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Exploration of the mechanism of Shenbai Fuzheng granules in improving cancer-related fatigue in non-small cell lung cancer based on network pharmacology and molecular docking

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Abstract: **Background**: Non-small cell lung cancer (NSCLC) is frequently complicated by cancer-related fatigue (CRF), which severely impairs quality of life. Shenbai Fuzheng Granules (SFG) have been reported for clinical use, but their mechanisms remain unclear. **Objectives**: This study aims to generate mechanistic hypotheses for SFG in alleviating CRF secondary to NSCLC using network pharmacology and molecular docking. **Methods**: In this *in silico* study, SFG constituents were retrieved from Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP; oral bioavailability ≥30%, drug-likeness ≥0.18); structures from PubChem; targets predicted via SwissTargetPrediction (probability ≥0.10) and mapped through UniProt. NSCLC/CRF targets were collected from GeneCards and OMIM. A TCM-ingredient-disease-target network was built with Cytoscape 3.10.0; hub nodes were identified by degree, betweenness and closeness centrality. A protein-protein interaction network was constructed using STRING (Homo sapiens; minimum score 0.900). Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment were performed in the Database for Annotation, Visualization and Integrated Discovery (DAVID) with Benjamini–Hochberg correction (adjusted $p < 0.05$). Molecular docking used AutoDock Vina 1.1.2 with PDB structures; reliability was assessed by re-docking co-crystallized ligands. **Results**: After deduplication, 244 compounds mapped to 1,067 unique targets and 550 NSCLC/CRF targets from GeneCards/OMIM.Six hub ingredients were identified: α-tocopherol (vitamin E; from Amomi Fructus), baicalein, phaseollinisoflavan, luteolin, chrysoeriol and quercetin. Six core targets (*TP53*, *STAT3*, *SRC*, *PIK3CA*, *AKT1*, *PIK3R1*) were top-ranked by combined centrality. KEGG pathways included PI3K–Akt, JAK–STAT and TNF signaling (adjusted $p < 0.05$). Docking predicted favorable binding affinities and plausible poses; experimental validation is required. **Conclusion**: This is the first study applying network pharmacology and molecular docking to generate testable hypotheses about SFG in CRF associated with NSCLC, providing a rationale for experimental validation prior to clinical application.

Keywords: Cancer-related fatigue; Molecular docking; Non-small cell lung cancer; Network pharmacology; Shenbai Fuzheng granules

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INTRODUCTION

Cancer-related fatigue (CRF) is one of the most frequently observed complications in patients with non-small cell lung cancer (NSCLC); more than a quarter of NSCLC patients experience moderate to severe fatigue during treatment, which significantly impacts treatment adherence and quality of life (Milzer *et al.,* 2023). The pathogenesis of CRF is complex and involves the combined effects of multiple factors, including the tumor itself, treatment-related factors and psychosocial factors. Recent studies have shown that neuro-immune dysregulation is one of its key driving factors. Elevated levels of pro-inflammatory cytokines released by immune cells in the tumor microenvironment are closely associated with the severity of CRF (Acharya and Kundu, 2024; Peppone *et al.,* 2019). Inflammation can also activate indole-2,3-dioxygenase (IDO) driving the conversion of tryptophan into the neurotoxic metabolite quinolinic acid, which leads to physical fatigue (Liu *et al.,* 2021). The hypothalamic-pituitary-adrenal (HPA) axis serves a core function in regulating stress responses, inflammatory processes and energy metabolism; dysfunction of the HPA axis in cancer patients can lead to cortisol secretion disorders, which can induce or exacerbate fatigue (Yang *et al.*, 2019; Kanter *et al.*, 2024). Skeletal muscle dysfunction and mitochondrial dysfunction are another key factors which contribute to fatigue; skeletal muscle is a highly metabolic tissue with a high demand for adenosine triphosphate (ATP). During cancer and its treatment, mitochondrial structure and function may become impaired, leading to abnormalities that hinder ATP synthesis. This results in skeletal muscle dysfunction, which in turn causes fatigue (Carvalho *et al.*, 2022; Zeng *et al.*, 2024; Yu *et al.*, 2024).

Although no specific pharmacological interventions are currently approved for CRF, several systematic reviews and meta-analyses have reported that traditional Chinese medicine may help alleviate CRF symptoms in cancer patients (Zhao *et al.*, 2020; Su *et al.*, 2014; Yang *et al.*, 2023) According to traditional Chinese medicine (TCM)

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theory, Shenbai Fuzheng Granules (SFG) are designed to tonify Qi, nourish the liver and strengthen the spleen. Clinically, SFG has been used as an adjunctive treatment for NSCLC and has been reported to improve symptoms of Qi deficiency and fatigue in patients. However, the bioactive compounds, key targets and pathway-level mechanisms underlying the effects of SFG on CRF secondary to NSCLC have not been systematically characterized. This study employs network pharmacology and molecular docking techniques to explore the potential active ingredients, core targets and signaling pathways that may underlie the effects of SFG on CRF associated with NSCLC, thereby generating mechanistic hypotheses for future validation. Through an integrative approach of network pharmacology and molecular docking, the present study explored the potential active ingredients, core targets and relevant signaling pathways that may be associated with the effects of SFG on CRF in the context of NSCLC. The aim is to explore, at the molecular level, potential mechanisms underlying its 'multi-component, multi-target and multi-pathway' approach to alleviating CRF, thereby providing mechanistic hypotheses to support future experimental validation.

MATERIALS AND METHODS

In silico screening of active ingredients and prediction of targets for SFG

SFG are composed of *Astragalus* (Huangqi), *Codonopsis Pilosula* (Dangshen), *Angelica Sinensis* (Danggui), *Poria Cocos* (Fuling), *Atractylodes Macrocephala* (Baizhu), *Pinelliae Rhizoma Praeparatum* (Fabanxia), *Ligustri Lucidi Fructus* (Nüzhenzi), *Cuscuta Chinensis* (Tusizi), *Epimedii Folium* (Yinyanghuo), *Polygonati Rhizoma* (Huangjing), *Amomi Fructus* (Sharen) and *Citri Reticulatae Pericarpium* (Chenpi). Each ingredient of SFG was used as a keyword to search the Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP) (https://www.tcmsp-e.com/tcmsp.php, accessed on December 16, 2024). Based on recommendations from the TCMSP platform and supporting literature, oral bioavailability (OB) ≥ 30% and drug-likeness (DL) ≥ 0.18 were set as screening thresholds to identify active compounds in SFG. An OB value ≥30% is a commonly applied threshold in the TCMSP, indicating that a compound possesses favorable absorption and metabolic properties; a DL score ≥0.18 indicates structural similarity to known drugs and thus a higher likelihood of serving as a drug candidate (Nogales *et al*., 2022, Wu *et al*., 2023a, Zhou *et al*., 2023). For the bioactive compounds identified from the TCMSP database, their two-dimensional molecular structures were retrieved from the PubChem database https://pubchem.ncbi.nlm.nih.gov, accessed on December 16, 2024 Compound structures acquired from PubChem were subsequently loaded into the SwissTargetPrediction platform http://swisstargetprediction.ch, accessed on December 16, 2024 for target prediction. To reduce the false-positive rate, only predictions with a probability greater than 0.1 were retained. Moreover, an intersection analysis of disease targets retrieved from multiple databases (e.g., GeneCards and OMIM, as described subsequently) was performed, which itself constitutes a form of cross-validation and effectively enhances the credibility of the identified targets (Wei *et al*., 2025).

Screening of key targets of SFG in treating NSCLC and CRF

Screening of key target for NSCLC

Retrieving "Non-small cell lung cancer" from the Gene Cards database https://www.genecards.org, accessed on December 21, 2024) yields a wealth of disease target information for NSCLC. Given the large number of targets, screening was performed based on their scores and those with a score of 29.59 or higher were selected as disease targets for NSCLC, In a parallel approach, the OMIM database https://omim.org, accessed on December 21, 2024 was interrogated with the term "Non-small cell lung cancer". The identified disease-associated targets were subsequently integrated with those sourced from GeneCards, followed by removal of duplicate entries to establish a comprehensive, non-repetitive catalog of therapeutic targets for NSCLC.

Screening of key target for CRF

For CRF, the GeneCards database was searched using the term "cancer-related fatigue," and targets with a GeneCards score ≥ 2.76 were selected. Subsequently, the OMIM database was searched using the same term, "cancer-related fatigue." The targets identified in OMIM were then merged with those obtained from GeneCards for CRF, followed by removal of duplicates to yield the final set of disease-associated molecular targets for CRF.

Common targets for NSCLC and CRF

The relevant target gene sets for NSCLC and CRF were co-submitted to the Weishengxin platform http://www.bioinformatics.com.cn, accessed on December 21, 2024) Utilizing the platform's inherent Venn diagram capabilities, the overlapping targets between the two sets were subsequently identified. The Weishengxin platform is a no-code online data analysis and scientific visualization platform designed specifically for biomedical researchers. It integrates commonly used bioinformatics analysis modules—including differential expression analysis, Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis and Gene Set Enrichment Analysis (GSEA)—and offers a more streamlined workflow than R or Python. This platform enables researchers without programming expertise to rapidly perform data analysis and generate publication-ready visualizations.

Intersection targets of drugs and diseases

The target genes of the bioactive constituents in SFG were intersected with the shared targets of NSCLC and CRF using the Weishengxin platform and Venn diagram

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analysis was performed to identify the overlapping targets between the drugs and the diseases.

Establishment of a traditional Chinese medicine-component-disease-target interaction network

Based on the predicted targets of the active constituents of SFG and the common targets of NSCLC and CRF, a file was constructed to present the network relationship of traditional Chinese medicine-ingredients-disease-targets. After completion of construction, the resultant file was imported into Cytoscape 3.10.0 to facilitate the construction of a visual network.

Generation of a protein-protein interaction network followed by identification of central therapeutic targets

The overlapping genes between disease-related targets identified through screening and drug-targeted proteins were submitted into the STRING 11.5 database https://cn.string-db.org, accessed on January 5, 2025, The analysis was performed with "Homo sapiens" as the organism and a high-confidence interaction threshold of 0.9. Disconnected nodes were removed to streamline the network architecture and a protein-protein interaction (PPI) network was subsequently constructed. The PPI network built using these parameters was exported as a TSV file and the resulting interaction data were loaded into Cytoscape 3.10.0 software. Using principles of network topology, the PPI network was visualized and core targets were identified based on degree centrality, betweenness centrality and closeness centrality.

Bioenrichment analysis and pathway annotation of key targets

To further investigate the biological relevance of the overlapping drug–disease targets, the target dataset was uploaded to the DAVID database https://davidbioinformatics.nih.gov, accessed on January 5, 2025 for comprehensive GO and KEGG signaling pathway enrichment analyses. For the GO enrichment analysis, which includes biological process (BP), cellular component (CC) and molecular function (MF), the ten most significantly enriched terms (p-value ≤ 0.05) were selected from each category. Then, using the Weishengxin platform, a clear and intuitive GO enrichment analysis bar chart was generated to visually present the enrichment results under each category. Regarding the KEGG signaling pathway enrichment analysis, the top 20 significantly enriched pathways were identified based on key indicators such as p-value, gene count and FDR. Similarly, using the Weishengxin platform, a KEGG enrichment bubble chart was generated to display the enrichment level and related information of different signaling pathways, with bubble size and color representing key metrics.

In silico validation of key active compounds and core targets via molecular docking

Based on degree value rankings, the six highest-ranked core targets from the PPI network and the six highest-ranked active ingredients from the TCM–ingredient–disease–target network were selected for subsequent molecular docking validation to confirm their interactions. The three-dimensional structures of the hub active ingredients were downloaded from PubChem as SDF files. These files were transformed into Chem3D 15.0 and converted to mol2 format, providing the ligand input files for molecular docking. Core target 3D structures were downloaded from the RCSB Protein Data Bank (PDB) https://www.rcsb.org, accessed on February 8, 2025 and processed using PyMOL 3.1.1 to delete water molecules and small-molecule ligands, thus preparing receptor input files for molecular docking. AutoDockTools 1.5.7 was used to add hydrogen atoms and compute partial atomic charges. After converting both ligands and receptors to PDBQT format and defining the docking grid box dimensions, molecular docking was performed with AutoDock Vina to calculate the minimum binding energy between core compounds and target proteins. Finally, the docking results were visualized using PyMOL (Huang *et al*., 2026).

RESULTS

Screening of bioactive constituents and putative target identification for SFG

A literature search was conducted using the chemical constituents of 12 traditional Chinese medicinal herbs (including Astragalus, Codonopsis pilosula and Angelica sinensis) as search keywords. Compounds were filtered based on the following criteria: OB≥ 30%, DL ≥ 0.18 and probability ≥ 0.1. 244 active compounds met all three criteria. Their sources and distributions are as follows: *Astragalus* (20), *Codonopsis Pilosula* (21), *Angelica Sinensis* (2), *Poria Cocos* (15), *Rhizoma Atractylodes Macrocephala* (7), *Pinelliae Rhizoma Praeparatum* (105), *Ligustri Lucidi Fructus* (13), *Cuscuta Chinensis* (11), *Epimedii Folium* (23), *Polygonati Rhizoma* (12), *Amomi Fructus* (10) and *Citri Reticulatae Pericarpium* (5). The targets corresponding to these compounds were compiled and deduplicated, yielding a total of 1,067 unique targets. As presented in table 1, an "Ingredient-Target" network file was subsequently built and loaded into Cytoscape software for visualization.

Acquisition of disease targets in NSCLC

Search for "non-small cell lung cancer" in the GeneCards database and OMIM database. Given the complexity of target information in the GeneCards database, 898 targets with a score ≥ 29.59 were selected and a further 398 disease-related targets were identified through the OMIM database. The targets identified from the two databases were consolidated and deduplicated, yielding a final set of 1,230 unique targets, which were designated as disease targets for NSCLC.

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Table 1: Some active substances of SFG.

Source	Mol ID	Name
Pinelliae Rhizoma Praeparatum	MOL004905	3,22-dihydroxy-11-oxo-delta (12)-oleanene-27-alpha-methoxycarbonyl-29-oic acid
Atractylodes Macrocephala	MOL000020	12-senecioyl-2E,8E,10E-atractylentriol
Amomi Fructus	MOL007180	Vitamin-E
Epimedii Folium	MOL004388	6-hydroxy-11,12-dimethoxy-2,2-dimethyl-1,8-dioxo-2,3,4,8-tetrahydro-1H-isochromeno[3,4-h] isoquinolin-2-ium
Astragalus	MOL000380	(6aR,11aR)-9,10-dimethoxy-6a,11a-dihydro-6H-benzofurano[3,2-c] chromen-3-ol
Polygonati Rhizoma	MOL002714	Baicalein
Pinelliae Rhizoma Praeparatum	MOL004833	Phaseolinisoflavan
Epimedii Folium	MOL000006	Luteolin
Epimedii Folium	MOL003044	Chryseriol
Pinelliae Rhizoma Praeparatum	MOL004961	Quercetin der.
Pinelliae Rhizoma Praeparatum	MOL002565	Medicarpin
Polygonati Rhizoma	MOL006331	4',5-dihydroxyflavone
Pinelliae Rhizoma Praeparatum	MOL004974	3'-methoxyglabridin
Astragalus	MOL000371	3,9-di-o-methylnissolin
Polygonati Rhizoma	MOL009766	Zhonghualiaoine 1
Cuscuta Chinensis	MOL000422	Kaempferol
Cuscuta Chinensis	MOL000354	Isorhamnetin
Pinelliae Rhizoma Praeparatum	MOL004990	7,2',4'-trihydroxy - 5-methoxy-3 - arylcoumarin
Pinelliae Rhizoma Praeparatum	MOL004989	6-prenylated eriodictyol
Pinelliae Rhizoma Praeparatum	MOL004988	Kanzonol F
Pinelliae Rhizoma Praeparatum	MOL000239	Jaranol

Acquisition of disease-related action targets for CRF

Search for "cancer related fatigue" in these two databases. In the GeneCards database, 1219 targets with a score ≥ 2.76 were selected. From the OMIM database, two additional targets were retrieved, which were combined with those from the GeneCards database. Following duplicate removal, a final set of 1,221 non-redundant targets were designated as disease-associated targets for CRF.

Acquisition of common targets for NSCLC and CRF

The previously identified relevant targets for NSCLC and CRF were imported into the Weishengxin platform for intersection analysis, resulting in 550 common targets.

Targets common to both pharmacological intervention and disease pathology

The active ingredient targets of SFG were intersected with the shared targets of NSCLC and CRF using the Weishengxin platform, yielding 145 common targets. Based on this result, a Venn diagram was constructed, as depicted in Fig. 1.

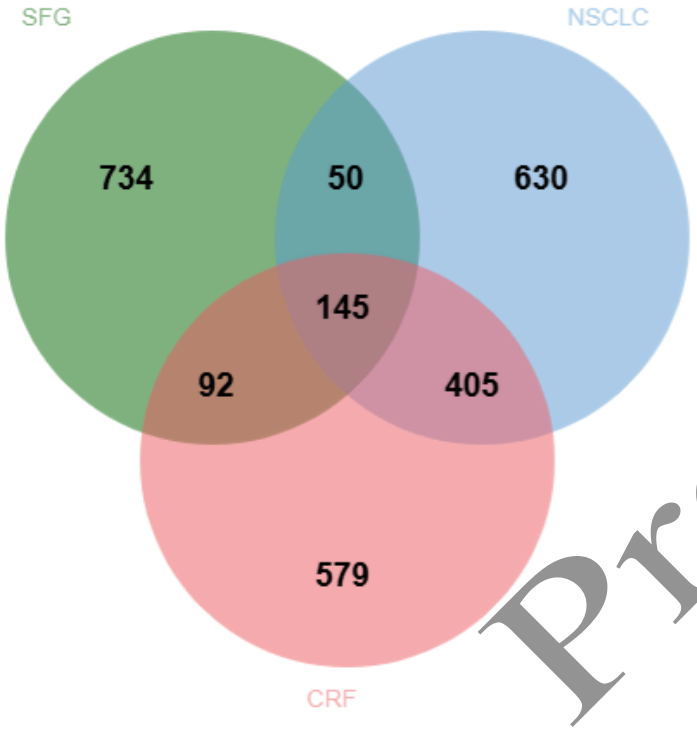
Establishment of an integrated TCM-ingredient-disease-target network

From the TCM–ingredient–disease–target network shown in Fig. 2, *Pinelliae Rhizoma Praeparatum* contains the most compounds, while *Angelica sinensis* contains the least. According to the degree value ranking, the top components are vitamin E, baicalein, phaseolinisoflavan, luteolin, chryseriol, quercetin der, which may be the key substances that exert their effects.

Building PPI network and obtaining hub targets

Using the 145 overlapping targets, a PPI network was established via the STRING database. The constructed network displayed 145 nodes, 672 edges and a mean degree centrality of 9.27. In this network, each node represents a protein and attributes such as node size and color which conveys distinct biological information. For instance, larger nodes typically indicate hub proteins that interact with a greater number of other proteins. Lines connecting two nodes denote physical or functional interactions between the corresponding proteins; additionally, the thickness and style of these lines encode supplementary information. For example, line thickness reflects the strength of the interaction. The PPI network was subsequently transferred into Cytoscape 3.10.0 for graphical representation (Fig. 3). Topological analysis of the PPI network was performed using the cytoNCA plugin, with the following criteria: betweenness centrality > 54.5339860609329, closeness centrality > 0.217320261437908 and degree > 7. This yielded 53 targets; The top six targets were identified as hub targets: *TP53*, *STAT3*, *SRC*, *PIK3CA*, *AKT1* and *PIK3R*.

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Fig. 1: Venn diagram of the intersection targets of SFG and CRF in NSCLC

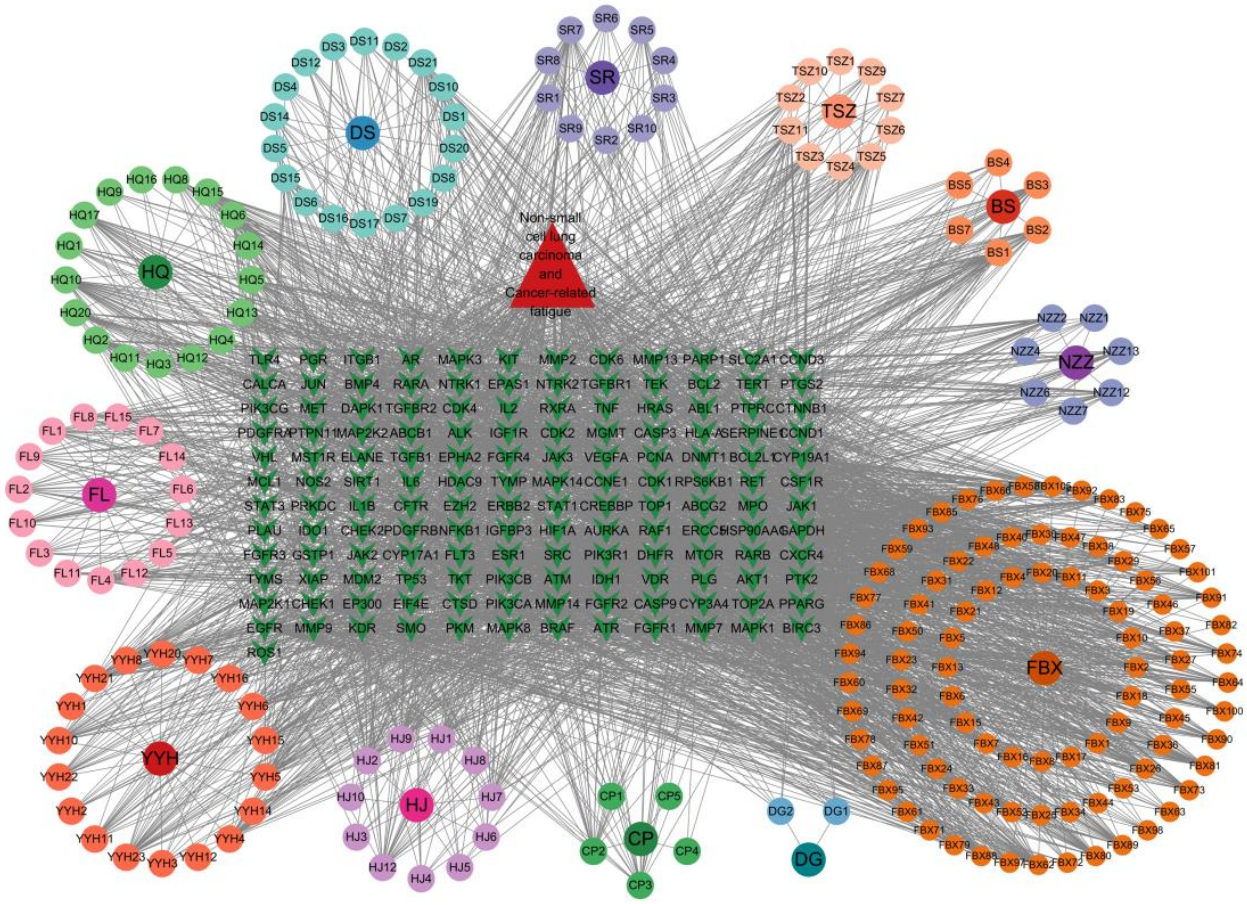


Fig. 2: Network diagram of SFG-ingredients-diseases-target

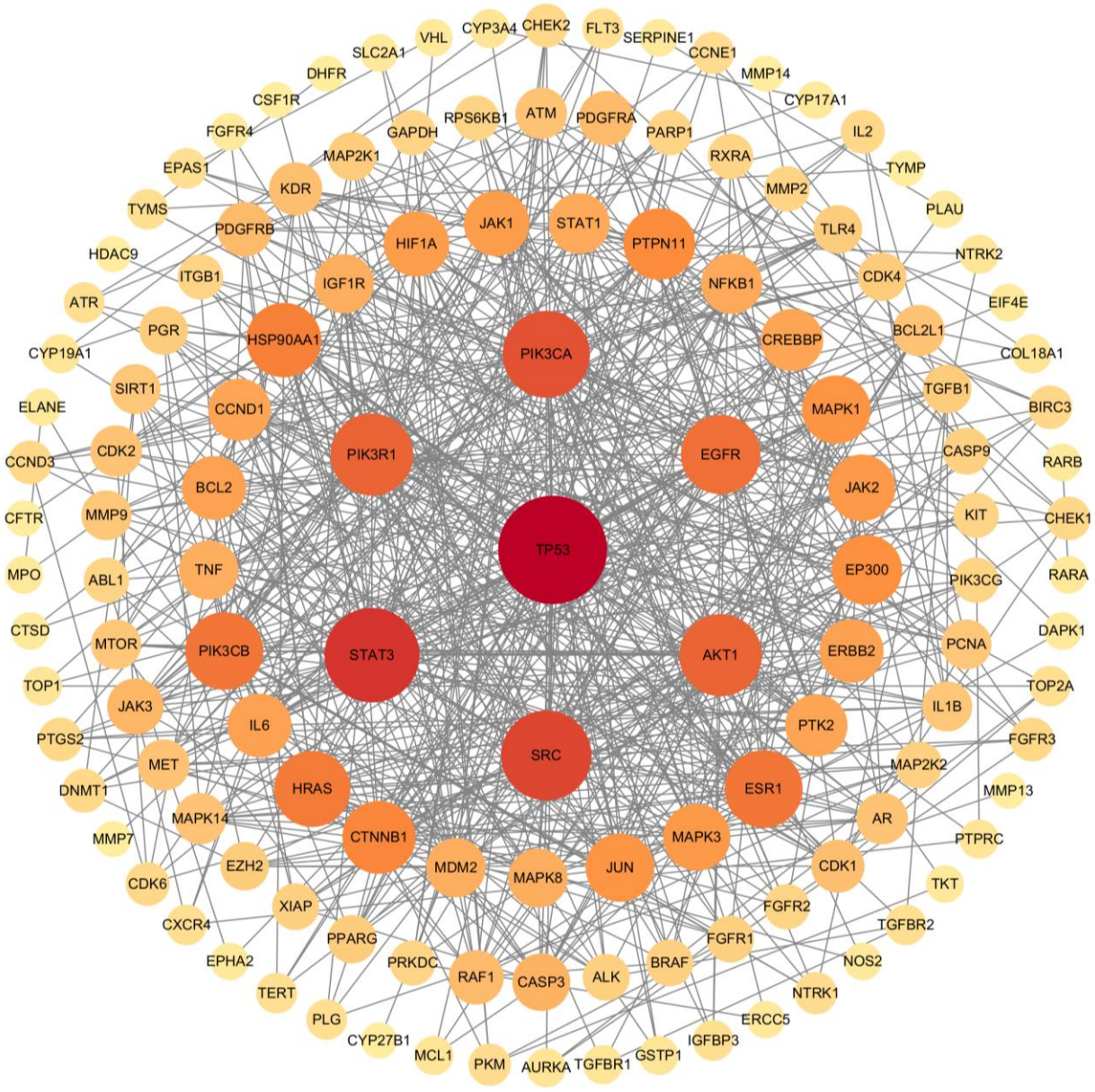


Fig. 3: PPI network diagram

GO and KEGG enrichment analysis

GO enrichment analysis

GO and KEGG enrichment analyses were performed via the DAVID database on the 145 intersecting targets that had been previously identified for treating CRF in NSCLC with SFG. The GO enrichment analysis yielded 842 terms associated with biological processes, 99 terms related to cellular components and 175 terms pertaining to molecular functions. The top 10 entries under each category were selected based on p-value and then visualized through the Weishengxin platform (Fig. 4). The results indicate that the potential mechanism of action of SFG may involve multidimensional biological regulation. At the biological process level, it is significantly enriched in key processes such as negative regulation of apoptosis, positive regulation of protein kinase activity and activation of the PI3K/Akt signaling pathway. At the molecular function level, it mainly involves protein kinase binding and ATPase activity.

KEGG enrichment analysis

A collection of 165 signaling pathways was identified as significantly enriched for the intersection targets through KEGG pathway analysis. The top 20 items were selected and visualized on the Weishengxin platform as shown in Fig. 5. After excluding prostate cancer, pancreatic cancer, human cytomegalovirus infection and other pathways unrelated to NSCLC-related fatigue, PI3K-Akt signaling pathway, HIF-1 signaling pathway, MAPK signaling pathway and cancer pathway were found to be mainly involved.

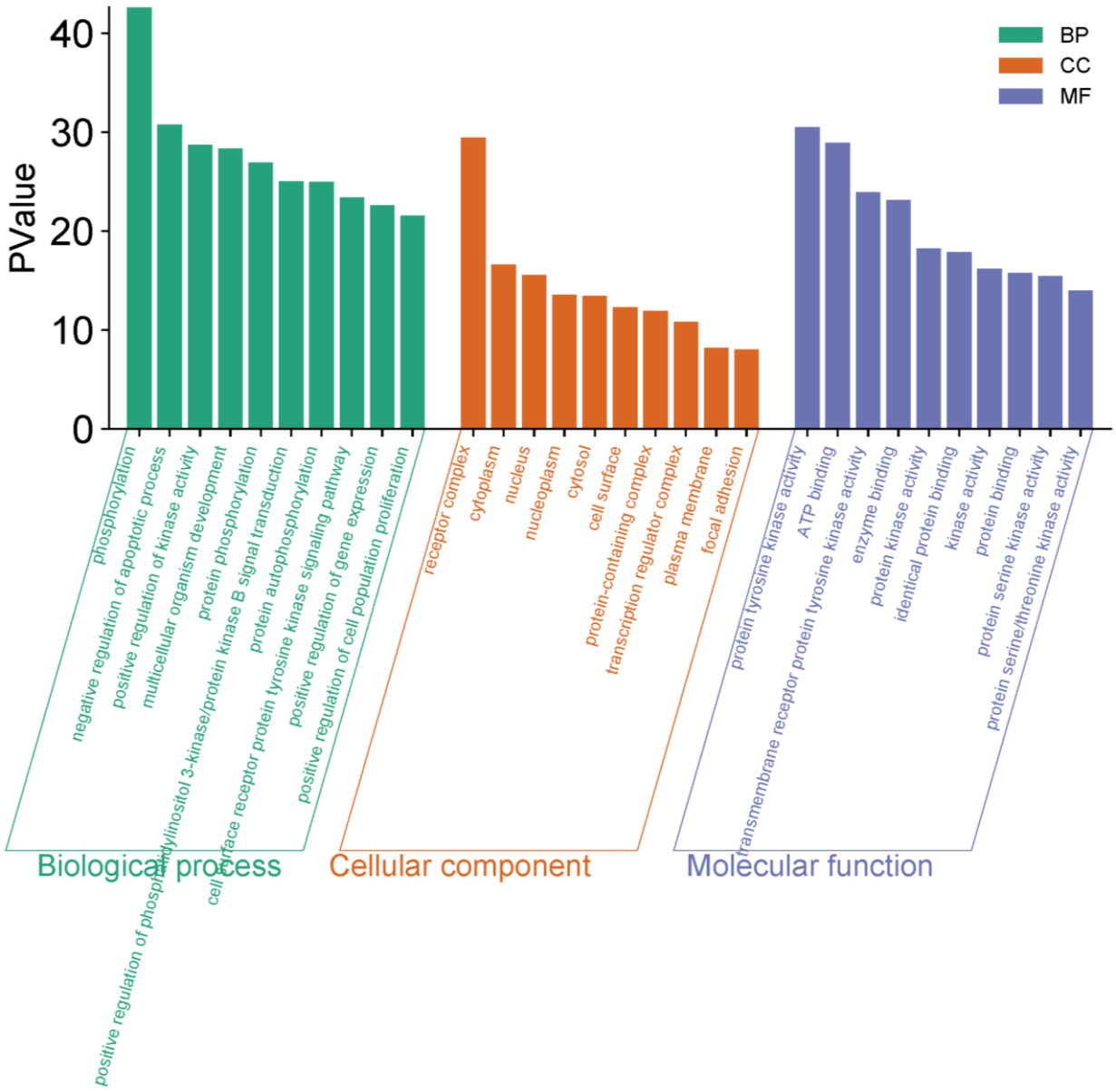


Fig. 4: GO analysis of SFG in the treatment of CRF in NSCLC

In silico validation of core targets of SFG in treating CRF in NSCLC

Molecular docking was performed between the 6 primary active compounds identified from screening and the 6 core targets, using binding energy to evaluate the binding activity of these compounds against their respective targets. Using binding energy as the evaluation metric, molecular docking was conducted between the six primary active compounds obtained from screening and the six core targets to assess the binding activity of each compound against its corresponding target. Lower binding energy corresponds to greater energy release, indicating higher binding stability between a compound and its target protein. This study employed a binding energy threshold of ≤ -5.0 kcal/mol to screen for compounds with potential binding activity. It is shown that the binding energies were all ≤ –5 kcal/mol (Table 2). TP53 exhibited the highest binding affinity for vitamin E, baicalin, genistein, luteolin, goldenseal flavonoids and quercetin. (Fig. 6).

DISCUSSION

CRF, a common complication of malignancy, exhibits a pathogenesis characterized by multifactorial interactions involving the disease itself, treatment-related factors and psychosocial influences. In NSCLC, for example, chemotherapy effectively controls tumor progression; however, clinical observations frequently identify symptoms including fatigue, weakness, dyspnea and sleep disturbance (Williams *et al*., 2025).

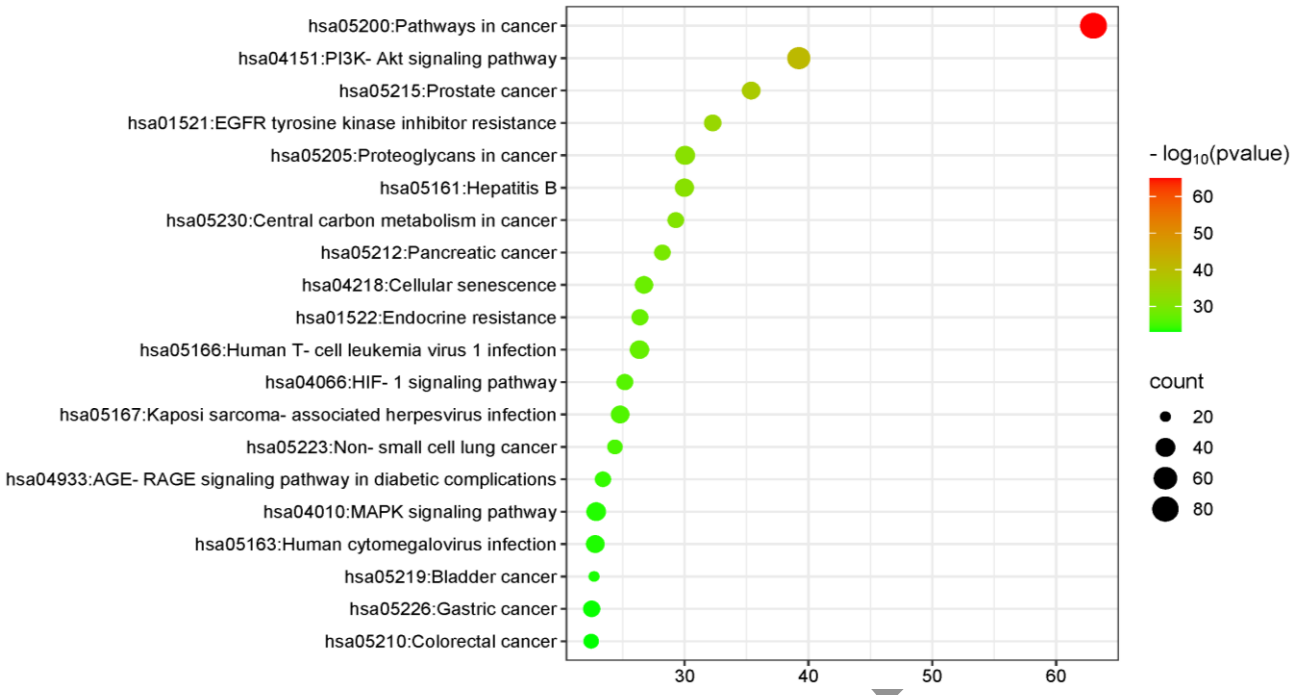


Fig. 5: KEGG analysis of SFG in the treatment of CRF in NSCLC.

At the pathophysiological level, modern medicine considers CRF to be closely associated with central nervous system dysfunction, inflammatory cytokine release, dysregulation of hypothalamic regulatory circuits and mitochondrial dysfunction (Yang *et al*., 2019). Conversely, traditional Chinese medicine views CRF as an overall manifestation of internal organ dysfunction, Qi and blood insufficiency and yin–yang disharmony (Yang *et al.*, 2023). SFG, a TCM compound formulation, is composed in accordance with the therapeutic principles of tonifying Qi and nourishing blood, invigorating the spleen and supplementing the kidney. Modern pharmacological studies have confirmed that multiple herbs in this formula exhibit diverse pharmacological activities, including immunomodulation, anti-inflammatory effects, antitumor activity and anti-fatigue effects. For example, active components in Astragalusi can modulate the tumor microenvironment by inhibiting NF-κB activation (Li Z *et al.*, 2024). *Codonopsis pilosula* ameliorates inflammation-driven fatigue via downregulation of pro-inflammatory cytokines like IL-6 and TNF-α (Meng *et al*., 2020). *Atractylodes Macrocephala* can synergistically exert anti-fatigue effects through immunomodulation, anti-inflammatory actions and inhibition of the Notch signaling pathway (Wang *et al.*, 2025).

In this *in silico* study identified a total of 244 active herbal compounds and their corresponding 1067 molecular targets through systematic screening. Among these, *Pinellia ternata*, *Epimedium*, *Astragalus* and *Codonopsis* contained the highest levels of active ingredients and the four herbs collectively exhibited the richest content of alkaloids and flavonoids. These compounds exert pharmacological effects through multiple mechanisms, including anti-inflammatory, antitumor and immunomodulatory activities. Topological network analysis indicates that vitamin E, baicalin, phaseolinisoflavan, luteolin, chrysoeriol and quercetin der are the key active components. Quercetin der alleviates CRF-associated muscle fatigue by inhibiting IL-17-induced nuclear translocation of NF-κB and enhancing oxidative phosphorylation efficiency in skeletal muscle (Yang *et al.*, 2024). Luteolin attenuates inflammation associated with CRF and facilitates tumor cell apoptosis through modulation of the NF-κB and MAPK cascades (Che *et al.*, 2020).Through inhibition of the NF-κB and JAK2/STAT3 signaling cascades, chrysoeriol downregulates pro-inflammatory cytokines like IL-6, IL-1β and TNF-α (Wu *et al*., 2020).

Topological analysis of the PPI network reveals complex interrelationships between the key targets of SFG and the core targets associated with CRF in NSCLC. The top-ranked targets include *TP53*, *STAT3*, *SRC*, *PIK3CA*, *AKT1* and *PIK3R1*, suggesting their important role in mediating the effects of SFG in alleviating CRF in NSCLC. Among these, *TP53*, a tumor suppressor gene, participates in the regulation of mitochondrial respiration and energy metabolism; its stress-induced activation may interfere with energy supply to skeletal muscle and contribute to fatigue development (Memme *et al.*, 2022).

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Table 2: Molecular docking results of core targets and key ingredients.

Target	PDB ID	Active ingredient	Mol ID	Binding energy/(kcal/mol)
TP53	7BWN	Vitamin E	MOL007180	-8.9
		Baicalein	MOL002714	-8.9
		Phaseolinisoflavan	MOL004833	-9.0
		Luteolin	MOL000006	-8.6
		Chrysoeriol	MOL003044	-8.4
		Quercetin der	MOL004961	-8.1
STAT3	6NJS	Vitamin E	MOL007180	-8.5
		Baicalein	MOL002714	-7.7
		Phaseolinisoflavan	MOL004833	-8.4
		Luteolin	MOL000006	-8.0
		Chrysoeriol	MOL003044	-7.9
		Quercetin der	MOL004961	-7.2
SRC	1A07	Vitamin E	MOL007180	-6.0
		Baicalein	MOL002714	-7.7
		Phaseolinisoflavan	MOL004833	-6.4
		Luteolin	MOL000006	-8.1
		Chrysoeriol	MOL003044	-7.3
		Quercetin der	MOL004961	-6.1
PIK3CA	2ENQ	Vitamin E	MOL007180	-6.9
		Baicalein	MOL002714	-6.8
		Phaseolinisoflavan	MOL004833	-6.9
		Luteolin	MOL000006	-6.4
		Chrysoeriol	MOL003044	-6.6
		Quercetin der	MOL004961	-6.1
AKT1	1H10	Vitamin E	MOL007180	-5.8
		Baicalein	MOL002714	-7.0
		Phaseolinisoflavan	MOL004833	-7.0
		Luteolin	MOL000006	-6.2
		Chrysoeriol	MOL003044	-6.3
		Quercetin der	MOL004961	-6.1
PIK3R1	1PHT	Vitamin E	MOL007180	-5.7
		Baicalein	MOL002714	-6.3
		Phaseolinisoflavan	MOL004833	-6.7
		Luteolin	MOL000006	-7.1
		Chrysoeriol	MOL003044	-6.1
		Quercetin der	MOL004961	-6.6

STAT3 is a key node in the IL-6/JAK/STAT3 inflammatory pathway; its aberrant activation can mediate the transmission of tumor-associated inflammatory signals to the central nervous system, leading to dysregulation of the HPA axis and abnormalities in neurotransmitter metabolism (Zhu *et al.*, 2025, Kanter *et al.*, 2024, Liu *et al.*, 2021). Meanwhile, the STAT3/HIF-1α/BNIP3 axis can induce mitochondrial autophagy in skeletal muscle, leading to impaired ATP synthesis (Wu *et al.*, 2023b). As a core molecule of the PI3K-AKT pathway, AKT1 participates in insulin signal transduction and glucose metabolism; its functional abnormalities can lead to energy metabolism disorders and are closely associated with CRF (Bae *et al.*, 2021, Chen *et al.*, 2024). Moreover, *SRC* promotes tumor invasion and metastasis by upregulating MMPs and VEGF (Liu *et al.*, 2020). Mutations in *PIK3CA* cause excessive activation of the PI3K-AKT pathway, consequently driving tumor proliferation and therapeutic resistance (Teruel *et al.*, 2025) meanwhile, PIK3R1 is critically involved in cell growth, metabolic regulation and glucose homeostasis (Teixeira *et al.*, 2025).

GO enrichment analysis revealed that SFG was significantly enriched in biological processes related to the negative regulation of apoptosis, modulation of protein kinase activity and regulation of gene expression. KEGG pathway analysis revealed that the PI3K-AKT, HIF-1, MAPK, IL-17 and TNF signaling pathways are significantly associated pathways. The PI3K-AKT signaling pathway is frequently abnormally activated in NSCLC due to genetic mutations, thereby promoting tumor cell proliferation; conversely, inactivation of this pathway can induce apoptosis (Zhou *et al.*, 2024, Li T *et al.*, 2024, Tan, 2020). The PI3K-AKT pathway also directly regulates protein synthesis and energy metabolism in skeletal muscle. Activation of this pathway enhances muscle protein utilization, thereby exerting anti-fatigue and muscle-hypertrophic effects (Fang *et al.*, 2022).

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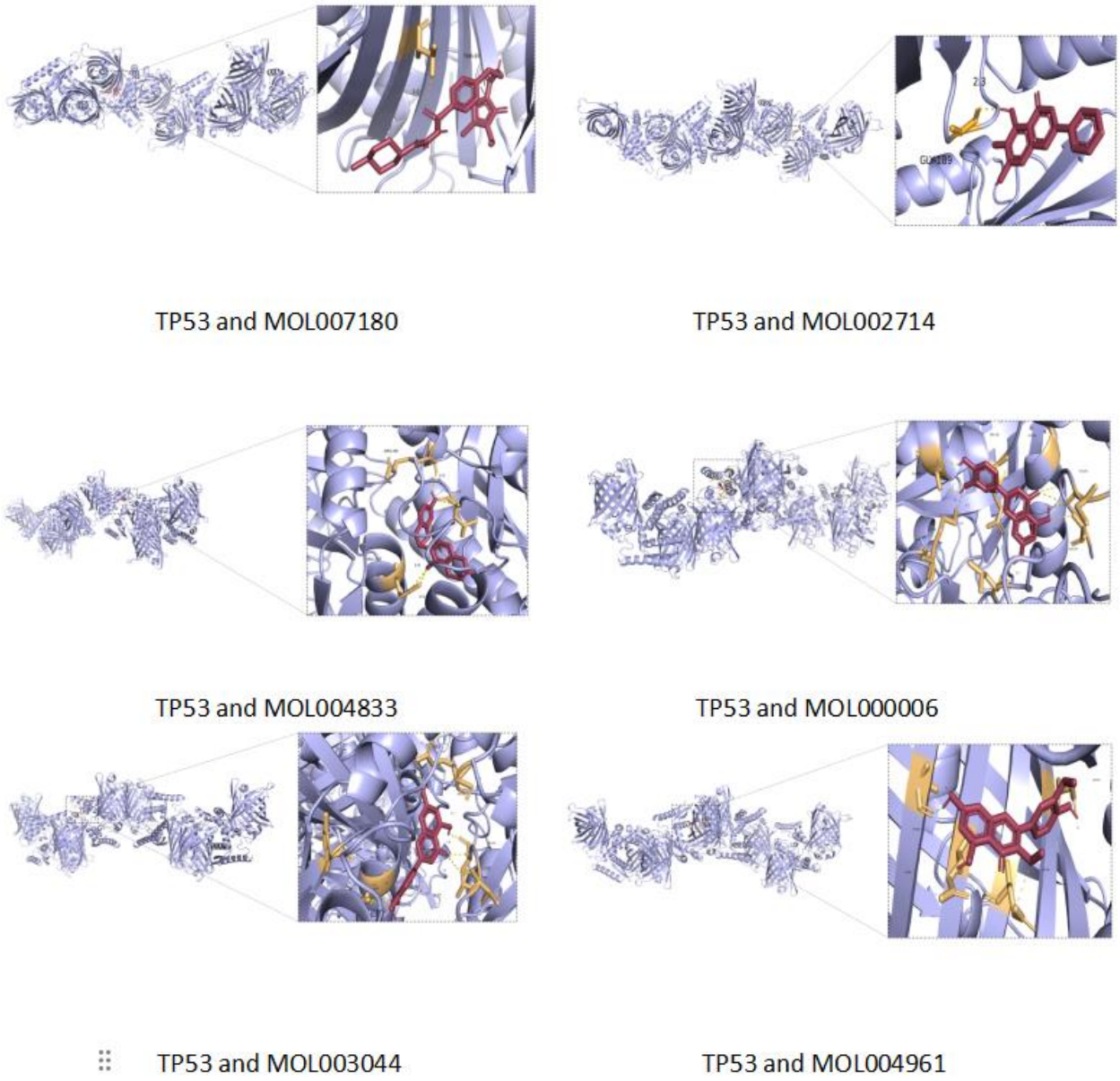


Fig. 6: Molecular docking mode diagram of TP53

Ginsenoside Rb1 elicits anti-fatigue effects via PI3K-AKT pathway activation, which triggers Nrf2 translocation to the nucleus and enhances the expression of antioxidant enzymes (Liu *et al.*, 2026). This dual functionality suggests that SFG may ameliorate CRF-associated impairments in skeletal muscle energy metabolism while simultaneously inhibiting tumor growth, potentially through moderate modulation of the PI3K-AKT pathway. Both the IL-17 and TNF signaling pathways are canonical pro-inflammatory pathways that promote CRF by inducing systemic inflammation and muscle wasting (Subudhi *et al.*, 2024). As an upstream regulator, TNF-α activates the NF-κB and MAPK pathways, inducing muscle atrophy and mitochondrial depletion, thereby directly driving fatigue (Xu *et al.*, 2024, Huang *et al.*, 2026). The tumor-associated inflammatory milieu dysregulates the STAT/HIF-1α/BNIP3 signaling cascade in skeletal muscle, thereby inducing excessive mitophagy and culminating in fatigue (Wu *et al.*, 2023b). SFG may alleviate fatigue in patients with NSCLC by orchestrating the PI3K-AKT, HIF-1, MAPK, IL-17 and TNF signal transduction pathways, thereby suppressing systemic inflammation and improving energy metabolism in skeletal muscle. Molecular docking validation demonstrated favorable binding of SFG's key compounds to core targets including TP53, STAT3, AKT1, SRC, PIK3CA and PIK3R; among these, TP53 exhibited the lowest binding free energy, suggesting it is one of the primary targets. This study is limited by its reliance on database-derived target prediction, which may introduce selection bias and incomplete target coverage. The screening thresholds used for compound and target

selection (e.g., OB, DL and prediction probability) may also have excluded potentially relevant bioactive constituents. In addition, target prediction tools may generate false-positive results and the molecular docking outcomes are hypothesis- generating rather than confirmatory of biological activity. Furthermore, the present study lacks validation of dose, bioavailability and pharmacokinetics, as well as clinical validation in NSCLC-related CRF. Therefore, the predicted compounds, targets and pathways require validation *in vitro*, *in vivo* and ultimately in clinical studies to confirm the potential mechanisms underlying the effects of SFG on CRF.

CONCLUSION

This *in silico* study used network pharmacology and molecular docking to generate hypotheses regarding the potential multi-component, multi-target and multi-pathway mechanisms by which SFG may influence CRF in NSCLC. The findings suggest possible involvement of inflammation-, metabolism- and immunity-related networks and provide a basis for future experimental validation.

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Authors' contributions
Changjing Feng: Writing - original draft, Visualization. Min Luo, Yuqian Lin & Yan Chen: Writing - review & editing. Jun Pang: Supervision, Project administration. All authors have read and agreed to the final manuscript.

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Data availability statement
The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethical approval
This study was approved by the Ethics Committee of the Affiliated Traditional Chinese Medicine Hospital of Southwest Medical University (Approval No.: KY2023002-FS01). All data used in this study were obtained from publicly available databases (TCMSP, PubChem. GeneCards, OMIM, etc.)

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

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