



Research



Exploring the mechanism of *Gentiana rigescens* Franch. in the treatment of pulmonary fibrosis based on network pharmacology

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Abstract

Pulmonary fibrosis (PF) is a severe chronic interstitial lung disease with high mortality, and there is currently a lack of definite and effective treatment methods. Studies have found that gentiopicroside, a secoiridoid glycoside compound derived from plants of the *Gentiana* genus, can significantly improve pulmonary inflammation and fibrosis lesions in mice with pulmonary fibrosis. However, the mechanism of its anti-fibrotic effect is unclear. Therefore, in this study, we employed network pharmacology's virtual computer technology to investigate the potential mechanism underlying the anti-pulmonary fibrosis effect of *Gentianae Radix et Rhizome* (Longdan in Chinese, GRR). Our findings offer valuable theoretical insights and serve as a guiding reference for future experimental investigations. A total of 10 active compounds and 920 drug-target proteins were identified from the TCMSP database. The compound-target-pathway-disease network showed that GRR could potentially treat PF by regulating the MDM2, ERBB2 and VEGFA, signaling pathways through its key targets, including AKT1, TNF, and MAPK1. The protein–protein interaction network revealed that these targets had strong interactions with each other, indicating a potential synergistic effect of GRR in treating PF. The GO and KEGG enrichment analyses further supported the potential anti-pulmonary fibrosis mechanisms of GRR, including regulating the inflammatory response, ECM-receptor interaction, and TGF-beta signaling pathways. Our study provides a systematic analysis of the potential anti-pulmonary fibrosis mechanisms of GRR based on network pharmacology. These findings could contribute to the development of novel treatments for PF and provide a basis for further experimental studies.

Article highlights

1. The anti-pulmonary fibrosis mechanism of GRR was investigated using network pharmacology methods
2. An effective pathway involving the interaction of compound-target-pathway-disease was identified
3. Several key target proteins were successfully identified, providing a basis for subsequent pharmaceutical experiments.

Keywords *Gentianae Radix et Rhizome* · *Gentiana rigescens* Franch. · Pulmonary fibrosis (PF) · Network pharmacology · TCMSP · GeneCards database

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Abbreviations

PF	Pulmonary fibrosis
Longdan in Chinese, GRR	Gentianae Radix et Rhizome

1 Introduction

Pulmonary fibrosis (PF) is a severe chronic fibrotic lung interstitial injury disease characterized by fibroblast proliferation, excessive extracellular matrix accumulation, inflammation, tissue structure damage, and progressive interstitial fibrosis, ultimately resulting in respiratory failure and high mortality rates [1]. Due to its complex pathogenesis, short median survival time after diagnosis, and lack of effective treatments, there is an urgent need to develop low-toxicity, high-efficiency, and cost-effective antifibrotic drugs [2]. Furthermore, for the recent outbreak of novel coronavirus pneumonia (CoronaVirus Disease 2019, COVID-19), two important changes occur in the progression of the disease from ordinary infection to severe or critical infection, which are significant manifestations of PF. Therefore, controlling the development of PF is of great significance in delaying the progression of COVID-19 [3]. Although the US Food and Drug Administration (FDA) has currently approved two drugs, nintedanib and pirfenidone, for the treatment of idiopathic PF [4], these drugs have severe adverse effects and are expensive, despite their antifibrotic, anti-inflammatory, and antioxidant properties [5–8], as well as their ability to inhibit the expression of various growth factors and cytokines [6, 8]. Therefore, there is an urgent need to develop new antifibrotic drugs that are low toxicity, high efficiency, and cost effective.

Gentianae Radix et Rhizome (Longdan in Chinese, GRR) in Chinese Pharmacopoeia is derived from the dried roots and rhizomes of *Gentiana scabra* Bge. and *Gentiana rigescens* Franch., that have long been used for heat-clearing and damp-drying in the medicinal history of China. *Gentiana rigescens* Franch., also known as Jianlongdan, Qingyudan, and Xiaoqinjiao, is a perennial herb in the Gentianaceae family, mainly found in Yunnan Province, and distributed in Sichuan, Guizhou, Guangxi, Hunan, and other regions [9]. Plants in the *Gentiana* genus contain various active components, such as iridoids, flavonoids, and terpenoids, which have multiple pharmacological activities, including anti-inflammatory, analgesic, hepatoprotective, antitumor, and antiviral effects [10]. Studies have found that raw materials and iridoid compounds from *Gentiana* plants can significantly improve pulmonary fibrosis in rats and mice [11, 12], and the iridoid glycoside compound gentiopicoside from *Gentiana* plants can significantly improve inflammation and fibrotic lesions in mouse lungs with PF [13]. Certain traditional Chinese medicine formulations, such as Fei Ning [14], contain GRR

as an ingredient. These formulations have demonstrated significant therapeutic efficacy in the treatment of pulmonary fibrosis, bronchitis, and other pulmonary injuries [15]. However, the precise mechanism underlying their anti-fibrotic effects remains elusive. As the pathogenesis of PF is complex and involves multiple targets, it is not conducive to traditional medical experiments. Therefore, this study used network pharmacology and virtual computer technology to theoretically explore the antifibrotic mechanism of action of GRR, providing theoretical references and guidance for subsequent experiments.

Network pharmacology technology is a new method based on computer virtual computing technology that integrates a large amount of information and allows for new discoveries by combining computational and experimental methods. The computational methods mainly include graph theory, statistical methods, data mining, modeling, and information visualization methods. Experimental methods include various high-throughput omics technologies as well as biological and pharmacological experiments. It integrates multidisciplinary technologies and contents such as systems biology and multidirectional pharmacology and explores the correlation between drugs and diseases from a holistic perspective, providing a reliable research platform for predicting key targets and pathways of drugs acting on diseases [16].

In TCM network pharmacology, a “network” is a mathematical and computable representation of various connections between herbal formulae and diseases, particularly in complex biological systems. By using basic network topology measurements, it is possible to characterize different drug treatments from a network perspective. Introducing “networks” into drug discovery combines the assessment of network topology and dynamics, providing a quantifiable description of complex biological systems and their responses to various drug/herbal treatments [16]. The present study employs a network pharmacology approach to predict the key targets and possible mechanisms of action of GRR in treating PF and establishes a “compound-target-pathway” relationship to provide a reference for further experimental research.

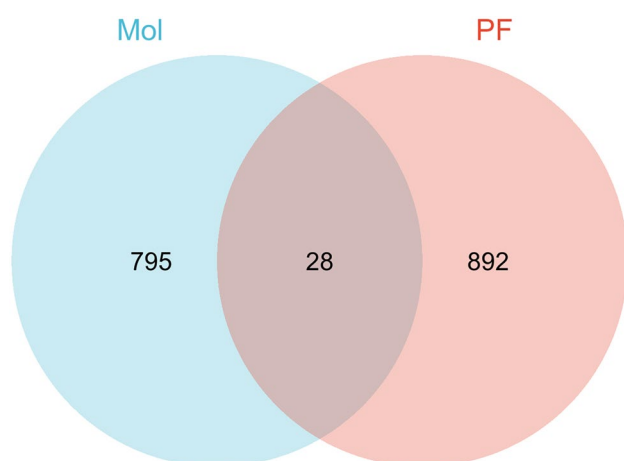
2 Result

2.1 Screening of active ingredients in GRR for oral administration

Following a rigorous screening and data collection process using the TCMSP database, 10 active compounds and 823 target proteins were identified based on a predetermined threshold of OB $\geq$ 30% and DL $\geq$ 0.18, as shown in Table 1. Moreover, to augment the analysis, the GeneCards

Table 1 Major active ingredients of GRR

Mol ID	Molecule name	OB(%)	DL
MOL003170	Gentisein	67.57	0.19
MOL003152	Gentisin	64.06	0.21
MOL000422	Kaempferol	41.88	0.24
MOL003155	Pranferin	52.14	0.28
MOL002322	Isovitexin	31.29	0.72
MOL003169	Gentiopicroside tetraacetate	32.44	0.75
MOL000359	Sitosterol	36.91	0.75
MOL003143	Gentirigenic acid	38.78	0.78
MOL003137	Leucanthoside	32.12	0.78
MOL001558	Sesamin	56.55	0.83

**Fig. 1** Venn diagram of intersection of *Gentiana yunnanensis* component targets and PF targets. Red PF indicates pulmonary fibrosis targets; blue Mol indicates active ingredient targets

database was utilized to retrieve a total of 920 target proteins associated with PF.

2.2 Construction of target networks for GRR and PF

A Venn diagram analysis was conducted to compare the target points of the constituents of GRR and those of PF. There were 28 common target points between the two, which may be the target points of GRR for treating PF, as shown in Fig. 1. Among the 10 chemical constituents, gentirigenic acid had the most common target points, as shown in Fig. 2.

2.3 Construction of a protein–protein interaction network of the targets of GRR in the treatment of PF

The target protein networks for GRR and PF were constructed. The networks consisted of 28 common

targets that were uploaded to the online STRING database (<https://string-db.org/>), and the corresponding protein–protein interaction (PPI) information was obtained by setting the medium confidence protein parameter score to > 0.4. A total of 24 important target proteins were obtained, as shown in Fig. 3. Six key targets were selected using Cytoscape 3.9.1 by calculating and filtering the betweenness value (≥ 37.94), closeness (≥ 0.015), and degree value (≥ 6.18). The key targets included MDM2 (mouse double minute 2 homolog), ERBB2 (Erb-B2 receptor tyrosine kinase 2), ESR1 (estrogen receptor 1), VEGFA (vascular endothelial growth factor A), B2M (beta-2-microglobulin), and INS (insulin), as shown in Table 2.

2.4 KEGG pathway enrichment analysis and GO functional enrichment analysis

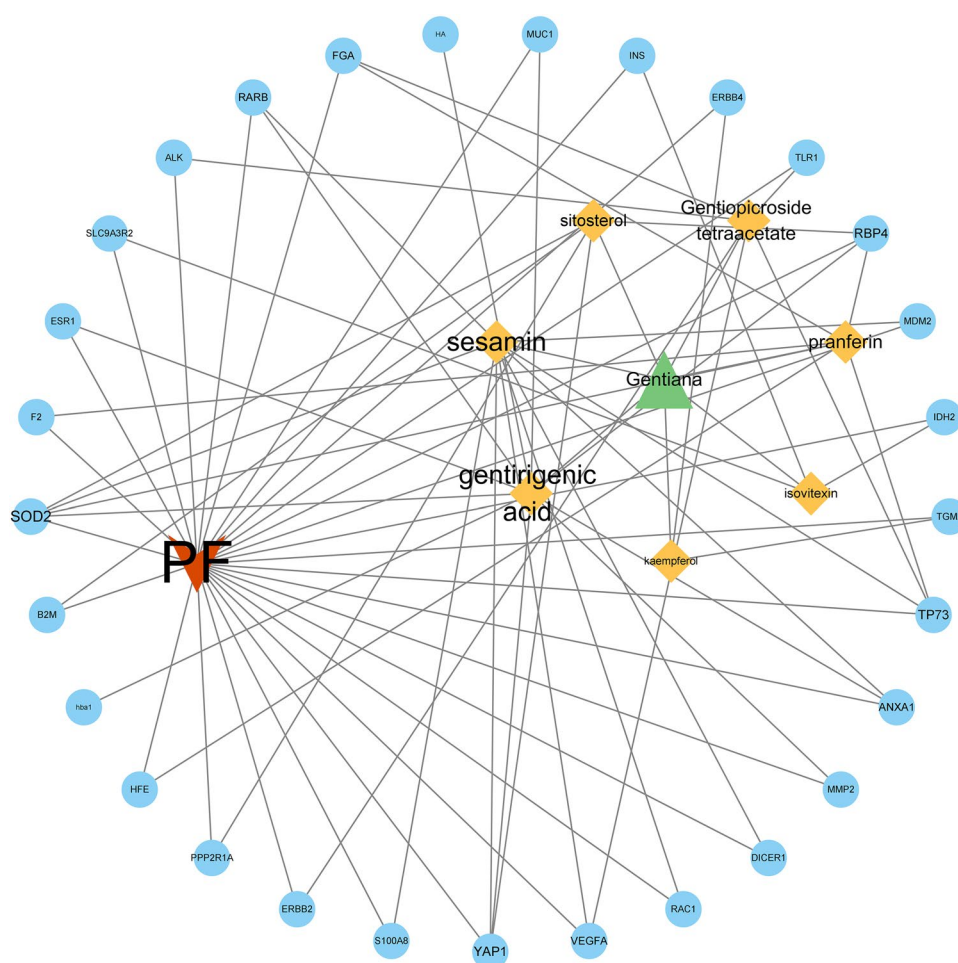
The KEGG pathway enrichment analysis results showed that a total of 75 related signaling pathways were obtained, including inflammation, cancer, and the endocrine system. The main pathways included pathways in cancer, carbon metabolism, fluid shear stress and atherosclerosis, protein processing in endoplasmic reticulum, insulin signaling pathway, bladder cancer, cysteine and methionine metabolism, proteoglycans in cancer, peroxisome, cAMP signaling pathway, HIF-1 signaling pathway, and Ras signaling pathway, as shown in Fig. 4. The top 10 pathways were selected, and a network diagram of ingredients, targets, pathways, and diseases was created using Cytoscape 3.9.1, as shown in Fig. 5. The more connections in the network, the greater the impact.

In the GO enrichment analysis, 20 biological functions were identified, including protein synthesis, enzyme synthesis, hormone response, protein receptor activity, transcription regulation, and cell proliferation. The main cellular components included the perinuclear region of the cytoplasm, secretory granule lumen, small molecule catabolic process, response to hormones, etc., as shown in Fig. 6.

3 Discussion

The pathological feature of PF is the repeated injury and repair of lung tissue, resulting in continuous damage to alveoli and proliferation of fibroblasts, ultimately leading to massive deposition of extracellular matrix in the lung interstitium, which is a common outcome of many lung diseases [17]. In the early stage of PF, pulmonary inflammation is the main manifestation, followed by the chronic inflammation and tissue repair phase, and ultimately, the excessive proliferation of fibroblasts and abnormal tissue repair result in the deposition of a large amount of

Fig. 2 Network map of *Gentiana yunnanensis* component targets and PF targets. The blue circles represent targets, the red triple arrows represent the disease PF, the green triangles represent GRR, the yellow diamonds represent active ingredients, and the font size is proportional to the number of connections



collagen fibers in the lung interstitium, leading to PF. The pathogenesis of PF is considered to be the abnormal activation and differentiation of myofibroblasts, which is a central link in the occurrence of PF [18]. Therefore, to improve PF, two key points need to be addressed: first, inflammation in the early stage needs to be suppressed, and second, abnormal cell proliferation in the later stage needs to be addressed. Through the intersection of target prediction for the components of GRR and the PF-related targets, it was found that there is good matching between the two.

The key target MDM2 encodes a nuclear E3 ubiquitin ligase. E3 ubiquitin ligases may have anti-inflammatory effects by promoting macrophage polarization to the M2 phenotype [19–21]. Ubiquitin E3 ligases can contribute to PF by regulating TGF- β -dependent pathways [22].

VEGFA (vascular endothelial growth factor A) is a member of the PDGF/VEGF growth factor family. It encodes a heparin-binding protein that exists as a disulfide-linked homodimer. This growth factor induces the proliferation and migration of endothelial cells and is critical for both physiological and pathological angiogenesis. In mice,

disruption of this gene results in abnormal embryonic blood vessel formation [23, 24]. During severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) infection, VEGF levels increase, thereby promoting inflammation by recruiting inflammatory cells and by increasing the level of angiotensin II (Ang II), one of the two products of SARS CoV-2 binding target angiotensin converting enzyme 2 (ACE2) [25]. Conversely, Ang II promotes the increase in VEGF, thus forming a vicious cycle in the release of inflammatory cytokines.

ERBB2 (Erb-B2 receptor tyrosine kinase 2) encodes a member of the epidermal growth factor (EGF) receptor family of receptor tyrosine kinases. The protein itself does not have a ligand binding domain and therefore cannot bind growth factors [26]. However, it does tightly associate with other ligand-bound EGF receptor family members to form heterodimers, stabilizing ligand binding and enhancing kinase-mediated activation of downstream signaling pathways such as those involving mitogen-activated protein kinase and phosphatidylinositol-3 kinase. It participates in transcriptional regulation in the nucleus and is associated with and activates transcription of the PTGS2/

Fig. 3 GRR action on a pulmonary fibrosis target PPI protein–protein interaction network diagram

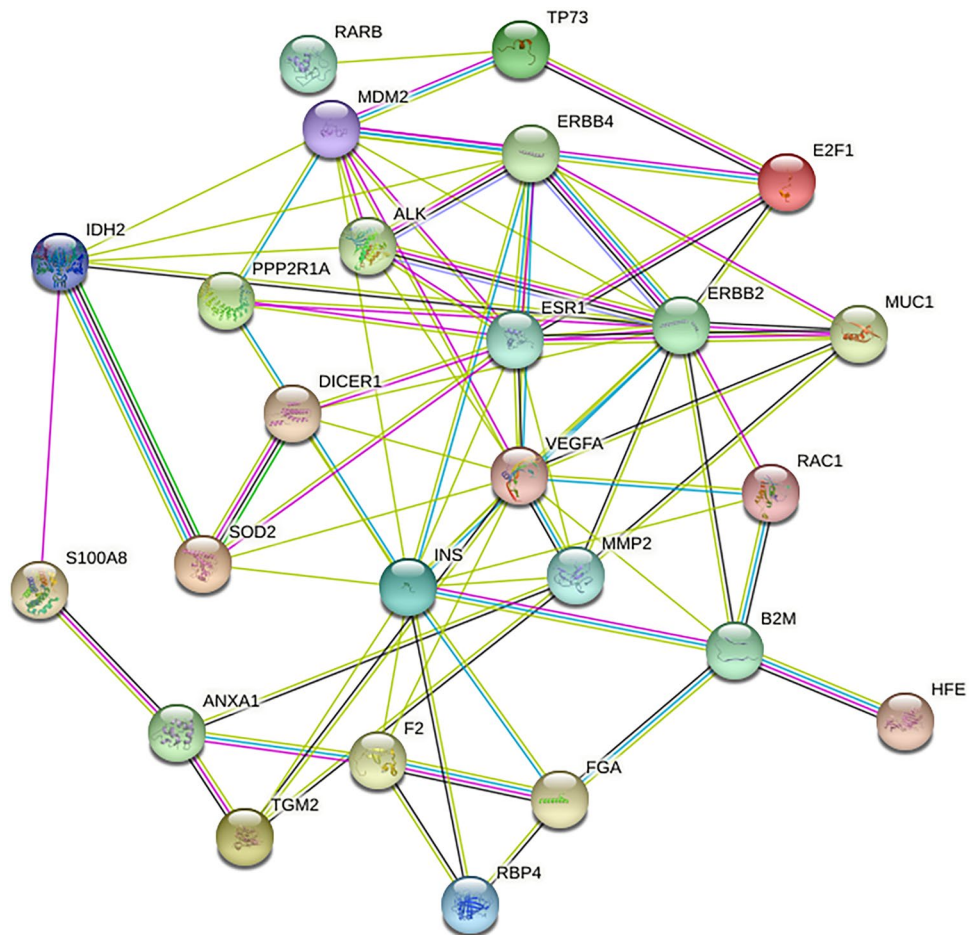


Table 2 Key anti-fibrotic targets of GRR

Name	Betweenness unDir	Closeness unDir	Degree unDir
MDM2	105.4549684	0.018181818	11
ERBB2	155.8865234	0.020833333	16
ESR1	47.49481367	0.018518519	13
VEGFA	103.3600595	0.020000000	15
B2M	69.14545455	0.016393443	7
INS	250.0285244	0.021276596	18

COX-2 promoter with the 5'-TCAATTC-3' sequence. It is also involved in the transcriptional activation of CDKN1A, which involves STAT3 and SRC. It participates in the transcription of rRNA genes through RNA Pol I and enhances protein synthesis and cell growth. Studies have provided evidence that the upregulation of the ERBB2 protein facilitates the growth, proliferation, and metastasis of non-small cell lung cancer (NSCLC) cells, particularly in lung adenocarcinoma patients, thus establishing ERBB2 as a crucial therapeutic target in tumor management [27]. Moreover, Huang et al. [28] have suggested DS8201a as a potential drug candidate targeting aberrations in the

ERBB2 pathway, while afatinib has demonstrated promising therapeutic effects against cancer cases harboring ERBB2 mutations.

Therefore, Gentiopicroside tetraacetate may exert its effects on the cancer-related ERBB2 pathway by inhibiting ERBB2 activity, thereby attenuating excessive fibroblast proliferation and abnormal tissue repair in the lungs, leading to a deceleration of the PF process.

The KEGG pathway enrichment analysis showed that GRR can act on multiple pathways, including carbon metabolism, protein processing in the endoplasmic reticulum, peroxisomes, cAMP signaling pathway, and Ras signaling pathway. Among them, the cancer signaling pathway, cAMP signaling pathway, and Ras signaling pathway are all related to abnormal cell proliferation. GO functional analysis indicated that GRR was associated with physiological functions such as protein synthesis, enzyme synthesis, hormone response, protein receptor activity, transcriptional regulation, and cell proliferation.

Due to practical constraints such as limited time and resources, experimental validation was not performed in this study. However, it is important to note that the data utilized in our research were derived from

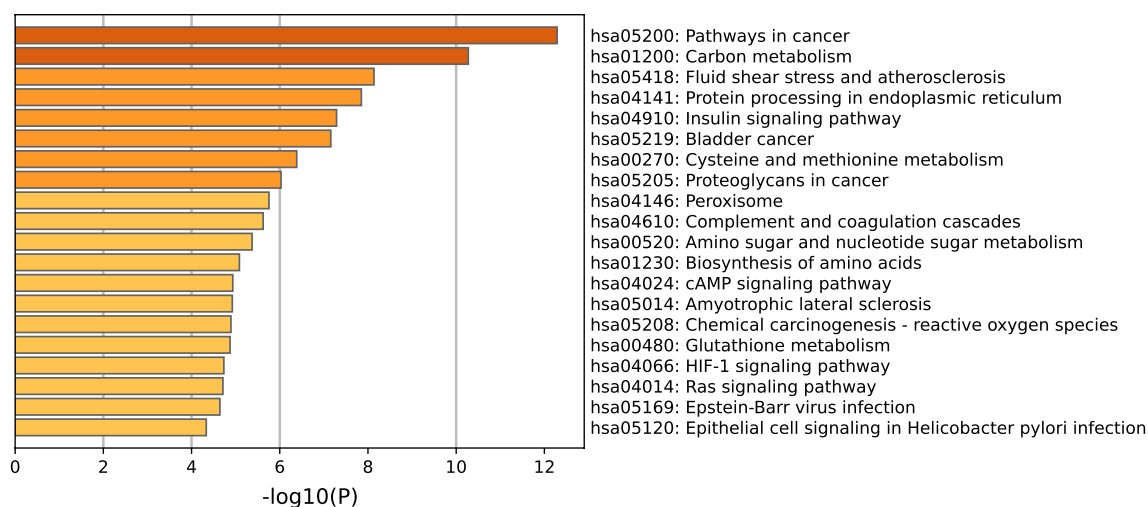
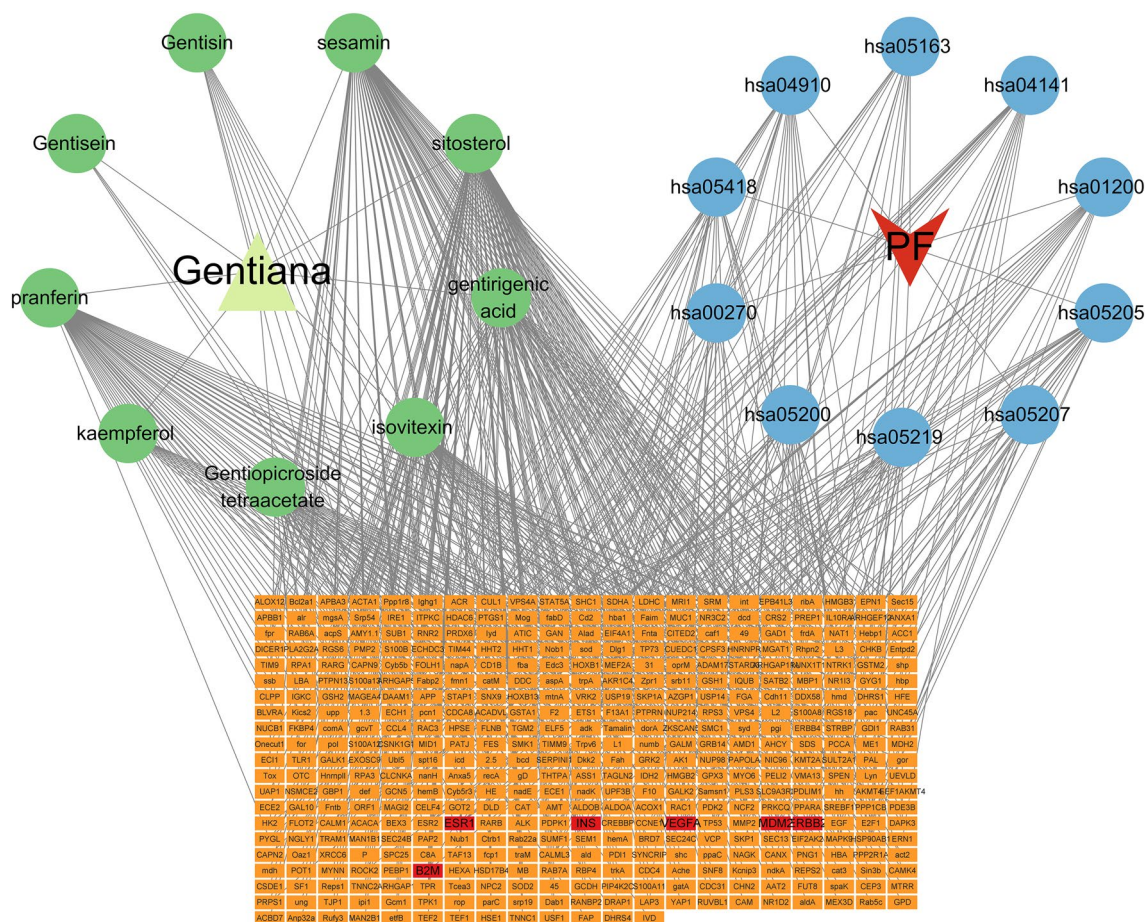


Fig. 4 Enrichment analysis of KEGG pathways for the target proteins of GRR



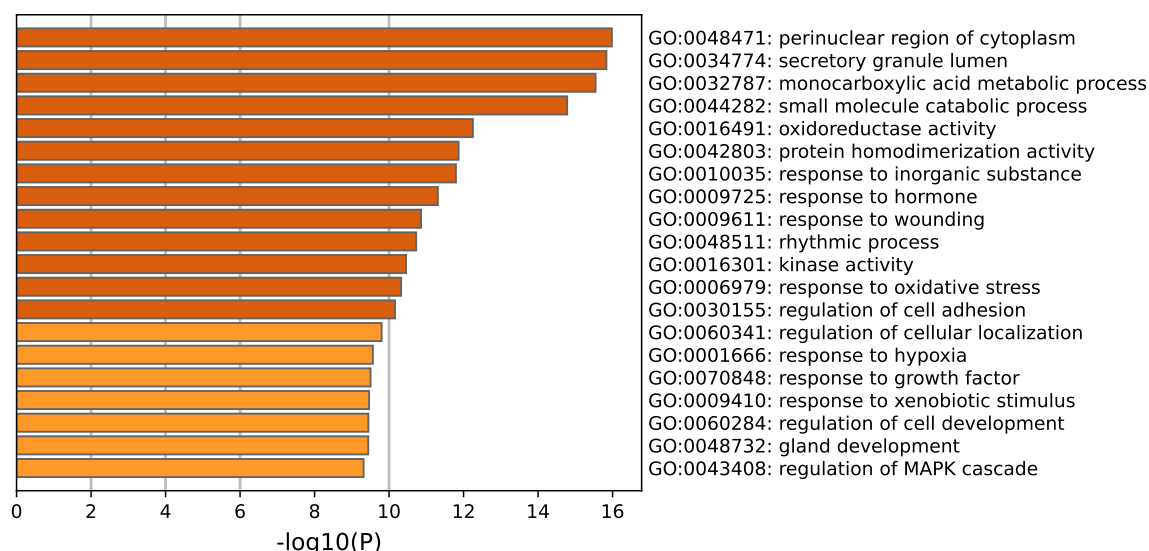


Fig. 6 Gene ontology (GO) molecular function enrichment analysis of the targets of GRR

well-established and highly credible public databases. The methods employed in our analysis are known for their minimal margin of error and high reproducibility.

Moreover, the congruence between our research findings and the conclusions drawn from other related experimental studies mutually reinforces and supplements our results. This convergence of evidence lends further support to the validity and reliability of our findings. It also underscores the value of our research in providing insightful guidance for future validation experiments.

While the absence of experimental validation in this study is acknowledged as a limitation, we are committed to conducting the necessary experimental investigations in subsequent research endeavors. By combining theoretical insights with empirical evidence, we aim to establish a comprehensive and robust framework that further consolidates our findings and contributes to the advancement of the field.

4 Conclusion

In summary, GRR can exert its therapeutic effect on PF through multiple active components, acting on multiple targets and pathways with complex mechanisms. Specifically, Gentiopicroside tetraacetate, as a major active compound in GRR, may decelerate fibroblast overproliferation and abnormal tissue repair in the lungs by inhibiting the activity of ERBB2. This study provides a theoretical basis for the anti-lung fibrosis effect of GRR and provides a scientific basis for its extensive use in the future.

5 Materials and methods

5.1 Software and databases

The databases used in this study include TCMSP [29], PubChem [30], PharmMapper [31], GeneCards [32], UniProt [33], STRING [34], and DAVID [35, 36]. Cytoscape 3.9.1 [37] software and its plugins were used for data visualization.

5.2 Methods

5.2.1 Screening of chemical components

Chemical components of GRR were collected from the TCMSP database. Considering that the main administration routes of GRR are decoction and oral administration, the thresholds of oral bioavailability (OB) and drug-like index (DL) are limited to $OB \geq 30\%$ and $DL \geq 0.18$, respectively. After screening and deduplication, a table of effective and active compounds was generated.

5.2.2 Construction of target networks for GRR and PF

PubChem was used to search and download the 2D and 3D structures of each compound, then the prepared compound structures were imported into PharmMapper. After running the program, predicted protein targets for each compound were obtained. After obtaining all compound targets, duplicates were removed, and UniProt was used to query the corresponding gene IDs for each target. PF-related target genes collected from the online human gene database GeneCards (<https://www.genecards.org/>) by searching the term "Pulmonary Fibrosis". UniProt was

used to standardize the protein target data, and a Venn diagram was used to identify the intersection between the disease targets and the active compound targets. Finally, Cytoscape 3.9.1 software was used to construct a visualized network diagram of the active compound targets and disease targets.

5.2.3 Construction of the protein–protein interaction network of GRR on PF targets

The target genes obtained in the previous step were uploaded to the STRING 11.0 database to obtain protein interaction information with a confidence protein parameter score greater than 0.40, and the target proteins were analyzed.

5.2.4 GO enrichment analysis and KEGG pathway analysis

The obtained common key target proteins were subjected to functional annotation and enrichment analysis using DAVID, and enrichment analysis was performed on the lung fibrosis target proteins and signaling pathways of GRR.

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Author contributions H-MX carried out the experiments. H-MX, and L-WH conceived the research, analyzed the data, and prepared the manuscript. L-HF and G-PF collected Signal pathway, interpretation of results. S-YQ and G-PF conceived the English polishing. All authors contributed to the article and approved the submitted version.

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Data availability The data used in this study were obtained from publicly available databases.

Declarations

Conflict of interest The authors declare that they have no Conflict of interest.

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