International Journal of Pharmacy and Pharmaceutical Research (IJPPR)
Volume 32, Issue 2, February 2026 ijppr.humanjournals.com ISSN: 2349-7203

In Silico Drug-Likeness, Network Pharmacology, and Docking Evaluation of Natural Compounds for Rheumatoid Arthritis

Gokula Krishnan.K[1], Kamalnath. A[2], Mukesh T[3], Renu. N[4], Keerthivasan. U[4] Sojarna.K*

*Assistant professor, Department of Pharmaceutical Chemistry, PSV College of Pharmaceutical Science and Research, Krishnagiri, Tamil Nadu 635 108 India.
[1,2,3,4] B. Pharm Final year students, PSV College of Pharmaceutical Science and Research, Krishnagiri, Tamil Nadu 635 108 India.

Received: 30 December 2025 Revised: 15 January 2026 Accepted: 30 January 2026

ABSTRACT

Rheumatoid arthritis (RA) is a systemic autoimmune disease in which chronic active synovitis leads to cartilage degradation and bone destruction resulting from aberrant immune responses. The current work was intended to investigate the druggability of certain phytoconstituents through the combined approach of network pharmacology, pharmacokinetic prediction, and molecular docking. Six active constituents, curcumin, luteolin, quercetin, capsaicin, berberine, and ginsenosides, were analysed for their drug-likeness and ADMET characteristics and the molecular interaction with RA-related targets. The pharmacokinetic impact analysis showed a desirable profile of absorption, distribution, metabolism and safety for the majority of the compounds with good Lipinski's rule compliance and low potential toxicity. A network pharmacology analysis revealed 130 common targets of phytochemical-associated proteins and RA-related genes. Protein–protein interaction network analysis also identified hub genes, including (but not limited to) AKT1, STAT3, EGFR, MTOR, and PTGS2, which were predicted to be central regulators of inflammatory and proliferative signalling pathways. GO and KEGG pathway enrichment analyses revealed that the most significantly enriched pathways were the PI3K–Akt, JAK–STAT, MAPK, VEGF and HIF-1 signalling pathways, indicating that kinase-mediated phosphorylation and cytokine signalling are major events in RA development. Molecular docking calculations with AKT1 (PDB ID: 3MVH) as a crucial target revealed high binding affinities, particularly for quercetin and luteolin, indicating stable ligand protein interactions in the active site. In summary, the results indicate a multi-target mode of action of therapy and provide in silico evidence that the considered phytoconstituents, particularly quercetin and luteolin, might be interesting candidates for further in vitro/in vivo studies for the treatment of rheumatoid arthritis.

Keywords: Rheumatoid arthritis, Network pharmacology, Molecular docking, AKT1, Phytoconstituents

1. INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterised by persistent synovial inflammation, pannus formation, cartilage degradation, and progressive bone erosion. It affects approximately 0.5-1% of the global population and significantly impairs physical function and quality of life (1). Pro-inflammatory cytokines, such as tumour necrosis factor-alpha (TNF-alpha), interleukin-1 beta (IL-1beta) and interleukin-6 (IL-6), are secreted by immune cells, T cells, B cells, macrophages and synovial fibroblasts, and initiate chronic inflammation and destruction of the joints (2). These mediators trigger several intracellular signalling pathways, such as NF-KB, MAPK, JAK/STAT, and PI3K/AKT, that play a role in the proliferation, angiogenesis, and activation of osteoclasts (3). Even though conventional disease-modifying antirheumatic drugs (DMARDs) and biologic therapies have become important to enhance the clinical outcomes, their prolonged use is not only commonly linked to adverse consequences but also to high cost and incomplete remission in some patients (4). So, the identification of safer and multi-target therapeutic agents has become one of the main areas of research. Network pharmacology has become one of the potent systems-level methods of understanding drug-target-disease interactions in recent years. In contrast to the historical paradigm of one drug, one target, network pharmacology investigates the concept of multi-component and multi-target effects, which is especially appropriate in this case with complex diseases, including RA (5). This method allows finding hub genes and important signalling pathways that contribute to the development of disease by combining bioinformatics databases, protein-protein interaction (PPI) networks, and pathway enrichment analysis (6). Several studies have successfully applied network pharmacology to identify hub genes such as TNF, IL6, AKT1, MAPK1 and STAT3 as key regulators in RA progression (7). In addition to target identification, early evaluation of pharmacokinetic and safety properties is essential in drug discovery. ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) profiling is used to predict oral bioavailability, metabolic stability, blood-brain barrier permeability, and possible toxicity, which

would reduce late-phase drug failure (8). Computational ADMET screening enhances efficiency in that it focuses on compounds that have good drug-like properties and safety profiles (9). Following target and pharmacokinetic prediction, molecular docking offers structural validation of the ligand-protein interactions. The affinities of binding, hydrophobic contacts, hydrogen bonds, and electrostatic interactions between candidate compounds and the main RA-interacting targets are calculated by docking methods. This approach facilitates mechanistic comprehension based on network pharmacology research and allows for the atomic-level explanation of binding mechanisms (10). Docking further improves dependability by assessing conformational stability and persistence of interest with the environment (physiological settings) when used in conjunction with molecular dynamics simulations. Since the pathogenesis of rheumatoid arthritis is complicated, and there are certain limitations in the available therapeutic options, the combination of ADMET analysis, network pharmacology, and molecular docking seems to be a logical and effective approach to finding new treatment options. The integrated in-silico screening allows identifying the target, conducting a pharmacokinetic evaluation, and validating the structures, thus enabling the process of identifying multi-target agents to enable effective management of rheumatoid arthritis.

2. Materials and methods

2.1 Phytoconstituent data retrieval

Based on an extensive literature review and analysis of available databases, phytoconstituents exhibiting significant immunosuppressive, anti-inflammatory, and analgesic activities were systematically identified. Among them, the most promising and widely reported bioactive compounds were Berberine, Curcumin, Capsaicin, Ginsenosides, Luteolin, and Quercetin. These phytoconstituents were selected as top candidates for further investigation based on their pharmacological relevance and reported therapeutic potential. The essential molecular information, including SMILES strings as well as two-dimensional and three-dimensional structural data, was retrieved from the PubChem database (11) to support subsequent computational and in silico analyses.

2.2 Pharmacokinetic and toxicity screening:

The toxicity and ADME profiles of the phytoconstituents were evaluated using in silico online platforms as a predictive pharmacokinetic characteristic of suitability and safety. Absorption, Distribution, Metabolism and Excretion parameters (Gastrointestinal absorption, lipophilicity, aqueous solubility and blood-brain barrier permeability) were analysed using SwissADME (12).The predictions of toxicological endpoints were assessed using the pkCSM webserver (13), which provides important toxicological values, including hepatotoxicity, hERG channel inhibition, mutagenicity, and acute toxicity. The combined compounds were found to have favourable absorption properties, encouraging physicochemical properties, and no severe toxicity risk, which justifies their potential for future experimental validation.

2.3 Network pharmacology

Phytochemicals target prediction

The target proteins or genes of the retrieved phytoconstituents were identified using the online web server Swiss target prediction (14). The canonical smile strings obtained from the PubChem web portal were used for obtaining the targets. The web tool is used to match the chemical structure of the retrieved bioactive compounds and assists in predicting which human protein binds with the phytocompounds.

Disease target identification

GeneCards web database (15), was used to identify the protein targets associated with Rheumatoid arthritis, which is an integrative database platform that gathers human phenotype data from model organism studies, scientific literature and manually curated gene-disease connections. The targets were obtained via a web portal by using the keyword “Rheumatoid arthritis”. All collected targets underwent deduplication in order to eliminate duplication and guarantee the accuracy and applicability of the final target collection. After that, downstream analysis was conducted using the revised list.

Overlapping targets

The phytoconstituent-specific target obtained from SwissTargetPrediction and the epilepsy-specific targets obtained from Genecards were compared. In order to perhaps outline proteins important to the pathophysiology of Rheumatoid arthritis, overlapping proteins that were concurrently represented in both datasets were analysed and identified using Venny 2.0 (16). These intersecting proteins were chosen for further in-depth research because they were thought to be core targets.

Protein- protein interaction

The protein-protein interaction analysis was used to determine the functional relationship between the identified target proteins and to explain the overall role of the proteins in the development of disease. The targets were added to the STRING online database (Version 11.5), and the organism was limited to Homo sapiens, and high-confidence interaction scores (≥0.7) were applied to assess reliability (17). Interactions between the database and experimentation, as well as curated ones, were added. The resultant data of interaction were also exported and read in TSV format, which was then exported to Cytoscape (version 3.10.1) to visualize the network and perform the topological analysis (18). The network analyser, named Cytohubba plugin, was used to retrieve the top 10 Hubgenes of the network based on the degree centrality with high regulatory effects (19). This method enabled the determination of the major Hub proteins that are involved in the pathogenic mechanism.

Gene ontology enrichment analysis

Gene ontology (GO) enrichment analysis was carried out to functionally characterise the set of proteins obtained from the PPI network. The set of proteins that are retrieved as hubgenes was listed to the ShinyGO 0.85.1 online web tool to enlist the ontological functions (20). The GO terms have been mapped to the three primary ontological domains such as Cellular components (CC), Molecular functions (MF) and biological process(BP). Only GO keywords with substantial enrichment (adjusted $p < 0.05$) were kept for interpretation. The Gene Ontology Consortium database was used to validate the hierarchical classifications and definitions of GO concepts. To find the main biological pathways and functional themes connected to the target protein set, the final enriched phrases were analysed.

KEGG pathway

KEGG (Kyoto Encyclopedia of Genes and Genomes) pathway enrichment analysis was applied to determine the biological pathways relevant to the proteins that were extracted in the protein-protein interaction (PPI) network (21). The obtained protein list was entered in the web tool ShinyGO 0.85.1, where relevant pathways were obtained and then overlain into KEGG pathway databases to identify statistically significant pathways. The false discovery rate (FDR) method was applied to adjust the P-Values based on various comparisons. The assignments and annotations of functional pathways were cross-validated with the KEGG database to ensure the correct pathway. This analysis has helped to identify major metabolic and signalling pathways that can be functionally applicable to the set of target proteins. Possible pathways of Rheumatoid arthritis found in the literature survey were considered for further investigation.

2.4 Molecular docking simulation

The two-dimensional and three-dimensional chemical structures of the phytochemical ligands were obtained from PubChem in SDF format. These structures were subjected to three-dimensional conformations, and energy minimisation was performed using the MMFF94 force field to yield stable conformations. Using Autodock tools (22), the water molecules and counterions were removed. The essential hydrogen atoms and Gasteiger charges were assigned. The optimised ligand structures were exported to dockable PDBQT format. The crystal structure of the target protein was downloaded from the RCSB protein data bank (23). A protein that has a resolution range between 1.5 Å and 2.5Å was chosen. The protein was evaluated using the wwPDB validation report, Ramachandran plot analysis and mutations. Ramachandran plot analysis (23) was performed using the Procheck server (24), evaluated for Phi and psi dihedral angle conformations. Proteins with greater than 75% of allowed regions and lower outliers were considered. The UCSF chimaera tool was used for the preprocessing of protein, including the removal of non-essential parameters (25). The castp 3.0 server was used to determine the volume of cavity, surface and pocket lining residues (26). Then the optimised protein structure was saved in PDBQT format. Docking simulations were carried out using Autodock tools (27) in which a grid box was specified around the protein with suitable centre coordinates. The genetic algorithm of Lamarckian was implemented using the default settings, and the program was run several times to give the stable binding conformations (28). Docked results were analysed based on the binding energies and the binding interactions between the ligand and the protein. The complex with low binding energy was considered to be the best-bound complex. Visualisation of the docked complexes was performed using BIOVIA Discovery Studio Visualizer (29), in which the hydrogen bonds, hydrophobic interactions, and electrostatic contacts were analysed. Two-dimensional and three-dimensional interaction maps were constructed to map amino acid residues that engaged the binding of the ligand, and a comparison of the interaction patterns was made between the studied compounds.

3 RESULT AND DISCUSSION

3.1 Physicochemical and Pharmacokinetic Analysis

The physicochemical characteristics of the desired phytochemicals indicate rather positive drug-like properties, and the detected differences affect oral bioavailability (Table 1). Curcumin, capsaicin, berberine and luteolin weigh less than 500 mg, which makes

them suitable to be administered orally. In quercetin and luteolin, the high topological polar surface area (TPSA) values (> 110) are associated with high polarity, which could decrease the membrane permeability, although there are no violations of the Lipinski rule. On the other hand, berberine and capsaicin have fewer TPSA (40.60 2 A), which is expected to be more permeable, but berberine is not a hydrogen bond donor. It was found that the ginsenosides had high molecular weights, a single Lipinski violation and high synthetic complexity, which was indicative of developmental issues. Finally, curcumin and capsaicin have the best-balanced physicochemical profiles, and more research could be necessary on compounds with large TPSA or synthetic complexity. The table indicates the physicochemical data.

Table 1: Physicochemical properties of six phytoconstituents

Compound	Formula	Molecular weight	Rotatable bonds	H-bond acceptors	H-bond donors	TPSA (A^{o2})	Lipinski violations
Curcumin	C21H20O6	368.38	8	6	2	93.06	0
Luteolin	C15H10O7	302.24	1	7	5	131.36	0
Quercetin	C30H52O2	444.73	4	2	2	40.46	1
Capsaicin	C20H18NO4 +	336.36	2	4	0	40.8	0
Berberine	C18H27NO3	305.41	10	3	2	58.56	0
Ginsenosides	C15H10O6	286.24	1	6	4	111.13	0

From the pharmacokinetic analysis, the absorption profile shows that the majority of the chosen phytochemicals display good oral bioavailability, and the gastrointestinal absorption as well as intestinal uptake vary between 77.97% and 97.97%. Curcumin, quercetin, berberine and capsaicin exhibit good gastrointestinal absorption. A positive response to $CaCO_2$ permeability of berberine, capsaicin and ginsenosides indicates a high possibility of transcellularization and berberine, capsaicin and ginsenosides have a high permeability and low permeability, respectively. More advantageous absorption phytochemicals with moderate lipophilicity and an increased membrane permeability such as Capsaicin and berberine, thus more likely to be found. In terms of metabolic interactions, the cytochrome P450 enzyme inhibiton of the compound differs, which suggests that the risk of drug-drug interactions are different. Curcumin has moderate effect on inhibiting CYP2C9 and CYP3A4, whereas quercetin, berberine, capsaicin, and luteolin inhibit CYP1A2, CYP2D6, and CYP3A4, so they are likely to have a greater impact on hepatic metabolism. Ginsenosides in contrast have no substantial effect on the CYP enzymes of interest indicating a relatively safer metabolic profile. Output and poisonousness parameters also support acceptable safety traits because total clearance values are ranging between -0.002 and 1.298. Berberis (1.298) and capsaicin (1.27) have a greater clearance meaning they are systemically eliminated faster whereas curcumin (-0.002) has a lower clearance meaning that it is retained longer. Luteolin (0.407), quercetin (0.372) and ginsenosides (0.495) exhibit moderate values of clearance indicating a balance distribution of elimination in general.

Table 2: Absorption, Distribution, Metabolism and Excretion parameters

Molecule	Absorption		Distribution		Metabolism		Excretion	
	LogS	LogP	BBB	CNS	CYP450	CYP3A4	RC	TC
Curcumin	-3.94	3.27	-0.51	-3.044	No	Yes	No	-0.002
Luteolin	-3.16	1.63	-0.288	-3.317	Yes	Yes	No	0.407
Quercetin	-7.71	5.01	-1.339	-3.317	No	No	No	0.372
Capsaicin	-4.55	0	0.633	-1.675	Yes	Yes	No	1.27
Berberine	-3.53	3.15	-0.349	-2.416	Yes	Yes	No	1.298
Ginsenosides	-3.71	1.86	-1.145	-2.405	Yes	Yes	No	0.495

LogS -Water solubility, **LogP-** Lipid solubility, **BBB-** Blood Brain Barrier permeability, **CNS-** CNS permeability, **CYP450-** Cytochrome P450 inhibitor, **CYP3A4**- CYP3A4 inhibitor, **RC**- Renal Clearance, **TC**-Total clearance

International Journal of Pharmacy and Pharmaceutical Research (IJPPR)
Volume 32, Issue 2, February 2026 ijppr.humanjournals.com ISSN: 2349-7203

2.2 NETWORK PHARMACOLOGY ANALYSIS

Compound target prediction analysis.

Swiss Target Prediction analysis has found hundreds of possible protein targets involved in each of the nine phytoconstituents. A large proportion of these targets belonged to a common functional class, including oxidoreductase, cytochrome P450 enzymes, carbonic anhydrases and membrane transporters. The interactions of phytochemicals curcumin, Quercetin, Ginsenoside, Berberine, Capsaicin and Luteolin with metabolic and detoxification enzymes were of a high probability type. These findings indicate that the phytoconstituents could have multitarget effects and operate through an integrated mechanism.

Disease target protein

The analysis of disease-target interaction showed that 1585 proteins had a role in rheumatoid arthritis association. Based on that, gene proteins with GIFts scores of 60 and above are shortlisted and utilised to find common overlapping genes. Critical signalling proteins. Analysis of compound-target prediction of curcumin, quercetin, ginsenoside, berberine, capsaicin and luteolin demonstrates that the compounds may be utilised in curing inflammatory and autoimmune diseases through interaction with different molecular targets. It is supposed that curcumin will keep TNF- 2, NF- - 2, COX- 2, JAK2 and STAT3 levels down to reduce the production of pro-inflammatory cytokines. It was predicted that quercetin inhibits inflammatory signalling, based on predicted interactions with PI3K/Akt, MAPK, TNF-2, and IL- 6. It is postulated that ginsenosides would mediate TLR4-mediated NF-kappaB and mediated MAPK, which would mediate immunomodulation. The principal effect of berberine is the stimulation of AMPK, NF-kB, TNF-alpha, and IL-1B, which implies that it suppresses inflammatory responses. The Capsaicin interactions are mainly with the TRPV1, NF-KB and COX-2, which support the analgesic and anti-inflammatory effects of Capsaicin. It is estimated that luteolin would inhibit JAK/STAT, NF- 0 and PI3K signalling pathways. Overall, these phytochemicals share their targets, such as TNF- 2, NF-KB, IL-6, and COX- 2, which highlight why they may be applicable in the treatment of rheumatoid arthritis.

Overlapping targets

The Venn diagram (Figure1) shows how targets are distributed and overlap in both List 1 and List 2, and 960 targets are found. In List 1, there are 151 unique targets (15.7 %) and in List 2, there are significantly more unique targets, 679 (70.7 %), so List 2 has most of the unique targets. The intersection area is made up of 130 common targets (13.5%), or shared molecular targets by the two lists. This overlap indicates that there is a significant overlap and may even be common biological pathways or mechanisms between the two datasets. Nonetheless, the proportion of unique portions in List 2 is more significant, suggesting that it has a broader coverage of its targets compared to List 1, which has a moderate level of shared targets with List 2. Altogether, the comparison shows similar and different target profiles, with List 2 having more target diversity, and the 130 similar targets showing that they could become the key candidates of interest in the future.

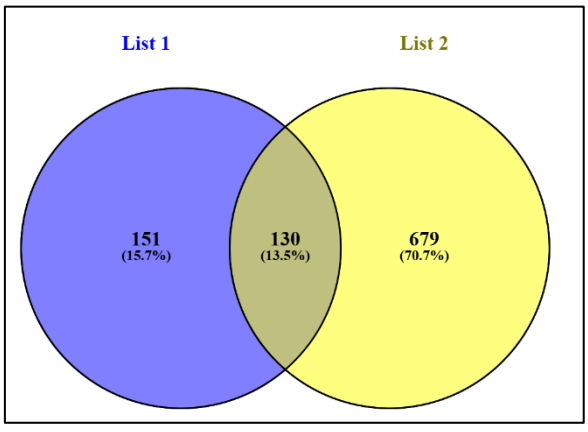


Figure 1: Overlapping targets (List1 – targets of six phytochemicals,

List 2- targets of Rheumatoid arthritis)

International Journal of Pharmacy and Pharmaceutical Research (IJPPR)
Volume 32, Issue 2, February 2026 ijppr.humanjournals.com ISSN: 2349-7203

Protein-protein interactions

The STRING-based protein–protein interaction network consisted of 130 nodes and 1759 edges, which is significantly higher than the expected number of 767 edges; a highly significant p-value on the enrichment of PPI interaction of less than 1.0 × 10 -6 indicates that the identified targets are biologically related and are not merely randomly linked. The average node degree of 27.1 implies that every protein has a wide range of partners, which supports a very dynamic system, whereas an average local clustering coefficient of 0.571 is a manifestation of strong modular organization and the existence of functional cluster of proteins that are closely interconnected. Analysis of degree-centrality had determined central hub proteins such as AKT1, EGFR, SRC, STAT3, ESR1, MTOR, HIF1A, GSK3B, MMP9, and PTGS2 that lie at the centre of the network and have a wide range of connections. These hubs play a central role in the regulation of key signalling cascades like the PI3K/AKT/mTOR, MAPK and JAK/STAT signalling pathways, as well as inflammatory and hypoxia-responsive signalling pathways. The PTGS 2 and MMP 9 are directly linked to the production of inflammatory mediators and the extracellular-matrix breakdown, and cell proliferation, survival, and angiogenesis are regulated by the AKT 1, MTOR and EGFR. STAT3 and HIF1A are also involved in cytokine signalling and adaptive response when under stress. The shortest path lengths between the highest-ranked nodes would suggest an efficient transmission of the signals and the cross-talk between the pathways are robust, which means that the immunological, inflammatory, and proliferative responses are coordinated. The central stylistic features of the dense core structure, the high connectivity and the high enrichment, in aggregate lead to a synergistic, multi target mechanism of action and therefore contribute to the idea of network pharmacology of therapeutic effects being the result of simultaneous activity in an interconnected series of molecular pathways as opposed to a single isolated target.

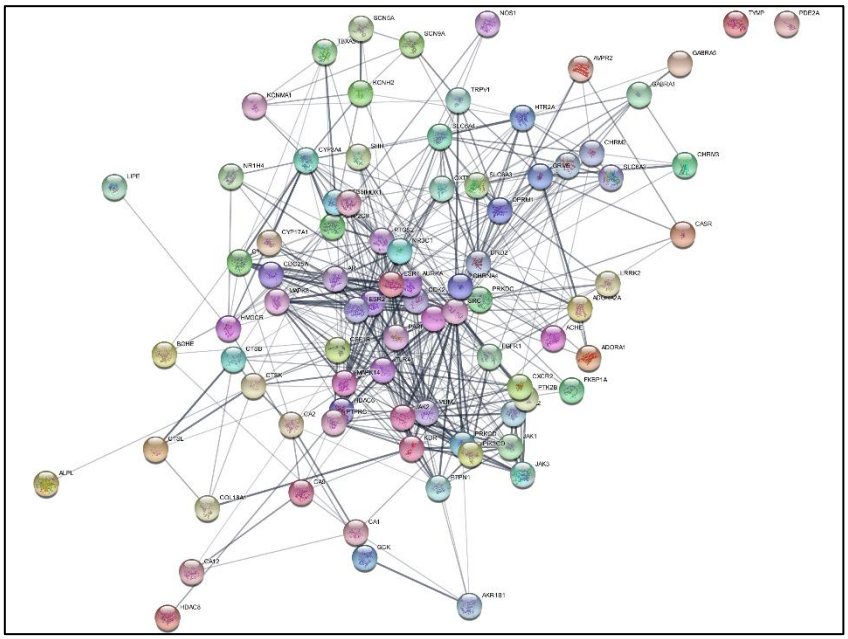


Figure 2: Protein-protein interaction of the overlapped target

Gene ontology analysis:

Biological process enrichment analysis:

Thus, the enrichment analysis depicts a series of protein phosphorylation events, particularly protein autophosphorylation and the PI3K/AKT signalling pathway. They also selected peptidyl-tyrosine phosphorylation, as well as cell migration, motivation, and proliferation. Altogether, this can be associated with active control of inflammation and growth-related processes. To summarise, PI3K-AKT and phosphorylation pathways, as well as receptor tyrosine kinases, can be considered important factors in the development of the disease.

International Journal of Pharmacy and Pharmaceutical Research (IJPPR)
Volume 32, Issue 2, February 2026 ijppr.humanjournals.com ISSN: 2349-7203

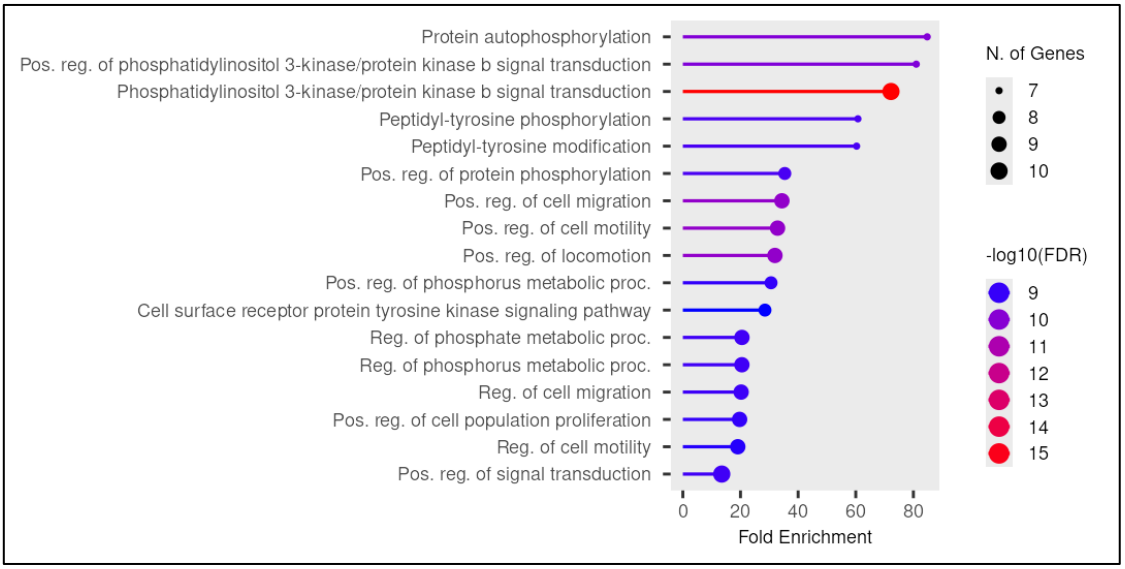


Figure 3: Plot of Gene Ontology Biological Process

Cellular component enrichment analysis

In a nutshell, the cellular component enrichment analysis reveals that the majority of our genes are primarily cell membrane-associated, such as the ruffle membrane, the leading-edge membrane, membrane rafts, and microdomains, and thus it appears that they are actively participating in cell movement and signal transduction. Enrichment of focal adhesions, cell-substrate junctions, and receptor complexes is also very abundant and indicates functions in cell adhesion and signal transduction. In addition to this, elements like the synapse, postsynapse, anchoring junctions, endosomes, and vesicles are augmented with implications in intracellular trafficking and communication. In brief, the target proteins appear to be largely dynamic membrane areas that are pertinent in signalling, adhesion, and general interaction between cells.

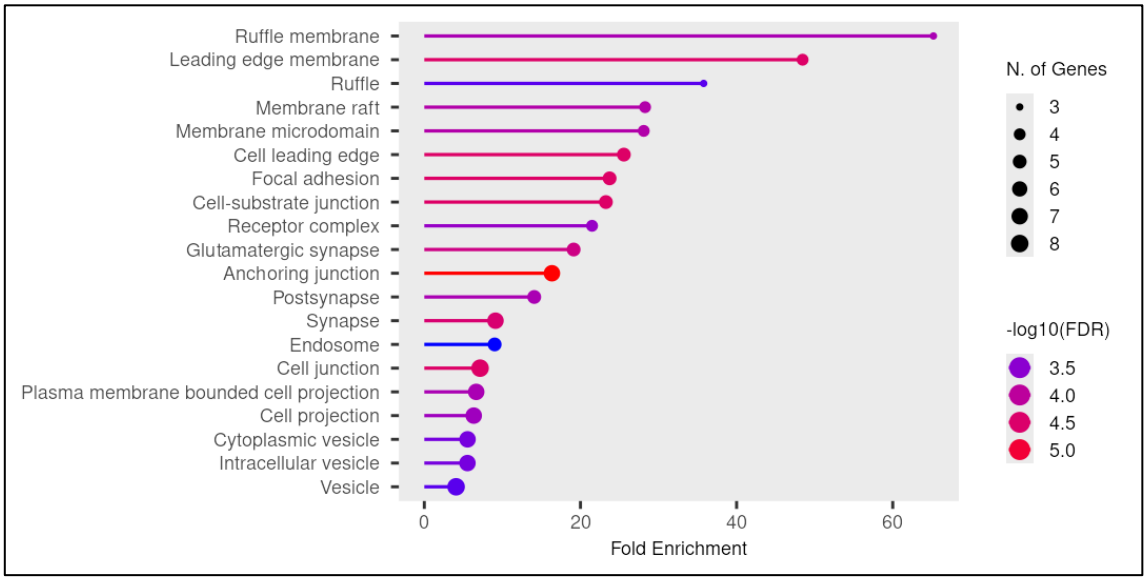


Figure 4: Plot of Gene Ontology Cellular components

Molecular function enrichment analysis:

The molecular function enrichment analysis shows a clear dominance of kinase-related activities. Protein tyrosine kinase activity shows maximum fold enrichment, which shows a crucial role of phosphorylation of tyrosine. Other terms highly enriched, such as protein kinase activity, phosphotransferase activity and protein kinase binding, contribute to the support of the presence of

phosphorylation-mediated signalling pathways. The activity of nucleotide binding and ATP binding functions, and the activity of enzymatic processes are enriched, proving the presence of active enzyme processes, as the enzyme, in this case, is a kinase that needs ATP to make an active complex. High values of the -log10(FDR) indicate a high level of statistical significance, with the number of genes contributing one term ranging between six and nine. Altogether, the results indicate that the dysregulated signal transduction via the introduction of kinase-dependent and nucleotide-dependent catalytic processes are the key aspects of the biological process itself.

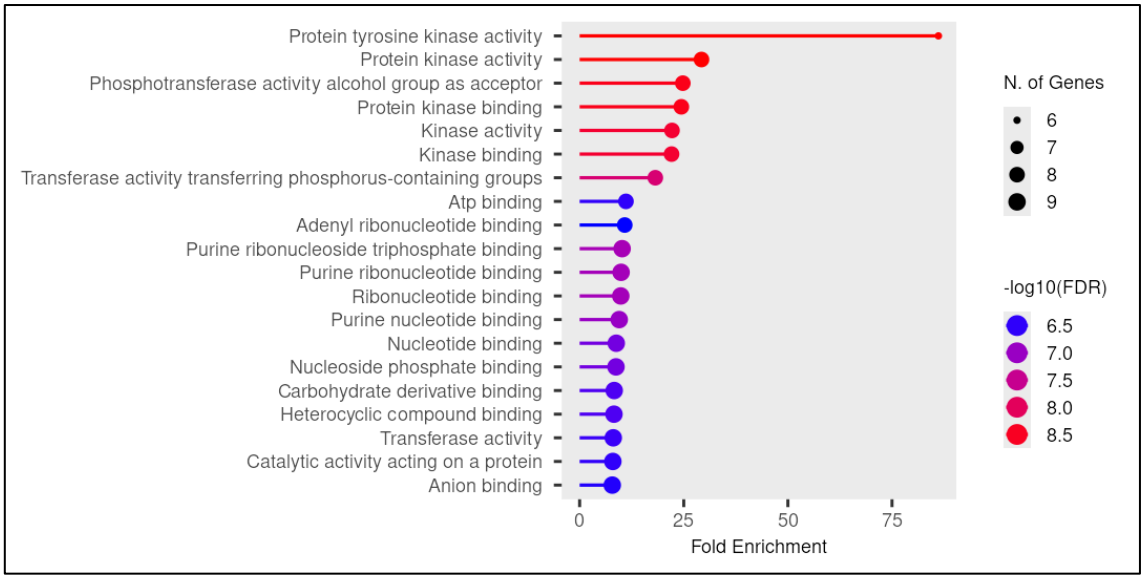


Figure 5: Plot of Gene Ontology Molecular functions

KEGG pathway analysis

The KEGG pathway analysis enrichment indicates that the obtained genes have an intensive involvement in a plethora of signalling pathways that regulate inflammation, immune homeostasis, cellular differentiation, and survival. EGFR tyrosine kinase inhibitor resistance is the highest hit, so it clearly indicates that the role of receptor tyrosine kinase signalling is significant. Next to it, the ErbB pathway appears, which controls the growth, differentiation, and inflammatory reactions by using PI3K–Akt and MAPK. VEGF signalling is not left behind, suggesting angiogenesis, particularly in long-term inflammatory diseases such as rheumatoid arthritis, in which the synovium becomes vascularized. Major immune and inflammatory pathways, including JAK-STAT, chemokine and HIF-1, are all enriched significantly. JAK-STAT plays a key role in mediating immunity by cytokines, and chemokines regulate the recruitment and migration of leukocytes to inflamed regions. HIF -1 shows that cells can adjust to low oxygen, which is typical of inflamed synovial tissue. Lastly, once again, PI3K -Akt underscores its key position in maintaining the survival, growth, and generation of inflammatory mediators of cells. Some cancer-related pathways as well, are visible, including general cancer, pancreatic cancer, proteoglycans in cancer, and the PD-1/PD-L1 checkpoint. This is demonstrated by the intersection where cancer and chronic inflammatory diseases have common mechanisms such as abnormal proliferation, angiogenesis and immune evasion. In general, the KEGG analysis informs us that the target proteins are mostly involved in the signalling of receptor tyrosine kinase, the immune pathways mediated by cytokines, angiogenesis, and cell survival mechanisms. This helps them to be relevant in the development of inflammatory disease and also indicates possible therapeutic targets.

International Journal of Pharmacy and Pharmaceutical Research (IJPPR)
Volume 32, Issue 2, February 2026 ijppr.humanjournals.com ISSN: 2349-7203

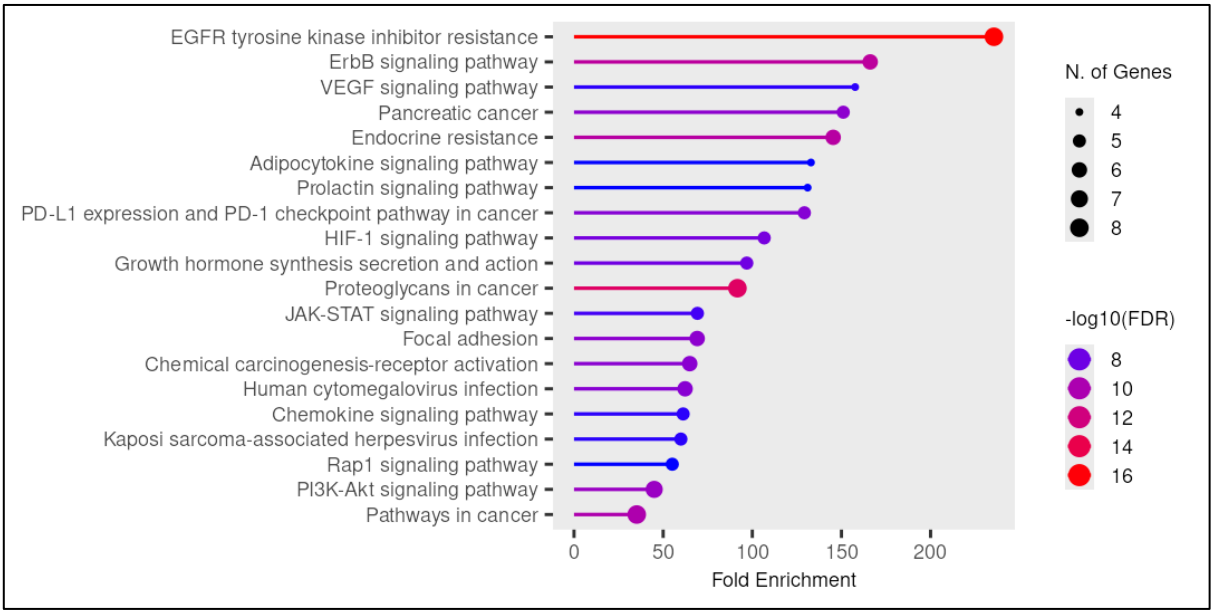


Figure 6: Plot of Gene Ontology KEGG pathways

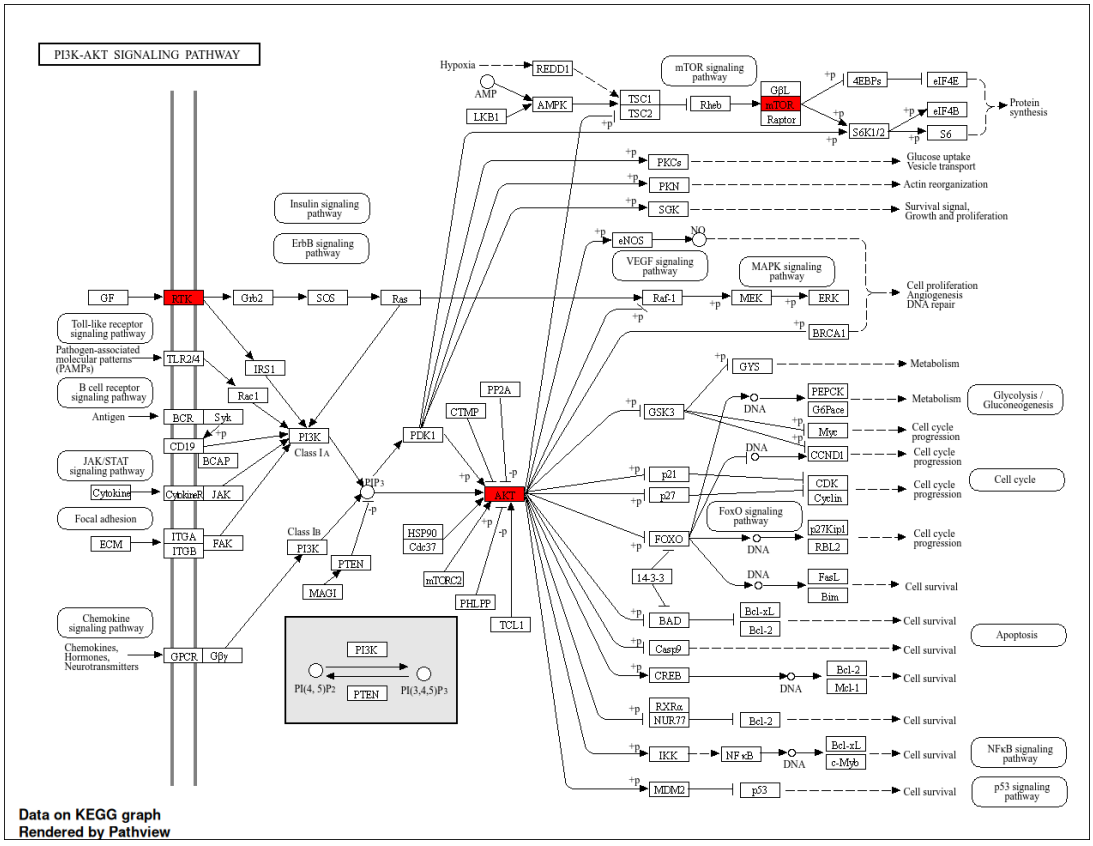


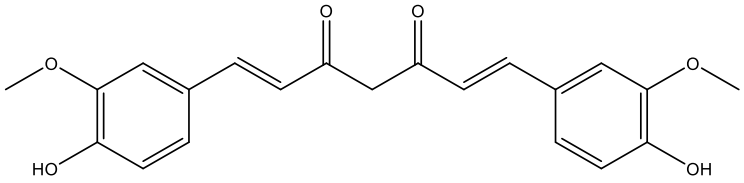
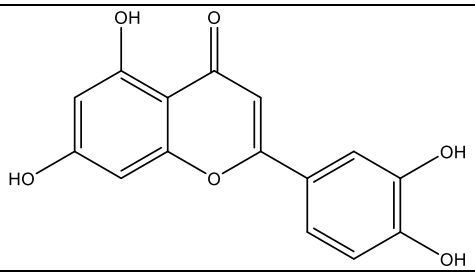
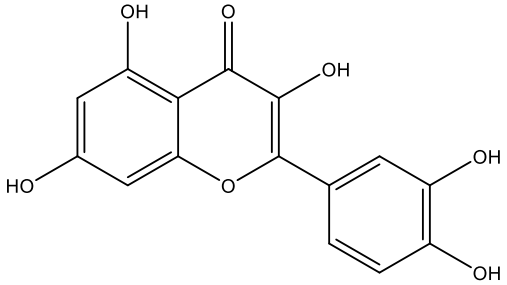
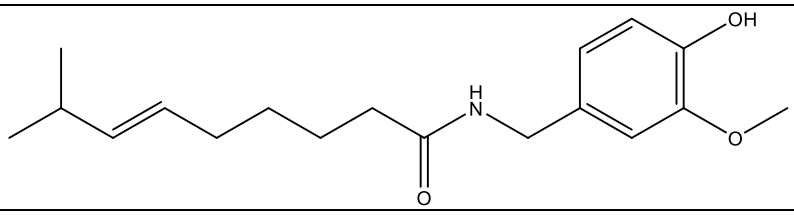
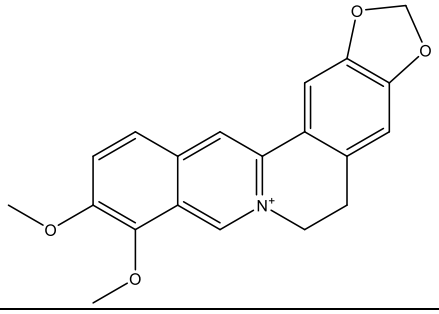
Figure 7: KEGG pathway of PI3K–Akt signalling pathway

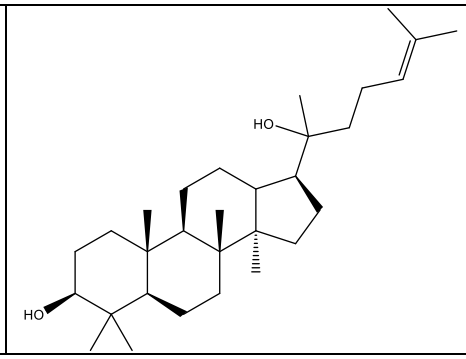
2.3 Molecular docking analysis

The two-dimensional structures of the chosen phytoconstituents were obtained in the PubChem database under SDF format, and were later translated into Three-dimensional structures using Chem3D. The minimisation of energy was done using the MMFF94 force field to form a stable conformation. The removal of water molecules and counter ions was done. AutoDock tools were used to

assign the charges of Gasteiger and the rotatable bonds were defined so that the ligand was flexible. The optimized ligands were then saved in PDBQT format to be used later in the docking analysis. The structure of the six phytoconstituents in two dimensions is below.

Table 3: Two-dimensional structures of 6 phytochemicals

Phytoconstituent name	Two-dimensional structure
Curcumin	
Luteolin	
Quercetin	
Capsaicin	
Berberine	

Ginsenosides	

Based on KEGG pathway enrichment and supporting literature, AKT1 is a key regulator in the process of rheumatoid arthritis, which controls the growth of synovial fibroblasts, the generation of pro-inflammatory cytokines, the survival of immune cells, angiogenesis, and osteoclast-mediated bone erosion via the PI3K/AKT signalling pathway, and can thus be considered an effective therapeutic target. Crystal structure of AKT1 (PDB ID: 3MVH) was obtained at the RCSB protein data bank and was identified using X-ray diffraction at a resolution of 2.01 A. The protein is made up of a single polypeptide chain that has 312 amino acid residues. Structural validation calculated using the Procheck server showed that 92.2 per cent of residues are located in the preferred regions, 5.3 per cent are found in the additionally allowed region, 1.4 per cent are found in the generously allowed region, and 1.1 per cent are found in the disallowed regions on the Ramachandran plot, which is a satisfactory level of stereochemical quality to use in docking study.

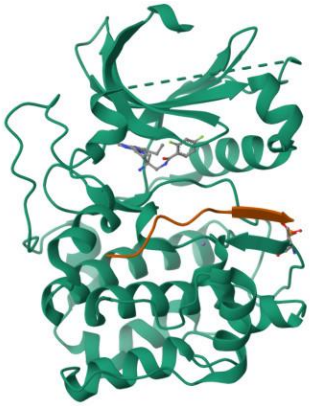


Figure 8: crystallographic structure of protein AKT1 (PDB: 3MVH)

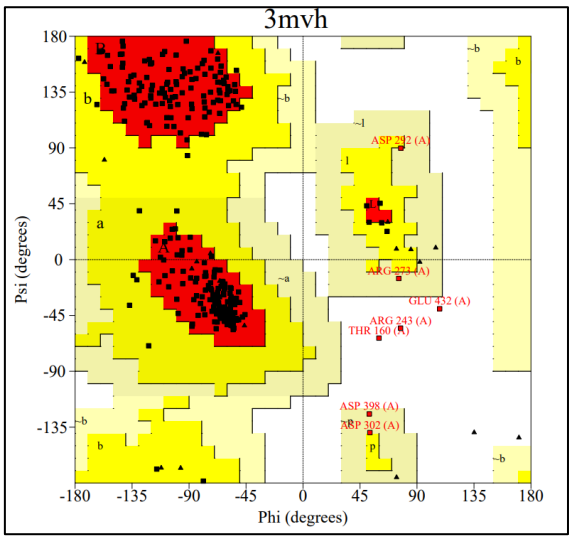


Figure 9: Ramachandran plot of protein AKT1 (PDB: 3MVH)

The molecular docking analysis shows that six phytocompounds have a good binding affinity towards the target protein AKT1 (PDB:3MHV) with binding energies between -8.55 and -10.7 kcal/mol, thus indicating a stable ligand-receptor complex in the active site. Quercetin was found to have the highest affinity (–10.7 kcal/ mol), with numerous interactions with residues GLU228, ALA230, LEU156, and ASP292, positive hydrogen binding and hydrophobic contacts with THR291 and MET281 and supported by electrostatic interactions. Luteolin (–10.4 kcal mol 1) formed a stable complex, mainly due to having a large number of non-polar contacts with residues VAL244, PHE245, LEU235, TYR253, LEU277, and LEU239; this indicates that the absence of hydrogen bonds is compensated by strong non-polar interactions. The same pattern of hydrophobic interaction was observed in ginsenosides, where the binding energy was -9.55 kcal/mol, showing this to be tightly bound in the binding cavity, although strongly stabilised by van der Waals forces. Berberine had a middle affinity (-9.1 kcal/mol), which was supported by hydrogen binding with THR211, as well as several hydrophobic and electrostatic interactions, giving the complex a moderate interaction pattern, which adds to the stability of the complex. Curcumin (binding energy of -8.55 kcal/mol) interacted with HIS194, GLU191, THR195, and GLY159 by forming several hydrogen bonds with these residues, hydrophobic, and electrostatic interactions, but its binding energy is relatively low in comparison with that of quercetin and luteolin. The binding energy of capsaicin with MET306 was found to be -8.7 kcal mol -1, and with HIS265 was found to be -, which explained its moderate affinity. Overall, the binding energies and interaction network analysis show that quercetin and luteolin are more promising in terms of their binding potential in comparison to the other compounds under consideration and, therefore, the level of their suitability as the most promising inhibitors of the target protein of interest.

Table 4: Docking score and interaction of six phytochemicals with the target protein AKT1 (PDB: 3MVH)

Compound	**Binding energy (Kcal/mol)**	**Interactions**		
		Conventional Hydrogen Bond	**Hydrophobic interactions**	**Electrostatic interactions**
Curcumin	-8.55	HIS194, GLU191, THR195, GLY159	PHE161, ALA177, MET227, LEU295, LEU181, VAL164, MET281	LYS179, ASP292
Luteolin	-10.4		VAL244, PHE245, LEU235, TYR253, LEU277, LEU275, LYS276, ALA250, LEU239	
Quercetin	-10.7	GLU228, ALA230, LEU156, ASP292	THR291, MET281	VAL164, ALA177, MET227
Capsaicin	-8.7		MET306	HIS265
Berberine	-9.1	THR211	ALA230, LYS289, TYR229, ALA177, VAL164, MET281, LEU156	THR291, GLY157, GLU234
Ginsenosides	-9.55		VAL244, PHE245, ALA250, LEU239, THR253, ILE257, LEU275, LYS276, LEU277	

4. Conclusion

In this work, an integrated in silico approach based on network pharmacology, ADMET properties, and molecular docking was adopted to explore the six phytoconstituents for their anti-rheumatoid arthritis activity. Through the network analyses, we showed that a majority of highly shared targets among disease and drug hub proteins, including AKT1, STAT3, EGFR, MTOR, and PTGS2 are involved, signifying that disease advancement of rheumatoid arthritis is modulated by intertwined inflammatory and kinase-regulated signalling cascades. Gene ontology (GO) and KEGG enrichment analyses consistently showed enrichment in PI3K–Akt, JAK–STAT, MAPK, VEGF, and HIF-1 pathways, highlighting the role of phosphorylation-dependent signal transduction and cytokine-mediated immune regulation in the pathogenicity of the disease. Pharmacokinetics prediction indicated good drug-likeness and safety for the majority of compounds, and molecular docking suggested stable binding of the key target AKT1 (PDB: 3MVH) with quercetin and luteolin exhibited the highest binding affinity among the tested phytochemicals in silico. Taken together, the results indicate a multi-targeted mechanism for therapy and provide evidence that selected phytoconstituents, namely **quercetin and luteolin,** could be promising candidates for in-depth validation in the application for rheumatoid arthritis treatment.

5. REFERENCES:

1. Smolen JS, Aletaha D, McInnes IB. Rheumatoid arthritis. The Lancet [Internet]. 2016 Oct;388(10055):2023–38. Available from: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(16)30173-8/abstract
2. Aletaha D, Smolen JS. Diagnosis and Management of Rheumatoid Arthritis. JAMA [Internet]. 2018 Oct 2;320(13):1360–72. Available from: https://jamanetwork.com/journals/jama/article-abstract/2705192
3. McInnes IB, Schett G. The Pathogenesis of Rheumatoid Arthritis. New England Journal of Medicine. 2011 Dec 8;365(23):2205–19.
4. Guo Q, Wang Y, Xu D, Nossent J, Pavlos NJ, Xu J. Rheumatoid arthritis: Pathological mechanisms and modern pharmacologic therapies. Bone Research. 2018 Apr 27;6(1).
5. Hopkins AL. Network pharmacology: the next paradigm in drug discovery. Nature Chemical Biology. 2008 Oct 20;4(11):682–90.
6. LI S, ZHANG B. Traditional Chinese medicine network pharmacology: theory, methodology and application. Chinese Journal of Natural Medicines. 2013 Mar;11(2):110–20.
7. Chen T, Li S, Lian D, Hu Q, Hou H, Niu D, et al. Integrated Network Pharmacology and Experimental Approach to Investigate the Protective Effect of Jin Gu Lian Capsule on Rheumatoid Arthritis by Inhibiting Inflammation via IL-17/NF-κB Pathway. Drug design, development and therapy. 2023 Dec 1;Volume 17:3723–48.
8. Di L, Kerns E, Carter G. Drug-Like Property Concepts in Pharmaceutical Design. Current Pharmaceutical Design. 2009 Jul 1;15(19):2184–94.
9. Yang H, Lou C, Sun L, Li J, Cai Y, Wang Z, et al. admetSAR 2.0: web-service for prediction and optimization of chemical ADMET properties. Wren J, editor. Bioinformatics. 2018 Aug 28;35(6):1067–9.
10. Meng XY, Zhang HX, Mezei M, Cui M. Molecular Docking: A Powerful Approach for Structure-Based Drug Discovery. Current Computer Aided-Drug Design [Internet]. 2011 Jun 1;7(2):146–57. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC3151162/
11. PubChem. PubChem [Internet]. Nih.gov. National Library of Medicine; 2004. Available from: https://pubchem.ncbi.nlm.nih.gov/
12. Daina A, Michielin O, Zoete V. SwissADME: a Free Web Tool to Evaluate pharmacokinetics, drug-likeness and Medicinal Chemistry Friendliness of Small Molecules. Scientific Reports. 2017 Mar 3;7(1):1–13.
13. Pires DEV, Blundell TL, Ascher DB. pkCSM: Predicting Small-Molecule Pharmacokinetic and Toxicity Properties Using Graph-Based Signatures. Journal of Medicinal Chemistry [Internet]. 2015 Apr 22;58(9):4066–72. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4434528/#ref1
14. Daina A, Michielin O, Zoete V. SwissTargetPrediction: updated data and new features for efficient prediction of protein targets of small molecules. Nucleic Acids Research. 2019 May 20;47(W1):W357–64.
15. Venny 2.1.0 [Internet]. bioinfogp.cnb.csic.es. Available from: https://bioinfogp.cnb.csic.es/tools/venny/index.html
16. Szklarczyk D, Kirsch R, Koutrouli M, Nastou K, Mehryary F, Hachilif R, et al. The STRING database in 2023: protein–protein association networks and functional enrichment analyses for any sequenced genome of interest. Nucleic Acids Research. 2022 Nov 12;51(D1):D638–46.
17. Doncheva NT, Morris JH, Gorodkin J, Jensen LJ. Cytoscape StringApp: Network Analysis and Visualization of Proteomics Data. Journal of Proteome Research. 2019 Feb 1;18(2):623–32.
18. Chin CH, Chen SH, Wu HH, Ho CW, Ko MT, Lin CY. cytoHubba: identifying hub objects and sub-networks from complex interactome. BMC Systems Biology. 2014;8(Suppl 4):S11.
19. Ge SX, Jung D, Yao R. ShinyGO: a graphical gene-set enrichment tool for animals and plants. Valencia A, editor. Bioinformatics. 2019 Dec 27;36(8):2628–9.
20. Carbon S, Mungall C. Gene Ontology Data Archive. Zenodo (CERN European Organization for Nuclear Research). 2024 Jan 17;
21. Minoru Kanehisa, Miho Furumichi, Sato Y, Matsuura Y, Ishiguro-Watanabe M. KEGG: biological systems database as a model of the real world. Nucleic Acids Research. 2024 Oct 17;53(D1).
22. Morris GM, Huey R, Lindstrom W, Sanner MF, Belew RK, Goodsell DS, et al. AutoDock4 and AutoDockTools4: Automated docking with selective receptor flexibility. Journal of Computational Chemistry. 2009 Dec;30(16):2785–91.
23. RCSB PDB [Internet]. Rcsb.org. Available from: https://www.rcsb.org/
24. Ramachandran GN, Ramakrishnan C, Sasisekharan V. Stereochemistry of polypeptide chain configurations. Journal of Molecular Biology. 1963 Jul;7(1):95–9.
25. Laskowski RomanA, Rullmann JAntoonC, MacArthur MalcolmW, Kaptein R, Thornton JanetM. AQUA and PROCHECK-NMR: Programs for checking the quality of protein structures solved by NMR. Journal of Biomolecular NMR. 1996 Dec;8(4).
26. Pettersen EF, Goddard TD, Huang CC, Meng EC, Couch GS, Croll TI, et al. UCSF ChimeraX: Structure visualization for researchers, educators, and developers. Protein Science. 2020 Oct 22;30(1):70–82.
27. Trott O, Olson AJ. AutoDock Vina: Improving the Speed and Accuracy of Docking with a New Scoring function, Efficient optimization, and Multithreading. Journal of Computational Chemistry. 2009;31(2).
28. Meng XY, Zhang HX, Mezei M, Cui M. Molecular Docking: A Powerful Approach for Structure-Based Drug Discovery.

Current Computer Aided-Drug Design [Internet]. 2011 Jun 1;7(2):146–57. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC3151162/
29. Discovery Studio [Internet]. Dassault Systèmes. 2023 [cited 2024 Jan 20]. Available from: https://www.3ds.com/products/biovia/discovery-studio

How to cite this article:
Sojarna.K et al. Ijppr.Human, 2026; Vol. 32 (2): 413-426.
Conflict of Interest Statement: All authors have nothing else to disclose.