



RNA signaling in medicinal plants: An overlooked mechanism for phytochemical regulation

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ABSTRACT

Background/objective: Medicinal plants are invaluable sources of bioactive phytochemicals critical for global health. This mini review explores the role of RNA signaling in regulating phytochemical production in medicinal plants, highlighting its potential for optimizing their therapeutic potential.

Methods: This mini review integrates insights from recent studies published in Scopus and Web of Science (2019–2025) on RNA-mediated signaling, including small RNAs (sRNAs), long non-coding RNAs (lncRNAs), and messenger RNAs (mRNAs).

Results: RNA signaling is revealed as a pivotal mechanism in secondary metabolite regulation, mediating stress-induced compound synthesis and environmental interactions. Notable findings include the role of siRNAs in activating alkaloid pathways and lncRNAs in regulating phenolic compound biosynthesis. RNA-directed DNA methylation and systemic RNA signaling further highlight its versatility in phytochemical regulation.

Conclusion: RNA signaling enhances medicinal plant research, unlocking therapeutic potential through bioactive compound production. The study calls for focused research to bridge knowledge gaps and translate laboratory findings into field applications.

1. Introduction

Medicinal plants have been an integral part of drug discovery and therapeutic practices, offering a rich reservoir of bioactive compounds collectively known as phytochemicals. These natural products form the basis of numerous pharmaceuticals and have played a pivotal role in addressing global health challenges [1,2]. Despite significant advancements in understanding the biochemistry of these plants, the molecular mechanisms regulating their secondary metabolite production remain inadequately explored. RNA signaling, a critical component of plant molecular biology, has emerged as a fundamental yet underappreciated mechanism influencing various physiological and biochemical processes. RNA molecules, including small RNAs (sRNAs), long non-coding RNAs (lncRNAs), and messenger RNAs (mRNAs), not only regulate gene expression but also act as systemic signals mediating plant responses to environmental cues and internal developmental signals [3]. However,

their role in shaping the phytochemical landscapes of medicinal plants has largely been overlooked. Despite the increasing recognition of RNA signaling in plant biology, its specific regulatory roles in medicinal plants remain poorly characterized compared to its well-established functions in model plants and staple crops. A thorough review of recent literature reveals that most studies focus on stress tolerance, development, and pathogen response, while direct investigations into RNA-mediated regulation of phytochemicals in medicinal plants are still scarce ([4]; [5]). This underrepresentation underscores the rationale for considering RNA signaling as an overlooked mechanism within the context of medicinal plant research. This study is justified by the need to bridge the knowledge gap in RNA-mediated pathways and their implications for enhancing the therapeutic potential of medicinal plants. By advancing our understanding of these mechanisms, the study seeks to lay the groundwork for innovative biotechnological applications, such as RNA-based metabolic engineering and plant breeding strategies.

Abbreviations: DNA, Deoxyribonucleic acid; lncRNAs, Long non-coding RNAs; mRNAs, Messenger RNAs; RNA, Ribonucleic acid; RdDM, RNA-directed DNA methylation; sRNAs, Small RNAs.

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Furthermore, elucidating RNA signaling pathways can contribute to optimizing phytochemical production in diverse environmental conditions, addressing the global demand for sustainable and effective medicinal plant-based therapies [6]. This investigation aligns with the growing need for sustainable approaches to enhance medicinal plant productivity and therapeutic efficacy, emphasizing its relevance to both scientific advancement and public health. This mini review seeks to illuminate the potential of RNA signaling in regulating phytochemical biosynthesis, emphasizing its implications for medicinal plant research. By unraveling these RNA-mediated pathways, we can unlock new opportunities to enhance the production and diversity of medicinal compounds, bridging a critical gap in plant molecular biology and biotechnology. Here, we present the entire text using concise sections and headings to improve the coherence and comprehension of the entire work.

2. Methodology

This mini review study integrates a thorough analysis of recent advancements in RNA signaling and its role in phytochemical regulation in medicinal plants. A thorough literature search was conducted and peer-reviewed articles from 2019 to 2025 published in English in databases such as Scopus, PubMed, Web of Science, and Google Scholar, were selected. Keywords included "RNA signaling," "medicinal plants," "phytochemical biosynthesis," "microRNA," "small RNAs," "lncRNAs," "RNA-directed DNA methylation," and "secondary metabolites." A total of 96 articles were included based on their focus on RNA-mediated regulation in plants, particularly medicinal species as well as those emphasizing secondary metabolite biosynthesis and stress-induced phytochemical production were included. Studies on non-plant species or those lacking specific relevance to phytochemical regulation were excluded. The results were presented and discussed using concise sections and headings for better coherence and comprehension of the entire work.

3. RNA signaling: A primer

RNA signaling in plants encompasses diverse molecules and pathways that orchestrate cellular and systemic processes. RNA molecules serve as dynamic signaling entities that regulate plant development, environmental responses, and biochemical pathways [3]. Among the various types of RNA involved in signaling, small RNAs (sRNAs) such as microRNAs (miRNAs) and small interfering RNAs (siRNAs) play pivotal roles in post-transcriptional gene regulation. These molecules guide the degradation or translational repression of target mRNAs, thereby fine-tuning gene expression [7]. miRNAs can translocate inside plants and between plants and other organisms, modulating gene expression and phenotypic traits ([8]). Diverse RNA types, such as mRNAs and short RNAs, traverse locally through plasmodesmata and systemically through phloem, impacting plant development, nutrition distribution, and stress responses [9]. Extracellular vesicles have surfaced as prospective carriers for short RNA transfer between species, safeguarding RNA from degradation and enabling targeted delivery to recipient cells [10]. Intercellular and interspecies RNA trafficking is essential for plant physiology, encompassing gene silencing, pathogen defence, and symbiotic interactions [11].

3.1. MicroRNAs (miRNAs)

miRNAs are endogenously transcribed non-coding RNAs, 20–24 nucleotides in length, generated from single-stranded RNA precursors (pri-miRNA) that form hairpin structures [12]. They undergo processing by Drosha and Dicer enzymes to form mature miRNA molecules. miRNAs primarily bind to complementary sequences in target mRNAs to induce cleavage or inhibit translation. They are pivotal in fine-tuning gene expression, especially transcription factors regulating phenolic,

flavonoid, and terpenoid biosynthesis under stress conditions or developmental cues in medicinal plants [13,14]. Fig. 1 illustrates the mechanism of action of miRNA. In phytochemical regulation, miRNAs modulate the expression of transcription factors such as MYB, bHLH, and WRKY, which directly control genes in flavonoid, phenolic, and terpenoid biosynthetic pathways [15,16]. For example, miR156 targets SPL transcription factors, indirectly affecting anthocyanin biosynthesis; miR858 regulates MYB transcription factors controlling phenolic compound synthesis ([17]; [18]). Under stress conditions, miRNAs are upregulated to enhance the biosynthesis of antioxidant compounds like flavonoids and phenolic acids [19,20].

3.2. Small interfering RNAs (siRNAs)

siRNAs are typically 21–24 nucleotides long and are derived from long double-stranded RNAs (dsRNAs) of endogenous or exogenous origin. Their biogenesis involves cleavage by Dicer enzymes, and their mechanism of action is highly specific due to perfect base-pairing with their target mRNA sequences [21]. In medicinal plants, siRNAs mediate post-transcriptional gene silencing through mRNA cleavage or transcriptional gene silencing via RNA-directed DNA methylation (RdDM) [22]. siRNAs regulate key genes involved in alkaloid and terpenoid biosynthetic pathways during stress-induced secondary metabolite production [23]. Fig. 2 illustrates the mechanism of action of siRNA. In phytochemical regulation, siRNAs typically silence structural genes encoding key enzymes (e.g., alkaloid synthases, terpene synthases) via mRNA cleavage or RdDM pathways [24]. In medicinal plants like *Datura stramonium*, siRNAs have been shown to regulate genes involved in tropane alkaloid biosynthesis by silencing competing metabolic pathways, thus channeling resources toward specific secondary metabolites [25].

3.3. Long non-coding RNAs (lncRNAs)

lncRNAs are non-protein-coding transcripts longer than 200 nucleotides, transcribed by RNA polymerase II or III. They exert regulatory effects at transcriptional, post-transcriptional, and epigenetic levels. Mechanisms include acting as scaffolds for protein complexes, decoys for transcription factors, or guides for chromatin modifiers [26]. In medicinal plants, lncRNAs modulate the expression of biosynthetic gene clusters involved in phenolic and flavonoid production by interacting with histone modification enzymes or RNA-binding proteins ([27]). Fig. 3 illustrates the mechanism of action of lncRNA. In phytochemical regulation, lncRNAs modulate the transcription of biosynthetic gene clusters by interacting with chromatin modifiers such as histone methyltransferases or DNA methyltransferases [28]. Some lncRNAs act as molecular scaffolds recruiting epigenetic regulators to gene promoters of phenolic or terpenoid biosynthesis pathways [29]. lncRNAs may also function as decoys that bind transcription factors, preventing them from activating competing pathways, thus fine-tuning the production of desired phytochemicals [30].

3.4. Summary of mechanisms of action

Mechanisms such as RNA silencing and the movement of RNA molecules between cells or over long distances further underscore the versatility of RNA signaling [31]. Recent studies on RNA-mediated signaling in plants have highlighted the significance of mobile RNAs in intercellular and long-range communication. Messenger RNAs (mRNAs), beyond their traditional role in protein synthesis, can also act as mobile signals, transmitting information across plant tissues to coordinate growth and stress responses [32]. mRNAs and short RNAs (sRNAs) function as mobile signaling molecules, traversing plasmodesmata and phloem to modulate several biological processes [33]. Mobile mRNAs assemble into ribonucleoprotein complexes during transport, engaging with plasmodesmata to guarantee mobility and selectivity

Mechanisms of Action of miRNA in Medicinal Plants

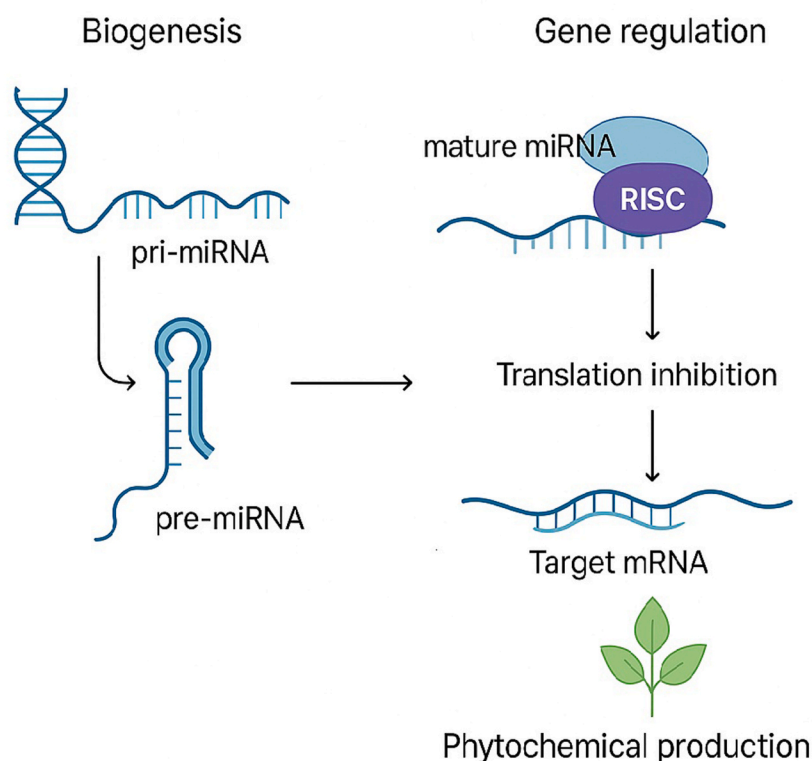


Fig. 1. Mechanism of action of miRNA.

[33]. Small RNAs, such as microRNAs and siRNAs, are integral to RNA interference and possess the ability to traverse cells, tissues, and even different species [34]. Research is being focused on the processes of sRNA transport, signal amplification, and responses of recipient tissues [34]. Collectively, these mechanisms highlight the critical role of RNA in maintaining plant homeostasis and facilitating intricate biochemical processes. Table 1 summarizes the key differences among siRNAs, miRNAs, and lncRNAs based on length, origin, biogenesis, target specificity, mechanism of gene regulation, and roles in secondary metabolite production. The graphical abstract provides a schematic representation of RNA signaling mechanisms influencing phytochemical production in medicinal plants. It illustrates the distinct roles of miRNAs, siRNAs, and lncRNAs in modulating gene expression pathways involved in secondary metabolite biosynthesis. It highlights RNA-directed DNA methylation, RNA interference, and systemic RNA transport as key processes underpinning this regulatory network.

4. Role of RNA signaling in medicinal plants

Emerging evidence suggests that RNA signaling plays a crucial role in the production of secondary metabolites—the bioactive compounds central to medicinal plants' therapeutic properties. These bioactive compounds, often produced in response to environmental and developmental cues, are tightly regulated by complex molecular networks in which RNA molecules are key players ([43,44]). By elucidating these RNA-mediated pathways, researchers can better understand the intricate regulatory networks governing phytochemical production and identify novel targets for enhancing the therapeutic potential of medicinal plant. Some of the RNA signaling roles in bioactive compounds are outlined below.

4.1. RNA signaling and stress-induced phytochemical production

One of the most evident links between RNA signaling and secondary metabolite production is observed under stress conditions. Small interfering RNAs (siRNAs), for instance, are known to mediate gene silencing pathways that activate secondary metabolite production during pathogen attack or environmental stress [45]. For example, siRNAs targeting key genes in alkaloid biosynthesis pathways have been implicated in enhancing the production of these pharmacologically important compounds [25]. Fig. 4 illustrates provides a schematic representation of RNA-mediated regulation of phytochemical biosynthesis.

4.2. Long non-coding RNAs in phenolic compound regulation

Long non-coding RNAs (lncRNAs) have also been identified as critical regulators of secondary metabolism. In medicinal plants, lncRNAs interact with transcription factors or chromatin-modifying complexes to modulate the expression of genes involved in phenolic compound biosynthesis [46]. These compounds, including flavonoids and tannins, are essential for plant defense and human health applications [47].

4.3. Epigenetic modulation via RNA signaling

Beyond direct gene regulation, RNA signaling intersects with epigenetic mechanisms to control phytochemical production. RNA-directed DNA methylation (RdDM) and histone modification pathways, often mediated by small RNAs, contribute to the fine-tuning of secondary metabolic pathways [48]. RdDM is a biological mechanism wherein non-coding RNA molecules facilitate the insertion of DNA methylation to particular DNA regions [48]. This layer of regulation underscores the versatility of RNA signaling in adapting medicinal plants to dynamic environmental and developmental contexts.

Mechanisms of Action of siRNA in Medicinal Plants

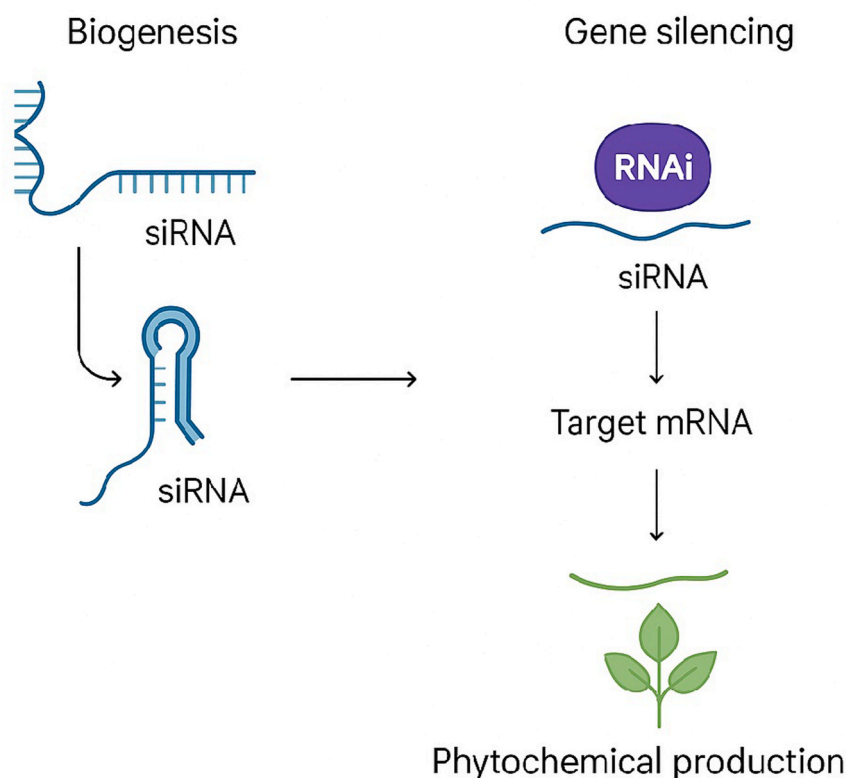


Fig. 2. Mechanism of action of siRNA.

5. RNA-based regulation and environmental interactions

The role of RNA signaling in medicinal plants extends beyond internal regulatory networks to encompass interactions with the environment. Medicinal plants often face a variety of environmental stressors, including drought, pests, pathogens, and nutrient deficiencies, all of which can influence secondary metabolite production [1]. RNA molecules mediate these responses, enabling plants to adapt their phytochemical profiles to changing conditions [49]. By exploring these RNA-mediated environmental interactions, scientists can uncover novel strategies to optimize the growth and metabolite profiles of medicinal plants under diverse conditions, further enhancing their therapeutic potential. Some of the notable regulatory effects are highlighted below.

5.1. Mediating stress responses

Environmental stress triggers RNA signaling pathways that upregulate or modify the production of secondary metabolites. For example, microRNAs play crucial roles in mediating drought tolerance by regulating genes associated with osmoprotectants and antioxidants, indirectly influencing secondary metabolite synthesis (F. [50]). Similarly, RNA signaling pathways have been shown to activate defense-related compounds, such as terpenoids and alkaloids, during pathogen attacks [51].

5.2. Rhizosphere interactions and microbial influence

RNA signaling also mediates interactions between medicinal plants and their rhizosphere microbial communities. Mobile RNAs transmitted through root exudates can influence microbial behavior, promoting beneficial symbiotic relationships or inhibiting pathogenic microbes

[52]. These interactions, in turn, shape the secondary metabolite profiles of medicinal plants by modulating their stress response and nutrient acquisition pathways [53].

5.3. Long-distance RNA signaling

Long-distance RNA signaling enables plants to integrate environmental signals into systemic responses. For instance, mobile RNAs can travel from stressed tissues to distant parts of the plant, coordinating a unified response that optimizes resource allocation and secondary metabolite production [34,54]. This systemic signaling mechanism ensures that medicinal plants can effectively adapt to localized and global environmental challenges, enhancing their resilience and phytochemical output [55].

6. Harnessing RNA signaling for biotechnological advancements

The insights gained from RNA signaling in medicinal plants offer transformative opportunities for biotechnological applications. By leveraging RNA-based regulatory pathways, it is possible to enhance the biosynthesis and diversity of phytochemicals, optimize plant resilience, and improve overall productivity [56]. The following are key applications of RNA signaling in biotechnology.

6.1. RNA interference for metabolic engineering

RNA interference technology can be employed to silence specific genes and redirect metabolic flux toward the biosynthesis of desired secondary metabolites [57]. For example, targeting key regulatory nodes in the flavonoid or alkaloid pathways can result in a higher yield of these valuable compounds [58]. Such approaches are particularly

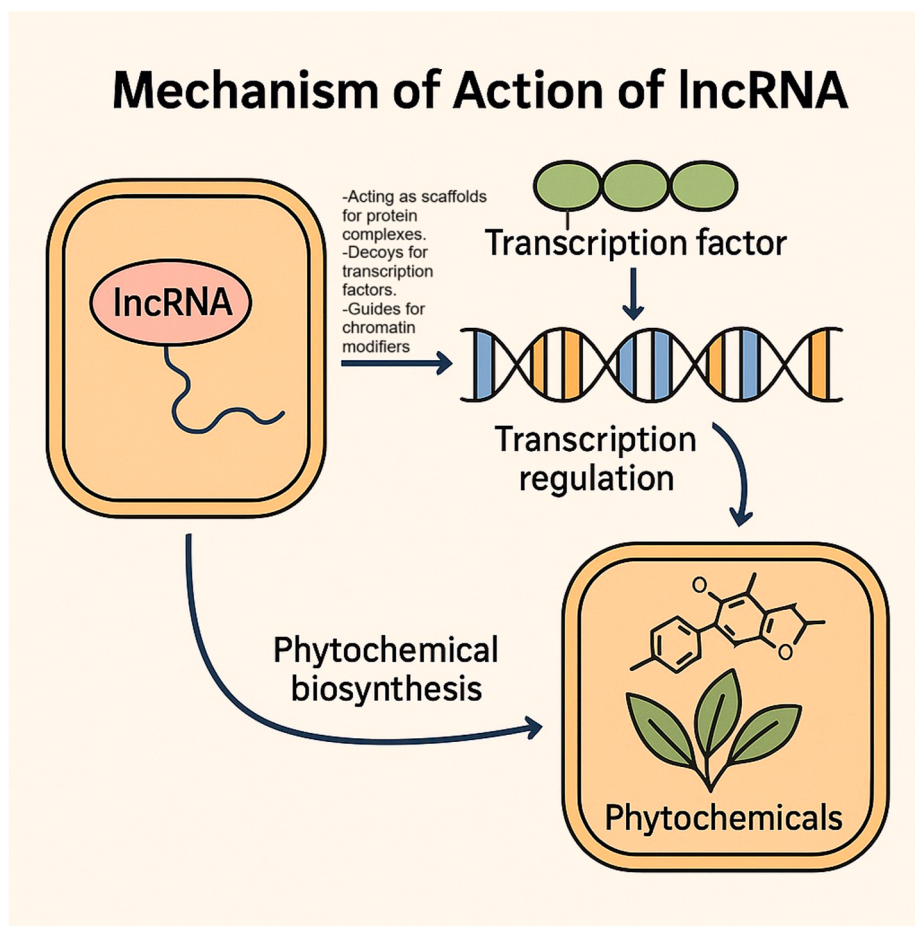


Fig. 3. Mechanism of action of lncRNA.

Table 1

A presentation clarifying the differences between siRNA, miRNA, and lncRNA.

Feature	miRNA	siRNA	lncRNA	References
Length	~20–24 nucleotides	~21–24 nucleotides	>200 nucleotides	[34]
Origin	Endogenously encoded single-stranded RNA	Derived from double-stranded RNA (dsRNA)	Transcribed from non-coding regions of DNA	[[35]]
Biogenesis	Processed from primary miRNA (pri-miRNA) by Drosha & Dicer	Dicer enzyme cleaves long dsRNA	Transcribed by RNA Polymerase II/III	[36]
Mechanism of Action	Partial or perfect base pairing; causes mRNA degradation or translation inhibition	Perfect base pairing with target mRNA; induces cleavage	Regulates transcription, chromatin modification, or acts as scaffolds or decoys	[[37]; [38]]
Main Function	Fine-tunes gene expression, development, stress adaptation	Gene silencing, antiviral defense, stress response	Epigenetic regulation, transcriptional and post-transcriptional control	[36]
Target Specificity	Moderate (often with mismatches)	High (due to perfect complementarity)	Broad (DNA, RNA, proteins)	[39]
Role in Phytochemical Regulation	Modulates transcription factors involved in phytochemical synthesis	Regulates key biosynthetic genes in secondary metabolite pathways	Regulates chromatin state or transcription factors controlling phytochemical biosynthesis	[40,41]
Mobility	Mobile across cells, tissues, and species	Cell-autonomous and non-cell-autonomous movement	Generally acts within nucleus or cytoplasm; may interact with mobile proteins	[42]

valuable for medicinal plants with complex and poorly understood metabolic networks.

6.2. Synthetic biology and RNA-based tools

Synthetic biology provides innovative RNA-based tools such as riboswitches and RNA scaffolds that can be used to modulate gene expression dynamically [59]. These tools can precisely control the expression of enzymes and regulatory proteins involved in secondary metabolism, enabling the fine-tuning of phytochemical production in response to developmental or environmental signals [60].

6.3. RNA-based plant breeding

RNA molecules can serve as biomarkers for selecting elite medicinal plant varieties with enhanced secondary metabolite profiles [61]. The integration of RNA sequencing and functional genomics enables the identification of RNA signatures associated with high-yield or stress-resilient phenotypes, accelerating the breeding of superior medicinal plant lines [62].

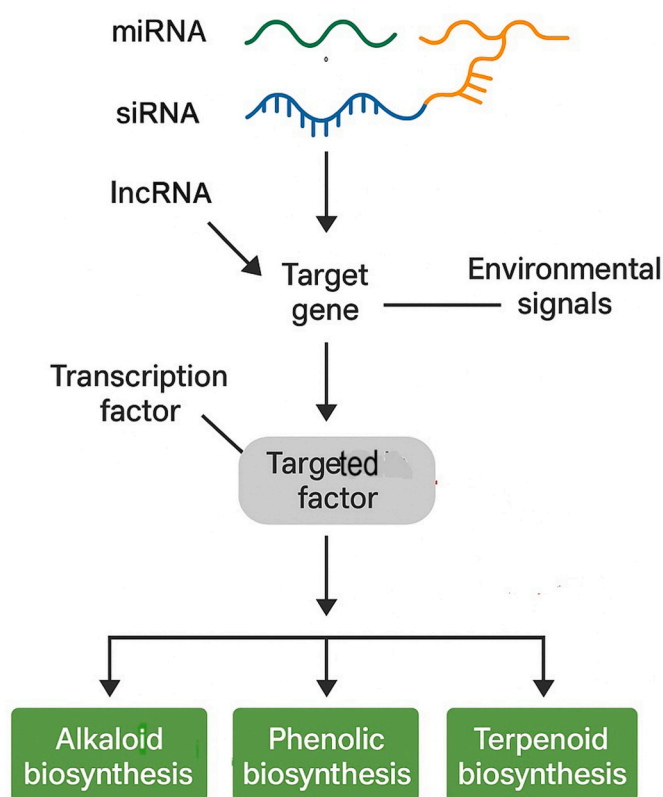


Fig. 4. RNA-mediated regulation of phytochemical biosynthesis.

7. Challenges in applying RNA-based approaches and proposed mitigating strategies

While the role of RNA signaling in medicinal plants holds immense promise, several challenges and questions remain. Overcoming these challenges requires innovative methodologies, improved bioinformatics tools, and a deeper understanding of plant biology. Some of these challenges and the accompanying mitigating strategies are highlighted below.

- i **Complexity of Plant Genomes:** Medicinal plants often have large, complex genomes with repetitive sequences, polyploidy, and high levels of genetic variation. This makes it difficult to generate high-quality reference genomes and interpret RNA sequencing data accurately ([63]). Advances in high-throughput sequencing, bioinformatics, and systems biology are crucial for unraveling these complexities and constructing comprehensive RNA regulatory models (“(PDF) Comprehensive Review of Antiretroviral Therapy Effects on Red Blood Cells in HIV Patients,” [64]).
- ii **Addressing Tissue-Specific and Temporal Dynamics:** Medicinal plants produce bioactive compounds in specific tissues or under particular environmental conditions. Isolating and analyzing RNA from these tissues requires precise sampling and often, tissue-specific RNA extraction methods, which can be labor-intensive [65]. Understanding how these spatial and temporal dynamics shape secondary metabolite biosynthesis requires the integration of single-cell RNA sequencing and advanced imaging techniques ([63]). Such approaches will provide finer resolution insights into RNA-mediated regulation at various stages of plant development and stress response.
- iii **Translating Laboratory Insights to Field Applications:** A significant hurdle in RNA signaling research lies in translating laboratory

discoveries to field conditions. Medicinal plants often grow in diverse and unpredictable environments where multiple stressors interact [1]. Developing RNA-based strategies that are effective across these variable conditions will require rigorous field studies and adaptable biotechnological solutions.

- iv **Ethical and Ecological Considerations:** RNA-based interventions in medicinal plants must be evaluated for potential ecological impacts, particularly on plant-microbe interactions and surrounding ecosystems [66]. Ensuring that RNA technologies align with environmental and ethical guidelines will be essential for their acceptance and widespread application [67].
- v **Post-Transcriptional Modifications:** RNA molecules in plants undergo various modifications (e.g., alternative splicing, methylation) that can complicate the interpretation of gene expression and functional analysis, requiring sophisticated analytical tools [68].

8. Future research directions

To unlock the potential of RNA signaling in medicinal plants, advanced tools and methodologies are imperative. High-throughput transcriptomics and CRISPR-based technologies could provide detailed insights into RNA signaling networks. Comparative studies across medicinal plant species may reveal conserved and unique RNA-mediated regulatory mechanisms. Additionally, integrating RNA signaling research with sustainable agricultural practices could enhance the cultivation and therapeutic value of medicinal plants.

9. Conclusion

RNA signaling represents a critical yet overlooked mechanism in the regulation of phytochemical biosynthesis. By elucidating its role, researchers can pave the way for innovative approaches to medicinal plant optimization, with far-reaching implications for plant science and human health. This study calls for a concerted effort to investigate RNA signaling pathways, ensuring that their potential is fully harnessed in the quest for sustainable and effective therapeutic solutions.

CRediT authorship contribution statement

Esther Ugo Alum: Writing – review & editing, Writing – original draft, Software, Methodology, Investigation, Conceptualization. **Chidozie Dennis Udechukwu:** Writing – review & editing, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation. **David Chukwu Obasi:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Methodology, Investigation.

Ethics approval

Not applicable.

Availability of data and material

All data are utilized in the manuscript.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

Data will be made available on request.

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