To explore the mechanism of action of *Irpex lacteus* treatment of hyperuricemia from the perspective of network pharmacology

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**Abstract**

**Objective**: To explore the active ingredients and mechanism of *Irpex lacteus* against HUA (hyperuricemia) by using network pharmacology and molecular docking technology.

**Methods**: Through literature search and collection, drug-like screening, target prediction, construct a target library of chemical components related to *Irpex lacteus*; search and construct HUA disease target library through disease database. The PPI network of the crossover gene between the components of *Irpex lacteus* and HUA was constructed using STRING and Cytoscape; the GO function enrichment analysis of the crossover genes and the enrichment analysis of the KEGG signaling pathway were realized through the Metascape database; the purpose of the "target-signal pathway" network was to analyze its specific mechanism of action; molecular docking to verify the binding ability of the main active ingredients and key targets.

**Results**: 56 active ingredients were screened, the core target of PPI network mitogen-activated protein kinase 3 (MAPK3), mitogen-activated protein kinase 1 (Mitogen-activated protein kinase 1, MAPK1), etc.; involved 1387 GO biological processes, 48 cell components, and 113 molecular functions; signaling pathway involved AGE-RAGE signaling pathway in diabetes complications, PI3K-Akt signaling pathway, IL-17 signaling pathway, etc.; molecular docking results show that the core component tremutins A/C/E had good docking activity with each target.

**Conclusion**: The related products of *Irpex lacteus* can treat HUA through multiple components, multiple targets, and multiple pathways, which could provide reference for further research and development.

1. Introduction

After a series of laborious processes such as discovery of lead compounds, structural modification, and evaluation of therapeutic quality, many highly selective single-targeted drugs have been developed in traditional drug discovery, and the problems of drug resistance and inefficiency have gradually emerged. Network pharmacology is a comprehensive interdisciplinary discipline based on systems biology, proteomics and other multidisciplinary theories, taking into account the interactions between target molecules and biological effector molecules in the body, and predicting drug efficacy by constructing drug-target-mechanism networks, which can develop unused natural products and expand the drug space of target proteins related to various complex diseases systematically[1].

HUA is a metabolic disorder in which fasting uric acid levels are higher than normal (420umol/L) in patients on a normal purine diet. Several studies have shown a causal relationship between HUA and the development of gout, diabetes, and cardiovascular diseases[2-4]. In recent years, with the improvement of people's living standard, the age of the onset of HUA has gradually changed from older
people with poor metabolism to younger people, and it is necessary to find safe and effective uric acid lowering drugs.

*Irpex lacteus* (Fr.) Fr is a common wood-rotting fungus, widely distributed in China, as the main raw material of Yi Shen Kang, an effective medicine for glomerulonephritis[5]. Some patients with nephritis associated with HUA and gout reported lower blood uric acid levels and relief of joint swelling and pain while on the drug. The preliminary basic research group found[6], mycelial polysaccharide was not the only pharmacodynamic substances, *Irpex lacteus* fermentation had a good effect on HUA mice and gouty arthritis rats, fermentation and other small molecules in the mycelium also played a therapeutic role. This study intends to make target prediction by network pharmacology and molecular docking on the active compounds related to *Irpex lacteus*, analyze the pathway mechanism of its treatment of HUA, and provide a reference for its further research and development.

2.Materials and methods

2.1.Ingredient acquisition and pretreatment

Search for the *Irpex lacteus* fruiting body, the relevant chemical composition of the fermentation products through CNKI, Wanfangdata, PubMed database, using the structure drawing software ChemDraw 17.1 to draw the structure of candidate compounds and save, import structure optimization software Chem 3D 17.1, optimize the mechanical structure, minimize energy, saved as mol2 format to prepare molecular docking. In order to screen drug-like molecules for better pharmacokinetic properties, the ADME properties of compounds are usually evaluated according to Lipinski's five-fold rule[7]. The five-fold rule is molecular weight MW ≤ 500, lipid-water partition coefficient MLOGP ≤ 4.15, number of rotatable bonds ≤ 10, number of hydrogen bond acceptors HBR ≤ 10, number of hydrogen bond donors HBD ≤ 5. The active compounds in mol2 format were converted to Canonical SMILES by the OpenBabel-2.4.1, a chemical structure file conversion software, uploaded to the pharmacokinetic and drug similarity evaluation platform SwissADME (http://www.swissadme.ch/index.php), was used to get structural information and ADME parameters of each compound, to predict the passive absorption (HIA) and blood-brain permeation (BBB) properties of each compound, and to screen for compounds with good pharmacokinetic properties[8].

2.2.Compound target prediction

The targeting platforms SwissTargetPrediction (http://www.swisstarget.prediction.ch) and QSAR (quantitative structure-activity relationship) based models for predicting compounds based on similarities to the 2D and 3D structures of known compounds TargetNet (http://targetnet.scbdd.com/calcnet/index/) for target prediction[9-10], SMILES was used as a standard upload format for compounds, and the top 20 items of Prob values of targets got from SwissTargetPrediction and TargetNet were selected, with TargetNet Prob values ≥ 0.8. The resulting target proteins were imported into the protein database Uniprot (https://www.uniprot.org) to convert the protein names into gene symbols and construct a library of targets for the components related to the *Irpex lacteus*.

2.3.Acquisition of disease targets

With the keyword "Hyperuricemia" in CTD (http://ctdbase.org/), MalaCards (https://www.malacards.org/), the Comparative Toxicogenomics Database, and the Human Disease Database. DisGeNET (https://www.disgenet.org) retrieves HUA disease-related targets[11-13], and the screening rules were CTD: Inference Score > 20; DisGeNET: Score-gda ≥ 0.1; MalaCards: no rule restriction. The above screening results were combined to construct the HUA disease target library.

2.4.Protein-Plus-Induced Interaction (PPI) Network Construction

Intersection of constituent targets with disease targets to get potential targets to treat HUA with *Irpex lacteus*, and protein interplay analysis of targets using the STRING 11.0 (https://string-db.org/) platform[14], organism set to Homo sapiens, set minimum required interaction score to
maximum (0.900), hide no connection target, export to TSV format file and import Cytoscape 3.7.2 for NetworkAnalyzer, the color of each node was rendered from green to red in increasing degree values.

2.5. Analysis of mechanisms of action
Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyzes were performed using the Metascape database (http://metascape.org/), a library of Integrates multiple databases such as GO, KEGG, UniProt and DrugBank for short data update cycles[15]. Upload the text file of the list of target genes got in 1.2, restrict the species to human, select custom mode, perform GO annotation and KEGG pathway enrichment analysis, perform enrichment calculation and P-value conversion on the first 20 entries of the GO and KEGG analysis results, and upload the text file in a standard format to draw bubble maps of the results.

2.6. Constituent-target-pathway mapping
The resulting components, targets, and pathways were imported into cytoscape to construct component-target and target-pathway diagrams, which were eventually merged into component-target-pathway diagrams, in which the components, targets, and pathways were represented by nodes of different colors and shapes, and the relationships between the nodes were represented by edges.

2.7. Molecular docking
Molecular docking is a computational method for predicting the preferred position and conformation of one molecule (ligand) relative to another (receptor), which can predict the binding strength or binding affinity between receptor and ligand. Screen the targets with the highest degree-value in the PPI results and download the crystal structure files of the corresponding proteins from the Protein Structure Database PDB (http://www.rcsb.org)[16], remove water and remove organic were done with Pymol[17], AutoDockTools for hydrogenation (Edit→Hydrogens→Add) processing and saving it as a pdbqt format file. Importing the sdf format file of core components related to component-target-pathway network into Chem 3D 17.1, save it as mol 2 format file, import it into AutoDockTools 1.5.6, and save it as pdbqt format file after hydrogenation, charge and Root, then construct the target protein ligand binding site with reference. Girdbox coordinates, molecular docking via AutoDock Vina, balloon mapping of docking results via Microbiotics platform, import of most stable complexes into Protein-Ligand Interaction Profiler (PLIP, https://projects.biotec.tudresden.de/plip-web/plip/), recognizes non-covalent interactions between proteins and ligands[18], finally, graphics optimization was performed via PyMOL.

3. Results

3.1. Compound screening results
A total of 63 compounds were obtained by searching the relevant literature[19-29], compounds 1-53 were obtained from the fermentation products of *Irpex lacteus* and 54-64 were obtained from the fruiting bodies of *Irpex lacteus*. According to the preliminary screening of the compounds obtained according to the five principles of drug-like five, the number of violations ≥ 2 that is, the compound may not be orally absorbed and poor biofilm permeability, as shown in Table 1, compounds 53-56, 58, 60-61 rule violation is more obvious, so they were removed from the composition library, and finally got 56 active compounds.

| Serial Number | Molecular Formula | Molecular Mass | Rotatable Keys | HBR(D) | MLOGP violation | TPSA | WLOGP |
|---------------|-------------------|----------------|----------------|--------|-----------------|------|-------|
| 1             | C_{13}H_{18}O_{3} | 246.30         | 0              | 3(1)   | 2.38            | 46.53| 2.12  |
| 2             | C_{13}H_{16}O_{3} | 244.29         | 0              | 3(1)   | 2.56            | 46.53| 2.91  |
| 3             | C_{13}H_{22}O_{3} | 250.33         | 0              | 3(1)   | 2.56            | 46.53| 2.29  |
|  | C<sub>13</sub>H<sub>20</sub>O<sub>5</sub> | 280.32 | 0 | 5(2) | 0.88 | 0 | 79.29 | 0.54 |
|---|---|---|---|---|---|---|---|---|
| 5 | C<sub>13</sub>H<sub>20</sub>O<sub>4</sub> | 264.32 | 0 | 4(1) | 1.71 | 0 | 59.06 | 1.42 |
| 6 | C<sub>15</sub>H<sub>20</sub>O<sub>3</sub> | 248.32 | 0 | 3(1) | 2.47 | 0 | 46.53 | 2.21 |
| 7 | C<sub>15</sub>H<sub>20</sub>O<sub>4</sub> | 264.32 | 1 | 4(2) | 1.62 | 0 | 66.76 | 1.19 |
| 8 | C<sub>15</sub>H<sub>20</sub>O<sub>4</sub> | 264.32 | 2 | 4(2) | 2.43 | 0 | 74.6 | 2.54 |
| 9 | C<sub>15</sub>H<sub>22</sub>O<sub>3</sub> | 250.33 | 0 | 3(1) | 2.56 | 0 | 46.53 | 2.44 |
| 10 | C<sub>15</sub>H<sub>22</sub>O<sub>3</sub> | 250.33 | 0 | 3(1) | 2.56 | 0 | 46.53 | 2.29 |
| ... | ... | ... | ... | ... | ... | ... | ... | ... |
| 53 | C<sub>34</sub>H<sub>48</sub>O<sub>8</sub> | 584.74 | 4 | 8(2) | 4.24 | 2 | 119.36 | 5.72 |
| 54 | C<sub>34</sub>H<sub>48</sub>O<sub>8</sub> | 598.77 | 5 | 8(1) | 4.43 | 2 | 108.36 | 5.81 |
| 55 | C<sub>34</sub>H<sub>46</sub>O<sub>8</sub> | 582.72 | 4 | 8(2) | 4.16 | 2 | 119.36 | 5.49 |
| 56 | C<sub>34</sub>H<sub>46</sub>O<sub>8</sub> | 596.75 | 5 | 8(1) | 4.34 | 2 | 108.36 | 5.58 |
| 57 | C<sub>31</sub>H<sub>40</sub>O<sub>5</sub> | 492.65 | 3 | 5(1) | 4.30 | 1 | 72.83 | 5.71 |
| 58 | C<sub>31</sub>H<sub>40</sub>O<sub>6</sub> | 506.63 | 3 | 6(1) | 4.22 | 2 | 89.90 | 5.80 |
| 59 | C<sub>31</sub>H<sub>40</sub>O<sub>6</sub> | 492.65 | 3 | 5(1) | 4.30 | 1 | 72.83 | 5.71 |
| 60 | C<sub>31</sub>H<sub>40</sub>O<sub>6</sub> | 508.65 | 3 | 6(2) | 4.30 | 2 | 93.06 | 5.32 |
| 61 | C<sub>31</sub>H<sub>42</sub>O<sub>6</sub> | 510.66 | 3 | 6(2) | 4.24 | 2 | 85.22 | 5.22 |
| 62 | C<sub>31</sub>H<sub>42</sub>O<sub>6</sub> | 510.66 | 1 | 6(2) | 3.65 | 1 | 93.06 | 4.65 |
| 63 | C<sub>31</sub>H<sub>44</sub>O<sub>7</sub> | 528.68 | 0 | 7(4) | 2.94 | 1 | 116.45 | 3.55 |

Visual assessment of the HIA and BBB properties of 63 compounds based on the molecular position of the combined WLOGP and TPSA parameters[30], see Figure 1 for more details. The white area shows a high probability of passive absorption from the gastrointestinal tract and the yellow area (yolk) shows a high probability of brain penetration. There are areas of intersection between the yolk and the white area. In addition, these points are shown in blue if they were predicted to be PGP+ active transport efflux, otherwise these points are shown in red (PGP-). In this example, compounds numbered 53-56 were predicted not to be absorbed and not to cross the blood-brain barrier (outside the egg), compounds 4, 27-28, and 58-63 were predicted to be well absorbed but not to enter the brain (in the white) and PGP+ (blue dots), and a portion of the other compounds were predicted to cross the BBB by passive transport (in the yolk) but to be actively transported out of the brain (blue dots), another part of the compound in the yolk region is expected to be permeable to brain function and unaffected by active transport (red dots).

Figure 1. Assessment of gastrointestinal passive absorption and blood-brain barrier permeability of 63 compounds
3.2. Results of access to potential therapeutic targets

56 components of the *Irpex lacteus* were predicted by SwissTargetPrediction and TargetNet, and 290 and 164 targets were obtained after screening and weighting, respectively, and 379 component targets were obtained after synthesis; 686, 32 and 58 HUA-related targets were retrieved after CTD, MalaCards, and DisGeNET search and screening, 727 HUA disease-associated targets were obtained after merging and de-emphasis. 95 intersecting targets were obtained after mapping of component targets to disease targets by venn diagram (Figure 2).

3.3. PPI Network Analysis Results

There were 71 nodes, 239 edges and the average node degree (degree) is 6.73. The color of the nodes was used to reflect the size of the degree, the closer the color was to red, the higher the corresponding degree value. The nodes with degree values less than the mean value were detailed in Figure 3. Topological analysis got the network core targets, MAPK3, MAPK1, RELA, PIK3CA, HSP90AA1, JUN and other targets with the greatest correlation between them, and some node properties were shown in Table 1.

![Figure 2. Venn's diagram of components(A) and HUA(B) targets](image)

**Table 2. Attributes of the top 10 nodes in degree value ranking**

| Gene    | Degree | Proximity to centrality | Mean shortest path length | Topology coefficient |
|---------|--------|-------------------------|---------------------------|----------------------|
| MAPK3   | 23     | 0.5109                  | 1.9571                    | 0.2240               |
| MAPK1   | 23     | 0.5147                  | 1.9429                    | 0.2133               |
| RELA    | 20     | 0.4930                  | 2.0286                    | 0.2370               |
| PIK3CA  | 19     | 0.4403                  | 2.2714                    | 0.2218               |
| HSP90AA1| 19     | 0.4575                  | 2.1857                    | 0.2071               |
| JUN     | 19     | 0.4861                  | 2.0571                    | 0.2295               |
| MAPK8   | 16     | 0.4667                  | 2.1429                    | 0.2630               |
| ESR1    | 15     | 0.4459                  | 2.2429                    | 0.2681               |
| MAPK14  | 14     | 0.4459                  | 2.2429                    | 0.2776               |
3.4 Results of Mechanism Analysis

In the Metascape, GO enrichment analysis was performed on 95 overlapping genes, and 1387 biological processes (BP), 48 cellular components (CC), and 113 molecular functions (MF) were obtained. Cyan markings, Enrichment scores in the vertical coordinates show the proportion of hits of candidate targets in the corresponding GO process, see Figure 4 for details. In the BP category, response to lipopolysaccharide, response to molecule of bacterial origin. Cellular response to lipid ranked high; in the CC category, membrane raft, membrane micro-domain, membrane region ranked high; in the MF category, nuclear receptor activity, transcription factor activity, steroid hormone receptor activity ranked high.

Figure 3. PPI network diagram of intersecting targets

Figure 4. Top 10 results of GO enrichment analysis for each BP/CC/MF group.
KEGG enrichment analysis yielded 68 signaling pathways, and the top 20 pathways were selected according to the logP value from smallest to largest, involving AGE-RAGE signaling pathway, PI3K-Akt signaling pathway, IL-17 signaling pathway, HIF-1 signaling pathway, and Th17 cell differentiation in diabetes complications. The Y-axis represents the name of the pathway, the X-axis enrichment value was the enrichment proportion of input genes in the pathway, the bubble area represents the count value (the number of target genes concentrated in the corresponding pathway), and the bubble color represents the enrichment significance (-LogP value), the larger the -LogP value, the higher the enrichment significance, see Figure 5 for details.

![Figure 5. Top 20 results of KEGG enrichment analysis.](image)

### 3.5 Component-Target-Pathway Network Construction Results

The network relationship between 56 active components, 47 intersection targets and 20 signaling pathways were constructed by Cytoscape software, with triangular nodes representing components, circular nodes representing targets and rounded rectangular nodes representing pathways. The higher the node degree value, the stronger the core effect and the closer the color was to red, the network contains 123 nodes, 514 edges, each active ingredient corresponds to multiple targets, multiple targets enrich multiple pathways, ingredient numbers 52 (degree value 19, below), 18(10), 51(9), 1(9), 6(9), 50(7), 3(7) have the highest degree centrality, the target Nos2, HSP90AA1, ESR2 and the signaling pathway PI3K-Akt are most important in this network and may play a central role in the treatment of HUA. For details, see Figure 6.
3.6. Molecular docking results

The essential components numbered 52 (L-3), 18 (Concenolides A), 51 (L-2), 1 (tremutins A), 6 (tremutins F), 50 (L-1), and 3 (tremutins C) were selected (Table 3) to be identical to the core targets in the PPI network, MAPK3 (PDB ID: 6GES), MAPK1 (PDB ID: 6RQ4), RELA (PDB ID: 6QHL), PIK3CA (PDB ID: 3ZIM), HSP90AA1 (PDB ID: 4BQG), and JUN (PDB ID: 5FV8) were molecularly docked, and the smaller the binding free energy $\Delta G$ score indicates that the receptor was associated with the more stable the binding of the ligands, the greater the likelihood of interaction. The results showed that tremutins A had the lowest binding energies to MAPK3 (binding free energy $\Delta G = -8.3$ kcal/mol), MAPK1 (-9.1 kcal/mol), RELA (-9.4 kcal/mol), PIK3CA (-8.1 kcal/mol), HSP90AA1 (-9.0 kcal/mol) had the lowest binding energy to JUN was for compound tremutins C (-6.3 kcal/mol). From Figure 7, we can see it that compounds 1, 3, and 6 have a stable binding capacity to each core target.

Table 3. Important ingredients for a central role

| Serial Number | Compound Name | Structure | Reference |
|---------------|---------------|-----------|-----------|
| 1             | tremutins A   | ![Structure](image) | [29]       |
Figure 7. Docking results of core components to primary targets

The complex of RELA and tremutins A with the lowest binding energy (Figure 8 a) was selected for non-covalent interaction analysis, and the results showed that the ligand has hydrophobic interactions with ILE-219, ILE-218, ILE-128, and ILE-168 residues, hydrogen-bonding interactions with LYS-122,
ASN-42, and SER-45 residues, and hydrogen-bonding interactions with LYS-122 residues to produce salt bridging effects, as detailed in Figure 8b.

![Figure 8. RELA and tremutins A complex (a) and their interactions (b)](image)

4. Discussions

Natural products and their derivatives account for about 50% of clinically used drugs, and for their structural diversity, multi-target activity and weak toxic side effects, they have become the major research trend and candidate source for targeted drugs in recent years. Luo, Fang et al. found that most of the natural products have docking activities with 104 cancer-related protein targets[31]. Medicinal fungi are an important reservoir of natural products, and many compounds have a wide range of clinical applications, with small molecules of fungal origin, such as erythromycin, penicillin, cephalosporins, and statins[32], all having good therapeutic effects. In this study, 56 active compounds with good pharmacokinetic properties associated with *Irpex lacteus* were screened, and the PPI network construction results showed that the relevant core targets for the compounds to exert HUA therapeutic effect were MAPK3, MAPK1, RELA, PIK3CA, HSP90AA1, JUN, and the molecular docking also verified that the core compounds had stable binding force with the above targets.

GO and KEGG analysis showed that the mechanism of action of *Irpex lacteus* against HUA involves pathological changes in glucose metabolism, inflammatory response, lipid metabolism, renal function and its corresponding organs, which also suggests a high correlation between diseases related to the body's metabolic system, with the main signaling pathways being the AGE-RAGE signaling pathway, PI3K-Akt signaling pathway, IL-17 in diabetes complications. HUA is closely related to diabetes, and the action of advanced glycosylated receptors (RAGE) and AGEs can lead to the production of reactive oxygen species (ROS), and oxidative stress occurs when ROS and antioxidants cannot counterbalance each other, thus inducing the release of inflammatory cytokines such as nuclear factor κB (NF-κB) or other pathways, and aggravating the related inflammatory response[33-34]. High uric acid can affect insulin resistance and pancreatic B cell function through multiple signaling pathways[35], chronic HUA can lead to uric acid deposition in pancreatic B cells, impairing their normal function, which is directly related to the development of diabetes[36]. In patients with chronic kidney disease, decreased uric acid clearance and increased blood uric acid levels delay tubular epithelial-mesenchymal trans-differentiation (EMT) is an effective way to control the development of chronic kidney disease, while high levels of blood uric acid upregulate the PI3K/Akt signaling pathway, which then induces EMT[37], promotion of interstitial fibrosis changes. interleukin 17 (IL-17) is secreted by Th17 cells and can promote the aggregation of inflammation-related factors that play a role in the development of chronic inflammation. IL-17 is highly expressed in autoimmune diseases such as rheumatoid arthritis and psoriasis[38]. Rui-Ming Shen et al. investigated the expression of IL-17 and NF-κB in acute gouty arthritis (AGA) and its significance. The results showed that sodium rate caused a significant increase...
in the expression levels of IL-17 and p-NF-κB p65 in synovial tissues of rats in the AGA model, resulting in an increased inflammatory response[39].

5. Conclusion

In summary, through network pharmacology and molecular docking to investigate the mechanism of action of *Irpex lacteus* in the treatment of HUA, L-3, Conocenolides A, L-2 and other core components act on MAPK3, MAPK1, RELA and other targets, through the AGE-RAGE signaling pathway, PI3K-Akt signaling pathway, IL-17 signaling pathway in diabetic complications, etc. pathways to exert therapeutic effects. For the limitations of the computational systems biology approach, the consistency between the actual therapeutic effect and the predicted results cannot be guaranteed. This study will be followed by *in vivo* and *in vitro* experiments on relevant target pathways to verify the prediction results of network pharmacology and molecular docking.

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