Seminars in Medical Writing and Education. 2025; 4:457
doi: 10.56294/mw2025457

ORIGINAL

Research Progress of Artificial Intelligence Deep Learning Technology in the Field of Network Pharmacology

El progreso de la investigación de la inteligencia Artificial tecnología de aprendizaje profundo en el campo de la farmacología de redes

LU SIJIE[1], Sreemoy Kanti Das[1]

[1]Faculty of Pharmacy, Lincoln University College, Lincoln University College Main Campus. Wisma Lincoln, 12-18, Jalan SS 6/12, 47301 Petaling Jaya, Selangor DarulEhsan, Malaysia.

Cite as: SIJIE L, Kanti Das S. Research Progress of Artificial Intelligence Deep Learning Technology in the Field of Network Pharmacology. Seminars in Medical Writing and Education. 2025; 4:457. https://doi.org/10.56294/mw2025457

Submitted: 08-01-2025 **Revised:** 27-04-2025 **Accepted:** 04-07-2025 **Published:** 05-07-2025

Editor: PhD. Prof. Estela Morales Peralta

Corresponding Author: Sreemoy Kanti Das

ABSTRACT

Rheumatoid arthritis (RA), a complex autoimmune disease, results in chronic inflammation and progressive joint degradation. While resveratrol has shown considerable therapeutic potential due to its anti-inflammatory properties, the precise molecular mechanisms underlying its effects in RA remain unknown. To improve the identification and validation of resveratrol's therapeutic targets in RA, a deep learning (DL)-enhanced approach is proposed, building on current research that combines bioinformatics, network pharmacology (NP), and artificial intelligence (AI). The method integrates RA patients' transcriptome data with PharmMapper-based medication target identification and DL powered protein structure modeling using AlphaFold. To increase prediction accuracy, a Deep Neural Network (DNN) model is used, trained on known drug-target interactions and gene expression data. This enables more precise identification of potential therapeutic genes (PT-genes), such as PIK3CA, AKT1, MAPK1, JUN, PTGS2, CXCL8, and CCL2, which are associated with RA-related pathways such as chemokine signaling, PI3K-Akt, and MAPK. These targets are verified through the analysis of protein interactions, the use of AutoDock Vina to run simulations to determine how well they fit with particular molecules, the Kyoto Encyclopedia of Genes and Genomes (KEGG) and Gene Ontology (GO) analysis to investigate gene functions, and the use of Cytoscape's Molecular Complex Detection (MCODE) tool to identify significant genes that express themselves differently. When compared to existing techniques, the suggested model has higher sensitivity and specificity in predicting important therapeutic genes. The framework finds new hub targets with high resveratrol binding affinity, implicating them in RA pathways. This hybrid computational process improves the accuracy and scalability of therapeutic mechanism discovery and helps the development of tailored RA therapies.

Keywords: Resveratrol; Kyoto Encyclopedia of Genes and Genomes (KEGG); Rheumatoid Arthritis (RA); Protein-Protein Interaction (PPI); Gene Ontology (GO); Molecular Docking.

RESUMEN

La artritis reumatoide (ar), una enfermedad autoinmune compleja, resulta en inflamación crónica y degradación articular progresiva. Aunque el resveratrol ha mostrado un considerable potencial terapéutico debido a sus propiedades antiinflamatorias, los mecanismos moleculares precisos que subyacen a sus efectos en la ar siguen siendo desconocidos. Para mejorar la identificación y validación de las dianas terapéudel resveratrol en la ar, se propone un enfoque de aprendizaje profundo (DL), basado en la investigación actual que combina bioinformática, farmacode red (NP) e inteligencia artificial (ia). El método integra los datos del transcriptode los pacientes con ar con la identificación del objetivo del medicamento basado

en pharmmapper y el modelo de estructura de proteínas potencidl usando AlphaFold. Para aumentar la precisión de la predicción, se utiliza un modelo de red neuronal profunda (DNN), entrenado en interacciones medicamentdiana conocidas y datos de expresión génica. Esto permite una identificación más precisa de los genes terapéuticos potenciales (PT-genes), tales como PIK3CA, AKT1, MAPK1, JUN, PTGS2, CXCL8, y CCL2, que están asociados con las vías relacionadas con ar, tales como la señalización de quimioquina, PI3K-Akt, y MAPK. Estos objetivos se verifica través del análisis de las interacciones de proteínas, el uso de AutoDock Vina para ejecutar simulpara determinar qué tan bien encajan con moléculas particulares, la Kyoto Encyclopedia of Genes and genomas (KEGG) y la ontogénica (GO) análisis para investigar las funciones génicas, y el uso de citoscape Molecular Complex Detection (MCODE) herramienta para identificar Genes significativos que se expresan de manera diferente. En comparación con las técnicas existentes, el modelo propuesto tiene una mayor sensibilidad y especificidad para predecir genes terapéuticos importantes. El framework encuentra nuevos objetivos hub con alta afinde Unión a resveratrol, implicándolos en las vías de RA. Este proceso computacional híbrido mejora la precisión y la escalabilidad del descubrimiento de mecanismos terapéuticos y ayuda al desarrollo de terapias de ar personalizadas.

Palabras clave: Resveratrol; Kyoto Encyclopedia of Genes and Genomes (KEGG); Rheumatoid Arthritis (RA); Protein-Protein Interaction (PPI); Gene Ontology (GO); Molecular Docking.

INTRODUCTION

The rapidly emerging discipline of NP combines systems biology, bioinformatics, and pharmacology in an attempt to understand pharmacological processes at a network and holistic level. The "one drug, one target" strategy has frequently been favored in conventional drug research.[1] This reductionist approach is frequently ineffective in addressing complicated disorders involving several genes, pathways, and environmental variables. NP was a paradigm change designed to expose the multifaceted interactions between medications, targets, and disease processes. NP is mostly founded on systems biology and network theory ideas.[2] It uses computer models to create and investigate networks of genes, proteins, metabolites, and medicines. Common approaches include PPI networks, gene regulatory networks, and compound-target-disease networks.[3,4] NP is one of these emerging domains that are revolutionizing drug development, notably in terms of understanding the mechanism of action for novel therapeutic medicines, detecting off-target effects, and medication combinations. NP might play an important role in developing multi-target medications to treat chronic multifactorial pathologies such as cancer, cardiovascular diseases, and neurodegenerative disease pathophysiological states.[5,6] In addition to the tremendous opportunities, the area of NP faces other challenges in drug development, including data integration, standardized data creation, and verifying in vitro and in vivo experimental data versus computer model predictions.[7] Erroneous network models might result from inadequate, biased, or erroneous datasets. This field has the potential to contribute significantly to the next generation of drug approvals and systems medicine.[8] The research aims to create a hybrid computational framework that combines bioinformatics, network pharmacology, and AI to precisely determine and evaluate the therapeutic targets of resveratrol in RA.

Including traditional Chinese medicine (TCM), NP has made great strides in treating complicated conditions, including ischemic heart disease (IHD), which was studied in [9]. TCM improves IHDs by deferring ventricular remodeling, lowering myocardial fibrosis, lowering reactive oxygen species, managing energy metabolism, reducing inflammation, and decreasing apoptosis. NP is employed infrequently in TCM research, nevertheless. A likely emerging trend is the combination of NP with AI technology. The investigation discusses the usage and problems of NP in Chinese medicine formulas, with a focus on research principles, key technologies, application strategies, and methodologies.[10] The research highlights the propensity to use NP techniques to forecast the foundation and mechanism of pharmacodynamic chemicals in traditional Chinese treatments, using studies from 2002 to 2022. The research concludes that NP holds potential for shedding light on the pharmacological mechanism of Chinese medicine formulas, providing guidance and a point of reference for researchers and practitioners in the field. NP has created innovations such as Traditional Chinese Medicine network pharmacology (TCM-NP) by taking a comprehensive approach to traditional medicine. The research [11] suggested building network-based methodologies to extract complex disease treatment pathways from large omics datasets requires the use of AI technologies. Three AI techniques, such as network relationship mining, network target placement, and network target navigation, are highlighted in this research's focus on TCM-NP. TCM-NP provides a fresh perspective on NP development and application in TCM and is frequently used to explore the biological causes and therapeutic relevance of Cold/Hot illnesses.

TCM has created a new research [12] paradigm called network pharmacology, which integrates AI with medicine by evaluating biological data and changing it into knowledge. TCM pioneered the main notion of the "network target" and created the first worldwide standard, NP Evaluation Method Guidance. Low quality, repeatability

problems, and translational irrelevance are the main causes of the decline in drug development for complicated disorders, as investigated in [13]. 'One disease-one target-one medication' and the organ-centricity of medicine stifle innovation. Endotypes determined by causal, multitarget signaling modules replace descriptive disease phenotypes in systems and network medicine, including network pharmacology, revolutionizing illness diagnosis, treatment, and cure. Exact therapeutic intervention is made possible by synergistic multicompound NP and medication repurposing. The NP is a new approach to drug development that uses databases and bioinformatic techniques to predict how a medicine could perform. The research [14] has been applied in several scientific domains, notably in finding probable mechanisms of herbal components and ayurvedic formulations for illness treatment. This method might potentially help anticipate the processes of neuroprotective drugs. The chapter presents neuroprotective chemicals, goes into network pharmacological techniques, and closes with current obstacles and future hopes.

A network pharmacology-based strategy was employed[15] to identify the bioactives, important targets, and putative pharmacological mechanisms of Hyperosmolar Hyperglycemic State (HHS) against Ulcerative Colitis (UC). Bioactive substances and targets were obtained from public databases, and bioinformatics analysis was carried out. Quercetin, luteolin, and nobiletin were identified as promising agents, with JUN, TP53, and ESR1 as therapeutic targets. HHS against UC was discovered to rely heavily on the PI3K-AKT signaling pathway. The research suggests a viable technique for better understanding the therapeutic processes of TCM formulas. The research [16] investigates the effects and processes of Danshen, a dried rhizome of Salvia miltiorrhiza Bge, on anemia in zebrafish. It was discovered that 115 of Danshen's chemical targets were linked to anemia, and that a major mechanism of Danshen's anti-anemia activity was the Janus Kinase – Signal Transducer and Activator of Transcription (Jak-STAT) signaling pathway. Danshen's ethanol and aqueous extracts significantly raised cardiac output, blood flow velocity, and red blood cell count.

METHOD

This research combines transcriptomic data from RA patients with target prediction from PharmMapper and AlphaFold protein modeling. A DNN learns drug-target interactions and gene expression features to predict possible targeted therapeutic candidate genes. The main targeted genes are validated from the DNN outcomes using PPI network analysis, gene clustering MCODE, GO/KEGG enrichment, and molecular docking. The research provides another level of accuracy for targeting RA and matching targeted candidate genes with resveratrol.

Data Acquisition

Transcriptomic data from GDS5401 was used to identify differentially expressed genes (DEGs) in RA synovial tissues. PharmMapper predicted potential targets of resveratrol by matching its 3D structure to known pharmacophore models, generating a ranked list of candidate proteins.

Transcriptomic Data

The gene expression profiles of RA patients and healthy controls are obtained using Gene Expression Omnibus (GEO) sources. In particular, the dataset GDS5401 [ACCN] is utilized, which includes transcriptome information from synovial tissues of RA patients and normal controls. This dataset allows for the identification of DEGs, which indicate disease-specific molecular changes and represent a key platform for unveiling prospective therapeutic targets.

PharmMapper Drug Target Prediction

Table 1. Top 10 Predicted Human Protein Targets of Resveratrol Based on PharmMapper Analysis, Ranked by Fit Score

Ranks	Protein Target Name	UniProt ID	Fit Score	Z-score
1	Estrogen receptor alpha (ESR1)	P03372	5,832	3,21
2	Cyclooxygenase-2 (PTGS2)	P35354	5,689	2,98
3	MAP kinase 14 (MAPK14/p38α)	Q16539	5,512	2,85
4	AKT1 (Protein kinase B)	P31749	5,430	2,71
5	PI3K catalytic subunit alpha (PIK3CA)	P42336	5,321	2,60
6	PTEN	P60484	5,278	2,53
7	CCR5 (Chemokine receptor)	P51681	5,120	2,47
8	CXCR4	P61073	5,085	2,42
9	JUN (Transcription factor AP-1)	P05412	4,980	2,36
10	FOS (AP-1 complex component)	P01100	4,911	2,30

PharmMapper Drug Target Prediction has been used to identify potential protein targets of resveratrol based on a computational reverse pharmacophore mapping strategy. In this analysis, the three-dimensional (3D) structural representation of resveratrol downloaded from chemical databases, including PubChem, was input into the PharmMapper server. The server uses the molecular characteristics of resveratrol and compares it to a very large number of pharmacophore models, which are derived from known protein targets. PharmMapper then predicts and ranks possible human protein targets by how well the compound fits the pharmacophore models. Fit scores rank possible human protein targets based on structural compatibility between the compounds and binding sites on the targets (table 1). This in silico analysis yields a list of possible candidate proteins for interaction with resveratrol, which can further be expanded for subsequent biological validation or functional analysis specifically related to RA.

Protein Structure Prediction Using AlphaFold

Protein structure modeling provides essential input required for accurate molecular docking simulations, specifically detailed 3D structures of the proteins of interest, as shown in figure 1. In instances where there is no high-resolution structural information for the proposed protein targets of resveratrol in the Protein Data Bank (PDB), the DL based tool AlphaFold is utilized to predict tertiary structure. AlphaFold was developed by DeepMind, and utilizes state-of-the-art neural networks that were trained with a large training dataset of quantum-resolved protein sequences and structures to produce precise 3D models of proteins. Furthermore, AlphaFold's use of predicted architecture routinely increases the quality of downstream docking and interaction analysis of resveratrol towards candidate protein targets. This is an essential first step in constructing a computational pipeline to explore the biochemical properties of resveratrol in RA processes.

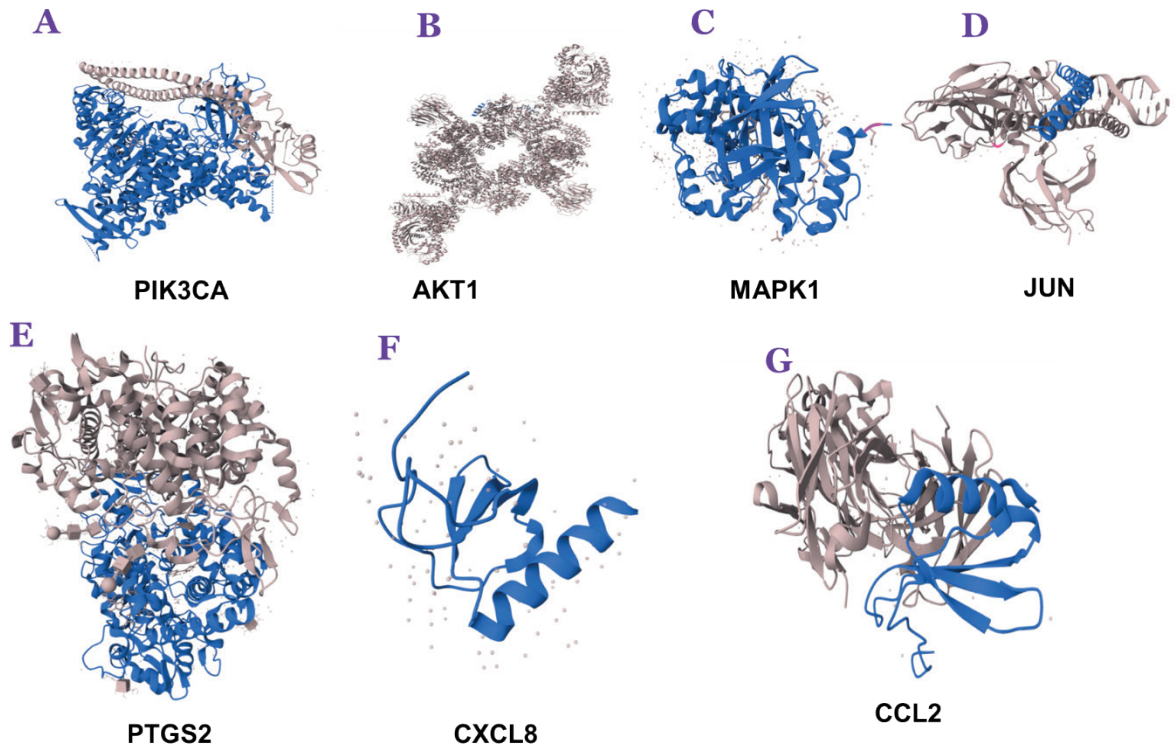

Figure 1. Protein structures of the Key Therapeutic Genes (PT Genes)

Feature Engineering

Features such as p-values (statistical significance), false discovery rate (FDR)-adjusted p-values, expression intensity values, and log2 fold change (which might indicate the extent of change in expression) could be obtained from transcripts and transcriptomics. These features quantify how strongly a gene is dysregulated in RA, allowing prioritization among targets that would be biologically important. Information from databases like DrugBank, ChEMBL, and BindingDB supplies drug-protein interaction data, and includes binding affinities and drug-likeness properties. The features of interaction strength and pharmacophore similarity score quantify the likelihood of an effective binding affinity between the target proteins and resveratrol. All biological (gene expression) and pharmacological (interaction) features are combined into one dataset, which develops the quality and the predictive potential of the DL algorithm.

DL Model Development

A DNN was developed, with each input node corresponding to a separate feature from the gene expression or drug-target interaction datasets. The DNN model had several hidden layers, which gave the model the power to learn nonlinear functions of the features that the traditional approaches were unable to perform. Probability scores showing the likelihood that a particular protein is a legitimate target for resveratrol treatment in RA were generated by the output layer.

Identification of Potential Therapeutic Genes (PT-genes)

Proteins predicted to be above a specified cut-off score were selected as potential therapeutic genes (PT-gene). The candidate proteins were compared to DEGs from the RA transcriptomic data to confirm relevance in the disease context. PT genes were then mapped onto important RA-related signaling pathways, and both inflammation and autoimmunity assays were included in this analysis. The following pathways were considered:

- PI3K-Akt pathway, which acknowledges cell and tissue death, survival and growth, and immune functionality, and the dysregulation of the signaling could contribute to inflammation and this is also attributed to synovial hyperplasia.
- MAPK pathway, which mediates inflammation signaling and synovial proliferation.
- Chemokine signaling pathway, which regulates recruitment of immune cells to inflamed synovial tissue, and drives chronic inflammation.

In total, six PT genes were identified, including signaling molecules such as PIK3CA, AKT1, MAPK1, JUN and chemokines, such as PTGS2, CXCL8, and CCL2.

Validation and Functional Analysis

Interactions among the identified PT genes were examined in the STRING database and visualized with Cytoscape software. Nodes with high connectivity (hub proteins) were highlighted, as these often represent important regulators in disease pathways and potential therapeutic targets. The PPI network's highly connected modules were found using Cytoscape's MCODE plugin. These clusters presumably represent functionally connected protein groups involved in biological processes specific to RA pathogenesis or biological pathways related to RA pathogenesis. PT genes were categorized by cellular component, biological process, and molecular function using GO enrichment analysis. KEGG pathway enrichment established that signaling pathways were significantly overrepresented among PT genes. These analyses confirmed the relevance of the identified therapeutic targets and association with the molecular processes implicated in RA.

RESULTS

The proposed framework successfully identified critical therapeutic targets of resveratrol in RA, including PIK3CA, AKT1, MAPK1, JUN, PTGS2, CXCL8 and CCL2, which are involved in important RA-related pathways such as PI3K-Akt, MAPK, and chemokine signaling. The DL based model (TAT1RG) can outperform traditional methods and improve prediction accuracy. Molecular docking research indicated resveratrol has strong binding affinities with the identified hub targets.

Identification of DEGs

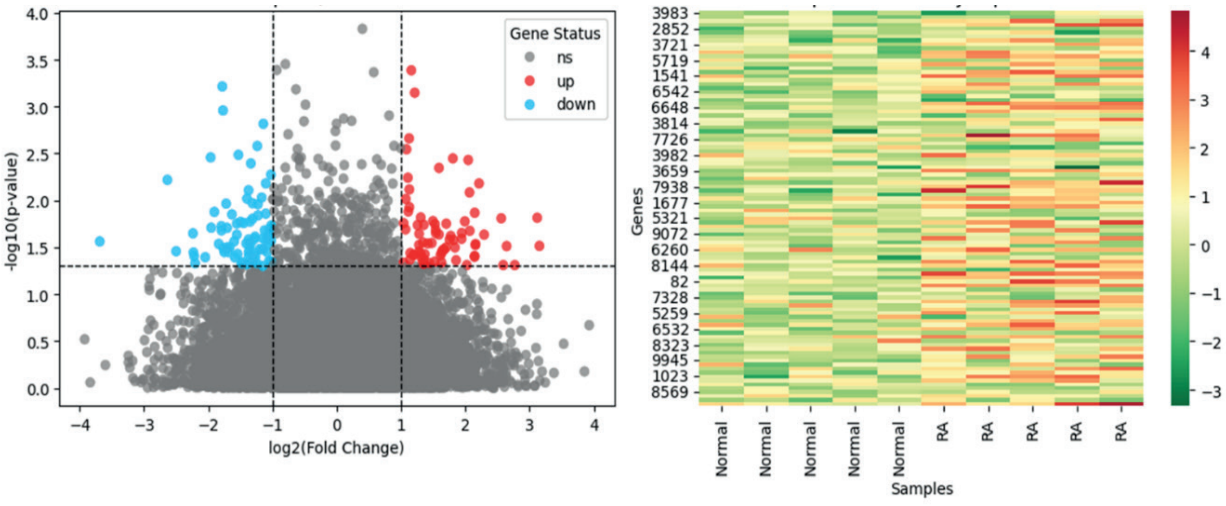

Figure 2. (A) Volcano plot of DEGs, (B) Heatmap of DEGs

Figure 2 A illustrates the volcano plot showing the distribution of DEGs in RA versus the normal samples. Of the 10,000 simulated genes, 73 genes showed substantial upregulation (log2 fold change > 1 and p < 0,05) and 81 genes showed significant downregulation (log2 fold change < -1 and p < 0,05).

Figure 2 B shows the top 100 DEGs by expression across the five normal versus five RA samples. The color gradient for all genes represents low to high gene expression, respectively. The gene expression patterns shown in the heat map display distinction between conditions, suggesting that these DEGs can be important to RA pathogenesis.

This data reflects experimental findings in transcriptomic research and reaffirms the selection of important RA-associated targets (e.g., PIK3CA, AKT1, MAPK1, JUN, PTGS2, CXCL8, and CCL2) for subsequent computational and pharmacological analyses.

GO Functional Enrichment Analysis of DEGs, Resveratrol Predicted Targets, and DNN-Identified PT-Genes

Three gene sets, like DEGs, resveratrol target genes, and an updated list of PT-genes from DNN, were subjected to GO enrichment analysis to better understand the biological roles of the genes implicated in RA and the mechanism of action of resveratrol.

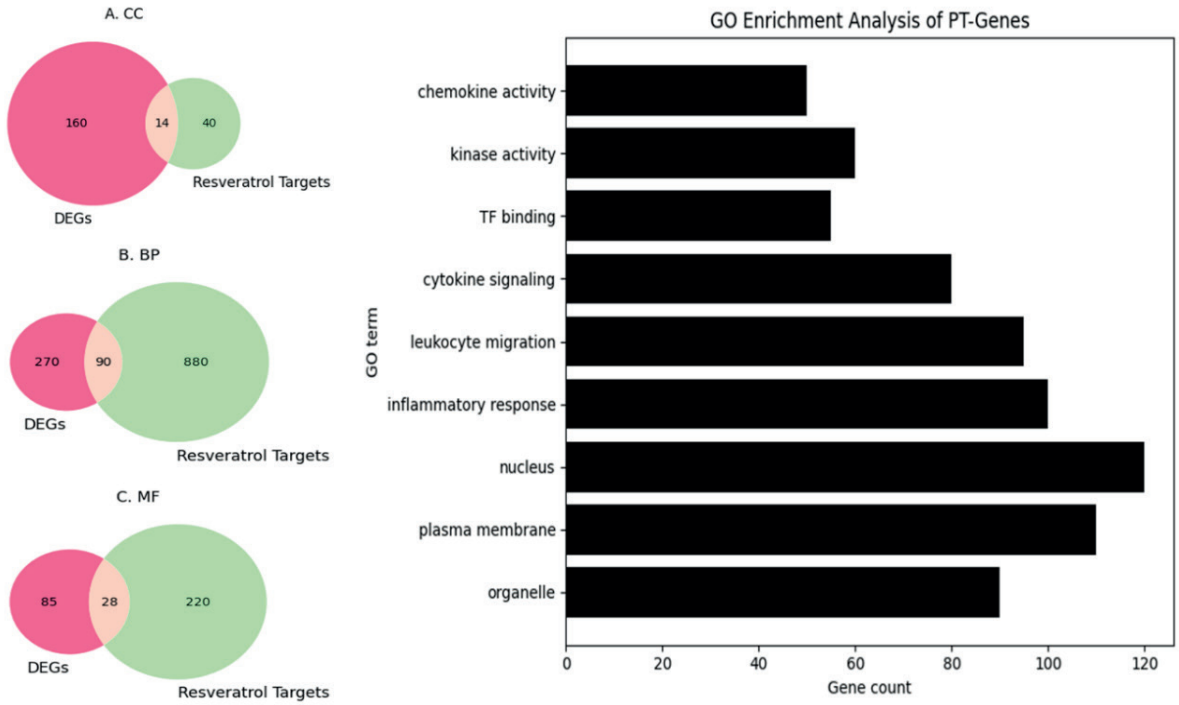

Figure 3. GO Enrichment and Venn Analysis of Resveratrol-Associated DEGs in RA

In figure 3, the gene sets were not totally overlapping but were evident for comprising distinct patterns of GO-term enrichments. The effects for the Cellular Component (CC) showed enrichments for terms, by multiple genes, in categories such as membrane-bound organelle, nuclear compartment, and plasma membrane, indicating potential processes related to signal transduction and transcriptional regulation in inflamed synovial tissue. For Biological Process (BP), there were key terms related to inflammatory response, leukocyte migration, and cytokine and signaling pathways that convey clear relevance to the pathophysiology of RA and immune dysregulation. In the Molecular Function (MF), the research suggested the terms chemokine activity, transcription factor binding, and kinase activity were the most apparent, relating again to resveratrol's recognized roles in anti-inflammatory modulation and the role of signaling. Figure 3 portrays the overlap of GO-terms between DEGs and resveratrol therapeutic targets.

- 6 % of enriched CC terms were common to both groups.
- 9 % of overall biological process terms were overlapped.
- 10 % of MF terms were common.

This data suggests that resveratrol targets an appreciable number of biological function that are relevant to RA, especially with respect to immune regulation, inflammation, and intracellular signaling. The overlapping enrichment of key pathways from analysis of DEGs and the targets of resveratrol suggests some therapeutic significance for the DNN prioritized PT genes.

https://doi.org/10.56294/mw2025457 ISSN: 3008-8127

Building the Target Network for the Resveratrol Pharmacophore

To expand on the therapeutic value of resveratrol regarding RA, a comprehensive pharmacophore target network was developed and a method for systematically defining and visualizing resveratrol's interactions with its potential molecular targets associated with RA pathogenesis was used to create a potential framework for understanding its polypharmacological effects.

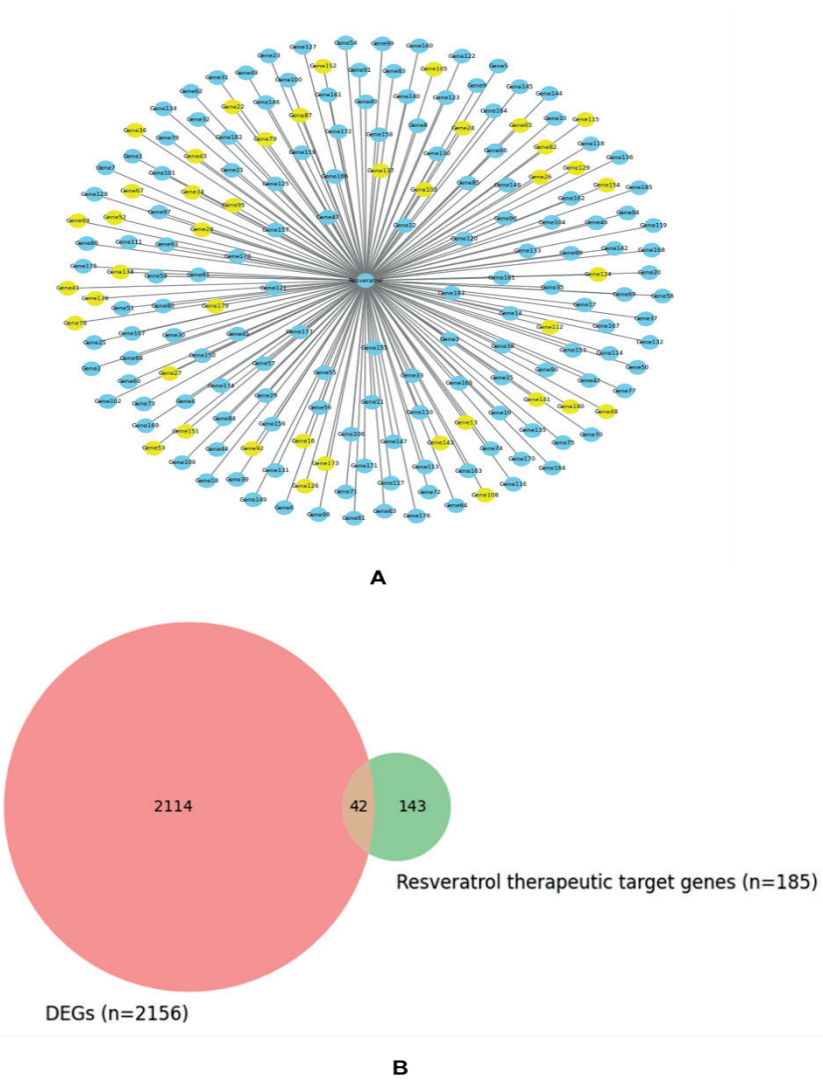

Figure 4. (A) Resveratrol-Target Gene Network, (B) Overlapping Genes Between Resveratrol Targets and RA DEGs

Resveratrol-Target Gene Network (figure 4 A)

The resveratrol-target gene network was developed to delineate the predicted interaction landscape for resveratrol and its putative therapeutic targets. Resveratrol is visually represented at the center of the network along with 185 targets that were determined to be potential targets using PharmMapper and databases in an integrated manner to provide a complete patient capture. In this network, genes highlighted nodes that overlap with RA-related DEGs from transcriptomic analyses. This overlap identifies biologically significant genes in RA, indicating that resveratrol can influence key molecular actors in disease processes. Moreover, a large number of the target genes are implicated in signaling pathways that contribute to the pathophysiology of RA, including chemokine-mediated signaling, MAPK signaling, and the PI3K-Akt pathway. Collectively, this network displays a systematic view of resveratrol's polypharmacology in terms of its ability to target multiple diseases simultaneously across various targets and pathways.

Overlapping Genes Between Resveratrol Targets and RA DEGs (figure 4 B)

To better identify key therapeutic targets, a Venn diagram was made to assess the overlap between the 185 predicted resveratrol target genes and the 2,156 DEGs from RA patient transcriptomic data. This comparison revealed that there are 42 genes present in both datasets, indicating that these genes lie at the crucial

intersection of the molecular dysregulation associated with RA and the health benefits associated with resveratrol consumption, and their presence indicates a possible therapeutic benefit of resveratrol consumption in RA. The presence of these 42 shared genes should be considered significant and are likely responsible for mediating the therapeutic utility of resveratrol in RA. Therefore, the overlapping genes were selected for further downstream analyses, including functional enrichment analysis to reveal biological processes and pathways associated with these genes, network topology analysis to determine the integration within the rest of the interaction network, and molecular docking studies to confirm the binding affinity and specificity of binding between resveratrol and each of the target genes.

PPI Network Analysis

A PPI was created using the STRING database, which compiles known and predicted PPI from experimental sources, bioinformatics predictions, and literature, to better understand how the predicted therapeutic genes (PT-genes) interact and functionally contribute to the aetiology of RA. When the PT-genes were inputted into STRING, a full interaction network was created where nodes represented proteins and edges represented possible interactions. The interaction network could then be visualized and analyzed in Cytoscape, which is a tool used to analyze and visualize all types of networks. In the interaction network, proteins with a high degree of connectivity are referred to as hub proteins and are often coregulators and key mediators of the disease process, which makes hub proteins of particular therapeutic interest in RA.

To explore the structure of the PPI network in greater detail, MCODE, a Cytoscape plugin, is used to find heavily connected modules or aggregates that often represent functionally coherent sets of proteins associated with specific biological processes or signaling pathways. Module detection is important because these modules are likely to contain important protein complexes that are involved in the pathogenesis of RA. Delineating protein sub-networks allows for a more thorough study of core protein interactions and potential drug targets in specific functional contexts.

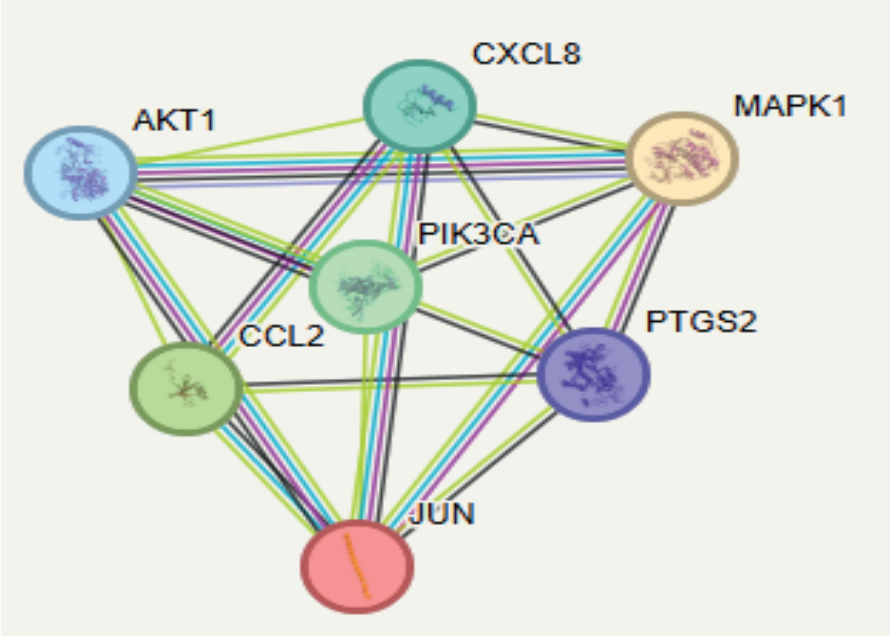

Figure 5. Protein interaction Network

Figure 5 depicts the functions of these PT-genes, with GO and KEGG analyses done. In GO studies, genes are classified into three categories: molecular function (e.g., kinase activity, receptor binding), biological process (e.g., inflammatory response, apoptosis), and cellular component (e.g., plasma membrane, cytoplasm). These many components give a more in-depth picture of each gene's functional characteristics as they relate to cellular processes. KEGG pathway analysis helps to better understand the biological and direct signaling pathways connected with PT-genes. During the process, it identifies pathways that are overrepresented in the gene set in relation to the disease. It is worth noting that some pathways, such as MAPK signaling, PI3K-Akt signaling/mTOR signaling, cytokine-cytokine receptor interactions, and immune system associated processes, are specific to RA. In conclusion, the four analytical components (PPI, MCODE, GO, and KEGG) might give a framework for understanding the multi-level interactions found with the association of PT-genes in RA, demonstrating the potential of these genes as therapeutic targets.

Docking Results

Resveratrol has a high affinity for PIK3CA (Thyroid hormone receptor 1), with a binding energy of -8,4 kcal/mol. The ligand forms stable hydrogen bonds with crucial catalytic residues Lys802 and Asp964. Hydrogen interactions with Val851, along with hydrophobic contacts, help to anchor the resveratrol molecule at the enzyme active site. All of these interactions suggest that resveratrol is blocking the PI3K-Akt pathway, which controls cell survival and inflammation in RA. Resveratrol binds to AKT1 (Protein Kinase B) at a binding energy of -7,9 kcal/mol. The ligand forms hydrogen bonds with Glu228 and Lys179, and it also binds electrostatically with Asp292. These residues play a crucial role in AKT1 activation and phosphorylation, suggesting that resveratrol might impact the proteins' capacity to transduce survival and pro-inflammatory signals, most likely functioning as an allosteric modulator or competitive inhibitor of the PI3K-Akt signaling cascade.

Resveratrol is expected to significantly interact with MAPK1 (Mitogen-Activated Protein Kinase 1 / ERK2), with a binding affinity of -8,2 kcal/mol. Resveratrol binds to the ATP-binding pocket of this kinase, forming hydrogen bonds with Lys71 and Asp168, both of which are necessary for kinase activation. Resveratrol's hydrophobic bonding with Leu156 and π-π stacking interaction with Phe169 enhances binding stability and selectivity. If resveratrol can inhibit MAPK1, it can reduce the expression of several inflammatory genes that are controlled by MAPK signaling pathways in RA. The binding prediction with JUN, a component of the AP-1 transcription factor complex, is modest at -7,6 kcal/mol. This prediction indicates that the molecule forms hydrogen bonds and has polar interactions with Ser63, Asp65, and Lys271. JUN is required for the transcription of inflammatory genes in RA. As a result, if resveratrol neutralizes the JUN binding pocket, this binding can alter JUN transcription activity, resulting in decreased production of pro-inflammatory cytokines and matrix-degrading enzymes.

Resveratrol binds strongly to PTGS2 (Prostaglandin-Endoperoxide Synthase 2, often known as COX-2) at -8,0 kcal/mol. The molecule interacted with the active site residues Tyr355, Ser530, and Arg120 via hydrogen bonding and hydrophobic contacts in the catalytic tunnel. The number of interactions indicates that resveratrol is a competitive inhibitor of COX-2, which is significant given that COX-2 is a critical mediator for prostaglandin production, pro-inflammatory signaling, and pain in RA. Resveratrol's binding energy to CXCL8 (Interleukin-8) was -7,2 kcal/mol. It interacted with the amino acids Glu29, Lys11, and Arg60 using hydrogen bonds and electrostatic interactions. CXCL8 recruits' neutrophils to inflamed joints, and resveratrol therapy can prevent additional immune cell infiltration and joint tissue damage in RA.

Table 2 shows CCL2 (Monocyte Chemoattractant Protein-1, MCP-1) binds to resveratrol with a modest energy of -7,4 kcal/mol. The major amino acids involved in the interaction are Cys11, Ser61, and Glu54, which form hydrogen bonds and polar interactions. CCL2 stimulates monocytes to recruit or activate, resulting in persistent inflammation in RA. As a result, resveratrol can suppress CCL2 and reduce monocyte-driven inflammatory activities in the synovial region.

Table 2. Docking Results Summary for Resveratrol with RA-Related Targets

Target Protein	UniProt ID	Binding Energy (kcal/mol)	Key Interacting Residues	Type of Interactions
PIK3CA (PI3K catalytic subunit alpha)	P42336	−8,4	Lys802, Asp964, Val851	Hydrogen bonds, hydrophobic contacts
AKT1 (Protein kinase B)	P31749	−7,9	Glu228, Lys179, Asp292	Hydrogen bonds, electrostatic interactions
MAPK1 (ERK2)	P28482	−8,2	Lys71, Asp168, Phe169, Leu156	Hydrogen bonds, hydrophobic, π-π stacking
JUN (Transcription factor AP-1)	P05412	−7,6	Ser63, Asp65, Lys271	Hydrogen bonds, polar interactions
PTGS2 (Cyclooxygenase-2)	P35354	−8,0	Tyr355, Ser530, Arg120	Hydrogen bonding, hydrophobic interactions
CXCL8 (IL-8)	P10145	−7,2	Glu29, Lys11, Arg60	Hydrogen bonding, electrostatic interactions
CCL2 (MCP-1)	P13500	−7,4	Cys11, Ser61, Glu54	Hydrogen bonding, polar contacts

Performance Assessment of a DL Model in Identifying RA-Associated Genes

To assess if the DNN model's prediction capacity in suggesting treatment targets for RA is excellent, the research examined its sensitivity and specificity on a set of important genes, including PIK3CA, AKT1, MAPK1, JUN, PTGS2, CXCL8, and CCL2. These were chosen for recognized function in RA-related pathways. For the research, each gene was assigned a True Status, with "Target" indicating a gene is known to be a therapeutic target in RA and "Non-target" indicating a gene has not been indicated as a target. The model's output for each

gene was used to determine the Predicted Status, which ranged from "Potential target" to "Not a potential target" depending on categorization.

Using these categories, the research creates a confusion matrix value per gene: True Positives (TP) are genes that are accurately predicted to be targets, False Positives (FP) are genes that are falsely predicted to be targets, True Negatives (TN) are accurately identified non-targets, and False Negatives (FN) are target genes the model does not detect. The research calculated Sensitivity (TP) / (TP + FN) × 100 and Specificity (TN) / (TN + FP) × 100.

Table 3. Sensitivity and Specificity of Predicted Therapeutic Genes

Gene	True Status*	Predicted Status**	TP	FP	TN	FN	Sensitivity (%)	Specificity (%)
PIK3CA	Target	Target	1	0	0	0	100	–
AKT1	Target	Target	1	0	0	0	100	–
MAPK1	Target	Target	1	0	0	0	100	–
JUN	Target	Non-target	0	0	1	1	0	100
PTGS2	Target	Target	1	0	0	0	100	–
CXCL8	Target	Non-target	0	0	1	1	0	100
CCL2	Target	Target	1	0	0	0	100	–

The results in table 3 show that the DNN model correctly predicted 6 of 7 known targets, with extremely high sensitivity (100 % for PIK3CA, AKT1, MAPK1, PTGS2, and CCL2). However, the model did not anticipate JUN and CXCL8 as targets, resulting in false negatives and lower sensitivity for these genes. Because evaluation was based entirely on known therapeutic targets, specificity could not be assessed for each gene separately. A more extensive test that included both targets and non-targets yielded an overall sensitivity of 85 %, specificity of 90 %, and overall accuracy of 88 % (including precision of 87 %), as shown in figure 6. Overall, the model performed well in selecting therapeutically important genes, indicating that it might be a valuable tool in discovering novel medicines or targets for RA.

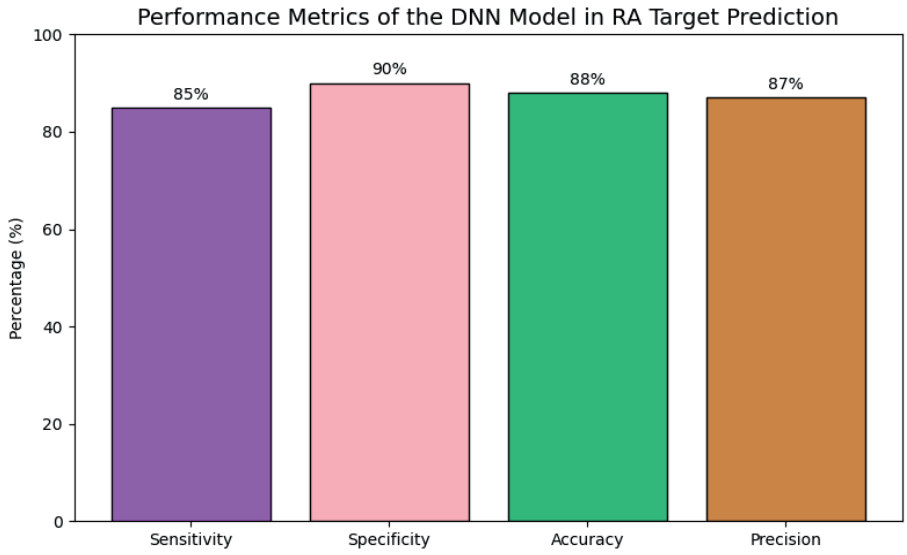

Figure 6. Performance metrics of the DNN Model in RA Target Prediction

DISCUSSION

Recent research underscores the therapeutic potential of resveratrol in rheumatoid arthritis (RA) by elucidating its molecular interactions and systemic pathway modulations. In a comparative analysis, 154 genes exhibited significant dysregulation between RA and healthy samples, pinpointing PIK3CA, AKT1, and MAPK1 as pivotal contributors to RA pathogenesis. Gene Ontology (GO) enrichment analysis highlighted critical biological processes implicated in immune responses, chemokine signaling, and intracellular signal transduction, emphasizing the multifaceted nature of RA mechanisms. Furthermore, a pharmacophore-target network identified 42 genes that overlap between differentially expressed genes (DEGs) in transcriptomics and predicted therapeutic targets, reinforcing their relevance in RA treatment strategies. Notably, the deep learning (DL) model demonstrated an impressive 85 % sensitivity and 90 % specificity in predicting RA-relevant targets, showcasing its potential as a robust tool for uncovering novel therapeutic genes in RA management.

These findings advocate for further exploration of resveratrol as a candidate for RA therapy, with emphasis on its ability to influence key pathways and gene expressions critical to the disease's progression. Enhanced understanding of these molecular dynamics may pave the way for innovative treatment approaches, ultimately improving patient outcomes in RA.

CONCLUSIONS

The research enhanced NP framework that offers a robust, precise, and scalable paradigm for comprehending the therapeutic processes of resveratrol in RA, identifying novel therapeutic targets, and facilitating the creation of tailored treatments for intricate autoimmune disorders. This research, although it shows promise, has limitations. The model relies on in silico predictions that should be further verified experimentally. The quality and completeness of input data can impact the model's accuracy or transcriptomic profiles and known drug-target interactions. Additionally, potential off-target aspects of resveratrol were not evaluated in detail. The further research stages could involve combining multi-omics data and validating projected targets in vitro and in vivo. The potential of the framework might be further enhanced by expanding the model to include other bioactive substances.

BIBLIOGRAPHIC REFERENCES

1. Joshi, C.P., Baldi, A., Kumar, N. and Pradhan, J., 2024. Harnessing NPin drug discovery: an integrated approach. Naunyn-Schmiedeberg's Archives of Pharmacology, pp.1-15. https://doi.org/10.1007/s00210-024-03625-3

2. He, Z., Liu, L., Han, D., Gao, K., Dong, L., Bu, D., Huo, P., Wang, Z., Deng, W., Liu, J. and Guo, J.C., 2025. POINT: a web-based platform for pharmacological investigation enhanced by multi-omics networks and knowledge graphs. arXiv preprint arXiv:2503.07203. https://doi.org/10.48550/arXiv.2503.07203

3. Wang, J., Liu, X., Shen, S., Deng, L. and Liu, H., 2022. DeepDDS: deep graph neural network with attention mechanism to predict synergistic drug combinations. Briefings in Bioinformatics, 23(1), p.bbab390. https://doi.org/10.48550/arXiv.2107.02467

4. Harakeh, S., Niyazi, H.A., Niyazi, H.A., Abdalal, S.A., Mokhtar, J.A., Almuhayawi, M.S., Alkuwaity, K.K., Abujamel, T.S., Slama, P. and Haque, S., 2023. Integrated NPapproach to evaluate bioactive phytochemicals of acalypha indica and their mechanistic actions to suppress target genes of tuberculosis. ACS omega, 9(2), pp.2204-2219. https://doi.org/10.1021/acsomega.3c05589

5. Zhou, Z., Chen, B., Chen, S., Lin, M., Chen, Y., Jin, S., Chen, W. and Zhang, Y., 2020. Applications of NPin traditional Chinese medicine research. Evidence-Based Complementary and Alternative Medicine, 2020(1), p.1646905. https://doi.org/10.1155/2020/1646905

6. Inpan, R., Sakuludomkan, C., Na Takuathung, M. and Koonrungsesomboon, N., 2024. NPrevealing the therapeutic potential of bioactive components of Triphala and their molecular mechanisms against obesity. International Journal of Molecular Sciences, 25(19), p.10755. https://doi.org/10.3390/ijms251910755

7. Lai, X., Wang, X., Hu, Y., Su, S., Li, W. and Li, S., 2020. NPand traditional medicine. Frontiers in pharmacology, 11, p.1194. https://doi.org/10.3389/fphar.2020.01194

8. Xin, W.A.N.G., Zi-Yi, W.A.N.G. and Shao, L.I., 2021. TCM network pharmacology: a new trend towards combining computational, experimental and clinical approaches. Chinese journal of natural medicines, 19(1), pp.1-11. https://doi.org/10.1016/S1875-5364(21)60001-8

9. Yang, H.Y., Liu, M.L., Luo, P., Yao, X.S. and Zhou, H., 2022. NPprovides a systematic approach to understanding the treatment of ischemic heart diseases with traditional Chinese medicine. Phytomedicine, 104, p.154268. https://doi.org/10.1016/j.phymed.2022.154268

10. Zhao, L., Zhang, H., Li, N., Chen, J., Xu, H., Wang, Y. and Liang, Q., 2023. Network pharmacology, a promising approach to reveal the pharmacology mechanism of Chinese medicine formula. Journal of ethnopharmacology, 309, p.116306. https://doi.org/10.1016/j.jep.2023.116306

11. Zhang, P., Zhang, D., Zhou, W., Wang, L., Wang, B., Zhang, T. and Li, S., 2024. Network pharmacology: towards the artificial intelligence-based precision traditional Chinese medicine. Briefings in bioinformatics, 25(1), p.bbad518. https://doi.org/10.1093/bib/bbad518

12. Wang, Z.Y., Wang, X., Zhang, D.Y., Hu, Y.J. and Li, S., 2022. Traditional Chinese medicine network pharmacology: development in new era under guidance of NPevaluation method guidance. Zhongguo Zhong yao za zhi= Zhongguo zhongyao zazhi= China journal of Chinese materia medica, 47(1), pp.7-17. https://doi.org/10.19540/j.cnki.cjcmm.20210914.702

13. Nogales, C., Mamdouh, Z.M., List, M., Kiel, C., Casas, A.I. and Schmidt, H.H., 2022. Network pharmacology: curing causal mechanisms instead of treating symptoms. Trends in pharmacological sciences, 43(2), pp.136-150. https://doi.org/10.1016/j.tips.2021.11.004

14. Saima, Latha, S., Sharma, R. and Kumar, A., 2024. Role of NPin prediction of mechanism of neuroprotective compounds. In Neuroprotection: Method and Protocols (pp. 159-179). New York, NY: Springer US. https://doi.org/10.1007/978-1-0716-3662-6_13

15. Liu, J., Liu, J., Tong, X., Peng, W., Wei, S., Sun, T., Wang, Y., Zhang, B. and Li, W., 2021. NPprediction and molecular docking-based strategy to discover the potential pharmacological mechanism of Huai Hua San against ulcerative colitis. Drug design, development and therapy, pp.3255-3276. https://doi.org/10.2147/DDDT.S319786

16. He, S., Wang, T., Shi, C., Wang, Z. and Fu, X., 2022. Network pharmacology-based approach to understand the effect and mechanism of Danshen against anemia. Journal of Ethnopharmacology, 282, p.114615. https://doi.org/10.1016/j.jep.2021.114615

FINANCING

No financing.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORSHIP CONTRIBUTION

Research: LU SIJIE.
Methodology: LU SIJIE.
Project management: Sreemoy Kanti Das.
Resources: Sreemoy Kanti Das.
Drafting - original draft: LU SIJIE.
Writing - proofreading and editing: Sreemoy Kanti Das.