Modern Chemistry
2026, Vol. 14, No. 3, pp. 98–108
https://doi.org/10.11648/j.mc.20261403.13

Research Article

Integrative Network Pharmacology Analysis of *Tripterygium Wilfordii* Against Rheumatoid Arthritis

Rohan Mohite, Pragati Pujari, Sneha Pawar*, Kumudini Pawar, Komal Laddha, Mayuri Bapu Chavan, Meera Deshmukh, Pranati Tilak

Pharmacy Department, Tilak Maharashtra Vidyapeeth's Lokmanya Tilak Institute of Pharmaceutical Sciences, Pune, India

Abstract

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease characterized by persistent synovial inflammation, progressive cartilage destruction, bone erosion and joint deformity, leading to severe disability and reduced quality of life. Tripterygium wilfordii Hook. F. (Thunder God Vine), a well-known medicinal plant in traditional Chinese medicine has been extensively used for the treatment of autoimmune and inflammatory disorders due to its potent immunosuppressive and anti-inflammatory properties. Although conventional therapies are effective, they are often associated with adverse effects and incomplete disease remission, highlighting the need for safer and effective therapeutic strategies. This study aimed to explore the molecular mechanisms underlying the therapeutic effects of *Tripterygium wilfordii* against RA using a network pharmacology approach. Active phytoconstituents including triptolide, celastrol, and wilforlide A, were identified from the Traditional Chinese Medicine Systems Pharmacology (TCMSP) database and PubChem. Potential molecular targets were predicted using Swiss Target Prediction, while RA-associated genes were retrieved from the GeneCards and DisGeNET databases. Overlapping targets were identified through Venn analysis, followed by Protein–Protein Interaction (PPI) network construction using the STRING database. Hub genes were screened using the CytoHubba plugin in Cytoscape, and Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses were performed to elucidate the biological functions and signaling pathways involved. The analysis identified TNF, IL6, AKT1, MAPK1, and NF-κB as major hub targets involved in inflammatory and immune responses. KEGG pathway enrichment analysis highlighted the PI3K–Akt, MAPK, TNF, and NF-κB signaling pathways as key mechanisms mediating the therapeutic effects. These findings suggest that *Tripterygium wilfordii* exerts anti-rheumatic activity through a multi-component, multi-target, and multi-pathway mode of action, providing valuable insights into its pharmacological basis and supporting its potential as a promising therapeutic candidate for rheumatoid arthritis.

Keywords

Network Pharmacology, NF-κB, PI3K-Akt Pathway, Rheumatoid Arthritis, TNF *Tripterygium Wilfordii*

*Correspondence: Sneha Pawar (shivank.sneha853@gmail.com)

Received: 24 July 2026; **Accepted:** 8 August 2026; **Published:** 20 September 2026

1. Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by chronic inflammation of synovial joints, leading to cartilage degradation and bone erosion [1-5] The disease affects approximately 0.5-1% of the global population and significantly reduces quality of life [1, 4]. The pathogenesis of RA involves complex interactions between immune cells, cytokines, and signaling pathways such as TNF-α, IL-6, and NF-κB [2, 3, 6-8]. Conventional treatments include NSAIDs, corticosteroids, and disease-modifying antirheumatic drugs (DMARDs), but these often produce adverse effects with long-term use [1, 4].

Tripterygium wilfordii Hook F, commonly known as Thunder God Vine, has been used in traditional Chinese medicine for centuries to treat inflammatory and autoimmune diseases [9-11]. Its bioactive compounds, including triptolide and celastrol have demonstrated strong anti-inflammatory, immunosuppressive, and anti-proliferative effects [9, 10, 12, 13].

Network pharmacology provides a holistic approach to understanding the interactions between drugs, targets, and diseases. Unlike the traditional "one drug-one target" model, this approach explores multi-target mechanisms, making it particularly suitable for herbal medicines. This study aims to elucidate the molecular mechanisms of *Tripterygium wilfordii* in RA treatment using a network pharmacology framework [14-19].

Tripterygium wilfordii Hook F (Thunder God Vine), a traditional Chinese medicinal plant, has demonstrated considerable therapeutic promise in inflammatory and autoimmune conditions [9-13]. Its principal bioactive constituents triptolide, celastrol, and wilforlide A have shown potent anti-inflammatory and immunosuppressive activities in preclinical studies, while clinical evidence supports meaningful improvements in RA disease activity [9, 10, 12, 13]. Despite this, the precise molecular mechanisms underlying its therapeutic effects remain incompletely understood, largely because its multi-constituent nature renders conventional single-target pharmacological approaches inadequate [14, 15, 17-19].

Network pharmacology, integrating bioinformatics, cheminformatics' and systems biology provide a rational framework to decode such multi-component, multi-target herb-disease interactions [14-19]. It bridges the gap between traditional empirical knowledge and modern evidence-based pharmacology by systematically identifying active compounds, core therapeutic targets, and enriched biological pathways [15-31].

Therefore, the study was undertaken to systematically elucidate the molecular mechanisms of *Tripterygium wilfordii* in RA through a network pharmacology approach, to provide a scientific foundation for its further development as a validated therapeutic agent [9-19].

2. Materials and Methods

2.1. Collection of Active Compounds

Active compounds of *Tripterygium wilfordii* were obtained from:

1) *TCMSP database*- It provides comprehensive data on the pharmacokinetic properties of traditional Chinese medicinal compounds
2) *PubChem*-It offers detailed chemical structures, molecular properties, and biological activity information.

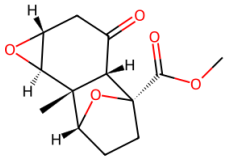
Screening criteria:

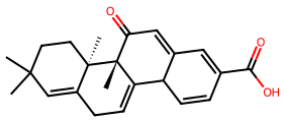
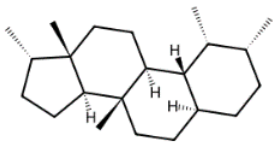
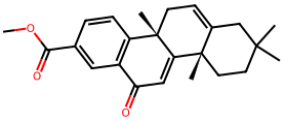
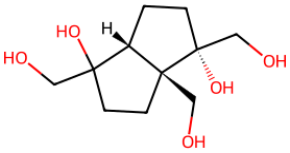
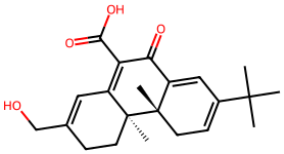
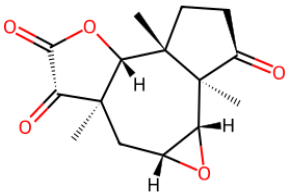
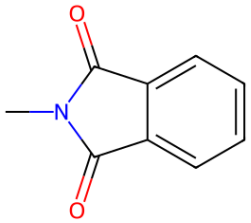
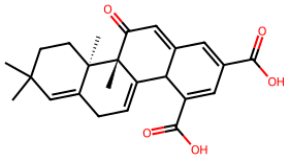
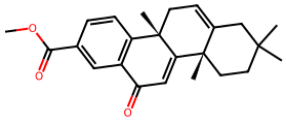
1) *Oral bioavailability (OB ≥ 30%)*- It was set at ≥30%, indicating the proportion of an orally administered compound that reaches systemic circulation and is available to exert therapeutic effects.
2) *Drug-likeness (DL ≥ 0.18)*- It evaluates the structural and physicochemical similarity of a compound to known therapeutic drugs, thereby predicting its potential as a viable drug candidate

Major compounds identified:

1) *Triptolide*- recognized for its potent anti-inflammatory, immunosuppressive, and anti-proliferative activities
2) *Celastrol*- exhibits significant antioxidant, anti-inflammatory, and immunomodulatory properties by regulating multiple signaling pathways involved in autoimmune diseases.
3) *Wilforlide A*- demonstrated promising anti-inflammatory and immune-regulating effects, contributing to the overall therapeutic efficacy of *Tripterygium wilfordii*.

Table 1. *Top 10 Active Phytochemicals of Tripterygium wilfordii with SwissADME-Derived Pharmacokinetic Properties and 2D Chemical Structures.*

No.	Compound	Molecular Formula	MW (g/mol)	OB (%)	DL	HBA	HBD	LogP	TPSA (Å²)	2D Structure
1	Triptolide	C20H24O6	360.40	33.45	0.14	6	0	1.85	79.90	

No.	Compound	Molecular Formula	MW (g/mol)	OB (%)	DL	HBA	HBD	LogP	TPSA (Å²)	2D Structure
2	Celastrol	C29H38O4	450.61	47.25	0.21	4	2	5.80	74.60	
3	Wilforlide A	C30H48O3	472.70	39.55	0.20	3	1	6.20	49.69	
4	Tripterin	C30H40O4	480.63	42.18	0.22	4	0	5.96	52.60	
5	Euonyminol	C15H24O6	300.34	30.72	0.11	6	5	-0.85	107.22	
6	Deme-thylzeylasteral	C29H36O5	468.60	51.33	0.25	5	2	5.44	87.99	
7	Triptonide	C20H22O6	358.38	36.10	0.16	6	0	1.65	79.90	
8	Wilforgine	C9H7NO2	161.16	41.22	0.09	3	0	0.72	46.17	
9	Salaspermic acid	C30H38O6	498.61	44.67	0.23	6	2	5.02	111.13	
10	Pristimerin	C30H40O4	480.	48.91	0.26	4	0	6.10	52.60	

Abbreviations: MW = Molecular Weight; OB = Oral Bioavailability (%); DL = Drug-Likeness; HBA = Hydrogen Bond Acceptors; HBD = Hydrogen Bond Donors; LogP = Partition Coefficient; TPSA = Topological Polar Surface Area. Active compounds were selected based on OB ≥ 30% and DL ≥ 0.18.

2.2. Target Identification

The first step involves collecting potential molecular targets from two separate angles. Compound-related targets are predicted using Swiss Target Prediction, a web tool that uses the chemical structure of a compound to computationally estimate which human proteins it may interact with Disease-related targets for rheumatoid arthritis (RA) are gathered from GeneCards, a comprehensive gene database [22], and DisGeNET, a platform that links genes and variants to known human diseases based on curated evidence [23].

2.3. Common Target Screening

Once both sets of targets are collected, they are compared to identify genes or proteins shared between the compound and the disease. This intersection is visualized using a Venn diagram generated by the Vinny online tool. Only the overlapping targets that appear in both lists are carried forward, since these represent potential therapeutic points where the compound could influence the disease biology [15-19].

2.4. Protein-Protein Interaction (PPI) Network

The shared targets are then uploaded to the STRING database, which maps known and predicted physical or functional interactions between proteins [21]. A confidence threshold of 0.7 is applied to retain only high-quality interactions and filter out weak or unreliable associations. The resulting network is imported into Cytoscape, a widely used bioinformatics tool, for visual exploration and topological analysis of how these proteins relate to one another [25].

2.5. Hub Gene Identification

Within the PPI network, not all nodes are equally important. The CytoHubba plugin in Cytoscape is used to rank proteins by their topological significance [26]. The MCC (Maximal Clique Centrality) algorithm is applied because it is considered one of the most accurate methods for identifying hub nodes proteins that are highly interconnected and therefore likely to play central regulatory roles in the disease-drug interaction network [26].

2.6. Gene Ontology (GO) Analysis

GO analysis is performed to understand what biological roles the common targets collectively serve. It is divided into three categories: Biological Process (what cellular or physiological functions the genes participate in), Molecular Function (the biochemical activities of the gene products, such as binding or catalysis), and Cellular Component (the specific locations within the cell where these proteins are found and active). Together, these categories provide a layered functional profile of the target set [29].

2.7. KEGG Pathway Analysis

KEGG (Kyoto Encyclopedia of Genes and Genomes) pathway analysis identifies which major biological signaling or metabolic pathways are significantly enriched among the common targets [30, 31]. Using the STRING or KEGG database, genes are mapped to established pathways and statistically ranked [21, 30, 31]. The top enriched pathways reveal the broader mechanistic context through which the compound might exert its therapeutic effects against RA [15-19].

3. Literature Review

Network pharmacology, first proposed by Hopkins (2008), represents a paradigm shift from the reductionist "one drug-one target" approach to a systems-level understanding of drug action [14, 18]. This approach integrates bioinformatics, systems biology, and pharmacology to explore the multi-target mechanisms of drugs, particularly herbal medicines [15-19].

3.1. Rheumatoid Arthritis — Pathogenesis and Current Treatment

Rheumatoid arthritis (RA) is driven by persistent immune activation involving T cells, B cells, macrophages, and synovial fibroblasts. Pro-inflammatory cytokines such as TNF-α, IL-6, IL-1β, and IL-17 play central roles in perpetuating synovial inflammation, pannus formation, and articular destruction [1-7, 32]. The NF-κB, MAPK, and PI3K-Akt signaling pathways serve as critical intracellular mediators orchestrating this inflammatory cascade [8, 32-34].

Conventional disease-modifying antirheumatic drugs (DMARDs), such as methotrexate, and biological agents targeting TNF-α (e.g., infliximab and etanercept) have substantially improved patient outcomes but are associated with risks including immunosuppression, infections, and high treatment costs [1, 2, 4, 6]. Consequently, there is considerable interest in identifying alternative therapeutic options, particularly those derived from traditional herbal medicines [9, 11].

3.2. *Tripterygium wilfordii* — Traditional and Modern Evidence

Tripterygium wilfordii, a traditional Chinese medicinal herb, has been used extensively for the treatment of autoimmune and inflammatory disorders [9-11]. Modern pharmacological studies have confirmed that its principal bioactive constituents including triptolide and celastrol possess anti-inflammatory, immunosuppressive, and antiproliferative properties [9, 10, 12, 13].

Triptolide has been shown to inhibit NF-κB-mediated signaling and suppress the production of pro-inflammatory cytokines while modulating T-cell activity [8, 12, 13]. Celastrol likewise exhibits potent anti-inflammatory effects by regulating oxidative stress and inflammatory signaling pathways and

reducing immune cell-mediated inflammation in affected tissues [10, 12].

Network pharmacology databases such as TCMSP, Swiss Target Prediction, GeneCards, DisGeNET, and STRING provide the computational infrastructure necessary for identifying active compounds, predicting molecular targets, and mapping disease-relevant pathways [20-24]. The integration of these resources with Cytoscape-based network visualization and topological analysis tools, together with Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses, has enabled researchers to systematically elucidate the polypharmacological mechanisms of herbal medicines and their multi-target therapeutic effects [15-19, 25-31].

4. Plant Profile

Taxonomy: Kingdom: Plantae; Clade: Angiosperms; Clade: Eudicots; Order: Celastrales; Family: Celastraceae; Genus: *Tripterygium*; Species: *Tripterygium wilfordii* Hook. f. Common Names: Thunder God Vine, Lei Gong Teng (Chinese), Three-winged Fruit Vine.

Tripterygium wilfordii is a perennial woody climbing vine valued for its potent bioactive constituents. It has slender, twining woody stems with light brown to grey bark, simple alternate ovate to elliptic leaves with finely serrated margins and pointed apices, and small white to pale green bisexual flowers arranged in axillary or terminal panicles. The plant produces characteristic three-winged capsules and possesses thick woody roots, which are the primary source of its pharmacologically active compounds. *Tripterygium wilfordii* is native to East Asia, primarily distributed in China, Korea, and Japan. It commonly grows in forest margins, mountain slopes, and shrublands under temperate and subtropical climatic conditions. The medicinally important parts of *Tripterygium wilfordii* include the root, root bark, and leaves, with the root bark being the richest source of pharmacologically active phytochemicals. Tripterygium wilfordii contains several bioactive phytochemicals, including diterpenoids (triptolide and tripdiolide), triterpenoids (celastrol), alkaloids, sterols, and glycosides. Among these, triptolide and celastrol are the principal active constituents and have been extensively investigated for their potent anti-inflammatory, immunosuppressive, and pharmacological activities.

Figure 1. *Tripterygium wilfordii (Ray Wood, Castle Howard, North Yorkshire, UK, August 2022). [https://davisla.wordpress.com/2014/09/09/tripterygium-wilfordii/]*

5. Pharmacological Activities

The plant exhibits multiple biological activities:

5.1. Anti-Rheumatic Activity

The plant has a well-established use in the management of rheumatoid arthritis (RA), a chronic autoimmune disease characterized by synovial inflammation and progressive joint destruction [1-5]. Its bioactive compounds suppress pro-inflammatory mediators, inhibit osteoclast-mediated bone resorption, and downregulate matrix metalloproteinases (MMPs) involved in cartilage degradation [6-8, 12, 32-34]. Clinical and experimental studies have demonstrated that *Tripterygium wilfordii* exhibits significant anti-rheumatic effects, supporting its traditional therapeutic use in RA [9, 10, 12, 13].

5.2. Anti-Inflammatory Activity

The plant potently inhibits key pro-inflammatory cytokines, including TNF-α and IL-6, primarily through suppression of the NF-κB signaling pathway, a central regulator of inflammatory gene expression [6-8, 12]. Inhibition of inflammatory mediators contributes to its analgesic and anti-inflammatory effects. Its multi-target mode of action provides broader therapeutic potential than conventional single-target anti-inflammatory agents [12, 14, 15, 17-19].

5.3. Anticancer Activity

Experimental studies indicate that constituents of *Tripterygium wilfordii*, particularly triptolide, inhibit tumor cell proliferation, induce apoptosis, and interfere with oncogenic signaling pathways [10, 12, 13]. These effects involve activation of apoptotic mechanisms and modulation of pathways associated with cell survival and proliferation, including PI3K/Akt signaling [12, 13, 33] suggesting potential anticancer activity that warrants further investigation.

5.4. Immunosuppressive Activity

The plant exhibits potent immunosuppressive properties by modulating T-cell and B-cell responses and reducing the production of inflammatory cytokines involved in autoimmune diseases [9, 10, 12, 13]. These immunomodulatory effects contribute to its therapeutic utility in disorders such as rheumatoid arthritis and other immune-mediated inflammatory conditions [1-5, 9].

5.5. Antioxidant Activity

The plant contains bioactive phytochemicals, including terpenoids and polyphenolic constituents, that may contribute to antioxidant activity by reducing oxidative stress and supporting cellular defense mechanisms [10, 11]. Such antioxidant effects may complement its anti-inflammatory and therapeutic properties in chronic diseases associated with oxidative damage [11, 12].

6. Molecular Mechanism of Action

The therapeutic effects of *Tripterygium wilfordii* in rheumatoid arthritis can be explained through its active constituents and their interactions with key molecular targets.

Triptolide, one of the major diterpenoid compounds isolated from *Tripterygium wilfordii*, exhibits potent anti-inflammatory and immunosuppressive activities. Triptolide, one of the bioactive compounds, exhibits strong anti-inflammatory activity by inhibiting transcription factors such as NF-κB and AP-1. It suppresses cytokine production (TNF-α, IL-6) and reduces T-cell activation, thereby modulating the immune response. In addition, it inhibits T-cell activation and proliferation, decreases macrophage-mediated inflammatory responses, and promotes apoptosis of pathogenic immune cells, ultimately restoring immune homeostasis and reducing joint damage associated with RA.

Celastrol, another compound, has been shown to inhibit oxidative stress and inflammatory signaling. It blocks NF-κB activation and reduces the expression of adhesion molecules, limiting immune cell infiltration into synovial tissues. celastrol modulates multiple intracellular signaling pathways, including the PI3K–Akt and MAPK pathways, which regulate cell survival, apoptosis, and inflammatory responses. Through these mechanisms, celastrol helps suppress synovial hyperplasia, cartilage degradation, and bone erosion, thereby slowing the progression of rheumatoid arthritis.

These bioactive compounds regulate cytokine signaling, apoptosis, immune cell activation and oxidative stress pathways, resulting in reduced inflammation, modulation of immune responses, and protection against cartilage destruction in rheumatoid arthritis.

Collectively, the bioactive constituents of *Tripterygium wilfordii* target multiple inflammatory mediators and signaling pathways, including TNF, NF-κB, MAPK, and PI3K–Akt, resulting in reduced cytokine production, modulation of immune cell activity, inhibition of oxidative stress, and restoration of immune balance. This coordinated regulation of diverse molecular targets supports the therapeutic potential of *Tripterygium wilfordii* as a multi-component, multi-target, and multi-pathway treatment strategy for rheumatoid arthritis.

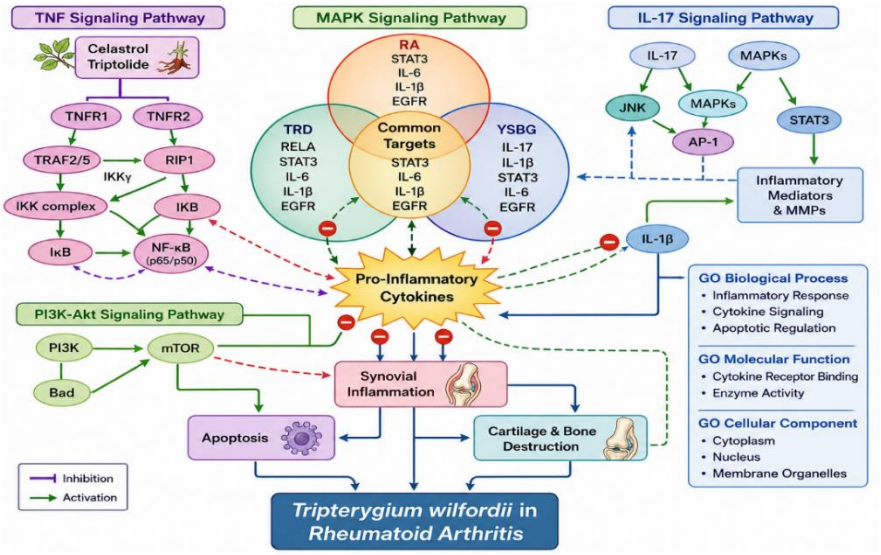


Figure 2. *Suppression of immune overactivation.*

7. Limitations of the Study

Despite providing valuable insights, this study has certain limitations that must be acknowledged.

Firstly, the study is based entirely on in silico (computational) methods, including database mining and network analysis. While these approaches are powerful for hypothesis generation, they lack experimental validation. Secondly, the accuracy of results depends on database reliability.

Databases such as GeneCards, STRING, and Swiss Target Prediction may contain incomplete or predicted data, which can influence the outcomes. Thirdly, the study does not consider pharmacokinetic factors such as bioavailability, metabolism, and toxicity *in-vivo*. For instance, compounds like triptolide are known to have potential toxicity, which may limit their clinical application. Lastly, the complex interactions within biological systems cannot be fully captured through network pharmacology alone. Therefore, *in-vitro* and *in-vivo* studies are essential to confirm these findings.

8. Results

8.1. Active Compounds and Targets

A total of key bioactive compounds was identified from *Tripterygium wilfordii*, including triptolide and celastrol which showed strong interactions with multiple protein targets associated with rheumatoid arthritis [9, 10, 12, 13, 20, 24].

8.2. Common Targets

Target screening and integration of disease- and compound-related datasets identified approximately 100-150 overlapping targets between *T. wilfordii* and rheumatoid arthritis, supporting the herb's multi-target therapeutic potential [15-19, 22-24].

Table 2. *Candidate Therapeutic Target Genes of Tripterygium wilfordii Against Rheumatoid Arthritis.*

Common Target (Gene Name)	UniPort ID
TNF	P01375
NFKB1	P19838
IKBKB	O14920
AKT1	P31749
CASP3	P42574
ABCB1	P08183
CYP3A4	P08684
ESR1	P03372
AR	P10275
HMGCR	P04035
HSP90AA1	P07900

8.3. Protein-Protein Interaction Network

The PPI network revealed highly interconnected nodes. Key proteins included:

1) TNF
2) IL6
3) AKT1
4) MAPK1
5) NFKB1

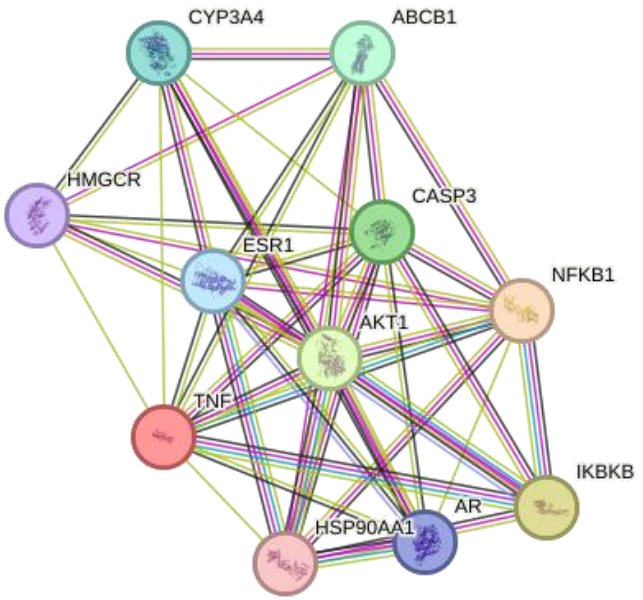


Figure 3. *Protein–Protein Interaction (PPI) network of the common target genes between Tripterygium wilfordii and rheumatoid arthritis constructed using the STRING database.*

These proteins play central roles in inflammation and immune response.

8.4. Hub Genes

Top hub genes identified:

1) TNF
2) IL6
3) STAT3
4) AKT1
5) JUN

These genes are critical regulators of RA progression.

8.5. Gene Ontology Analysis

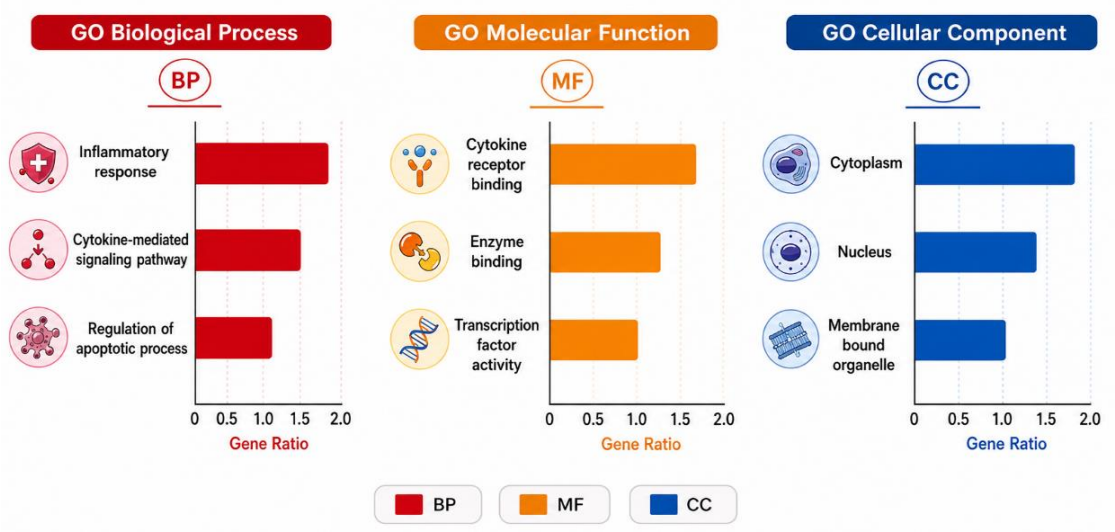


Figure 4. *Gene Ontology (GO) enrichment analysis of the common target genes between Tripterygium wilfordii and rheumatoid arthritis.*

8.6. KEGG Pathway Analysis

Significant pathways identified:

1) TNF signaling pathway
2) NF-κB signaling pathway
3) PI3K-Akt signaling pathway
4) MAPK signaling pathway
5) IL-17 signaling pathway

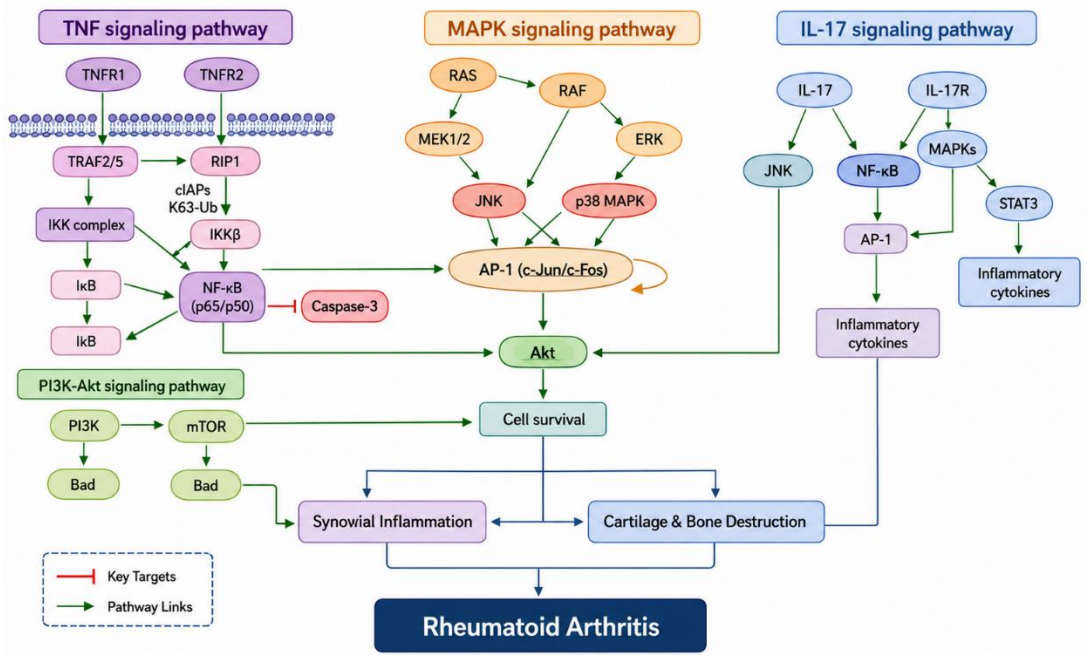


Figure 5. *Schematic illustration of the major signaling pathways involved in the therapeutic mechanism of Tripterygium wilfordii against rheumatoid arthritis based on KEGG pathway enrichment analysis.*

These pathways are strongly associated with RA pathogenesis. The above schematic representation focuses on the major signaling pathways involved in the therapeutic action of *Tripterygium wilfordii* against rheumatoid arthritis, including the

TNF, MAPK, PI3K–Akt, and IL-17 pathways. These pathways interact with key molecular targets such as TNF, NF-κB, AKT, JNK, ERK, Caspase-3, and AP-1, which play pivotal roles in regulating inflammatory responses, cytokine production, apoptosis, synovial inflammation, cell survival, and cartilage and bone degradation.

9. Discussion

The study demonstrates that Tripterygium wilfordii acts through multiple bioactive compounds targeting several proteins involved in inflammation and immune regulation. Triptolide and celastrol are key compounds responsible for inhibiting inflammatory cytokines such as TNF-α and IL-6 [10, 12, 13].

The network pharmacology analysis highlights the importance of signaling pathways such as NF-κB and PI3K-Akt, which regulate immune responses and cell survival [8, 33]. The multi-target nature of *T. wilfordii* makes it a promising candidate for RA treatment [15, 17, 19]. The present study provides a comprehensive network pharmacology-based insight into the therapeutic mechanisms of *Tripterygium wilfordii* in rheumatoid arthritis (RA). Unlike conventional pharmacological approaches that focus on single targets, this study highlights the multi-component and multi-target nature of herbal medicine, which is particularly relevant for complex diseases like RA [14, 15, 17, 18].

One of the most significant findings of this study is the identification of key inflammatory mediators such as TNF-α and IL-6 as central nodes in the protein-protein interaction network. These cytokines are well-established contributors to RA pathogenesis, playing critical roles in synovial inflammation, pannus formation, and joint destruction [1-7]. The inhibition of TNF-α has already been successfully translated into clinical therapies (e.g., monoclonal antibodies like infliximab), which further validates the importance of these targets [6]. The ability of *T. wilfordii* compounds such as triptolide and celastrol to modulate these cytokines suggests a strong therapeutic potential comparable to existing biologics [9, 10, 12, 13].

Additionally, the NF-κB signaling pathway emerged as a crucial pathway in this study. NF-κB is a master regulator of inflammatory gene expression and is persistently activated in RA patients. Activation of NF-κB leads to the transcription of pro-inflammatory genes, including TNF-α, IL-1β, and IL-6. The suppression of NF-κB signaling by bioactive compounds of *T. wilfordii* indicates a mechanism through which inflammation can be effectively controlled at the transcriptional level [12, 13]. The PI3K-Akt signaling pathway also plays a vital role in cell survival, proliferation, and immune regulation. In RA, abnormal activation of this pathway contributes to synovial hyperplasia and resistance to apoptosis in fibroblast-like synoviocytes (FLS) [33]. The identification of AKT1 as a hub gene suggests that *T. wilfordii* may help restore apoptotic balance and reduce synovial tissue overgrowth [12, 33].

Similarly, the MAPK signaling pathway, including ERK, JNK, and p38 kinases, is involved in transmitting extracellular inflammatory signals into intracellular responses. These kinases regulate the production of cytokines and matrix metalloproteinases (MMPs), which are responsible for cartilage degradation [34]. By targeting MAPK1, *T. wilfordii* may reduce joint damage and inflammation simultaneously [12, 34] Another important pathway identified is the IL-17 signaling pathway, which is closely associated with Th17 cell-mediated immune responses. IL-17 promotes the recruitment of neutrophils and enhances inflammation in synovial tissues [32]. The modulation of this pathway further supports the immunosuppressive role of *T. wilfordii* [12, 32]. Overall, the integration of these pathways demonstrates that *Tripterygium wilfordii* does not act through a single mechanism but rather exerts a synergistic therapeutic effect by regulating multiple biological processes simultaneously. This multi-target approach may reduce drug resistance and improve treatment outcomes compared with single-target therapies [14, 15, 17-19].

Future research should validate these findings through *in-vitro*, *in-vivo*, and clinical studies to confirm efficacy, safety, and optimal dosing. Additionally, molecular docking, molecular dynamics simulations, and omics approaches (proteomics and transcriptomics) can further elucidate the underlying mechanisms and support the therapeutic development of *Tripterygium wilfordii* for rheumatoid arthritis.

10. Conclusion

This study confirms that *Tripterygium wilfordii* exerts therapeutic effects in rheumatoid arthritis through a multi-component, multi-target, and multi-pathway mechanism, consistent with the principles of network pharmacology [14, 15, 17-19]. Key targets such as TNF, IL6, and AKT1, along with critical signaling pathways including NF-κB and PI3K-Akt, play a central role in mediating its pharmacological actions [6-8, 33]. The integration of network pharmacology analysis highlights the ability of bioactive compounds like triptolide and celastrol to regulate complex inflammatory networks and immune responses involved in RA pathogenesis [9, 10, 12, 13, 15].

Furthermore, the modulation of pathways such as MAPK and IL-17 suggests a broader regulatory effect on cytokine production, synovial inflammation, and joint destruction [32, 34]. These findings provide mechanistic insights into how *T. wilfordii* can simultaneously target multiple biological processes, offering an advantage over conventional single-target therapies [14, 15, 17, 19]. The results also emphasize its potential role in restoring immune balance and inhibiting disease progression in rheumatoid arthritis [1-8, 12, 33].

Overall, this study supports the traditional use of *Tripterygium wilfordii* and establishes a scientific foundation for its development as a promising therapeutic agent for rheumatoid arthritis [9-11]. However, further experimental validation, including *in -vitro*, *in- vivo*, and clinical studies, is essential to confirm its efficacy, safety, and pharmacokinetic profile before clinical application [9, 10, 13].

Abbreviations

RA	Rheumatoid Arthritis
TCMSP	Traditional Chinese Medicine Systems Pharmacology Database
PPI	Protein–Protein Interaction
GO	Gene Ontology
KEGG	Kyoto Encyclopedia of Genes and Genomes
STRING	Search Tool for the Retrieval of Interacting Genes/Proteins
OB	Oral Bioavailability
DL	Drug-Likeness
BP	Biological Process
MF	Molecular Function
CC	Cellular Component
TNF	Tumor Necrosis Factor
IL	Interleukin
NF-κB	Nuclear Factor Kappa B
PI3K	Phosphoinositide 3-Kinase
AKT	Protein Kinase B
MAPK	Mitogen-Activated Protein Kinase
JNK	c-Jun N-terminal Kinase
ERK	Extracellular Signal-Regulated Kinase
AP-1	Activator Protein-1
CASP3	Caspase-3
AKT1	AKT Serine/Threonine Kinase 1
STAT3	Signal Transducer and Activator of Transcription 3
ESR1	Estrogen Receptor Alpha
AR	Androgen Receptor
HMGCR	3-Hydroxy-3-Methylglutaryl-CoA Reductase
HSP90AA1	Heat Shock Protein 90 Alpha Family Class A Member 1
ABCB1	ATP-Binding Cassette Subfamily B Member 1
CYP3A4	Cytochrome P450 Family 3 Subfamily A Member 4
IKBKB	Inhibitor of Nuclear Factor Kappa-B Kinase Subunit Beta
NFKB1	Nuclear Factor Kappa B Subunit 1
DMARDs	Disease-Modifying Antirheumatic Drugs
FLS	Fibroblast-Like Synoviocytes
MMPs	Matrix Metalloproteinases
MCC	Maximal Clique Centrality
UniProt	Universal Protein Resource

Acknowledgments

The authors would like to express their sincere gratitude to the Tilak Maharashtra Vidyapeeth's Lokmanya Tilak Institute of Pharmaceutical Sciences, Pune team for encouragement and support during the course of this research. Their valuable suggestions and academic assistance contributed significantly to the successful completion of this study.

The authors also acknowledge the developers and maintainers of publicly available databases and bioinformatics resources, including TCMSP, Swiss Target Prediction, GeneCards, DisGeNET, STRING, UniPort, Drug Bank, Gene Ontology (GO), and KEGG, which provided essential data for the network pharmacology analysis conducted in this work.

Author Contributions

Rohan Mohite: Conceptualization, Methodology, Writing – original draft

Pragati Pujari: Investigation, Visualization

Sneha Pawar: Formal Analysis, Software

Kumudini Pawar: Resources, Validation

Komal Laddha: Writing – review & editing

Mayuri Bapu Chavan: Validation, Writing – review & editing

Meera Deshmukh: Project administration, Supervision

Pranati Tilak: Project administration

Conflicts of Interest

The authors declare no conflicts of interests.

References

[1] Smolen JS, Aletaha D, McInnes IB (2016) Rheumatoid arthritis. Lancet 388: 2023-2038.

[2] McInnes IB, Schett G (2011) The pathogenesis of rheumatoid arthritis. N Engl J Med 365: 2205-2219.

[3] Firestein GS (2003) Evolving concepts of rheumatoid arthritis. Nature 423: 356-361.

[4] Scott DL, Wolfe F, Huizinga TW (2010) Rheumatoid arthritis. Lancet 376: 1094-1108.

[5] Klareskog L, Catrina AI, Paget S (2009) Rheumatoid arthritis. Lancet 373: 659-672.

[6] Feldmann M, Maini RN (2003) TNF as a therapeutic target. Nat Med 9: 1245-1250.

[7] Tanaka T, Narazaki M, Kishimoto T (2014) IL-6 in inflammation. Cold Spring Harb Perspect Biol 6: a016295.

[8] Hayden MS, Ghosh S (2011) NF-κB in immunity. Cell Res 21: 223-244.

[9] Tao X, Cush JJ, Garret M, Lipsky PE (2001) Clinical efficacy of Tripterygium wilfordii. Arthritis Rheum 44: 1737-1743.

[10] Brinker AM, Ma J, Lipsky PE, Raskin I (2007) Medicinal chemistry of Tripterygium. Phytochemistry 68: 732-766.

[11] Jiang WY (2013) Therapeutic wisdom in traditional Chinese medicine. J Tradit Complement Med 3: 125-129.

[12] Liu Q (2011) Triptolide and celastrol in inflammatory diseases. Int Immunopharmacol 11: 377-383.

[13] Unveiling the Anticancer Mechanism of Myristicin: A Computational Study on DHODH Targeting in UV-Induced Melanoma MS Bhosle, MR Kajbaje, MD Borawake, MA Ranade… - International Journal of Medical and Pharmaceutical …, 2025(6): 1311-1317.

[14] Hopkins AL (2008) Network pharmacology: the next paradigm in drug discovery. Nat Chem Biol 4(11): 682-690.

[15] Li S, Zhang B (2013) Traditional Chinese medicine network pharmacology. Chin J Nat Med 11: 110-120.

[16] Zhang R, Zhu X, Bai H, Ning K (2019) Network pharmacology databases. Brief Bioinform 20: 1774-1785.

[17] Zhou W, Wang Y, Lu A, Zhang G (2016) Systems pharmacology in herbal medicine. BMC Syst Biol 10(Suppl 1): S3.

[18] Hopkins AL (2007) Network pharmacology in drug discovery. Nat Chem Biol 3: 682-690.

[19] Li X, Xu X, Wang J, et al (2014) Systems pharmacology approach. Mol Biosyst 10: 252-261.

[20] Ru J, Li P, Wang J, et al (2014) TCMSP: a database of systems pharmacology. J Cheminform 6: 13.

[21] Szklarczyk D, Gable AL, Nastou KC, et al (2021) STRING database in 2021. Nucleic Acids Res 49: D605-D612.

[22] Stelzer G, Rosen N, Plaschkes I, et al (2016) GeneCards Suite. Curr Protoc Bioinformatics 54: 1.30.1-1.30.33.

[23] Snnehaa Bhosle1*, Komal Laddha 2, Dr. Meera Deshmukh3, Dr. Pranati Tilak4 (2025) In-Silico & Biological Activity Evaluation of Herbal and Synthetic Compound for the Treatment of Arthritis: A comparative ADMET Analysis. Journal of Technology Vol 13; Issue 7: 976-995.

[24] Daina A, Michielin O, Zoete V (2019) SwissTargetPrediction. Nucleic Acids Res 47: W357-W364.

[25] Shannon P, Markiel A, Ozier O, et al (2003) Cytoscape: a software environment for biomolecular interaction networks. Genome Res 13(11): 2498-2504.

[26] Chin CH, Chen SH, Wu HH, et al (2014) cytoHubba: identifying hub objects in networks. BMC Syst Biol 8(Suppl 4): S11.

[27] Wishart DS, Feunang YD, Guo AC, et al (2018) DrugBank database. Nucleic Acids Res 46: D1074-D1082.

[28] UniProt Consortium (2021) UniProt: the universal protein database. Nucleic Acids Res 49: D480-D489.

[29] Ashburner M, Ball CA, Blake JA, et al (2000) Gene Ontology: tool for unification of biology. Nat Genet 25: 25-29.

[30] Kanehisa M, Goto S (2000) KEGG database. Nucleic Acids Res 28: 27-30.

[31] Kanehisa M, Furumichi M, Sato Y, et al (2021) KEGG for integration. Nucleic Acids Res 49: D545-D551.

[32] Gaffen SL (2009) IL-17 signaling pathway. Nat Rev Immunol 9: 556-567.

[33] Manning BD, Cantley LC (2007) AKT/PKB signaling pathway. Cell 129: 1261-1274.

[34] Pearson G, Robinson F, Beers Gibson T, et al (2001) MAPK pathways. Endocr Rev 22: 153-183.