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• *Review* •

Integrating "Pathway-Target-Active Ingredient" to Explore the Mechanism and Clinical Research of Shexiang Baoxin Pills in Treating Coronary Artery Lesions

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Abstract: Objective: To analyze the mechanism of Shexiang Baoxin Pills (SBP) against coronary artery lesions (CAL) via network pharmacology and validate it clinically. Methods: SBP components and targets were screened via TCMSP, TCMID, and Swiss Target Prediction. Intersecting with CAL targets from GeneGards formed a "drug-ingredient-target-disease" network. STRING and DAVID supported PPI topology, GO annotation, and KEGG enrichment. A "pathway-target-ingredient" network clarified the formula's multi-target, multi-pathway synergy. Clinical efficacy, serum vascular endothelial growth factor (VEGF) and angiopoietin-1 (Ang-1) levels, adverse reactions, and major adverse cardiovascular events (MACE) were compared among 240 patients with severe CAL, divided into control groups (no SBP) and experimental groups (SBP for 6 months). Results: Network pharmacology analysis identified 94 potential therapeutic targets of SBP for CAL. Core targets included tumor necrosis factor (TNF), interleukin 1 beta (IL1B), AKT serine/threonine kinase 1 (AKT1), insulin (INS), and RELA proto-oncogene, NF-kB subunit (RELA). Enriched pathways involved lipid metabolism and atherosclerosis. Clinical results showed that the total effective rates in all experimental groups were significantly higher than those in the control groups ($P < 0.05$). No statistically significant differences were observed in the adverse reactions or MACE between groups ($P > 0.05$). Serum levels of VEGF and Ang-1 were significantly elevated in all experimental groups compared to the control groups ($P < 0.05$). Conclusion: SBP exerts therapeutic effects through multi-component, multi-target, and multi-pathway actions, safely improving clinical outcomes in patients with CAL , with angiogenesis promotion as a key mechanism.

Keywords: Shexiang Baoxin Pill; Coronary artery lesions; Network pharmacology; Mechanism of action

1 Introduction

The pathogenesis of coronary artery lesions (CAL) is complexand mainly linked to inflammatory responses, vascular endothelial cell injury, oxi-

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dative stress, and other factors (Chen and Yang, 2024; Myszko et al., 2025). In the diagnosis and treatment of complex diseases, traditional Chinese medicine demonstrates its unique advantages due to its multi-component, multi-target synergistic effects (Yu et al., 2025). Shexiang Baoxin Pill (SBP) is composed of borneol, artificial bezoar, cinnamon, ginseng extract, musk, toad venom, and storax. It has the effects of aromatic warming and invigorating qi to strengthen the heart, and exerts a certain therapeutic effect on diseases such as coronary heart disease with angina pectoris, myocardial infarction, and chest bi syndrome caused by qi stagnation and blood stasis (Yang et al., 2021). At present, it is also used for the long-term prevention and treatment of coronary heart disease (Lu et al., 2018). Research has confirmed that SBP promote coronary vascular neogenesis in animals (Zhang et al., 2017; Zhang et al., 2020), but clinical studies are currently lacking to determine whether they can promote coronary vascular neogenesis in humans for the treatment of CAL. Research has found that the expression of angiopoietin-1 (Ang-1) and vascular endothelial growth factor (VEGF) can indirectly reflect the processes of vascular neogenesis and repair (Su et al., 2022; Melincovici et al., 2018). This study hypothesizes that SBP may promote coronary vascular angiogenesis in humans by upregulating Ang-1 and VEGF expression, activating complex signaling pathways, and regulating cellular functions and gene activation. Network pharmacology serves as an effective approach for studying compound traditional Chinese medicines, offering an intuitive means to reveal the intricate biological relationships among herbal components, targets, and diseases (Luo et al., 2020). Therefore, this study aims to explore the potential key targets, primary compounds, and signaling pathways of SBP in treating CAL through network pharmacology. It further analyzes the therapeutic effects of Shexiang Baoxin Pills on patients with CAL and its influence on serum Ang-1 and VEGF expression via clinical research. This approach validates the clinical efficacy of SBP and its role in human coronary vascular angiogenesis, providing valuable reference for subsequent studies.

2 Materials and Methods

2.1 Relevant Mechanisms

2.1.1 Database

This study aims to investigate the therapeutic mechanisms of SBP against CAL based on network pharmacology, with detailed information on the relevant databases provided in Table 1.

2.1.2 Identification of Active Components and Targets in SBP

The active components and their corresponding targets of the five traditional Chinese medicines, namely ginseng, borneol, bezoar, storax, and cinnamon, were obtained using the TCMSP. Using oral bioavailability (OB) ≥ 30% and drug similarity (DL) ≥ 0.1 as criteria (Shen et al., 2017), we screened the active components from the aforementioned five Chinese herbal medicines and identified the corresponding targets for each compound. For components not retrievable from the TCMSP database—musk and toad venom—searches were conducted using the TCMID database. Active compounds were screened via PubChem and SwissADME databases, followed by target prediction for potential active substances using the Swiss Target Prediction database. Target selection was performed by setting a “probability” threshold of 0.3.

Table. 1 Database

Database	Website
Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP)	https://old.tcmsp-e.com/tcmsp.php
UniProt	https://www.uniprot.org/
Traditional Chinese Medicine Integrated Database (TCMID)	https://www.megabionet.org/tcmid
PubChem	https://pubchem.ncbi.nlm.nih.gov/
SwissADME	http://www.swissadme.ch/
Swiss Target Prediction	http://swisstargetprediction.ch/
GeneGards	https://www.genecards.org/
String	https: //string-db. org/
David	https://david.ncifcrf.gov/

2.1.3 Acquisition and Intersection of CAL Target Genes

Using “coronary artery lesion” as the keyword, disease targets were retrieved from the GeneGards database, excluding targets with a relevance score below 1. Using the Venny online tool (https://bioinfogp.cnb.csic.es/tools/venny/), we input the target gene list for CAL and the target gene list for the active ingredients of SBP to extract the intersecting target genes and generate a Venn diagram.

2.1.4 Construction of Protein-Protein Interaction (PPI) Networks

A PPI network was constructed based on the String database to identify target proteins of SBP in treating CAL. CytoScape 3.9.1 software was employed for network topology analysis to elucidate the interaction mechanisms among key targets. Core targets were selected using a filtering criterion of node degree values exceeding the average.

2.1.5 Constructing the “Drug-Active Ingredient–Target–Disease” Network for Shexiang Baoxin Pills in Treating CAL

Organize the correspondence between the drug's active ingredients and their shared target points. Import this data into Cytoscape 3.9.1 software to generate a “drug-active ingredient-target-disease” network diagram. Simultaneously, analyze the topological parameters of the target points using Network Analyzer. Sort them based on the magnitude of their degree connectivity values to identify core active ingredients.

2.1.6 GO Functional Enrichment Analysis and KEGG Enrichment Analysis

Upload the intersecting targets to the DAVID database, set the species to Homo sapiens, and conduct Gene Ontology (GO) functional enrichment analysis with a threshold of $P<0.01$, covering biological process (BP), cellular component (CC), and molecular function (MF). Concurrently, perform Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis. Generate bubble plots using the MicroBioinformatics web portal.

2.1.7 Construction of the "Pathway-Target-Active Ingredient" Network for SBP in the Treatment of CAL

The enriched KEGG pathways for SBP in treating CAL, along with the involved key genes and

effective compound components, were imported into Cytoscape 3.9.1 software to construct a "pathway-target-active ingredient" network.

2.2 Clinical Studies

2.2.1 General Information

From July 2020 to June 2021, a total of 240 inpatients diagnosed with severe CAL via coronary angiography at the Department of Cardiology, Nanxishan Hospital of Guangxi Zhuang Autonomous Region, were recruited. These patients were categorized as follows: (1)Control Group 1 (n=40): Patients who did not undergo percutaneous coronary intervention (PCI) with stent implantation; (2) Control Group 2 (n=40):Patients who underwent PCI with stent implantation; (3) Single-Vessel Lesion Group (n=40): Patients with single-vessel coronary artery lesions who underwent PCI with stent implantation; (4) Double-Vessel Lesion Group (n=40):Patients with double-vessel coronary artery lesions who underwent PCI with stent implantation; (5) Triple-Vessel Lesion Group (n=40): Patients with triple-vessel coronary artery lesions who underwent PCI with stent implantation; (6) Experimental Group 1 (n=40):Patients who did not undergo PCI with stent implantation.

Inclusion Criteria: (1)complete clinical data; (2) moderate to severe lesions according to the Gensini score (Melincovici et al., 2018). Exclusion Criteria: (1) left ventricular dysfunction; (2) severe renal insufficiency; (3) Iodine allergy; (4) Severe respiratory disease. This study obtained informed consent from participants and their families and was approved by the hospital's Medical Ethics Committee.

2.2.2 Treatment Methods

Both Control Group 1 and Control Group 2 received guideline-directed secondary prevention therapy for coronary heart disease, administered for 6 months. The specific medication regimen was as follows: Aspirin enteric-coated tablets (Manufacturer: Bayer S.p.A; National Drug Approval Number: J20171021; Specification: 100 mg/tablet): 100 mg orally, once daily. Clopidogrel bisulfate tablets (Manufacturer: Shenzhen Salubris Pharmaceuticals Co., Ltd.; National Drug Approval Number: H20000542; Specification: 25 mg/tablet): 75 mg orally, once daily. Isosorbide mononitrate tablets (Manufacturer: Lunan Better Pharmaceutical Co., Ltd.; National Drug Approval Number: H10940039; Specification: 20 mg/tablet): 20 mg orally, twice daily. Metoprolol tartrate tablets (Manufacturer: AstraZeneca Pharmaceuticals Co., Ltd.; National Drug Approval Number: H32025391; Specification: 25 mg/tablet): 50 mg orally, twice daily. Rosuvastatin calcium tablets (Manufacturer: AstraZeneca Pharmaceuticals Co., Ltd.; National Drug Approval Number: J20170008; Specification: 10 mg/tablet): 5 mg orally, once daily.

The Single-Vessel Lesion Group, Double-Vessel Lesion Group, Triple-Vessel Lesion Group, and Experimental Group 1 all received combined therapy consisting of guideline-directed secondary prevention medication (identical to the regimen for Control Group 1 and Control Group 2) plus SBP. The Shexiang Baoxin Pills (Manufacturer: Shanghai Hutchison Pharmaceuticals Co., Ltd.; National Drug Approval Number: Z31020068; Specification: 22.5 mg/pill) were administered orally at a dose of 22.5 mg, three times daily (morning, noon, and evening). All groups underwent treatment for a duration of 6 months.

2.2.3 Observation Indicators

(1) Efficacy: After 6 months of treatment, efficacy was assessed according to the “Guidelines for Clinical Research on Cardiovascular System Drugs” and the “Guidelines for Clinical Research

on New Traditional Chinese Medicine Drugs" Primary outcome measures included changes in symptom severity, attack frequency, and Traditional Chinese Medicine (TCM) syndrome scores. Grading criteria were as follows: Markedly Effective: ≥80% reduction in angina symptoms and attack frequency during equivalent physical exertion, no limitations on physical activity, and ≥70% reduction in TCM syndrome scores. Effective: Symptoms such as angina pectoris and attack frequency reduced by 50%–80%, TCM syndrome score reduced by 30%–70%; Ineffective: Symptoms such as angina pectoris and attack frequency reduced by <50% or increased, TCM syndrome score reduced by <30%. Total Effective Rate (%) = [(Number of markedly effective cases + Number of effective cases) / Total number of cases] × 100% (Wei et al., 2022).

(2) Safety Indicators: During treatment, closely monitor patients for major adverse cardiovascular events (MACE) and adverse drug reactions. MACE primarily includes cardiac death, non-fatal myocardial infarction, non-fatal stroke, hospitalization for worsening symptoms, severe hepatic or renal impairment, serious arrhythmias, and any form of revascularization (e.g., repeat PCI or bypass surgery). Adverse drug reactions mainly encompass palpitations, headache, dizziness, nausea, vomiting, and abnormal hepatic or renal function.

(3) Serological Markers: Vascular Endothelial Growth Factor (VEGF), Angiopoietin-1 (Ang-1). Venous blood samples were collected from all patients prior to drug administration to measure Ang-1 and VEGF expression levels. Regular follow-up visits were conducted post-discharge, with serum Ang-1 and VEGF expression levels sampled at 1 month, 3 months, and 6 months post-treatment. Ang-1 and VEGF were measured using ELISA kits purchased from Shanghai Baiwo Biotechnology Co., Ltd. and Shanghai Jining Biological Products Co., Ltd., respectively. Testing procedures strictly followed the kit instructions.

2.2.4 Statistical Methods

Data were analyzed using SPSS 23.0 statistical software. Measurement data conforming to a normal distribution were expressed as mean ± standard deviation () and compared between groups using the t-test (for two groups) or one-way ANOVA (for multiple groups). Subgroup comparisons were conducted using the LSD-t test, while comparisons within groups before and after treatment were performed using repeated measures ANOVA. Count data were expressed as numbers and percentages [n (%)] and compared between groups using the chi-square test. The significance level was set at 0.05.

3 Results

3.1 Network Pharmacology Findings

3.1.1 Primary Active Ingredients of SBP and Their Corresponding Targets

A total of 92 active ingredients were identified from the seven medicinal herbs constituting SBP, including 32 from ginseng, 27 from musk, 10 from cinnamon, 9 from toad venom, 8 from storax, 5 from bezoar, and 1 from borneol. These ingredients corresponded to 649 potential targets, with 189 unique targets retained after removing duplicates.

3.1.2 Targets for CAL and Intersection Targets with SBP

A database search identified 6,993 target points associated with CAL. After intersecting these with the target points of the Active Ingredients in Shexiang Baoxin Pills, 94 potential therapeutic target points were screened. See Figure 1 for details.

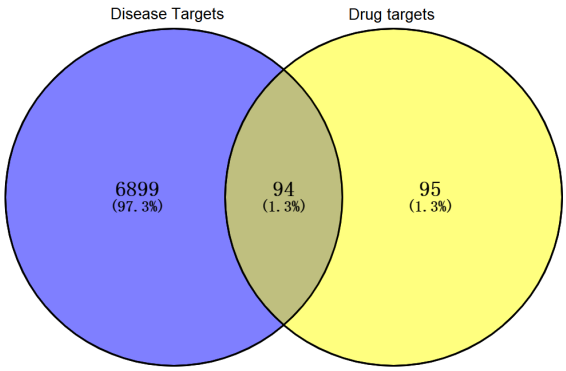

Figure. 1 Veen Diagram of Drug Targets for SBP and Disease Targets for CAL

3.1.3 Core Targets of SBP in Treating CAL

A PPI network comprising 94 intersecting targets was constructed using the String database and visualized via Cytoscape 3.9.1 (Figure 2). Core targets were further screened through network topology analysis, with a selection criterion of Degree values exceeding 8.02 (mean value), ultimately yielding 30 core targets (Figure 3). The top five core targets by degree value were TNF, IL1B, AKT1, INS, and RELA. These are presumed to be key targets mediating the therapeutic effects of SBP in treating CAL.

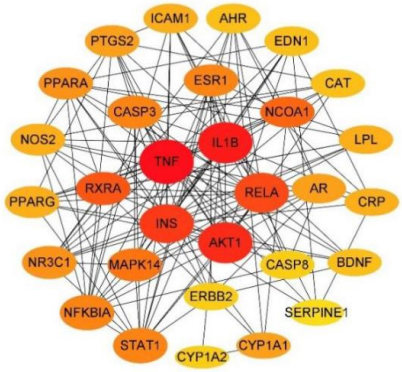

Figure. 3 Drug-Disease Core Target Network Diagram (Degree > 8.02)

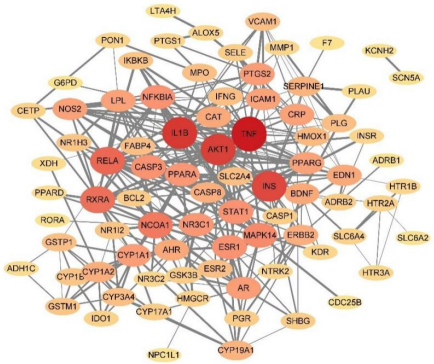

Figure. 2 PPI Network Diagram of Potential Target Molecules for SBP in Treating CAL

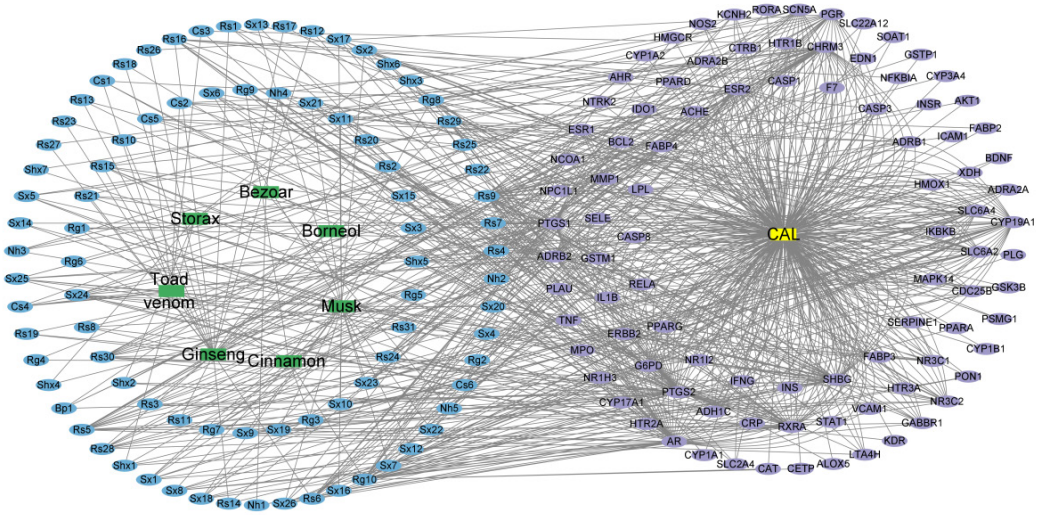

Figure. 4 Drug-Active Ingredient-Target-Disease Network Diagram. Note: CAL=coronary artery lesions, Rs = Ginseng, Rg = Cinnamon, Shx = Storax, Bp = Borneol, Nh = Bezoar, Cs = Toad Venom, Sx = Musk; Blue circles represent active ingredients, purple circles represent targets.

3.1.4 The "Drug-Active Ingredient-Target-Disease" Network of SBP in Treating CAL

Analysis of the 94 intersecting targets using Cytoscape 3.9.1 generated a “drug-Active Ingredient-target-disease” network diagram illustrating the mechanism of SBP in treating CAL. This network comprises 188 nodes and 872 edges, as shown in Figure 4. The top five Active Ingredients by efficacy were: kaempferol, oleic acid, stigmasterol, beta-sitosterol, and fumarine.

3.1.5 GO Enrichment Analysis and KRGG Pathway Enrichment Analysis

GO enrichment analysis revealed that 94 intersecting targets were significantly associated with 559 GO terms, including 422 BP, 49 CC, and 88 MF terms. The top five most significant and highly enriched GO terms (P<0.01) from the

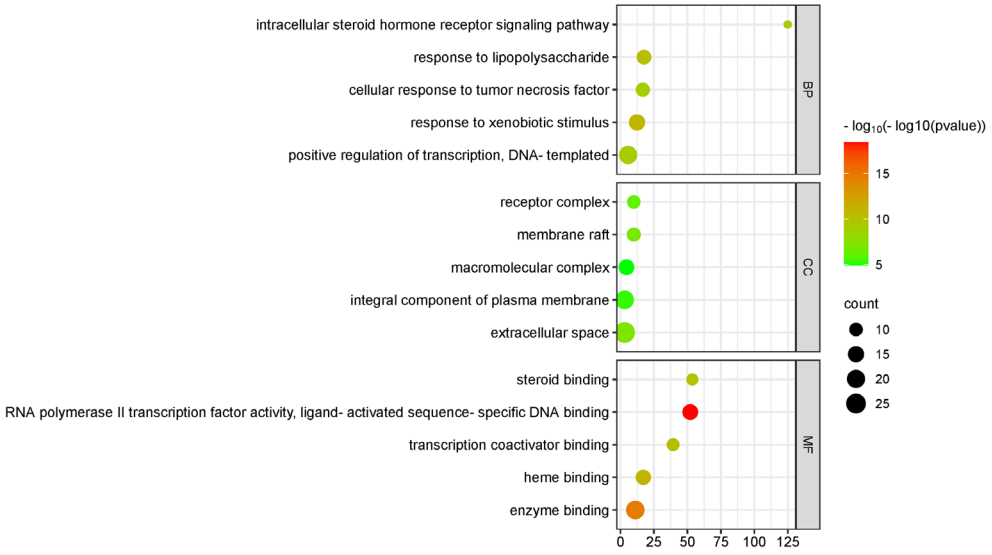

Figure. 5 GO Enrichment Analysis Plot

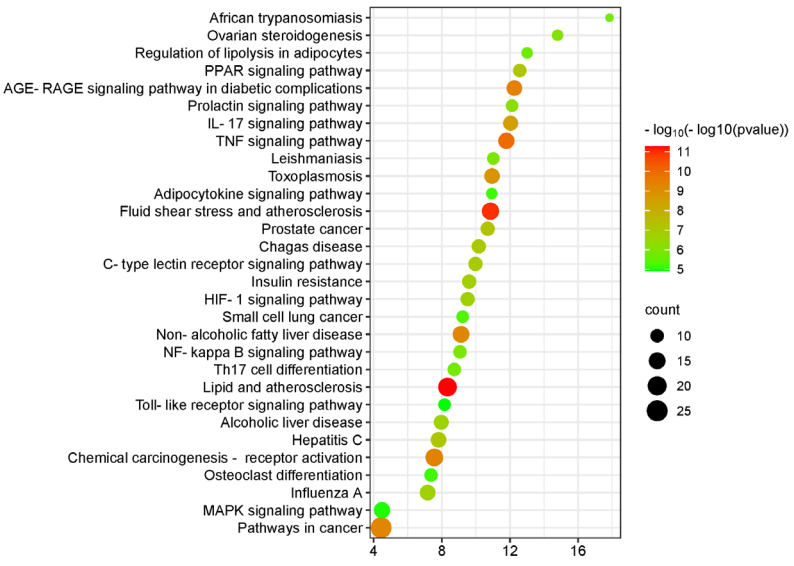

Figure. 6 KEGG Pathway Enrichment Analysis Diagram

BP, CC, and MF analyses were selected for visualization, as shown in Figure 5. KEGG pathway enrichment analysis identified 119 pathways, with Lipid and atherosclerosis, Fluid shear stress and atherosclerosis, TNF signaling pathway, and AGE-RAGE signaling pathway in diabetic complications emerging as the primary therapeutic pathways. The top 30 pathways were selected for bubble chart visualization (Figure 6). The color gradient from green to red indicates progressively decreasing P-values and increasing reliability.

3.1.6 The "Pathway-Target-Active Ingredient" Network of SBP in Treating CAL

The top 30 KEGG pathways enriched for SBP in treating CAL were selected in ascending order of P-values. These pathways, along with their key genes (core targets) and Active Ingredients, were input into Cytoscape 3.9.1 software to construct a “pathway-target-Active Ingredient” network, as shown in Figure 7. The top five Active Ingredients by degree value were kaempferol, oleic acid, stigmasterol, ginsenoside rh2, and beta-sitosterol. These ingredients are likely the core components responsible for SBP' therapeutic effects on CAL.

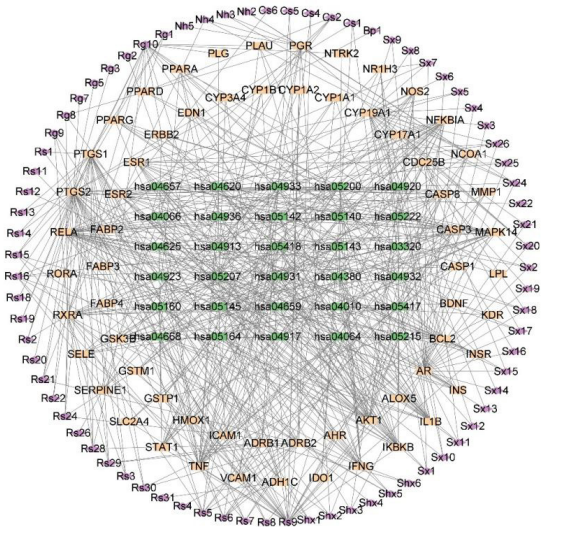

Figure. 7 “Pathway-Target-Active Ingredient” Network of SBP in Treating CAL. Note: Rs = Ginseng, Rg = Cinnamon, Shx = Storax, Bp = Borneol, Nh = Bezoar, Cs = Toad Venom, Sx = Musk; Orange circles represent active ingredients, purple circles represent targets, and green squares represent pathways.

3.2 Clinical Study Results

3.2.1 Comparison of General Characteristics Among Groups

There were no statistically significant differences between patient groups in terms of gender distribution, mean age, disease duration, and body mass index ($P > 0.05$), as detailed in Table 2, indicating comparability.

Table. 2 Comparison of General Conditions $\bar{\chi} \pm s$, n=40)

Group	Gender (Male/Female)	Age (years)	Disease duration (years)	Body Mass Index-(kg/m^{-2})
Control Group 1	24/16	57.15±11.12	3.51±1.03	25.78±3.64
Control Group 2	23/17	55.83±8.56	3.32±0.89	26.01±3.75
Single-Vessel Lesion Group	20/20	56.73±9.20	3.62±1.15	26.18±3.79
Double-Vessel Lesion Group	22/18	58.21±11.24	3.59±1.09	25.98±3.72
Triple-Vessel Lesion Group	21/19	56.29±10.15	3.47±0.96	25.71±3.24
Experimental Group 1	22/18	55.54±7.90	3.54±1.05	26.22±4.10
F/χ^2 value	1.010	0.393	0.410	0.120
P value	0.962	0.853	0.841	0.988

3.2.2 Comparison of Response Rates Among Different Patient Groups After 6 Months of Treatment

Among patients who did not undergo stent implantation, the total effective rate in Experimental Group 1 (62.50%) was significantly higher than that in Control Group 1 (40.00%) after six months of treatment, with a statistically significant difference ($P < 0.05$). Details are shown in Table 3. Among patients who underwent stent implantation, after six months of treatment, the total effective rate in all groups receiving combined treatment with Shexiang Baoxin Pills was higher than that in Control Group 2, which received only standard therapy (72.50%). Specifically, the Single-Vessel Lesion Group achieved the highest total effective rate (95.00%), followed by the Double-Vessel Lesion Group (87.50%) and the Triple-Vessel Lesion Group (82.50%). Intergroup comparisons demonstrated statistically significant differences ($P < 0.05$), as detailed in Table 4.

3.2.3 Comparison of VEGF and Ang-1 Levels Before and After Treatment in Two Groups of Patients Who Did Not Undergo Stent Implantation

Following treatment, VEGF and Ang-1 levels in Experimental Group 1 were significantly higher than those in the control group (all $P < 0.001$ for intergroup comparisons). Both groups exhibited a trend of increasing VEGF and Ang-1 levels over time (P for time < 0.001 for both), but the increase in VEGF and Ang-1 levels over time was more pronounced in the experimental group 1 (P for interaction < 0.001). See Tables 5 and 6.

3.2.4 Comparison of Various Indicators Among Four Groups of Patients Following Stent Implantation

After treatment, VEGF and Ang-1 levels in all groups showed an increasing trend over time (P for time effect < 0.001 for both). However,

Table. 3 Comparison of Efficacy Rates Between Control Group 1 and Experimental Group 1 After 6 Months of Treatment [n(%), n=40]

Group	Markedly Effective	Effective	Ineffective	Total Effective Rate
Control Group 1	10(25.00)	6(15.00)	24(60.00)	16(40.00)
Experimental Group 1	13(32.50)	12(30.00)	15(37.50)	25(62.50)
χ^2 value				4.053
P value				0.044

Table. 4 Comparison of 6-Month Efficacy Rates Among 4 Groups of Patients Undergoing Stent Implantation [n(%), n=40]

Group	Markedly Effective	Effective	Ineffective	Total Effective Rate
Control Group 2	17(42.50)	12(30.00)	11(27.50)	29(72.50)
Single-Vessel Lesion Group	30(75.00)	8(20.00)	2(5.00)	38(95.00)
Double-Vessel Lesion Group	25(62.50)	10(25.00)	5(12.50)	35(87.50)
Triple-Vessel Lesion Group	20(50.00)	13(32.50)	7(17.50)	33(82.50)
χ^2 value				8.107
P value				0.044

Table. 5 Comparison of Serum VEGF Levels Before and After Treatment Between the Two Groups ($\overline{\chi} \pm s$, pg/ml)

Group	n	Before treatment	One month after treatment	Three months after treatment	Six months after treatment
Control Group 1	40	208.85±11.27	227.66±13.78	241.40±15.81	253.07±16.93
Experimental Group 1	40	210.82±12.54	300.43±16.92	350.94±17.81	394.49±20.10
t value		0.739	21.092	29.089	34.038
P value		0.462	<0.001	<0.001	<0.001

Note: Between-group F = 759.400, P < 0.001; time-effect F = 2102.000, P < 0.001; interaction F = 284.800, P < 0.001.

Table. 6 Comparison of Serum Ang-1 Levels Before and After Treatment in the Two Groups ($\overline{\chi} \pm s$, pg/ml)

Group	n	Before treatment	One month after treatment	Three months after treatment	Six months after treatment
Control Group 1	40	228.43±13.79	238.34±14.03	247.45±14.81	259.38±15.38
Experimental Group 1	40	227.40±15.14	283.52±19.53	334.91±21.63	387.55±22.62
t value		0.315	11.881	21.104	29.637
P value		0.754	<0.001	<0.001	<0.001

Note: Between-group F = 438.700, P < 0.001; time-effect F = 1105.000, P < 0.001; interaction F = 202.000, P < 0.001.

the VEGF and Ang-1 levels in the single-vessel lesion group, double-vessel lesion group, and triple-vessel lesion group were all higher than those in Control Group 2 (all P < 0.05). A significant interaction effect was observed between group and time (P for interaction < 0.001 for both), with the triple-vessel lesion group showing the most pronounced increase in VEGF and Ang-1 levels over time. See Tables 7 and 8 for details.

3.2.5 Adverse Drug Reactions and Occurrence of MACE

Among patients who did not undergo stent implantation, the total incidence of MACE in Experimental Group 1 was 17.50%, lower than the 25.00% in Control Group 1; however, the difference was not statistically significant (P

Table. 7 Comparison of Serum VEGF Levels Among Groups at Different Time Points ($\overline{\chi} \pm s$)

Time	Group	VEGF (pg/mL)	F value	*P* value	Multiple Comparison Results
Before treatment	Control Group 2	212.18±12.68	1.028	0.382	/
	Single-Vessel Lesion Group	214.35±13.57			
	Double-Vessel Lesion Group	211.80±12.74			
	Triple-Vessel Lesion Group	209.38±11.75			
One month after treatment	Control Group 2	223.29±14.308	195.037	<0.001	D>C>B>A
	Single-Vessel Lesion Group	287.52±16.58			
	Double-Vessel Lesion Group	304.06±18.33			
	Triple-Vessel Lesion Group	318.72±19.10			

Time	Group	VEGF (pg/mL)	F value	*P* value	Multiple Comparison Results
Three months after treatment	Control Group 2	231.77±15.69	275.841	<0.001	D>C>B>A
	Single-Vessel Lesion Group	311.11±19.87			
	Double-Vessel Lesion Group	337.20±22.06			
	Triple-Vessel Lesion Group	351.96±23.15			
Six months after treatment	Control Group 2	247.36±18.94	345.297	<0.001	D>C>B>A
	Single-Vessel Lesion Group	347.13±21.89			
	Double-Vessel Lesion Group	370.02±23.31			
	Triple-Vessel Lesion Group	396.40±24.14			

Note: (1) A = Control Group 2, B = Single-vessel lesion group, C = Double-vessel lesion group, D = Triple-vessel lesion group. (2)Between-group F = 1396.000, P < 0.001; time-effect F = 750.000, P < 0.001; interaction F = 97.370, P < 0.001.

Table. 8 Comparison of Serum Ang-1 Levels Among Groups at Different Time Points ($\overline{\chi} \pm s$)

Time	Group	Ang-1 (ng/ml)	F value	*P* value	Multiple Comparison Results
Before treatment	Control Group 2	231.59±14.99	1.545	0.205	/
	Single-Vessel Lesion Group	229.53±14.56			
	Double-Vessel Lesion Group	236.42±15.10			
	Triple-Vessel Lesion Group	233.59±15.14			
One month after treatment	Control Group 2	249.48±15.02	110.998	<0.001	D>C>B>A
	Single-Vessel Lesion Group	298.92±22.33			
	Double-Vessel Lesion Group	316.67±23.03			
	Triple-Vessel Lesion Group	331.01±23.79			
Three months after treatment	Control Group 2	253.92±17.64	198.513	<0.001	D>C>B>A
	Single-Vessel Lesion Group	335.15±25.12			
	Double-Vessel Lesion Group	356.88±26.49			
	Triple-Vessel Lesion Group	381.35±28.60			
Six months after treatment	Control Group 2	267.10±19.65	260.709	<0.001	D>C>B>A
	Single-Vessel Lesion Group	353.91±25.86			
	Double-Vessel Lesion Group	388.59±26.82			
	Triple-Vessel Lesion Group	413.17±27.01			

Note: (1) A = Control Group 2, B = Single-vessel lesion group, C = Double-vessel lesion group, D = Triple-vessel lesion group. (2)Between-group F = 948.900, P < 0.001; time-effect F = 507.000, P < 0.001; interaction F = 64.440, P < 0.001.

> 0.05). Among patients who underwent stent implantation, the total MACE incidence in Control Group 2 was 12.50%, which was higher than that in the single-vessel lesion group, double-vessel lesion group, and triple-vessel lesion group, yet the difference also did not reach statistical significance (P > 0.05). See Table 9 for details.

Among patients who did not undergo stent implantation, there were 4 cases (10.00%) of total adverse drug reactions in Experimental Group 1 and 2 cases (5.00%) in Control Group 1, with no statistically significant difference in the incidence of adverse reactions between the two groups (P > 0.05). Among patients who underwent stent implantation, the incidence of adverse drug reactions was 5 cases (12.50%) in the single-vessel lesion group, 4 cases (10.00%) in the double-vessel lesion group, 5 cases (12.50%) in the triple-vessel

Table. 9 Incidence of MACE in Each Group [n(%), n=40]

Group	Heart failure	Unstable angina pectoris	Nonfatal acute myocardial infarction	Ischemia-driven repeat revascularization	Severe arrhythmia	Total MACE
Control Group 1	2 (5.00)	4 (10.00)	1 (2.50)	0 (0.00)	3 (7.50)	10 (25.00)
Experimental Group 1	1 (2.50)	3 (7.50)	1 (2.50)	0 (0.00)	2 (5.00)	7 (17.50)
Control Group 2	0 (0.00)	3 (7.50)	0 (0.00)	0 (0.00)	2 (5.00)	5 (12.50)
Single-Vessel Lesion Group	0 (0.00)	1 (2.50)	0 (0.00)	0 (0.00)	0 (0.00)	1 (2.50)
Double-Vessel Lesion Group	0 (0.00)	1 (2.50)	0 (0.00)	1 (2.50)	0 (0.00)	2 (5.00)
Triple-Vessel Lesion Group	1 (2.50)	2 (5.00)	1 (2.50)	0 (0.00)	0 (0.00)	4 (10.00)

Table. 10 Incidence of Adverse Drug Reactions in Each Group [n(%), n=40]

Group	Palpitation	Headache/ dizziness	Nausea/vomiting	Abnormal liver/ kidney function	Total adverse drug reactions	Total MACE
Control Group 1	0 (0.00)	1 (2.50)	1 (2.50)	0 (0.00)	2 (5.00)	10 (25.00)
Experimental Group 1	1 (2.50)	2 (5.00)	1 (2.50)	0 (0.00)	4 (10.00)	7 (17.50)
Control Group 2	0 (0.00)	2 (5.00)	0 (0.00)	1 (2.50)	3 (7.50)	5 (12.50)
Single-Vessel Lesion Group	1 (2.50)	1 (2.50)	3 (7.50)	0 (0.00)	5 (12.50)	1 (2.50)
Double-Vessel Lesion Group	0 (0.00)	1 (2.50)	2 (5.00)	1 (2.50)	4 (10.00)	2 (5.00)
Triple-Vessel Lesion Group	0 (0.00)	2 (5.00)	3 (7.50)	0 (0.00)	5 (12.50)	4 (10.00)

lesion group, and 3 cases (7.50%) in Control Group 2. Comparisons of adverse reaction incidence between these groups also showed no statistically significant differences ($P > 0.05$). For details, please refer to Table 10.

4 Discussion

CAL is a common cardiac condition characterized by the narrowing of one or more coronary artery branches, which obstructs blood flow and leads to chest pain or heart attack. Improving coronary blood flow and slowing or reversing the progression of atherosclerosis are key strategies in the treatment of coronary artery lesions (Li et al., 2021). In clinical practice, TCM can be formulated based on the disease mechanism and pharmacological properties of medicinal substances, following principles such as "sovereign, minister, assistant, and envoy" and "seven modes of compatibility," to achieve synergistic therapeutic effects or antagonistic effects aimed at reducing toxicity and enhancing efficacy. The most crucial component in SBP is musk, which functions to promote blood circulation, remove blood stasis, and induce resuscitation. Cinnamon, ginseng, toad venom, and storax serve as minister herbs, respectively contributing to replenishing qi and activating stagnation, warming yang and unblocking meridians, inducing resuscitation and relieving pain, and exerting aromatic warming and unblocking effects. Artificial bezoar and borneol act as assistant herbs, providing effects such as reducing swelling, alleviating pain, and inducing resuscitation (Zhang et al., 2018). Given the multi-component and multi-target characteristics of TCM formulas, this study comprehensively employs network pharmacology and clinical validation methods to systematically elucidate the molecular mechanisms of SBP in treating coronary artery lesions, thereby providing a scientific basis for its clinical application.

This study employed network pharmacology methods to analyze the Active Ingredients, drug targets, and key pathways responsible for the therapeutic effects of SBP in CAL. The results indicate that the primary active compounds of SBP in the treatment of CAL include kaempferol, oleic acid, stigmasterol, β-sitosterol, fumarine, ginsenoside rh2, among others. These effective components mainly act on key targets such as TNF, IL1B, AKT1, INS, and RELA. Through pathways including Lipid and atherosclerosis, Fluid shear stress and atherosclerosis, TNF signaling pathway, and AGE-RAGE signaling pathway in diabetic complications, they regulate nuclear receptor activity, DNA-binding transcription activator activity, steroid binding, cytokine receptor binding, and participate in coronary artery inflammation and immune responses—such as lipopolysaccharide response, oxidative stress response, steroid hormone response, and other biological processes related to CAL (Zhao et al., 2020; Jin et al., 2021; Dabeek and Marra, 2019; Feng et al., 2018; Kurano et al., 2018). Its mechanism of action primarily involves anti-inflammatory and antioxidant effects. TNF and IL-1β are classic pro-inflammatory cytokines and core regulatory molecules in the body's inflammatory response and immune response. Their primary functions are to initiate and amplify inflammatory reactions. In addition to regulating cell growth and apoptosis (van Loo and Bertrand, 2023), TNF can also synergistically induce VEGF production with IL-1β by activating the NF-κB or HIF-1α pathways, participating in the complex regulation of the angiogenesis process (Papadopoulos, 2023). In endothelial cells, AKT1 is the predominant AKT subtype, regulating inflammation, immunity, and

cellular metabolism through signaling pathways including Fluid shear stress and atherosclerosis and AGE-RAGE signaling pathway in diabetic complications. It can directly phosphorylate nitric oxide synthase (eNOS) at Ser1177 to produce nitric oxide (NO) (Huang et al., 2020). NO is a major endothelium-derived regulator of vascular tone and can promote the expression of VEGF in the body, thereby facilitating angiogenesis. Additionally, AKT1 is involved in the regulation of endothelial cell proliferation/apoptosis by Ang-1. It can attract vascular smooth muscle cells and pericytes to surround and support endothelial cells, forming a complete vessel wall and maintaining the maturation and functional integrity of the vascular structure (Ha et al., 2022). A study analyzing the GSE18612 and GSE64554 gene profiles of epicardial adipose tissue in patients with CAL concluded that the AKT1 gene can serve as a major biomarker and therapeutic target for CAL (Zhou et al., 2019). INS, on the other hand, is a key protein regulating the body's energy metabolism, and insulin resistance is one of the critical risk factors leading to CAL (Di Pino and DeFronzo, 2019). RELA is a transcription factor of the NF-κB family, which can regulate cell adhesion, infiltration, metastasis, and many other processes. Its elevated expression promotes the occurrence and progression of atherosclerosis (Li et al., 2022). In summary, the primary mechanism by which SBP treat CAL may involve improving the angiogenesis microenvironment by inhibiting inflammatory factors such as TNF and IL1B, while simultaneously activating AKT1 signaling to promote VEGF expression and NO production, and cooperating with Ang-1 to collectively facilitate vasodilation, structural neovascularization, and stabilization.

It is worth noting that the predictive results of network pharmacology are largely based on database information and virtual computations. Whether the component-target-pathway associations it reveals can actually occur in humans, and whether the associated molecular-level changes ultimately translate into clinical efficacy, still require validation through clinical trials. The aforementioned network pharmacology analysis suggests that promoting angiogenesis may be one of the core mechanisms by which Shexiang Baoxin Pills treat coronary artery lesions. This process is closely associated with the regulation of key targets such as AKT1, TNF, and IL1B, and its potential pathways include inducing VEGF expression to promote angiogenesis and cooperating with Ang-1 to maintain vascular stability. To validate this mechanism, this study further conducted a clinical trial. By analyzing changes in serum VEGF and Ang-1 levels in patients before and after treatment and correlating them with clinical efficacy, the study aims to systematically evaluate, at the clinical level, whether Shexiang Baoxin Pills promote therapeutic angiogenesis through the regulation of VEGF/Ang-1. This approach provides an integrated evidence framework linking "mechanism to efficacy" for its application in treating coronary artery lesions.

This study found that in terms of clinical efficacy, among patients who did not undergo stent implantation, the total effective rate in Experimental Group 1 was significantly higher than that in Control Group 1 ($P < 0.05$). Among patients who underwent stent implantation, the total effective rates in the single-vessel, double-vessel, and triple-vessel lesion groups were all higher than that in Control Group 2, with statistically significant differences between groups (all $P < 0.05$). Regarding safety, the incidence of adverse drug reactions was similar across all

groups, with no statistically significant differences ($P > 0.05$). In groups receiving combined SBP treatment, the incidence of MACE showed a numerical decreasing trend compared to the control groups, although the intergroup differences did not reach statistical significance ($P > 0.05$), a result that may be related to the relatively small sample size. Furthermore, regardless of whether they had undergone percutaneous coronary stent implantation, patients with severe coronary artery lesions who took SBP exhibited significantly higher serum levels of Ang-1 and VEGF compared to those who did not receive the medication ($P < 0.05$). This result forms a closed-loop validation with the aforementioned network pharmacology findings, indicating that SBP safely and effectively improve clinical outcomes in patients with CAL through the mechanism of "regulating AKT1/TNF/IL1B → upregulating VEGF and synergizing with Ang-1 → promoting angiogenesis and structural stability."

5 Conclusion

SBP may act through key active compounds such as kaempferol, oleic acid, stigmasterol, β-sitosterol, fumarine, and ginsenoside rh2, targeting critical hubs including TNF, IL1B, AKT1, INS, and RELA, and regulating pathways related to Lipid and atherosclerosis, as well as the TNF signaling pathway, thereby safely and effectively improving clinical efficacy in patients with CAL. Moreover, promoting angiogenesis represents one of the core therapeutic mechanisms of SBP in treating CAL.

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Author Contributions

The authors confirms they responsibility for the following: study conception and design, datacollection, analysis and interpretation of results, and manuscript preparation.

Consent statement

This study adhered to the principles of the Helsinki Declaration and obtained approval from the Ethics Committee of Nanxishan Hospital, Guangxi Zhuang Autonomous Region. The study obtained the informed consent of all respondents.

Availability of Data and Materials

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Conflicts of Interest

The authors have no conflicts of interest to disclose concerning the manuscript.

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