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Integrating network pharmacology and Mendelian randomization to explore potential targets of Fufang Banmao capsule against non-small cell lung cancer

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Abstract: **Background**: Fufang Banmao Capsule (FBC) is clinically applied in the treatment of non-small cell lung cancer (NSCLC), yet its underlying pharmacological mechanism remains to be fully elucidated. **Objectives**: This study aimed to systematically elucidate the pharmacological actions of FBC against NSCLC by integrating network pharmacology and Mendelian randomization approaches. **Methods**: Active components and potential targets of FBC were retrieved from the BATMAN-TCM database, while NSCLC-related therapeutic targets were collected from OMIM, TTD, and DisGeNet. Enrichment analysis and a "Herbs-Ingredients-Targets-Pathways" network were constructed. Core targets were further identified through protein-protein interaction and Mendelian randomization analyses, followed by colocaliza tion tests and molecular docking validation. **Results**: A total of 152 potential FBC targets for NSCLC were identified, with seven candidates shortlisted. Among these, TNF and PIK3CA emerged as key protective targets ($P<0.0025$, $OR<1$). Colocalization analysis suggested possible shared genetic causality of TNF and PIK3CA single nucleotide polymorphisms with increased NSCLC risk. Molecular docking confirmed strong binding interactions between these targets and active FBC compounds such as resveratrol. **Conclusion**: The findings provide a theoretical foundation and new research directions for further investigation into the anti-NSCLC mechanism of FBC, supporting future innovation in therapeutic strategies.

Keywords: Fufang banmao capsule; Mendelian randomization; Mechanism; NSCLC; Network pharmacology; Traditional Chinese medicine

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INTRODUCTION

Non-small cell lung cancer (NSCLC) is the prevalent form of lung cancer, comprising around 85% of all lung cancer cases (Gridelli *et al*., 2015). Compared to small cell carcinoma, NSCLC grows and divides slower, often spreading later, with three-quarters of patients diagnosed at locally intermediate to advanced or metastatic stages (Molina *et al*., 2008). Traditional treatments for NSCLC, including surgery, radiotherapy and systemic chemotherapy (Ettinger *et al*., 2021), have limited benefits for patients with moderately advanced or metastatic disease due to the cancer's pathological characteristics and resistance to chemotherapy (Crucitta *et al*., 2022). While molecular targeted therapy and immunotherapy have emerged as promising treatment options for NSCLC in recent years (Ettinger *et al*., 2023), these therapies also face challenges with drug tolerance and adverse effects (Wu and Lin, 2022; Shyam Sunder *et al*., 2023). The ongoing challenge in NSCLC treatment lies in discovering safer and more effective therapies that not only extend patients' survival but also maintain their quality of life. Traditional Chinese medicine (TCM) has garnered increasing attention as a potential alternative or adjuvant therapy for lung cancer (LC) due to its unique therapeutic characteristics (Wang *et al*., 2023a; Li *et al*., 2021b). TCM offers the advantage of a novel pharmacological mechanism with lower toxic side effects compared to classical radiotherapy, while achieving comparable therapeutic outcomes (Zhang *et al*., 2021; Qi *et al*., 2015). One such TCM compound preparation is Fufang Banmao Capsule (FBC), which comprises 11 herbs, including Cantharides, Ginseng and Astragalus, and is approved by the Chinese Pharmacopoeia for treating primary liver tumors, lung tumors, rectal tumors, and malignant lymphomas (Liu *et al*., 2019). Modern research has demonstrated FBC's inhibitory effects on multiple tumor cells via various pathways, such as cell proliferation, apoptosis, and immunomodulation (Han *et al*., 2012; Sun *et al*., 2017; Cao *et al*., 2007). Yet, there remains a dearth of studies on FBC's mechanism of action specifically for NSCLC. Network pharmacology utilizes advanced technologies like histology, high-throughput screening, network visualization and analysis to elucidate complex relationships among drugs, genes, targets, and diseases. This holistic approach has greatly facilitated the discovery of active ingredients in TCM and the

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comprehension of its overall mechanism (Zhao *et al*., 2023). Meanwhile, Drug-target Mendelian randomization (MR) employs genetic variation in drug-target gene proxies as instrumental variables to assess the causal relationship between drugs and diseases through randomization, minimizing the impact of confounding factors (Ference, 2022). This study aims to explore and elucidate the potential therapeutic targets and mechanisms of FBC in treating NSCLC using network pharmacology and MR, thus providing a novel theoretical foundation and clinical guidance for FBC's application in NSCLC treatment.

MATERIAL AND METHODS

Identifying active constituents and targets in FBC

Eleven Chinese herbs, including Cantharides, Ginseng, and Astragalus, were retrieved from the BATMAN-TCM 2.0 database (http://bionet.ncpsb.org.cn/batman-tcm/). This online bioinformatics database specializes in providing comprehensive data on the interactions between multiple active ingredients and human target proteins, enhancing modern TCM research and elucidating its pharmacological mechanisms (Kong *et al*., 2024). In this study, we set the search parameters in BATMAN-TCM 2.0 to a Confidence Score cutoff of 0.95 (LR=278), an Adjusted P value cutoff of 0.05, and a Druggable Score of ≥0.1. We then downloaded the details of the ingredients that met these criteria, along with data on their known and predicted targets.

Collection of NSCLC-related targets

To obtain relevant genes and protein targets associated with NSCLC, we performed a comprehensive search in three databases: The Online Mendelian Inheritance in Man (OMIM) (Amberger *et al*., 2015), the Therapeutic Target Database (TTD) (Zhou *et al*., 2024b), and DisGeNET (Pinero *et al*., 2017). By utilizing search terms like "Non-Small Cell Lung Carcinoma" and "Non-Small Cell Lung Cancer", we were able to compile a comprehensive collection of disease-associated targets. Through meticulous consolidation and removal of duplicate entries, we curated a unique dataset that provides valuable insights into NSCLC. This approach ensures that the information gathered is precise and pertinent to the study of NSCLC.

Relationship construction

By intersecting the obtained compound targets with the disease targets, we determined the potential targets of FBC in treating NSCLC. We organized the FBC targets and disease-related targets into two distinct groups using an online drawing tool and created a Venn diagram to visualize their set relationships. Next, we entered the identified potential targets of FBC for NSCLC treatment into the STRING database to generate a protein-protein interaction (PPI) network (Szklarczyk *et al*., 2023). The core genes were then screened using the CytoHubba plugin in Cytoscape 3.10.1.

Enrichment analysis of FBC on anti-NSCLC targets

Using the DAVID database (Dennis *et al*., 2003), we identified shared targets between FBC and NSCLC and conducted Gene Ontology (GO) function analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis on these targets. The top 10 GO pathways, ranked by their enrichment factors, and the top 25 KEGG pathways were selected for visualization.

Construction of the "Herbs-ingredients-targets-pathways" network

Using Cytoscape 3.10.1, we constructed a comprehensive "Herbs-Ingredients-Targets-Pathways" network. In this network, nodes represent active ingredients, targets, and pathways, with edges indicating that a compound has a specific potential target. Subsequently, we analyzed the overall network characteristics using the network analyzer plugin.

MR analysis

Our study aimed to investigate the potential causal relationship between specific genetic targets and NSCLC through Mendelian Randomization (MR) analysis. We obtained single nucleotide polymorphisms (SNPs) of core genes from the IEU Open GWAS database as exposure factors and NSCLC data from the FinnGen database as endpoint factors. By using the R software packages 'TwoSampleMR' and 'MRPRESSO', we conducted MR analysis to pinpoint candidate targets associated with NSCLC (Zhou *et al*., 2024a). The selection of instrumental variables (IVs) was meticulously done, adhering to strict criteria. We only included SNPs with genome-wide significance ($P < 5 \times 10^{-8}$), and used the PLINK algorithm for SNP clustering with specified parameters. SNPs exhibiting potential multidirectional effects were excluded, along with weak IVs having an F statistic below 10 (Boef *et al*., 2015). Various MR methods were employed to confirm the causality, with the inverse variance weighted (IVW) as the primary method and others such as MR Egger, weighted median, simple mode, and weighted mode as supportive measures (Liu *et al*., 2023). A significance level of $P < 0.05$ for the IVW method indicated a possible causal link, while a Bonferroni-corrected threshold of $P < 0.0025$ ($\alpha = 0.05/20$) was applied to adjust for multiple testing. The results were portrayed through odds ratios (ORs) with corresponding 95% confidence intervals (CIs), where an OR >1 denoted a risk factor and <1 indicated a protective factor. Visualization tools like scatter plots, forest plots, and funnel plots were utilized to present the findings. Sensitivity analyses were conducted to evaluate the robustness of the MR results, including assessments for heterogeneity, horizontal multiplicity, and leave-one-out analyses. In conclusion, our MR analysis revealed potential causal relationships between certain genetic targets and NSCLC, shedding light on the underlying mechanisms that could contribute to the development of

this type of lung cancer. These findings hold implications for future research and potential therapeutic interventions targeting the identified genes.

eQTL colocalization analysis

The data on expression quantitative trait loci (eQTLs) for the target genes were sourced from the eQTLGen consortium's website. To further analyze the genetic associations, a colocalization study was conducted using Bayesian methods with the R software 'Coloc' and the 'locuscompare' package (Luo *et al*., 2023). This method aimed to determine if the genetic variants identified in Genome-Wide Association Studies (GWAS) overlapped with the eQTLs, indicating a shared genetic component. The colocalization analysis considered five hypotheses (Wang *et al*., 2023b): H0 suggested that the SNPs in the overlapping region were not associated with either trait, while H1 and H2 proposed associations with only one of the traits. H3 posited that SNPs were associated with both traits but at different loci, and H4 suggested association with both traits at the same locus.

The key indicator of a successful colocalization was the posterior probability of H4 (PP.H4) being at least 50%, signifying a likely shared genetic mechanism. By evaluating the hypotheses and calculating the posterior probabilities, researchers could determine the strength of evidence for colocalization between GWAS and eQTL associations. This approach helped to uncover potential genetic links between complex traits and gene expression, shedding light on the underlying mechanisms of disease and variation.

Molecular docking verification

The interaction between core targets and the active compounds from the FBC was investigated through a molecular docking assessment. Small molecule structures were obtained from the PubChem database (Kim *et al*., 2023b) and converted to pdb format for docking analysis. Protein structures were sourced from the Protein Data Bank for the study. The CB-Dock2 database was utilized to validate the molecular docking process, which uses curvature-based cavity detection and Autodock Vina software for accurate predictions (Liu *et al*., 2022b). CB-Dock2 ranks the binding modes based on Vina scores and offers a 3D visualization of these modes.

Binding poses are sorted by binding energy for further analysis. PyMOL and LigPlot+ were then employed to delve deeper into the binding modes, affinity, and critical interactions between the compounds and targets. Through this comprehensive approach, valuable insights into the molecular recognition and binding characteristics of the active compounds with their respective targets were gained. The methodology employed in this study provides a robust framework for evaluating the plausibility of interactions between core targets and active compounds, enhancing our understanding of their potential therapeutic effects.

Statistical analysis

The study utilized statistical tests in R software (version 4.4.0) with a significance threshold of $P < 0.05$. To account for multiple comparisons, the Bonferroni correction was applied to adjust the significance level. This rigorous approach ensures the reliability and accuracy of the study's findings.

RESULTS

Active ingredients in FBC and potential targets for treatment

Fig. 1 and Table 1 provide an overview of 11 Chinese herbs found in FBC, showcasing their detailed information. Utilizing the BATMAN-TCM 2.0 database, researchers identified a total of 230 active ingredients and 786 corresponding targets, shedding light on the complex therapeutic potential of these traditional medicinal herbs (Table S1).

Disease-related targets of NSCLC

A thorough search was conducted in the OMIM, TTD, and DisGeNet databases using the keywords "Non-Small Cell Lung Carcinoma" or "Non-Small Cell Lung Cancer" to identify relevant genes or protein targets. This search revealed a total of 943 pieces of information related to NSCLC, including genes and proteins (Table S2). The comprehensive analysis provided valuable insights into the molecular aspects of NSCLC, highlighting potential targets for further research.

Network pharmacology analysis

As depicted in Fig. 2A, an intersection analysis was performed between the FBC-related targets and the NSCLC -related-targets, revealing 152 common genes at the intersection. Subsequently, an PPI network was constructed among these genes (Fig. 2B). The top 20 degree-ranked targets were obtained by core target screening using the CytoHubba plugin, as shown in Fig. 2E. Table 2 provides further information on the core targets.

In order to delve deeper into the potential mechanisms of FBC for NSCLC, we utilized the DAVID database to analyze 152 genes at the intersection. The results of our GO enrichment analysis unveiled 903 statistically significant terms, encompassing 725 biological process (BP) terms, 73 cell component (CC) terms, and 103 molecular function (MF) terms. Furthermore, the KEGG enrichment analysis highlighted 167 statistically significant pathway entries. These findings shed light on the complex and intricate pathways involved in the therapeutic effects of FBC on NSCLC, providing valuable insights for future research in this area.

Table 1: The Fufang Banmao Capsule, including 11 herbs.

Herbs (Chinese name)	English name	Latin name	Part Used	Weight
BAN MAO	Cantharides	*Mylabris phalerata* Pallas; *Mylabris cichorii* Linnaeus	Dried body	23.8g
REN SHEN	Ginseng	*Panax ginseng* C. A. Mey.	Roots and rhizomes	59.5g
HUANG QI	Astragalus	*Astragalus membranaceus* (Fisch.) Bun	Roots	297.5g
CI WU JIA	Manyprickle Acathopanax Root	*Acanthopanax senticosus* (Rupr,et Maxim.) Harms	Roots	297.5g
SAN LENG	Common Burreed Rhizoma	*Sparganium stoloni erum* Buch. -Ham.	Rhizomes	95g
BAN ZHI LIAN	Barbed Skullcap Herba	*Scutellaria barbata* D. Don.	Whole herb	357g
E ZHU	Zedoray Rhizome	*Curcuma phaeocaulis* Valeton	Rhizomes	95g
SHAN ZHU YU	Asiatic Cornelian Cherry Fruit	*Cornus officinalis* Sieb. et Zucc.	Fruits	119g
NV ZHEN ZI	Glossy Privet Fruit	*Ligustrum lucidum* Ait.	Fruits	119g
XIONG DAN	Bear Gall	*Selenarctos thibetanus* G. Cuvier	Dried bile	2.4g
GAN CAO	Licorice Root	*Glycyrrhiza uralensis* Fisch.	Roots and rhizomes	59.5g

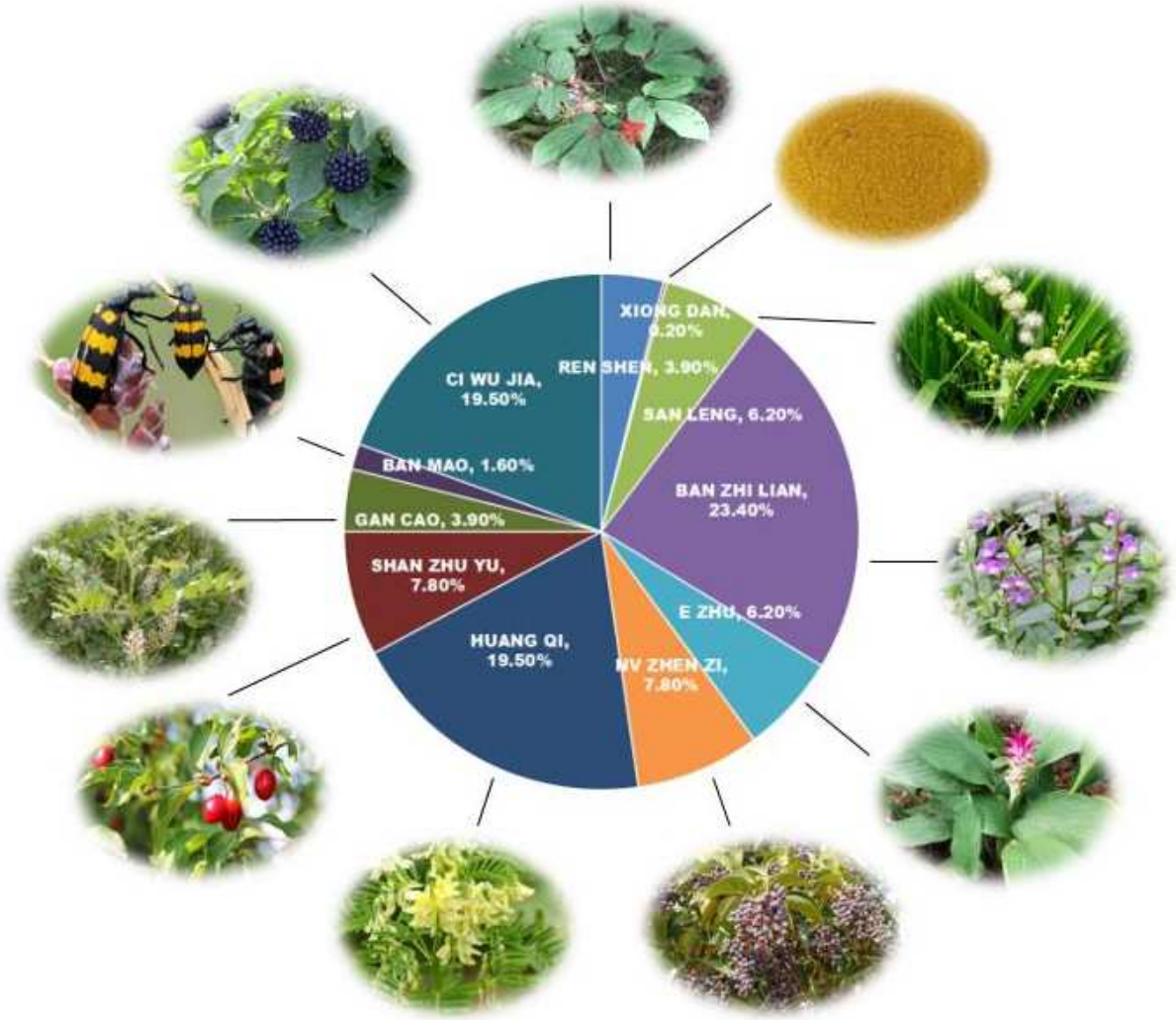

Fig. 1: Compositions of the Fufang Banmao capsule.

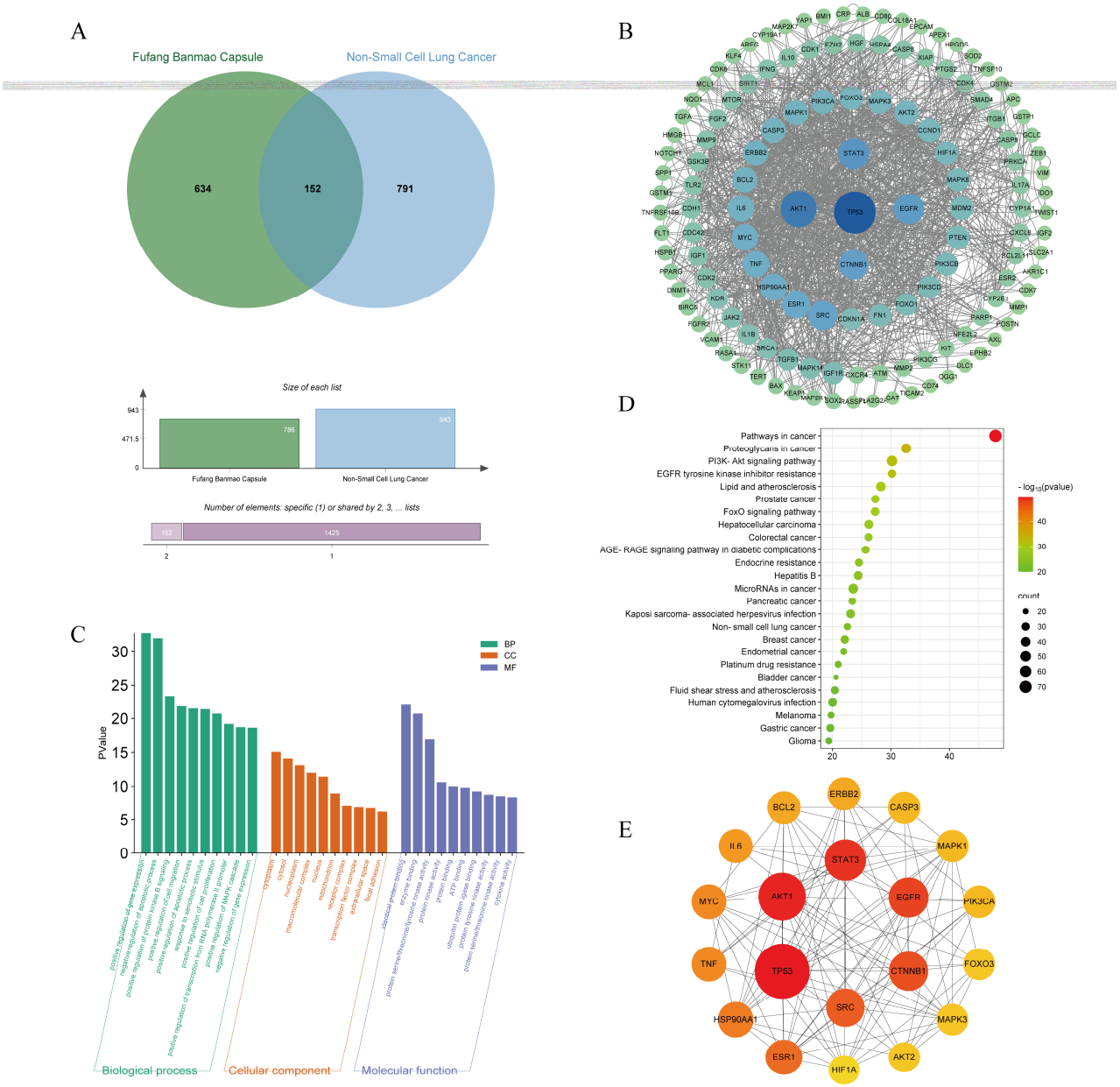

Fig. 2: Analysis of the targets associated with FBC and NSCLC. (A) Venn diagram of FBC and NSCLC-associated targets. Includes 786 FBC-related targets (left), 943 NSCLC-related targets (right), and 152 intersection targets (center). (B) FBC anti-NSCLC PPI network. A larger area indicates larger nodes, blue color indicates higher association, lighter color less association, and the core target is the target in the inner circle. (C) GO enrichment analysis. fold enrichment (y-axis), term (x-axis); green, orange and purple represent the 15 core results for BP, CC, and MF, respectively. (D) KEGG pathway enrichment analysis (DAVID). Pathways (Y-axis), FDR (X-axis), and P-values (color change). Bubble size indicates the number of genes enriched in the pathway. (E) Degree top 20 core target networks. Darker color indicates larger Degree values.

The bar chart in Fig. 2C highlights the top 10 enrichment terms for BP, CC, and MF with the highest gene counts. Concerning BP, significant enrichment is observed in positive regulation of gene expression, negative regulation of apoptotic process, protein kinase B signaling, cell migration and apoptotic process. Meanwhile, CC is predominantly enriched in cytoplasm, cytosol, nucleoplasm, macromolecular complex, and nucleus. As for MF, the main enrichments include identical protein binding, enzyme binding, protein kinase activities for serine/threonine/tyrosine, and general protein binding. These findings shed light on the diverse and complex biological processes at play within these cellular components, emphasizing the importance of various molecular functions in regulating key cellular activities.

A

Disease	Gene	nsnp	method	pval	OR(95% CI)
NSCLC	PIK3CA	9	MR Egger	0.110	0.650 (0.410 to 1.031)
		9	Weighted median	**<0.0025**	0.749 (0.639 to 0.877)
		9	Inverse variance weighted	**<0.0025**	0.774 (0.661 to 0.906)
		9	Simple mode	**0.017**	0.741 (0.610 to 0.900)
		9	Weighted mode	**0.015**	0.745 (0.618 to 0.897)
	TNF	92	MR Egger	0.313	0.933 (0.816 to 1.067)
		92	Weighted median	**<0.0025**	0.858 (0.801 to 0.920)
		92	Inverse variance weighted	**<0.0025**	0.834 (0.792 to 0.878)
		92	Simple mode	**0.009**	0.801 (0.681 to 0.942)
		92	Weighted mode	**<0.0025**	0.836 (0.752 to 0.930)

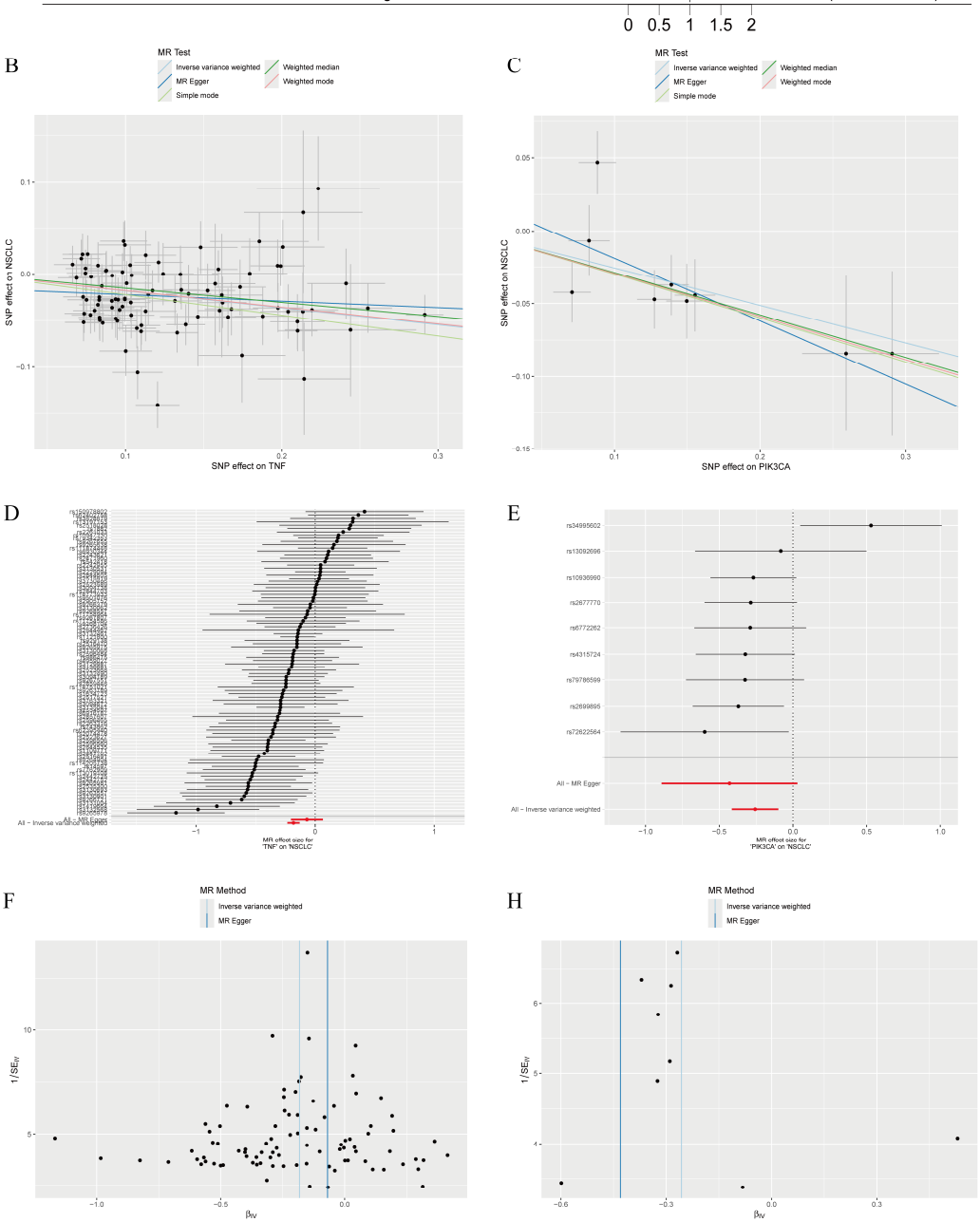

Fig. 3: The results of Mendelian randomization analysis. (A) The forest plot of the causal relationships between TNF, PIK3CA, and NSCLC. (B, C) The scatter plot of the Mendelian randomization (MR) analysis for relationship of two key targets (B: TNF; C: PIK3CA) and NSCLC. (D, E) Forest plots of the MR analysis for diagnostic significance of two key targets (D: TNF; E: PIK3CA) on NSCLC. (F, G) Funnel plots of the MR analysis for two key targets (F: TNF; G: PIK3CA) on NSCLC.

Table 2: Information of core targets.

Gene symbol	Gene name	Degree
TP53	tumor protein p53	100
AKT1	AKT serine/threonine kinase 1	80
STAT3	signal transducer and activator of transcription 3	64
EGFR	epidermal growth factor receptor	60
CTNNB1	catenin beta 1	58
SRC	SRC proto-oncogene, non-receptor tyrosine kinase	56
ESR1	estrogen receptor 1	52
HSP90AA1	heat shock protein 90 alpha family class A member 1	48
MYC	MYC proto-oncogene, bHLH transcription factor	46
TNF	tumor necrosis factor	46
IL6	interleukin 6	44
ERBB2	erb-b2 receptor tyrosine kinase 2	42
BCL2	BCL2 apoptosis regulator	42
MAPK1	mitogen-activated protein kinase 1	40
CASP3	caspase 3	40
PIK3CA	phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha	40
FOXO3	forkhead box O3	38
AKT2	AKT serine/threonine kinase 2	38
MAPK3	mitogen-activated protein kinase 3	38
HIF1A	hypoxia inducible factor 1 subunit alpha	36

Table 3: Information for seven candidate targets causally associated with NSCLC.

id.exposure	id.outcome	method	nsnp	pval	pleio_pval
eqtl-a-ENSG00000141510	finngen_R10_C3_LUNG_NONSMALL_EXALLC	IVW	6	0.023451	0.801078
eqtl-a-ENSG00000142208			32	0.024591	0.500213
eqtl-a-ENSG00000080824			45	0.034526	0.9819
eqtl-a-ENSG00000136997			10	0.024533	0.699777
eqtl-a-ENSG00000232810			92	4.8E-12	0.07661
eqtl-a-ENSG00000164305			41	0.041282	0.805727
eqtl-a-ENSG00000121879			9	0.001416	0.455479

Table 4: Heterogeneity and pleiotropy assessment.

Outcome	Exposure	Cochran Q test			MR-Egger		
		Q	Q df	Q P-value	Intercept	se	Pleiotropy Test p-value
finngen_R10_C3_LUNG_NONSMALL_EXALLC	eqtl-a-ENSG00000232810	152.69	91	5.51E-05	-0.015	0.0086	0.08
	eqtl-a-ENSG00000121879	12.88	8	0.116	0.024	0.0305	0.46

* $P < 0.05$

Table 5: The binding energy values obtained from molecular docking analysis.

Targets	Ingredients	Binding Score (kcal/mol)
TNF	Cantharidin	-7.0
TNF	METHYL PALMITATE	-7.1
TNF	Resveratrol	-8.2
PIK3CA	Resveratrol	-8.5

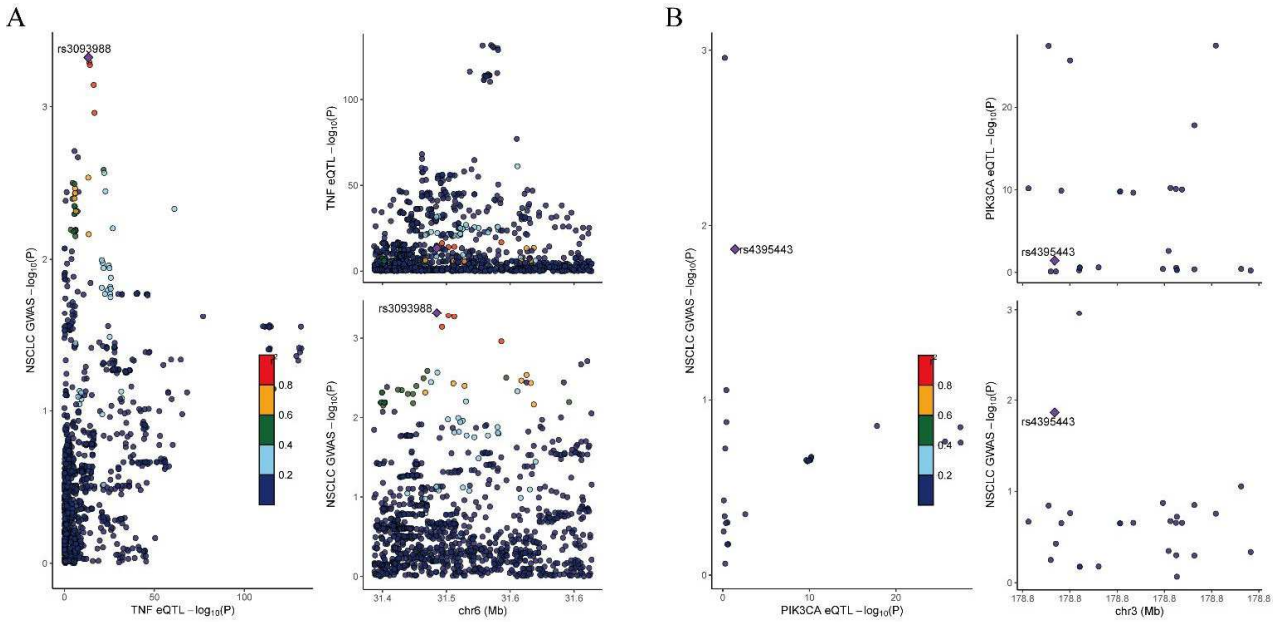

Fig. 4: The results of eQTL colocalization analysis. (A) TNF. (B) PIK3CA. The left plot represents the -log10(P) distribution of SNPs and eQTL in GWAS, with smaller p-values above the y-axis. The two plots on the right represent the eQTL and GWAS distributions with subplots, respectively (horizontal coordinates are the loci of SNPs, vertical coordinates represent the -log10(P) values of SNPs in the GWAS/eQTL data). The rsid with the smallest summed p-value in both data is labelled as the pioneer SNP.

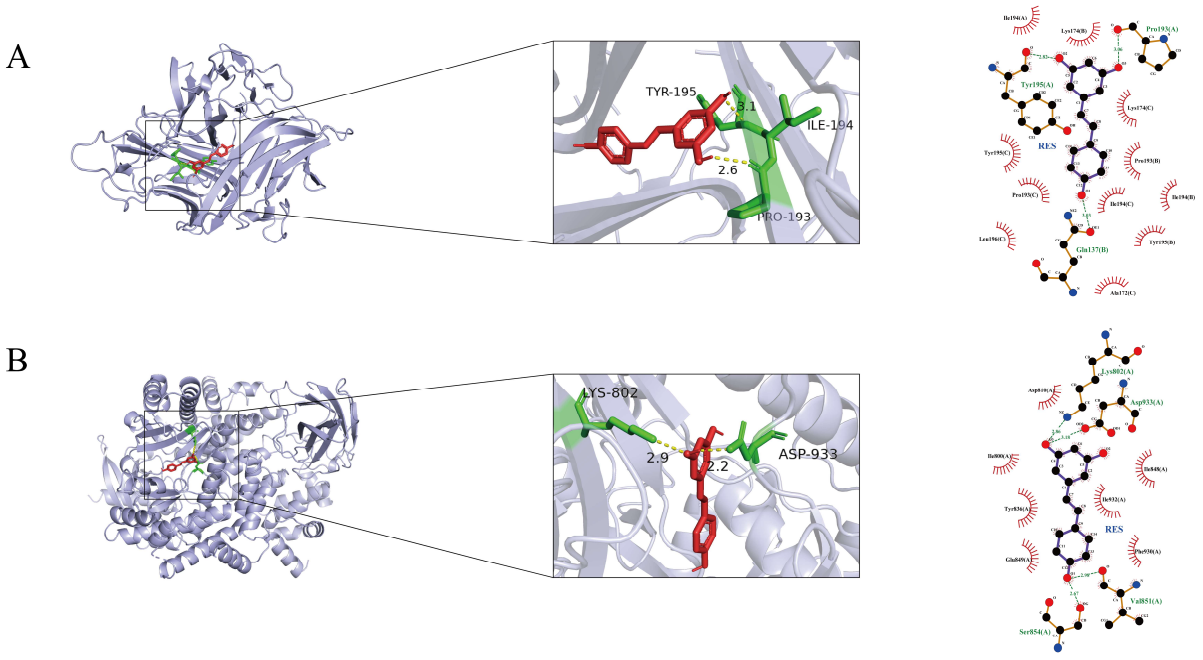

Fig. 5: Visual results of molecular docking between pharmacodynamic molecules and core targets. (A) TNF docked to Resveratrol. (B) PIK3CA docked to Resveratrol. *RES*, Resveratrol.

Fig. 2D displays the ten most notably correlated KEGG pathways, with the top five being pathways connected to cancer, PI3K-Akt signaling, proteoglycan in cancer, lipids and atherosclerosis, and resistance to epidermal growth factor receptor tyrosine kinase inhibitors. These pathways play crucial roles in various biological processes.

Construction of Herbs-Ingredients-Targets-Pathways Network

By establishing the connections between target-pathway and ingredient-target, we constructed a comprehensive Herbs-Ingredients-Targets-Pathways network (Fig. S1). This integrated network comprises 11 herbs, 131 compounds, 152 target proteins, and 136 pathways,

indicating that FBC possesses a multi-compound, multi-target, and multi-pathway characteristic. Each herb is indispensable in tumor treatment, and every ingredient molecule contributes to the overall therapeutic effect of FBC in NSCLC through their respective local pharmacological actions. The top 10 degree compounds were resveratrol, methyl palmitate, formononetin, tauroursodeoxycholic acid, deoxycic acid, cantharidin, SCHEMBL 11962424, raffinose, stearic acid, beta-elmene, and these core compounds may be the main material basis of FBC for the treatment of NSCLC.

MR analysis

By MR analysis, we identified seven candidate genes—Cellular tumor antigen p53 (TP53), AKT1, HSP90AA1, MYC, TNF, CASP3, and PIK3CA—that potentially exhibit causal relationships with NSCLC. By employing the inverse variance weighted (IVW) method with a significance threshold of $P<0.05$, we initially selected these genes. However, upon applying the horizontal multiplicity analysis, no significant associations emerged for the selected candidates at $P>0.05$. To ensure statistical rigor, we further subjected our findings to the Bonferroni correction (adjusted p-value = 0.05/20) (Table 3, Fig. 3A). Upon this refined analysis, TNF and PIK3CA emerged as notably significant, revealing a negative association with the risk of NSCLC. Specifically, elevated levels of these genes seemed to confer a protective effect against NSCLC. This inverse relationship was supported by the IVW results and further underscored by their odds ratios (OR) being less than 1, indicating a decreased likelihood of NSCLC with higher TNF and PIK3CA expression levels. This protective association was visually represented in scatter plots where both TNF and PIK3CA demonstrated a negative correlation with NSCLC risk ($OR < 1$) (Fig. 3B, 3C). The forest plots, depicting the MR effect sizes, also consistently showed estimates below 0, confirming their potential protective roles (Fig. 3D, 3E). To ensure that our findings were not influenced by random chance or biases, we constructed funnel plots, which revealed that our MR analysis adhered to Mendel's second law of independent assortment, indicating that our results were not skewed by any particular sample or subset (Fig. 3F, 3G). Additionally, we conducted a comprehensive series of sensitivity analyses to detect any underlying heterogeneity or horizontal pleiotropy. While Cochran's Q test indicated heterogeneity ($p < 0.001$) among our results, this was mitigated by using the random-effects IVW method, which effectively accommodates variability across studies, thus preserving the robustness of our findings (as detailed in Table 4). Moreover, the MR-Egger intercept evaluation provided further reassurance, yielding a P-value greater than 0.05, suggesting no significant pleiotropic effects influencing our results. In other words, there was no indication that unmeasured confounders were influencing our observed associations. Additionally, leave-one-out (LOO) analyses were conducted to assess the potential bias in effect sizes for individual instrumental variables (IVs) (Figs. S2-3). These analyses demonstrated that the exclusion of any single IV did not notably alter the effect sizes, reinforcing the reliability of our findings. In conclusion, through meticulous MR analysis and rigorous validation steps, we have identified TNF and PIK3CA as potential protective factors against NSCLC. Their inverse association with NSCLC risk adds a new dimension to our understanding of NSCLC genetics and could pave the way for future research exploring these genes' mechanisms and potential therapeutic applications.

eQTL co-location analysis

We sequenced SNPs situated within a ± 100kb region between two genes, TNF and PIK3CA, and NSCLC risk. We then employed Bayesian co-localization to evaluate the evidence for common causal variants between these key target genes and NSCLC. The results demonstrated that SNPs linked to TNF expression and NSCLC risk exhibited a posteriori probability of pathogenic variants at the TNF locus of 7.56% (PH1 = 83.60%, PH2 = 0.00%, PH3 = 8.88%, and PH4 = 7.56%). The results demonstrated that the SNPs associated with PIK3CA expression and NSCLC risk exhibited a pathogenic variant at the PIK3CA locus with a posteriori probability of 2.94% (PH1 = 96.60%, PH2 = 0.00%, PH3 = 0.46%, PH4 = 2.94%). The results of the colocalization analyses indicated that the possibility of co-causality between TNF and PIK3CA gene expression and SNPs associated with NSCLC risk was low, but could not be completely excluded. Finally, the R software 'locuscompare' package was used to demonstrate the chain imbalance of SNPs and the distribution of lead SNPs (Fig. 4).

Molecular Docking

Molecular docking was utilized to determine the binding capacity between the core active ingredient and the key target. The findings from the molecular docking are outlined in Table 5, showcasing the binding energies. It is widely acknowledged that a binding energy below -5 kcal/mol signifies a strong binding activity between a protein and a small molecule (Liu *et al*., 2022a). The results from the molecular docking analysis revealed that the core active ingredient, resveratrol, displayed a superior docking affinity of -8.1 kcal/mol with TNF, showcasing a significant binding capacity (Fig. 5A). Similarly, the docking affinity of resveratrol with PIK3CA was measured at -8.5 kcal/mol, indicating a robust binding capacity (Fig. 5B).

DISCUSSION

The utilization of FBC, a modern preparation rooted in TCM beliefs, has sparked significant interest and investigation within the realm of anti-tumor therapy (Li *et al*., 2022b). Comprised of a combination of 11 Chinese

herbs, including Cantharides, Ginseng, and Astragalus, FBC is meticulously crafted using contemporary pharmaceutical techniques to create a potent formula capable of delivering powerful anti-tumor benefits. Beyond directly targeting malignant cells, FBC also serves to modulate and enhance the body's immune function, with a specific focus on bolstering cellular immune responses. This unique approach not only aids in fortifying the body's defenses against tumors but also aligns with the fundamental TCM principle of "strengthening the vital Qi and consolidating the foundation" (Cao *et al*., 2007; Han *et al*., 2012; Liu *et al*., 2020). In clinical settings tailored to address specific cancer types, FBC is frequently integrated into comprehensive treatment strategies alongside traditional anti-tumor methodologies such as chemotherapy and radiotherapy. Through such combined approaches, FBC has showcased remarkable synergistic effects. For example, when incorporated into the treatment plan for primary liver cancer, FBC has proven to significantly elevate treatment response rates compared to therapies that rely solely on supportive care. Moreover, the inclusion of FBC has been instrumental in minimizing the undesirable side effects typically associated with chemotherapy, like immunosuppression. The incorporation of FBC into combination therapies has yielded encouraging outcomes, leading to improvements in patient survival rates (Liu *et al*., 2020; Liu *et al*., 2019). Its distinctive anti-tumor properties, coupled with its relatively mild side effect profile, have made FBC a favored option among patients, particularly those seeking to mitigate the adverse effects commonly linked to chemotherapy. Overall, the growing body of evidence supporting the efficacy of FBC in conjunction with conventional anti-tumor treatments underscores its potential as a valuable asset in the fight against cancer.

The intricate network of 'Herbs-Ingredients-Targets-Pathways' has unveiled the key components responsible for the therapeutic efficacy of FBC in treating NSCLC. Among these components, resveratrol stands out as a potent polyphenolic compound with promising anti-cancer properties. Studies have shown that resveratrol can trigger autophagy and apoptosis in NSCLC cells, as well as sensitize them to chemotherapy by influencing various signaling pathways such as Akt/NF-κB and NGFR/AMPK/mTOR (Rasheduzzaman *et al*., 2018; Li *et al*., 2022a). Formononetin, an isoflavonoid, has also been found to inhibit tumor growth in NSCLC by blocking the EGFR/Akt/Mcl-1 axis (Yu *et al*., 2020). Cantharidin, a natural toxin, emerges as a potential anti-cancer agent due to its unique cytotoxicity and ability to suppress the migration and invasion of NSCLC cells through the inhibition of protein phosphatase 5 and activation of AMPK signaling (Kim *et al*., 2013; Hsieh *et al*., 2017). Moreover, beta-elemene, a sesquiterpene isomer, exhibits significant inhibitory effects on NSCLC by inducing iron-dependent cell death (Zhao *et al*., 2024), restraining cancer cell proliferation (Feng *et al*., 2022), and enhancing sensitivity to chemotherapy and radiotherapy (Li *et al*., 2011; Xu *et al*., 2023).While compounds like methyl palmitate, tauroursodeoxycholic acid, deoxycholic acid, SCHEMBL11962424, raffinose, and stearic acid show promising interactions within the network analysis regarding NSCLC-related targets, there is a lack of direct evidence demonstrating their specific therapeutic effects on NSCLC. Therefore, further research is imperative to understand their potential in treating NSCLC. In essence, the therapeutic benefits of FBC in NSCLC are attributed to the combination of active ingredients working synergistically through diverse mechanisms. These mechanisms include inhibiting cancer cell growth, promoting apoptosis, modulating signaling pathways, and enhancing the efficacy of chemotherapy. The intricate interplay of these components underscores the multifaceted approach of FBC in combating NSCLC, offering a promising avenue for future research and development in cancer treatment.

Lung cancer remains one of the most prevalent and deadly cancer types worldwide, with non-small cell lung cancer (NSCLC) being the most common subtype, accounting for approximately 85% of all cases. The identification of key genes and molecular pathways involved in NSCLC pathogenesis is essential for the development of targeted therapies and improved prognosis for patients. Through the construction of a protein-protein interaction (PPI) network and the identification of core targets, a number of genes closely related to NSCLC pathogenesis have been uncovered, including TP53, AKT1, HSP90AA1, MYC, TNF, CASP3, and PIK3CA.The TP53 gene encodes the p53 protein, a critical tumor suppressor known for its role in regulating the cell cycle, promoting DNA repair, and inducing apoptosis to prevent tumor formation (Kaur *et al*., 2019; Tang *et al*., 2020). Mutations in TP53 have been closely linked to various cancers, with recent studies highlighting the central role of the TP53 gene in NSCLC. These studies have shown the predictive significance of TP53 for ALK-positive NSCLC prognosis (Canale *et al*., 2022; Zeng *et al*., 2021), its impact on patient prognosis and therapeutic responses, including immunotherapy and cisplatin resistance, and its crucial value in cancer treatment and prognostic assessment (Jiang *et al*., 2023; Kim *et al*., 2023a). The AKT1 gene encodes a serine/threonine protein kinase that is a key component of the PI3K/AKT signaling pathway, crucial for cell survival, cell cycle progression, and cell growth (Fresno Vara *et al*., 2004). Inhibiting AKT1 phosphorylation and activation has been shown to inhibit NSCLC cell proliferation and induce apoptosis, suggesting that molecular targeted therapy against AKT1 could provide more precise and effective treatment options for NSCLC patients (Jin *et al*., 2023; Tian *et al*., 2022). Heat shock

protein 90 (HSP90), encoded by the HSP90AA1 gene, is a molecular chaperone that plays a crucial role in folding and stabilizing cancer-related proteins (Zuehlke *et al*., 2015). High expression of HSP90AA1 in NSCLC has been associated with reduced overall survival, and inhibition of HSP90 has shown promise in diminishing the pro-survival effects of AKT1 phosphorylation and its downstream factors, mTOR and BAD, providing a new avenue for NSCLC treatment (Niu *et al*., 2021). The MYC gene encodes the Myc protein, a transcription factor that regulates cell growth and proliferation. Targeted therapies against MYC have emerged as a promising strategy for NSCLC treatment (Duffy *et al*., 2021), with studies showing a significant correlation between MYC expression and the immune checkpoint biomarker PD-L1 in NSCLC (Kim *et al*., 2017). TNF plays a crucial role in inflammation, immune responses, and tumor development and progression (Balkwill, 2009). TNF-α has demonstrated potent anti-tumor activity, and precise regulation of TNF function is essential for NSCLC treatment (Josephs *et al*., 2018; Wang, 2008). CASP3 encodes Caspase-3, a key enzyme in executing apoptosis. Activation of Caspase-3 directly triggers apoptosis (Eskandari and Eaves, 2022).

It has been reported that certain small molecules of natural origin can induce apoptosis in NSCLC cells by activating Caspase-3 activity (Guo *et al*., 2024; Li *et al*., 2021a). PIK3CA encodes the phosphatidylinositol-3-kinase catalytic subunit alpha, a crucial molecule upstream of the PI3K/AKT signaling pathway. Mutations in PIK3CA have been linked to a poor prognosis in patients with solid malignancies (Alqahtani *et al*., 2019) and have the potential to induce drug resistance in NSCLC patients undergoing treatment with epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) (Liu *et al*., 2024). The development of specific inhibitors represents a novel approach to targeted therapy against PIK3CA (Hanan *et al*., 2022). These core targets represent key players in NSCLC pathogenesis and provide a valuable molecular basis for understanding the disease process, guiding precision therapy, and assessing prognosis. Furthermore, the significant causal relationship between elevated expression levels of TNF and PIK3CA and decreased risk of NSCLC, as identified by MR analysis, underscores the potential of these genes as therapeutic targets. The accuracy of key gene screening has been verified through colocalization analysis and molecular docking, paving the way for further research into targeted therapies for NSCLC.

The investigation conducted in this study utilized a comprehensive and multifaceted approach, which integrated network pharmacology, Mendelian randomization, colocalization analysis, and molecular docking techniques. The primary objective was to elucidate the mechanism of action of the Chinese herbal formula FBC in the treatment of NSCLC. While existing research has mainly focused on the clinical efficacy of FBC, our in-depth analysis aimed to fill a crucial gap in the understanding of the mechanistic basis of this therapeutic agent. FBC has garnered attention for its multi-target action profile, which distinguishes it as a valuable asset in the realm of cancer therapy. The combination of various active ingredients within FBC exhibits not only a direct impact on tumor cell proliferation but also influences the immune microenvironment of the host, making it a noteworthy candidate for inclusion in combination treatment regimens (Wang *et al*., 2021). With the rise of precision medicine and personalized therapy, FBC's multifaceted approach sheds light on novel strategies to combat tumor heterogeneity and therapeutic resistance. The synergy between FBC and other anticancer drugs presents an opportunity to expand treatment options and develop tailored therapeutic approaches that cater to the specific characteristics of individual patients' tumors. Future research endeavors should focus on determining the optimal dosage, timing, duration, and precise mechanisms of action when combining FBC with different anticancer agents, with an emphasis on validating its safety and efficacy through rigorous clinical trials. Furthermore, harnessing modern molecular biology tools and bioinformatics methods to dissect the complex network of targets affected by FBC will provide critical insights for achieving personalized and precise tumor therapy. The exploration of FBC in the context of combination therapy holds great promise for revolutionizing current approaches to cancer treatment, offering new avenues for breakthroughs and instilling hope in patients battling NSCLC. In light of the transformative potential of FBC in combination therapy for NSCLC, further investigations are warranted to validate and deepen our understanding of its intricate relationship with the disease. By delving into the complex interplay between FBC and NSCLC, we can pave the way for enhanced treatment strategies and improved outcomes for patients facing this challenging malignancy.

Despite the promising findings presented in this study on the potential benefits of FBC in NSCLC, it is important to acknowledge the limitations that may affect the interpretation of the results. While network pharmacology and Mendelian randomization methods offer valuable insights into drug mechanisms, the predictive outcomes generated still require validation through in vitro and in vivo experiments. In order to strengthen the credibility of these findings, future research should incorporate additional experimental validation. Furthermore, this study mainly focused on the active ingredients and targets of FBC, neglecting the impacts of metabolism, distribution, and pharmacokinetics in vivo. Exploring these aspects would provide a more thorough understanding of how FBC works in the treatment of

NSCLC. Additionally, while the therapeutic potential of FBC in NSCLC is highlighted in this study, further research should investigate its efficacy and mechanisms in other types of cancer for a more comprehensive assessment of its benefits.

CONCLUSION

This study delves into the intricate mechanisms of action of FBC in treating NSCLC, utilizing a combination of network pharmacology, molecular docking, MR, and colocalization analyses. The identified key targets, TNF and PIK3CA, were shown to play a causal role in reducing the risk of NSCLC development. Molecular docking further confirmed the strong binding affinity between the active components of FBC and these crucial targets. The findings of this study enhance our understanding of how FBC functions in NSCLC treatment, paving the way for potential therapeutic applications. It lays a solid groundwork for future exploration of FBC's therapeutic potential in NSCLC, offering valuable insights for precision medicine approaches and drug development strategies. Moreover, this study underscores the importance of integrating in vitro and in vivo experiments in future studies to strengthen and complement the current findings. Further research is necessary to elucidate the impact of FBC's active components on in vivo metabolism, distribution, and pharmacokinetics, providing a more comprehensive understanding of FBC's mechanism of action in NSCLC therapy. Additionally, future investigations should focus on exploring the therapeutic effects and mechanisms of FBC in other types of cancer, expanding its potential applications beyond NSCLC. By continuing to unravel the intricacies of FBC's mechanisms, we can potentially unlock new avenues for cancer treatment and improve patient outcomes.

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Authors' contributions
ZC.W contributed to the paper writing and data analysis, YY.H and Z.F contributed to searching the database and data collection, DS.W contributed to summarizing all the tables, CH.L contributed to drawing the figures, and XD.S contributed to designing the project.

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Data availability statement
The datasets presented in this study are included in the article/Supplementary Materials. Further inquiries can be directed to the corresponding author.

Ethical approval
All data referenced from the GWASs cited in this work have undergone transparent publication and are publicly accessible, thereby obviating ethical scrutiny concerns.

Conflict of interest
There are no conflict of interest.

Supplementary data
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