Exploration of the Molecular Mechanisms of *Codonopsis pilosula* in Treating Immune Deficiency Based on Network Pharmacology, Bioinformatics, and Molecular Docking

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Abstract [**Objectives**] To investigate the potential molecular mechanisms of *Codonopsis pilosula* in the treatment of immune deficiency using network pharmacology, bioinformatics analysis, and molecular docking. [**Methods**] Active compounds of *C. pilosula* were retrieved from the TCMSP database using oral bioavailability (*OB*) ≥30% and drug-likeness (*DL*) ≥0.18 as screening criteria, followed by further optimization using SwissADME. Potential targets of the active compounds were predicted using the Prediction. charite and GeneCards databases. A protein-protein interaction (PPI) network was constructed using the STRING database and visualized with Cytoscape to identify core targets. Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses were performed using the DAVID database. Molecular docking between key active compounds and core target proteins was carried out using SwissDock, and the docking results were visualized with PyMOL. [**Results**] A total of 21 active compounds were initially identified from the TCMSP database. After pharmacokinetic evaluation, four potential bioactive compounds were screened, namely Perlolyrine (MOL002140), 7-methoxy-2-methyl isoflavone (MOL003896), Frutinone A (MOL005321), and Glycitein (MOL008400). Due to database availability and target prediction feasibility, only two compounds (7-methoxy-2-methyl isoflavone and Glycitein) were included in subsequent analyses. Therefore, the results of this study primarily reflect the potential mechanisms of these two isoflavone components. Venn analysis identified 63 overlapping targets. PPI network analysis revealed 14 core targets. GO and KEGG enrichment analyses indicated that these targets were mainly involved in inflammation-related processes, amino acid metabolism, and immune defense. Molecular docking showed that except for the Glycitein-HSP90AA1 pair (−2.253 kcal/mol), which exhibited no significant binding activity, most ligand-target pairs had binding energies lower than −5 kcal/mol. [**Conclusions**] This study computationally predicts that 7-methoxy-2-methyl isoflavone and Glycitein from *C. pilosula* may exert therapeutic effects on immune deficiency through a multi-target and multi-pathway mode of action. These findings provide a theoretical basis for further experimental validation and clinical application of *C. pilosula* in the prevention and treatment of immune deficiency.

Key words Network pharmacology, Bioinformatics, Molecular docking, *Codonopsis pilosula*, Immune deficiency

1 Introduction

Immune deficiency is a pathological condition characterized by impaired immune function, leading to increased susceptibility to infections, tumors, and other diseases[1]. It may arise from congenital defects, chronic diseases, aging, or external factors such as stress and malnutrition. With population aging and the increasing prevalence of chronic diseases, the incidence of immune dysfunction continues to rise, posing a significant burden on public health. Current therapeutic strategies for immune deficiency mainly include immunomodulatory drugs, nutritional support, and symptomatic treatment. However, these approaches often show limited efficacy and may be associated with adverse effects. Therefore, it is of great significance to explore novel therapeutic strategies with multi-target and multi-pathway characteristics.

Codonopsis pilosula is a traditional Chinese medicinal herb with a sweet taste and neutral nature, entering the spleen and lung meridians. According to *Compendium of Materia Medica*, it has the functions of tonifying the middle energizer, replenishing qi, nourishing blood, and promoting fluid production. It is widely used in classical prescriptions, such as Shengmai decoction and Shenmai injection, for conditions including qi-yin deficiency, chest obstruction, and palpitations. As a medicinal and edible plant, *C. pilosula* contains abundant bioactive components, including polysaccharides, saponins, alkaloids, flavonoids, and other compounds[2-4]. Modern pharmacological studies have demonstrated that its active constituents, such as polysaccharides, volatile oils, and flavonoids, can inhibit the generation of reactive oxygen species, attenuate inflammatory responses, stabilize mitochondrial function, and optimize myocardial energy metabolism[5]. In addition, it plays important roles in neuroprotection, anti-aging, antioxidation, and antitumor activities[6]. Previous studies have shown that *C. pilosula* can upregulate Bcl-2, downregulate Bax/Caspase-3, and activate the AMPK-AKT signaling pathway to maintain myocardial energy metabolism. It can also improve neuronal function and reduce neurodegeneration, thereby slowing the progression of Alzheimer's disease (AD)[7]. Furthermore, it has been reported to enhance cerebral blood circulation, reduce ischemic injury, and alleviate chronic cerebral ischemia[8]. Moreover, *C. pilosula* can regulate immune function in sepsis[9], rheumatoid arthritis[10], allergic asthma[11], and other immune-related diseases[12], thereby reducing inflammatory responses and controlling disease progression.

However, due to its multi-component, multi-target, and

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multi-pathway characteristics, the pharmacological mechanisms of *C. pilosula* are difficult to fully elucidate using traditional single-factor experimental approaches. Network pharmacology, which systematically analyzes the interactions among herbs, components, targets, and signaling pathways, has emerged as a novel paradigm for modern TCM research[13]. This approach integrates databases and tools such as TCMSP, SwissTargetPrediction, STRING, and Cytoscape to screen active compounds, predict potential targets, construct protein-protein interaction (PPI) networks, and perform GO and KEGG enrichment analyses, thereby enabling efficient identification of core pathways prior to experimental validation. Bioinformatics, an interdisciplinary field combining biology, mathematics, and computer science, focuses on the acquisition, organization, and analysis of large-scale biological data, particularly the structural and functional characteristics of biomolecules and genomic and proteomic information[14-15]. Molecular docking is a computational simulation method used to evaluate the binding interactions between active compounds and target proteins. By exploring the spatial complementarity between ligands and receptors, it predicts binding modes and affinities. This technique enables high-throughput screening of candidate compounds and identification of key amino acid residues, and is widely applied in drug discovery and protein function annotation[16].

In this study, a systematic network of active components, potential target genes, and signaling pathways of *C. pilosula* was constructed based on network pharmacology. Molecular docking was further employed to validate the interactions between active compounds and core target proteins. By integrating network pharmacology predictions with molecular docking verification, this study aims to elucidate the molecular mechanisms of *C. pilosula* in the treatment of immune deficiency.

2 Materials and methods

2.1 Screening of active components The active components and corresponding targets of *C. pilosula* were retrieved from the Traditional Chinese Medicine Systems Pharmacology Database (TCMSP)[17]. Screening criteria were set as oral bioavailability (OB) ≥30%[18] and drug-likeness (DL) ≥0.18[19].

2.2 Further screening of bioactive compounds The SMILES structures of the selected compounds were obtained from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/)[20]. If unavailable in PubChem, the compound structures were downloaded from the TCMSP database and converted into SMILES format using NovoPro (https://www.novopro.cn/tools/mol2smiles.html). Although preliminary screening had been performed based on OB and DL values, further evaluation of pharmacokinetic properties was conducted using SwissADME (http://www.swissadme.ch/). Compounds with high gastrointestinal absorption (GI absorption = "High") and at least two "Yes" parameters in drug-likeness were retained as effective bioactive components[21].

2.3 Prediction of targets for active compounds The SMILES of the screened active compounds were imported into the Prediction. charite database (https://prediction.charite.de/)[22], with the species limited to Homo sapiens. Potential targets of each compound were obtained, and duplicate targets were removed to generate a comprehensive target set. Of the four compounds identified after TCMSP and SwissADME screening, Perlolyrine and Frutinone A did not yield valid target prediction results (Probability = 0) in this database. Despite attempts with alternative databases (*e.g.*, SwissTargetPrediction), no reliable targets could be obtained due to structural specificity or database coverage limitations. Therefore, subsequent analyses were performed only on 7-methoxy-2-methyl isoflavone and Glycitein.

2.4 Identification of common targets between active compounds and disease Disease-related targets were collected from the GeneCards database using "immune deficiency" as the keyword[23]. The intersection between disease targets and compound-related targets was identified using an online Venn analysis tool, and a Venn diagram was generated to visualize the overlapping targets[24].

2.5 Enrichment analysis of common targets To further investigate the biological functions and signaling pathways associated with the common targets, Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses were performed using the DAVID database (https://david.ncifcrf.gov/)[25]. The screening criteria were set as $P < 0.05$ and $q < 0.05$[26]. The results were visualized using the Bioinformatics platform (https://www.bioinformatics.com.cn/), and an integrated network of drug-target-GO function-KEGG pathway-disease was constructed.

2.6 Construction of PPI network and identification of core targets The intersecting targets were imported into the STRING database (https://cn.string-db.org/) to obtain protein-protein interaction (PPI) data[27]. The PPI network was visualized using Cytoscape software[28] Network topology analysis was performed using the CentiScaPe plugin in Cytoscape, and key targets were screened based on the parameters of degree, betweenness centrality, and closeness centrality[29].

2.7 Molecular docking validation Molecular docking was conducted using the SwissDock platform (https://www.swissdock.ch/) to evaluate the binding affinity between active compounds and core targets[30]. The MOL2 format files of ligands were obtained from the TCMSP database, while the three-dimensional structures of target proteins were downloaded from the Protein Data Bank (PDB) (https://www.rcsb.org/)[31]. Prior to docking, water molecules and endogenous ligands were removed from protein structures using PyMOL software[32]. Docking results were screened based on the lowest binding energy (≤ −5 kcal/mol), and the optimal docking conformations were visualized using PyMOL.

3 Results and analysis

3.1 Prediction of active components A total of 21 candidate active components of *C. pilosula* were identified from the TCMSP

database using the screening criteria of $OB \geqslant 30\%$ and $DL \geqslant 0.18$. After further pharmacokinetic evaluation, four potential bioactive compounds were ultimately selected (Table 1), namely, MOL002140 (Perlolyrine), MOL003896 (7-methoxy-2-methyl isoflavone), MOL005321 (Frutinone A), and MOL008400 (Glycitein).

Table 1 Potential active components of *Codonopsis pilosula*

No.	Compound ID	Compound Name	MW	*OB*//%	*DL*
1	MOL002140	Perlolyrine	264.30	65.95	0.27
2	MOL003896	7-Methoxy-2-methyl isoflavone	266.31	42.56	0.20
3	MOL005321	Frutinone A	264.24	65.90	0.34
4	MOL008400	glycitein	284.28	50.48	0.24

3.2 Identification of common targets To explore the mechanism of *C. pilosula* in treating immune deficiency, target prediction was performed for the screened bioactive compounds. Among the four compounds identified after TCMSP and SwissADME screening, Perlolyrine and Frutinone A could not be included in subsequent analyses because no valid target prediction data were available in the Prediction. charite database (all predictions had Probability = 0), and reliable targets could not be retrieved from alternative databases. As a result, only two compounds (7-methoxy-2-methyl isoflavone and Glycitein) were retained for target prediction. The targets of these two compounds were then predicted, and after excluding targets with Probability = 0, a total of 107 unique targets were obtained. Meanwhile, 10 560 disease-related targets for immune deficiency were retrieved from the GeneCards database, and the top 5 000 targets ranked by relevance score were selected for subsequent analysis. By intersecting the disease targets with the compound-related targets, a total of 63 common targets were identified (Fig. 1).

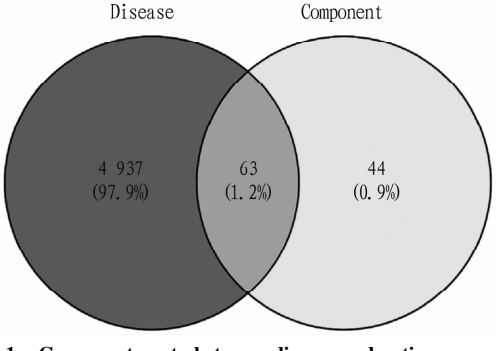

Fig. 1 Common targets between disease and active components of *Codonopsis pilosula*

3.3 Enrichment analysis of common targets To further investigate the biological functions and signaling pathways associated with these targets, GO and KEGG enrichment analyses were performed on the 63 intersecting targets. The GO enrichment results indicated that, in the biological process (BP) category, a total of 20 enriched terms were identified. The key targets were mainly involved in processes such as response to xenobiotic stimulus, inflammatory response, positive regulation of cell population proliferation, and response to amphetamine. In the cellular component (CC) category, eight enriched terms were identified, with targets mainly localized in the histone deacetylase complex, ficolin-1-rich granule lumen, nuclear speck, and cytosol. In the molecular function (MF) category, 22 enriched terms were obtained, primarily involving histone deacetylase activity (including H4K5, H4K8, H4K16, H3K14, H4K12, and H3K9), as well as protein lysine deacetylase activity.

Based on the *p*-value ranking ($P < 0.05$), the top 10 BP and MF terms, along with all CC terms (8 items), were selected to construct the GO bubble plot (Fig. 2).

KEGG pathway enrichment analysis identified 21 significantly enriched pathways. The results indicated that *C. pilosula* may exert therapeutic effects on immune deficiency by regulating pathways such as Alcoholism, Phenylalanine metabolism, Tyrosine metabolism, and Neutrophil extracellular trap formation (Fig. 3). In the bubble plots, the size of each circle represents the number of genes involved in the corresponding pathway, while the color intensity reflects the significance level (*p*-value). A smaller *p*-value corresponds to a deeper red color, indicating a higher degree of enrichment. Overall, these findings suggest that *C. pilosula* exerts therapeutic effects on immune deficiency through multiple biological functions and signaling pathways, particularly by regulating processes related to alcoholism, amino acid metabolism, and immune defense.

It should be noted that the KEGG pathway "Alcoholism" appeared as a significantly enriched term. This may be attributable to the high proportion of metabolic enzymes (*e. g.*, MAOA, MAOB, CYP2D6) among the target set and does not necessarily reflect core pathophysiological mechanisms of immune deficiency. Immune-relevant pathways are prioritized in the discussion.

3.4 Construction of PPI network and identification of core targets A total of 63 common targets of *C. pilosula* and immune deficiency were imported into the STRING database for further analysis to identify key targets. After removing isolated nodes, a PPI network was constructed (Fig. 4). Topological analysis of the network was performed using the CentiScaPe plugin in Cytoscape. Based on the threshold values of degree, betweenness centrality, and closeness centrality, 14 key targets associated with immune deficiency intervention were identified as core targets (highlighted in red). These targets included HSP90AA1, MCL1, ESR1, CYP2D6, PGR, XDH, TYR, MAOA, MAOB, IL2, PPARA, CDK4, PIK3CA, and CYP19A1.

3.5 Molecular docking analysis To further evaluate whether the active compounds of *C. pilosula* could bind to the core target proteins, molecular docking analysis was performed. The top five core targets ranked by degree value (PGR, PIK3CA, HSP90AA1, ESR1, and MCL1) were selected for docking validation with two key active compounds, 7-methoxy-2-methyl isoflavone (MOL003896) and glycitein. The specific docking combinations are presented in Table 2.

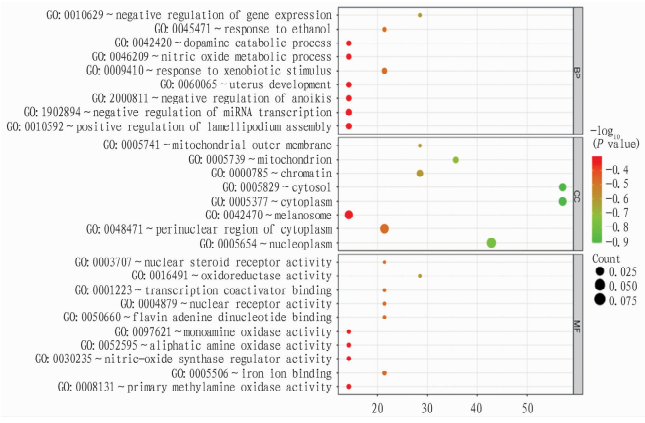

Fig. 2 GO enrichment bubble plot of intersecting targets

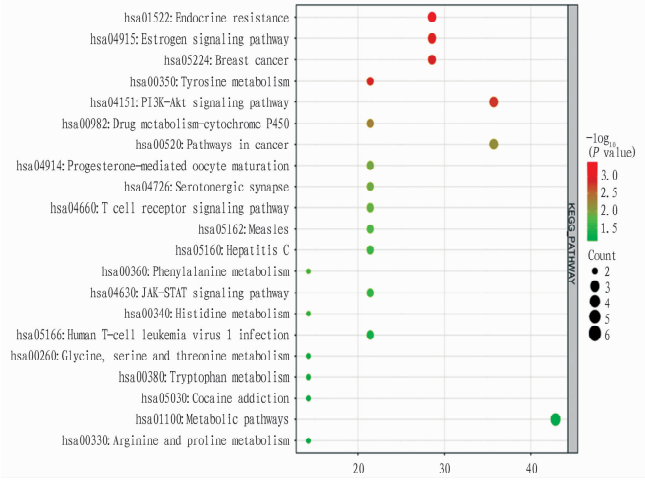

Fig. 3 KEGG pathway enrichment bubble plot of intersecting targets

The molecular docking results provided detailed binding modes and interaction sites between ligands and target proteins. The results showed that, except for the interaction between glycitein and HSP90AA1 (−2.253 kcal/mol), all other ligand-target pairs exhibited strong binding affinity (≤ −5 kcal/mol), suggesting generally stable interactions.

The docking conformations with the highest scores and binding energies below −5 kcal/mol were selected for visualization using PyMOL (Fig. 5). As shown in Fig. 5: In panel (a), the protein PGR formed hydrogen bonds with 7-methoxy-2-methyl isoflavone (MOL003896) at GLY-186 and ALA-184, with bond lengths of 2.3 Å and 3.5 Å, respectively, suggesting a stable hydrogen bond network at the active site that may enhance binding

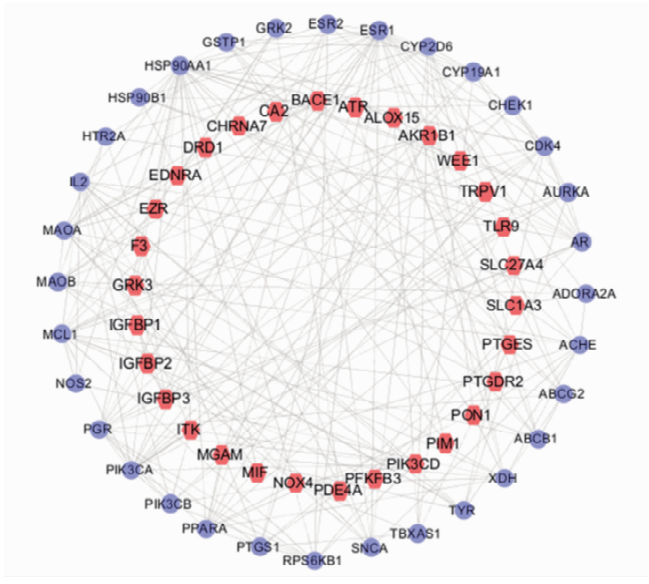

Fig. 4 PPI network of intersecting targets

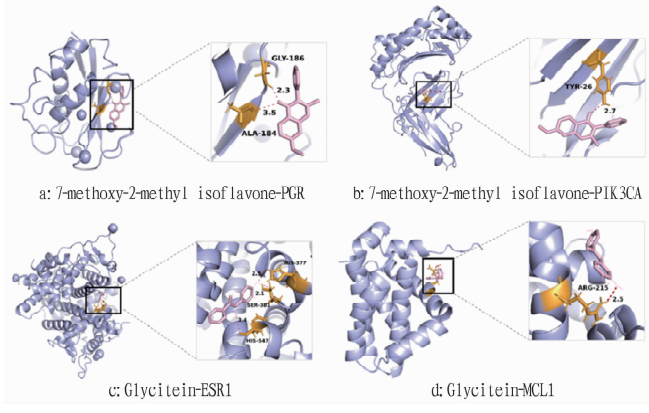

Fig. 5 Molecular docking results of ligand-receptor interactions

specificity. In panel (b), PIK3CA formed a hydrogen bond with the ligand at the TYR-26 residue (2.7 Å), indicating a close interaction and highlighting the anchoring role of aromatic amino acids in ligand binding. In panel (c), ESR1 formed multiple hydrogen bonds with the ligand at HIS-377, SER-381, and HIS-547, with bond lengths ranging from 2.1 to 2.7 Å, suggesting strong affinity within the catalytic core region and potential regulatory effects on protein function. In panel (d), MCL1 formed a hydrogen bond with the ligand at ARG-215 (2.5 Å), indicating that positively charged amino acid residues may enhance ligand binding stability through electrostatic interactions.

Table 2 Molecular docking results of key targets

No.	Compound	Target	Protein ID	Binding affinity//kcal/mol	Binding Activity
1	7-methoxy-2-methyl isoflavone	PGR	7OVY	−7.077	Strong
2	7-methoxy-2-methyl isoflavone	PIK3CA	9ASF	−7.194	Strong
3	Glycitein	HSP90AA1	5J80	−2.253	No significant binding
4	Glycitein	ESR1	7NFB	−6.927	Moderate
5	Glycitein	MCL1	6UDV	−5.521	Moderate

Besides, stable hydrogen bonds and hydrophobic interactions were observed between ligands and multiple amino acid residues. The binding conformations were structurally reasonable with stable energy distributions, suggesting that the selected ligands possess high binding affinity and favorable target specificity. These findings provide a solid theoretical basis for subsequent molecular dynamics simulations and pharmacodynamic validation.

4 Conclusions

In this study, an integrated strategy combining network pharmacology, bioinformatics analysis, and molecular docking was employed to systematically explore the potential mechanisms of *C. pilosula* in the treatment of immune deficiency. Four potential bioactive compounds (Perlolyrine, 7-methoxy-2-methyl isoflavone, Frutinone A, and glycitein) were identified by compound screening. Among them, 7-methoxy-2-methyl isoflavone and glycitein were further subjected to target prediction, enrichment analysis, PPI network construction, and molecular docking based on database availability. The downstream analysis identified 14 core targets, including HSP90AA1, MCL1, ESR1, CYP2D6, PGR, XDH, TYR, MAOA, MAOB, IL2, PPARA, CDK4, PIK3CA, and CYP19A1, suggesting that *C. pilosula* may exert therapeutic effects against immune deficiency through multiple targets and pathways. However, because the downstream network analysis and docking validation were performed on only two representative compounds, and all findings were based on in silico prediction, further *in vitro* and *in vivo* experiments are still required to validate these results.

References

[1] RIVIÈRE JG, PALACÍN PS, BUTTE MJ. Proceedings from the inaugural artificial intelligence in primary immune deficiencies (AIPID) conference [J]. Journal of Allergy and Clinical Immunology, 2024, 153(3): 637 – 642.

[2] GAO W, GUO H, NIU M, *et al.* circPARD3 drives malignant progression and chemoresistance of laryngeal squamous cell carcinoma by inhibiting autophagy through the PRKCI-Akt-mTOR pathway [J]. Molecular Cancer, 2020, 19(1): 166.

[3] BAILLY C. Anticancer properties of lobetyolin, an essential component of Radix Codonopsis (Dangshen) [J]. Natural Products and Bioprospecting, 2021, 11(2): 143 – 153.

[4] LUAN F, JI Y, PENG L, *et al.* Extraction, purification, structural characteristics and biological properties of the polysaccharides from *Codonopsis pilosula*: A review[J]. Carbohydrate Polymers, 2021, 261: 117863.

[5] WANG JN, KAN CD, LEE LT, *et al.* Herbal extract from *Codonopsis pilosula* (Franch.) Nannf. enhances cardiogenic differentiation and improves the function of infarcted rat hearts[J]. Life, 2021, 11(5): 422.

[6] LAN XY, ZHOU L, LI X, *et al.* Research progress of *Codonopsis* Radix and prediction of its Q-markers[J]. Zhongguo Zhong Yao Za Zhi, 2023, 48(8): 2020 – 2040. (in Chinese)

[7] XIE Q, HU X, ZHAO X, *et al.* Effects and mechanism of extracts rich in phenylpropanoids-polyacetylenes and polysaccharides from Codonopsis Radix on improving scopolamine-induced memory impairment of mice [J]. Journal of Ethnopharmacology, 2024, 319(Pt 1): 117106.

[8] WANG J, LI Q, CHU S, *et al.* Impact of *Codonopsis* decoction on cerebral blood flow and cognitive function in rats with chronic cerebral ischemia[J]. Journal of Ethnopharmacology, 2024, 323: 117585.

[9] CHOI SH, KIM SY, KIM KM, *et al.* Fermented sprouts of *Codonopsis lanceolata* suppress LPS-induced inflammatory responses by inhibiting NF-kappaB signaling pathway in RAW 264.7 macrophages and CD1 mice [J]. Pharmaceutics, 2023, 15(7): 1793.

[10] WANG YJ, ZHONG XY, WANG XH, *et al.* Activity of *Codonopsis canescens* against rheumatoid arthritis based on TLRs/MAPKs/NF-kappaB signaling pathways and its mechanism[J]. Zhongguo Zhong Yao Za Zhi, 2022, 47(22): 6164 – 6174. (in Chinese)

[11] SEO YS, KIM HS, LEE AY, *et al.* *Codonopsis lanceolata* attenuates allergic lung inflammation by inhibiting Th2 cell activation and augmenting mitochondrial ROS dismutase (SOD2) expression [J]. Scientific Reports, 2019, 9(1): 2312.

[12] ZOU YF, ZHANG YY, FU YP, *et al.* A polysaccharide isolated from *Codonopsis pilosula* with immunomodulation effects both *in vitro* and *in vivo*[J]. Molecules, 2019, 24(20): 3632.

[13] HOPKINS AL. Network pharmacology: The next paradigm in drug discovery[J]. Nature Chemical Biology, 2008, 4(11): 682 – 690.

[14] WANG J, GUO L, WU JS, *et al.* Current status of bioinformatics research in the era of big data[J]. Journal of Nanjing University of Posts and Telecommunications (Natural Science Edition), 2017, 37(4): 62 – 67. (in Chinese)

[15] FOULKES AC, WATSON DS, GRIFFITHS C, *et al.* Research techniques made simple: Bioinformatics for genome-scale biology[J]. Journal of Investigative Dermatology, 2017, 137(9): e163 – e168.

[16] AGUIAR C, CAMPS I. Molecular docking in drug discovery: Techniques, applications, and advancements[J]. Current Medicinal Chemistry, 2024. https://doi.org/10.26434/chemrxiv-2024-gmhtx.

[17] RU J, LI P, WANG J, *et al.* TCMSP: A database of systems pharmacology for drug discovery from herbal medicines[J]. Journal of Cheminformatics, 2014, 6(1): 13.

[18] XU X, ZHANG W, HUANG C, *et al.* A novel chemometric method for the prediction of human oral bioavailability[J]. International Journal of Molecular Sciences, 2012, 13(6): 6964 – 6982.

[19] TAO W, XU X, WANG X, *et al.* Network pharmacology-based prediction of the active ingredients and potential targets of Chinese herbal Radix Curcumae formula for application to cardiovascular disease [J]. Journal of Ethnopharmacology, 2013, 145(1): 1 – 10.

[20] KIM S, CHEN J, CHENG T, *et al.* PubChem 2023 update[J]. Nucleic Acids Research, 2023, 51(D1): D1373 – D1380.

[21] DAINA A, MICHIELIN O, ZOETE V. SwissADME: A free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules [J]. Scientific Reports, 2017, 7: 42717.

[22] DAINA A, MICHIELIN O, ZOETE V. SwissTargetPrediction: Updated data and new features for efficient prediction of protein targets of small molecules[J]. Nucleic Acids Research, 2019, 47(W1): W357 – W364.

[23] STELZER G, ROSEN N, PLASCHKES I, *et al.* The GeneCards suite: From gene data mining to disease genome sequence analyses[J]. Current Protocols in Bioinformatics, 2016, 54: 1 – 30.

[24] BARDOU P, MARIETTE J, ESCUDIÉ F, *et al.* jvenn: An interactive Venn diagram viewer[J]. BMC Bioinformatics, 2014, 15(1): 293.

[25] HUANG DW, SHERMAN BT, LEMPICKI RA. Systematic and integrative analysis of large gene lists using DAVID bioinformatics resources [J]. Nature Protocols, 2009, 4(1): 44 – 57.

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poxia-inducible factor-mediated resistance to tyrosine kinase inhibitors in hepatocellular carcinoma[J]. China Pharmacy, 2024, 35(10): 1280 – 1284. (in Chinese)

[12] HU X, LING D. Nanotechnology-based tumor metabolic reprogramming: Insights into nutrient-delivery and metabolism reactivation therapy[J]. Acta Pharmaceutica Sinica B, 2024, 14(10): 4619 – 4621.

[13] LIU X, REN B, REN J, *et al.* The significant role of amino acid metabolic reprogramming in cancer[J]. Cell Communication and Signaling, 2024, 22(1): 380.

[14] SUN JC, XING JH, TAN RX, *et al.* Curcumol reverses temozolomide resistance in glioma cells by regulating the UTX/ MGMT axis[J]. Journal of Southern Medical University, 2023, 43(10): 1697 – 1705. (in Chinese)

[15] ABDEL-MAKSOUD YT, ABDELHASEB AH, ABDO AA, *et al.* Responsive mesoporous silica nanocarriers in glioma therapy: A step forward in overcoming biological barriers[J]. World Journal of Clinical Oncology, 2025, 16(9): 108731.

[16] DI FILIPPO LD, DE CARVALHO SG, DUARTE JL, *et al.* A receptor-mediated landscape of druggable and targeted nanomaterials for gliomas [J]. Materials Today Bio, 2023, 20: 100671.

[17] LUO J, JUNAID M, HAMID N, *et al.* Current understanding of gliomagenesis: From model to mechanism[J]. International Journal of Medical Sciences, 2022, 19(14): 2071 – 2079.

[18] RAHBAN M, JOUSHI S, BASHIRI H, *et al.* Characterization of prevalent tyrosine kinase inhibitors and their challenges in glioblastoma treatment[J]. Frontiers in Chemistry, 2024, 11: 1325214.

[19] LE RHUN E, PREUSSER M, ROTH PL, *et al.* Molecular targeted therapy of glioblastoma[J]. Cancer Treatment Reviews, 2019(80): 1 – 13.

[20] LIU K, WANG HJ, SUN ZQ, *et al.* Expression and clinical significance of VEGF, EGFR and HER-2in patient with gastric cancer[J]. Chinese Journal of Cancer Prevention and Treatment, 2015, 22(10): 781 – 785. (in Chinese)

[21] ZHANG C, DING JL, MAIMAITIYIMING T, *et al.* Expression and significance of P53 and EGFR in glioma tissues[J]. Medical Information, 2020, 33(7): 94 – 96. (in Chinese)

[22] CUI X, ZHAO J, LI G, *et al.* Blockage of EGFR/AKT and mevalonate pathways synergize the antitumor effect of temozolomide by reprogramming energy metabolism in glioblastoma[J]. Cancer Communications, 2023, 43(12): 1326 – 1353.

[23] ZHENG Y, ZENG Y, XI M, *et al.* Epithelial-mesenchymal transition states and metabolic reprogramming related signatures predict prognosis and therapeutic responses in HER2-positive breast cancer[J]. Journal of Clinical Laboratory Analysis, 2025, 39(22): e70119.

[24] VANDER HEIDEN MG, CANTLEY LC, THOMPSON CB. Understanding the Warburg effect: The metabolic requirements of cell proliferation [J]. Science, 2009, 324(5930): 1029 – 1033.

[25] FUKUSHI A, KIM HD, CHANG YC, *et al.* Revisited metabolic control and reprogramming cancers by means of the Warburg effect in tumor cells[J/OL]. International Journal of Molecular Sciences, 2022, 23 (17): 10037[2023 – 12 – 14].

[26] BI J, CHOWDHRY S, WU S, ZHANG W, *et al.* Altered cellular metabolism in gliomas: An emerging landscape of actionable co-dependency targets[J]. Nature Reviews Cancer, 2020, 20(1): 57 – 70.

[27] YANG W, XIA Y, JI H, *et al.* Nuclear PKM2 regulates β-catenin transactivation upon EGFR activation[J]. Nature, 2011, 480(7375): 118 – 122.

[28] JIANG H, JEDOUI M, YE J. The Warburg effect drives dedifferentiation through epigenetic reprogramming[J]. Cancer Biology & Medicine, 2024, 20(12): 891 – 897.

(From page 51)

[26] YE Y, HUANG Z, CHEN M, *et al.* Luteolin potentially treating prostate cancer and COVID-19 analyzed by the bioinformatics approach: Clinical findings and drug targets[J]. Frontiers in Endocrinology, 2021, 12: 802447.

[27] SZKLARCZYK D, GABLE AL, LYON D, *et al.* STRING v11: Protein-protein association networks with increased coverage, supporting functional discovery in genome-wide experimental datasets[J]. Nucleic Acids Research, 2019, 47(D1): D607 – D613.

[28] SHANNON P, MARKIEL A, OZIER O, *et al.* Cytoscape: A software environment for integrated models of biomolecular interaction networks [J]. Genome Research, 2003, 13(11): 2498 – 2504.

[29] SCARDONI G, PETTERLINI M, LAUDANNA C. Analyzing biological network parameters with CentiScaPe[J]. Bioinformatics, 2009, 25 (21): 2857 – 2859.

[30] BUGNON M, RÖHRIG UF, GOULLIEUX M, *et al.* SwissDock 2024: Major enhancements for small-molecule docking with attracting cavities and AutoDock Vina[J]. Nucleic Acids Research, 2024, 52(W1): W324 – W332.

[31] BURLEY SK, BHIKADIYA C, BI C, *et al.* RCSB Protein Data Bank: Powerful new tools for exploring 3D structures of biological macromolecules for basic and applied research and education in fundamental biology, biomedicine, biotechnology, bioengineering and energy sciences [J]. Nucleic Acids Research, 2021, 49(D1): D437 – D451.

[32] ALEXANDER N, WOETZEL N, MEILER J. bcl::Cluster: A method for clustering biological molecules coupled with visualization in the Pymol Molecular Graphics System[J]. IEEE International Conference on Computational Advances in Bio and Medical Sciences, 2011, 2011: 13 – 18.