In-silico Analysis of THC/CBD-Responsive miRNA–Target Interactions and Pathway Associations in Humans

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Abstract

Cannabinoids such as cannabidiol (CBD) and Δ9-tetrahydrocannabinol (THC) exert diverse immunological and cellular effects, yet the post-transcriptional mechanisms underlying these responses remain insufficiently defined. Emerging evidence suggests that microRNAs (miRNAs) may mediate cannabinoid-induced regulatory changes; however, an integrated overview of cannabinoid-responsive miRNAs and their downstream targets is lacking. This study employed an in-silico framework to systematically identify miRNAs with altered expression following THC, CBD, or combined THC+CBD exposure. Fourteen cannabinoid-responsive miRNAs were curated from human studies and animal models with validated human orthologs. Predicted human mRNA targets were retrieved using TargetScan, incorporating canonical seed matches and weighted context++ scores, which were subsequently classified into high-, moderate-, and low-confidence interaction groups. Target genes associated with three major signaling pathways including NF-κB/TLR, JAK/STAT, and PI3K/AKT were selected for pathway-focused analysis. A total of 39 miRNA–mRNA interactions were identified, with the PI3K/AKT pathway receiving the highest interaction density. Network visualization in Cytoscape revealed miR-126-5p and miR-1972 as the primary central regulators, each targeting multiple components across NF-κB/TLR, JAK/STAT, and PI3K/AKT pathways. Key genes such as STAT1, STAT3, TLR4, IRAK1, IRAK4, and AKT emerged as prominent convergence points. This study provides a mechanistic framework linking THC- and CBD-responsive miRNAs to key inflammatory, immune, and survival pathways, offering a valuable foundation for guiding future molecular validation and the development of cannabinoid-based therapeutic applications.

Keywords: microRNA, In-silico analysis, miRNA–mRNA interactions

1. Introduction

Cannabinoids are a diverse class of bioactive molecules produced by Cannabis sativa, with Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD) representing the most extensively characterized compounds due to their broad biochemical and physiological effects in humans

(Atakan, 2012). These phytocannabinoids primarily act through the endocannabinoid system (ECS), a regulatory network composed of CB1 and CB2 receptors, endogenous ligands, and metabolic enzymes that maintain neurological, immunological, and metabolic homeostasis (Lu & Mackie, 2016). Through both receptor-dependent and receptor-independent mechanisms, cannabinoids modulate neurotransmission, inflammatory signaling, oxidative stress, pain perception, and cell-survival pathways, reflecting their wide biological significance (Pertwee, 2008; Chokchaisiri, 2025).

The biomedical relevance of cannabinoids has grown substantially, supported by clinical evidence demonstrating benefits in chronic pain, epilepsy, spasticity, neurodegenerative disorders, anxiety, and inflammation, which has led to the approval of cannabinoid-based therapeutics in multiple regions (Pisanti et al., 2017). Beyond therapeutic applications, cannabinoids influence immune function, cytokine release, and cell-fate decisions such as apoptosis and proliferation, suggesting broader implications in fields such as oncology and immunology (Kogan & Mechoulam, 2007). Because the ECS serves as a master regulatory system, exogenous cannabinoids can trigger complex pathway-level responses requiring systematic investigation (Zou & Kumar, 2018).

MicroRNAs (miRNAs)—short non-coding RNAs that repress gene expression through sequence-specific binding to target mRNAs—represent a key post-transcriptional regulatory layer that shapes numerous biological processes, including inflammation, neural communication, immunity, and metabolism (Bartel, 2018). Emerging studies show that cannabinoids can modulate miRNA expression profiles. For example, CBD alters inflammatory miRNA networks in microglia (Juknat et al., 2019), whereas THC regulates miRNAs associated with cytokine production, neuronal differentiation, and cell survival (Nagarkatti et al., 2009).

Cannabinoid-responsive miRNAs are predicted to target key signaling pathways including NF-κB/TLR, JAK/STAT, and PI3K/AKT, which are strongly associated with cannabinoid-mediated immune modulation and cell-survival effects (Rom & Persidsky, 2013). However, current knowledge remains fragmented, with prior studies focusing on isolated miRNAs or individual molecules rather than constructing an integrated regulatory landscape.

To address this knowledge gap, the present study employs an in-silico framework to systematically identify THC- and CBD-responsive miRNAs, predict their corresponding human mRNA targets, and map their interactions across major inflammatory and survival pathways. This integrative approach aims to construct a systems-level miRNA–mRNA regulatory network that clarifies how cannabinoid-responsive miRNAs modulate key biological signaling pathways, thereby establishing a mechanistic basis for future experimental studies.

1.1 Research Objective

To construct a systems-level miRNA–mRNA regulatory network for investigating cannabinoid-responsive miRNAs play essential roles in controlling key biological signaling pathways in the human body.

2. Material and methods

2.1 Identification of Cannabinoid-Responsive miRNAs

Cannabinoid-responsive microRNAs were identified through structured literature screening of peer-reviewed studies reporting altered miRNA expression following exposure to THC, CBD, or combined THC+CBD treatment. All miRNAs, human-derived miRNAs and conserved miRNAs reported in animal models, were collected and organized according to their associated cannabinoid condition and subsequently visualized using a Venn diagram to evaluate the overlap and unique subsets of miRNAs responsive to THC, CBD, and THC+CBD. The resulting miRNA panel served as the basis for downstream target prediction and network analysis.

2.2 Selection of Key Signaling Pathways and Candidate Genes

Three signaling pathways known to play central roles in cannabinoid-associated immunological and cellular responses—NF-κB/TLR, JAK/STAT, and PI3K/AKT—were predefined based on established biological relevance reported across multiple peer-reviewed studies. For each pathway, representative human genes were selected through literature-based curation, emphasizing genes consistently identified as core regulators or downstream effectors within these signaling cascades. Only protein-coding genes with annotated 3′ untranslated regions (3′UTRs) were retained to ensure compatibility with miRNA target prediction. The resulting gene panels, consisting of 10–15 key genes per pathway, served as the reference sets for downstream interaction analysis.

2.3 Prediction of miRNA–mRNA Interactions

Predicted miRNA–mRNA interactions were obtained using TargetScan (version 8.0). All canonical seed matches were retrieved and treated as a combined dataset. Weighted context++ scores for all predicted interactions were extracted without exclusion. Each interaction was subsequently classified into confidence categories based on context++ score thresholds: high-confidence (≤ −0.3), moderate-confidence (−0.3 to −0.1), and low-confidence (−0.1 to 0). Interactions corresponding to genes within the NF-κB/TLR, JAK/STAT, and PI3K/AKT pathways were retained for downstream analyses. For each miRNA and its associated target genes, mean and minimum context++ scores were computed to represent overall and strongest predicted regulatory effects. These confidence attributes were incorporated into the final dataset for network visualization and interpretation.

2.4 Network Construction and Visualization

An integrated miRNA–mRNA interaction network was constructed by combining the curated node attributes with the predicted interaction pairs in an edge table. Node attributes included molecule type (miRNA or gene), cannabinoid responsiveness (THC, CBD, or THC+CBD), pathway assignment, species origin, and context++ score metrics. The edge table contained interaction directionality and associated context++ scores. Both tables were imported

into Cytoscape (version 3.10.4), where nodes and edges were automatically merged using shared identifiers.

3. Results and discussion

3.1 Identification of Cannabinoid-Responsive miRNAs

A total of 14 cannabinoid-responsive miRNAs were identified from peer-reviewed studies and compiled into a curated dataset (Table 1). These included seven human miRNAs (let-7-5p, miR-1972, miR-21-5p, miR-126-5p, miR-760, miR-302c-3p, and miR-200bc-3p) and seven conserved miRNAs from animal models with validated human orthologs (miR-122-5p, miR-155-5p, miR-146-5p, miR-27-3p, miR-17-5p, miR-19-3p, and miR-21-5p).

Table 1: List of THC-, CBD-, and THC+CBD-Responsive miRNAs for Downstream Target Prediction

miRNA	species_origin	cannabinoid_response
let-7-5p	human	CBD
miR-1972	human	CBD
miR-21-5p	human	CBD
miR-126-5p	human	CBD
miR-760	human	CBD
miR-302c-3p	human	CBD
miR-200bc-3p	human	CBD
miR-122-5p	animal-with-human-ortholog	THC
miR-155-5p	animal-with-human-ortholog	CBD
miR-146-5p	animal-with-human-ortholog	CBD
miR-27-3p	animal-with-human-ortholog	THC+CBD
miR-17-5p	animal-with-human-ortholog	THC
miR-19-3p	animal-with-human-ortholog	THC
miR-21-5p	animal-with-human-ortholog	THC+CBD

When grouped by cannabinoid condition, CBD-responsive miRNAs represented the largest subset (n = 9), consisting of both human-derived and ortholog-derived sequences. THC-responsive miRNAs accounted for three entries, while two miRNAs (miR-27-3p and miR-21-5p) were reported under combined THC+CBD exposure.

Venn diagram visualization (Figure 1) demonstrated no overlap among the three treatment categories, indicating that THC, CBD, and combined THC+CBD each induced distinct miRNA expression signatures. However, miR-21-5p appeared in two categories consists of CBD-responsive human miRNA and THC+CBD-responsive ortholog-derived miRNA.

Because the CBD-responsive form of miR-21-5p was derived from human data and therefore carried higher relevance for downstream human-focused analysis, only the human CBD-responsive miR-21-5p was retained for further processing. Consequently, the dataset used for TargetScan prediction and network analysis was refined to 13 unique miRNAs.

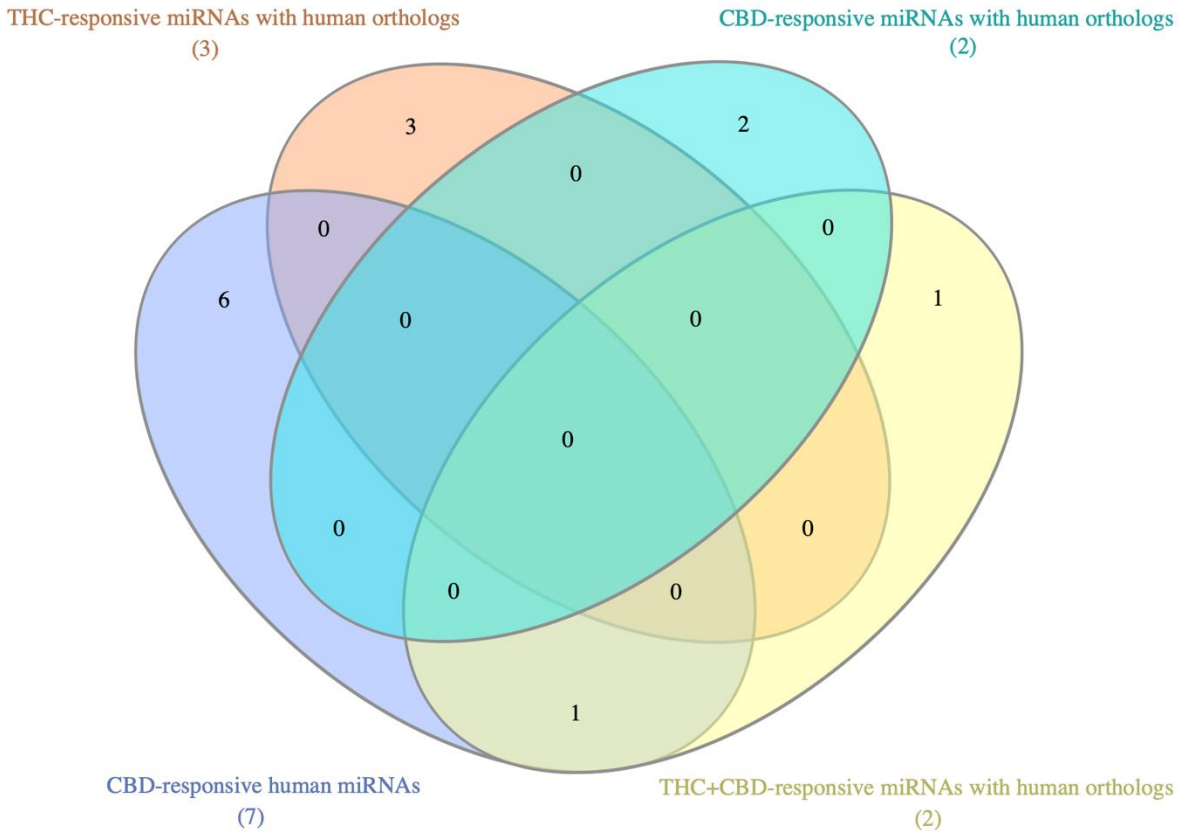

***Figure 1**: Venn diagram of THC-, CBD-, and THC+CBD-responsive miRNAs. Distribution of 14 cannabinoid-responsive miRNAs identified from human studies and validated animal models. CBD-responsive miRNAs formed the largest group. No overlap was observed among the three exposure conditions. miR-21-5p appeared in both CBD-responsive human miRNAs group and THC+CBD-responsive miRNAs with human ortholog group. Therefore, only the human CBD-responsive human miRNAs group was retained for downstream analyses.*

3.2 TargetScan-Based Prediction of miRNA–mRNA Interactions

TargetScan analysis yielded a total of 39 predicted miRNA–mRNA interactions across the three predefined pathways (NF-κB/TLR, JAK/STAT and PI3K/AKT). The interaction set included 15 low-confidence, 12 moderate-confidence, and 12 high-confidence predictions based on weighted context++ scores ranging from 0 to −0.60.

The PI3K/AKT pathway contained the highest number of predicted interactions, involving key genes such as AKT1, AKT2, AKT3, FOXO3, PTEN and PIK3R1. The JAK/STAT pathway accounted for the second-largest group, including interactions with STAT1, STAT3, JAK2, and SOCS3, while the NF-κB/TLR pathway yielded fewer but notable targets such as TLR4 and IRAK1.

Among individual miRNAs, miR-126-5p and miR-1972 contributed the most predicted interactions, with multiple moderate- and high-confidence binding events across pathways. Several strong interactions (context++ □ –0.30) were identified, including let-7-5p□TSC1, miR-126-5p□MYD88, miR-146-5p□TRAF6, miR-146-5p□IRAK1, miR-17-5p□STAT3, miR-19-3p□TSC1, miR-19-3p□SOCS3, miR-19-3p□PTEN, miR-1972□IRAK4, miR-27-3p □TSC1, miR-302c-3p□SOCS1 and miR-302c-3p□AKT3.

Cannabinoid exposure categories revealed that CBD-responsive miRNAs accounted for most interactions, including the majority of high-confidence predictions, whereas THC-responsive miRNAs contributed fewer but selective targets (e.g., miR-122-5p, miR-17-5p, miR-19-3p). THC+CBD exposure uniquely contributed high-confidence interactions involving miR-27-3p

Table 2 Predicted miRNA–mRNA Interactions Based on TargetScan Analysis

miRNA	Target gene	Pathway	Context score	Confidence groups	Cannabinoid response
let-7-5p	STAT3	JAK/STAT	-0.05	Low-confidence	CBD
let-7-5p	AKT2	PI3K/AKT	-0.05	Low-confidence	CBD
let-7-5p	TSC1	PI3K/AKT	-0.37	High-confidence	CBD
miR-122-5p	FOXO3	PI3K/AKT	-0.19	Moderate-confidence	THC
miR-126-5p	TLR4	NFkB/TLR	0.00	Low-confidence	CBD
miR-126-5p	JAK2	JAK/STAT	-0.01	Low-confidence	CBD
miR-126-5p	STAT1	JAK/STAT	-0.01	Low-confidence	CBD
miR-126-5p	AKT3	PI3K/AKT	-0.01	Low-confidence	CBD
miR-126-5p	SOCS3	JAK/STAT	-0.02	Low-confidence	CBD
miR-126-5p	FOXO3	PI3K/AKT	-0.02	Low-confidence	CBD
miR-126-5p	STAT3	JAK/STAT	-0.04	Low-confidence	CBD

miRNA	Target gene	Pathway	Context score	Confidence groups	Cannabinoid response
miR-126-5p	TRAF6	NFkB/TLR	-0.11	Moderate-confidence	CBD
miR-126-5p	MYD88	NFkB/TLR	-0.40	High-confidence	CBD
miR-146-5p	TRAF6	NFkB/TLR	-0.49	High-confidence	CBD
miR-146-5p	IRAK1	NFkB/TLR	-0.56	High-confidence	CBD
miR-155-5p	FOXO3	PI3K/AKT	-0.26	Moderate-confidence	CBD
miR-17-5p	TLR4	NFkB/TLR	0.00	Low-confidence	THC
miR-17-5p	AKT3	PI3K/AKT	-0.15	Moderate-confidence	THC
miR-17-5p	PTEN	PI3K/AKT	-0.21	Moderate-confidence	THC
miR-17-5p	STAT3	JAK/STAT	-0.47	High-confidence	THC
miR-19-3p	TSC1	PI3K/AKT	-0.36	High-confidence	THC
miR-19-3p	SOCS3	JAK/STAT	-0.49	High-confidence	THC
miR-19-3p	PTEN	PI3K/AKT	-0.61	High-confidence	THC
miR-1972	TLR4	NFkB/TLR	0.00	Low-confidence	CBD
miR-1972	AKT1	PI3K/AKT	-0.01	Low-confidence	CBD
miR-1972	IRAK1	NFkB/TLR	-0.04	Low-confidence	CBD
miR-1972	PTEN	PI3K/AKT	-0.14	Moderate-confidence	CBD
miR-1972	TRAF6	NFkB/TLR	-0.19	Moderate-confidence	CBD
miR-1972	AKT2	PI3K/AKT	-0.26	Moderate-confidence	CBD
miR-1972	IRAK4	NFkB/TLR	-0.41	High-confidence	CBD
miR-200bc-3p	PTEN	PI3K/AKT	-0.08	Low-confidence	CBD
miR-200bc-3p	AKT2	PI3K/AKT	-0.10	Moderate-confidence	CBD

miRNA	Target gene	Pathway	Context score	Confidence groups	Cannabinoid response
miR-21-5p	STAT3	JAK/STAT	-0.25	Moderate-confidence	CBD
miR-27-3p	FOXO3	PI3K/AKT	-0.06	Low-confidence	THC+CBD
miR-27-3p	STAT1	JAK/STAT	-0.19	Moderate-confidence	THC+CBD
miR-27-3p	TSC1	PI3K/AKT	-0.30	High-confidence	THC+CBD
miR-302c-3p	SOCS3	JAK/STAT	-0.41	High-confidence	CBD
miR-302c-3p	AKT3	PI3K/AKT	-0.41	High-confidence	CBD
miR-760	SOCS3	JAK/STAT	-0.17	Moderate-confidence	CBD

3.3 Network Construction and Visualization

An integrated miRNA–mRNA regulatory network was constructed in Cytoscape using all predicted interactions derived from TargetScan. The final network consisted of 13 miRNAs connected to 15 pathway-associated genes, forming a multi-pathway interaction landscape encompassing NF-κB/TLR, JAK/STAT, and PI3K/AKT signaling (Figure 2).

Network visualization revealed several high-connectivity miRNAs, including miR-126-5p, and miR-1972, each targeting multiple genes across different pathways. miR-126-5p emerged as one of the most central nodes, forming edges with STAT1, STAT3, SOCS3, JAK2, TLR4, TRAF6, AKT3, FOXO3 and MYD88, while miR-1972 targeted TLR4, TRAF6, AKT1, AKT2, PTEN, IRAK1, and IRAK4.

High-confidence edges (thicker lines) were predominantly distributed among PI3K/AKT components—particularly interactions involving AKT2, AKT3, PTEN, and FOXO3—highlighting this pathway as a major hub of miRNA regulation. miR-302c-3p, miR-760, and miR-200bc-3p collectively produced several strong PI3K/AKT-related predictions.

Interactions within the JAK/STAT pathway were concentrated around STAT3, STAT1, JAK2 and SOCS3, with miR-21-5p, miR-27-3p, miR-760, miR-126-5p, and miR-302c-3p being the most frequent regulators. Meanwhile, NF-κB/TLR signaling contributed fewer nodes but displayed strong regulatory links, including high-confidence targeting of IRAK1, IRAK4, and TLR4 by miR-146-5p, miR-1972, and miR-17-5p.

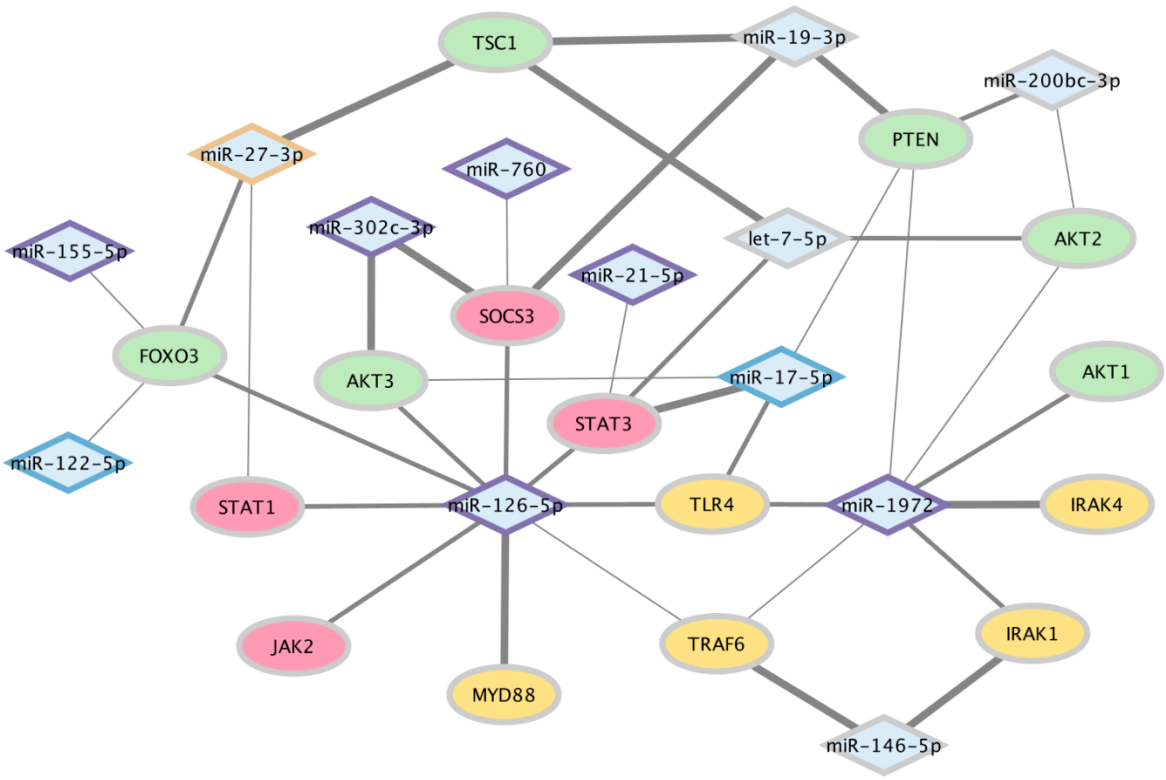

Figure 2*. Integrated miRNA–mRNA regulatory network predicted from cannabinoid-responsive miRNAs. Cytoscape visualization of the predicted miRNA–mRNA regulatory network constructed from 13 cannabinoid-responsive miRNAs and pathway-associated genes. Circle node colors represent pathway membership (PI3K/AKT, JAK/STAT, NF-κB/TLR), while edge thickness reflects interaction confidence based on TargetScan context++ scores. Two miRNAs—miR-126-5p and miR-1972—emerge as central regulators, each targeting multiple key components across inflammatory, immune, and cell-survival pathways, including STAT3, TLR4, AKT3, IRAK1, and IRAK4.*

4. Discussion

This study provides a systems-level characterization of cannabinoid-responsive miRNAs and their predicted regulatory interactions across three major signaling pathways—NF-κB/TLR, JAK/STAT, and PI3K/AKT—which collectively orchestrate inflammatory, immune, and cell-survival processes. The predominance of CBD-responsive miRNAs observed in this dataset aligns with prior transcriptomic and post-transcriptional evidence demonstrating that CBD exerts broader immunoregulatory effects than THC (Juknat et al., 2019). Several of these miRNAs, including miR-21-5p and miR-126-5p, have well-established roles in endothelial

function, immune cell activation, and inflammatory resolution (Kozela et al., 2010), reinforcing their mechanistic relevance within CBD-mediated pathways.

THC-responsive miRNAs such as miR-122-5p, miR-17-5p, and miR-19-3p were associated with regulatory nodes linked to cytokine production, metabolism, and neuronal survival, consistent with reports of THC's selective modulation of immune and neuronal signaling (Nagarkatti et al., 2009). The absence of overlap between THC-, CBD-, and THC+CBD-responsive miRNAs further underscores the distinct molecular signatures induced by each cannabinoid, in accordance with evidence that THC and CBD differentially engage receptor-dependent and intracellular pathways (Pertwee, 2008). Although miR-21-5p was reported in both CBD-responsive human datasets and THC+CBD ortholog datasets, only the human-derived form was retained to preserve translational relevance, yielding a final set of 13 candidate miRNAs for regulatory modeling.

The integration of ortholog-derived miRNAs highlights the evolutionary conservation of miRNA sequences and supports their translational applicability to human regulatory predictions (Bartel, 2018). Subsequent TargetScan-based analysis generated 39 miRNA–mRNA interactions spanning the three signaling pathways. The PI3K/AKT pathway exhibited the highest density of predicted interactions, consistent with its established involvement in cannabinoid-mediated effects on apoptosis, cell survival, and metabolic regulation (Rom & Persidsky, 2013). High-confidence predictions including let-7-5p□TSC1, miR-126-5p□MYD88, miR-146-5p□TRAF6, miR-146-5p□IRAK1, miR-17-5p□STAT3, miR-19-3p□TSC1, miR-19-3p□SOCS3, miR-19-3p□PTEN, miR-1972□IRAK4, miR-27-3p □TSC1, miR-302c-3p□SOCS1 and miR-302c-3p□AKT3 suggest potent regulatory influence and delineate priority candidates for functional validation.

Network topology analysis identified miR-126-5p and miR-1972 as central regulatory nodes targeting multiple pathway components, including JAK2, STAT1, STAT3, TLR4, IRAK1, IRAK 4, and AKT family members. These miRNAs may function as key modulators of inflammatory and survival pathways, consistent with the broader role of miRNAs as coordinated regulators of signaling networks rather than isolated effectors (Bartel, 2018). Additional convergence on shared hubs such as STAT1, STAT3, TRL4 and IRAK1 suggests that cannabinoid-responsive miRNAs may collectively fine-tune pathway output through multi-layered regulatory mechanisms.

Taken together, these findings reveal a coherent miRNA-centered regulatory architecture engaged by cannabinoid exposure and provide mechanistic insight into how THC and CBD may shape downstream biological responses. The study establishes a predictive framework that identifies high-value miRNA–mRNA interactions and regulatory hubs for experimental prioritization. Importantly, the network-level approach used here offers a conceptual scaffold for future functional studies and supports the rational development of targeted cannabinoid-based therapeutic strategies.

5. Conclusion

This study provides a systems-level framework that delineates how THC- and CBD-responsive miRNAs may modulate key inflammatory and survival pathways through coordinated regulatory interactions. By integrating human and ortholog-derived miRNAs with TargetScan-based predictions, the analysis identifies 13 cannabinoid-responsive miRNAs and highlights the PI3K/AKT, JAK/STAT, and NF-κB/TLR pathways as major regulatory targets. Network modeling reveals miR-126-5p and miR-1972 as central regulators that converge on critical signaling hubs, including STAT1, STAT3, TLR4, IRAK1, IRAK4, and AKT isoforms, suggesting multi-layered miRNA-mediated control of cannabinoid-responsive pathways. Collectively, these findings establish a predictive regulatory architecture that clarifies the mechanistic basis of cannabinoid-induced molecular responses and provides prioritized miRNA–mRNA interactions for future experimental validation and therapeutic exploration.

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