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Molecular Mechanisms of Active Compounds in Goji Berries: From Bioinformatics Screening to Target Pathway Analysis

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Abstract:

Lycium barbarum(goji berry) paired with traditional Chinese tea are known for their rejuvenating effects on the liver and kidneys, improving eyesight, and moisturizing the lungs. However, its multi-component, multi-target pharmacological mechanisms remain to be fully elucidated. Bioinformatics approaches provide powerful tools for systematically unraveling the complex mechanisms of traditional medicines. The purpose of this article is to systematically predict the active compounds in *Lycium barbarum* through bioinformatics methods, explore the potential pharmacological mechanisms of *Lycium barbarum*, and determine their potential targets. According to analysis, 45 potential active compounds have been identified, including quercetin, β-sitosterol, and stigmasterol, were screened from the TCMSP database based on oral bioavailability (OB ≥ 30%) and drug-likeness (DL ≥ 0.18) criteria. Their corresponding target proteins were predicted and a protein-protein interaction (PPI) network was constructed, identifying AKT1, TP53, and VEGFA as core target proteins. From the results of GO and KEGG analysis, it can be seen that these targets play important roles in some human life activities, such as responding to external stimuli and regulating the MAPK cascade, and were enriched in pathways like Some cancer-related pathways and AGE-RAGE signaling pathways. Molecular docking simulations further validated strong binding interactions between the core active compounds and targets. This study systematically reveals the multi-target mechanisms of *Lycium barbarum* through integrated bioinformatics, providing a scientific basis for its further application in preventing diabetes, cancer and cardiovascular diseases.

Keywords: *Lycium barbarum*; bioactive compounds; bioinformatics; protein-protein interaction network; pathway enrichment analysis.

1. Introduction

Lycium barbarumL (goji berry), the dried ripe fruit of the Solanaceae, is a historically valued medicinal and edible resource in China. Its therapeutic properties, documented in classical texts such as Shennong Ben Cao Jing and Compendium of Materia Medica, include "nourishing Yin and kidneys, improving vision, boosting energy, and moistening the lungs" [1]. In the field of traditional Chinese medicine, goji berries are used to treat symptoms such as blurred eyes, eye fatigue, liver and kidney deficiency, and dry cough caused by blood dysfunction. Research in modern pharmacology has shown that goji berries can play a certain role in improving reproductive function, protecting the liver, nourishing the kidneys, anti-tumor effects, and immune regulation [2]. These broad pharmacological effects are attributed to its rich bioactive compounds, including *Lycium barbarum* polysaccharides (LBP), flavonoids (e.g., quercetin), carotenoids, and phytosterols (e.g., β-sitosterol, stigmasterol).

Although research on the pharmacological activity of goji berries has been extensive, existing studies often focus on single components or pathways, without fully revealing their synergistic mechanisms. This will limit further research and application of goji berries. The latest advances in network pharmacology and bioinformatics provide new methods for deciphering the complex mechanisms of traditional drugs [3]. [Bioinformatics is an interdisciplinary field that integrates computer science, statistics, and biology, capable of efficiently processing, visualizing, and analyzing large biological experimental data. Its applications in network pharmacology include high-throughput screening, target prediction and network construction, mechanism interpretation, and preliminary validation [4]. For high-throughput screening, databases such as TCMSP help to quickly screen potential active compounds based on OB and OD [5]. For target prediction and network construction, platforms such as STRING and DisGeNET can predict target proteins and construct protein-protein interaction (PPI) networks to identify central targets [6]. For mechanism explanation, tools such as Cytoscape and its plugin GlueGO can be used for GO and KEGG pathway enrichment analysis, which can predict biological processes and signaling pathways [7-9]. For validation, molecular docking software such as AutoDock Vina can simulate the interactions between bioactive compounds and target proteins, providing structural simulation analysis for experimental validation [10].

This review aims to systematically review and integrate the analysis of active ingredients, targets, and pharmacological mechanisms of goji berries based on bioinformatics. By constructing a multi-level compound gene target network and validating it through molecular docking, we aim to elucidate the molecular mechanisms behind its efficacy. This work provides a theoretical basis and research direction for further pharmacological research, clinical application, and development of medicinal and edible products of goji berries.

2. Screening of Active Ingredients in Goji Berries Based on Bioinformatics

2.1 Screening Databases and Criteria

The Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP) is an important database for searching traditional Chinese medicine compounds, their absorption, distribution, metabolism, excretion characteristics, and target information. In order to identify active compounds with high drug potential, oral bioavailability (OB ≥ 30%) and drug similarity (DL ≥ 0.18) are widely used screening criteria. These two standards ensure the selection of compounds with good pharmacokinetic characteristics, improving the reliability of subsequent analysis.

2.2 Screening Results and Analysis of Potential Bioactive Compounds

Applying these standards to the active compounds of wolfberry in TCMSP, 45 potential active compounds were screened. These compounds are the basis of their pharmacological effects and can be divided into three categories. The first type is flavonoids, such as quercetin, which have certain antioxidant, anti-inflammatory, and anti-tumor effects. The second type is phytosterols, including β-sitosterol, stigmasterol and campesterol, which are involved in lipid regulation, anti-inflammation and immunomodulation. The third type covers other compounds like amygdalin, cycloartenol and ethyl linolenate, which are associated with diverse pharmacological activities. This screening outcome highlights the chemical diversity of *Lycium barbarum* and provides a foundation for target prediction and mechanistic studies.

3. Target Prediction and PPI Network Construction of Lycium barbarum Compounds

3.1 Screening and Characteristics of Core Target Proteins

Import the human genes corresponding to 45 active compounds into the STRING database and set the species as

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humans for analysis to obtain a network diagram. The resulting data were visualized as a network using Cytoscape(see Fig. 1). The CytoHubba plugin was employed to identify the top 10 hub targets based on algorithms such as Degree and MCC(see Fig. 2). These core targets (e.g., AKT1, TP53, VEGFA, IL6, CASP3, JUN, EGFR, MYC, ESR1, RELA) are central nodes in the network and are critically involved in apoptosis, inflammation, angiogenesis, cell proliferation, and survival, reflecting the core pharmacological functions of *Lycium barbarum* [11].

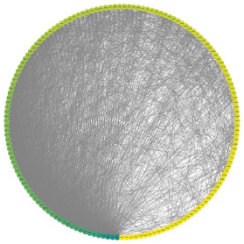

Fig. 1 Target Protein-Protein Interaction Network Graph

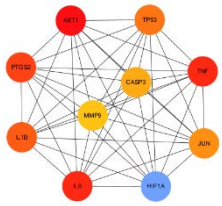

Fig. 2 Target Core Target Protein Network

3.2 Construction and Interpretation of PPI

PPI is composed of the interaction lines between target proteins. Denser connectivity indicates stronger functional associations among targets, suggesting cooperative regulation of physiological or pathological processes. The network visually demonstrates that the effects of *Lycium barbarumare* mediated through a highly interconnected target network rather than isolated targets, underscoring the multi-target and synergistic nature of traditional medicine.

4. KEGG and GO Analysis of Active Ingredients in Goji Berries and Their Corresponding Human Target Genes

In order to elucidate the biological functions of human genes related to the effects of active ingredients in goji berries on the human body, GO and KEGG pathway enrichment analysis was performed using the ClueGO plugin in Cytoscape [8]. The GO analysis encompassed three categories: biological process, cellular component and molecular function.

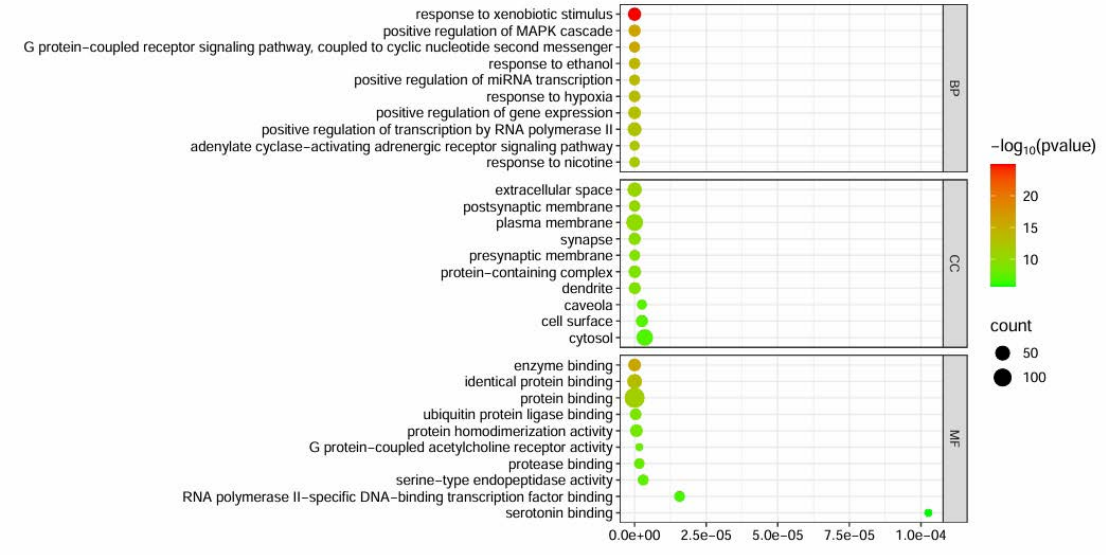

Fig. 3 Target GO Enrichment Analysis Results Diagram

GO enrichment analysis revealed significant functional annotations for the target proteins of *Lycium barbarum*(see Fig. 3). For Biological Process (BP), the most significantly enriched processes were response to xenobiotic stimulus, which is consistent with the herb's role in aiding detoxification and maintaining homeostasis; enrichment in positive regulation of MAPK cascade and G protein-coupled receptor signaling pathway also suggests modulation of core signaling pathways that influence cell growth, differentiation, metabolism, and stress response [12]. For Cellular Component (CC), target proteins were predominantly localized in the extracellular space, plasma membrane, and synapse, an observation that indicates involvement in intercellular communication, membrane receptor signaling, and neural regulation and provides a mechanistic basis for the herb's traditional use in improving visual acuity and cognitive function. For Molecular Function (MF), the most enriched functions were enzyme binding, followed by identical protein binding and protein binding; this implies the bioactive compounds likely interact directly with enzymes or other proteins to modulate their activity, thereby influencing downstream metabolic and signaling cascades and forming a key molecular mechanism for their pleiotropic effects.

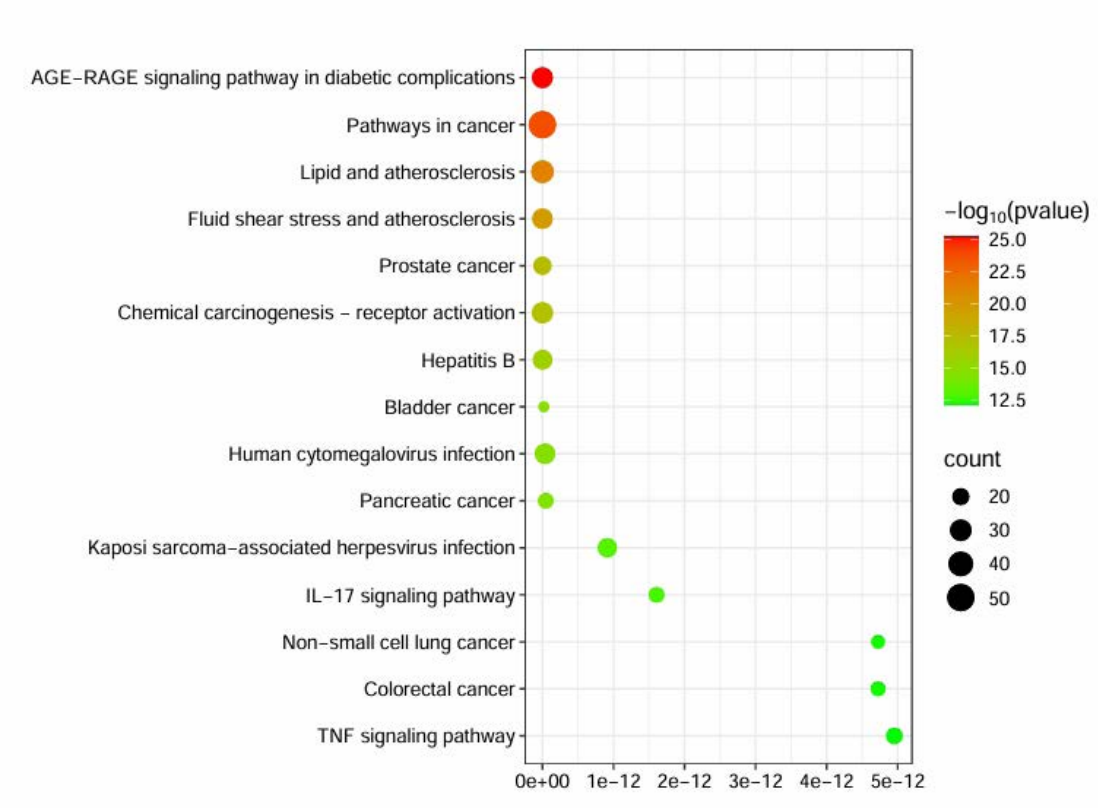

Fig. 4 Target KEGG Enrichment Analysis Results Diagram

KEGG pathway enrichment analysis directly links target protein clusters to well-characterized disease or functional pathways, and the results demonstrated significant enrichment of *Lycium barbarum* targets in three key pathways(see Fig. 4). The enrichment of AGE-RAGE pathway provides a scientific mechanism explanation for the traditional use of *Lycium barbarum* in treating diabetes by nourishing yin, as well as modern evidence supporting its hypoglycemic effects and protection of pancreatic β-cells, which suggests *Lycium barbarum* may mitigate diabetes and its complications by modulating this pathway[2]. For Pathways in cancer, the enrichment of targets in this broad pathway aligns with reported experimental results showing that *Lycium barbarum* polysaccharides and flavonoids (e.g., quercetin, daidzein) inhibit cancer cell proliferation and induce apoptosis, and this reveals its potential multi-target anticancer mechanisms[13]. For Lipid and atherosclerosis, enrichment in this pathway correlates with the lipid-lowering, anti-inflammatory, and anti-atherosclerotic effects of phytosterols and other compounds in *Lycium barbarum*, scientifically supporting its potential in maintaining cardiovascular health [14]. These pathway enrichment results systematically connect the active compounds, targets, traditional efficacy, and modern pharmacological findings of *Lycium barbarum*, forming a coherent "compound-target-pathway-efficacy" network.

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5. Molecular Docking Validation of Lycium barbarum Bioactive Compounds and Target Proteins

5.1 Core Tools and Workflow for Molecular Simulation

To validate the reliability of bioinformatics predictions at the three-dimensional structural level, molecular docking simulations were performed, and the primary workflow involved four key steps [10]. First, the 3D structures of key active compounds (e.g., quercetin, β-sitosterol) were retrieved from the PubChem database. Second, crystal structures of core target proteins (e.g., AKT1, TP53) were obtained from the RCSB PDB database, followed by the removal of water molecules and the addition of hydrogen atoms. Third, ligands and receptors were prepared using AutoDock Tools for format conversion and charge calculation. Fourth, molecular docking calculations were performed within the active site of target proteins using AutoDock Vina to simulate binding modes.

5.2 Molecular Docking Results and Analysis

Evaluate the results of docking through binding affinity. A lower binding energy value indicates a more stable interaction between the active compound and the receptor. The analysis showed that key active compounds in *Lycium barbarum*, such as quercetin binding to AKT1, exhibited binding energies below -7.0 kcal/mol, suggesting spontaneous and stable binding. Visualization analysis confirmed that these compounds fit well into the active cavities of the target proteins through intermolecular forces, including hydrogen bonds, hydrophobic interactions, and van der Waals forces. These results provide atom-level evidence supporting direct interactions between the predicted active compounds and their targets, adding structural biological validation to the prior network pharmacology findings.

5.3 Advantages and Innovations of the Bioinformatics Approach

This study integrates a comprehensive bioinformatics workflow from active compound screening and target prediction to network construction, pathway analysis, and molecular validation, and the advantages and innovations of this approach include four aspects [3, 4]. The first is systematicity: this approach moves beyond the "single-compound, single-target" research model and comprehensively reveals the mechanism of action of *Lycium barbarum* at a systems level. The second is the integration of prediction and validation: the combination of high-throughput prediction with preliminary computational validation through molecular docking enhances result reliability and provides a clear direction for subsequent experiments. The third is mechanistic depth: directly linking the pharmacological effects of *Lycium barbarum* to specific molecular pathways of major diseases like diabetes, cancer, and cardiovascular conditions allows for deeper mechanistic interpretation. The fourth is efficiency and cost-effectiveness: providing focused hypotheses and clear priorities for further wet-lab experimentation reduces research blindness and saves resources and time.

6. Conclusion

This paper successfully applies integrated bioinformatics approaches to systematically elucidate the multi-compound, multi-target, and multi-pathway pharmacological mechanisms of *Lycium barbarum*(goji berry). KEGG enrichment analysis shows that some compounds, such as quercetin and β - sitosterol, can regulate key targets, including AKT1, TP53 and VEGFA, which are widely involved in key pathways related to diabetes complications, cancer and atherosclerosis. GO analysis further highlighted their roles in response to xenobiotic stimuli, enzyme binding, and cellular signaling transduction. Molecular docking simulations provided preliminary validation of strong binding interactions between these compounds and targets. These findings not only offer a scientific basis and theoretical foundation for the clinical application and further development of goji berry in preventing and managing chronic diseases like diabetes, cancer, and cardiovascular conditions but also demonstrate the significant value of bioinformatics in modernizing research on traditional Chinese medicines. However, these computational predictions require further validation through in vitro and in vivo experiments. Future research should focus on experimental verification of the identified core targets and pathways, and explore the synergistic effects of goji berry within compound formulas to fully uncover its scientific connotation.

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