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Research article

Clinical efficacy and potential mechanism of ginseng polysaccharides in the treatment of non-small cell lung cancer based on meta-analysis associated with network pharmacology

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ABSTRACT

Background: The ginseng polysaccharide injection is a well-known traditional Chinese medicine often employed as a supplementary treatment for cancer. This treatment can not only alleviate the adverse effects caused by tumor radiotherapy and chemotherapy but also enhance the immune system of individuals diagnosed with lung cancer. It is important to acknowledge the efficacy of ginseng polysaccharide injection in the treatment of non-small cell lung cancer (NSCLC). However, these small-sample studies may have certain biases, and the underlying mechanisms of ginseng polysaccharides therapy for NSCLC are still unclear.

Methods: The present study involved a systematic review of the literature on randomized controlled trials (RCTs) focusing on using ginseng polysaccharide injection as a therapeutic approach for NSCLC. Seven databases were searched for eligible studies published before April 2023. Two researchers independently managed data extraction, risk of bias assessment, and data analyses using RevMan 5.3 software. In network pharmacology, we thoroughly searched the relevant literature on ginseng polysaccharides (GPs) and the PubChem database. This search aimed to identify the main active ingredients and targets associated with ginseng polysaccharides. Subsequently, we compared these targets with those of NSCLC and utilized bioinformatics techniques to analyze and explore their potential interactions.

Results: A total of 11 RCTs involving 845 patients with NSCLC were included in the meta-analysis. The meta-analysis revealed that ginseng polysaccharide injection combined significantly improved the objective response rate [RR = 1.45, 95% CI (1.26, 1.67), $P < 0.00001$]. Furthermore, it was observed that ginseng polysaccharide injection increased the serum levels of $CD4^+$ T-lymphocytes ($CD4^+$ T) [MD = 8.98, 95% CI (5.18, 12.78), $P < 0.00001$], and decreased the serum levels of $CD8^+$ T-lymphocytes ($CD8^+$ T) [MD = −2.68, 95% CI (−4.66, −0.70), $P = 0.008$]. Through network pharmacology analysis, a total of 211 target genes of GPs and 81 common targets were identified. GAPDH, EGFR, VEGFA, JUN, SRC, CASP3, STAT3, CCND1, HSP90AA1, and MMP9 were identified as the core target proteins. Additionally, KEGG enrichment analysis

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revealed 122 relevant signaling pathways, including Pathways in cancer, PD-L1 expression and PD-1 checkpoint pathway in cancer, and Proteoglycans in cancer.
Conclusion: Ginseng polysaccharide injection can improve the ORR of patients with NSCLC, increase the serum levels of $CD4^+$ T, and decrease the serum levels of $CD8^+$ T. The potential mechanism may be associated with the PD-1/PD-L1 signaling pathway.

1. Introduction

Lung cancer is a leading cause of cancer-related deaths globally. Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancer cases, while small-cell lung cancer (SCLC) accounts for approximately 15% [1,2]. By 2023, it is estimated that there will be 238,140 new cases of lung cancer in the United States, resulting in approximately 127,070 deaths (20.8% of all cancer deaths) [3].

Treatments for NSCLC include surgery, radiotherapy, chemotherapy, targeted therapy, and immunotherapy [4]. Drug resistance remains a challenge in current lung cancer treatment, as even the most effective therapies fail to sustainably suppress tumor response, ultimately resulting in resistance and tumor recurrence [5,6]. In addition, the adverse events produced during long-term treatment are one of the most important reasons for declining the quality of life of patients [7]. Currently, it has been found that the immune system plays an important role in suppressing tumor development and progression. Immunotherapy, especially immune checkpoint inhibitors (e.g., PD-1/PD-L1 inhibitors), has shown promise in prolonging the survival of patients with advanced lung cancer, with fewer adverse reactions compared to other treatments [8]. Ginseng, one of the most commonly used Chinese medicines in clinical practice, contains various active ingredients, including saponins, polysaccharides, volatile oils, amino acids, etc. Relevant studies have demonstrated that ginseng polysaccharides (GPs) play an indispensable role in immunomodulation, antitumor, antioxidant effects, etc [9,10]. Recent studies suggest that GPs can not only play an anti-tumor role through immunomodulation, but also improve the sensitivity of patients with advanced NSCLC to PD-1/PD-L1 immunotherapy by combining with αPD-1 monoclonal antibody, thus enhancing the anti-tumor efficacy [11].

Many first-line chemotherapeutic agents for lung cancer (e.g., paclitaxel, vincristine) are natural drug extracts. Therefore, further investigation is needed to explore the potential advantage of GPs as a new therapeutic agent for lung cancer. Given that multiple randomized controlled trials (RCTs) have evaluated the efficacy of GPs for adjuvant therapy for lung cancer, we conducted this meta-analysis to summarize the current evidence. Meanwhile, we also predicted the potential mechanism of GPs in the treatment of NSCLC by the use of network pharmacology.

2. Materials and methods

2.1. Meta-analysis

2.1.1. Literature search strategy

A comprehensive search was conducted in the following databases: PubMed, Embase, Cochrane Library, China National Knowledge Infrastructure (CNKI), Weipu Information Chinese Journal Service Platform (VIP), and Wanfang Data Knowledge Service Platform (Wanfang Data). A combination of free words and subject words was used as the search method. The search terms were ("Carcinoma, Non-Small-Cell Lung"[Mesh]) AND ((((((((((Carcinoma, Non Small Cell Lung[Title/Abstract]) OR (Carcinomas, Non-Small-Cell Lung [Title/Abstract])) OR (Lung Carcinoma, Non-Small-Cell[Title/Abstract])) OR (Lung Carcinomas, Non-Small-Cell[Title/Abstract])) OR (Non-Small-Cell Lung Carcinomas[Title/Abstract])) OR (Non-Small-Cell Lung Carcinoma[Title/Abstract])) OR (Non Small Cell Lung Carcinoma[Title/Abstract])) OR (Carcinoma, Non-Small Cell Lung[Title/Abstract])) OR (Non-Small Cell Lung Carcinoma[Title/Abstract])) OR (Non-Small Cell Lung Cancer[Title/Abstract])) OR (Nonsmall Cell Lung Cancer[Title/Abstract])) AND (ginseng polysaccharide injection[Title/Abstract]) OR (ginseng polysaccharides[Title/Abstract])) OR (GPs[Title/Abstract]. We reviewed articles published in any language before April 2023.

2.1.2. Inclusion and exclusion criteria

Inclusion criteria: ①RCTs; ②studies where patients were diagnosed with NSCLC according to Chinese Common Malignant Tumor Diagnostic and Treatment Criteria [12]; ③studies where control groups were treated with regular chemotherapy, while intervention groups were treated with ginseng polysaccharide injection and regular chemotherapy; ④studies where outcomes included at least one of the following: objective response rate, immune function ($CD4^+$ T-lymphocytes, $CD8^+$ T-lymphocytes), or long-term survival.

Exclusion criteria: ①studies where intervention groups were treated with other traditional Chinese; ②studies with incomplete data; ③duplicated published literature.

2.1.3. Inclusion of literature risk of bias assessment

Data extraction and quality evaluation of the included literature were independently conducted by two investigators. In case of disagreement, a third investigator was consulted for discussion and negotiation. The extracted data included the first author, publication time, patient age, lung cancer stage, intervention, and course of treatment. Quality evaluation was performed using the risk-of-bias assessment method recommended by the Cochrane Assistance Network.

2.1.4. Statistics and analysis of data

For dichotomous variables, odds ratios (OR) with 95% confidence intervals (CI) were selected as effect sizes, while mean differences (MD) were used as the effect size for continuous variables. The I-square (I^2) test was used to assess heterogeneity among the included studies, and a fixed-effect model was used for studies with insignificant heterogeneity ($I^2 < 50\%$); otherwise, a random-effect model was used. Publication bias was evaluated using the funnel plot. The statistical analyses mentioned above were conducted using RevMan 5.3 and Stata 12 software.

2.2. Network pharmacology

2.2.1. Collection of ginseng polysaccharide components and their potential targets

The main active components of GPs were identified by reviewing relevant literature from both domestic and international sources. The SMILES numbers of these main components of ginseng polysaccharides were obtained from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/) and inputted into the SwissTargetPrediction database (http://www.swisstargetprediction.ch/) to predict their potential targets.

2.2.2. Acquisition of targets related to NSCLC

To identify potential targets associated with NSCLC, the OMIM (Online Mendelian Inheritance in Man, https://www.omim.org/) and GeneCards Suite databases (https://www.genecards.org/) were utilized to search for potential disease targets using the keyword "non-small cell lung cancer".

2.2.3. Acquisition of targets common to disease and drug

To determine the potential targets of GPs for treating NSCLC, the drug targets obtained in Section 2.2.1 were compared with the disease targets obtained in Section 2.2.2 through the online Wayne software Venny 2.1.0 (https://bioinfogp.cnb.csic.es/tools/venny/). A Venn diagram was then created to illustrate the results.

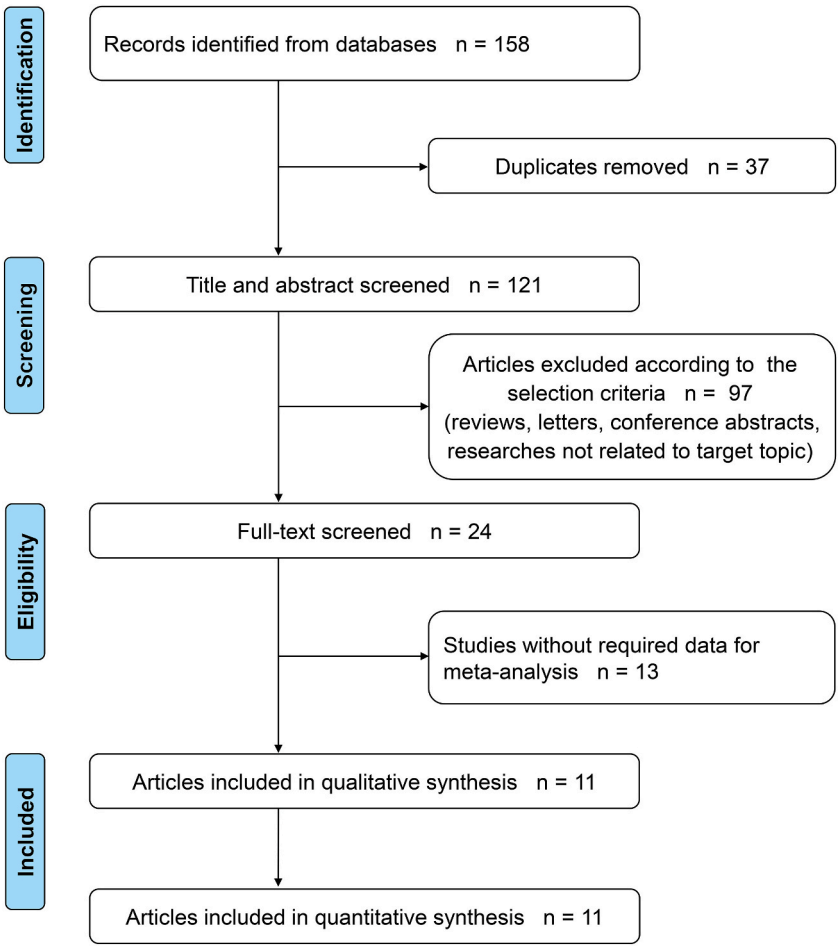


Fig. 1. Flowchart of literature search and screening.

2.2.4. Constructing of "drug -target-disease" network diagrams"

Using Cytoscape software, a "drug-target-disease" network diagram was created to illustrate the links between GPs and NSCLC. The diagram was then analyzed topologically.

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

To illustrate the role of target proteins in the network, an analysis was conducted on the common targets of GPs and NSCLC using the STRING database (https://string-db.org/). The analysis primarily concentrated on the species *Homo sapiens*, with a screening criterion of a combined score > 0.4. The PPI networks of the intersecting targets were obtained, and the resulting TSV files obtained from STRING analysis were imported into Cytoscape software to visualize the network. Topological analysis was performed to determine the degree value and filter the core targets based on their size. The node color shades and sizes varied according to the degree value.

2.2.6. GO and KEGG enrichment analysis

To characterize and annotate the function of the target genes, as well as to explore the signaling pathway involved. The intersecting targets screened in 1.2.4 were uploaded to the DAVID database (https://david.ncifcrf.gov). Gene Ontology (GO) gene function and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis were performed to obtain information on biological processes (BP), cellular components (CC), molecular functions (MF), and key KEGG pathways of the intersecting targets. For KEGG pathway key information, p-value <0.05 was the inclusion criteria. The data results were visualized using bioinformatics.com.cn to screen the biological processes and potential signaling pathways involved in the GPs treatment of NSCLC.

3. Results

3.1. Meta-analysis

3.1.1. Search results

A total of 11 RCTs were finally included, with 845 patients in total, 429 in the treatment group, and 416 in the control group. The detailed literature screening flowchart is shown in Fig. 1.

3.1.2. Baseline information about the included studies

Three studies included patients aged >60 years [13–15]. Eight articles included patients ranging from 30 to 80 years old [16–23]. Control groups received regular chemotherapy, while intervention groups were treated additionally with ginseng polysaccharide injection. Six articles administered the injection intravenously [14,15,17,19,21,23], while five articles used intramuscular injection [13,16,18,20,22]. The treatment duration ranged from 30 to 126 days. More details are provided in Table 1.

3.1.3. Quality assessment of the included literature

Five studies described randomized assignment methods [15–18,20], which were evaluated as having a low risk of bias. Two studies

Table 1
Characteristics of included studies.

Study	Age	Sample (T/C)	Interventions (T/C)		Duration (days)	Outcomes
Zeng et al., 2001	40–70	31/32	Chemotherapy therapy and ginseng polysaccharide injection	Chemotherapy therapy	30	①
Fan et al., 2016	40–73	43/44	Chemotherapy therapy and ginseng polysaccharide injection	Chemotherapy therapy	42	①
Ge et al., 2015	41–79	65/65	Chemotherapy therapy and ginseng polysaccharide injection	Chemotherapy therapy	84	①②③
Li et al., 2013	38–77	40/40	Chemotherapy therapy and ginseng polysaccharide injection	Chemotherapy therapy	42–56	①③
Liang et al., 2020	41–78	50/50	Chemotherapy therapy and ginseng polysaccharide injection	Chemotherapy therapy	56	①
Liang et al., 2013	60–73	26/24	Chemotherapy therapy and ginseng polysaccharide injection	Chemotherapy therapy	112	①
Tu et al., 2016	60–88	60/48	Chemotherapy therapy and ginseng polysaccharide injection	Chemotherapy therapy	21–28	①②
Wang et al., 2022	41–77	24/24	Chemotherapy therapy and ginseng polysaccharide injection	Chemotherapy therapy	84–126	①②
Wang et al., 2022	42–73	40/40	Chemotherapy therapy and ginseng polysaccharide injection	Chemotherapy therapy	84	①
Zhang et al., 2004	≥60	34/33	Chemotherapy therapy and ginseng polysaccharide injection	Chemotherapy therapy	60	②
Zhu et al., 2013	**30–79**	**16/16**	**Chemotherapy therapy and ginseng polysaccharide injection**	**Chemotherapy therapy**	**120**	**①**

T: treatment group; C: control group; ① objective response rate; ② immune function; ③long-term survival rate.

mentioned "randomization" without a detailed method description and were considered to have an unclear risk of bias [13,21]. Two studies allocated patients according to patients' preferences [14,19], while one study allocated patients based on the order of treatment [22]. These studies were considered to have a high risk of bias. One study did not provide any details about the allocation method used, therefore it was classified as having an uncertain risk of bias [23]. All studies did not mention the allocation concealment and blind method and were regarded as having an uncertain risk of bias. Details are presented in Fig. 2.

3.1.4. Meta-analysis of outcome indicators

ORR: A total of 10 studies including 810 patients reported the ORR [13,15–23]. The heterogeneity across studies was not significant ($I^2 = 0\%$) and a fixed-effect model was used. The meta-analysis indicated that the ORR of patients in treatment groups was markedly higher than that of patients in control groups [RR = 1.45, 95% CI (1.26, 1.67), $P < 0.00001$]. Please see Fig. 3A.

Long-term survival: A total of 2 studies including 210 patients reported six-month survival rates [20,22]. The heterogeneity across studies was significant ($I^2 = 92\%$) and a random-effect model was used. The meta-analysis indicated that there was no statistically significant difference in the comparison between patients in treatment groups and those in the control groups [RR = 1.39, 95% CI (0.74, 2.63), $P = 0.31$]. The two studies also reported one-year survival rates. The heterogeneity across studies was not significant ($I^2 = 0\%$) and a fixed-effect model was used [20,22]. The meta-analysis indicated that there was no statistically significant difference between the treatment groups and those in the control groups [RR = 1.26, 95% CI (0.99, 1.60), $P = 0.06$]. Please see Fig. 3B.

Immune function: A total of 4 studies including 354 patients reported the content of $CD4^+$ T in the peripheral blood of patients [14,15,17,20]. The heterogeneity across studies was significant ($I^2 = 74\%$) and a random-effect model was used. The meta-analysis indicated that the content of $CD4^+$ T in the peripheral blood of patients in treatment groups was higher than that of patients in control groups [MD = 8.98, 95% CI (5.18, 12.78), $P < 0.00001$]. The four studies also reported the content of $CD8^+$ T in the peripheral blood of patients [14,15,17,20]. The heterogeneity across studies was not significant ($I^2 = 37\%$), and a fixed-effect model was used. The meta-analysis indicated that the content of $CD8^+$ T in the peripheral blood of patients in treatment groups was lower than that of patients in control groups [MD = −2.68, 95% CI (−4.66, - 0.70), $P = 0.008$]. Please see Fig. 3C.

3.1.5. Publication bias analysis

A funnel plot was drawn for the results of ORR. No significant publication bias was found according to the visual assessment of the funnel plot. Please see Fig. 4.

3.2. Network pharmacology

3.2.1. Search results for the main components and potential targets of GPs

By conducting an extensive examination of both domestic and international literature, we have successfully identified six distinct chemical constituents present in GPs that exhibit notable pharmacological effects. These constituents include D-Glucose, D-Galactose, Cytarabine, L-Rhamnose, D-Galacturonic acid, and L-Arabinose [24,25]. To further validate our findings, we proceeded to search for the names of these components in the PubChem database and retrieved their respective SMILES numbers. Following a meticulous screening and analysis process, we were able to ascertain a total of 211 target genes that are closely associated with GPs from the SwissTargetPrediction database.

3.2.2. Search results for non-small cell lung cancer disease-related target

We conducted a thorough search of the OMIM database for the keyword "non-small cell lung cancer", yielding a total of 1505 targets. Furthermore, we utilized the GeneCards Suite database and applied a Relevance score of ≥25.6, resulting in 2004 targets. After merging the targets from both databases and eliminating duplicates, we successfully obtained a final set of 3277 targets.

3.2.3. Results of the intersection between drugs and diseases

The intersection was analyzed between the two sets of targets obtained in 2.2.1 and 2.2.2. Using the online Wayne software Venny

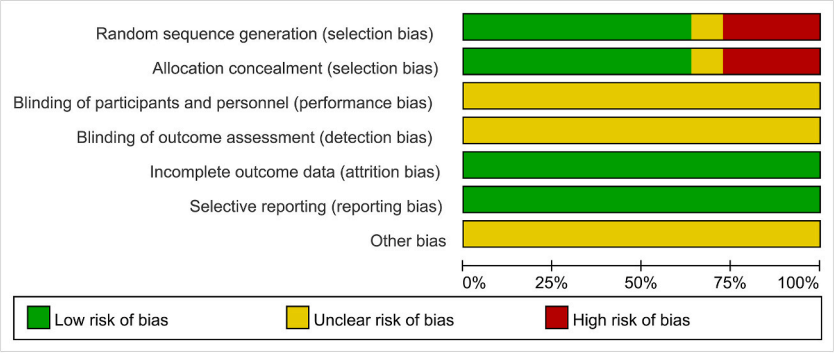
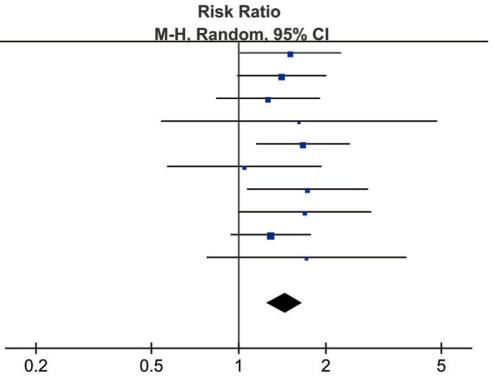


Fig. 2. Quality assessment of the included literature: Assessment for risk of bias across all included literature.

A

Study or Subgroup	Treatment group Events	Total	Control group Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Fan et al 2016	28	43	19	44	12.3%	1.51 [1.01, 2.26]
Ge et al 2015	38	65	27	65	16.0%	1.41 [0.99, 2.00]
Li et al 2013	24	40	19	40	11.7%	1.26 [0.84, 1.91]
Liang et al 2013	7	26	4	24	1.7%	1.62 [0.54, 4.83]
Liang et al 2020	35	50	21	50	14.4%	1.67 [1.15, 2.42]
Tu et al 2016	17	60	13	48	5.3%	1.05 [0.57, 1.93]
Wang et al 2022	19	24	11	24	8.6%	1.73 [1.07, 2.79]
Wang et al 2023	22	40	13	40	7.2%	1.69 [1.00, 2.87]
Zeng et al 2001	25	31	20	32	19.6%	1.29 [0.94, 1.78]
Zhu et al 2013	12	32	7	32	3.2%	1.71 [0.78, 3.79]
Total (95% CI)		**411**		**399**	**100.0%**	**1.45 [1.26, 1.67]**
Total events	227		154			

Heterogeneity: Tau² = 0.00; Chi² = 3.68, df = 9 (P = 0.93); I² = 0%



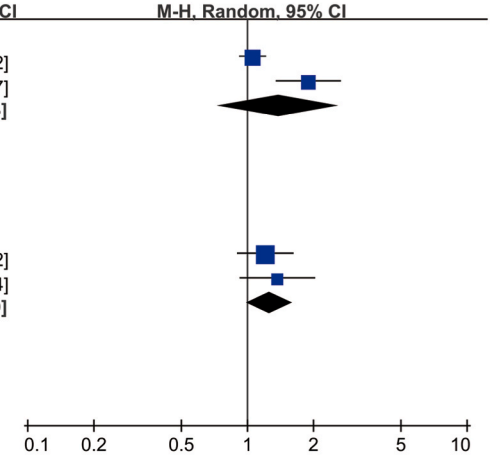
B

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.1.1 6-month survival						
Ge et al 2015	57	65	54	65	53.0%	1.06 [0.92, 1.22]
Li et al 2013	36	40	19	40	47.0%	1.89 [1.35, 2.67]
Subtotal (95% CI)		**105**		**105**	**100.0%**	**1.39 [0.74, 2.63]**
Total events	93		73			

Heterogeneity: Tau² = 0.19; Chi² = 11.86, df = 1 (P = 0.0006); I² = 92%
Test for overall effect: Z = 1.01 (P = 0.31)

2.1.2 1-year survival						
Ge et al 2015	41	65	34	65	64.1%	1.21 [0.90, 1.62]
Li et al 2013	26	40	19	40	35.9%	1.37 [0.92, 2.04]
Subtotal (95% CI)		**105**		**105**	**100.0%**	**1.26 [0.99, 1.60]**
Total events	67		53			

Heterogeneity: Tau² = 0.00; Chi² = 0.25, df = 1 (P = 0.62); I² = 0%
Test for overall effect: Z = 1.91 (P = 0.06)



C

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
3.1.1 CD4+（%）								
Ge et al 2015	44.2	6.1	65	35.9	5.9	65	32.9%	8.30 [6.24, 10.36]
Tu et al 2016	41	8	60	35	9	48	28.8%	6.00 [2.75, 9.25]
Wang et al 2022	45.23	10.68	24	28.06	9.68	24	19.8%	17.17 [11.40, 22.94]
Zhang et al 2004	41.33	11.19	34	35.27	14.76	34	18.4%	6.06 [-0.17, 12.29]
Subtotal (95% CI)			**183**			**171**	**100.0%**	**8.98 [5.18, 12.78]**

Heterogeneity: Tau² = 10.31; Chi² = 11.51, df = 3 (P = 0.009); I² = 74%
Test for overall effect: Z = 4.63 (P < 0.00001)

3.1.2 CD8+（%）								
Ge et al 2015	34.2	6.1	65	36.9	6.5	65	37.6%	-2.70 [-4.87, -0.53]
Tu et al 2016	34	8	60	35	7	48	28.5%	-1.00 [-3.83, 1.83]
Wang et al 2022	23.06	6.02	24	28.69	5.89	24	22.9%	-5.63 [-9.00, -2.26]
Zhang et al 2004	34.37	9.7	34	35.18	13.09	34	10.9%	-0.81 [-6.29, 4.67]
Subtotal (95% CI)			**183**			**171**	**100.0%**	**-2.68 [-4.66, -0.70]**

Heterogeneity: Tau² = 1.48; Chi² = 4.74, df = 3 (P = 0.19); I² = 37%
Test for overall effect: Z = 2.66 (P = 0.008)

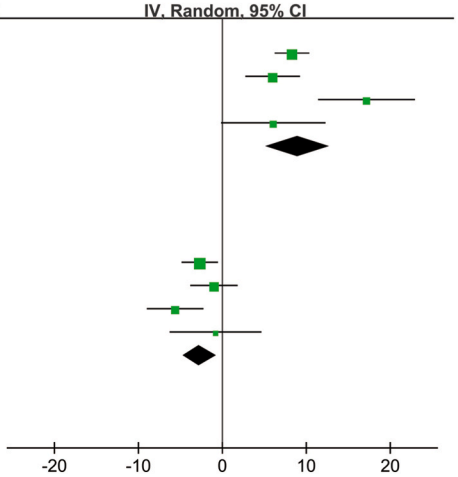


Fig. 3. Results of a meta-analysis: (A) Results of the objective response rate: Forest plot comparing ORR in treatment groups and control groups, ORR = objective response rate; (B) Results of long-term survival of the included studies: Forest plot comparing long-term survival in treatment groups and control groups; (C) Results of immune function in the included studies: Forest plot comparing immune function in treatment groups and control groups.

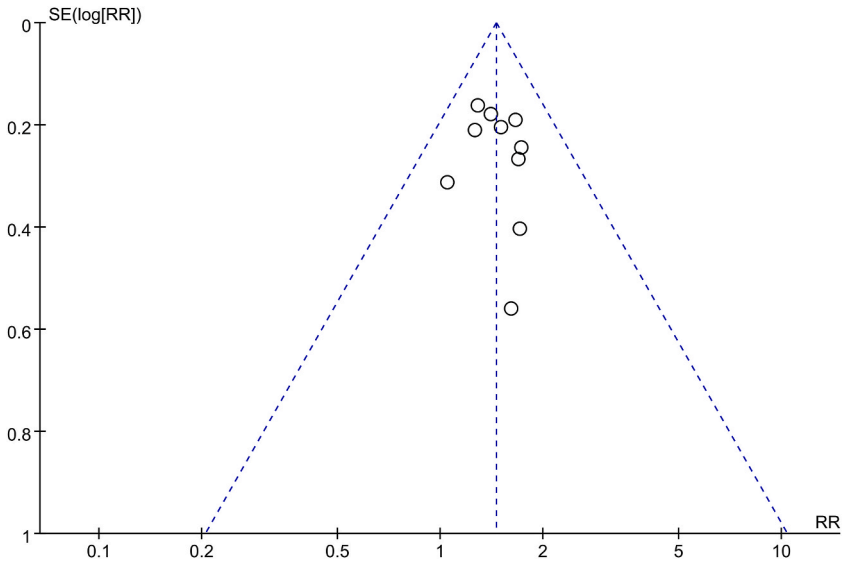


Fig. 4. Funnel diagram.

2.1.0, Venn diagrams were generated. The blue circle represents the GPs targets, and the yellow circle represents the NSCLC targets, revealing a total of 81 intersecting targets. Please see Fig. 5A.

3.2.4. "Drug -target-disease" network diagrams

By utilizing Cytoscape, we successfully developed an interaction network that establishes connections between GPs and NSCLC. This network encompasses a total of 218 nodes and 619 edges. Notably, distinct colors are assigned to different entities within the network: purple represents NSCLC, pink represents GPs, yellow signifies the predicted targets of GPs, and blue symbolizes the intersection of targets of NSCLC and GPs. It indicates that GPs play a therapeutic role in NSCLC through multi-targets. Please see Fig. 5B.

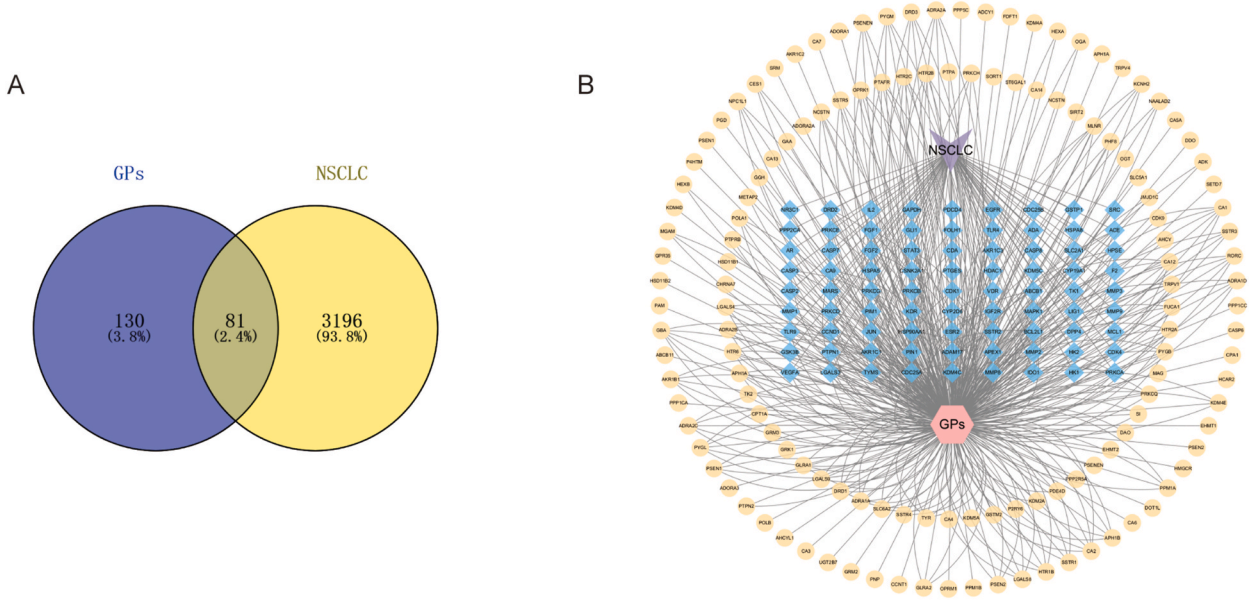


Fig. 5. Results of network pharmacology: (A) Venn diagram: Intersection targets of ginseng polysaccharides and non-small cell lung cancer. The blue circle represents the ginseng polysaccharides target, and the yellow circle represents the non-small cell lung cancer targets. GPs = ginseng polysaccharides, NSCLC = non-small cell lung cancer; (B) GPs for lung cancer treatment: "drug-target-disease" network diagrams: Purple represents NSCLC, pink represents GPs, yellow signifies the predicted targets of GPs, and blue symbolizes the intersection of targets of NSCLC and GPs. GPs = ginseng polysaccharides, NSCLC = non-small cell lung cancer.

3.2.5. Results of the construction and analysis of the PPI network

The intersection targets acquired in section 2.2.3 were imported into the STRING database to produce a PPI network graph. This graph, comprising 80 nodes and 1512 edges, was saved in TSV format and then imported into Cytoscape to further analyze and obtain the visual pattern graph. As shown in Fig. 6A, the nodes represent targets, while the edges represent interactions between these targets. In this graph, the size of a node and the intensity of its color increase as the degree value increases. Similarly, the thickness of an edge and the intensity of its color increase as the combined score value increases. The top 10 targets screened according to the degree value, as shown in Fig. 6B, were GADPH, EGFR, VEGFA, JUN, SRC, CASP3, STAT3, CCND1, HSP90AA1, and MMP9, which play crucial roles in GPs treatment of NSCLC.

3.2.6. GO bioassay and KEGG pathway analysis

The analysis of the 81 intersecting targets from section 2.2.3 resulted in the identification of 319 biological processes, 61 cellular components, and 95 molecular functions through GO enrichment analysis. For further investigation, the top 10 entries were selected for visual analytics, as depicted in Fig. 7A. Moreover, the targets were subjected to KEGG enrichment analysis using the David database. This analysis yielded a sum of 122 entries with $p < 0.05$. The top 20 relevant pathways were selected for visualization, as shown in Fig. 7B, including Pathways in cancer, PD-L1 expression and PD-1 checkpoint pathway in cancer, and Proteoglycans in cancer signaling pathways.

4. Discussion

Lung cancer continues to be a significant global health issue with the increase of morbidity and mortality. The present study demonstrates that co-administration of ginseng polysaccharides significantly improved the treatment response rate, which may be associated with the improvement of immune function in patients with NSCLC.

In recent years, immunotherapy has emerged as a new means of clinical treatment for lung cancer, specifically through the use of monoclonal antibodies that target immune checkpoint proteins [26]. Immune checkpoints play a crucial role in maintaining the balance of the immune system, ensuring autoimmune homeostasis. By regulating the activity of T-lymphocytes, immune checkpoints can effectively suppress tumor growth and exert anti-tumor effects [27]. Programmed cell death protein-1 (PD-1), an immune checkpoint, is expressed on activated T-lymphocytes, B-lymphocytes, and monocytes. Conversely, programmed death protein ligand-1 (PD-L1), its ligand, is commonly found in high levels within tumor cells [28]. The activation of the PD-1/PD-L1 signaling pathway occurs when PD-1 and PD-L1 molecules interact. This activation leads to the negative regulation of the immune response mediated by T-lymphocytes, ultimately inhibiting the elimination of tumor cells by T-lymphocytes. Consequently, this process enables tumor cells to evade the immune system [29,30]. Immune checkpoint inhibitors can disrupt the interaction between PD-1 and PD-L1, effectively alleviating the inhibitory impact of tumor cells on T-lymphocytes. As a result, this facilitates the activation, proliferation, and

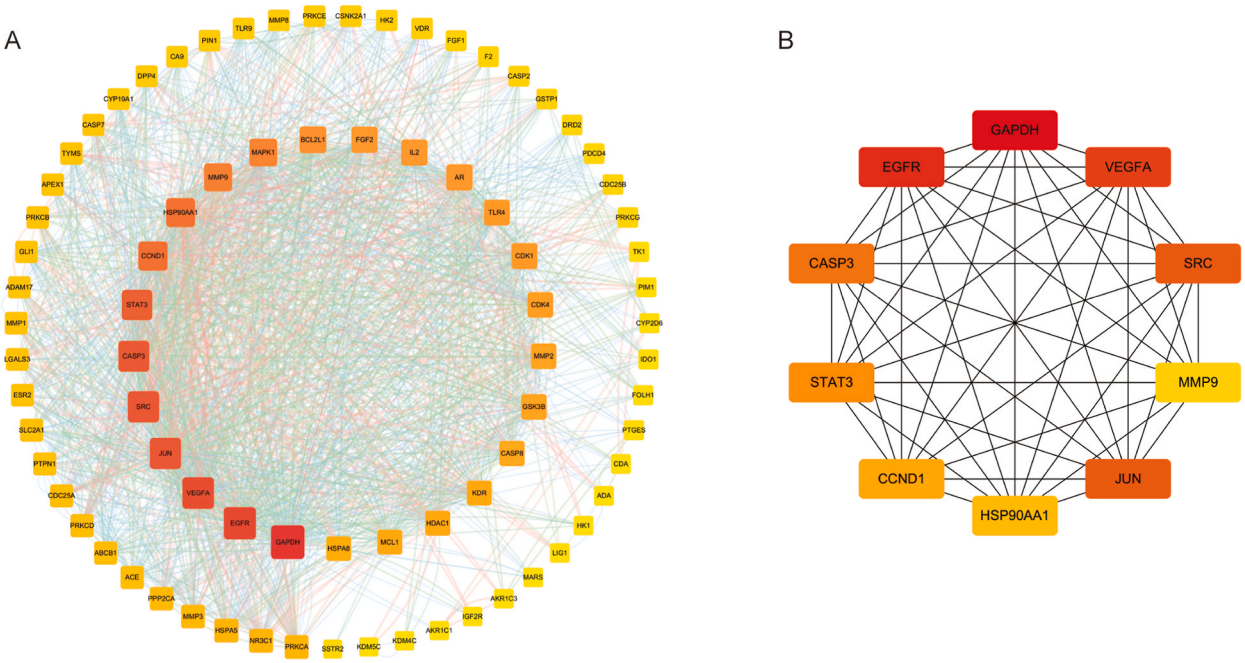


Fig. 6. Network diagram of PPI: (A) PPI network analysis of GPs for the treatment of NSCLC. The larger the node, the higher the degree of the target. GPs = ginseng polysaccharides, NSCLC = non-small cell lung cancer, PPI = Protein-protein interaction; (B) Core target map: The top 10 targets screened by the degree value.

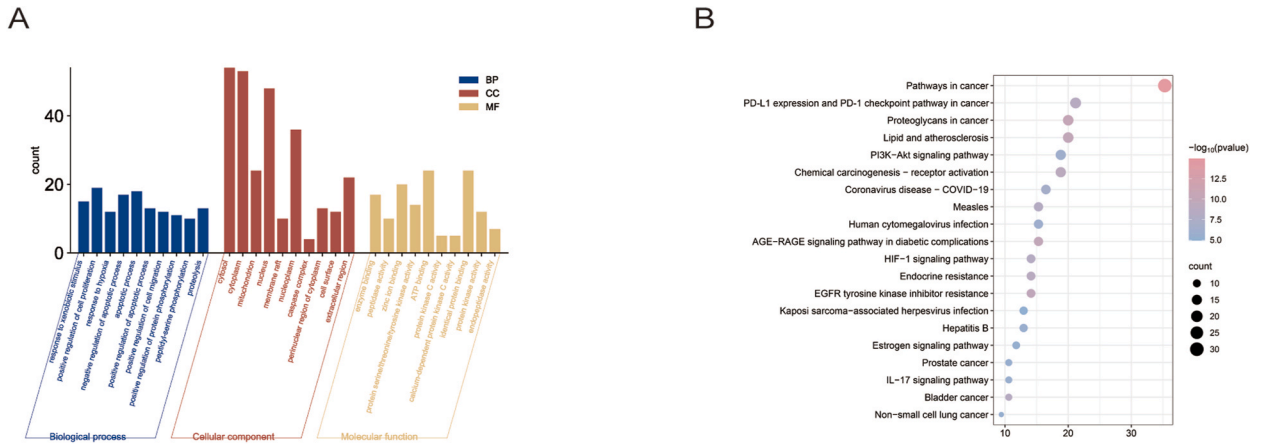


Fig. 7. Results of GO enrichment analysis and KEGG enrichment analysis: (A) The top 10 significant enriched terms in BP, CC, and MF. BP = biological process, CC = cellular component, MF = molecular function, GO = Gene Ontology; (B) The top 20 significant enriched pathways in KEGG, KEGG = Kyoto Encyclopedia of Genes and Genomes.

differentiation of T-lymphocytes, enhancing the body's anti-tumor immune function [31,32].

However, it should be noted that there are numerous potential immune-mediated adverse events. Among them, most NSCLC patients have low lung reserve, and those receiving treatment with anti-PD-1 antibodies are at a higher risk of developing pneumonia. This implies that the lung reserve of such patients may further deteriorate and even be fatal [33,34]. In this meta-analysis, few included trials reported results on adverse events of ginseng polysaccharides. However, several clinical studies have shown that ginseng polysaccharides can alleviate adverse reactions caused by immunotherapy. Therefore, more trials are needed to further evaluate the efficacy and safety of combination therapy of ginseng polysaccharides and other immunotherapeutic drugs in patients with NSCLC. Moreover, some studies suggested that these polysaccharides can activate immune cells such as T-lymphocytes, B-lymphocytes, and NK cells, thereby enhancing immune response and improving the anti-tumor effects of immunotherapy [35–39].

$CD4^+$ and $CD8^+$ T expression levels, as well as the $CD4^+/CD8^+$ T ratios, can serve as indicators of the body's immune function [40]. $CD4^+$ T can modulate intrinsic and adaptive immunity that is associated with tumors. They can also stimulate the production of cytokines and hinder the growth of tumors [41,42]. In contrast, $CD8^+$ T has a detrimental impact on the immune response as it hinders the functioning of $CD4^+$ T and B-lymphocytes. Consequently, this inhibition leads to a suppression of both antibody formation and cellular immune response [43]. The decrease in the ratio of $CD4^+/CD8^+$ T indicates a decrease in the immune function of the body. Studies have demonstrated that individuals with lung cancer often experience a weakened immune system, as evidenced by a significant decrease in the presence of $CD4^+$ T in their peripheral blood compared to healthy individuals. Conversely, the level of $CD8^+$ T is higher in lung cancer patients, resulting in a lower $CD4^+/CD8^+$ T ratio [44–46]. However, blocking the PD-1/PD-L1 signaling pathway has demonstrated efficacy in elevating $CD4^+$ T levels in the peripheral blood of individuals with lung cancer, simultaneously decreasing $CD8^+$ T levels. Consequently, the $CD4^+/CD8^+$ T ratio rises, thereby mitigating immune suppression induced by tumor cells [47,48]. These findings suggest that modulating the PD-1/PD-L1 signaling pathway can enhance immune function and enhance the body's anti-tumor ability, as indicated by changes in the expression levels of various T-lymphocyte subpopulations in the peripheral blood.

The disease now known as "lung cancer" was not specifically labeled as such in ancient Chinese medical literature. Instead, it was identified by its clinical symptoms and signs, such as "pulmonary masses", "xiben", "cough", "phlegm and fluid retention", "wheezing" and so on. Lung cancer primarily affects the lungs and is associated with the liver, spleen, and kidney. According to Zhou Zhongying, a master of Chinese medicine, the basic pathogenesis of lung cancer is the deficiency of qi and blood in internal organs, which leads to congestion and blockage of cancerous toxins in the lungs. Over time, the cancerous toxin can generate pathological substances such as phlegm, blood stasis, heat, and others, which can also be agglutinated with them to eventually form a tumor [49]. Hence, the underlying factors contributing to lung cancer are phlegm, blood stasis, heat, toxicity, and deficiency. The disease is characterized by a combination of healthy qi deficiency and excessive pathogen. The key approach to treating lung cancer is to strengthen the positive aspects and eliminate the negative ones. This entails enhancing the body's ability to resist the disease by regulating the body's qi, blood, yin, and yang, while also eliminating the pathological factors that contribute to cancer. Consistent with what modern medicine states, strengthening the body's immune ability and immune monitoring could effectively inhibit the growth, metastasis, and immune evasion of tumor cells [50–52].

The immunomodulatory properties of GPs are widely acknowledged, as they activate various immune processes and stimulate the production of different cytokines [9,41,53]. The study revealed that in immunosuppressed models, GPs can increase the ratio of $CD4^+/CD8^+$ T in peripheral blood. This correction of immunosuppression enhances the immune function of the body and maintains the homeostasis of the internal environment, thus exerting an anti-tumor effect [54]. The therapeutic concept of GPs can control tumor growth by modulating the immune response through T-lymphocytes is consistent with the basic principle of traditional Chinese medicine in the treatment of lung cancer, which is "to reinforce the healthy qi to eliminate pathogenic factors".

After conducting a comprehensive review of the available literature, this study has revealed the following findings: (1) the administration of ginseng polysaccharide injection can enhance the objective response rate in patients with lung cancer; (2) this injection has the potential to increase the expression level of $CD4^+$ T and decrease the expression level of $CD8^+$ T in peripheral blood of patients.

Furthermore, a network pharmacological analysis conducted as part of this study revealed that GPs contain a total of 216 potential active ingredients. We found the key anti-cancer targets of GPs were GADPH, EGFR, VEGFA, JUN, SRC, CASP3, STAT3, CCND1, HSP90AA1, and MMP9. The study revealed a significant upregulation of GADPH expression in human lung tumor tissue when compared to normal tissue adjacent to the tumor [55,56]. While GADPH itself may not serve as a direct therapeutic target, it can indirectly target other pathways, such as glycolysis [57]. EGFR is regarded as a cancer-driver gene and displays multiple carcinogenic effects, including stimulation of DNA synthesis, cell proliferation, cell migration, and invasion [58]. The clinical trial findings have shown that the utilization of EGFR-TKIs shows better efficacy and higher survival rates but inevitably has the disadvantage of drug resistance [59]. Recent studies have discovered that CASP3 not only exerts anti-cancer effects by promoting apoptosis, but its mechanisms of anticancer activity may also involve angiogenesis, immune response, and inflammatory reactions [60,61]. After the inhibition of CASP3, a noticeable decrease in the migratory and invasive abilities of the tumor cells was observed, while increasing their sensitivity to radiotherapy [62]. STAT3 is an oncogene that promotes the proliferation, motility, and progression of cancer cells. Downregulation or knockout of STAT3 inhibits the proliferation and angiogenesis of tumor cells and reduces the immune escape of tumor cells [63,64]. CCND1 is a crucial regulatory factor in tumor cells, which is capable of promoting tumor cell proliferation and inducing cell cycle arrest at the S phase [65]. siRNAs targeting CCND1 inhibit cancer progression by inducing apoptosis and suppressing tumor cell stemness and epithelial-mesenchymal transition [66]. HSP90AA1 can regulate a variety of biological processes. Clinical observations indicate that high expression of HSP90AA1 is associated with shorter overall survival. Silencing of this protein inhibits the aberrantly activated AKT1 and ERK signaling pathways in tumor tissues, thereby suppressing tumor cell proliferation, migration, and invasion [67]. Cellular JUN (c-JUN) has carcinogenic potential, and it has been found that the JNK/c-JUN signaling pathway plays a key role in the development of lung cancer [68]. MMP9 can cleave mature E-calmodulin, which promotes the escape of tumor cells from the primary site [69]. Furthermore, MMP9 is involved in various biological processes such as tumor-related inflammatory responses, angiogenesis, and tumor microenvironment formation [70].SRC regulates epithelial-mesenchymal transition in the tumor microenvironment, thereby promoting the migration and invasion of tumor cells. Additionally, inhibition of SRC expression down-regulates the signaling cascade associated with tumorigenesis and progression, thereby exerting anti-cancer effects [71,72]. Angiogenesis is critical for tumor growth and metastasis, and angiogenesis is dependent on VEGFA [73]。

By acting on relevant pathways, these active ingredients contribute to the effective treatment of lung cancer. The enrichment results of GO biological analysis and KEGG pathway analysis yielded numerous relevant pathways. The therapeutic effect of GPs on lung cancer mainly involves the regulation of the PD-1/PD-L1 signaling pathway to modulate immune function and exert anti-tumor efficacy. To summarize, GPs could treat NSCLC by modulating the PD-1/PD-L1 signaling pathway. This modulation leads to an increase in the expression of $CD4^+$ T and the ratio of $CD4^+/CD8^+$ T in peripheral blood. Simultaneously, it reduces the expression of $CD8^+$ T, correcting the immunosuppressive state induced by tumor cells. Ultimately, this enhances the body's anti-tumor immune function.

Furthermore, this study still has the following shortcomings: (1) The studies included in this meta-analysis were predominantly single-center studies with small sample sizes, which introduces some heterogeneity and limits the evidence strength of the meta-analysis results. The lack of multi-center, large-sample randomized controlled trials to some extent affects the robustness of the evidence; (2) The quality of most of the included studies was generally low, with insufficient mention of allocation concealment and blinding, resulting in subjective results and bias in implementation and measurement; (3) All of the included studies were conducted in China, which could lead to racial bias; (4) The treatment plans included in the various studies are not consistent, and there are differences in the duration of treatment under the same plan, which could have a potential impact on the results; (5) Ginseng polysaccharide injection did not demonstrate an enhancement in the overall survival rate of patients over a prolonged period. Nevertheless, it is important to note that the limited number of available studies may contribute to the lack of statistical significance in the conclusions drawn. Consequently, it is imperative to conduct extensive and multicenter clinical trials on a larger scale to accurately assess the clinical effectiveness of Ginseng polysaccharide injection; (6) The potential of ginseng polysaccharide injection as an adjuvant therapeutic agent is acknowledged. However, it is important to note that the main efficacy index, in this particular study, was ORR rather than OS. OS is considered the gold standard for evaluating patients' benefits in terms of survival time. Therefore, based on these findings, it cannot be definitively concluded that ginseng polysaccharide injection provides benefits in OS for lung cancer treatment; (7) The potential mechanism of action of GPs in the treatment of NSCLC was predicted based on network pharmacology with the help of computer simulation. However, experimental verification is still required to confirm its actual mechanism of action.

5. Conclusion

In this study, the therapeutic effectiveness of GPs on lung cancer and its potential mechanism was comprehensively assessed using meta-analysis and network pharmacology technology. The meta-analysis indicated that ginseng polysaccharide injection can enhance the objective response rate among individuals diagnosed with NSCLC. Additionally, ginseng polysaccharide injection was found to elevate the expression of $CD4^+$ T and decreased the expression of $CD8^+$ T in the peripheral blood of patients with lung cancer. By conducting the analysis of network pharmacological, we have identified a total of 216 potential targets, 81 common targets, and 122 related pathways of GPs. Hence, it can be inferred that the advantages of GPs are significant in the treatment of NSCLC, which can act on multiple targets and pathways.

Data availability statement

All data relevant to the study are included in the article.

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CRediT authorship contribution statement

Qi Zhao: Writing – review & editing, Writing – original draft, Data curation. **Le Bai:** Writing – original draft, Data curation. **Dongwei Zhu:** Writing – review & editing, Visualization. **Tingyuan Li:** Writing – review & editing. **Jie Xu:** Writing – review & editing. **Yong Xu:** Supervision. **Xianmei Zhou:** Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Abbreviations

BP	Biological processes
CASP3	Cysteinyl aspartate specific proteinase 3
CC	Cellular components
CCND1	Cyclin D1
$CD4^+$ T	$CD4^+$ T-lymphocytes
$CD8^+$ T	$CD8^+$ T-lymphocytes
CI	Confidence intervals
CNKI	China National Knowledge Infrastructure
DAVID	Database for Annotation, Visualization and Integrated Discovery
EGFR	Epidermal growth factor receptor
GAPDH	Glyceraldehyde-3-phosphate dehydrogenase
GO	Gene ontology
GPs	Ginseng polysaccharides
HSP90AA1	Heat Shock Protein 90 Alpha Family Class A Member 1
I^2	I-square
KEGG	Kyoto Encyclopedia of Genes and Genomes
MD	Mean differences
MF	Molecular functions
MMP9	Matrix Metalloproteinase-9
NK cells	Natural killer cells
NSCLC	Non-small cell lung cancer
OMIM	Online Mendelian Inheritance in Man
OR	Odds ratios
ORR	Objective response rate
OS	Overall survival
PD-1	Programmed cell death protein-1
PD-L1	Programmed Death Protein Ligand-1
PPI	Protein-protein Interaction
RCTs	Randomized controlled trials
RR	Relative risk
SCLC	Small-cell lung cancer
SRC	Sarcoma
STAT3	Signal transducer and activator of transcription 3
VEGFA	Vascular endothelial growth factor A
VIP	Weipu Information Chinese Journal Service Platform
Wanfang Data	Wanfang Data Knowledge Service Platform

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