Perspectives

Acupuncture and
Herbal Medicine

HerbRNome: exploring the mysteries of traditional Chinese medicine from a new perspective

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Since the proposal of the "central dogma," various types of RNA have been discovered, including messenger RNA (mRNA), ribosomal RNA (rRNA), and transfer RNA (tRNA). These RNAs are further classified into coding and non-coding RNAs (ncRNAs). The modernization of research on traditional Chinese medicines (TCMs) has led to the increasing availability of whole-genome sequences for medicinal plants and the initiation of RNome (ie, the complete set of all RNA species) projects for TCMs. In this article, from the perspective of mRNAs involved in the transmission and expression of genetic information and ncRNAs involved in the regulation of gene function in herbal taxa, we emphasize the importance of the discovery of novel functional ncRNA components in TCMs through the construction of systematic herbal mRNA libraries and an herbal ncRNA functional database for TCMs. This research area could revolutionize research and development focused on nucleic acid drugs and pesticides, opening up a new dimension for the modernization of TCMs.

Herbal mRNAs involved in genetic information transfer and expression

In the transmission and expression of genetic information, coding RNAs in herbs transfer genetic information from herbal DNA to the cytoplasm to direct protein synthesis. By constructing transcriptome libraries for herbs across different developmental stages, organs, and regions, we can uncover the regulatory mechanisms underlying herbal gene expression in diverse environments and comprehensively characterize the biosynthesis and regulation of secondary metabolites. Given the central role of mRNAs in genetic information processing, transcriptomics research focused on mRNAs shows great potential in various areas of herbal research, such as variety identification, phylogenetic analyses, genuineness identification, and molecular breeding[1].

Self-regulation of herbal ncRNAs

Once regarded as nonfunctional "dark matter," ncRNAs are now recognized as key factors in gene regulation. The most studied ncRNAs include microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular ncRNAs (circRNAs). Widespread in TCM plants, ncRNAs regulate growth and development as well as responses to biotic and abiotic stresses, thereby contributing to survival and reproduction. For instance, temperature is a key environmental factor affecting the yield and quality of *Astragalus*[2]. MiRNAs in *Astragalus* regulate cold stress responses and are candidate genes for molecular breeding to enhance cold tolerance. During growth, medicinal plants produce secondary metabolites with high biological activity, crucial for the pharmaceutical industry. Some ncRNAs regulate the biosynthesis of these metabolites; for example, miR5298b upregulates genes involved in paclitaxel biosynthesis, boosting its accumulation in *Taxus chinensis*[3]. Herbal RNAs have important regulatory functions in growth, stress resistance, and secondary metabolite production. Their use in molecular-assisted breeding could yield valuable secondary metabolites, advancing the generation of high-quality and high-grade Chinese medicinal materials.

Cross-kingdom regulation of herbal ncRNAs

In addition to self-regulation, herbal ncRNAs also exert cross-kingdom regulation (Figure 1). MIR2911, a honeysuckle-encoded microRNA, is highly stable in honeysuckle decoction, and mice fed the honeysuckle decoction show significantly elevated levels of MIR2911 in the peripheral blood and lungs[4]. Further analyses have revealed that MIR2911 effectively inhibits the replication of various influenza A viruses (including H1N1, H5N1, and H7N9) in mice, rescues viral infection-induced body weight loss, and reduces mortality associated with viral infection. Accordingly, herbal miRNAs can serve

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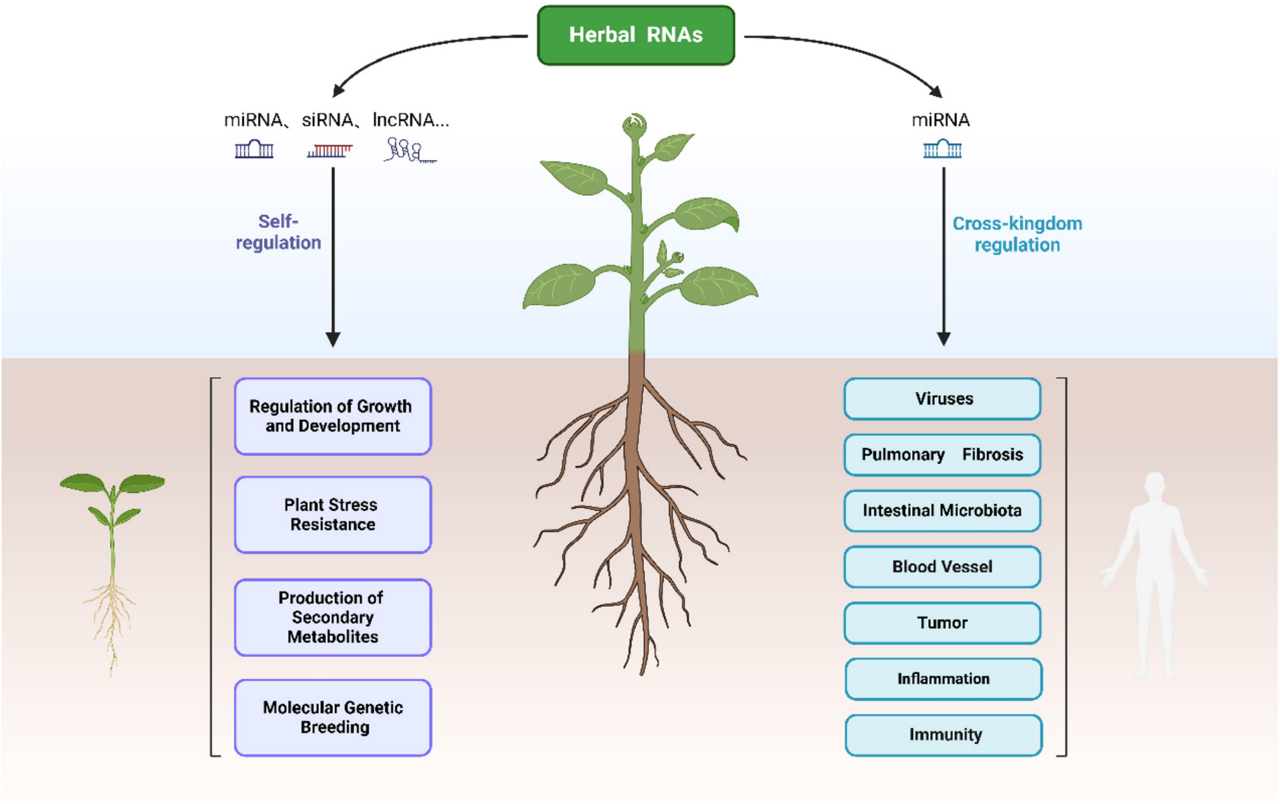

Figure 1. Self-regulation and cross-kingdom regulation of herbal RNAs. lncRNA: Long non-coding RNA; miRNA: MicroRNA; siRNA: Small interfering RNA.

as active ingredients in TCM. Subsequent research on the cross-kingdom regulation of herbal ncRNAs has yielded amazing findings. For instance, the small RNA HJT-sRNA-m7 from *Rhodiola crenulata* can alleviate bleomycin-induced lung fibrosis in mice[5]. Similarly, the small RNA BZL-sRNA-20 from *Scutellaria barbata* D. Don reduces the expression levels of pro-inflammatory factors in bronchoalveolar lavage fluid and plasma in a mouse model of lipopolysaccharide-induced acute lung injury and restores lung function[6]. Additionally, ncRNAs from TCM, such as *Salvia miltiorrhiza*[7], *Gastrodia elata*[8], and *Taraxacum mongolicum*[9], also demonstrate cross-kingdom regulatory effects. These studies not only validate the efficacy of herbal ncRNAs from TCM but also provide a basis for the development of novel small nucleic acid drugs utilizing these herbal ncRNAs.

HerbRNome research aims and process

The modernization of TCM necessitates addressing the limitations of conventional compositional analyses and elucidating systemic mechanisms underlying self-regulation and cross-kingdom regulation[10]. Based on the aforementioned research findings and to meet the multi-faceted and multi-level demands of modern TCM research and development, we hereby propose the concept of HerbRNome and introduce the related HerbRNomics research initiative. This initiative comprises the following three key components (Figure 2): Construction of HerbRNome databases: develop comprehensive databases of herbal RNAs profiles from various developmental stages (temporal), organs (spatial), and geographical origins (environmental) for medicinal plants, fungi, and animals; functional studies of herbal RNAs: investigate the roles of herbal RNAs in genetic information transmission and expression as well as in self-regulation. This includes identifying functional genes that confer resistance to environmental stresses and promote the biosynthesis of important secondary metabolites, thereby guiding and facilitating molecular-assisted breeding aimed at producing high-quality and high-grade medicinal materials; exploration of cross-kingdom regulatory mechanisms: explore the modes and mechanisms of cross-kingdom regulatory functions of herbal RNAs. This will provide a theoretical foundation and research framework for the development of novel therapeutic agents, such as small nucleic acid drugs and pesticides derived from and inspired by TCMs.

Application scenarios and research implications of HerbRNome

Construction of an HerbRNome database and discovery of functional genes

Gene expression exhibits temporal and spatial specificity. HerbRNome research on TCMs at different developmental stages, in various organs, and of different origins can help to identify functional genes and elucidate the mechanisms of specific regulatory genes. Bioactive secondary metabolites derived from TCMs are a valuable source of new drugs. Cloning the genes encoding key enzymes and employing metabolic engineering to produce the

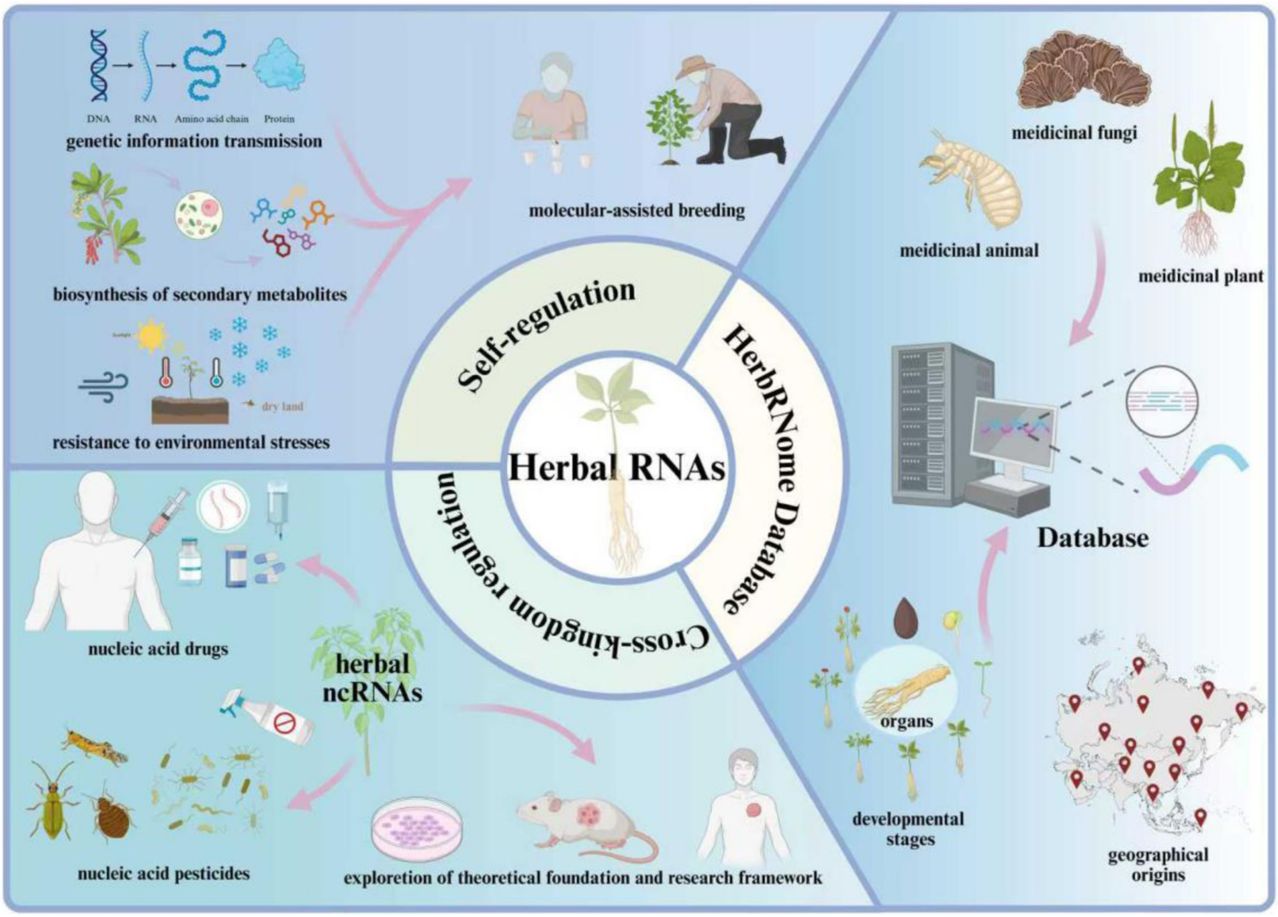

Figure 2. Overview of HerbRNome research. ncRNAs: Non-coding RNAs.

pharmacologically active components of medicinal plants are important approaches in drug research and development. The rapid development of RNA sequencing technology enables herbal RNA transcriptomics analyses aimed at the discovery of functional genes that regulate the biosynthesis of active ingredients in TCMs and the exploration of biosynthetic pathways, providing a basis for developing new drugs containing these active ingredients.

Exploring the self-regulatory mechanism of herbal ncRNAs and developing molecular-assisted breeding strategies

The increasing demand for traditional Chinese medicinal materials (TCMMs), driven by the growth of the TCM industry, has led to expansions in the range and quantity of TCMM varieties cultivated. The primary aim of cultivating TCMMs is to produce medicinal plant products, and breeding strategies influence the yield and quality of TCMM products. Unlike crop breeding, breeding TCMMs requires maintaining stable biological traits and ensuring the controllability of medicinal components. While the application of ncRNAs in the molecular-assisted breeding of crops has developed rapidly in recent years, their application in TCMM breeding has been relatively slow. However, with the release of medicinal plant genome sequences and reductions in the cost of high-throughput transcriptome sequencing, there are now significant opportunities for the molecular-assisted breeding of TCMMs with a high quality and grade.

Expanding the cross-kingdom regulatory functions of herbal ncRNAs and promoting the development of nucleic acid drugs

Numerous studies have confirmed that herbal ncRNAs from TCM can exert regulatory effects on mammalian pathological processes through cross-kingdom mechanisms. Herbal ncRNAs from TCM may be responsible for the observed therapeutic effects, supporting their applications in the development of small nucleic acid drugs. Conducting HerbRNome research on TCM enables the identification of ncRNAs with cross-kingdom regulatory functions. These ncRNAs can then undergo nucleic acid modifications to develop small nucleic acid drugs. This research strategy is expected to establish a new paradigm for developing nucleic acid drugs. Furthermore, further analyses of the delivery mechanisms of cross-kingdom regulatory herbal ncRNAs will provide new insights into the delivery of small nucleic acid drugs.

The scope of applications of HerbRNome is not limited to the aforementioned principal areas but will extend to various research fields, such as herbal plant variety identification, authenticity identification (Dao-di Herbs), and small RNA pesticide development. The scope of HerbRNome research will not be confined to the aspects outlined here; any studies related to herbal RNAs fall within its domain. In the future, HerbRNome research will unravel the mysteries of herbal biology, elucidate the scientific basis of the therapeutic effects of medicinal herbs, and expand the applications of TCM. The ultimate goal of HerbRNome research is to enhance China's capacity for innovation in TCM research and accelerate the modernization and industrialization of TCMs.

Conflict of interest statement

Weidong Zhang is the editorial board member of this journal and other authors declare no conflict of interest.

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Author contributions

Yu Tian and Hai Shang contributed to investigating writing and revising—original draft preparation. GuiBo Sun participated in conceptual discussion. Weidong Zhang contributed to conceptualization, review and editing, funding acquisition. All authors have read and agreed to the published version of the manuscript.

Ethical approval of studies and informed consent

Not applicable.

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Data availability

Not applicable.

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