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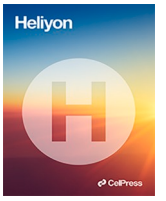

Research article

Combining bioinformatics, network pharmacology, and artificial intelligence to predict the mechanism of resveratrol in the treatment of rheumatoid arthritis

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ABSTRACT

Background: Rheumatoid arthritis (RA) is a chronic autoimmune disorder that causes joint inflammation and destruction, resulting in significant physical and economic burdens. Finding effective and targeted therapy for RA remains a top priority. Resveratrol is a potential candidate with anti-inflammatory and immunomodulatory properties for RA treatment. This study aims to determine the therapeutic targets and signaling pathways of resveratrol in the treatment of RA.
Methods: The GSE205962 dataset downloaded from The Gene Expression Omnibus (GEO) database was used to obtain the differentially expressed genes (DEGs) in blood samples from the patients and the healthy. PharmMapper database and Cytoscape (v3.9.1) were applied to construct the resveratrol pharmacophore target network. Gene functional enrichment analysis, including the Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis, was based on the BiNGo plug-in of Cytoscape and David's online tool. The intersection of the target genes of resveratrol and the DEGs were considered potential therapeutic genes (PT-genes). The Protein-Protein Interaction (PPI) network of PT-genes was constructed using the STRING tool, and the key therapeutic genes (KT-genes) were determined using the cytoHubba plug-in based on the Maximal Clique Centrality (MCC) algorithms. Molecular docking validation of resveratrol and therapeutic targets was performed based on the protein structure of KT-genes predicted by AlphaFold.
Results: A total of 2202 DEGs and 47PT-genes were identified. GO analysis showed that the three groups of genes, the DEGs, the resveratrol target genes, and the PT-genes, have similar results for the top-five gene functional enrichment. PT-genes were closely related to the pathways of metabolic pathways, pathways in cancer, proteoglycans in cancer, insulin signaling pathway, and chemokine signaling pathway. The common pathway enriched by KEGG for the DEGs, and the resveratrol target genes was up to 36 %. The nine KT-genes were ABL1, ANXA5, CASP3, HSP90AA1, LCK, MAP2K1, MAPK1, PIK3R1, and RAC1, and the lowest free energy indicating the resveratrol/protein affinity were −8.4, −7.4, −6.4, −6.7, −8.0, −7.9, −7.4, −6.7, and −7.9, respectively.

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Conclusion: Nine KT-genes were identified and validated as the most potential therapeutic targets in the treatment of RA with resveratrol, which provide new insights into therapeutic mechanisms and may improve the efficiency of drug development.

1. Introduction

Rheumatoid arthritis (RA) is a complex autoimmune disorder characterized by chronic inflammation and joint destruction, leading to a significant impact on an individual's quality of life and causing morbidity. Epidemiological studies have revealed that the prevalence of RA is 0.42 % in China, 0.35 % in Western Europe, and 0.38 % in North America [1,2]. The main therapeutic approaches for RA involve various drugs, including disease-modifying antirheumatic drugs, non-steroidal anti-inflammatory drugs, and glucocorticoids. However, these drugs are known to have serious long-term side effects such as gastrointestinal reactions, bone marrow transplantation, liver and kidney toxicity, and infection. Despite advances in comprehending the immunological basis of RA, discovering effective therapeutic options with minimal side effects continues to be a significant challenge.

Resveratrol, a non-flavonoid polyphenolic compound, exhibits various pharmacological activities including anti-tumor [3], antioxidant [4], anti-inflammatory [5], anti-aging [6], immunoregulation [7], and neuroprotection [8], and effects on therapy of RA [9]. Previous studies revealed that resveratrol could effectively inhibit RA fibroblast-like synoviocytes cell apoptosis [10], and decrease the serum levels of malondialdehyde, Interleukin 6, and tumor necrosis factor alpha, Interleukin 1β and arthritis index scores in arthritic rats compared to the arthritic control rats [11], Recently, a randomized controlled clinical trial indicated the clinical and biochemical markers of RA in the resveratrol-treated group were significantly lower compared to the control group [12]. Although in vivo and in vitro experiments suggest that resveratrol has therapeutic effects on RA, the mechanisms of resveratrol involved in RA progression remain unknown. However, despite the positive results from experiments conducted both in vivo and in vitro, we still don't fully understand how resveratrol works to treat RA.

Recently, the integration of bioinformatics, network pharmacology, and artificial intelligence has emerged as a powerful approach to unravel complex biological processes and accelerate drug discovery. Bioinformatics techniques enable the systematic analysis and integration of omics data, shedding light on molecular interactions and signaling pathways associated with disease [13]. Network pharmacology provides a holistic perspective by considering the intricate interplay between drugs, targets, and biological networks [14]. AI algorithms, particularly machine learning and deep learning methods excel at the prediction of protein structure, facilitating the identification of potential therapeutic interventions [15].

In this research, we used bioinformatics and network pharmacology methods to find out the important genes and pathways that are targeted by resveratrol for treating RA. Additionally, we carried out molecular dynamics validation using AlphaFold and molecular docking techniques.

2. Materials and methods

2.1. Gene expression data collection and preprocessing

The gene expression dataset for the whole blood sample of RA patients, GSE205962, was downloaded from the Gene Expression Omnibus (GEO) database (http://www.ncbi.nlm.nih.gov/geo). GSE205962 was based on the GPL16043 platform and consisted of four healthy samples and 16 RA samples. Differentially expressed genes (DEGs) were identified using the online analysis tool GEO2R (https://www.ncbi.nlm.nih.gov/geo/geo2r). Absolute log2 fold change (logFC) > 1 and a P value < 0.05 were set as the cutoff criteria. The ggplot package was used to draw the heatmap and volcano plot. The methods of DEG screening and gene functional enrichment analysis were based on a previous study [16].

2.2. Resveratrol pharmacophore target network construction

According to the structure of resveratrol, the possible target genes of resveratrol were predicted based on the PharmMapper database, the most widely used online database for drug target prediction [17]. The screening criteria were set as top 300 highest scores, and the species were limited only to *Homo sapiens*. The gene names were calibrated using the UniProt database. The resveratrol target network was constructed and visualized using Cytoscape software (v3.9.1).

The intersection of the target genes of resveratrol and the DEGs obtained from GSE205962 was considered a potential therapeutic genes (PT-genes) for the treatment of RA.

2.3. GO and KEGG analysis

Gene functional enrichment analysis, including the Cell Composition (CC), Biological Process (BP), Molecular Function (MF) and signaling pathway, were performed using the Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) Analysis. The DEGs, resveratrol target genes, and PT-genes were input into the BiNGo plug-in of Cycloscape (v3.9.1) for enrichment analysis in GO, respectively. The significance level was set $P < 0.05$, and the *Homo sapiens* species was selected. KEGG pathway analysis was performed using David's online tool. The visualization was done using the dplyr package and the ggplot 2 package.

2.4. Protein-Protein interaction network analysis of PT-genes

The Protein-Protein Interaction (PPI) network of PT-genes was constructed using Multiple protein module of the online database resource Search Tool for the Retrieval of Interacting Genes (STRING) (https://string-db.org). A combined score >0.4 was considered statistically significant. The PPI network of the results was depicted using Cytoscape 3.9.1 software. The top 10 hub genes were determined using the cytoHubba plug-in based on the Maximal Clique Centrality (MCC) algorithms. And the key modules (scores >4) were identified using the MCODE plug-in. The intersection of the top 10 hub genes calculated by cytoHubba and the genes of key modules obtained from the MCODE was considered a key therapeutic gene (KT-genes) for the treatment of RA.

2.5. Protein structure prediction using AlphaFold

AlphaFold is an AI system developed by DeepMind that predicts a protein's 3D structure from its amino acid sequence [18]. It regularly achieves accuracy competitive with experimentation. The protein codes of the human species corresponding to the KT-genes were downloaded from the UniProt database. The online structure prediction in AlphaFold was used to predict the structure of proteins corresponding to the protein codes. And a PDB format file of the corresponding protein structure was output.

2.6. Molecular docking

The mol2 structure file of resveratrol was input into AutoDockTools (v1.5.7), set as ligands, and saved in pdbqt format. The proteins corresponding to the KT-genes were input into AutoDockTools in PDB format and output in pdbqt format after dehydration and hydrogenation pretreatment. The docking box is set to encompass the entire protein structure. Finally, AutoDockvina was used for molecular docking verification to output the binding results of protein and resveratrol, and the minimum free energy was selected for visualization [19].

2.7. Statistical analysis

R (4.1.0) was used for bioinformatics analysis, and the R package was used for statistical analysis [16]. GEO2R uses the moderated t-statistic for comparing 2 groups of Samples in GSE205962. Enrichment of GO terms in differentially gene sets was assessed based on Fisher's exact test statistic. $P < 0.05$ was considered statistically significant.

3. Results

3.1. Identification of DEGs in RA

A total of 14636 genes were detected in the GSE205962 dataset, and 2202 DEGs were identified using the GEO2R. A volcano plot displays the expression level of all genes (Fig. 1A). DEGs, including 44 downregulated genes and 2158 upregulated genes, were

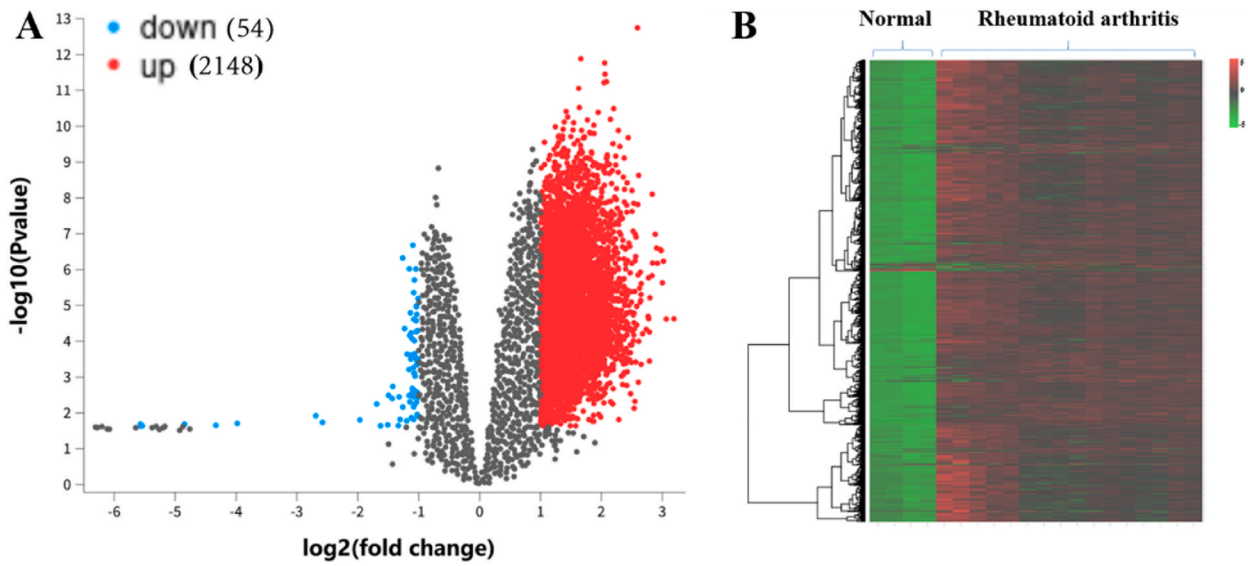

Fig. 1. Expression profile of the GSE205962 dataset. (A) Volcano map of detected genes. Each dot represents a gene. Blue dots represent downregulated genes, and red dots represent upregulated genes. The screening criteria for significant genes were $|\log2FC| > 1$ and $P < 0.05$. (B) Heatmap display of the clustering of the differentially expressed genes (DEGs). Green represents low expression, red represents high expression.

selected for heat map display based on their corresponding log2FC values (Fig. 1B).

3.2. Construction of the resveratrol pharmacophore target network

To create a target network map of resveratrol, pharmacophore target genes were predicted by the PharmMapper database, and 215 target genes for resveratrol were successfully annotated by the UniProt annotation database. The annotated genes were imported into Cytoscape software to construct the pharmacophore network of resveratrol and target genes (Fig. 2A). A total of 47 PT-genes were obtained using the intersection of the target genes of resveratrol and the DEGs in RA (Fig. 2B).

3.3. GO analysis

GO analysis shows that the three groups of genes, the DEGs, the resveratrol target genes, and the PT-genes, have similar results for the top-five gene functional enrichment (Fig. 3). The CC of these genes was mainly enriched in the intracellular, cytoplasm, and organelle. In the BP category, cellular process, metabolic process and biological regulation were co-enriched terms among the three groups. At the level of the MF aspect, catalytic activity and protein binding were significantly co-enriched. On the whole, the proportion of co-enriched terms of the DEGs and the resveratrol target genes was 8 %, 7 %, and 8 % in CC, BP, MF, respectively (Fig. 4).

3.4. KEGG analysis

The DEGs mainly participate in pathways of amyotrophic lateral sclerosis, pathways of neurodegeneration, pathways in cancer, Alzheimer disease (Fig. 5A). The top 5 KEGG enrichments of resveratrol target genes were metabolic pathways, pathways in cancer, PI3K-Akt signaling pathway, chemical carcinogenesis, lipid, and atherosclerosis (Fig. 5B). PT-genes are closely related to the pathways of metabolic pathways, pathways in cancer, proteoglycans in cancer, insulin signaling pathway, chemokine signaling pathway (Fig. 5C). Significantly, the common pathway enriched by KEGG for the DEGs, and the resveratrol target genes was up to 36 % (Fig. 5D).

3.5. Construction of PPI network and identification of KT-genes

The PPI network of PT-genes is shown in Fig. 6. There are 149 edges and 41 nodes in the network diagram. A total of two key modules with 17 key genes in the PPI network were identified using the MCODE plug-in (Fig. 7A). And the top 10 network key genes were obtained using the cytoHubba plug-in based on the MCC algorithms (Fig. 7B and C). The key genes determined by these methods were intersected to obtain nine KT-genes. The 9 KT-genes were ABL1, ANXA5, CASP3, HSP90AA1, LCK, MAP2K1, MAPK1, PIK3R1,

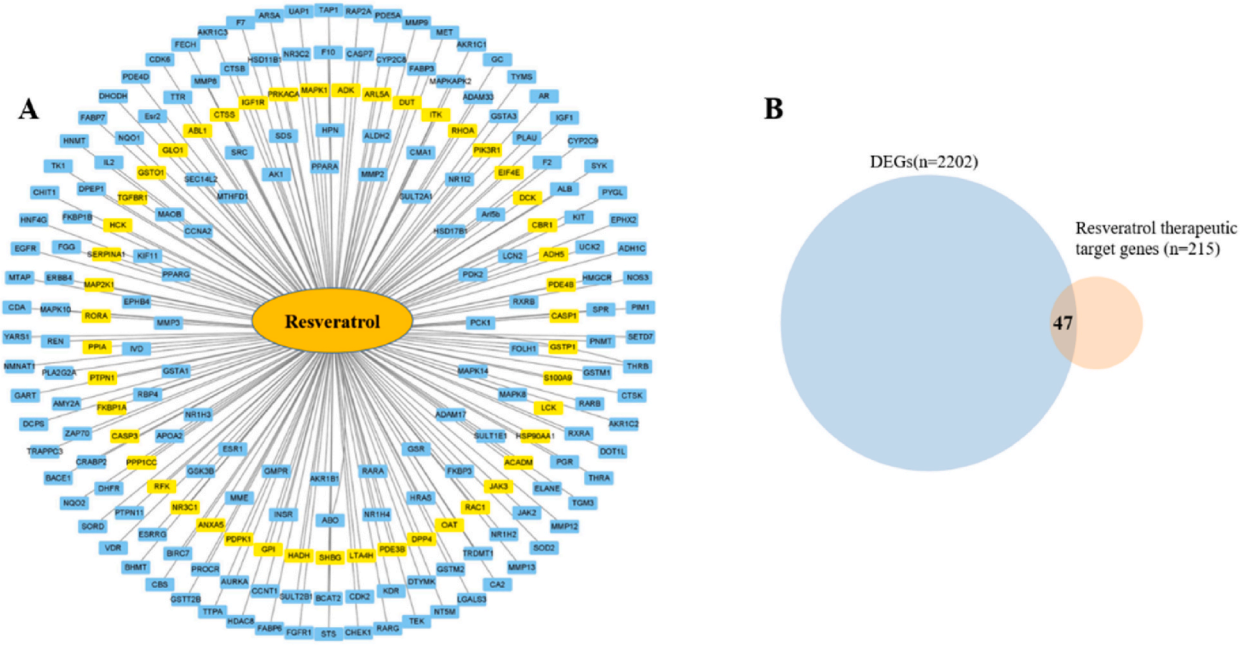

Fig. 2. Pharmacophore target network of resveratrol. (A) Drug-target network. Resveratrol is located at the center of the network. Target genes are located around the drug core. Potential therapeutic genes (PT-genes) for the treatment of rheumatoid arthritis are marked yellow. (B) The intersection of the target genes of resveratrol and the DEGs obtained from GSE205962 was considered a PT-genes.

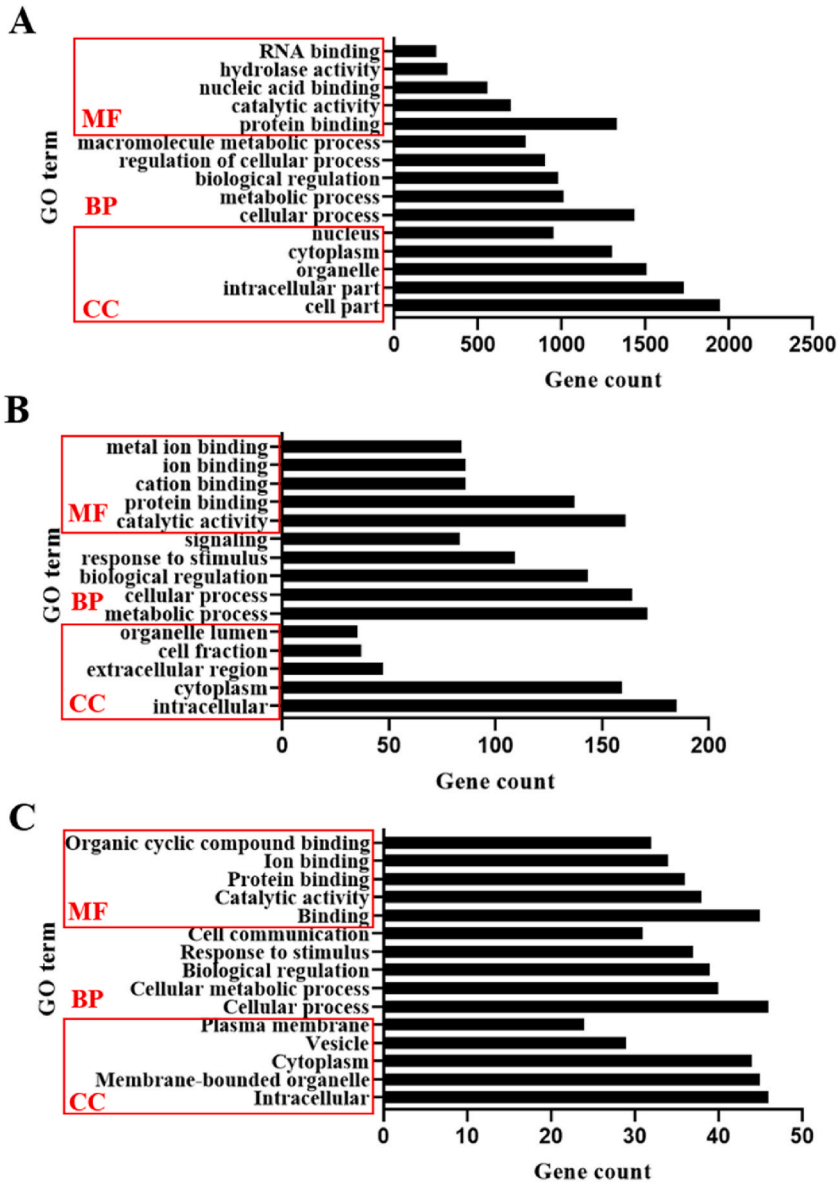

Fig. 3. The top 5 cellular component (CC), biological process (BP), and molecular function (MF), enriched by RA-related differentially expressed genes (DEGs) (A), resveratrol target genes (B), and potential therapeutic genes (PT-genes) (C).

and RAC1 (Fig. 7D).

3.6. AlphaFold prediction of the protein structure of resveratrol therapeutic targets

Human protein numbers for KT-genes, including P00519-ABL1, P08758-ANXA5, P42574-CASP3, P07900-HSP90AA1, P06239-LCK, Q02750-MAP2K1, P28482-MAPK1, P27986-PIK3R1, and P63000-RAC1, were found in the Uniprot online database. AlphaFold was successfully used to predict their protein structures (Fig. 8).

3.7. Molecular docking validation of resveratrol and therapeutic targets

All of the proteins corresponding to KT-genes were successfully validated by molecular docking (Table 1). The lowest free energy of ABL1, ANXA5, CASP3, HSP90AA1, LCK, MAP2K1, MAPK1, PIK3R1, and RAC1, were −8.4, −7.4, −6.4, −6.7, −8.0, −7.9, −7.4, −6.7, and −7.9, respectively. Notably, resveratrol also formed hydrogen bonds with the proteins of LCK, MAPK1, PIK3R1, and RAC1. Molecular docking with the lowest free energy was selected for a separate presentation (Fig. 9).

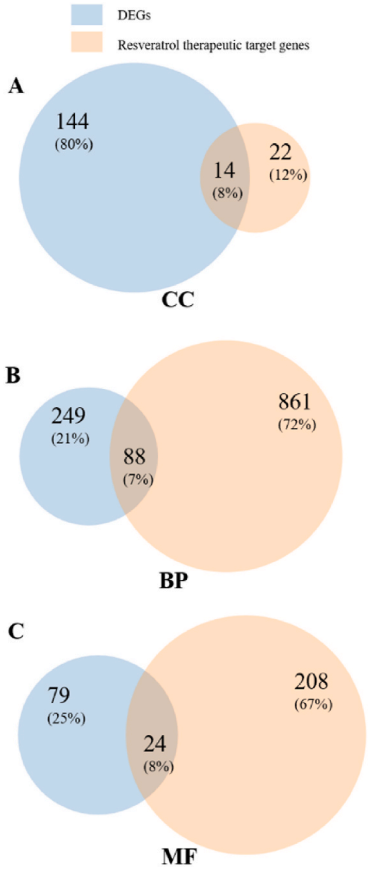

Fig. 4. Venn diagram of the Gene Ontology (GO) terms for differentially expressed genes (DEGs) and resveratrol target genes. (A) Cellular component (CC). (B) Biological process (BP). (C) Molecular function (MF).

4. Discussion

Although clinical remission or low disease activity is the therapeutic goal for RA, many patients do not reach this target or achieve it but remain dependent on medication with serious complications, implying that new therapies are still required. Resveratrol has demonstrated utility with no serious adverse effects either alone or as an adjuvant in some clinical trials [20,21] and is a tremendous potential drug for RA. However, the mechanism of resveratrol in treating RA is not fully understood. Previous studies on the treatment of RA with resveratrol have mostly been limited to the effects of single mechanisms such as cytokines, inflammation, and oxidative stress [22]. This study is the first to comprehensively analyze the key targets and signaling pathways of resveratrol in RA treatment by combining the overall gene expression characteristics of RA and the pharmacophore target network of resveratrol.

In this study, both the similar results for the top-five gene functional enrichment and the considerable number of PT-genes indicate the close and complicated relationship between resveratrol and RA. KEGG analysis results revealed PT-genes are closely related to the pathways of metabolic pathways, pathways in cancer, proteoglycans in cancer, insulin signaling pathway, chemokine signaling pathway.

The first three are the general categories of signal pathways, including various specific signal pathways, such as carbohydrate/energy/lipid/amino acid/glycan metabolism, ERK/PI3K/WNT/NOTCH/TGFB/JAK-STAT/HIF-1/apoptosis signaling. Although there is still a lack of research on the regulation of RA metabolism by resveratrol, some signaling including apoptosis [23], TGFB [24], HIF-1 [25], PI3K [26], JAK-STAT [27], WNT [28] and ERK signaling [29], have been confirmed to be involved in the treatment of RA with resveratrol. The insulin signaling pathway is involved in regulating various physiological processes, such as metabolism, autophagy, protein synthesis, and cell growth. Lorna Gallagher et al. found insulin resistance is significantly associated with BMI and synovitis in RA in a cohort study [30]. Another research showed resveratrol partially ameliorates diabetes-associated dysregulation in GK rats [31]. It's possible that resveratrol may have a better effect on RA patients with metabolic disorders. Blocking chemokine receptors has led to inhibition of inflammatory Th1cells resulting in decreased synovitis. Chemokine included CCL2/3/19 was reported to be a convenient marker for RA treatment [32]. The anti-inflammatory effect of resveratrol may be an important cornerstone for its treatment of RA. In vivo experiments, resveratrol significantly reduces the serum levels of IL-1β, C reactive protein, and prostaglandin E2 in antigen-induced arthritis model [33].

A total of 9 KT-genes, including ABL1, ANXA5, CASP3, HSP90AA1, LCK, MAP2K1, MAPK1, PIK3R1, and RAC1, were identified. In

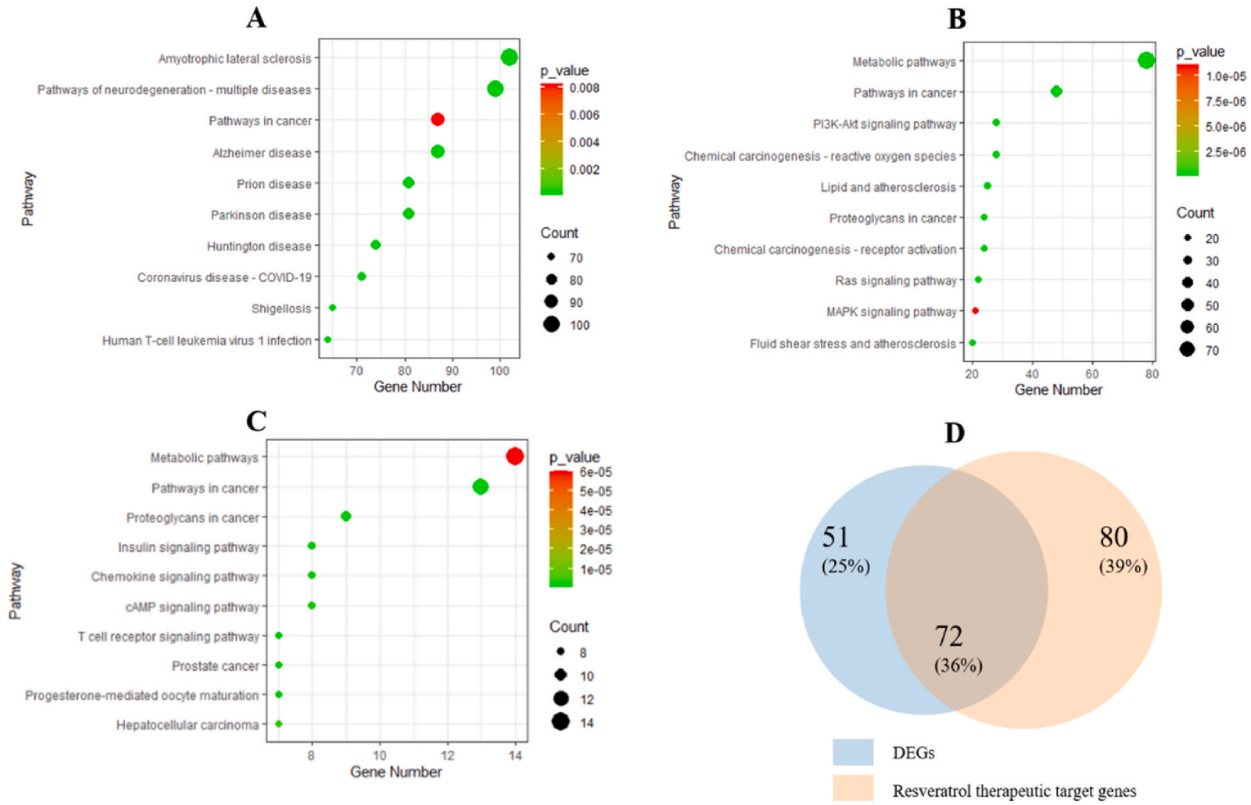

Fig. 5. Top 10 Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment maps of RA-related differentially expressed genes (DEGs) (A), the resveratrol target genes (B), and the potential therapeutic genes (PT-genes) (C). Venn diagram of the KEGG pathway of DEGs and the resveratrol target genes (D).

addition, the lowest free energy of KT-genes showed resveratrol could combine with the proteins corresponding to KT-genes in excellent bonding stability. All of these genes were significantly upregulated. The proteins encoded by these genes are involved in cell proliferation, differentiation, apoptosis, inflammation, and even insulin metabolism, which may play a crucial role in the treatment of RA with resveratrol.

ABL1 and LCK are members of the Src family of protein tyrosine kinases (PTKs) involved in a variety of cellular processes, including cell division, adhesion, differentiation, and response to stress. ABL1 plays an important role in various cancers, while its roles remain unclear in RA. In vivo data demonstrated that the inhibition of ABL1 suppressed the inflammatory cytokines and ameliorated the lung injury score of pneumonia mice [34], which indicating the potential for inflammatory regulation of ABL1. LCK has a pivotal role in T-cell signaling, and its expression is restricted to lymphoid cells. Accumulated activated T cells are related to the synovitis and bony erosions in RA [35], an LCK-selective inhibitor would be expected to have a significantly improved safety profile for the treatment of RA [36]. Study has confirmed that LCK had remarkably higher expression in synovial tissue of RA patients [37]. Previous bioinformatics analyses have also shown that LCK might be a potential hub gene for RA [38].

ANXA5 belongs to the annexin family of calcium-dependent phospholipid-binding proteins and has potential roles in cell signaling, inflammation, growth, and differentiation. Previous studies suggested that ANXA5 upregulation alters the proliferation, morphology, and rough endoplasmic reticulum of murine hepatocarcinoma cells, and enhances in vitro migration and invasions [39]. The relationship between RA and the upregulated ANXA5 in RA blood samples needs further research.

CASP3 plays a central role in the execution phase of cell apoptosis. The unbalanced regulation of apoptosis leads to abnormal expansion or excessive apoptosis of synovial cells contributing to the pathogenesis of RA. A variety of NSAIDs, such as oxaprozin, indomethacin, diclofenac, and zaltoprofen, can inhibit the proliferation of synovial cells and induce apoptosis [40]. Experimental study have shown that sinomenine can inhibit osteoclast survival in vitro through caspase-3-mediated apoptosis in treating rheumatoid arthritis [41]. In vitro research showed that resveratrol induced apoptosis of human rheumatoid arthritis synovial cells by activating caspase 3 [42].

HSP90AA1 is an inducible molecular chaperone that functions as a homodimer. Bin Yang et al. found that geldanamycin, an HSP90 inhibitor, dose-dependently inhibited TNF-α-induced rheumatoid arthritis fibroblast-like synoviocytes (RAFLS) proliferation, and promoted RAFLS apoptosis [43]. Another research evaluated the anti-inflammation ability of a novel small molecule inhibitor of HSP90 and suggested it could potently inhibit cytokine production in vitro and correct the scores for inflammation in vivo [44]. In addition, supplemental resveratrol reduces oxidative stress in heat-stressed, black-boned chickens by modulating the expression of

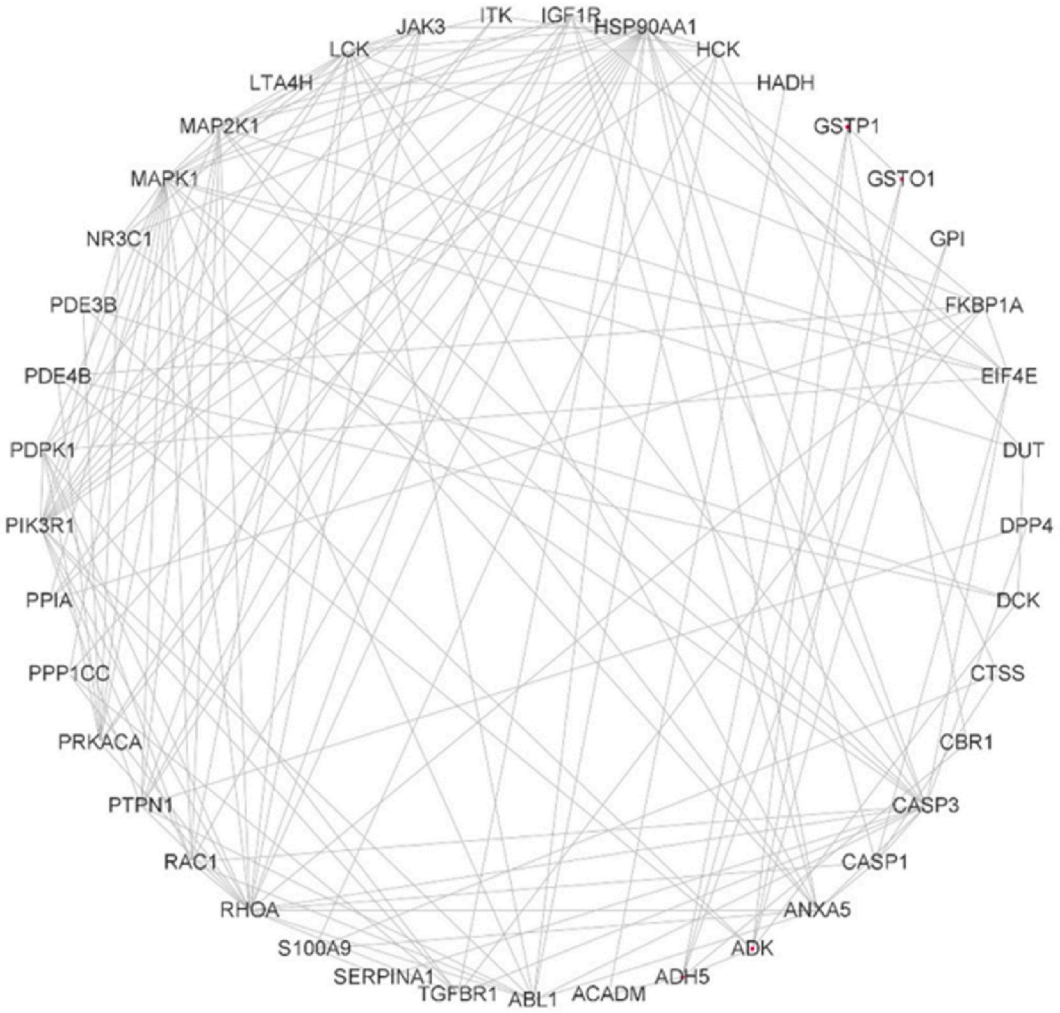

Fig. 6. The Protein-Protein Interaction network (line) of potential therapeutic genes (dots) for the treatment of rheumatoid arthritis.

heat-shock genes. Guo et al. demonstrate that Guizhi-Shaoyao-Zhimu decoction upregulates HSP90AA1 to reduce synovial inflammation and prevent cartilage destruction during RA progression in vivo and in vitro experiment [45].

MAPK1 encodes a member of the mitogen-activated protein (MAP) kinase, also known as extracellular signal-regulated kinases (ERKs) and acts as an integration point for multiple biochemical signals. MAP2K1 acts as a MAP kinase. MAPK inhibitors are considered as promising potential agents in treatment of RA [46]. Previous research demonstrated intervention of herbal active monomers including apigenin and diosgenin can significantly induce the apoptosis of RA-FLS by regulating ERKs and MAPK pathways [47]. Significantly, Guliang Yang et al. explored the effect of resveratrol on the rat arthritis model and in vitro RA model and found that resveratrol inhibits MAPK signaling pathways, to suppress the inflammatory response and cell proliferation and provokes cell apoptosis in the synovial tissue [11].

Phosphoinositide 3-kinase regulatory subunit 1 (PIK3R1) plays a crucial role in insulin metabolism [48]. The protein encoded by RAC1 is a GTPase, involved in the control of cell growth, cytoskeletal reorganization, and the activation of protein kinases. RAC1 inhibitory peptide showed the effect of reducing paw swelling and antibody production in mice with collagen-induced arthritis [49]. Additionally, another RAC1 inhibitor revealed a similar effect in mice models of RA through its regulation of platelet microparticle formation [50].

Resveratrol is likely to participate in regulating the occurrence and development of RA through the products encoded by these KT-genes. Currently, only PIK3R1, MAPK1, HSP90AA1, and RAC1 have been reported to be involved in the pathogenesis of RA, the specific effects of other KT-genes in the treatment of RA with resveratrol still need further experimental exploration.

The limitations of this study should be acknowledged. Firstly, the gene expression data was derived from the blood samples of RA patients. Low gene expression concentration in blood samples often results in false negative results, which means that the results cannot directly reflect the characteristics of joint lesions in RA. Besides, the intricate network of interactions between resveratrol and RA may not be fully captured by in silico models due to the reliance on computational predictions and the inherent complexity of the

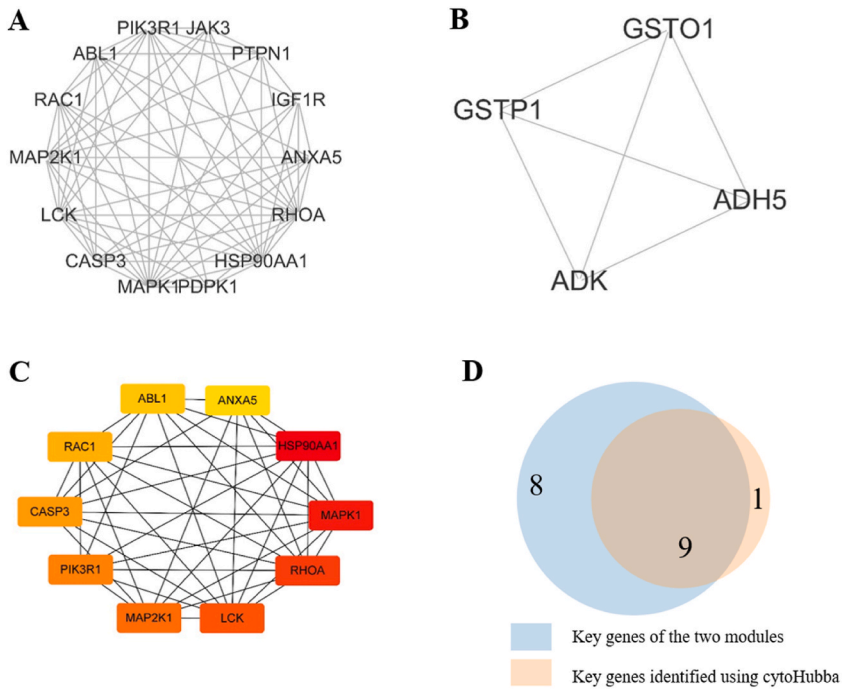

Fig. 7. Key therapeutic genes (KT-genes) screening. (A, B) The key modules (scores >4) of the Protein-Protein interaction networks of PT-genes. (C) The top 10 key genes calculated by cytoHubba. (D) The Venn diagram of the top 10 hub genes calculated by cytoHubba and the genes of key modules.

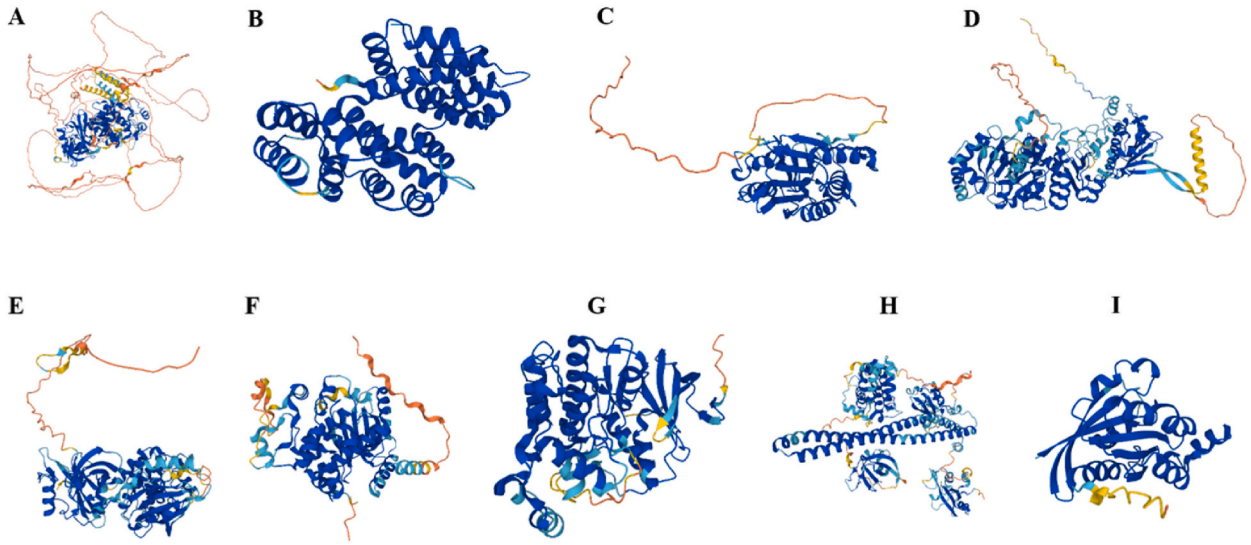

Fig. 8. Protein structures of the key therapeutic genes (KT-genes) predicted by the artificial intelligence AlphaFold. (A) Predicted protein structure of ABL1. (B) Predicted protein structure of ANXA5. (C) Predicted protein structure of CASP3. (D) Predicted protein structure of HSP90AA1. (E) Predicted protein structure of LCK. (F) Predicted protein structure of MAP2K1. (G) Predicted protein structure of MAPK1. (H) Predicted protein structure of PIK3R1. (I) Predicted protein structure of RAC1.

RA pathogenesis. And AlphaFold cannot guarantee that all predicted structures of protein are correct. Last but not least, the validation of molecular docking experiments is not sufficient. Further validation of the specific effects of these key drug targets in in vitro and in vivo experiments is still needed in the future.

Table 1
Binding energy values of resveratrol to therapeutic targets.

Target	Drug	Binding energy (kcal/mol)	Hydrogen bonds
ABL1	Resveratrol	−8.4	0
ANXA5	Resveratrol	−7.4	0
CASP3	Resveratrol	−6.4	0
HSP90AA1	Resveratrol	−6.7	0
LCK	Resveratrol	−8.0	1
MAP2K1	Resveratrol	−7.9	0
MAPK1	Resveratrol	−7.4	2
PIK3R1	Resveratrol	−6.7	1
RAC1	Resveratrol	−7.9	1

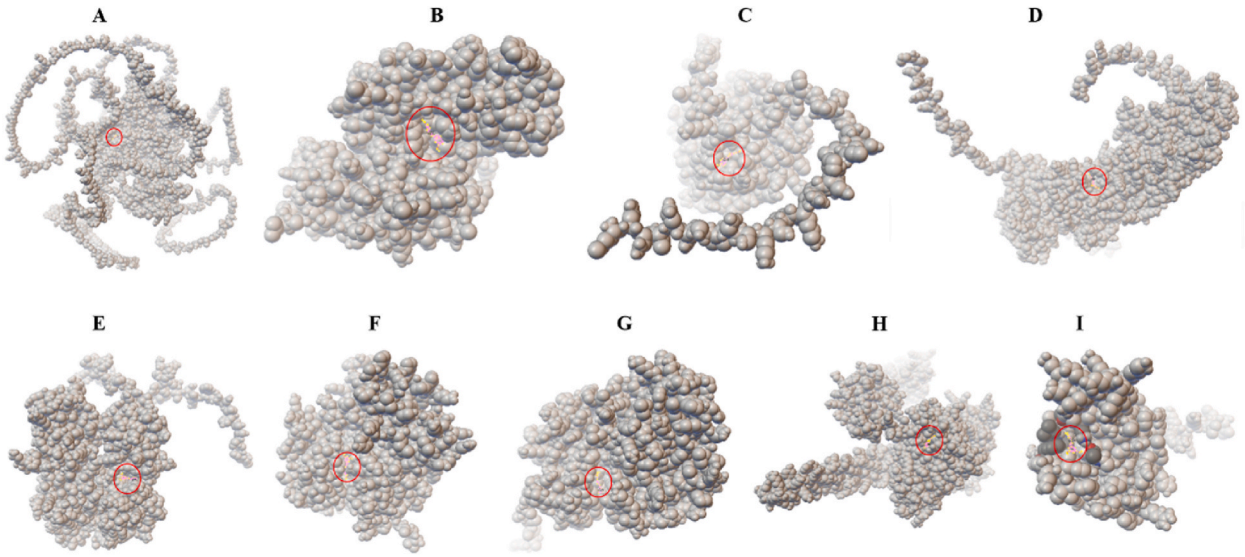

Fig. 9. Molecular docking of the small-molecule ligand resveratrol (red circle) to the protein receptor of the key therapeutic genes (KT-genes). (A) Molecular docking display diagram of ABL1. (B) Molecular docking display diagram of ANXA5. (C) Molecular docking display diagram of CASP3. (D) Molecular docking display diagram of HSP90AA1. (E) Molecular docking display diagram of LCK. (F) Molecular docking display diagram of MAP2K1. (G) Molecular docking display diagram of MAPK1. (H) Molecular docking display diagram of PIK3R1. (I) Molecular docking display diagram of RAC1.

5. Conclusion

In this study, gene functional enrichment and signaling pathways of both resveratrol targets and DEGs in RA were comprehensively described. And 9 KT-genes, ABL1, ANXA5, CASP3, HSP90AA1, LCK, MAP2K1, MAPK1, PIK3R1, and RAC1, were identified and validated as the most potential therapeutic targets in the treatment of RA with resveratrol. These results provide new direction for the interaction mechanisms of resveratrol in RA treatment, which may improve the efficiency of drug development.

Ethics approval and consent to participate

Not applicable.

Consent to publish

All the authors read the final manuscript and approved for publication.

Availability of data and materials

The public datasets analyzed in this study can be found in the online GEO database.

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CRediT authorship contribution statement

Piaoqi Zeng and Haohan Huang contributed equally to this work. Dongsheng Li: Writing – review & editing, Visualization, Validation, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

Not applicable.

Abbreviations

RA	Rheumatoid arthritis
GEO	Gene Expression Omnibus
DEGs	Differentially expressed genes
GO	Gene Ontology
KEGG	Kyoto Encyclopedia of Genes and Genomes
PT-genes	potential therapeutic genes
PPI	Protein-Protein Interaction
KT-genes	key therapeutic genes
MCC	Maximal Clique Centrality
CC	Cell Composition
BP	Biological Process
MF	Molecular Function

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