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Research article

# Multi-Target Pharmacological Evaluation of Embelin and Piperine against Rheumatoid Arthritis: A Network Pharmacology and Molecular Docking Study

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**Abstract**

Rheumatoid arthritis is a chronic autoimmune inflammatory illness that causes synovial inflammation, cartilage degradation, joint deterioration, and increasing disability. Conventional medicinal techniques are frequently linked with side effects and poor long-term success, prompting the search for safer multitarget phytotherapeutics. The present study used an integrated network pharmacology and molecular docking technique to examine Embelin and Piperine's antiarthritic potential. SwissTargetPrediction and PubChem were used to identify potential Embelin and Piperine targets, while the GeneCards database was used to find rheumatoid arthritis-associated targets. To discover critical hub genes, common targets were studied using protein-protein interaction (PPI) networks. GO and KEGG pathway enrichment analysis revealed a considerable involvement of inflammatory and immune-regulatory pathways, notably the PI3K-Akt signaling pathway. The Key hub genes discovered were HSP90AA1, SRC, PIK3CA, JAK2, PTK2, and MET. Piperine binds strongly to HSP90AA1 (-7.2 kcal/mol) and JAK2 (-7.5 kcal/mol), similar to the standard treatment Tofacitinib (-7.5 kcal/mol), according to a molecular docking investigation. Embelin had a positive affinity with HSP90AA1 (-6.1 kcal/mol) and JAK2 (-5.8 kcal/mol). These data indicate that Embelin and Piperine may have antiarthritic properties through multitarget regulation of inflammatory and immunological pathways.

## 1. Introduction

Arthritis is a chronic musculoskeletal disorder characterized by inflammation, pain, stiffness, swelling, and progressive joint degeneration, leading to impaired mobility and reduced quality of life. It comprises nearly 100 distinct joint disorders affecting connective tissues, cartilage, bones, ligaments, and synovial membranes. The pathogenesis of arthritis involves inflammatory mediators, immune responses, oxidative stress, cartilage degradation, and bone erosion. Cytokines such as TNF-α, IL-1β, IL-6, prostaglandins, and matrix metalloproteinases contribute to persistent inflammation, joint destruction, and pain. Arthritis includes several forms such as osteoarthritis, rheumatoid arthritis, gouty arthritis, psoriatic arthritis, ankylosing spondylitis, and juvenile idiopathic arthritis. Osteoarthritis is the most prevalent degenerative joint disorder associated with aging, obesity, trauma, and mechanical stress, whereas rheumatoid arthritis is a chronic autoimmune disease characterized by synovial inflammation and progressive cartilage and bone destruction [1-7].

The global burden of arthritis has increased considerably due to aging populations, obesity, sedentary lifestyle, and metabolic disorders. Osteoarthritis affects more than 500 million people worldwide, while rheumatoid arthritis affects approximately 0.5-1% of the global population and is more common in women. Current treatment strategies include NSAIDs, corticosteroids, DMARDs, biologics, physiotherapy, exercise, and surgical interventions. However, long-term use of these therapies is associated with

adverse effects including hepatotoxicity, nephrotoxicity, immunosuppression, and increased risk of infections. Consequently, natural phytoconstituents with anti-inflammatory and antioxidant properties have gained significant attention as alternative therapeutic agents [8-13]. Embelin, a naturally occurring benzoquinone derivative isolated from the fruits of Embelia ribes Burm., exhibits anti-inflammatory, antioxidant, anticancer, analgesic, antibacterial, hepatoprotective, cardioprotective, immunomodulatory, and antiarthritic activities. Its anti-inflammatory effects are mainly attributed to inhibition of TNF-α, IL-1β, COX-2, and NF-κB signaling pathways, thereby reducing oxidative stress, joint swelling, and cartilage degeneration in arthritic conditions. Similarly, piperine, the major alkaloid present in Piper nigrum and Piper longum, possesses anti-inflammatory, antioxidant, analgesic, anticancer, immunomodulatory, neuroprotective, and antiarthritic activities. Piperine suppresses cytokines, prostaglandins, nitric oxide generation, and NF-κB signaling pathways, resulting in reduced synovial inflammation and cartilage degradation. Additionally, piperine enhances the bioavailability of several phytoconstituents and therapeutic agents [14-22].

In recent years, network pharmacology has evolved as a powerful systems-level method to understanding the complicated relationships between bioactive chemicals, target proteins, signaling pathways, and illnesses. This computational technique, when combined with molecular docking, allows for the identification of new therapeutic targets as well as the evaluation of ligand-protein binding affinities, which speeds up drug discovery and mechanistic research. Despite several studies demonstrating the individual anti-inflammatory and antiarthritic effects of embelin and piperine, limited information is available regarding their combined molecular mechanisms against rheumatoid arthritis. Since rheumatoid arthritis involves multiple signaling pathways, inflammatory mediators, oxidative stress, and immune dysregulation, a multitarget therapeutic strategy may provide improved therapeutic outcomes.

## 2. Materials and Methods

### 2.1 Chemical Candidates and Compound Related Targets

The literature was used to aid the chemical selection process. The selected bioactive compounds were then searched in the PubChem database to obtain their chemical structures and SMILES notations. Potential target proteins linked with these chemicals, with potential scores higher than zero, were then predicted using the Swiss Target Prediction Database.

### 2.2 Identification of Rheumatoid Arthritis-Related Targets

We searched the GeneCards database for possible targets related with Rheumatoid arthritis. This database combines data from several sources to provide complete information on human genes. The selected targets were collated for additional study and classified as Rheumatoid arthritis-related targets [23].

### 2.3 Venn Diagram

We developed a Venn diagram to assess the overlap between Rheumatoid arthritis -associated targets and possible targets for Embelin and Piperine.

### 2.4 Protein-Protein Interaction (PPI) Network

The STRING database (https://string-db.org/) collects known and projected protein-protein interactions, including functional and physical correlations. For this study, we utilized STRING [24] to look at the connections between the chemicals in our analysis and the targets associated with Rheumatoid arthritis, finding potential therapy targets. To build a reliable protein-protein interaction (PPI) network for these targets, we employed the "Homo sapiens" organism with a confidence level of 0.9. This confidence score is commonly employed because it strikes a good balance between sensitivity and specificity, resulting in a credible criteria for interaction prediction. As a consequence, only proteins with interaction scores of 0.9 or higher were included to the PPI network, increasing the accuracy of our potential target identification.

### 2.5 Functional Enrichment and Pathway Analysis

To identify key pathways and related Gene Ontology (GO) concepts, all potential therapeutic targets were analyzed using pathway and GO enrichment analyses in the String database [25] (https://string-db.org/). This investigation shed light on the biological processes (BP), molecular functions (MF), and cellular components (CC) connected with the targets. Pathways and GO keywords having a significance level of $p < 0.05$ were chosen for further study.

### 2.6 Building a Compound-Target Network

The compound-target interaction network was created by linking the targets associated with each chemical. Cytoscape 3.10.2 (Cytoscape Consortium, San Diego, CA, USA) was used to visualize the network [25]. Nodes in the network represent drugs and their targets, while edges show their interactions.

### 2.7 Molecular Docking

Molecular docking investigations were carried out in accordance with the previously published approach described by Ahmad et al. (2024). The three-dimensional structures of target proteins were obtained from the Protein Data Bank, while ligand structures were obtained from PubChem. AutoDock Vina was used to investigate binding affinity and protein-ligand interactions. The docked complexes with the lowest binding energy were chosen and visualized using PyMOL and Discovery Studio, following the previously defined computational process [24-25].

## 3. Result and Discussion

### 3.1 Potential Therapeutic Targets of Compounds Used to Treat Rheumatoid Arthritis

Employing Rheumatoid arthritis as a keyword, data were extracted from the GeneCards database, providing 5160 target genes. Among them, 100 targets were identified as shared by the chemicals and Rheumatoid arthritis-related genes, indicating prospective therapeutic targets for compounds used to treat Rheumatoid arthritis. A Venn diagram (Figure 1) depicts these overlapping targets.

### 3.2 Construction of the Compound-Target Network

To investigate the signaling pathways and functional functions of the identified target genes, we used Cytoscape data analysis. This strategy made it easier to create a sophisticated compound-target network, as seen in Figure 2. The network highlights the pharmacological pathways by which the chemicals may impact Rheumatoid arthritis therapy, with a focus on interactions with 147 target proteins. Network analysis shows that different components are converging across numerous targets, implying that these bioactive chemicals may have synergistic effects. These interactions may improve the therapeutic efficacy of these drugs not just in the treatment of rheumatoid arthritis, but also in other associated disorders.

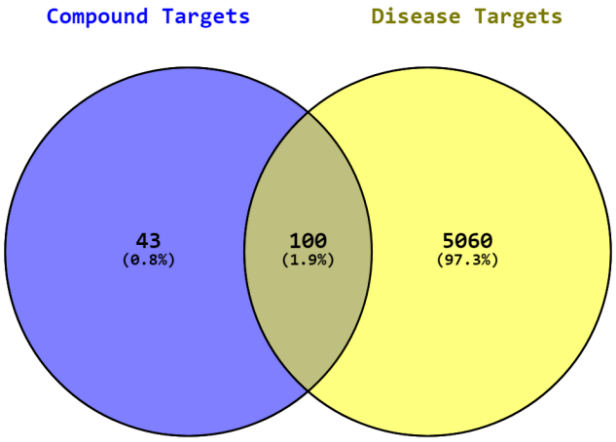



**Figure 1. Venn Plot.**

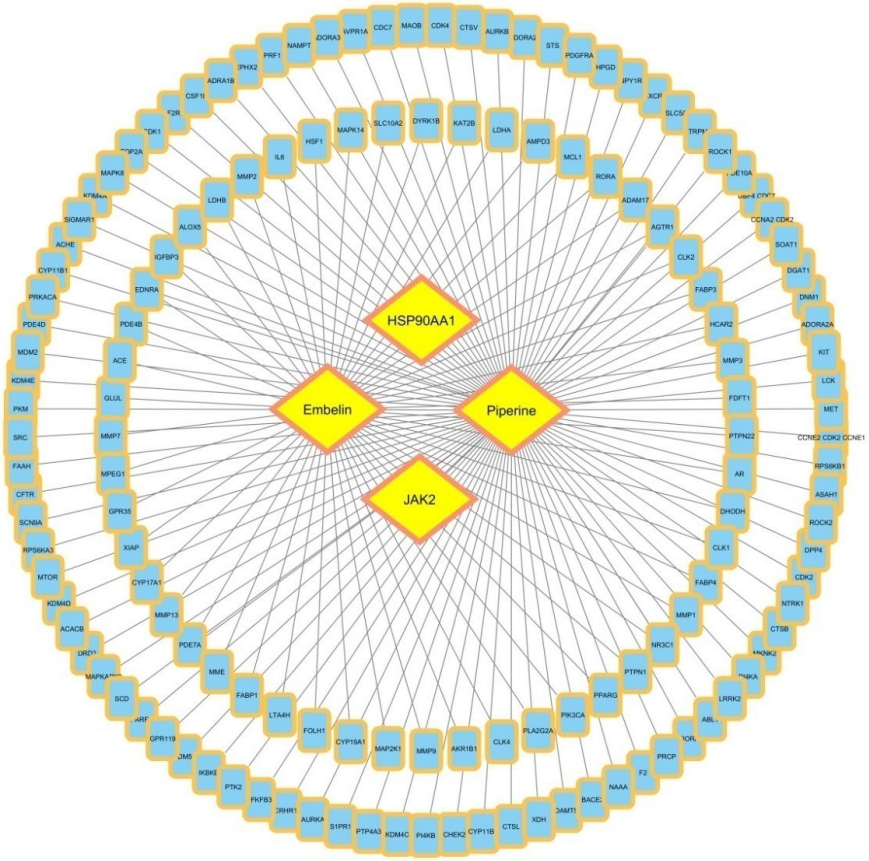



**Figure 2. Compound Target Network.**

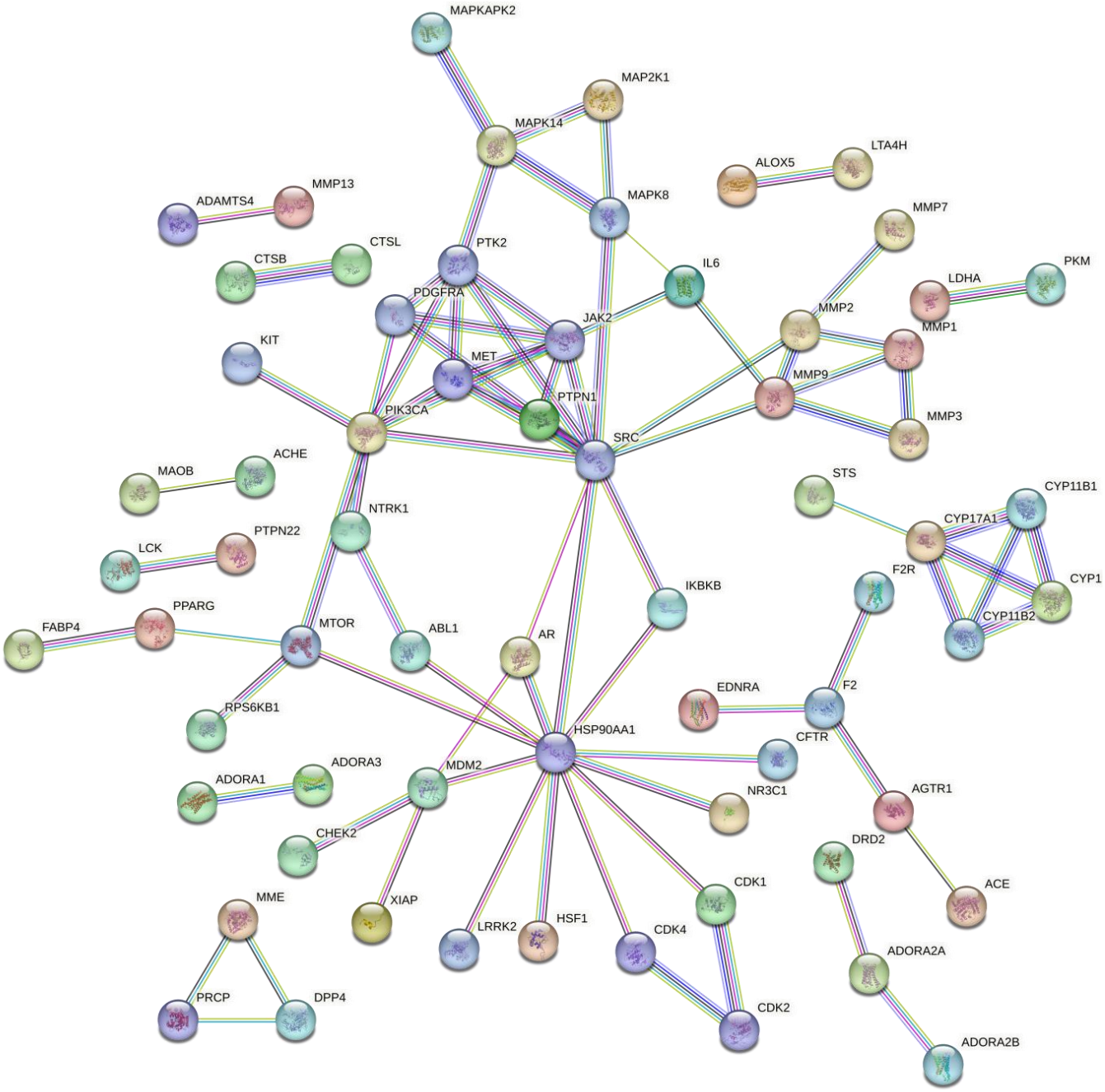



**Figure 3. PPI Network.**

### 3.3 PPI Network Visualization and Analysis

The STRING database was used to investigate interactions between 100 putative medicinal targets. The final protein-protein interaction (PPI) network included 99 nodes and 83 edges, with an average node degree of 1.68 and a local clustering coefficient of 0.479 (Figure 3). In this network, nodes represent individual proteins, while edges represent the relationships between them. A higher degree value indicates a more important involvement for the protein in the network. Following a filtering procedure based on specified criteria, numerous hub genes were found, including HSP90AA1, SRC, PIK3CA, JAK2, PTK2, MET, MMP9, CYP17A1, MAPK14, and MAPK8. These proteins, which include biological enzymes and cytokines, play critical roles in a variety of regulatory processes such as signal transduction and protein phosphorylation. Among these genes, the top five nodal targets were HSP90AA1, SRC, PIK3CA, JAK2, PTK2, and MET. The substantial connections between these genes and other possible therapeutic targets highlight their relevance in Rheumatoid arthritis therapy.

### 3.4 GO enrichment analyses

To determine the molecular processes by which drugs exert their effects on rheumatoid arthritis, we performed Gene Ontology (GO) enrichment analysis on 100 possible

therapeutic targets linked with these medicines using the string database. This study divided into three categories: biological process (BP), molecular function (MF), and cellular component. The top ten GO keywords found in each category are displayed in a bar plot, with data described in Tables 1 (BP), 2 (MF), and 3 (CC), as well as (Figure 4A), 4B), and 4C. In the visualizations, the size of each bar correlates to the number of enriched genes linked with that GO word, while the color gradient indicates the importance of the p value, with deeper colors representing lower p values. A higher bar indicates a greater number of enriched therapeutic genes inside the associated GO word, implying a stronger link with Rheumatoid arthritis therapy than the other terms.

### 3.5 KEGG Pathway Enrichment Analyses

The pathways related with possible therapeutic targets for Rheumatoid arthritis therapy were discovered using KEGG pathway enrichment analysis. Signaling pathways were obtained using the string database. The top ten signaling pathways were then shown in a bar graph (Table 4 and Figure 5), sorted by P value in ascending order. The study revealed that the main targets were significantly enriched in the PI3K-Akt signaling pathway (Figure 5A).

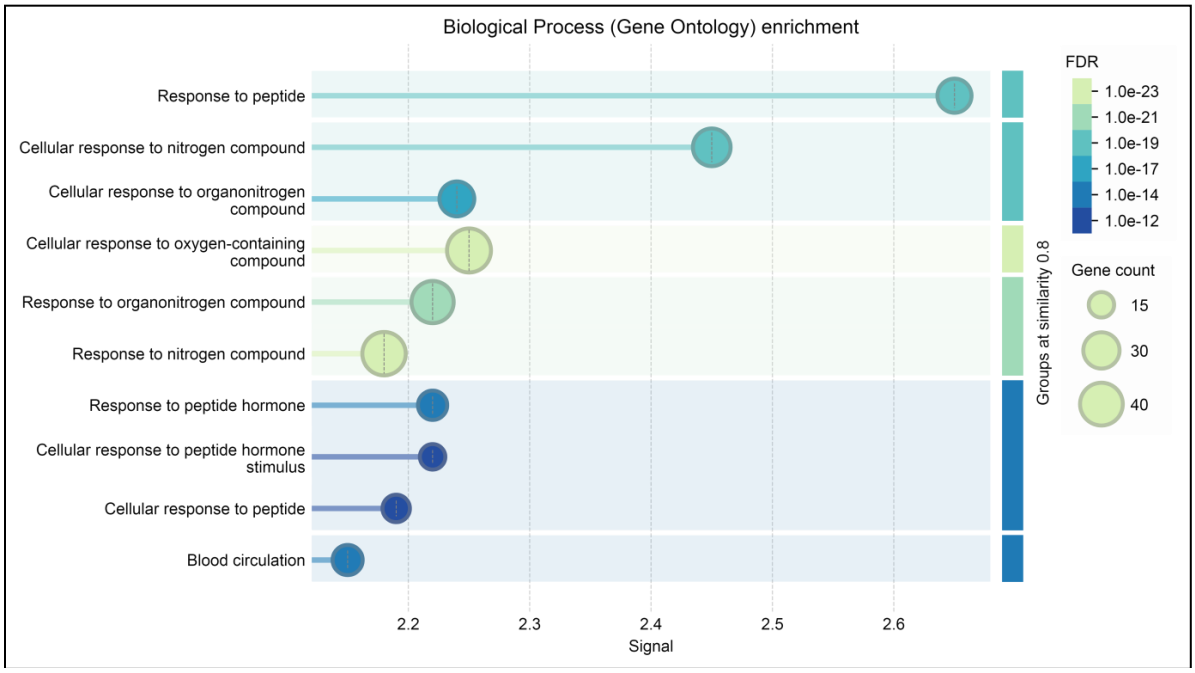



**Figure 4A. Biological Process.**

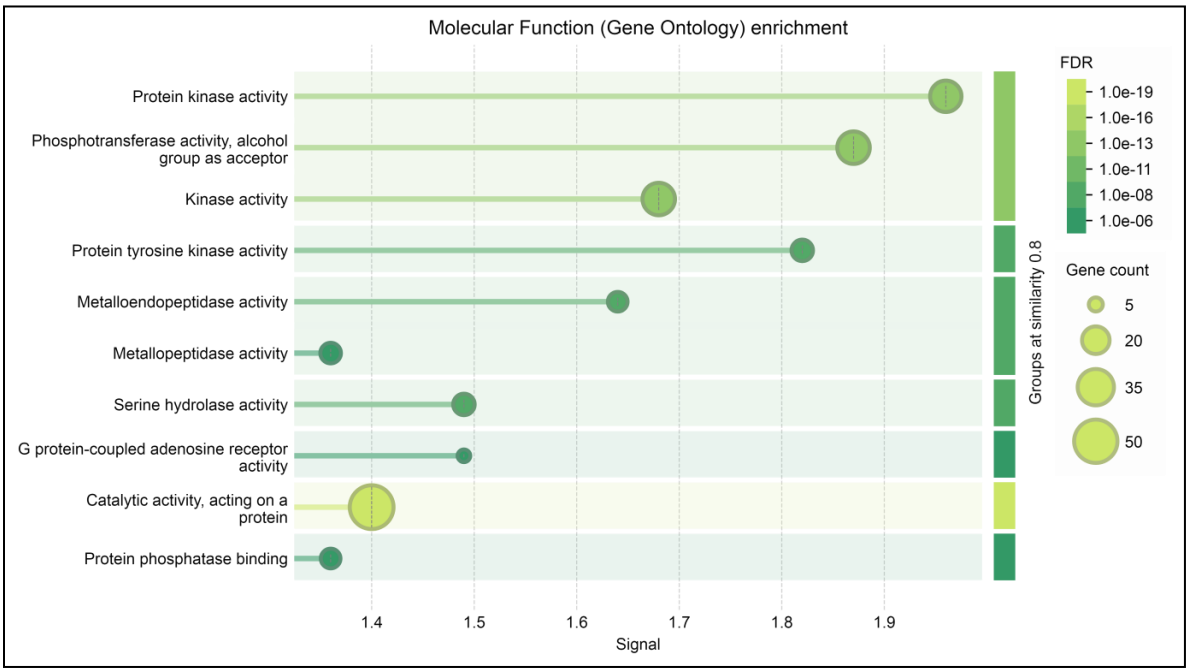



**Figure 4B. Molecular Function.**

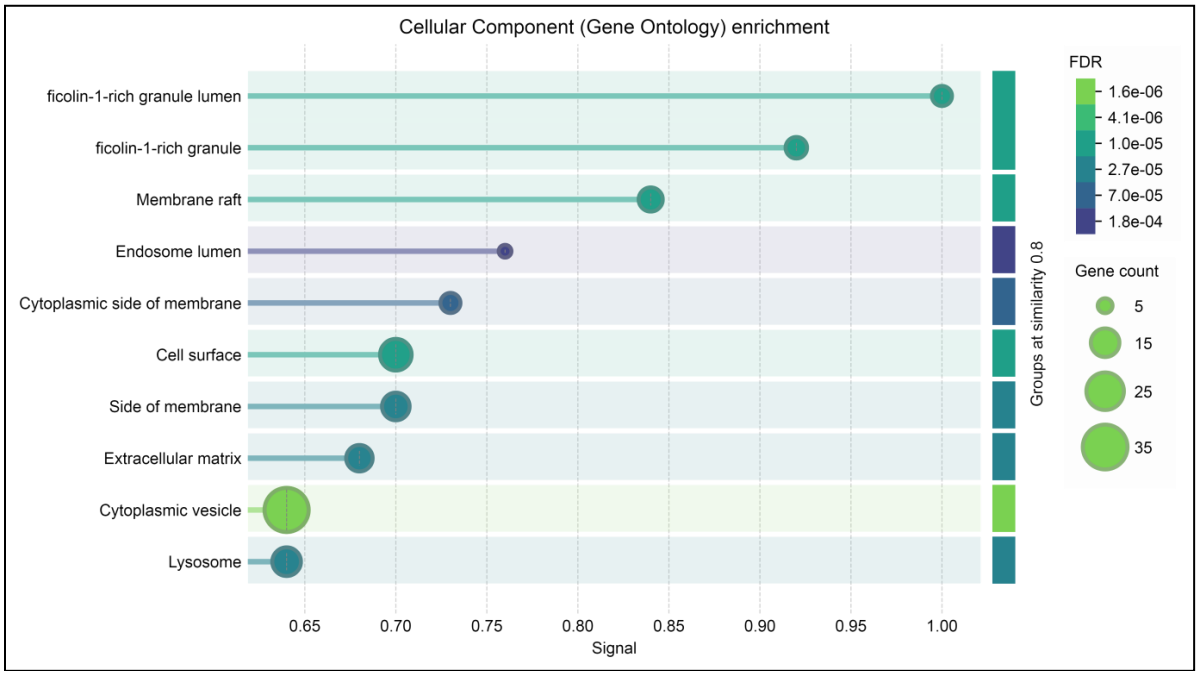



**Figure 4C. Cellular Components.**

**Table 1. Biological Process.**

| Description | Observed gene count | False discovery rate |
|---|---|---|
| Response to oxygen-containing compound | 53 | 8.79E-28 |
| Response to organic substance | 64 | 2.97E-27 |
| Response to chemical | 74 | 3.87E-27 |
| Regulation of biological quality | 68 | 9.24E-24 |
| Cellular response to oxygen-containing compound | 42 | 2.09E-23 |
| Regulation of multicellular organismal process | 60 | 3.48E-23 |

**Table 2. Molecular Function.**

| Description | Observed gene count | False discovery rate |
|---|---|---|
| Catalytic activity | 77 | 9.13E-21 |
| Catalytic activity, acting on a protein | 51 | 9.32E-19 |
| Phosphotransferase activity, alcohol group as acceptor | 28 | 1.55E-14 |
| Protein kinase activity | 26 | 2.25E-14 |
| Ion binding | 71 | 6.08E-14 |
| Kinase activity | 28 | 1.94E-13 |

**Table 3. Cellular Components.**

| Description | Observed gene count | False discovery rate |
|---|---|---|
| Endomembrane system | 52 | 1.99E-06 |
| Vesicle | 45 | 1.28E-05 |
| Cytoplasmic vesicle | 34 | 1.62E-05 |
| Cell periphery | 57 | 1.62E-05 |
| Cytoplasm | 85 | 2.42E-05 |
| Intracellular membrane-bounded organelle | 85 | 3.37E-05 |

**Table 4. KEGG Pathway.**

| Description | Observed gene count | False discovery rate |
|---|---|---|
| **Pathways in cancer** | 30 | 8.38E-21 |
| **PI3K-Akt signaling pathway** | 19 | 3.82E-12 |
| **Endocrine resistance** | 12 | 2.06E-11 |
| **Apoptosis** | 12 | 5.37E-10 |
| **Human cytomegalovirus infection** | 14 | 5.37E-10 |
| **Prostate cancer** | 11 | 5.37E-10 |

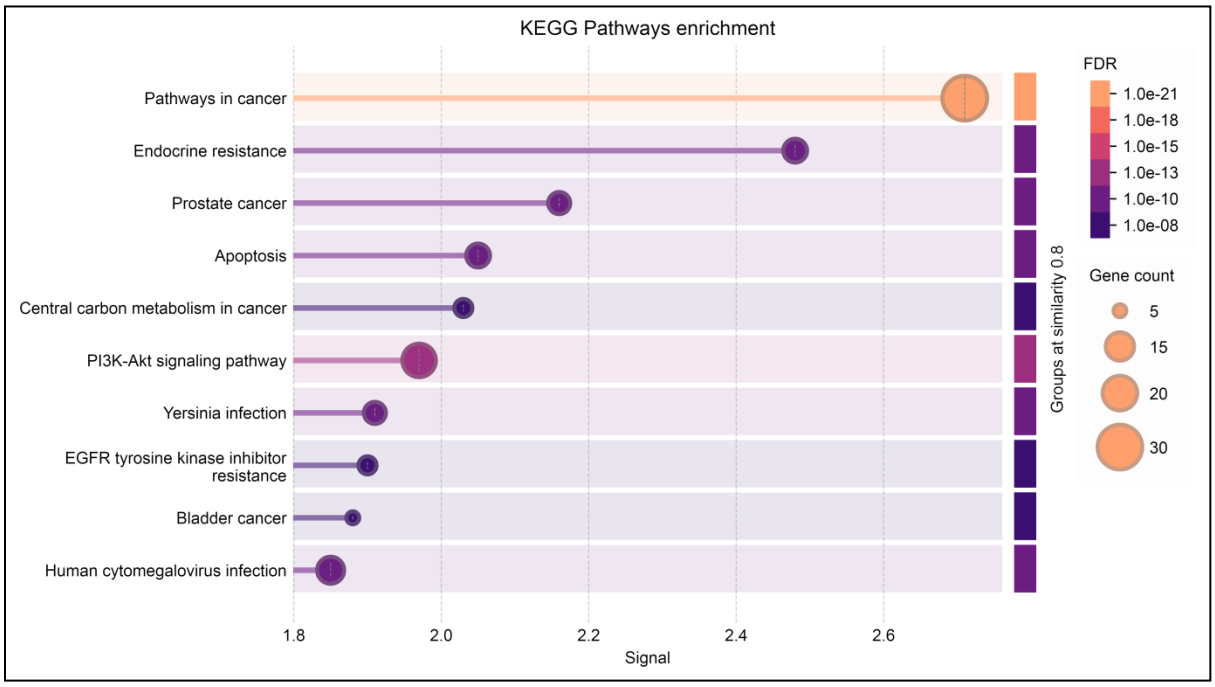



**Figure 5. KEGG Pathway.**

## Molecular docking

Molecular docking (MD) studies of Embelin, Piperine with key breast cancer-associated targets, including HSP90AA1 (node degree = 12) and JAK2 (node degree = 7), were performed using AutoDock Vina to evaluate binding affinities and interaction profiles. The docking analysis assessed parameters include binding affinity (kcal/mol), interacting amino acid residues. The obtained docking results demonstrated favorable ligand-protein interactions and are summarized in Table 5 and illustrated in Figure 6.

The molecular docking study was performed to evaluate the binding affinity of Embelin and Piperine against rheumatoid arthritis-associated target proteins HSP90AA1 (PDB ID: 3K99) and JAK2 (PDB ID: 6E2Q), using Tofacitinib as the reference standard. Binding affinity was assessed based on docking scores expressed in kcal/mol, where lower binding energy indicates stronger ligand-protein interaction and higher complex stability. Among the investigated compounds, Tofacitinib demonstrated the highest binding affinity toward HSP90AA1 with a docking score of -7.7 kcal/mol, confirming its strong interaction with the target protein. Piperine also exhibited significant binding affinity against HSP90AA1 with a docking score of -7.2 kcal/mol, suggesting stable interaction and potential inhibitory activity comparable to the standard compound. In contrast, Embelin showed comparatively moderate interaction with HSP90AA1, exhibiting a docking score of -6.1 kcal/mol. Similarly, docking analysis against JAK2 (PDB ID: 6E2Q) revealed that both Tofacitinib and Piperine displayed strong binding affinity with docking scores of -7.5 kcal/mol, indicating favorable molecular interactions within the active binding pocket of the target protein. Embelin showed lower binding affinity toward JAK2 with a docking score of -5.8 kcal/mol. The observed interactions suggest that Piperine may possess significant inhibitory potential against JAK2-mediated inflammatory signaling pathways involved in rheumatoid arthritis pathogenesis.

The strong binding interactions of Piperine with both HSP90AA1 and JAK2 may be attributed to its hydrophobic interactions, hydrogen bonding, and favorable molecular orientation within the active site residues of the proteins. Since HSP90AA1 and JAK2 are critically involved in inflammatory cytokine signaling, immune regulation, synovial inflammation, and progression of rheumatoid arthritis, inhibition of these targets may contribute to anti-inflammatory and disease-modifying effects. The docking results suggest that Piperine demonstrated promising binding affinity comparable to the standard drug Tofacitinib,

indicating its potential therapeutic relevance against rheumatoid arthritis-associated molecular targets. Embelin also exhibited moderate interaction profiles, supporting its possible contribution as a multitarget phytochemical candidate for rheumatoid arthritis management.

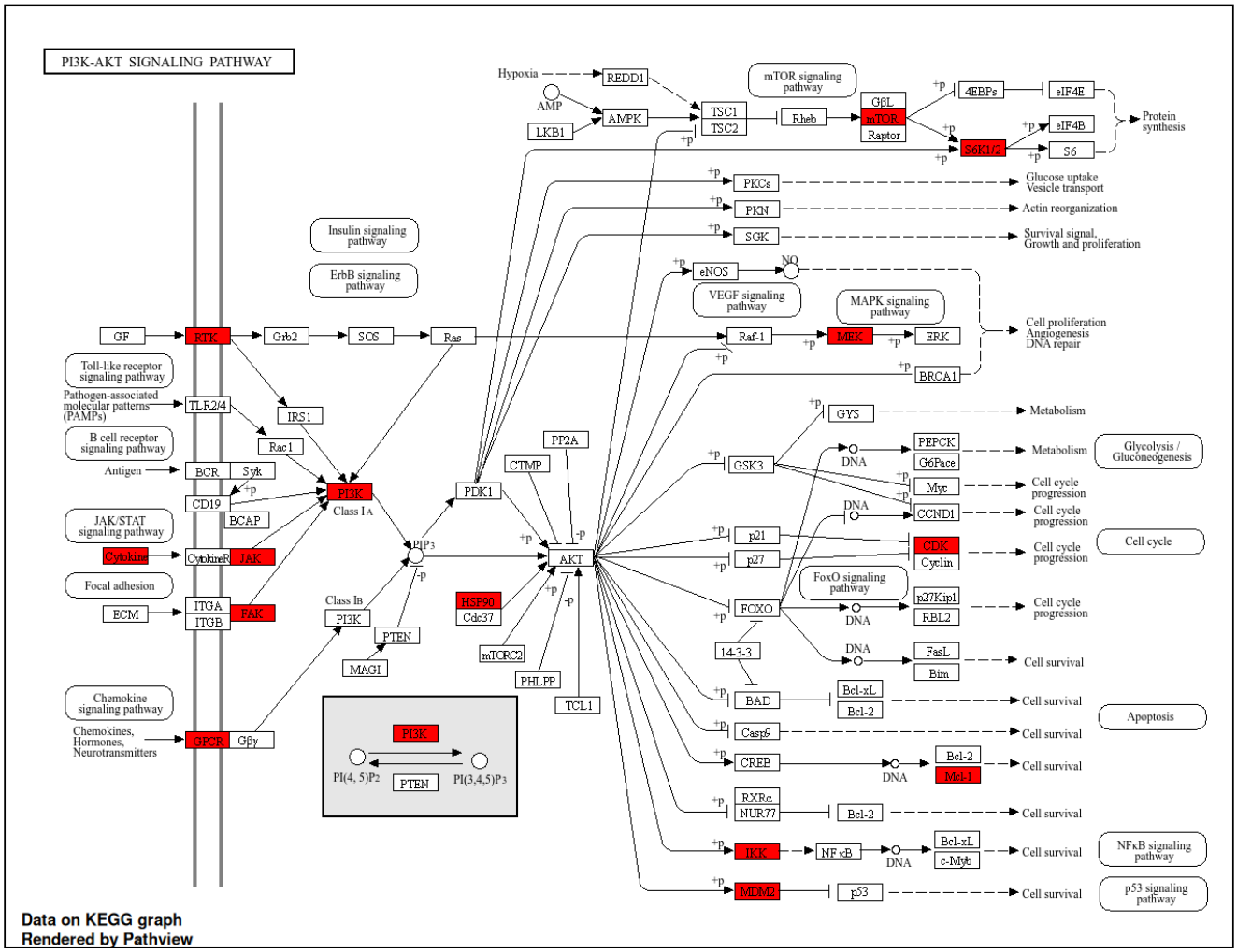



**Figure 5A. PI3K-AKT Pathway.**

**Table 5. Molecular Docking Analysis.**

| Sr. No. | Compound | Target Protein | PDB ID | Binding Energy (kcal/mol) | Interpretation |
|---|---|---|---|---|---|
| **1** | Tofacitinib | HSP90AA1 | 3K99 | -7.7 | Exhibited strong binding affinity toward HSP90AA1 protein. |
| **2** | Embelin | HSP90AA1 | 3K99 | -6.1 | Showed moderate binding interaction with HSP90AA1. |
| **3** | Piperine | HSP90AA1 | 3K99 | -7.2 | Demonstrated good binding affinity against HSP90AA1 target protein. |
| **4** | Tofacitinib | JAK2 | 6E2Q | -7.5 | Displayed strong interaction and stable binding with JAK2 protein. |
| **5** | Embelin | JAK2 | 6E2Q | -5.8 | Revealed comparatively lower binding affinity toward JAK2. |
| **6** | Piperine | JAK2 | 6E2Q | -7.5 | Showed strong binding affinity comparable to standard ligand against JAK2. |

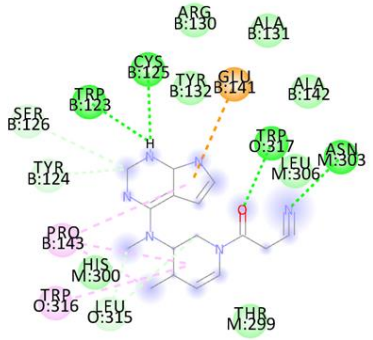
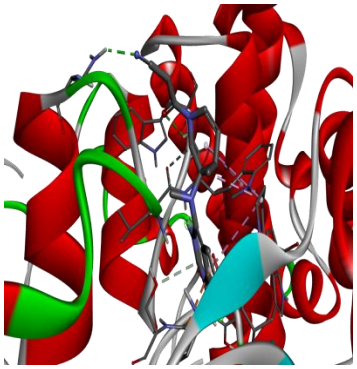
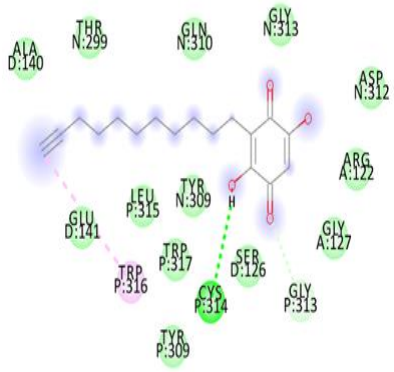
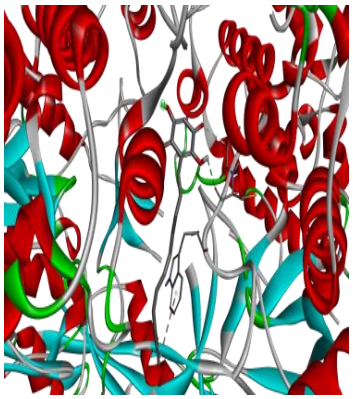
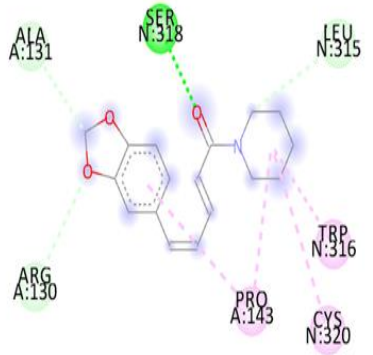
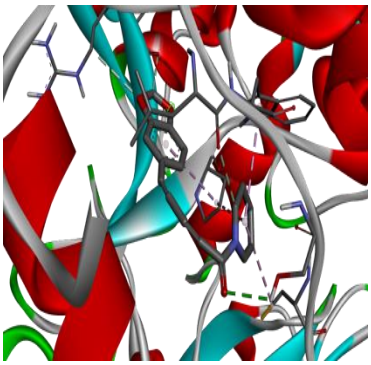
| Compound/Targets | 2D | 3D |
|---|---|---|
| Tofacitinib-(6E2Q) |  |  |
| Embelin-(6E2Q) |  |  |
| Piperine-(6E2Q) |  |  |

**Figure 6. Illustrates 2D and 3D docking poses of Tofacitinib, Embelin and Piperine with protein JAK2 (6E2Q).**

## 4. Conclusion

The research used integrated network pharmacology and molecular docking analysis to show that Embelin and Piperine had therapeutic promise against rheumatoid arthritis. The discovery of hub genes and enhanced signaling pathways emphasized their function in regulating inflammatory and immunological responses associated with rheumatoid arthritis. Molecular docking experiments confirmed the phytochemicals' significant binding affinities with critical therapeutic targets, specifically HSP90AA1 and JAK2. Overall, the data indicate that Embelin and Piperine may be viable multitarget phytoconstituents for rheumatoid arthritis therapy, providing a scientific foundation for further experimental and clinical validation.

### Author Contribution

Sulaiman Ahmad performed the literature survey, target identification, and manuscript preparation. Shaikh Mahmad Kaif conducted molecular docking studies and pathway

analysis. Dr. Shaikh Mehmood Dawood supervised the research work, reviewed the manuscript, and approved the final version for publication.

## Funding Statement

The authors declare that no financial support or funding was received for this study.

## Conflict of Interest

The authors declare that there are no conflicts of interest regarding the publication of this manuscript.

## Ethics Approval and Consent to Participate

This study was entirely based on computational and *in silico* methodologies including network pharmacology and molecular docking approaches. Therefore, ethical approval and informed consent were not required as no human participants or experimental animals were involved in the study.

## Consent for Publication

All authors have read and approved the final version of the manuscript for publication.

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## Declaration of Generative AI

During the preparation of this manuscript, generative artificial intelligence (AI)-assisted tools were utilized only for language refinement, grammatical correction, and improvement of scientific readability.

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