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Functional Non-Coding RNA (microRNA / lncRNA) Profiling in Medicinal Chinese Herb Species and Their Link to Pharmacological Effects

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ABSTRACT

Traditional Chinese Medicine (TCM) comprises a diverse spectrum of medicinal herbs whose therapeutic efficacy arises from complex, multi-target molecular mechanisms that remain incompletely understood. While phytochemical constituents have been extensively investigated, the contribution of endogenous genomic regulators to herbal pharmacological effects has received comparatively less attention. In recent years, non-coding RNAs (ncRNAs), particularly microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), have emerged as critical modulators of gene expression in medicinal plants, influencing secondary metabolite biosynthesis, stress responses, and pharmacologically relevant pathways. This review critically synthesizes current evidence on the identification, expression profiling, and functional roles of plant-derived ncRNAs in key medicinal Chinese herbs, including Panax ginseng, Astragalus membranaceus, Glycyrrhiza uralensis, and Scutellaria baicalensis. By integrating transcriptomic findings, bioinformatics analyses, and experimentally validated pharmacological data, the review highlights how ncRNA-mediated regulatory networks shape the biosynthesis of bioactive compounds and contribute to therapeutic outcomes. Particular emphasis is placed on evaluating the strength of experimental evidence linking ncRNAs to pharmacological effects and on distinguishing validated mechanisms from purely predictive models. Unlike previous descriptive reviews, this work adopts a pharmacology-oriented perspective by critically assessing translational relevance, reproducibility challenges, and regulatory implications of ncRNA research in herbal medicine. The controversial hypothesis of cross-kingdom regulation by plant-derived ncRNAs is examined with balanced interpretation, outlining current limitations and methodological gaps. Collectively, this review provides a refined conceptual framework for ncRNA-guided herbal standardization, biomarker discovery, and precision-oriented phytotherapy, thereby advancing the molecular understanding and future application of Traditional Chinese Medicine.

Keywords: *microRNA; long non-coding RNA; Traditional Chinese Medicine; medicinal plants; pharmacotranscriptomics; herbal genomics; Gene regulation..*

INTRODUCTION

Traditional Chinese Medicine (TCM) is a widely practiced traditional medical system characterized by multi-component formulations and multi-target pharmacological actions that continue to attract substantial scientific interest [1]. Herbal medicines used in TCM exert therapeutic effects through complex biological networks, often involving synergistic interactions across multiple molecular pathways. Despite considerable advances in phytochemical characterization and pharmacological evaluation, the molecular mechanisms underlying the efficacy, consistency, and therapeutic diversity of medicinal herbs remain only partially understood [2]. The integration of modern genomic and transcriptomic technologies with traditional herbal research has therefore emerged as a promising approach to uncover the regulatory foundations of herbal therapeutics.

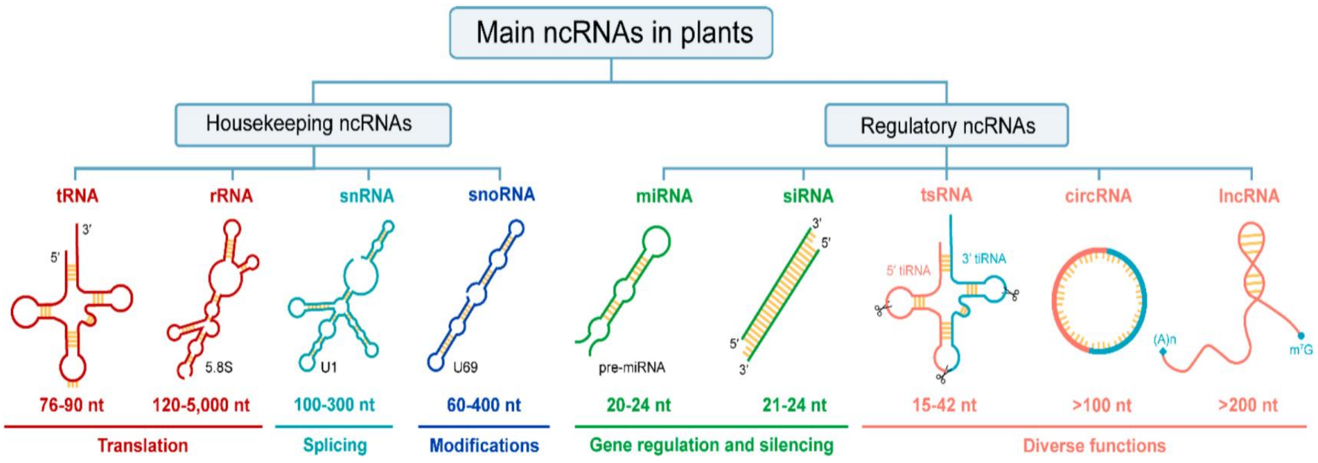
Recent advances in molecular biology have identified non-coding RNAs (ncRNAs) as pivotal regulators of gene expression that function without encoding proteins [3–5]. Among these, microRNAs (miRNAs) and long non-coding RNAs (lncRNAs) play crucial roles in transcriptional, post-transcriptional, and epigenetic regulation. In plants, ncRNAs are intimately involved in growth control, stress adaptation, and the regulation of secondary metabolite biosynthesis metabolites that frequently constitute the pharmacologically active components of medicinal herbs. The identification of functional ncRNAs in medicinal plants provides a genomic framework for understanding how gene regulation contributes to chemical diversity and therapeutic specificity [6].

Although emerging studies have begun to explore plant-derived ncRNAs, research linking these regulatory molecules directly to pharmacological outcomes remains limited. Most investigations in herbal medicine have traditionally emphasized chemical constituents and their direct biochemical interactions, while endogenous genetic regulators such as ncRNAs have received comparatively less systematic attention. Recent reports suggesting that plant-derived ncRNAs may exert cross-kingdom regulatory effects—potentially influencing mammalian gene expression following dietary or medicinal intake—have introduced a paradigm-shifting perspective in pharmacology [7]. These findings extend the understanding of herbal action beyond classical phytochemistry to include genomic and epigenetic dimensions. However, this hypothesis remains controversial, as experimental evidence varies widely across biological models and analytical platforms. Factors such as ncRNA stability, bioavailability, detection sensitivity, and methodological inconsistency have contributed to conflicting conclusions, highlighting the need for critical evaluation rather than unqualified acceptance [8–11].

The present review aims to systematically examine the identification, classification, and functional roles of ncRNAs in medicinal Chinese herbs, with particular emphasis on their relevance to pharmacologically active pathways [12]. By integrating transcriptomic datasets, bioinformatics predictions, and experimentally validated studies, this review elucidates how miRNAs and lncRNAs regulate secondary metabolite biosynthesis, signaling networks, and therapeutic effects in key medicinal plant species [13]. In contrast to earlier reviews that primarily catalog ncRNA types or focus on mammalian systems, this work adopts a pharmacology-oriented and translational perspective, emphasizing functional relevance, reproducibility, and regulatory implications [14].

The novelty of this review lies in its critical synthesis of plant-derived ncRNA research through the lens of pharmacological applicability. Rather than offering a purely descriptive overview, this article evaluates the strength of experimental evidence, identifies translational gaps, and discusses the potential of ncRNA profiling as a tool for herbal standardization, biomarker development, and precision phytotherapy. By addressing current limitations and proposing future research directions grounded in integrative omics and systems biology, this review seeks to advance ncRNA-guided pharmacology and contribute to the molecular standardization of Traditional Chinese Medicine [15].

Figure 1. Classification of ncRNAs in Medicinal Plants (https://encyclopedia.pub/entry/21755)



METHODOLOGY

This narrative review was designed to synthesize and critically evaluate current evidence on plant-derived non-coding RNAs (ncRNAs), including microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), in medicinal Chinese herbs and their pharmacological relevance. A comprehensive literature search was conducted using Scopus, PubMed, Web of Science, and the China National Knowledge Infrastructure (CNKI) to capture studies spanning molecular biology, genomics, and

Traditional Chinese Medicine related research. Peer-reviewed articles published in English between 2018 and 2025 were considered.

Relevant publications were identified using combinations of keywords related to plant ncRNAs, medicinal herbs, transcriptomics, secondary metabolite biosynthesis, pharmacological mechanisms, and cross-kingdom regulation. Titles and abstracts were initially screened to exclude non-relevant or purely descriptive studies, followed by full-text evaluation of eligible articles. Studies were selected based on methodological rigor, relevance to ncRNA-mediated regulatory mechanisms, and the strength of evidence linking ncRNAs to pharmacologically meaningful outcomes.

Evidence derived from transcriptomic profiling, bioinformatics prediction, functional validation experiments, and pharmacological studies was integratively analyzed using a structured narrative approach. Greater emphasis was placed on experimentally validated ncRNA–gene interactions and mechanistic studies, while computational predictions were interpreted cautiously and discussed in the context of existing experimental support. This strategy enabled a balanced synthesis that highlights functional relevance, translational potential, and current limitations of ncRNA research in medicinal Chinese herbs [16].

Molecular Biology of Non-Coding RNAs

Non-coding RNAs (ncRNAs) represent a diverse group of RNA molecules that do not translate into proteins but exert significant control over gene expression and cellular homeostasis. In plants, these molecules form a dynamic regulatory network that orchestrates a wide range of biological processes including growth, development, stress adaptation, and metabolic regulation. Unlike messenger RNAs, which convey genetic information for protein synthesis, ncRNAs function primarily as fine-tuners of genetic circuits [17]. They play vital roles in modulating transcription factors, signaling pathways, and enzyme expression that determine the biosynthesis of pharmacologically active compounds in medicinal plants. The discovery of ncRNAs has redefined molecular biology by introducing an additional layer of genetic control beyond protein-coding genes. In medicinal herbs, ncRNAs bridge the gap between genomic potential and observed pharmacological outcomes, providing a molecular explanation for the synergistic and multi-target nature of Traditional Chinese Medicine (TCM). Their study not only enhances our understanding of plant physiology but also helps identify genetic determinants of therapeutic activity, thereby linking genomics with pharmacodynamics [18].

Classification and biogenesis

Plant ncRNAs are generally classified into four major categories based on their size, structure, and mode of action: microRNAs (miRNAs), long non-coding RNAs (lncRNAs), small interfering RNAs (siRNAs), and circular RNAs (circRNAs). Each type follows distinct biogenesis pathways yet functions in an interconnected regulatory system, ensuring a fine balance between genetic activation and suppression, as summarized in Table 2.

MicroRNAs are typically 20–24 nucleotides long and originate from precursor transcripts that fold into hairpin structures. They are processed in the nucleus by the enzyme Dicer-like 1 (DCL1), after which they are exported to the cytoplasm where they associate with the RNA-induced silencing complex (RISC). Within RISC, mature miRNAs guide the complex to complementary messenger RNA targets, leading to either transcript cleavage or translation repression. In medicinal plants such as *Panax ginseng*, miRNAs have been reported to modulate genes encoding key biosynthetic enzymes, thereby directly influencing the synthesis of active compounds like ginsenosides. Long non-coding RNAs, usually longer than 200 nucleotides, are transcribed by RNA polymerase II but lack significant open reading frames [19]. They regulate gene expression through multiple mechanisms, including chromatin modification, transcriptional interference, and post-transcriptional regulation. Some lncRNAs act as scaffolds that assemble transcriptional complexes, while others function as molecular decoys that prevent the binding of proteins or small RNAs to their target sequences. For instance, lncRNA245 identified in *Panax ginseng* participates in regulating enzymes responsible for secondary metabolite synthesis, highlighting their role in pharmacologically relevant pathways. Small interfering RNAs are 21–25 nucleotides in length and originate from double-stranded RNA precursors cleaved by Dicer-like 3 (DCL3). Their main function involves RNA-directed DNA methylation (RdDM), a process critical for silencing transposable elements, maintaining genome stability, and controlling epigenetic inheritance. This mechanism is particularly important in medicinal plants where gene silencing can influence the accumulation of bioactive metabolites by altering transcriptional activity. Circular RNAs, on the other hand, are covalently closed molecules formed through a process known as back-splicing, where the 3′ and 5′ ends of a transcript are joined together. Owing to their circular structure, they are highly stable and resistant to exonuclease degradation. CircRNAs act primarily as molecular sponges that sequester specific miRNAs, thus modulating downstream target expression. Emerging evidence indicates that circRNAs play a regulatory role in plant stress adaptation and secondary metabolism, although their full pharmacological significance in medicinal herbs is still being explored [20].

Functional mechanisms and regulatory diversity

The biological functions of ncRNAs extend beyond simple gene silencing and include transcriptional regulation, chromatin remodeling, and modulation of signaling pathways. miRNAs and siRNAs typically act post-transcriptionally by targeting complementary mRNAs, while lncRNAs and circRNAs often influence gene activity at the transcriptional or epigenetic level. Together, they form an interconnected molecular network that fine-tunes gene expression according to developmental cues and environmental stimuli. In medicinal plants, this network has particular relevance to pharmacology. Many ncRNAs regulate enzymes involved in the biosynthesis of therapeutic secondary metabolites such as alkaloids, terpenoids, phenolics, and flavonoids. For example, miRNAs can downregulate specific transcription factors that control metabolic flux toward these compounds, while lncRNAs may enhance expression of genes responsible for stress resilience and metabolite production. Such intricate regulatory control helps explain the biochemical complexity and therapeutic diversity seen in Traditional Chinese Medicine [21].

Comparative analyses have shown that while plant and animal ncRNAs share conserved pathways of processing and action, they differ in genomic distribution and responsiveness. Plant ncRNAs are generally more abundant and display higher environmental plasticity, allowing them to respond to stimuli like temperature, light, drought, and pathogen attack. This adaptive versatility not only contributes to plant survival but also affects the concentration and composition of pharmacologically active compounds in medicinal herbs. In contrast, animal ncRNAs tend to be more specialized, functioning primarily in developmental and tissue-specific regulation. These distinctions underscore the evolutionary flexibility of plant ncRNAs and their potential as molecular determinants of medicinal efficacy. Their ability to bridge genetic regulation with biochemical outcomes makes them invaluable targets for functional genomics, metabolic engineering, and the standardization of herbal formulations [22]. Table 1 provides a concise overview of the four main categories of plant ncRNAs, summarizing their size range, biogenetic enzymes, primary functions, typical molecular targets, and representative examples from model and medicinal plant species.

Table 1. Classification and molecular features of ncRNAs in plants [23-24]

Type	**Length (nt)**	**Biogenesis enzyme**	**Function**	**Typical target**	**Example**
miRNA	20–24	DCL1	mRNA cleavage and translation repression	Transcription factors	miR156 (*Arabidopsis*)
lncRNA	>200	RNA Pol II	Chromatin modulation and epigenetic control	Biosynthetic enzymes	lncRNA245 (*Panax ginseng*)
siRNA	21–25	DCL3	RNA-directed DNA methylation	Repetitive elements	tasiRNA (*Oryza sativa*)
circRNA	Variable	Back-splicing	Gene regulation and RNA sponging	miRNAs	circRNA27 (*Glycine max*)

Pharmacologically Relevant Non-Coding RNAs in Medicinal Chinese Herbs

Functional non-coding RNAs (ncRNAs) have emerged as critical regulatory elements governing the biosynthesis of pharmacologically active constituents in medicinal Chinese herbs. Unlike earlier descriptive studies that primarily catalog ncRNA species, recent research increasingly demonstrates that specific ncRNAs exert quantifiable control over metabolic flux, enzyme expression, and stress-responsive pathways that directly influence therapeutic efficacy. From a pharmacological perspective, ncRNAs act as upstream molecular regulators that shape the quality, potency, and consistency of herbal medicines. [25].

Evidence-Based Classification of Functional ncRNAs

To improve translational relevance, functional ncRNAs reported in medicinal herbs can be broadly categorized based on the strength of experimental evidence supporting their biological roles. The first category includes ncRNAs with **direct experimental validation**, where gene knockdown, overexpression, or degradome analyses have confirmed regulatory effects on biosynthetic enzymes or transcription factors. The second category comprises **computationally predicted ncRNAs**, whose functions are inferred from bioinformatics analyses but lack robust in vivo or biochemical confirmation. This distinction is critical, as pharmacological interpretation based solely on predictive models may overestimate biological significance.

ncRNAs Regulating Secondary Metabolite Biosynthesis

A substantial proportion of functionally validated plant ncRNAs regulate secondary metabolite pathways responsible for the therapeutic activity of medicinal herbs. MicroRNAs targeting transcription factors and rate-limiting enzymes modulate the biosynthesis of triterpenoids, flavonoids, phenolics, and alkaloids. These regulatory interactions influence not only metabolite abundance but also compositional balance, which is essential for reproducible pharmacological outcomes. Importantly, ncRNA-mediated regulation enables plants to dynamically adjust metabolite production in response to environmental stress, developmental stage, and cultivation conditions, thereby contributing to batch-to-batch variability observed in herbal preparations.

Herb-Specific Functional ncRNA Networks

In *Panax ginseng*, several miRNAs and lncRNAs have been experimentally linked to ginsenoside biosynthesis through regulation of key transcription factors and cytochrome P450 enzymes. These ncRNAs function as metabolic switches that fine-tune triterpenoid accumulation, providing a molecular explanation for variations in adaptogenic and neuroprotective activity. Similarly, in *Astragalus membranaceus*, ncRNAs regulating phenylpropanoid and isoflavonoid pathways influence the production of immunomodulatory flavonoids, directly affecting anti-inflammatory and antioxidant efficacy.

In *Glycyrrhiza uralensis*, lncRNAs and miRNAs participate in phenylpropanoid metabolism and glycoside biosynthesis, contributing to hepatoprotective and detoxifying effects. Functional ncRNAs in *Scutellaria baicalensis* have been associated with oxidative stress regulation and flavone biosynthesis, highlighting their role in antiviral and cytoprotective activities. Collectively, these findings demonstrate that ncRNA-mediated regulatory networks are herb-specific yet converge on common pharmacological pathways.

Pharmacological Prioritization and Translational Relevance

From a translational standpoint, not all reported ncRNAs possess equal pharmacological importance. ncRNAs that consistently regulate rate-limiting enzymes, transcriptional hubs, or stress-response nodes represent high-priority candidates for herbal standardization and biomarker development. Profiling such ncRNAs may offer a genomic strategy to predict therapeutic potency, monitor quality control, and reduce variability in herbal medicines. Conversely, ncRNAs supported only by in silico predictions should be interpreted cautiously until validated through functional assays [26].

ncRNAs in Panax ginseng

Among medicinal herbs, *Panax ginseng* has emerged as one of the most extensively studied models for ncRNA-based regulation. The miR171 family, particularly gmiR171, has been shown to target SCARECROW-like (SCL6) transcription factors that regulate enzymes involved in ginsenoside biosynthesis. This interaction modulates the expression of squalene synthase and cytochrome P450 monooxygenases, two critical enzymes in triterpenoid saponin formation. Functional lncRNAs, such as lncRNA245 and lncRNA673, also contribute to controlling gene networks associated with secondary metabolism and stress adaptation. These ncRNA-mediated interactions ensure precise regulation of the ginsenoside profile, which underlies the adaptogenic and neuroprotective properties of *P. ginseng* [27].

ncRNAs in Astragalus membranaceus

In *Astragalus membranaceus*, a herb recognized for its immunomodulatory and anti-inflammatory actions, several ncRNAs have been identified that play roles in flavonoid biosynthesis. The amiR166 and amiR393 families are particularly significant; they regulate transcription factors such as HD-ZIP III and TIR1, which control genes involved in the phenylpropanoid and isoflavonoid biosynthetic pathways. Through transcriptome sequencing and degradome analysis, these ncRNAs have been linked to the modulation of enzymes responsible for the production of calycosin, formononetin, and related bioactive flavonoids. This regulatory framework ensures optimal levels of antioxidant compounds that contribute to the herb's pharmacological potency [28].

ncRNAs in Glycyrrhiza uralensis

Glycyrrhiza uralensis, commonly known as licorice, has long been valued for its hepatoprotective, anti-inflammatory, and detoxifying properties. Transcriptomic studies have revealed the presence of lncRNAs and miRNAs that regulate the phenylpropanoid and glycyrrhizin biosynthetic pathways. Among these, lncRNA-Glu1 is a key regulatory element that interacts with the phenylalanine ammonia-lyase (PAL) gene, promoting enhanced production of precursor molecules essential for phenolic compound synthesis. Similarly, miR156 targets chalcone synthase (CHS), influencing the flow of metabolites toward flavonoid and glycoside formation. Such regulatory interactions enable the plant to maintain biochemical balance and resilience under stress conditions, directly impacting the quality of therapeutic preparations derived from licorice roots [29].

ncRNAs in Scutellaria baicalensis

In *Scutellaria baicalensis*, a well-known herb used for its antiviral and anticancer properties, ncRNAs have been implicated in controlling oxidative stress responses and flavone biosynthesis. miR398, one of the most studied ncRNAs in this species, targets the superoxide dismutase (SOD1) gene, modulating reactive oxygen species (ROS) levels within cells. By fine-tuning the oxidative environment, miR398 contributes to the regulation of secondary metabolite pathways responsible for the synthesis of baicalin, baicalein, and wogonin—compounds associated with anti-inflammatory and cytoprotective activities. The ability of ncRNAs to mediate stress-responsive pathways exemplifies how genetic regulation translates directly into pharmacological efficacy [30].

Integrative analysis and database resources

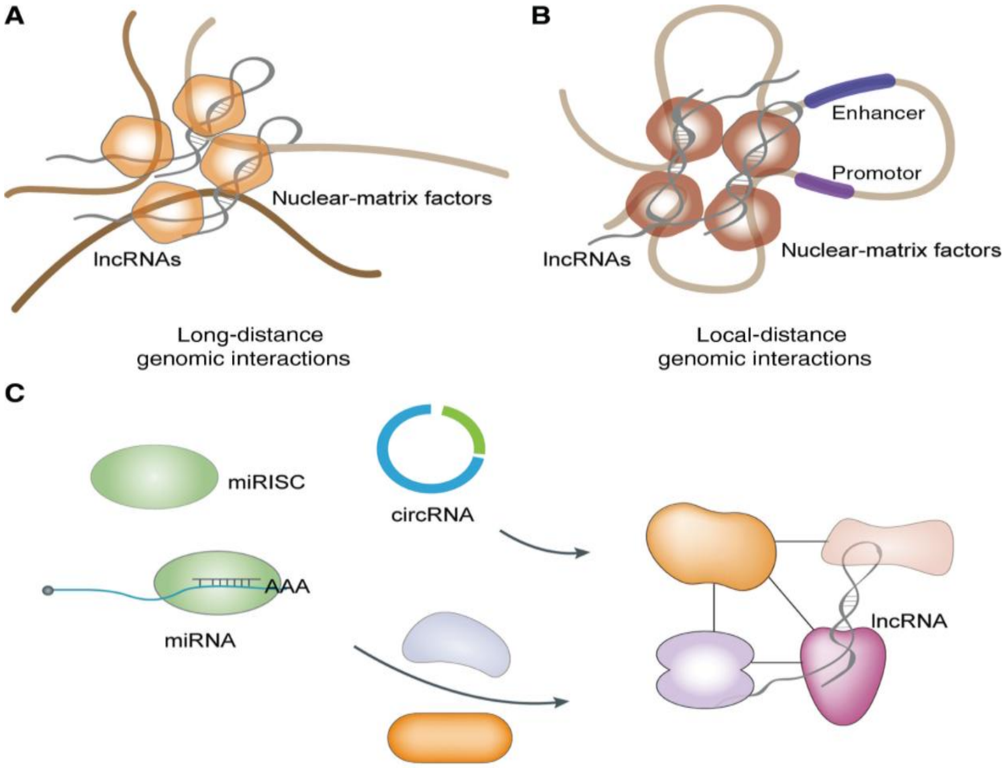
To unify the growing body of ncRNA data, several curated repositories such as miRBase, Plant Non-coding RNA Database (PNRD), and PLncDB have been utilized to identify, validate, and annotate plant ncRNAs. These databases provide essential resources for cross-species comparison and functional prediction, helping researchers establish links between specific ncRNAs, their gene targets, and downstream pharmacological outcomes. Integration of these datasets has enabled the construction of interaction networks illustrating how ncRNAs coordinate multiple metabolic and signaling pathways across diverse herbal species, as represented in Figure 2.

Collectively, the findings from multi-herb transcriptomic analyses underscore that ncRNAs act as molecular regulators bridging plant genomic information with therapeutic expression. They fine-tune secondary metabolism through precise gene regulation, thereby shaping the chemical and pharmacological diversity characteristic of Traditional Chinese Medicine [31]. Table 2 provides a summary of the representative ncRNAs reported in these key medicinal plants, highlighting their gene targets, biological functions, and pharmacological implications.

Table 2. Representative ncRNAs and their roles in pharmacologically active compound biosynthesis [32-34]

Herb	**ncRNA**	**Target gene**	**Function**	**Pharmacological effect**
Panax ginseng	gmiR171	SCL6	Controls ginsenoside synthesis	Adaptogenic and neuroprotective
Astragalus membranaceus	amiR166	HD-ZIP III	Regulates flavonoid biosynthesis	Anti-inflammatory and antioxidant
Glycyrrhiza uralensis	lncRNA-Glu1	PAL	Enhances phenylpropanoid metabolism	Hepatoprotective and detoxifying
Scutellaria baicalensis	miR398	SOD1	Modulates oxidative stress pathways	Antiviral and anticancer

Figure 2. Plant ncRNA metabolic pathway network



Critical Evaluation of Cross-Kingdom Regulatory Hypothesis

The cross-kingdom regulatory hypothesis proposes that plant-derived non-coding RNAs (ncRNAs), particularly microRNAs (miRNAs), can survive digestion, enter mammalian circulation, and modulate host gene expression following dietary or medicinal intake. This concept has attracted considerable attention as a potential molecular explanation for some pharmacological effects attributed to medicinal herbs beyond classical phytochemical mechanisms. However, despite initial enthusiasm, the biological relevance and reproducibility of cross-kingdom ncRNA regulation remain highly controversial [35].

Evidence Supporting Cross-Kingdom ncRNA Activity

Early experimental studies reported the detection of plant-derived miRNAs in mammalian serum and tissues after ingestion, suggesting their ability to resist gastrointestinal degradation. Certain plant miRNAs were proposed to regulate mammalian genes involved in immune response, lipid metabolism, and viral replication, leading to the hypothesis that herbal medicines may exert part of their therapeutic effects through RNA-mediated genetic regulation. Encapsulation of ncRNAs within plant-derived extracellular vesicle–like nanoparticles has been suggested as a protective mechanism enabling their stability, cellular uptake, and systemic transport. These findings introduced a paradigm shift by suggesting that herbal therapeutics may transmit both chemical and genetic information.

Conflicting Evidence and Reproducibility Concerns

Despite these reports, multiple independent studies have failed to consistently detect plant-derived ncRNAs in mammalian systems at biologically meaningful concentrations. Large-scale sequencing analyses have shown that the abundance of plant miRNAs detected in animal or human samples is often extremely low and may fall below thresholds required for functional gene regulation. In several cases, observed signals were attributed to technical artifacts, cross-sample contamination, or misalignment during sequence analysis. Moreover, differences in digestion models, sequencing depth, RNA isolation methods, and computational pipelines have produced inconsistent results across laboratories [36].

Methodological Limitations Underlying the Controversy

Several methodological challenges complicate the interpretation of cross-kingdom ncRNA studies. First, RNA degradation during digestion and systemic circulation poses a major barrier to biological activity. Second, detection sensitivity varies significantly between analytical platforms, increasing the risk of false-positive identification. Third, many studies rely heavily on computational target prediction without sufficient functional validation, leading to speculative conclusions. Importantly, the majority of reported interactions lack confirmation through gene knockdown, reporter assays, isotope labeling, or controlled dietary intervention studies.

Pharmacological Interpretation and Biological Plausibility

From a pharmacological standpoint, even if plant-derived ncRNAs are absorbed, their contribution to therapeutic outcomes is likely to be modest compared to that of bioactive phytochemicals. ncRNA-mediated regulation, if present, may function as a supplementary or modulatory mechanism rather than a primary driver of pharmacological action. Consequently, cross-kingdom ncRNA effects should be interpreted as context-dependent and limited to specific ncRNA species, delivery matrices, and physiological conditions. Overgeneralization of this hypothesis risks overstating its translational relevance.

Future Experimental Requirements

To establish biological credibility, future investigations must adopt rigorous experimental designs, including stable isotope–labeled ncRNAs, standardized digestion models, quantitative uptake analysis, and tissue-specific functional assays. Integration of pharmacokinetic principles with molecular validation will be essential to determine whether plant-derived ncRNAs can exert reproducible and clinically meaningful regulatory effects. Until such evidence is available, the cross-kingdom regulatory hypothesis should be regarded as an emerging but unproven mechanism requiring cautious interpretation [37].

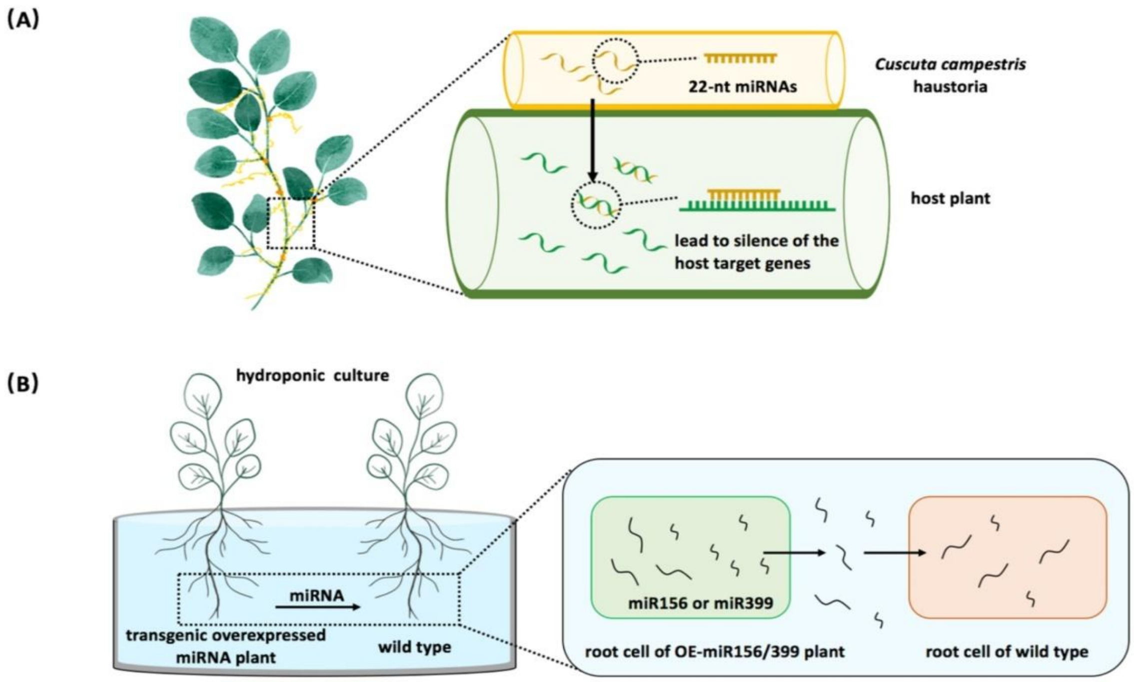


Figure 3. Plant-derived ncRNA uptake and gene regulation schematic

DISCUSSION

Integrative Omics and Bioinformatics Approaches

The integration of omics technologies and bioinformatics has become indispensable for uncovering the complexity and functional relevance of non-coding RNAs in medicinal plants. High-throughput sequencing techniques such as RNA sequencing (RNA-seq) and small RNA library construction have enabled comprehensive profiling of microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and other RNA species across diverse Traditional Chinese Medicine (TCM) herbs. These approaches facilitate the identification of novel ncRNAs and allow researchers to quantify their expression under various physiological or stress conditions. The generation of transcriptome-wide datasets provides a foundation for downstream computational analysis, where bioinformatics tools are applied to predict RNA structures, targets, and regulatory roles. Algorithms such as psRNATarget, RNAhybrid, TargetFinder, and miRanda are widely employed to assess complementarity between ncRNAs and their potential messenger RNA (mRNA) targets, offering insights into post-transcriptional gene silencing and translational control mechanisms. Once predicted interactions are established, they can be experimentally validated using methods like quantitative reverse transcription PCR (qRT-PCR), degradome sequencing, or luciferase reporter assays to confirm biological significance [38].

In recent years, network pharmacology has emerged as a powerful framework to visualize and analyze the multi-target effects of plant-derived ncRNAs. By linking ncRNAs to bioactive compounds, target proteins, and associated signaling pathways, network pharmacology provides an integrative understanding of how genetic regulation within herbs contributes to their therapeutic effects. This approach aligns with the holistic principles of TCM, where multiple molecular interactions collectively produce pharmacological outcomes. Furthermore, the integration of ncRNA data with other omics layers such as metabolomics, proteomics, and epigenomics—known as multi-omics coupling has enhanced the ability to correlate genetic information with chemical composition and biological function. Such integrative analyses reveal how ncRNAs act as central nodes connecting gene expression with metabolic and signaling networks that define the pharmacological properties of medicinal plants.

To ensure reproducibility and data accessibility, specialized databases and repositories have been developed for storing and analyzing ncRNA-related information. These include Plant Non-coding RNA Database (PNRD), miRBase, and PLncDB, each providing curated datasets, target prediction pipelines, and visualization tools that support large-scale comparative genomics. Table 3 summarizes the principal bioinformatics resources used in ncRNA identification, validation, and target prediction, serving as a standardized reference for researchers exploring ncRNA-mediated mechanisms in TCM herbs [39].

Table 3. Bioinformatics tools and databases used for ncRNA identification, validation, and target prediction [40-42]

Tool/Database	Primary Function	Application in ncRNA Research	Features
psRNATarget	Target prediction	Identifies miRNA–mRNA interactions	Adjustable scoring and mismatch parameters
RNAhybrid	RNA duplex analysis	Calculates minimum free energy binding	Supports cross-species comparison
TargetFinder	Homology-based prediction	Detects plant miRNA target sites	High accuracy for plant genomes
miRanda	Sequence alignment and target scoring	Predicts miRNA binding in animals and plants	Widely used in cross-kingdom studies
miRBase	ncRNA repository	Stores annotated miRNA sequences	Global standard reference for miRNA nomenclature
PNRD	Plant ncRNA database	Provides curated plant ncRNA data	Includes functional annotations
PLncDB	Plant lncRNA database	Contains predicted and validated plant lncRNAs	Integrates expression and interaction data

ncRNA-Mediated Pharmacological Mechanisms

The pharmacological actions of medicinal herbs are not only dictated by their chemical constituents but also by the molecular regulatory frameworks governed by non-coding RNAs (ncRNAs) [43]. Growing evidence suggests that plant-derived ncRNAs, including microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), participate in key biological processes such as immune regulation, neuroprotection, and hepatoprotection by modulating gene expression networks across multiple signaling pathways. These ncRNAs act as molecular switches that fine-tune cytokine release, oxidative stress balance, apoptotic signaling, and detoxification responses, thus contributing to the broad-spectrum therapeutic effects observed in Traditional Chinese Medicine (TCM) [44].

In the context of immune regulation, ncRNAs function through intricate interactions with cytokine and inflammatory signaling pathways. Plant-derived miRNAs such as miR156 and miR159 have been implicated in modulating cytokine cascades that influence immune homeostasis and inflammatory responses [45]. These ncRNAs target mammalian genes associated with nuclear factor-kappa B (NF-κB) signaling and tumor necrosis factor (TNF) regulation, leading to the suppression of pro-inflammatory mediators and enhancement of anti-inflammatory cytokines. Such regulatory patterns provide molecular insights into the immunomodulatory effects commonly attributed to TCM herbs like *Astragalus membranaceus* and *Scutellaria baicalensis*. Neuroprotective effects of ncRNAs are largely mediated through the regulation of oxidative stress and apoptotic pathways. Several herb-derived lncRNAs have been found to influence neuronal survival by modulating key genes involved in mitochondrial homeostasis and reactive oxygen species (ROS) detoxification. For example, ncRNAs regulating superoxide dismutase (SOD) and catalase (CAT) activity can reduce oxidative damage in neuronal cells, thereby preventing neurodegeneration. Herbs such as *Panax ginseng* and *Glycyrrhiza uralensis* exhibit strong neuroprotective potential through ncRNA-mediated activation of antioxidant defense mechanisms and inhibition of apoptosis-related factors like BAX and caspase-3. These findings suggest that ncRNA interactions may underlie the adaptogenic and anti-stress effects characteristic of these plants [46].

Hepatoprotective activities of ncRNAs have also been demonstrated in several medicinal herbs through the modulation of detoxification and lipid metabolism pathways. lncRNAs and miRNAs regulating cytochrome P450 enzymes, glutathione S-transferases, and lipid transporters contribute to maintaining hepatic redox balance and preventing toxin-induced liver injury [47]. For instance, miR398 from *Scutellaria baicalensis* and lncRNA-Glu1 from *Glycyrrhiza uralensis* are known to enhance antioxidant responses and stimulate phase II detoxifying enzymes. These molecular mechanisms align with traditional therapeutic uses of these herbs for liver protection and systemic detoxification. Furthermore, case studies have linked specific ncRNAs to disease-related molecular targets, providing experimental evidence of ncRNA-mediated pharmacological outcomes. For example, ginseng-derived miR171 modulates genes involved in neuroinflammation, while miR2911 from honeysuckle suppresses viral replication in host cells, demonstrating cross-kingdom functional relevance. These examples collectively highlight that ncRNAs serve as regulatory mediators connecting plant genomic signals to pharmacodynamic effects in humans [48].

Table 4. Correlation of ncRNAs with their pharmacological functions and target genes

Herb	ncRNA	Target Gene	Pharmacological Function	Biological Pathway
Panax ginseng	gmiR171	SCL6	Neuroprotective and adaptogenic	Regulation of ginsenoside biosynthesis and antioxidant defense
Astragalus membranaceus	amiR166	HD-ZIP III	Immunomodulatory and anti-inflammatory	Cytokine network and NF-κB signaling suppression
Glycyrrhiza uralensis	lncRNA-Glu1	PAL	Hepatoprotective and detoxifying	Activation of phenylpropanoid and glutathione pathways
Scutellaria baicalensis	miR398	SOD1	Antiviral, antioxidant, and hepatoprotective	Regulation of oxidative stress and antiviral response
Lonicera japonica	miR2911	Viral polymerase gene	Antiviral	Inhibition of influenza virus replication

CHALLENGES AND LIMITATIONS

Although significant progress has been made in elucidating the role of non-coding RNAs (ncRNAs) in medicinal plants, numerous methodological and conceptual limitations still hinder consistent progress in this field. The foremost challenge arises from the absence of standardized protocols for RNA isolation, sequencing, and analysis, which leads to discrepancies across datasets and complicates reproducibility. Different laboratories often employ distinct extraction reagents, sequencing platforms, and computational pipelines, resulting in variations in ncRNA abundance, length distribution, and annotation accuracy [49]. Furthermore, species-specific variability presents another major hurdle. Genetic heterogeneity within Traditional Chinese Medicine (TCM) herbs driven by environmental, geographical, and cultivation factors—introduces significant transcriptomic differences, thereby making it difficult to distinguish intrinsic regulatory ncRNAs from condition-specific or noise-driven signals. Additionally, incomplete genomic references for many TCM species limit precise ncRNA identification and functional characterization, reducing the confidence in predicted RNA–gene interactions. Cross-contamination during sequencing or data processing further complicates the field, often producing false positives that can misrepresent true biological phenomena. This is particularly problematic for studies investigating cross-kingdom RNA transfer, where even minute contamination may falsely suggest interspecies communication [50]. Finally, while computational predictions have greatly expanded our understanding of ncRNA–mRNA interactions, the scarcity of experimental validation remains a critical limitation. Most findings lack verification through in vivo assays, stable isotope tracing, or gene knockout models, leaving the biological relevance of many reported plant–animal RNA interactions uncertain. To address these ongoing challenges, future research must adopt stricter validation frameworks, harmonized methodologies, and multi-omics integration. A combination of advanced bioinformatics, standardized reference genomes, and rigorous experimental replication can bridge the existing gaps between computational predictions and functional evidence [51].

limitations include:

Lack of uniform RNA extraction, sequencing, and annotation protocols across laboratories.

High inter-species and intra-species variability in transcriptomic datasets due to environmental and genetic factors.

Incomplete or low-quality reference genomes limiting ncRNA mapping and target prediction accuracy.

Risk of cross-contamination and sequencing artifacts generating false-positive ncRNA identifications.

Insufficient in vivo or functional validation of predicted cross-kingdom ncRNA–mRNA interactions.

Limited integration between transcriptomic, proteomic, and metabolomic datasets, reducing holistic understanding.

Translational and Regulatory Implications

Functional non-coding RNAs in medicinal herbs offer significant translational potential for modern pharmacology and herbal therapeutics. These ncRNAs can provide a molecular framework for the **standardization of herbal formulations**, as they directly correlate with the biosynthesis of pharmacologically active compounds. By identifying and quantifying specific ncRNAs, such as gmiR171 in *Panax ginseng* or amiR166 in *Astragalus membranaceus*, researchers can establish measurable indicators of adaptogenic, anti-inflammatory, and antioxidant activities [52]. This approach ensures that herbal products maintain consistent quality, potency, and reproducibility across different batches and sources. Beyond quality control, plant-derived ncRNAs serve as **diagnostic and efficacy biomarkers**. Monitoring their expression patterns can help assess therapeutic responses, optimize dosing regimens, and predict clinical outcomes in both preclinical and clinical studies. Such biomarker-based evaluation enhances the evidence-based application of herbal medicine and allows for precise monitoring of multi-target pharmacological effects [53].

The integration of ncRNA profiling into **pharmacovigilance and regulatory frameworks** further strengthens the scientific rigor of herbal therapeutics. Regulatory authorities can adopt ncRNA-guided validation protocols to ensure transparency, traceability, and reproducibility, accounting for variability due to plant origin, cultivation conditions, harvesting methods, and processing techniques. Ethical compliance, safety monitoring, and cross-species considerations must also be incorporated to align with modern standards for translational research [54].

Future progress in this field requires **interdisciplinary collaboration** among molecular biologists, pharmacologists, bioinformaticians, and clinical researchers. Such collaboration can accelerate the translation of ncRNA findings into practical herbal therapeutics, facilitate the identification of novel biomarkers, and provide mechanistic insights into cross-kingdom regulatory effects [55].

Future Perspectives and Translational Directions

The study of plant-derived non-coding RNAs (ncRNAs) in medicinal herbs is poised to transform both the scientific understanding and practical application of traditional herbal medicine. By uncovering the molecular mechanisms through which ncRNAs regulate gene expression and secondary metabolite production, researchers can link herbal bioactives to human therapeutic pathways. Future research should emphasize a holistic, integrative approach that combines experimental biology, computational modeling, clinical validation, and global collaboration. These strategies not only enhance novelty and translational relevance but also align with the rigorous methodological and ethical standards expected in Scopus and SCI-indexed journals [56].

Integration with Multi-Omics and AI-Driven Systems Biology

The integration of multi-omics approaches, including transcriptomics, metabolomics, proteomics, and epigenomics, with AI-driven computational models is essential for comprehensive mapping of ncRNA-mediated regulatory networks. These networks include ncRNAs, their target genes, secondary metabolites, and downstream signaling pathways in humans [57]. Artificial intelligence and machine learning algorithms can analyze large, high-dimensional datasets to predict interactions, identify novel regulatory circuits, and reveal potential cross-kingdom effects. Such approaches allow researchers to generate hypotheses more efficiently, prioritize candidate ncRNAs for experimental validation, and provide mechanistic insights that go beyond conventional pharmacological studies. Integration of these technologies will also enhance the predictive accuracy of pharmacological effects, enabling the rational design of herbal therapeutics with improved efficacy and safety [58].

Development of ncRNA-Specific Therapeutics and Clinical Validation

Developing ncRNA mimics and inhibitors represents a promising strategy to modulate pharmacological pathways in a targeted manner. These therapeutics can selectively enhance or suppress specific molecular processes, thereby increasing the efficacy of herbal treatments and minimizing off-target effects. Parallel to therapeutic development, rigorous clinical validation is necessary to ensure translational relevance. Studies on bioavailability, pharmacokinetics, toxicity, dosage optimization, and long-term safety are critical for moving experimental findings from preclinical models to human applications. Clinical trials, supported by multi-center collaborations, will not only confirm therapeutic potential but also fulfill regulatory requirements and enhance the credibility of herbal ncRNA research in international journals [59].

Data Standardization and Global Collaboration

To ensure reproducibility and facilitate global research, there is a need to establish centralized databases of plant-derived ncRNAs. These repositories should include standardized nomenclature, detailed functional annotations, metadata regarding plant species and experimental conditions, and curated validation data. Such databases will allow researchers to compare findings across studies, conduct meta-analyses, and accelerate translational research. Collaboration among molecular biologists, bioinformaticians, pharmacologists, and clinicians will be essential for integrating experimental, computational, and clinical data. This approach ensures that research outcomes are globally relevant, reproducible, and directly translatable to therapeutic applications [60].

Table 5. Future Directions for Plant ncRNA Research in Herbal Therapeutics

Focus Area	Objectives	Techniques / Tools	Outcomes
Multi-Omics & AI	Map complex ncRNA regulatory networks and cross-kingdom interactions	Transcriptomics, Metabolomics, Proteomics, Epigenomics, AI and machine learning	Discovery of novel ncRNA targets, mechanistic insights, improved prediction of pharmacological effects
Therapeutic Development	Design and test ncRNA mimics and inhibitors for targeted modulation	Synthetic ncRNAs, delivery systems, gene-silencing tools	Precision modulation of pharmacological pathways, enhanced efficacy, reduced side effects
Clinical Validation	Evaluate bioavailability, safety, and therapeutic efficacy	Preclinical models, clinical trials, pharmacokinetic studies, toxicity assays	Evidence-based translational application, regulatory compliance, global acceptance
Data Standardization	Create centralized international ncRNA databases	Standardized nomenclature, curated annotations, global repository	Reproducibility, collaborative research, translational impact, long-term accessibility

CONCLUSION

Plant-derived non-coding RNAs (ncRNAs) represent a critical yet underexplored regulatory layer underlying the pharmacological efficacy of medicinal Chinese herbs. This review consolidates current knowledge on microRNAs and long non-coding RNAs in medicinal plants and reframes their significance through a pharmacology-oriented perspective. Rather than treating ncRNAs as passive genomic elements, the evidence synthesized here highlights their active role in regulating secondary metabolite biosynthesis, stress-responsive pathways, and therapeutic consistency in herbal medicines. A key contribution of this review is the distinction between experimentally validated ncRNA–pathway interactions and those inferred primarily through computational prediction, emphasizing the importance of evidence strength when interpreting pharmacological relevance. By prioritizing functionally characterized ncRNAs and critically evaluating controversial concepts such as cross-kingdom regulation, this work advances beyond descriptive cataloging and provides a balanced, mechanism-driven synthesis of the field. The analysis underscores that while ncRNA-mediated effects may complement classical phytochemical mechanisms, their translational relevance depends on rigorous validation, reproducibility, and biological plausibility. Importantly, this review highlights the potential of ncRNA profiling as a molecular tool for herbal standardization, quality control, and biomarker development. Integration of ncRNA data with multi-omics approaches and systems pharmacology frameworks offers a promising pathway toward precision-oriented phytotherapy, addressing long-standing challenges of variability and reproducibility in Traditional Chinese Medicine. Future progress will require standardized methodologies, integrative experimental designs, and translational studies that bridge plant genomics with pharmacodynamic outcomes. Collectively, this work positions ncRNAs as pharmacologically actionable regulators rather than ancillary molecular features, providing a conceptual and translational framework for future research. By aligning ncRNA biology with therapeutic relevance and regulatory considerations, this review contributes to the advancement of evidence-based, molecularly informed herbal pharmacology.

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