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Original Article

Systems-Level Network Pharmacology analysis of *Terminalia chebula* (*Haritaki*): Deciphering Multi-Target Mechanisms Across Inflammation-Metabolism-Immunity Axis

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ABSTRACT

Background: Chronic inflammatory disorders result from complex interactions among inflammation, metabolic dysregulation, and immune imbalance. Conventional single-target therapies often fail to address this complexity. *Terminalia chebula* (*Haritaki*), an important Ayurvedic medicinal plant, is traditionally used for inflammatory, metabolic, and immune-related disorders; however, its integrated molecular mechanisms remain insufficiently understood. **Objectives:** This study aimed to elucidate the systems-level, multi-target mechanisms of *Terminalia chebula* across the inflammation-metabolism-immunity axis using network pharmacology and molecular docking approaches. **Materials and Methods:** Bioactive compounds of *T. chebula* were screened from IMMPAT and Dr. Duke databases using ADME criteria. Potential targets were predicted using SwissTargetPrediction and BindingDB, while disease-related targets were obtained from GeneCards. Overlapping targets were analyzed through compound-target and protein-protein interaction networks, followed by hub gene identification and KEGG pathway enrichment. Molecular docking was performed to validate ligand-target interactions. **Results:** Thirty-two bioactive compounds and 150 overlapping targets were identified. Key phytoconstituents included quercetin, ellagic acid, and fatty acids, while hub genes comprised TNF, BCL2, ESR1, MMP9, EGFR, SRC, and CASP3. Enriched pathways involved Rap1, PI3K-Akt, MAPK, and PPAR signaling. Molecular docking demonstrated favorable binding affinities (≤-4 kcal/mol), supporting stable ligand-protein interactions. **Conclusion:** *Terminalia chebula* exerts therapeutic effects through coordinated multi-component, multi-target modulation of interconnected inflammatory, metabolic, and immune pathways, providing a scientific basis for its traditional use in complex chronic disorders.

Keywords: *Haritaki*, Inflammation-Metabolism-Immunity Axis, Molecular docking, Multi-target therapeutics, Network pharmacology, *Terminalia chebula*.

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INTRODUCTION

Inflammation is a vital biological process that acts as the body's first line of defense against harmful stimuli such as infections, damaged cells, along with irritants (Chavda *et al*., 2024). The interaction of inflammatory factors and metabolism is critical for physiological balance and progression of diseases, including immune dysregulation (Hu *et al*., 2024). This interrelated inflammation-metabolism-immunity axis is responsible for the development of a wide range of diseases, such as metabolic syndrome, autoimmune diseases, cardiovascular disease, and chronic inflammatory conditions (Rathmell, 2012; Xu *et al*., 2025). Formerly, drug discovery and development was mostly based on the "one target, only one disease" strategy. However, clinical data reveal that single-target medications are challenging to interfere with the entire disease network, are now prone to drug resistance, and have a low safety profile in clinical use (Zimmermann *et al*.,

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2007). As a result, multi-target therapy strategies that can alter associated molecular networks at the systems level are gaining widespread acceptance. In Ayurveda, *Haritaki* (*Terminalia chebula*) is highly valued for its exceptional therapeutic properties, it is referred to as the "King of Medicines" and is consistently ranked among the best in Ayurveda (Ratha and Joshi, 2013). Key signaling pathways like NF-κB, MAPK, PI3K-Akt, innate immunological pathways, and cytokines networks-central elements in the inflammation-metabolism-immunity axis-have been shown to be modulated by *T. chebula* in both experimental and clinical investigations (Haghani *et al*., 2022; Lee *et al*., 2025; Lopez *et al*., 2017). Additionally, emerging evidence suggests to its function in immune cell control, gut microbiome modification, lipid and glucose metabolism, and redox balance, suggesting a systems-level therapeutic impact as opposed to discrete pharmacological effects (Agrawal and Kulkarni, 2023; Sadhupati *et al*., 2024). The broad therapeutic efficacy of the herb can be explained by identifying important hub genes, signaling modules, and synergistic interactions through the construction of compound-target-pathway-disease networks (Jin *et al*., 2021). In addition to bridging the gap between contemporary systems biology and ancient Ayurvedic knowledge, this method offers a scientific justification for the integrative use of *Terminalia chebula* in complicated chronic conditions. Therefore, the present study aims to use a systems-level network pharmacology analysis to elucidate *Terminalia chebula's* multi-target mechanisms across the interconnected inflammation-metabolism-immunity axis providing novel insights into its holistic therapeutic potential and supporting evidence-based application in integrative medicine.

MATERIALS AND METHODS

Bio-active compounds screening of *T. chebula*

IMMPAT 2.0 and Dr. Duke's Ethnobotanical database were used to identify all the phytocompounds in *Haritaki* (Lans and Van Andel, 2020; Vivek-Ananth *et al*., 2023). ADME screening focused on GI absorption, bioavailability, and Lipinski rule to identify functionally active components in *T. chebula*. This was carried out using SwissADME database (Daina *et al*., 2017).

Target Screening of *T. chebula* bioactive compounds

Both SwissTargetPrediction (Daina *et al*., 2019) and BindingDB databases (Liu *et al*., 2024) were used to identify active ingredient targets in *T. chebula*. To simplify and standardize the analysis of data, the Uniprot library (Bateman *et al*., 2024) was employed to systematically convert the target's "protein name" into the "gene name."

Prediction of Targets related to inflammation-metabolism-immunity

The search plan comprised using the terms 'inflammation', 'metabolic disorder', and 'immune dysregulation' to obtain the relevant gene data set via GeneCard (Safran *et al*., 2021). The gene data collected via these searches were compiled, and duplicates were eliminated. Following data normalization with the UniProt library, we identified key targets for the inflammation-metabolism-immunity axis. An online mapping tool framework was used to create a Venn diagram correlating the active compounds of *T. chebula* with inflammation, metabolism, and immune targets.

Construction of Compound-Target Network

Using Cytoscape 3.7.2 to build the targeted compound network, the active compounds and their targets were imported, and a major compound-target-network diagram for *Haritaki* ameliorating inflammation-metabolic disorder-immune dysregulation was created.

Establishment of Protein-Protein Interaction (PPI) Network and Hub Gene Prediction

To build a PPI network with common targets, STRING database (Szklarczyk *et al*., 2024) was used, with '*Homo sapiens*' as the species. The PPI network was then examined using Cytoscape. The cytohubba pluggin was used to undertake a thorough study of the network, allowing for the estimation of degree scores, MNC (maximum neighbourhood component), and MCC (Maximum Clique Centrality). After review, hub targets were chosen for *in silico* molecular docking.

KEGG Enrichment Analysis and Pathway-Target Network Formation

KEGG enrichment studies were carried out on the intersecting target genes via the String database. A pathway- target network was constructed to establish the link among the enriched pathways and their potential targets.

Molecular Docking validation of hub genes and bio-active compounds

Molecular docking, a prominent computer-based structural technique for drug development, anticipate ligand-target interactions on a molecular level. Molecular docking was employed to see if the active components discovered using network pharmacology could bind to the key targets. The 3D structure of the target protein was obtained from the PDB Database (Bittrich *et al*., 2023). Concurrently, the structure of the bio-active compounds of *T. chebula* was obtained from Pubchem (Kim *et al*., 2024). Protein preparation were carried out by dehydrogenation and incorporating polar bonds via BIOVIA DS. To verify the target protein was entirely encompassed by the docking box, we uploaded the receptor and ligand pdbqt structures into AutoDock and put the target protein to the center of the grid. Finally, BIOVIA software was utilized to visualize the results.

Ethical Statement

As this study was based on *in silico* network pharmacology analysis using publicly available databases (IMMPAT, Dr. Duke, GeneCards), ethical approval was not required for this research.

Statistical Analysis

Data normalization and standardization were conducted using the UniProt library. In the PPI network, topological properties including degree scores, MNC, and MCC were used to identify hub genes. Pathway enrichment results were filtered using a False Discovery Rate (FDR) to ensure statistical significance.

RESULTS

Bioactive compounds screening of *T. chebula*

IMMPAT yielded 89 chemical components for *T. chebula*, while Dr Duke's database yielded 97. Chemical formula of *T. chebula* phytochemicals was validated by PubChem. Table 1 shows that 32 phytocompounds that met the ADME demand were identified as possible active phytocomponents utilizing SwissADME.

Target Screening of *T. chebula* bioactive compounds

Target screening of biologically active *T. chebula* compounds revealed 77 targets from the BindingDB database and 172 from SwissTargetPrediction. After de-duplication, thirty-two promising compounds from *T. chebula* were predicted to target 212 proteins.

Prediction of Targets related to inflammation-metabolism-immunity

A comprehensive search of the GeneCards database revealed 6375 targets linked with inflammation, 17411 targets linked to metabolic disorders, and 8858 targets linked with immunological dysregulation. A Venn diagram (Figure 1) identified 150 targets associated with *T. chebula* chemicals and inflammation, metabolism, and immunological dysregulation.

Construction of Compound-Target Network

Over 32 *T. chebula* compounds linked with the 150 common targets were imported into Cytoscape, resulting in a comprehensive Compound-Target (CT) network (Figure 2). The composite network has 182 nodes and 339 edges, an average of 3.725 neighbors, and network heterogeneity along with centralization of 1.198 and 0.141, respectively. It demonstrated a highly linked structure of multi-targeting chemicals and proteins. The main compounds were selected based on the order of their topological properties, with numerous compounds scoring reasonably high degree (>11). These included Quercetin, Ellagic Acid, Palmitoleic Acid, Oleic Acid, Linoleic Acid, Ricinoleic Acid, Shikimic Acid, L-Rhamnose, Anthraquinone, and Flavylium.

Establishment of Protein-Protein Interaction (PPI) Network and Hub Gene Prediction

The PPI network for *T. chebula* chemicals and inflammation-metabolism disorder-immune dysregulation

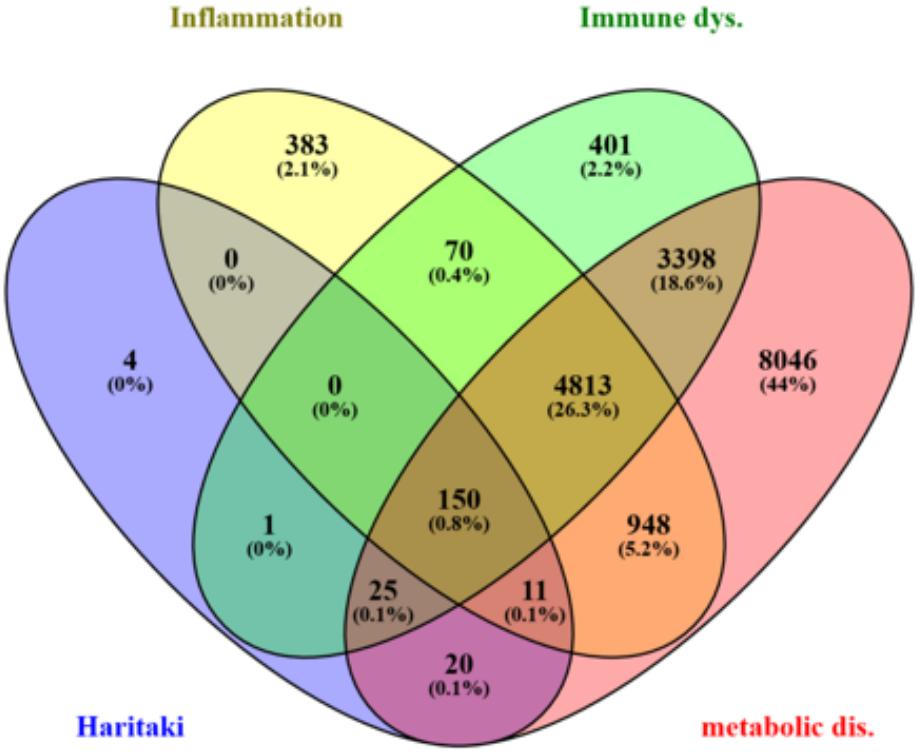

Figure 1: Venn diagram of *Haritaki* bioactive targets overlapping inflamation-metabolism-immunity axis.

Table 1: Bioactive phytochemicals of Haritaki identified via SwissADME.

Haritaki Compound	PubChem CID	GI absorption	Lipinski violation	Bioavailability score
3-Dehydroshikimic acid	439774	High	0	0.55
Anthraquinone	6780	High	0	0.55
Arjugenin	12444386	High	1	0.56
Arjunolic Acid	73641	High	0	0.56
Ascorbic Acid	54670067	High	0	0.56
Caffeic Acid	689043	High	0	0.56
Colosolic acid	15917996	High	1	0.56
Corosolic acid	6918774	High	1	0.56
Ellagic Acid	5281855	High	0	0.55
Ethyl gallate	13250	High	0	0.55
Ferulic acid	445858	High	0	0.55
Flavylium	145858	High	0	0.55
Gallic Acid	370	High	0	0.56
Linoleic Acid	5280450	High	0	0.55
L-Rhamnose	25310	High	0	0.55
Maslinic Acid	73659	High	1	0.56
Myristic Acid	11005	High	0	0.85
Oleic Acid	445639	High	1	0.85
Oxalic Acid	971	High	0	0.85
Palmitic Acid	985	High	1	0.85
Palmitoleic Acid	445638	High	0	0.85
p-Coumaric acid	637542	High	0	0.85
Phloroglucinol	359	High	0	0.55
Proline	145742	High	0	0.55
Pyrogallol	1057	High	0	0.55
Quercetin	5280343	High	0	0.55
Ricinoleic acid	643684	High	0	0.85
Shikimic Acid	8742	High	0	0.56
Stearic Acid	5281	High	1	0.85
Succinic Acid	1110	High	0	0.85
Syringic acid	10742	High	0	0.56
Vanillic Acid	8468	High	0	0.85

showed significant connections (at a confidence level of 0.7), as shown in the Figure 3. Based on MCC, MNC, and Degree values, the top seven ranking hub genes were BCL2, ESR1, TNF, MMP9, EGFR, SRC, and CASP3 (Figure 4).

KEGG Enrichment Analysis and Pathway-Target Network Formation

A pathway enrichment analysis was done using the anticipated 150 common targets to investigate pathways important to the Inflammation-Metabolism-Immunity Axis. A total of 170 pathways were found, and the top 20 were statistically extracted as shown in Table 2. These included the Rap1 signaling route, PI3K-Akt signaling pathway, MAPK signaling pathway, PPAR signaling pathway, and the endocrine resistance pathway (Figure 5). Additional Pathway-Target networks were built, as illustrated in Figure 6.

Molecular Docking validation of hub genes and bio-active compounds

The ten top-ranked compounds (Quercetin, Ellagic Acid, Palmitoleic Acid, Oleic Acid, Linoleic Acid, Ricinoleic Acid, Shikimic Acid, L-Rhamnose, Anthraquinone, and Flavylium)

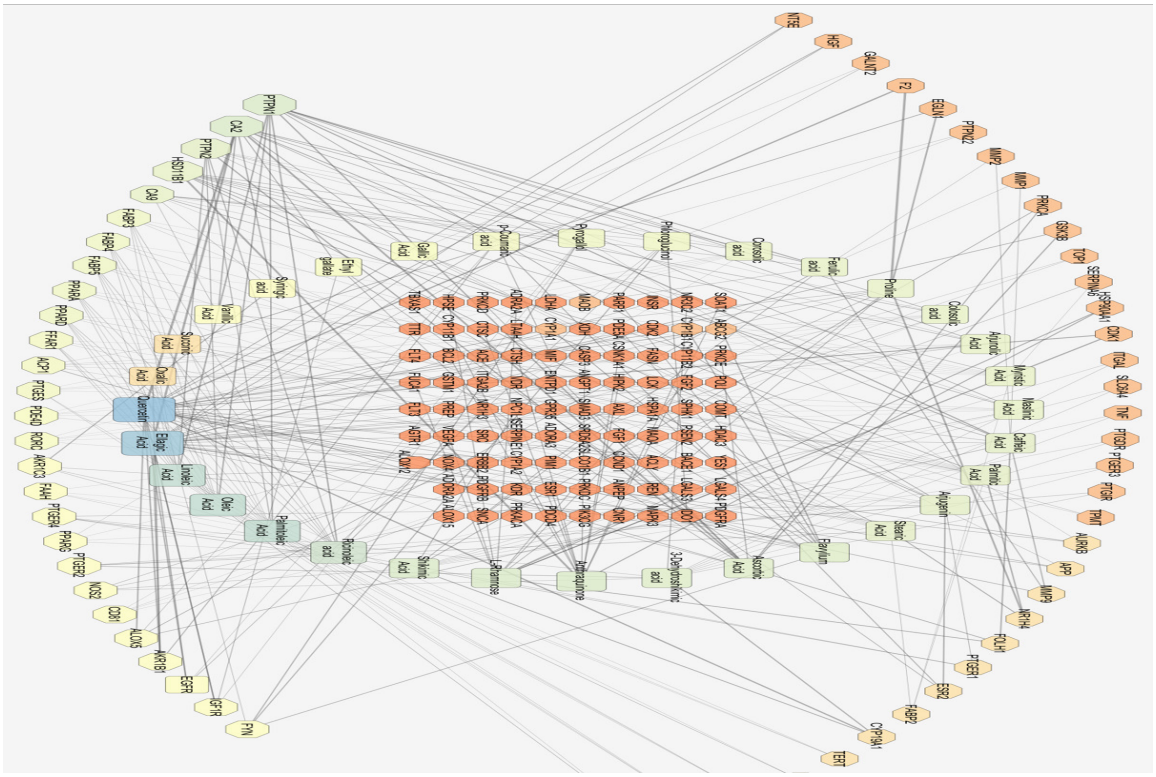

Figure 2: Compound-Target Network of *Haritaki* Across Inflammation-Metabolism-Immunity Axis.

Table 2: Pathway annotation obtained via STRING KEGG analysis.

Enriched pathway	Total gene count	Observed gene count	FDR
Pathways in cancer	515	39	1.97×10^{-24}
EGFR tyrosine kinase inhibitor resistance	77	14	1.16×10^{-12}
Proteoglycans in cancer	194	18	4.10×10^{-12}
Rap1 signaling pathway	201	18	5.40×10^{-12}
PI3K-Akt signaling pathway	349	22	5.40×10^{-12}
AGE-RAGE signaling pathway in diabetic complications	96	14	5.91×10^{-12}
Prostate cancer	97	13	1.05×10^{-10}
Focal adhesion	195	16	2.19×10^{-10}
MAPK signaling pathway	286	18	5.65×10^{-10}
Endocrine resistance	94	12	8.13×10^{-10}
PPAR signaling pathway	75	11	1.34×10^{-9}
MicroRNAs in cancer	159	14	1.42×10^{-9}
HIF-1 signaling pathway	102	12	1.52×10^{-9}
Steroid hormone biosynthesis	60	10	2.61×10^{-9}
Serotonergic synapse	108	12	2.61×10^{-9}
Ras signaling pathway	225	15	8.19×10^{-9}
Adherens junction	69	10	8.19×10^{-9}
Bladder cancer	40	8	4.41×10^{-8}
Melanoma	72	9	1.58×10^{-7}
Ovarian steroidogenesis	50	8	1.79×10^{-7}

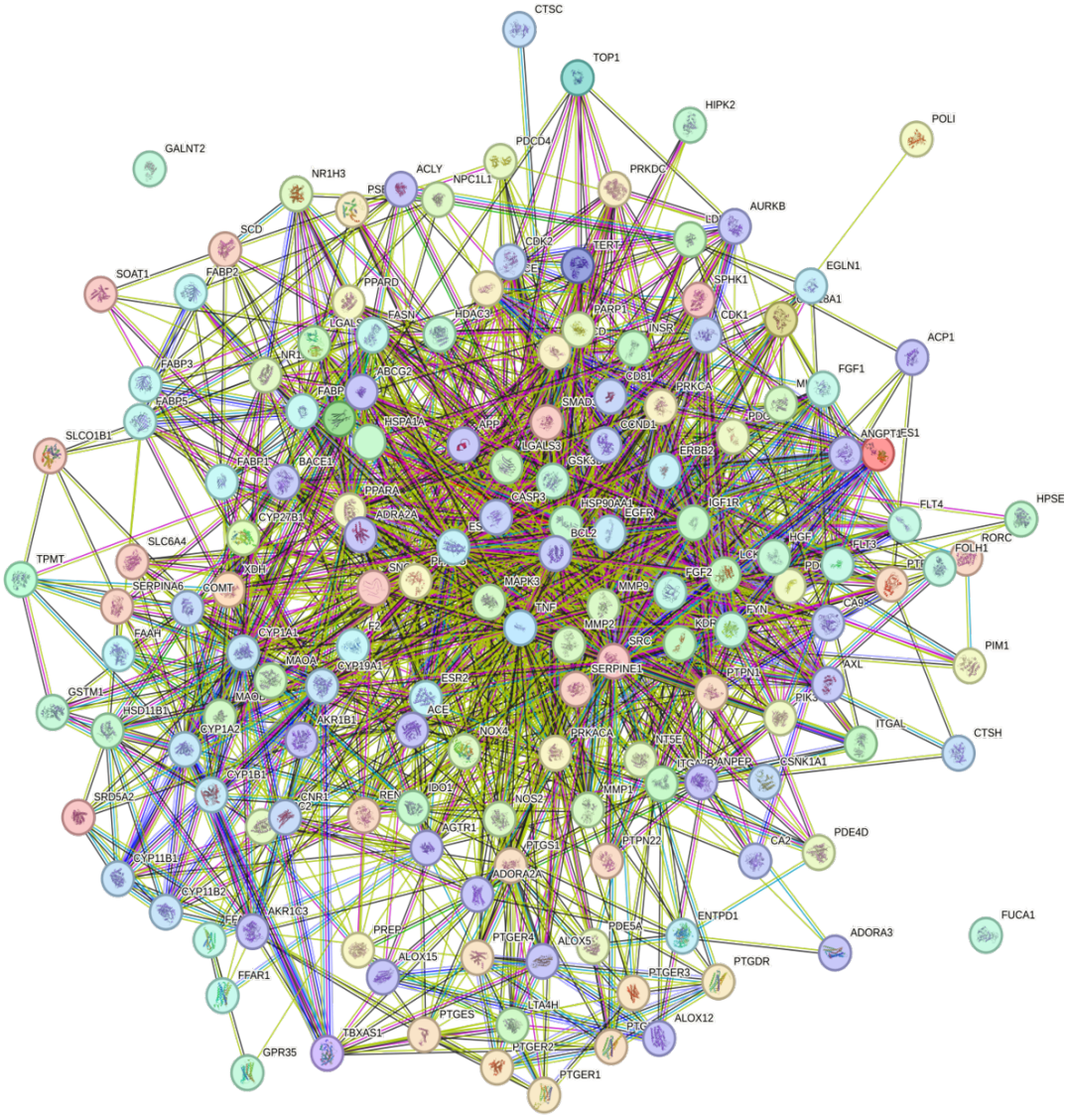

Figure 3: PPI of 150 targets associated with *T. chebula* chemicals and inflammation, metabolism, and immunological dysregulation.

predicted in the CT network were docked with seven hub targets relevant to the Inflammation-Metabolism-Immunity Axis (BCL2, ESR1, TNF, MMP9, EGFR, SRC, and CASP3). Most compounds had favorable binding energy scores (≤-4 kcal/mol). The Table 3 depicts the binding affinity metrics for hub genes and *T. chebula* bioactive compounds. Figure 7 shows the 3D docking poses and 2D Ligand Protein interaction photos of each target against the *Haritaki* phyto-constituent with the highest binding affinity.

DISCUSSION

The present study reflect that *Haritaki* have a multi-compound, multi-targeted, and multi- biological pathway effect. The comprehensive network of *Haritaki* Compound-Target and Pathway- Targ*et al*ong with PPI depicts mechanistic insight to immune dysregulation, metabolic imbalance, and persistent inflammation treatment. The results of this study show 150 potential targets for the modulation of Inflammation-Metabolism-Immunity Axis with *Haritaki* bioactive compounds. The seven hub targets, SRC, BCL2, TNF, CASP3, EGFR, ESR1 and MMP9, were also discovered in the network diagram as the potential targets. Previous study suggest that these genes play critical roles in inflammatory signaling, immune cell activation, survival, and apoptosis pathways (Byeon *et al*., 2012; Hobbs *et al*., 2011; Lee *et al*., 2007; Nehra *et al*., 2010; Zeng *et al*., 2016). Such multi-target regulation may explain *Haritaki's* long-term efficacy in chronic, complex disease conditions (Sagar *et al*., 2025). TNF, MMP9, EGFR, SRC, and ESR1 are the primary immunomodulatory regulators, affecting cytokine production, immune cell migration, epithelial-immune interactions, and immunological tolerance (Gilad *et al*., 2022; He *et al*., 2023; Holbrook *et al*., 2019; Kassi and Moutsatsou, 2010; Lu *et al*., 2014). Previous research states that modulation of TNF possibly mediated by polyphenols

Table 3: Binding affinity score of *Haritaki* bioactive-core hub gene.

Bioactive chemicals	Post docking binding affinity(kcal^{-1}) with hub genes						
	BCL2	ESR1	TNF	MMP9	EGFR	SRC	CASP3
Flavylium	-7.4	-8.7	-7.1	-6.8	-8.1	-8.1	-5.9
L-Rhamnose	-4.5	-5	-4	-5.1	-5.2	-4.7	-4.6
Palmitoleic Acid	-4.7	-6.2	-5.1	-4.5	-5.7	-6.1	-4.9
Oleic Acid	-5.3	-4.3	-4.8	-4.6	-5.9	-6.3	-4
Quercetin	-6.9	-8.5	-6.4	-6.8	-8.7	-8.3	-6.6
Linoleic Acid	-4.9	-6.9	-5	-5.6	-6.1	-6.2	-4.2
Ellagic Acid	-6.4	-7.6	-6.1	-7.8	-8.5	-9	-6.1
Ricinoleic acid	-4.8	-6.5	-5.3	-4.4	-6.1	-5.9	-4.4
Anthraquinone	-7.1	-8.6	-5.9	-6.9	-7.5	-8.6	-5.5
Shikimic Acid	-5.4	-6.2	-4.5	-5.4	-5.2	-5.4	-4.5

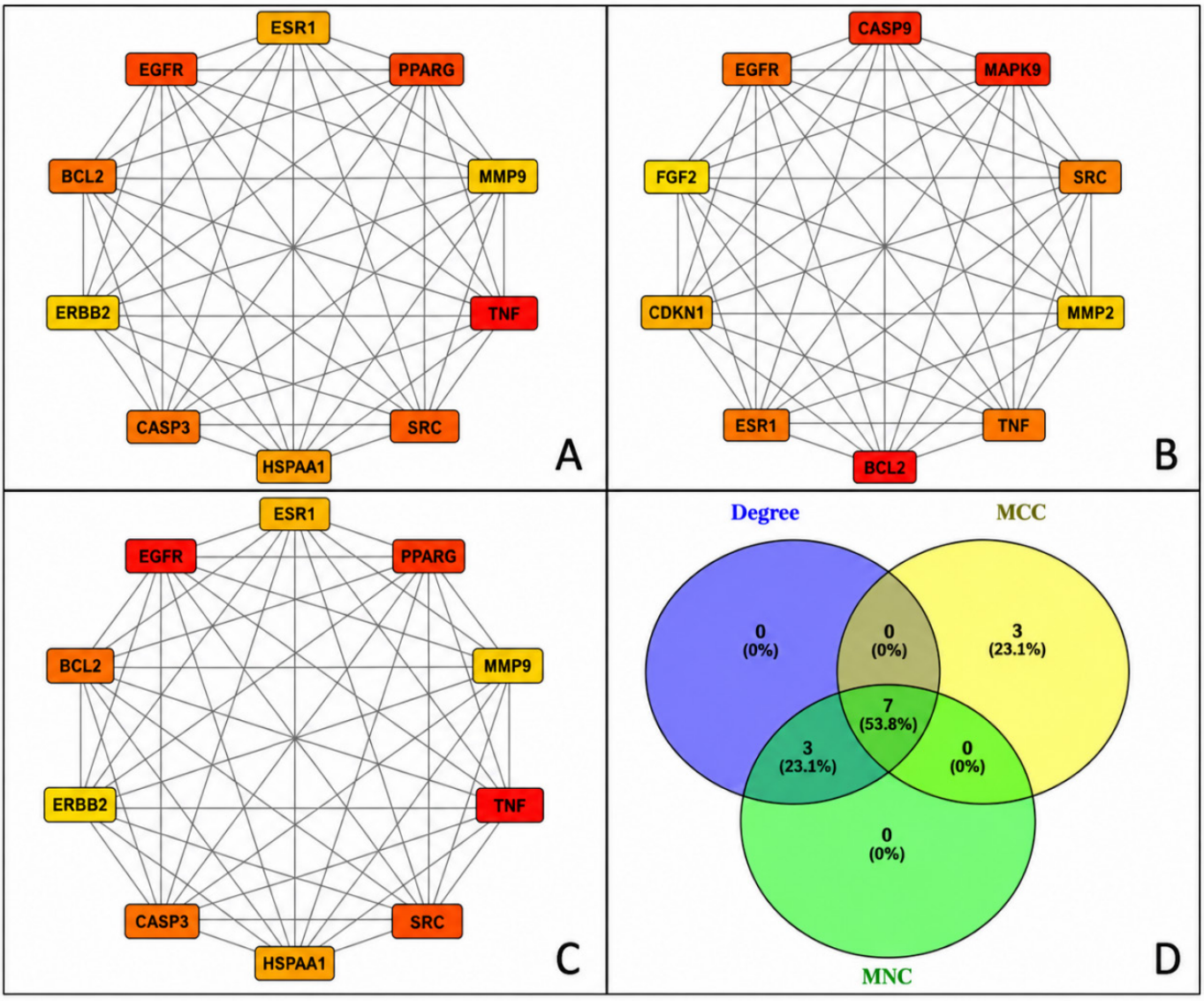

Figure 4: Hub gene obtained via Cytohubba based on Degree (A), MCC (B), MNC (C). Venn digram of core hub genes (D).

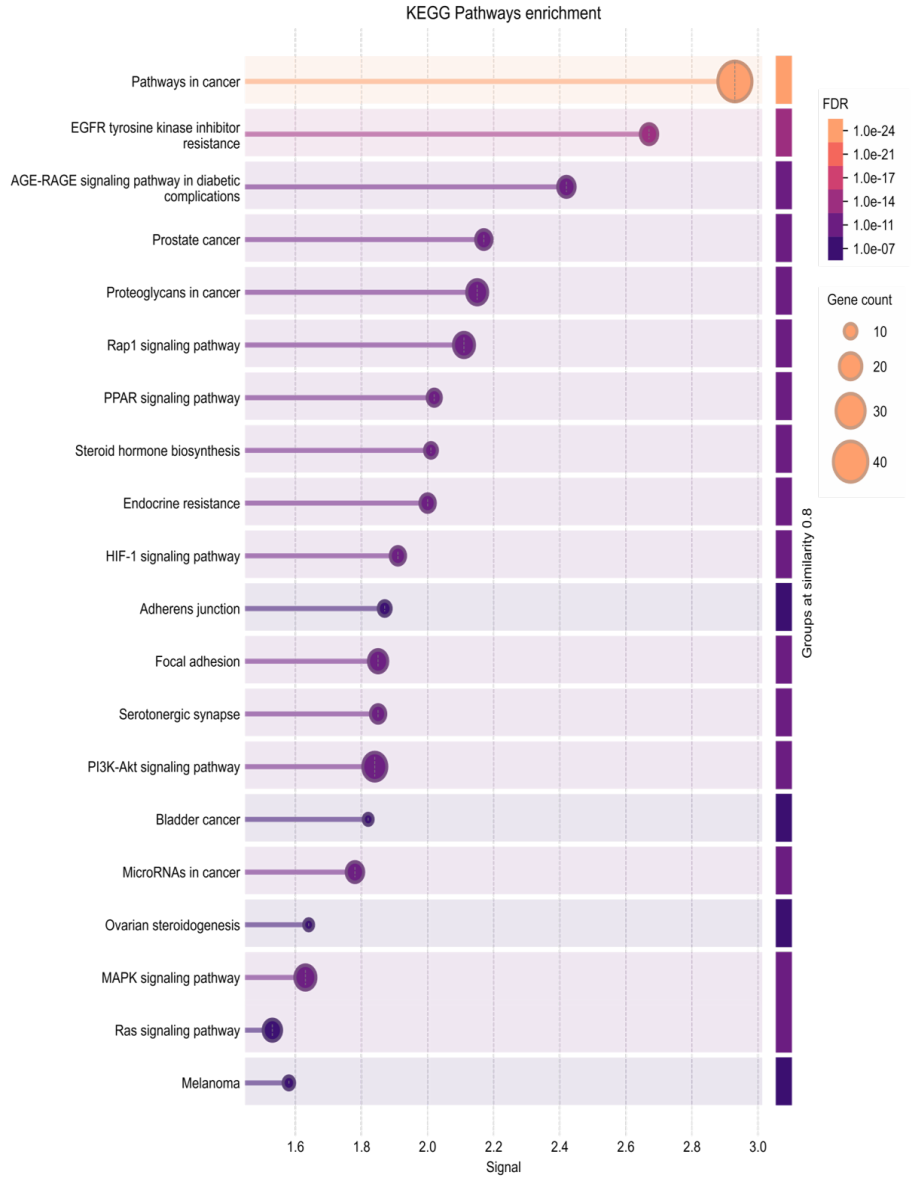

Figure 5: Pathway analysis illustrated via Bubble plot.

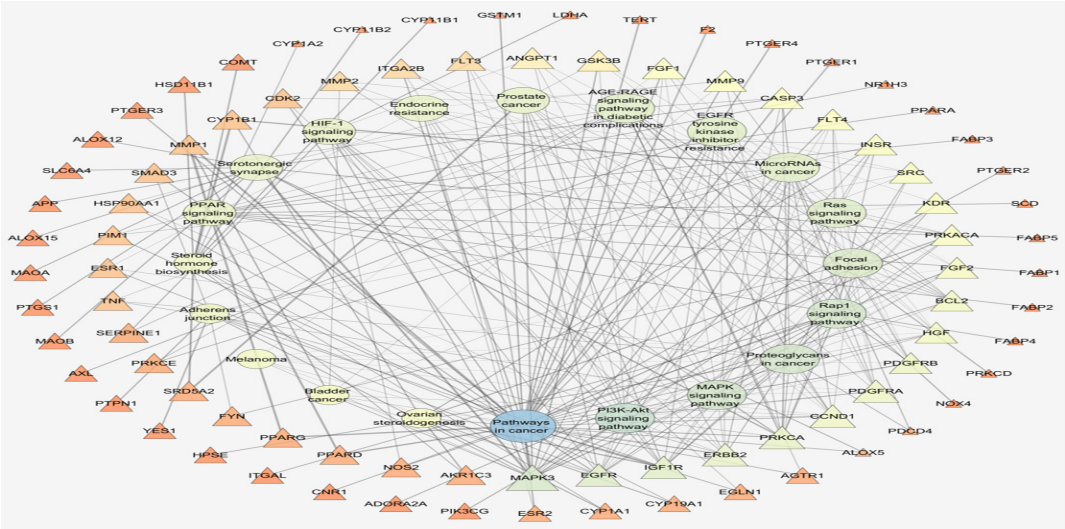

Figure 6: Enriched Pathway-Target Network.

such as quercetin and ellagic acid, may reduce chronic low-grade inflammation while preserving immune response (Gupta *et al.*, 2014). BCL2 and CASP3, on the other hand, are linked to molecular regulators of apoptosis, allowing for the elimination of immune cells through apoptosis (Hussar, 2022). Importantly, the combined activation of immunomodulatory and apoptotic targets supports immunological recalibration rather than indiscriminate suppressive, which promotes immune homeostasis (Hotamisligil, 2017; Sakaguchi, 2002). This balanced control is consistent with the Ayurvedic notion of *Rasayana*, which emphasizes increasing *Vyadhikshamatva* (disease resistance) while avoiding immune exhaustion. The incorporation of molecular docking results enhances these network predictions. *Haritaki's* bioactive compounds have high binding affinities (≤-4 kcal/mol) to essential protein targets in inflammation, metabolism, and immunological function. Pathway enrichment analysis found strong convergence in the RAP1, PI3K-Akt, and MAPK signaling pathways, emphasizing

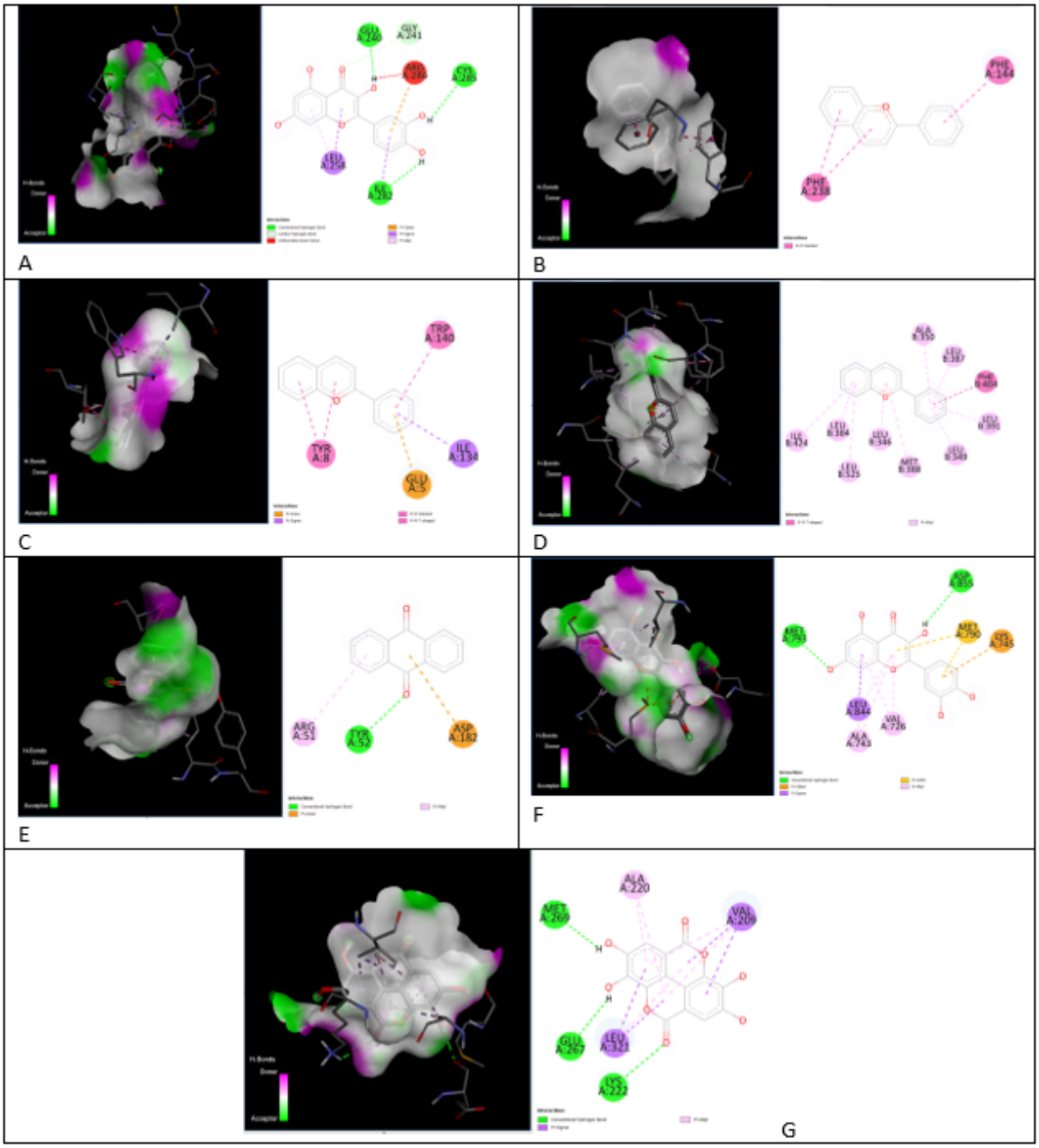

Figure 7: 3D and 2D view of *Haritaki* bioactive- hub gene with highest binding affinity.

the molecular link between inflammation and metabolism (Johnson and Lapadat, 2002; Raaijmakers and Bos, 2009). Rap1 signaling promotes immune activation through NF-κB-mediated cytokine production, while also modulating glucose-lipid metabolism, sensitivity to insulin, along with fatty acid oxidation (Jaśkiewicz *et al.*, 2018). The PI3K-Akt pathway is a key regulator of insulin, growth factor, and immune signaling, integrating metabolic functions like glucose absorption and lipogenesis with cell survival and inflammatory regulation (Acosta-Martinez and Cabail, 2022). Furthermore, the MAPK pathway, particularly through p38 and JNK, connects stress and inflammatory stimuli to inflammatory cytokines and immune activation while also regulating cellular energy detection and metabolic adaptability (Pua *et al.*, 2022). Modulation of these interconnected pathways suggests that *Haritaki* may mitigate inflammation-driven metabolic derangements. From a translational perspective, the identified multi-target and multi-pathway profile supports the potential application of *Haritaki* in complex disease clusters such as metabolic syndrome, atherosclerosis, non-alcoholic fatty liver disease, and chronic inflammatory disorders, (Bag *et al.*, 2013) where single-target pharmacological approaches often fail to achieve durable outcomes. The network identifies potential biomarkers, such as TNF-α, phosphorylated Akt, p38 MAPK, and caspase-3 activity, for further experimental validation *in vitro, in vivo*, and clinical trials. Nonetheless, this study features shortcomings typical of *in silico* network pharmacology, such as its dependence on computerized target prediction and a lack of dose-response contextualization (Li *et al.*, 2023). Thus, biochemical, cell-based, and clinical validation are required to establish expected interactions and therapeutic significance.

CONCLUSION

The present systems pharmacology investigation demonstrates that *Haritaki* (*Terminalia chebula*) exerts its therapeutic potential through multi-component, multi-target interactions, supported by stable molecular binding and network-level pathway regulation. These findings provide a scientific basis for its traditional use and highlight its promise as a therapeutic candidate for complex chronic disorders involving inflammation-metabolism-immunity crosstalk. Further experimental and clinical validation is warranted.

ACKNOWLEDGEMENT

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ABBREVIATIONS

IMMPAT: Indian Medicinal Plants, Phytochemistry And Therapeutics; **ADME:** Absorption, Distribution, Metabolism, and Excretion; **MNC:** maximum neighbourhood component; **MCC:** maximum clique centrality; **KEGG:** Kyoto Encyclopedia of Genes and Genomes; **PDB:** Protein Data Bank; **RAP-1:** Ras-related protein 1; **PI3K-Akt:** Phosphoinositide 3-Kinase - Protein Kinase B (Akt); **MAPK:** Mitogen-Activated Protein Kinase; **PPAR:** Peroxisome Proliferator-Activated Receptor; **BCL2:** B-cell lymphoma 2; **ESR1:** Estrogen Receptor 1; **TNF:** Tumor Necrosis Factor; **MMP9:** Matrix Metalloproteinase-9; **EGFR:** Epidermal Growth Factor Receptor; **SRC:** Proto-oncogene tyrosine-protein kinase Src; **CASP3:** Caspase-3.

CONFLICT OF INTEREST

The authors declare that there is no Conflict of interest.

AUTHOR CONTRIBUTIONS

Conceptualization: JP, PK; Study design and network pharmacology framework: SK, KP; Data collection and phytochemical screening: SK,KP; Target prediction and network construction: PrK, PJ; Pathway enrichment and functional analysis: PrK, PJ; Molecular docking and binding interaction analysis: RR, JP; Validation and interpretation of results: RR, JP; Visualization and figure preparation: JP, RR; Writing-original draft preparation: SK, KP; Writing-review and editing: RR, PJ, PK; Supervision and project administration: JP; Final approval of manuscript: All authors.

SUMMARY

This systems-level network pharmacology analysis explores the therapeutic mechanisms of *Haritaki* (*Terminalia chebula*) by elucidating its multi-component, multi-target actions across the inflammation-metabolism-immunity axis. *In silico* integration of phytochemicals, protein targets, and pathway networks reveals that Haritaki modulates interconnected signaling pathways rather than acting on single molecular targets. Key pathways, including PI3K-Akt, MAPK and Rap1 signaling, highlight crosstalk between immune regulation, inflammatory responses, oxidative stress, and metabolic homeostasis. Hub targets such as BCL2, EGFR, CASP3 and ESR1 indicate coordinated regulation of cytokine signaling and cellular stress responses. These findings provide a systems-level rationale for Haritaki's broad-spectrum efficacy and support its traditional Ayurvedic use in chronic inflammatory and metabolic disorders.

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