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RESEARCH ARTICLE

Research on the potential mechanism of ginsenoside Rg3 against gastric cancer based on network pharmacology

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ABSTRACT

Gastric cancer (GC) remains one of the most prevalent malignancies worldwide, particularly in East Asia. Despite advancements in treatment strategies, the prognosis for advanced GC patients remains unsatisfactory. Ginsenoside Rg3, a key bioactive component derived from Panax ginseng, has demonstrated significant antitumor effects in various cancers, including GC. This study systematically explores the potential mechanisms underlying the therapeutic effects of Ginsenoside Rg3, on GC, employing network pharmacology and molecular docking technologies. Key target genes and signaling pathways were identified, highlighting their critical roles in tumor cell proliferation, apoptosis, and metastasis. Molecular docking analyses revealed strong binding affinities between Ginsenoside Rg3, and crucial protein targets, supporting its direct interaction and functional modulation. The findings provide valuable insights into the molecular basis of Ginsenoside Rg3's anticancer activity and underscore its potential as a promising therapeutic candidate for GC. Future research and clinical studies are encouraged to validate these mechanisms and evaluate the clinical applicability of Ginsenoside Rg3.

Keywords: Ginsenoside Rg3; Network Pharmacology; Gastric Cancer; Multi-target Action; Signaling Pathway; Molecular Docking

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1. Introduction

Gastric cancer is one of the most common malignant tumors of the digestive system worldwide, with its high incidence and mortality rates posing a significant threat to human health. According to statistics from Globocan 2020, gastric cancer ranks fifth among newly diagnosed cancers globally and fourth in cancer-related mortality rates[1]. Despite the continuous development of methods such as surgery, chemotherapy, targeted therapy, and immunotherapy, many patients are already in the advanced stage at the time of diagnosis, resulting in limited treatment efficacy and low survival rates[2]. Therefore, developing effective and low-side-effect treatment options has become a key direction in gastric cancer research.

The application of natural products in cancer treatment has received widespread attention, with traditional Chinese medicine showing unique advantages due to its broad range of action targets and lower side effects[3]. Ginsenoside Rg3, a key active component of ginseng, exhibits significant anti-tumor effects by suppressing cell proliferation, inducing apoptosis, limiting angiogenesis, and reducing metastasis[4]. Network pharmacology provides a new perspective for studying the efficacy of natural products, effectively predicting potential mechanisms of action through systematic analysis of the

complex relationships between drugs, targets, and pathways[5]. Studies have found that Rg3 can exert anti-cancer activity by regulating multiple signaling pathways, such as PI3K/Akt, MAPK, and NF-kB[6]. In clinical applications, Rg3 is mainly used in the form of ginseng capsules in combination with chemotherapy, which not only enhances efficacy but also reduces chemotherapy toxicity[7]. However, the specific molecular mechanisms of Rg3 in gastric cancer treatment have not been fully clarified and require further investigation.

This study aims to systematically explore the mechanisms of action of ginsenoside Rg3 in gastric cancer treatment based on network pharmacology and molecular docking technology[8]. By screening potential targets of Rg3 and gastric cancer-related genes, combined with the construction of protein-protein interaction (PPI) networks and functional enrichment analysis, key targets and core pathways are identified, and the binding characteristics of the drug with targets are validated through molecular docking. Additionally, by reviewing relevant clinical studies, the practical application value of Rg3 in gastric cancer treatment is further verified[9], providing theoretical support and scientific basis for its development as an anti-gastric cancer drug.

2. Materials and methods

2.1. Potential target screening

2.1.1. Obtaining compound information and targets

The SMILES of ginsenoside Rg3 was obtained from PubChem. The properties of these two compounds, including physicochemical properties, absorption, distribution, metabolism, excretion, and toxicology, were evaluated using SwissADME (http://www.swissadme.ch) [10] and ADMETlab3.0 (https://admetmesh.scbdd.com[11] to assess the similarity in drug properties and safety of Rg3.

The targets of ginsenoside Rg3 were predicted and collected using SEA(https://sea.bkslab.org/)[12], SwissTargetPrediction(http://www.swisstargetprediction.ch/), and Herb (http://herb.ac.cn/) databases by integrating SMILES and three-dimensional structures. All database parameters were set to default options to generate the predicted target information for ginsenoside Rg3.

The obtained target information was merged and deduplicated to obtain the potential active targets of ginsenoside Rg3.

2.1.2. Collection of gastric cancer-related genes

Using "Gastric Cancer" as a keyword, we searched for gastric cancer genes in the Therapeutic Target Database （ http://db.idrblab.net/ttd/,TTD ） , Human Gene Database （ https://www.genecards.org,Gene Cards[13], DisGeNET(https://disgenet.org), and Online Mendelian Inheritance（https://omim.org/,OMIM） [14] in Man. Duplicates were removed, and the gene set was filtered for further analysis.

2.2. Target-pathway network construction

2.2.1. Construction of protein-protein interaction network (PPI)

STRING （ https://cn.string-db.org/[15] is an online biological database that can predict PPI networks. The intersection targets of ginsenoside Rg3 and gastric cancer were imported into the STRING database, with the species set to "Homo sapiens" and the confidence level set to 0.400 to obtain the required minimum interaction score. The network was visualized using Cytoscape 3.10.3, and the CytoNCA plugin was used to calculate the topological indices in the interaction network, including betweenness centrality (BC), closeness centrality (CC), degree centrality (DC), eigenvector centrality (EC), local average connectivity-based method (LAC), and network centrality (NC). The median of each topological index was used as a threshold to filter key targets. The MOCDE plugin was used to obtain key subnetworks, and the intersection with key targets was taken to obtain core targets.

2.2.2. Gene ontology (go) and kyoto encyclopedia of genes and genomes (kegg) enrichment analysis

To annotate the functions and pathways of the intersection targets, the DAVID database was used for GO and KEGG enrichment analysis, with $P < 0.05$ considered significantly enriched. The pathway enrichment analysis results were visualized using an online bioinformatics platform （http://www.bioinformatics.com.cn/）.

2.2.3. Construction and topological analysis of the "ginsenoside Rg3–target–pathway" network

Using Cytoscape 3.10.3[16], the intersection targets of ginsenoside Rg3 in treating gastric cancer and its KEGG enrichment pathway results were used to construct the "Ginsenoside Rg3–Target–Pathway" network. The CytoNCA plugin was used to obtain network topological information, using DC as the primary indicator and BC, CC, and EC as secondary indicators to filter the key core targets and pathways of ginsenoside Rg3 in treating gastric cancer.

2.3. Molecular docking analysis

2.3.1. Preparation of target protein structures

The ten core targets from section 2.1 were used for further molecular docking to study the interaction between the drug and the target. First, the three-dimensional structures of hub proteins with similar (or no) ligands to the studied compound were obtained from the RCSB Protein Data Bank[17]. The structure of ginsenoside Rg3 was downloaded from the Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform. Second, using AutoDock Tools 1.5.7, water was removed from the protein, and all hydrogens were added, followed by checking the charge balance and rotatable bonds of each molecule. Third, the entire protein or at least the receptor active center was surrounded in a grid for further docking. Fourth, semi-flexible docking of the receptor and corresponding ligands was performed using AutoDock Vina with default settings. Then, molecular docking was conducted using the vina-2.0 within the pyrx software to calculate binding energy and output result files. Finally, the results were visualized using PyMol software. The Affinity (kcal/mol) value represents the binding ability of the two; the lower the binding energy, the more stable the ligand-receptor interaction. Visualization analysis was performed using Pymol.

2.4. Clinical support evidence analysis

2.4.1. Data sources

To comprehensively evaluate the adjuvant efficacy of ginsenoside Rg3 in the treatment of gastric cancer, this study systematically reviewed clinical trial literature published between 2015 and 2024 on Shenyi Capsule containing ginsenoside Rg3 combined with chemotherapy. These studies were primarily sourced from databases such as PubMed, CNKI, Web of Science, and Embase, using search terms including “ginsenoside Rg3,” “Shenyi Capsule,” “gastric cancer,” “chemotherapy,” and “clinical trial.” The inclusion criteria were as follows:

Study subjects were patients diagnosed with gastric cancer;

The experimental group received Shenyi Capsule containing ginsenoside Rg3 in combination with chemotherapy, while the control group received chemotherapy alone;

The studies reported data on disease control rate (DCR), objective response rate (ORR), and adverse event incidence;

High-quality studies employing randomized controlled trial (RCT) or prospective cohort study designs;

Studies published within the last five years to reflect the latest clinical research progress.

Ultimately, 20 high-quality studies meeting the criteria were selected, encompassing clinical data from over 1,500 gastric cancer patients.

2.4.2. Data analysis

Clinical research results were integrated through literature review to assess the actual effect of Rg3 in adjuvant therapy for gastric cancer, discussing its mechanism of action in conjunction with network pharmacology results.

3. Results

3.1. Information and targets of ginsenoside Rg3

The properties of ginsenoside Rg3 obtained through SwissADME and ADMETlab indicate that this compound has ideal clinical application performance (**Figure 1** and **Table 1**). According to various drug similarity evaluation criteria, such as Lipinski's rule, Ghose's rule, Veber's rule, Egan's rule, Muegge's rule, bioavailability score, Pfizer's rule, GSK's rule, and Golden Triangle rule, ginsenoside Rg3 is found to be suitable as a drug. Due to its high clearance rate and relatively short half-life, it is recommended for safe and frequent administration. Toxicological evaluations indicate that adverse events requiring special attention in further clinical practice mainly involve hepatotoxicity (H-HT and DILI), nephrotoxicity (DIN), mutagenicity (AMES toxicity), and carcinogenicity (**Table 1**).

For ginsenoside Rg3, 106 target genes were obtained through SEA, 14 target genes through SwissTargetPrediction, and 10 target genes through Herb, resulting in a total of 120 unique target genes after removing duplicates.

Table 1. ADMET evaluation of ginsenoside Rg3.

Properties	Indicator	Ginsenoside Rg3
Physicochemistry properties	MW	784.5
	Water Solubility	Soluble
Medicinal Chemistry	Lipinski Rule	Rejected
	Pfizer Rule	Accepted
	GSK Rule	Rejected
	GoldenTriangle	Rejected
	PAINS	0
	Alarm_NMR Rule	0
	BMS Rule	1
Absorption	Caco-2 Permeability	-6.287
	Pgp-substrate	NO
Distribution	BBB permeant	NO
	PPB	78.7%
Metabolism	CYP1A2 inhibitor	NO
	CYP1A2 substrate	NO
Excretion	CL_{plasma}	0.711
	$T_{1/2}$	2.309
Toxicology	Carcinogenicity	0.27
	DILI	0.481
	Eye Corrosion	0.0
	Eye Irritation	0.006
	Respiratory	0.018

Properties	Indicator	Ginsenoside Rg3
	Human Hepatotoxicity	0.765
	Drug-induced Nephrotoxicity	0.984
	Drug-induced Neurotoxicity	0.004
	Ototoxicity	0.996
	Hematotoxicity	0.702
	Genotoxicity	0.193
	RPMI-8226 Immunitoxicity	0.154
	A549 Cytotoxicity	0.92

Table 1. (*Continued*)

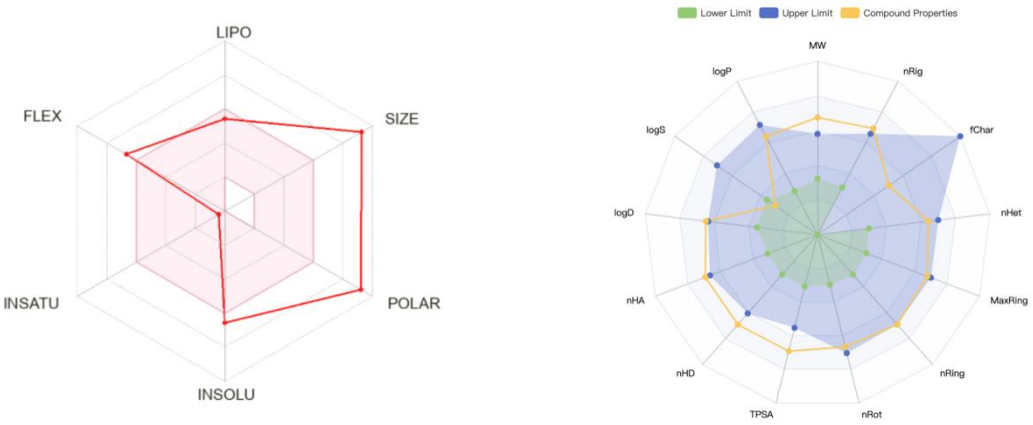

Figure 1. Bioavailability radar plots of ginsenoside Rg3.

3.2. Collection of gastric cancer-related genes

Using the Genecards database, 13,354 gastric cancer targets were obtained, 194 gastric cancer targets from the OMIM database, 48 gastric cancer targets from the TTD database, and 30 gastric cancer-related target genes from Disgenet, resulting in a total of 13,407 targets based on the four databases.

A total of 120 drug-related targets were retrieved, and subsequently, 13,407 gastric cancer-related target genes were retrieved from the four disease databases. By inputting the drug targets and disease targets into Venny (https://www.bioinformatics.com.cn/static/others/jvenn/example.html) and removing redundancies, it was found that ginsenoside Rg3 and gastric cancer share 112 common targets, which are listed in **Figure 2**.

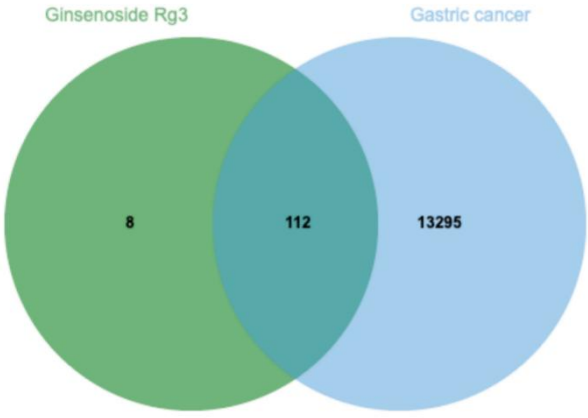

Figure 2. The venn diagram of the targets both in gastric cancer targets and ginsenoside Rg3 targets.

3.3. Construction of target-pathway network

The 112 common targets were used to construct a protein-protein interaction (PPI) network, which was visualized in Cytoscape. Genes were rearranged based on degree with gradient size and color (**Figure 3**). After calculating with the MCC algorithm, we identified 10 hub genes: IFNG, MMP9, EGFR, IL1B, JUN, PPARG, PTGS2, STAT3, IL2, TNF (**Figure 4**).

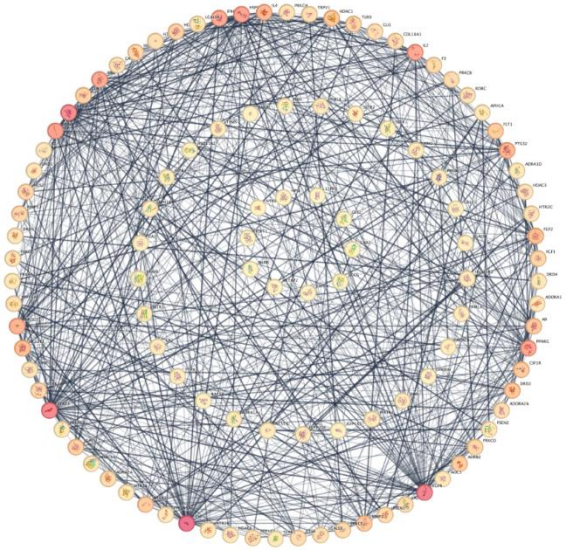

Figure 3. Protein-protein interaction network of 112 overlapping genes.

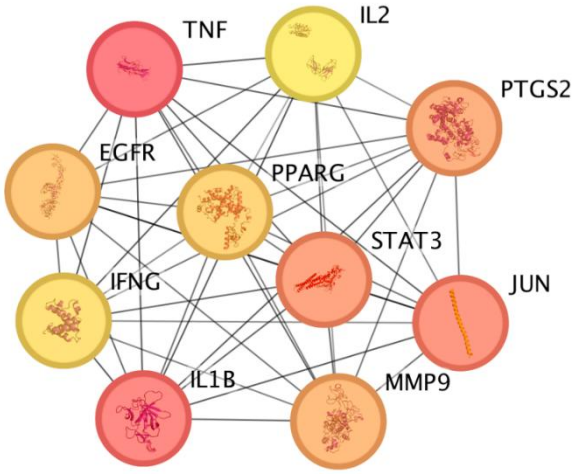

Figure 4. Interaction network of top 10 hub genes.

3.4. Gene ontology (go) and kyoto encyclopedia of genes and genomes (kegg) enrichment analysis

The intersection targets of ginsenoside Rg3 and gastric cancer were uploaded to the DAVID database for GO and KEGG enrichment analysis, with a significance level set at $P < 0.05$.

A total of 1,451 GO enrichment entries were obtained, including 1,905 biological processes (BP), 137 molecular functions (MF), and 94 cellular components (CC). The top 10 entries for BP, MF, and CC were selected based on P values, as shown in **Figure 5**.

The KEGG pathway enrichment results showed that a total of 109 relevant pathways were screened, and the top 10 entries were plotted in a horizontal bar chart, as seen in **Figure 6**. The top 10 pathways are neuroactive ligand-receptor interaction, calcium signaling pathway, insulin resistance, regulation of TRP channels by inflammatory mediators, AGE-RAGE signaling pathway in diabetic complications, cAMP

signaling pathway, inflammatory bowel disease, IL-17 signaling pathway, MAPK signaling pathway, and leishmaniasis. This indicates that ginsenoside can alleviate neuroinflammation and improve animal movement and neurological function by inhibiting the activation of the IL-17 signaling pathway, NLRP3 signaling pathway, MAPK signaling pathway, and regulation of TRP channels by inflammatory mediators, as well as the cAMP signaling pathway.

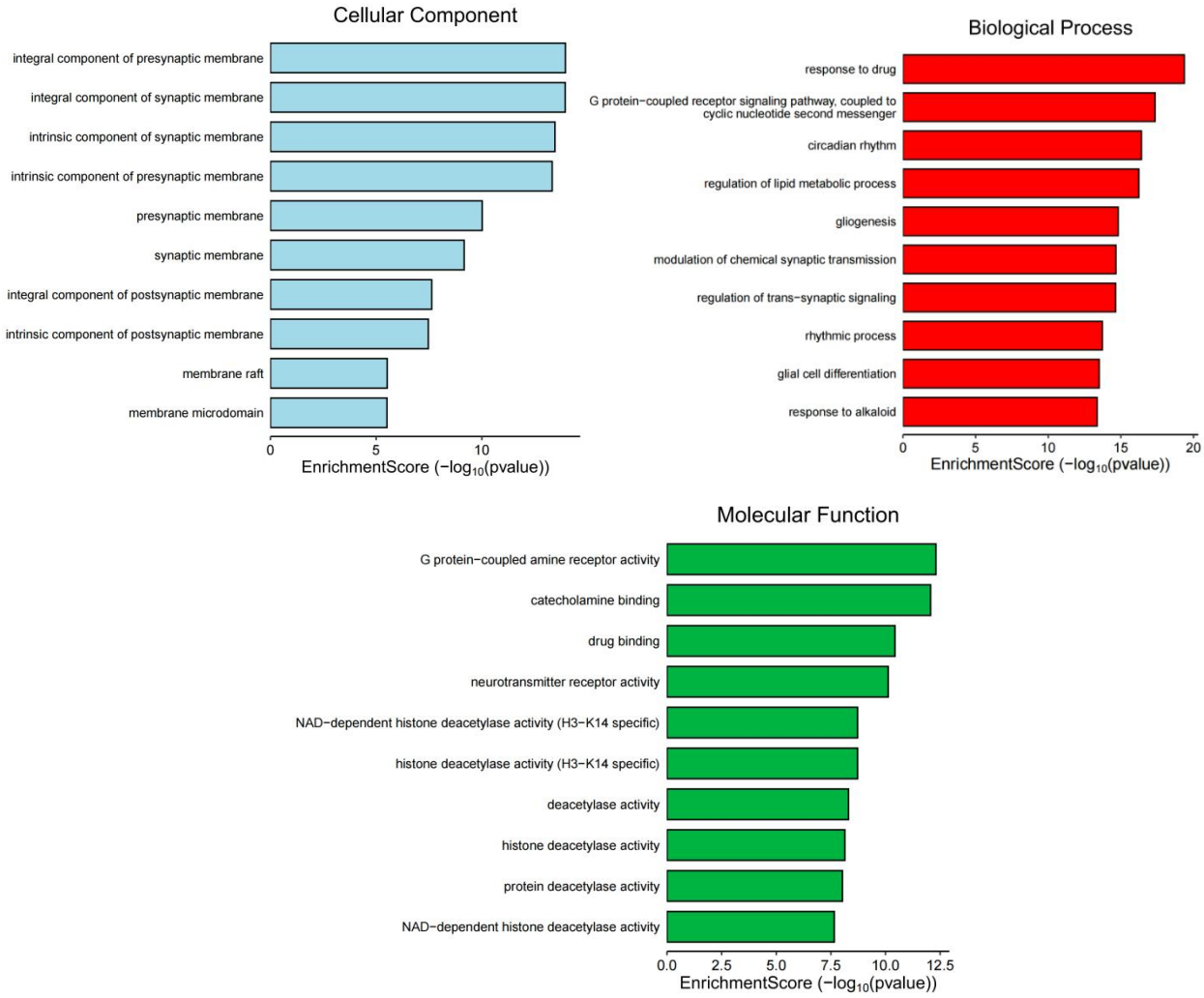

Figure 5. GO map of putative target genes.

3.5. Construction and topological analysis of the "ginsenoside Rg3–target–pathway" network

Based on target and pathway analysis, the network of active compounds and related targets shows the relationship between the compounds and targets. As shown in **Figure 7**, this compound, target, and pathway interaction network consists of 78 nodes and 144 edges.

3.6. Analysis of molecular docking results

The binding energy of ginsenoside with targets is shown in **Table 2**. Generally, a docking energy value less than -4.25 kcal/mol indicates a certain binding activity between the two, less than -5.0 kcal/mol indicates good binding activity, and less than -7.0 kcal/mol indicates strong binding activity. In the docking results, all targets had docking scores less than -4.25 kcal/mol, indicating that all targets can spontaneously bind with ginsenoside, and the binding affinity is strong, suggesting an important role in the treatment of gastric cancer. The specific molecular docking patterns are shown in **Figure 8**.

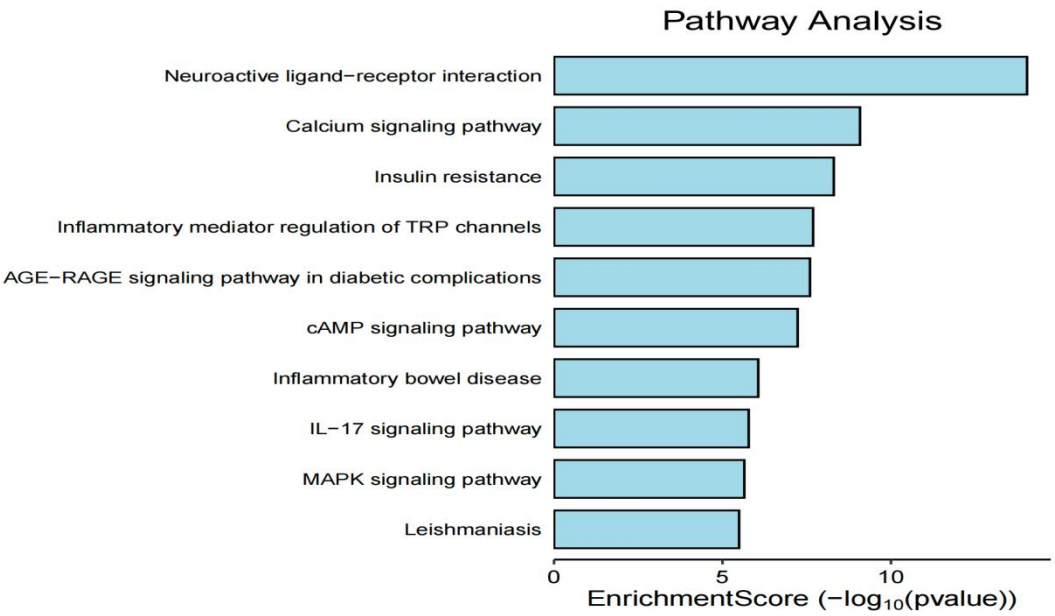

Figure 6. KEGG pathway analysis of putative target genes.

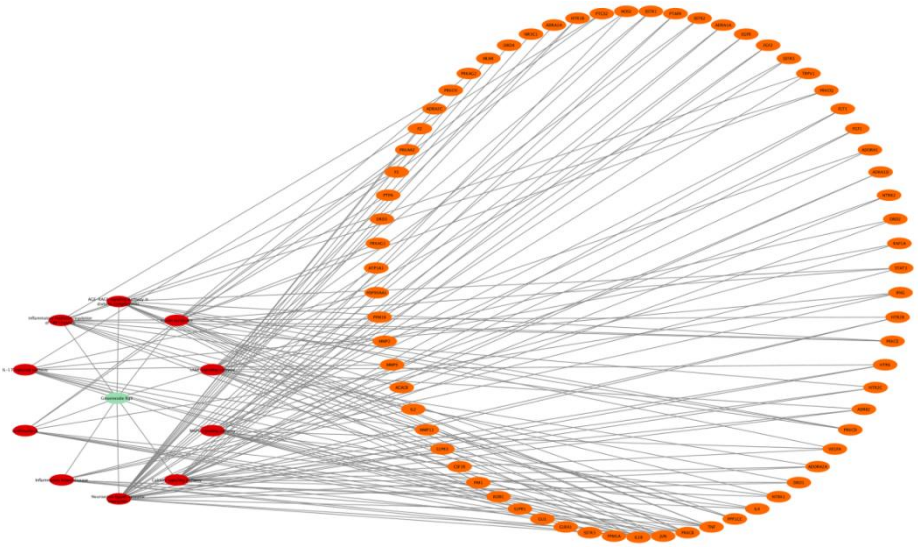

Figure 7. Drug-gc-targets-pathways PPI network.

Table 2. Binding energy of targets and compounds.

GENE	PPARG
IL2	-7.1
IL1B	-7.1
EGFR	-7.8
MMP9	-7.7
JUN	-5.6
TNF	-8.1
IFNG	-7.7
PPARG	-8.8
STAT3	-8.4

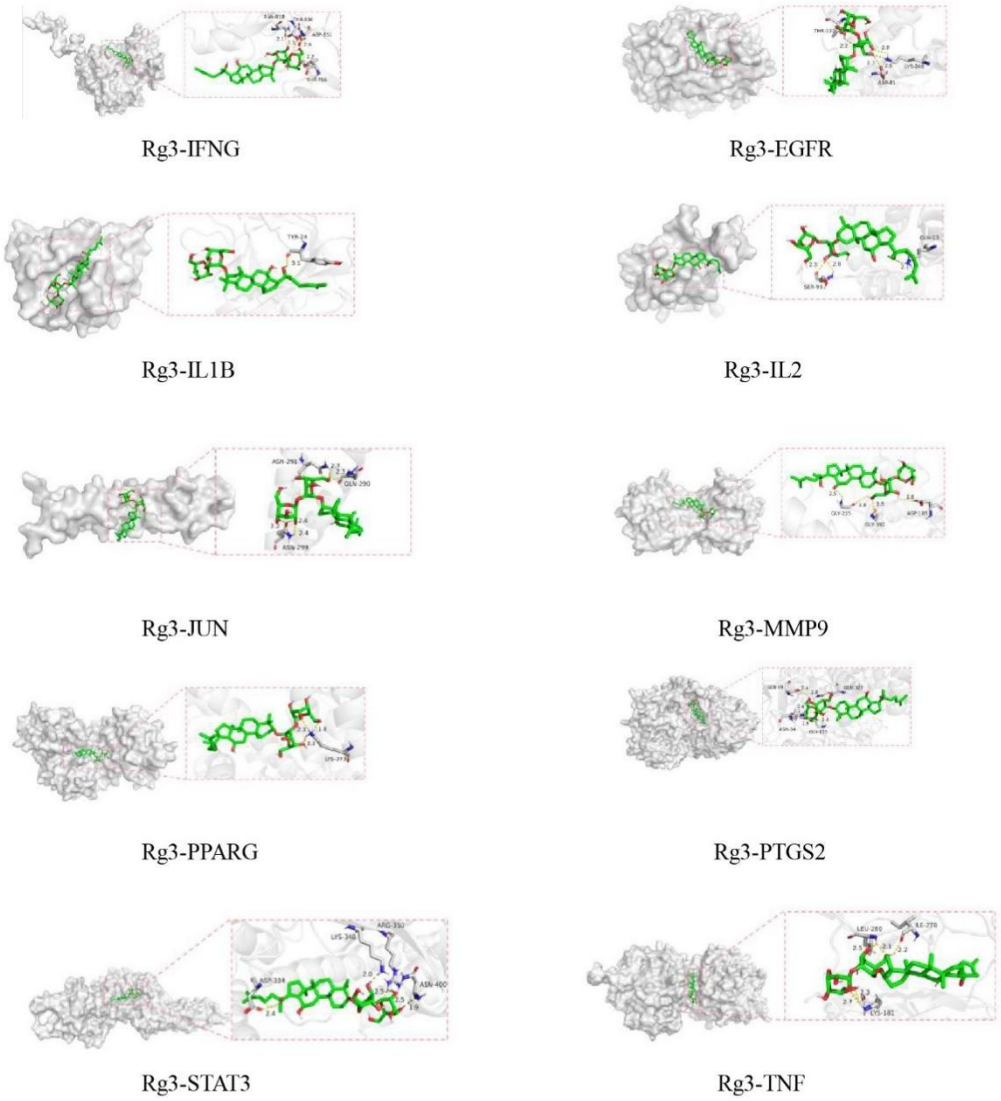

Figure 8. Molecular dockings of hub receptors and compounds.

4. Discussion

This study systematically analyzed the potential molecular mechanisms of ginsenoside Rg3 against gastric cancer using network pharmacology methods. The results indicate that Rg3 may regulate biological processes related to gastric cancer, such as cell proliferation, apoptosis, invasion, and metastasis, through multi-target and multi-pathway synergistic actions, demonstrating its potential as an adjuvant therapeutic agent[18]. Additionally, the clinical usage results of Shenyi capsules further support the practical application value of Rg3 in gastric cancer treatment. The following is an in-depth discussion of the research findings.

4.1. Clinical significance of pharmacokinetics and toxicology characteristics of ginsenoside Rg3

Pharmacokinetic and toxicological evaluations of ginsenoside Rg3 conducted through SwissADME and ADMETlab indicate that Rg3 has certain drug development potential. Although it has some limitations in traditional drug evaluation standards such as Lipinski's rule, for example, a larger molecular weight (784.5 Da) and lower Caco-2 permeability (-6.287), which may affect its oral bioavailability, its good water solubility compensates for this shortcoming, giving it potential clinical application prospects. Furthermore, a

higher plasma protein binding rate (78.7%) and a shorter half-life (2.3 hours) suggest that Rg3 is metabolized quickly in the body, recommending frequent or modified dosage forms, such as sustained-release formulations or targeted delivery technologies, to ensure effective drug concentration[19].

Toxicological evaluations show that Rg3 has potential risks of hepatotoxicity (H-HT score of 0.765) and nephrotoxicity (DIN score of 0.984) to some extent, which may be related to its metabolites or tissue-specific toxicity at high doses. However, its carcinogenicity (0.27) and mutagenicity (0.193) risks are low, indicating a higher safety profile for Rg3 in chemotherapy alternatives or adjuvant therapy. Future studies need to combine in vivo and in vitro experiments to assess the specific mechanisms of these toxic risks to ensure the safety of Rg3's clinical application.

4.2. Intersection analysis of ginsenoside Rg3 and gastric cancer-related targets

By integrating drug and disease target data, a total of 112 common targets were identified, covering multiple key aspects of gastric cancer occurrence, development, and anti-tumor responses. Some of these targets, such as EGFR, STAT3, and TNF, have been widely studied and validated to play critical roles in gastric cancer[20]. This suggests that Rg3 may intervene in the pathological processes of gastric cancer through multi-target synergistic actions.

The occurrence and development of gastric cancer typically involve multi-factorial and multi-pathway synergistic actions, making the multi-target action mechanism of drugs more suitable for the treatment needs of this complex disease. The 112 common targets screened through network pharmacology provide important clues for the mechanism of Rg3 against gastric cancer and also offer a clear molecular basis for subsequent research.

4.3. Significance of protein-protein interaction (PPI) network and key targets

PPI network analysis revealed the complex associations between common targets, further validating the anti-cancer potential of Rg3 through multi-pathway and multi-target synergistic actions. Among the 10 hub genes selected, TNF, STAT3, and EGFR are key regulatory factors in gastric cancer, participating in inflammatory responses, immune regulation, and shaping the tumor microenvironment, directly affecting the invasiveness and metastatic potential of gastric cancer[21].

Additionally, genes such as IL1B, IL2, and IFNG play important roles in tumor immune regulation. Studies have shown that gastric cancer patients often exhibit immune evasion, and Rg3 may rebalance the immune system's ability to recognize and eliminate tumor cells by activating or inhibiting these targets. Furthermore, the regulatory roles of PPARG and PTGS2 suggest that Rg3 may intervene in the proliferation and migration of gastric cancer cells by inhibiting tumor-associated inflammation and regulating lipid metabolism.

4.4. Biological mechanisms revealed by GO and KEGG analysis

GO functional enrichment analysis shows that the common targets of Rg3 play important roles in multiple biological processes, especially in inflammatory responses (such as cytokine secretion regulation) and immune response regulation. This result is consistent with the widely reported anti-inflammatory and immune-regulatory effects of Rg3. Molecular function (MF) analysis reveals that Rg3 targets mainly focus on cytokine receptor binding and protein phosphatase activity regulation, further supporting the hypothesis that Rg3 exerts anti-tumor effects by regulating signaling molecules[20].

The results of KEGG pathway enrichment analysis indicate that Rg3 exerts anti-gastric cancer effects by regulating multiple cancer-related pathways, including the IL-17 signaling pathway, MAPK[22] signaling pathway, and regulation of TRP channels by inflammatory mediators. The IL-17 signaling pathway has become a research hotspot in gastric cancer in recent years, as IL-17 promotes inflammatory responses and

immune suppression in the tumor microenvironment, participating in tumor occurrence and development[23]. Rg3's inhibition of this pathway may suppress tumor progression by reducing the secretion of inflammatory factors and restoring immune surveillance functions. Additionally, Rg3's regulation of the MAPK signaling pathway may further prevent the malignant growth of gastric cancer cells by intervening in cell proliferation and apoptosis processes[24].

4.5. Topological analysis of target-pathway network

The "Rg3–Target–Pathway" network constructed based on shared targets and pathways (**Figure 7**) highlights the potential of Rg3 to intervene in gastric cancer through multi-target and multi-pathway mechanisms. Network analysis indicates that Rg3 may regulate key molecules in tumor-related signaling pathways directly or indirectly. For example, ginsenoside Rg3 may attenuate the inflammatory response in gastric cancer by inhibiting the activation of IL-17 and its downstream pathways, such as STAT3 signaling[25]. By interfering with IL-17-induced angiogenesis, it may also suppress tumor growth and metastasis. This network topology provides insights for designing combination therapies in future studies, such as combining Rg3 with immune checkpoint inhibitors, which may enhance its anticancer efficacy.

4.6. Molecular docking validation of target binding ability

Molecular docking experiments further validated the high-affinity binding between Rg3 and key targets. Among them, PPARG (-8.8 kcal/mol) and PTGS2 (-8.9 kcal/mol) showed the strongest binding capabilities[26]. This indicates that Rg3 may exert its effects by regulating lipid metabolism, inhibiting inflammatory responses, and modulating the tumor microenvironment. As a key factor in regulating cell differentiation and metabolism, the high-affinity binding of PPARG suggests that Rg3 may impact the metabolic adaptability of gastric cancer cells; while PTGS2, as a key target of inflammatory factors, indicates that Rg3 may alleviate gastric cancer-related inflammatory states by inhibiting the production of pro-inflammatory prostaglandins.

The docking energy of TNF is -8.1 kcal/mol, making it one of the strongest binding targets, indicating that Rg3 may reduce the secretion of inflammatory factors by inhibiting TNF activity, thereby weakening the inflammatory microenvironment of gastric cancer. Additionally, the binding with STAT3 (-8.4 kcal/mol) and EGFR (-7.8 kcal/mol) validates the potential role of Rg3 in intervening in cancer signaling pathways.

The docking results show that Rg3 has good binding activity to key targets, providing theoretical support for the experimental results and further confirming the reliability of Rg3's multi-target action mechanism. These data provide an important basis for the targeted development of Rg3 in gastric cancer treatment and suggest that molecular docking models can serve as important tools for screening active components of traditional Chinese medicine and their targets.

4.7. Support and inspiration from clinical evidence

This study, by integrating clinical trial data and mechanistic analyses, further confirms the efficacy and safety of ginsenoside Rg3 in the adjuvant treatment of gastric cancer. Shenyi Capsule combined with chemotherapy significantly improves the disease control rate and objective response rate, while reducing chemotherapy-related adverse reactions and enhancing patients' quality of life. In the future, large-scale, multicenter randomized controlled trials are needed to further validate the efficacy and safety of Rg3[27]. Additionally, incorporating pharmacokinetic studies and developing novel drug delivery systems hold promise for enhancing the bioavailability and clinical value of Rg3.

5. Conclusion

This study systematically reveals the potential mechanisms of Rg3 in treating gastric cancer through network pharmacology, PPI network analysis, and molecular docking methods. Rg3 intervenes in

inflammatory responses, immune regulation, and cancer-related signaling pathways through comprehensive regulation of multiple targets and pathways, thereby inhibiting the occurrence and development of gastric cancer. Although clinical translation requires further research, the prospects for Rg3 in gastric cancer treatment are promising[28], providing important evidence for the development of new traditional Chinese medicine anti-cancer drugs.

Conflict of interest

The authors declare no conflict of interest.

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