

Molecular crosstalk between cannabinoid targets and uveitis-associated proteins: insights from network analysis



Mehrdad Motamed Shariati

Eye Research Center, Mashhad University of Medical Sciences, Mashhad, Iran
Head: prof. Siamak Zarei-Ghanavati; MD, MSc, FICO

HIGHLIGHTS

Δ 9-tetrahydrocannabinol (THC) interacts with key inflammatory mediators in immune-associated uveitis through PPARG and TRPV1, highlighting potential targets for cannabinoid-based therapeutic strategies.

ABSTRACT

Objectives: To map Δ 9-tetrahydrocannabinol (THC) interactions within a protein–protein interaction network of idiopathic anterior uveitis.

Methods: Uveitis-related proteins were identified from the literature; THC targets (CNR1, CNR2, PPARG, TRPV1) were integrated manually. STRING database interactions (score ≥ 0.7) were analyzed in Python using centrality measures and Louvain clustering.

Results: The network contained 215 nodes and 10,911 edges (density 0.47). IL-6, TNF, IFN- γ , and IL-17A were hubs. PPARG bridged THC to multiple cytokines, while TRPV1 linked THC to IL-1 β and IL-4. Clustering revealed cytokine and cannabinoid modules.

Conclusions: THC connects to key inflammatory mediators in idiopathic anterior uveitis via PPARG and TRPV1, suggesting translational targets for cannabinoid-based therapies.

Key words: idiopathic anterior uveitis, tetrahydrocannabinol, THC, protein–protein interaction, network, translational medicine

INTRODUCTION

Idiopathic anterior uveitis is the most common form of intraocular inflammation and a major cause of vision loss worldwide [1]. It is characterized by a dysregulated immune response in the anterior chamber of the eye, frequently driven by proinflammatory cytokines such as interleukin (IL)-6, tumor necrosis factor (TNF), interferon gamma (IFN- γ), and IL-17A [2, 3]. While corticosteroids remain the cornerstone of treatment, their long-term use is associated with substantial ocular and systemic side effects, and there remains an unmet need for safer, targeted therapies [4].

Cannabinoids, particularly Δ^9 -tetrahydrocannabinol (THC), have garnered increasing interest due to their immunomodulatory and anti-inflammatory properties [5]. THC exerts its effects primarily through cannabinoid receptors 1 and 2 (CNR1 and CNR2), but it also interacts with additional molecular targets such as peroxisome proliferator-activated receptor gamma (PPARG) and transient receptor potential vanilloid 1 (TRPV1) [6, 7]. Although experimental studies have suggested that cannabinoids may modulate ocular inflammation, the precise molecular pathways linking THC to uveitis-related proteins remain poorly defined.

Network biology offers a powerful framework for addressing this knowledge gap. Protein–protein interaction networks can capture the complexity of molecular crosstalk underlying disease pathogenesis and drug mechanisms [8]. By integrating literature-curated THC targets with uveitis-associated proteins and their extended interactors, systems-level analysis can reveal candidate mediators and signaling routes through which cannabinoids influence ocular immunity.

In this study, we constructed and analyzed a protein–protein interaction network linking THC to proteins implicated in idiopathic anterior uveitis. We aimed to:

- identify key hubs and bottlenecks within the network
- map the shortest molecular paths connecting THC to central inflammatory mediators
- explore modular organization to uncover functionally coherent communities.

METHODS

Literature review and protein selection

A comprehensive literature search was performed in PubMed, Scopus, and Web of Science to identify proteins previously implicated in the pathogenesis of idiopathic anterior uveitis. Selection criteria included experimental evidence of altered expression in uveitis, relevance to immune or inflammatory signaling, and prior association with intraocular inflammation. Based on this review, a curated list of 10 uveitis-related proteins (IL-6, IL-10, TNF, IFN- γ ,

IL-17A, IL-2, IL-1 β , HLA-B, IL-4, and TGF- β 1) [9–11] was compiled as seed nodes for network construction.

In parallel, cannabinoid-related proteins reported in the literature as direct or indirect molecular targets of THC were identified. These included CNR1, CNR2, peroxisome proliferator-activated receptor gamma (PPARG), and transient receptor potential cation channel subfamily V member 1 (TRPV1) [12, 13].

Integration of THC interactions

THC was treated as a novel node within the protein–protein interaction network. Its interactions with the 4 selected target proteins were manually curated from prior experimental and pharmacological reports. These connections were integrated into the network programmatically using custom Python scripts, ensuring that literature-derived links were explicitly represented alongside database-derived associations.

Network construction

The STRING v12 database (Homo sapiens, taxonomy ID: 9606) was queried via the API to retrieve experimentally validated and high-confidence interactions (combined score ≥ 0.7) for all seed proteins. To expand the interactome beyond direct partners, a multi-degree neighborhood strategy was implemented; for each round, neighbors of the current set of proteins were retrieved, and this process was repeated for two degrees of separation. The resulting dataset was parsed, filtered for redundancy, and used to construct an undirected weighted network in Python using the NetworkX library. Nodes represented proteins, and edges represented physical or functional associations, weighted by STRING confidence scores.

Network analysis

To characterize network topology, multiple graph-theoretical metrics were computed, including degree, betweenness, and closeness centrality. Network density, clustering coefficient, and diameter were also calculated. Community detection was performed using the Louvain algorithm (implemented in the python-louvain package) to identify functionally coherent protein modules. Shortest paths between THC and uveitis-related proteins were mapped to highlight potential molecular routes linking cannabinoid signaling with inflammatory processes.

Visualization

The network was visualized in Python using a spring layout algorithm, with node sizes scaled according to biological relevance (uveitis-related proteins, THC, and extended neighbors). Literature-curated THC interactions were highlighted distinctly from STRING-derived associations.

RESULTS

Network construction and global properties

The integration of literature-curated seed proteins and THC targets with STRING-derived neighbors resulted in a comprehensive protein–protein interaction network. The final network consisted of 215 nodes connected by 10,911 edges, with a network density of 0.4743 and an average clustering coefficient of 0.7288 (tab. 1). These metrics indicate a densely interconnected interactome with high local clustering, suggesting strong functional associations among the selected proteins and their extended neighbors.

TABLE 1

Main network characteristics.	
Number of nodes: 215	
Number of edges: 10911	
Network density: 0.4743	
Average clustering coefficient: 0.7288	
Top 10 hubs (degree centrality)	
	IL-6 (0.9579439252336448) IFN-γ (0.9579439252336448) IL-10 (0.9485981308411214) IL-4 (0.9205607476635513) IL-2 (0.911214953271028) CSF-2 (0.9065420560747662) IL-1B (0.8971962616822429) TNF (0.8925233644859812) CD4 (0.8878504672897196) IL-13 (0.8738317757009345)
Top 10 nodes (betweenness centrality)	
	IL-6 (0.01862794372648145) IL-10 (0.017744688435897) IFN-γ (0.017358452876245198) IL-1B (0.014910276923200492) TNF (0.014194180937935948) IL-4 (0.014163672734259905) IFN-γ (0.013624536392003561) IL-2 (0.0131062340778385) CD-4 (0.012388142403804826) CSF-2 (0.012170745376927953)
Shortest paths from THC to uveitis proteins	
	THC $\rightarrow$ IL-6: ['THC', 'PPARG', 'IL-6'] THC $\rightarrow$ IL-10: ['THC', 'PPARG', 'IL-10'] THC $\rightarrow$ TNF: ['THC', 'PPARG', 'TNF'] THC $\rightarrow$ IFN- γ : ['THC', 'PPARG', 'IFN- γ '] THC $\rightarrow$ IL-17A: ['THC', 'PPARG', 'IL-17A'] THC $\rightarrow$ IL-2: ['THC', 'PPARG', 'IL-2'] THC $\rightarrow$ IL-1B: ['THC', 'TRPV1', 'IL-1B'] THC $\rightarrow$ HLA-B: ['THC', 'PPARG', 'IL-2', 'HLA-B'] THC $\rightarrow$ IL-4: ['THC', 'TRPV1', 'IL-4'] THC $\rightarrow$ TGF- β 1: ['THC', 'PPARG', 'TGF- β 1']

Centrality analysis

Graph-theoretical analysis identified key hub proteins with high degree centrality. Interleukins (IL-6, IFN- γ , IL-10, IL-4, IL-2, IL-1 β , IL-13) and TNF were among the most connected nodes, alongside colony-stimulating factor 2 (CSF-2) and the T cell surface marker CD4. In terms of betweenness centrality, IL-6, IL-10, IFN- γ , IL-1 β , TNF, and IL-4 were again prominent, reflecting their role as critical mediators bridging network modules. Interestingly, PPARG, one of the cannabinoid-related targets, also ranked highly in betweenness, highlighting its potential role as a key mediator linking THC signaling with immune-inflammatory pathways.

Shortest path analysis from THC to uveitis proteins

Shortest path analysis revealed direct and indirect molecular routes by which THC may influence uveitis-associated proteins. Notably, THC connected to several cytokines (IL-6, IL-10, TNF, IFN- γ , IL-17A, IL-2, and TGF- β 1) primarily through PPARG, while TRPV1 mediated connections to IL-1 β and IL-4. In addition, HLA-B was linked to THC through a PPARG–IL-2 path. These findings suggest that cannabinoid receptors and related targets act as intermediaries bridging THC with central immunoregulatory proteins in anterior uveitis.

Community detection and modular organization

Application of the Louvain algorithm revealed distinct network modules, corresponding broadly to cytokine signaling clusters, T-cell activation pathways, and cannabinoid-related signaling. The modular structure supports the existence of biologically coherent communities, with PPARG and TRPV1 positioned at the interface between cannabinoid and immune-inflammatory modules.

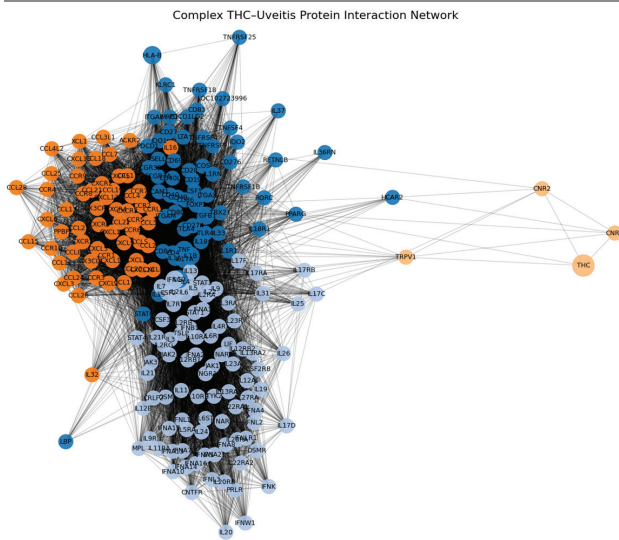
Visualization of the THC–uveitis interactome

The final network visualization is presented in figure 1, where uveitis-associated proteins are highlighted alongside THC and its targets. Distinct communities are visible, with the shortest paths from THC to core inflammatory mediators emphasized. This graphical representation underscores the integrative role of cannabinoid signaling within inflammatory networks of idiopathic anterior uveitis.

Nodes represent proteins, and edges represent physical or functional associations. Uveitis-related proteins are shown as enlarged nodes; THC is highlighted in green. Direct THC–target interactions (PPARG, CNR1, CNR2, TRPV1) were manually curated from the literature, while other edges were derived from STRING database queries (confidence score ≥ 0.7). Communities identified by the Louvain algorithm are color-coded, and shortest paths from THC to uveitis-related proteins are marked with bold red edges.

FIGURE 1

Extended protein–protein interaction network of idiopathic anterior uveitis with integrated THC interactions.



DISCUSSION

This study explored the molecular landscape connecting THC with proteins implicated in idiopathic anterior uveitis by integrating literature-curated cannabinoid targets into an extended protein–protein interaction network. By combining a comprehensive literature review with computational network biology, we provide new insights into the immunomodulatory potential of THC in the context of ocular inflammation.

The constructed network recapitulated many of the canonical inflammatory mediators that have long been associated with anterior uveitis, including IL-6, TNF, IFN- γ , IL-1 β , and IL-17A. These proteins were identified as hubs by both degree and betweenness centrality, underscoring their well-established role as master regulators of intraocular inflammation. Their emergence as central nodes validates the accuracy of our network reconstruction and demonstrates the effectiveness of network approaches in capturing biologically meaningful interactions. Importantly, these cytokines serve as convergence points for multiple immune pathways, including Th1, Th17, and macrophage-driven responses, all of which are implicated in the pathogenesis of uveitis [14, 15].

One of the most significant findings of our analysis was the identification of PPARG and TRPV1 as critical intermediaries bridging THC with uveitis-associated proteins. PPARG is a nuclear receptor with recognized anti-inflammatory properties, including suppression of proinflammatory cytokines and modulation of immune cell differentiation [16, 17]. Its high betweenness centrality indicates that it acts as a bottleneck connecting THC to central inflammatory nodes such as IL-6, TNF, and IFN- γ . This highlights

PPARG as a plausible mediator through which THC exerts transcriptional reprogramming of immune responses.

Similarly, TRPV1 (transient receptor potential cation channel subfamily V member 1), known for its role in nociception and neuroinflammation [18, 19], linked THC to IL-1 β and IL-4. This connection is particularly intriguing, as TRPV1 has been implicated in modulating both innate and adaptive immune responses. Its involvement suggests that ion channel–dependent signaling could represent an additional route through which cannabinoids influence ocular inflammation.

Community detection analysis revealed a modular organization of the network, with distinct clusters representing cytokine signaling, T-cell activation, and cannabinoid-related pathways. Such modularity is a hallmark of complex biological systems, where functional communities correspond to physiologically coherent processes [20]. The embedding of cannabinoid targets within these immune-related modules emphasizes that THC does not act in isolation but integrates into existing inflammatory circuitry. This supports the hypothesis that cannabinoid signaling intersects with immune-regulatory pathways relevant to anterior uveitis.

The translational relevance of these findings lies in their ability to generate mechanistic hypotheses that can be tested in preclinical and clinical contexts. Cannabinoid receptors and related targets have been extensively studied in systemic immunology, but their role in ocular inflammation remains underexplored. By identifying PPARG and TRPV1 as potential bridges between THC and inflammatory cytokines, our study suggests tangible molecular targets for future therapeutic strategies.

From a translational perspective, several avenues emerge:

1. **Drug repurposing and development:** Existing PPARG agonists and TRPV1 modulators could be investigated as adjunctive therapies in uveitis, potentially enhancing or mimicking the immunomodulatory effects of cannabinoids.
2. **Biomarker discovery:** Proteins positioned along the shortest paths between THC and cytokines may serve as biomarkers to monitor therapeutic response or disease activity in patients receiving cannabinoid-based interventions.
3. **Personalized medicine:** The network approach highlights inter-individual variability in immune–cannabinoid interactions, paving the way for precision medicine strategies where treatment is tailored based on molecular signatures of uveitis.

Several limitations should be considered. STRING-derived interactions combine experimental data with computational predictions and text mining, which may introduce uncertainty. THC–protein associations were manually curated from the literature and may not capture the full spectrum

of cannabinoid biology in ocular tissues. Furthermore, our analysis was confined to protein-level interactions; integration of transcriptomic, epigenomic, and metabolomic datasets would provide a more holistic understanding. Despite these limitations, the network-based approach provides a robust framework for hypothesis generation.

Future work should focus on experimental validation of the predicted THC–PPARG–cytokine and THC–TRPV1–cytokine axes in cellular and animal models of uveitis. Clinical translation will require assessing the safety, efficacy, and pharmacodynamics of cannabinoid-based therapies in controlled trials. Incorporating patient-derived molecular profiles could further bridge the gap between computational predictions and individualized treatment strategies.

CONCLUSION

In summary, our network analysis demonstrates that THC connects to central uveitis-associated cytokines primarily through PPARG and TRPV1, suggesting these molecules as key intermediaries in cannabinoid-mediated immune modulation. Beyond advancing our mechanistic understanding, these findings emphasize the translational potential of cannabinoids as modulators of ocular inflammation. By integrating literature curation with network biology, this study establishes a framework for bridging basic immunology with therapeutic innovation in idiopathic anterior uveitis.

All codes are available at: https://github.com/Mehrdad-Motamed-lab/THC_IAU/blob/main/THC__IAU.ipynb

CORRESPONDENCE

Mehrdad Motamed Shariati, MD

Eye Research Center, Khatam Al-Anbia Eye Hospital

Gharani Boulevard, Mashhad, Iran.

Tel: +989377388690

E-mail: Mehrdad_shariati2005@yahoo.com

ORCID

Mehrdad Motamed Shariati – ID – <https://orcid.org/0000-0001-8680-5560>

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