DOI: 10.53469/jcmp.2026.08(01).48

Study on the Mechanism of Xiaoyu Yin in Treating Postoperative Pain based on Network Pharmacology

Hui Yan, Yan Ma*, Wenpu Shi, Xiajing Zhang, Xude Sun

Department of Anesthesiology, The Second Affiliated Hospital of Shaanxi University of Chinese Medicine, Xianyang 712000, Shaanxi, China
**Correspondence Author*

Abstract: ***Postoperative pain is a common complication in surgery. Western medicine for pain relief has adverse reactions, while the traditional Chinese medicine Xiaoyu Decoction (derived from the experience of renowned traditional Chinese medicine practitioners) mainly focuses on "activating blood circulation and removing blood stasis". This study used network pharmacology to explore its mechanism of action. Firstly, compounds and targets of Xiaoyu Decoction were obtained from databases, and after ADME parameter screening, 26 active components and 118 drug targets were obtained. 820 disease targets of postoperative pain were retrieved, and the intersection was taken to obtain 55 potential action targets. A PPI network was constructed to screen out core targets; a compound-target network analysis diagram was constructed to discover key active components. GO and KEGG enrichment analysis showed that the targets were involved in oxidative stress response, apoptosis signaling pathways, etc. In conclusion, Xiaoyu Decoction may treat postoperative pain through the action of multiple components on multiple targets and regulation of multiple pathways, including inhibiting inflammation and regulating apoptosis, providing a basis for its clinical application.***

Keywords: Postoperative pain, Xiaoyu Decoction, Network pharmacology.

1. Introduction

Postoperative pain (Postoperative Pain) is a common complication of surgical procedures, referring to the pain sensation caused by tissue damage, inflammatory responses, etc., after surgery. It not only causes physical and psychological distress to patients but may also affect the postoperative recovery process [1,2].

From the perspective of pain generation mechanisms, surgical trauma leads to local tissue damage, releasing inflammatory mediators such as prostaglandins and bradykinins. These mediators stimulate nerve endings, generating pain signals that are transmitted to the central nervous system, resulting in pain perception [3]. Meanwhile, surgical stress can also affect the neuro-endocrine-immune network of the body, further exacerbating the pain response [4]. Failure to effectively control postoperative pain may lead to a series of adverse consequences, including impaired sleep quality and compromised immune function in patients. Additionally, it may delay the recovery of gastrointestinal function and prolong hospitalization duration [5].

Currently, the commonly used postoperative analgesia methods in clinical practice mainly include Western analgesics, such as opioids and nonsteroidal anti-inflammatory drugs (NSAIDs) [6]. However, these medications also have certain limitations in pain relief. Opioids may induce adverse reactions such as nausea, vomiting, respiratory depression, and constipation; nonsteroidal anti-inflammatory drugs (NSAIDs) may cause gastrointestinal mucosal injury and renal impairment [7]. In contrast, traditional Chinese medicine (TCM) demonstrates unique advantages in the treatment of postoperative pain.

Traditional Chinese Medicine (TCM) emphasizes holistic regulation in its therapeutic approach. TCM posits that postoperative pain is often associated with qi and blood stasis as well as meridian obstruction. Treatment is not merely about pain relief but involves methods such as regulating qi and blood, unblocking meridians, and reinforcing healthy qi to eliminate pathogens, thereby fundamentally improving the patient's physical condition and alleviating pain [8]. Studies indicate that blood-activating and stasis-resolving herbs like peach kernel and safflower can promote local blood circulation and reduce pain caused by blood stasis. Qi-tonifying herbs such as astragalus and codonopsis can enhance immune function and accelerate wound healing, indirectly relieving pain [9]. "Xiaoyu Yin" (Stasis-Resolving Decoction) is a category of TCM prescriptions characterized by their core efficacy of "activating blood circulation, resolving stasis, and dispersing stagnation." It evolved from the self-formulated prescriptions of renowned TCM practitioner Li Xueming, who developed this formula based on TCM theory and years of clinical experience, and is now widely applied.

2. Materials and Methods

2.1 Compounds of Xiaoyu Yin and Target Identification

The corresponding compounds of Astragalus membranaceus, Achyranthes bidentata, Peach Kernel, Rheum palmatum, and Plantago asiatica were identified through the Traditional Chinese Medicine Systematic Pharmacology Database and Analysis Platform (https://www.tcmsp-e.com/, TCMSP) and the Herbal Group Identification Database (http://herb.ac.cn/). Based on the principles of pharmacokinetic parameters (absorption, distribution, metabolism, excretion, ADME), compounds were screened according to the following criteria: oral bioavailability (OB) ≥30%, drug likeness (DL) ≥0.18, and blood-brain barrier permeability ≥-0.3. The compounds meeting these criteria and their corresponding target information were then entered into the Uniprot database (https://www.uniprot.org/) to obtain their gene names and gene IDs.

2.2 Postoperative Pain: Intersection of Disease Targets

and Drug Targets

Select the keyword "postoperative pain" to retrieve disease targets related to postoperative pain from the GeneCards database (https://www.genecards.org/), DrugBank database (https://www.drugbank.ca/), and TTD database (Therapeutic Target Database, http://bidd.nus.edu.sg/group/cjttd/TTD_HOME.asp). In the GeneCards database, select genes with a Relevance score ≥5.18. Merge the results from the four databases and remove duplicate targets to obtain disease targets. Match these disease targets with drug targets to derive the intersection, and the intersected targets are identified as potential therapeutic targets.

2.3 Construction and Analysis of Protein-Protein Interaction (PPI) Networks

The potential therapeutic targets of Xiaoyu Xieyin for postoperative pain were imported into the STRING database (https://string-db.org/) to obtain protein-protein interaction (PPI) data. The species selected was "Homo sapiens", with the minimum interaction threshold set as "Medium confidence" (>0.4), and all other settings kept as default. The resulting PPI network was saved in TSV format and imported into Cytoscape software for further analysis and visualization.

2.4 GO and KEGG Enrichment Analysis of Potential Target Sites

The potential target sites were imported into the biological information annotation database Metascape (http://metascape.org) with species selection set to human, using a significance level of $P<0.01$, for GO (Gene Ontology) enrichment and KEGG (Kyoto Encyclopedia of Genes and Genomes) pathway annotation analysis. The top 20 KEGG enriched pathways and the top 20 biological processes (BP), molecular functions (MF), and cellular components (CC) ranked by-Log10(p-value) were plotted as bubble charts.

2.5 Compound Active Ingredient-Target Network Construction

The predicted potential target sites were used as nodes to construct the compound active ingredient-target network using the software Cytoscape 3.7.2. The network was then visualized and subjected to topological parameter analysis to investigate the relationship between the compound active ingredient and the target sites.

3. Results

3.1 Active Components and Related Targets of Xiaoyu Yin

Through screening and analysis, 26 major active components of Xiaoyu Yin were identified. Among them, 2 were from Sichuan Achyranthes Root (Chuan Niuxi), 5 from Rheum palmatum (Dahuang), 12 from Astragalus membranaceus (Huangqi), 5 from Peach Kernel (Taoren), and 5 from Plantago asiatica (Cheqiancao). After merging the target prediction results and excluding duplicates, a total of 118 target genes were obtained.

3.2 Postoperative Pain and Drug Target Retrieval

After screening and removing duplicates from GeneCards, DrugBank, and TTD databases, 820 postoperative pain-related genes were identified. Intersection analysis with drug targets identified 55 shared targets, accounting for 6.2% of the total genes, as shown in Figure 1.

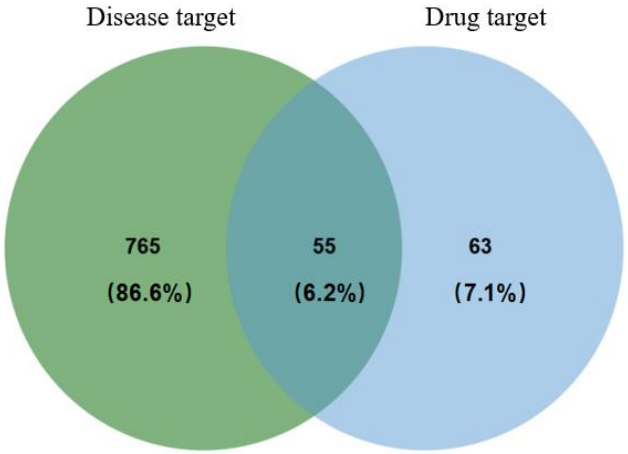

Figure 1: Venn diagram of drugs and disease targets

3.3 Target Gene Protein-Protein Interaction Analysis

The potential common interaction targets were imported into the STRING database (https://string-db.org/) to obtain the protein-protein interaction (PPI) network diagram (Figure 2). The circles in the diagram represent different proteins, and the straight lines represent the associations between proteins. This network diagram involves 54 nodes and 492 edges, with an average degree of 18.2 and an average local clustering coefficient of 0.725. The top 10 genes with higher degrees were screened, namely AKT1, PTGS2, ESR1, CSAP3, FOS, BCL2, PPARG, MMP9, TP53, and JUN genes. For detailed information, see Table 1.

Table 1

Gene name	Degree value	egg white ID	Name
AKT1	38	P31749	Serine/threonine protein kinase 1
PTGS2	36	P35354	Prostaglandin E2 peroxidase
ESR1	35	P03372	ER α
CASP3	34	P42574	Cystatin 3
FOS	34	P01100	proto-oncogene protein
BCL2	33	P10415	apoptotic protein
PPARG	33	P37231	peroxisome proliferator-activated receptor gamma
MMP9	32	P14780	matrix metalloproteinase
TP53	32	P04637	Cellular tumor antigen p53
JUN	31	P05412	proto-oncogene

3.4 Target Network Analysis of Active Components in Xiaoyu Yin

The relationship network between active components of anti-stasis and turbid-dampness-drinking compounds and their target sites was constructed and analyzed using Cytoscape 3.7.2, yielding 147 nodes and 483 edges, as illustrated in Figure 3. The top 5 compounds ranked by degree values were sitosterol alpha1 (TR1, α-sitosterol), GA120 (TR2), campesterol (TR3, rapeseed sterol), hederagenin (A1, hederagenin), and beta-sitosterol (B1, β-sitosterol). Among these, sitosterol alpha1 (α-sitosterol) exhibited the highest

degree value, involving the most target sites, suggesting its most significant therapeutic effects.

3.5 Potential Target GO and KEGG Enrichment Analysis

The GO annotation analysis consists of three components: biological process (BP, Figure 4), cellular component (CC, Figure 5), and molecularfunction (MF, Figure 6). The results indicate that the primary pathways involved include response to oxidative stress, apoptotic signaling pathway, and regulation of protein serine/threonine kinase activity.

KEGG pathway enrichment analysis identified 156 co-enriched pathways, among which the apoptosis signaling pathway (hsa04210: Apoptosis), PI3K-Aktsignaling pathway (hsa04151: PI3K-Aktsignaling pathway), IL-17signaling pathway (hsa04657: IL-17signaling pathway), calcium signaling pathway (hsa04020: calcium signaling pathway), and AGE-RAGE signaling pathway (ko04933: AGE-RAGE signaling pathway in diabetic complications) were significantly associated with postoperative pain. These pathways can serve as important targets for exploring the mechanism of Xiaoyu Yin in treating postoperative pain. The top 20 KEGG pathways ranked by-Log10(P) values were selected for further analysis (Figure 7). The results of GO-BP, CC, and MF are presented in Figures 4, 5, and 6, respectively.

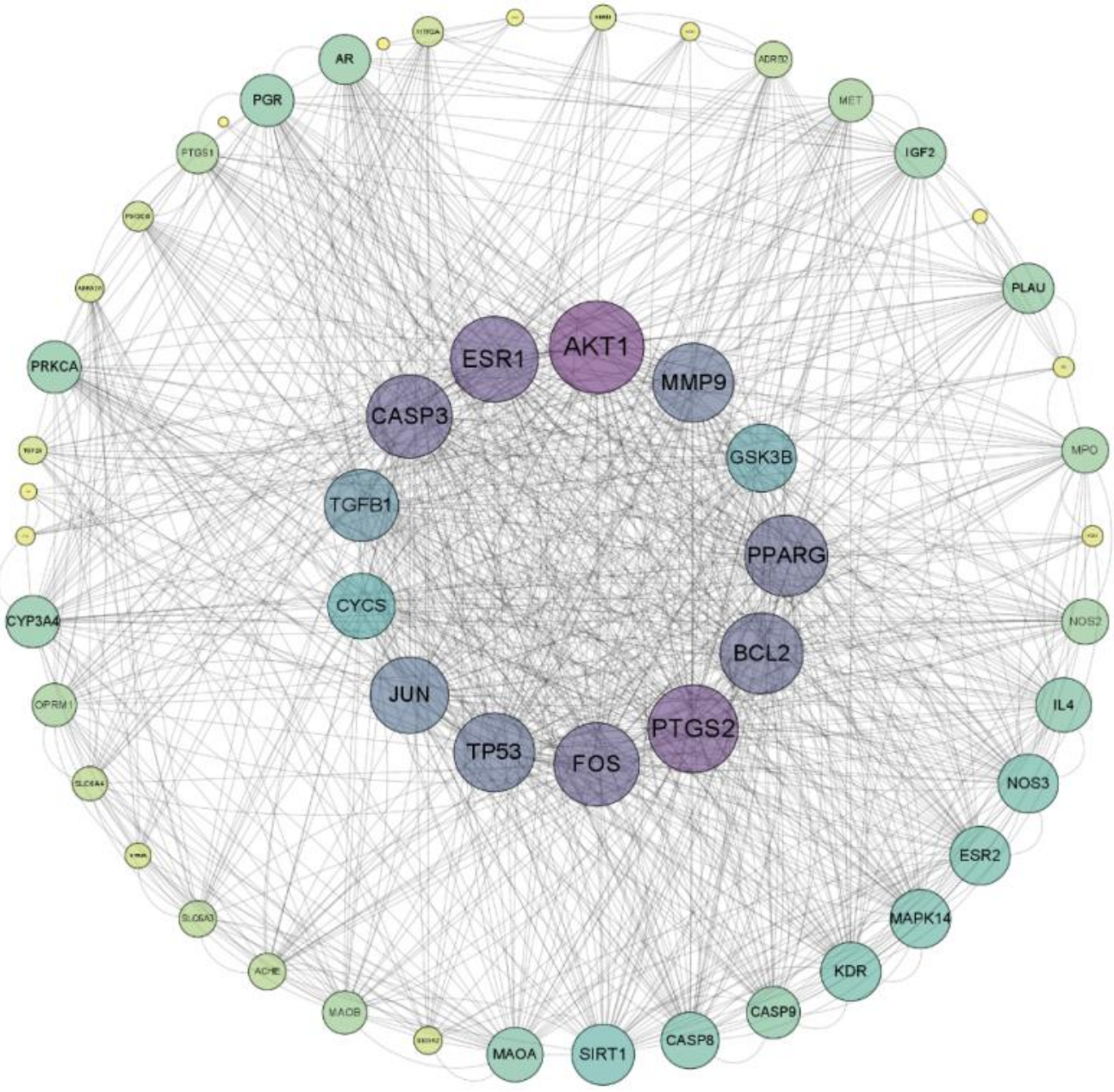

Figure 2: PPI network of target proteins in Xiaoyu Yin

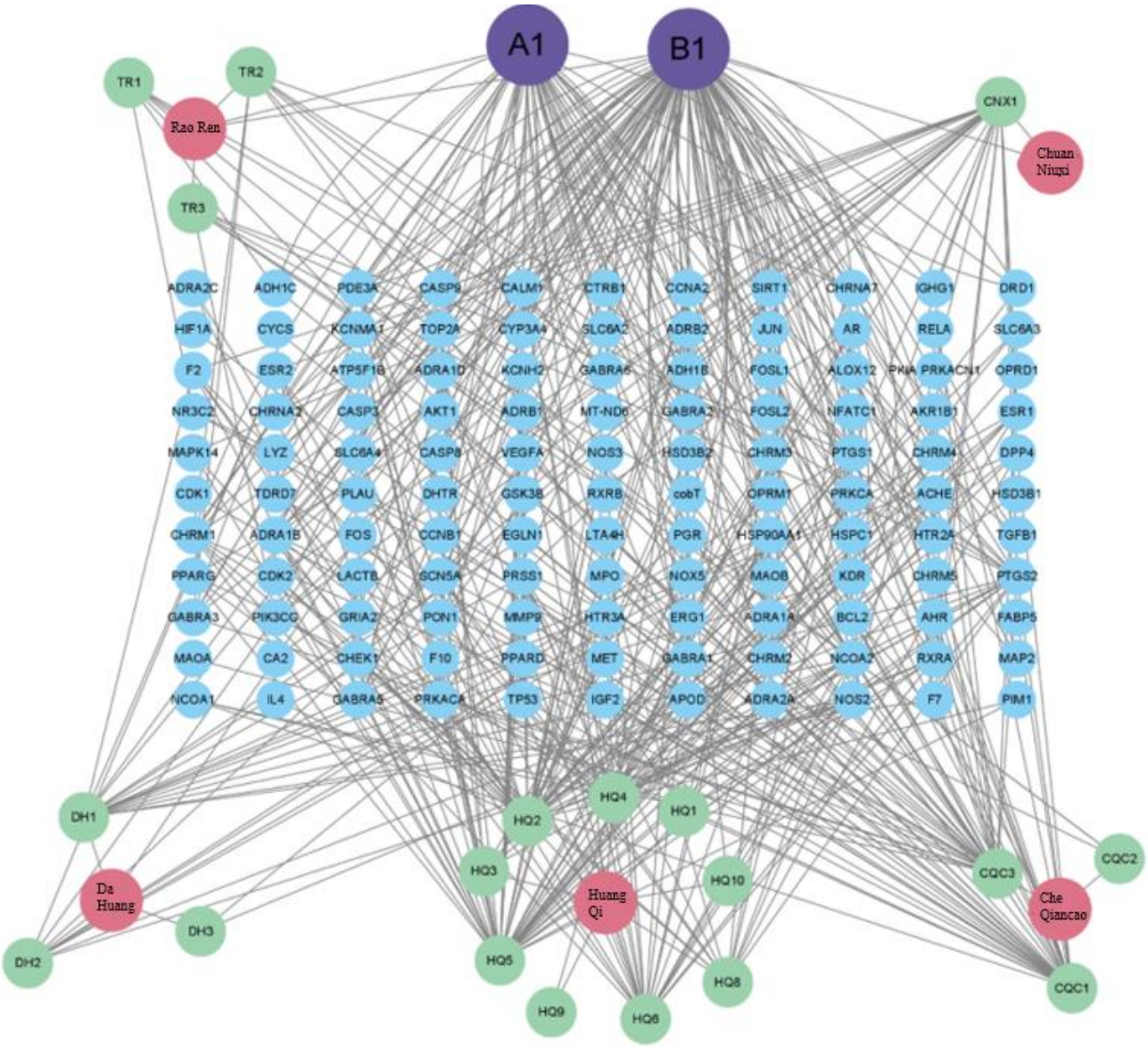

Figure 3: Compound Activity Component-Target Network Diagram of Xiaoyu Yin

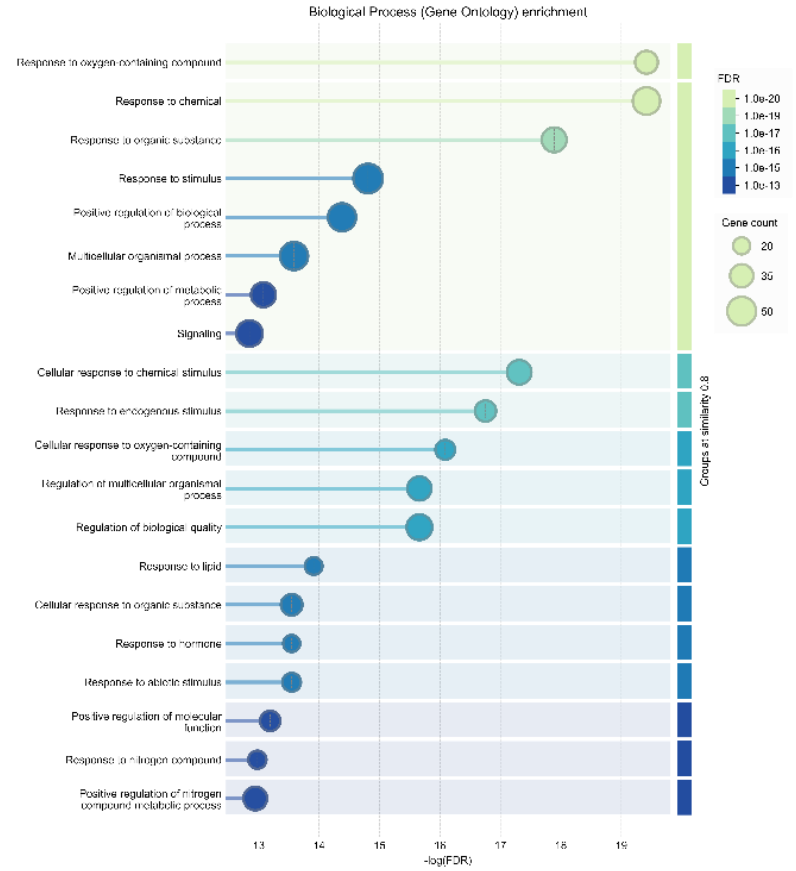

Figure 4: GO pathway analysis-BP

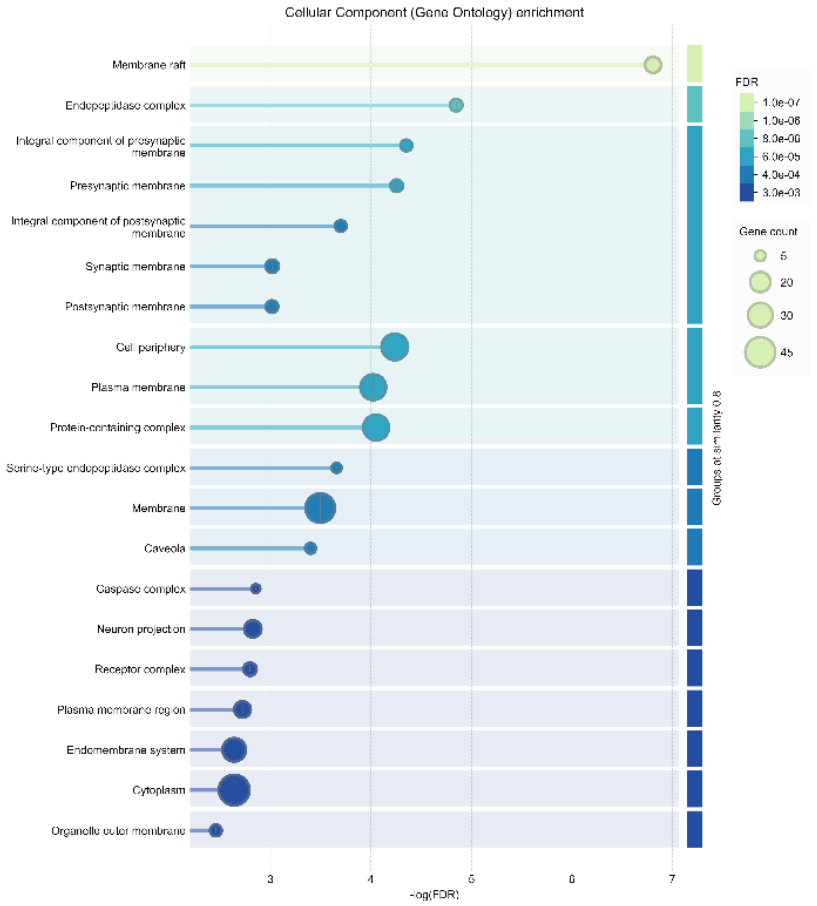

Figure 5: GO pathway analysis-CC

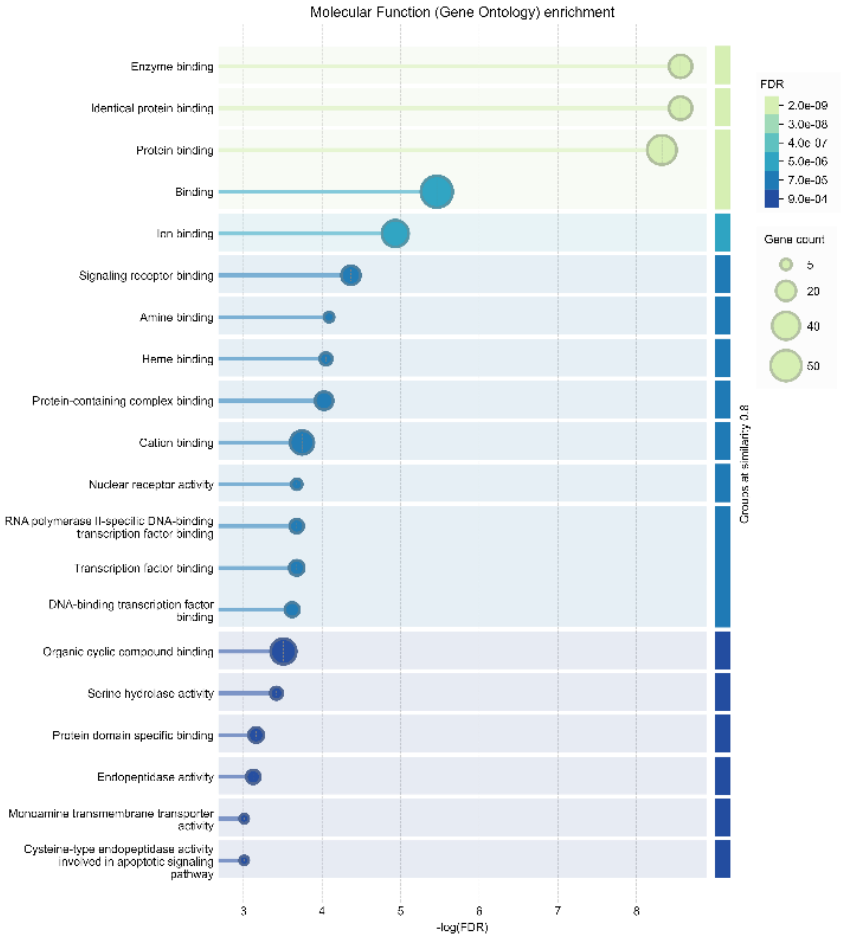

Figure 6: GO pathway analysis-MF

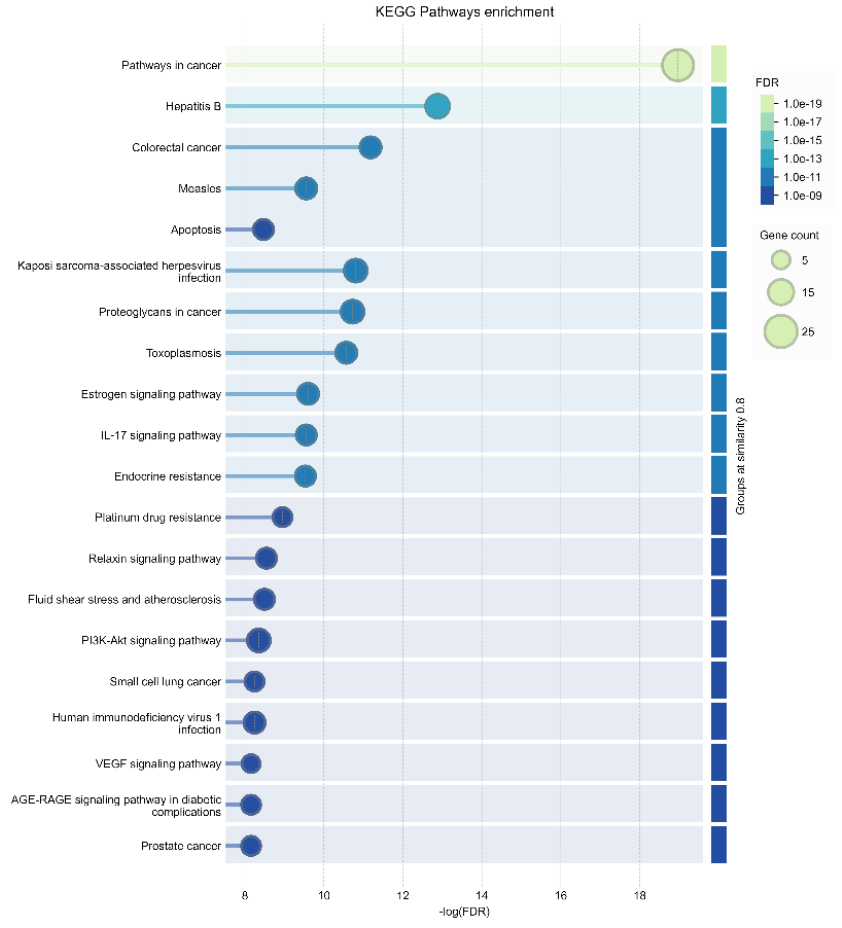

Figure 7: KEGG pathway analysis

4. Discussion

Postoperative pain, as a common complication of surgical procedures, involves core pathogenic mechanisms such as the release of inflammatory mediators triggered by tissue damage, abnormal neural signal transmission, and dysfunction of the neuroendocrine-immune network. Although Western analgesics exhibit rapid onset of action, the adverse effects of opioids (e.g., respiratory depression) and nonsteroidal anti-inflammatory drugs (NSAIDs) (e.g., gastrointestinal and renal damage) limit their long-term use [10]. Traditional Chinese Medicine (TCM) identifies “qi and blood stasis, meridian obstruction” as the key pathogenic mechanisms of postoperative pain, offering holistic regulatory advantages. This study employs network pharmacology to systematically elucidate the molecular mechanisms underlying postoperative pain treatment through dimensions such as active ingredient screening, target prediction, network construction, and pathway enrichment.

Network pharmacology screening identified 26 core active components of Xiaoyu Yin. Through target prediction, 118 drug targets were obtained. After intersection with 820 postoperative pain disease targets, 55 potential action targets were identified, which primarily target the core mechanisms of postoperative pain.

Topological analysis of compound-target networks revealed that the top 5 active components by degree value were α-sitosterol, GA120, raposide, ivy glycoside, and β-sitosterol, with α-sitosterol exhibiting the highest degree value and the most target interactions, suggesting its potential as the key active component in Xiaoyu Yin’s analgesic mechanism.Modern pharmacological studies have confirmed that stigmasterol compounds (α-and β-stigmasterol) exhibit significant anti-inflammatory and analgesic effects. These compounds reduce prostaglandin synthesis by inhibiting cyclooxygenase (COX) activity and regulate the release of inflammatory factors, which are directly related to the core mechanisms of postoperative pain-related inflammation [11]. Iberisoside has been reported to exert analgesic effects by modulating neurotransmitter release and inhibiting neuropathic pain-related signaling pathways [12]. These findings further validate the synergistic analgesic effects of the active components in Xiaoyu Yin, which are achieved through both direct inhibition of inflammatory mediator synthesis and modulation of neural signaling, as well as indirect improvement of local circulation and alleviation of blood stasis obstruction.

PPI network analysis revealed that the network constructed from 55 potential targets comprised 54 nodes and 492 edges. The top 10 core targets with the highest screening scores were involved in critical biological processes such as inflammation regulation, apoptosis, and neural signal transduction, which are closely associated with the onset and progression of postoperative pain. Among these, AKT1 and PTGS2 exhibited the highest values (38 and 36, respectively), making them the core targets.PTGS2, a key enzyme in prostaglandin synthesis, exhibits significantly elevated expression following surgical trauma and serves as one of the primary inflammatory mediators contributing to pain [13]. Xiaoyu Yin may directly block the initiation of pain signaling by inhibiting PTGS2 activity and reducing PGE2 release. AKT1, a core molecule in the PI3K-Akt signaling pathway, not only regulates cell survival and apoptosis but also participates <EndNote><Cite><Authorin pain modulation by influencing neurotransmitter receptor expression and modulating inflammatory cytokine release[14]. This mechanism aligns closely with the “neuro-endocrine-immune network dysfunction” underlying postoperative pain [15].

GO functional enrichment analysis and KEGG pathway enrichment analysis revealed that the most closely associated pathways with postoperative pain included the apoptosis signaling pathway (hsa04210), PI3K-Akt signaling pathway (hsa04151), IL-17 signaling pathway (hsa04657), calcium signaling pathway (hsa04020), and AGE-RAGE signaling pathway (ko04933). As a core pathway for cell survival and metabolism, the PI3K-Akt signaling pathway was preliminarily elucidated through network pharmacology in this study, revealing the “multi-component-multi-target-multi-pathway” mechanism of Xiaoyu Yin in treating postoperative pain [16]. The study confirmed that Xiaoyu Yin may act on key targets such as AKT1, PTGS2, and CASP3 through active components like α-sitosterol and ursolic acid, thereby regulating critical signaling pathways including PI3K-Akt, IL-17, and calcium signaling [17]. This mechanism exerts therapeutic effects on postoperative pain through multiple mechanisms, such as inhibiting inflammatory responses, modulating apoptosis, improving neural signal transmission, and alleviating oxidative stress. The findings are highly consistent with the traditional Chinese medicine theory of “activating blood circulation to resolve stasis and unblocking meridians,” providing a scientific basis for the clinical application and further mechanistic research of Xiaoyu Yin.

Fund Project

Qinchuangyuan Project in Xianyang City, Shaanxi Province (L2024-QCY-ZYYJJQ-257) (L2024-QCY-ZYYJJQ-280).

References

[1] Gao W, Li H, Li T, et al. Effects of S-ketamine on Postoperative Recovery Quality and Inflammatory Response in Patients Undergoing Modified Radical Mastectomy [J]. Pain Ther, 2023, 12(5): 1165-1178.

[2] Cheng Y, Xue F S, Li C W. Effects of the Different Doses of Esketamine on Postoperative Quality of Recovery in Patients Undergoing Modified Radical Mastectomy: A Randomized, Double-Blind, Controlled Trial [Letter] [J]. Drug Des Devel Ther, 2023, 17: 937-938.

[3] Li J, Xie X, Zhang J, et al. Novel Bedside Dynamic Nomograms to Predict the Probability of Postoperative Cognitive Dysfunction in Elderly Patients Undergoing Noncardiac Surgery: A Retrospective Study [J]. Clin Interv Aging, 2022, 17: 1331-42.

[4] Chen R, Sun Y, Lv J, et al. Effects of Dexmedetomidine on Immune Cells: A Narrative Review [J]. Front Pharmacol, 2022, 13: 829951.

[5] Liu Y, Li G, Liu Z, et al. Efficacy of Ultrasound-Guided Intercostal Nerve Block on Pain Management and Physiological Outcomes in Breast Cancer Mastectomy:

A retrospective study [J]. Medicine (Baltimore), 2024, 103(31): e38738.
[6] Yilmaz E T, Gulmez D D, Apan A, et al. A novel comparison of erector spinae plane block and paravertebral block in laparoscopic cholecystectomy [J]. Rev Assoc Med Bras (1992), 2024, 70(3): e20231457.
[7] Usman M A, Rabiu M B, Salahu D. A comparison of fascia iliaca compartment block with intravenous analgesia to improve pain control in patients with femoral fracture [J]. J West Afr Coll Surg, 2024, 14(3): 255-261.
[8] Zhu Q, Mao L N, Liu C P, et al. Antinociceptive effects of vitexin in a mouse model of postoperative pain [J]. Sci Rep, 2016, 6: 19266.
[9] Guo M, Wang X. Pathological mechanism and targeted drugs of ulcerative colitis: A review [J]. Medicine (Baltimore), 2023, 102(37): e35020.
[10] Chi K, Yang S, Zhang Y, et al. Exploring the mechanism of Tingli Pill in the treatment of HFpEF based on network pharmacology and molecular docking [J]. Medicine (Baltimore), 2024, 103(16): e37727.
[11] Wang L, Yuan L. Analysis of ginseng in the treatment of Interstitial Cystitis/Bladder Pain Syndrome based on network pharmacology [J]. Eur Rev Med Pharmacol Sci, 2022, 26(13): 4709-4720.
[12] Chen D, Zhong J, Jiang W, et al. Dietary phytic acid damages the intestinal mucus barrier and structural integrity in the grass carp (Ctenopharyngodon idella) [J]. Fish Shellfish Immunol, 2025, 161: 110300.
[13] Li X, Shao M, Liu Z, et al. Mechanistic Insights of Qingre Jiedu Recipe Based on Network Pharmacology Approach against Heart Failure [J]. Evid Based Complement Alternat Med, 2022, 2022: 9024394.
[14] Qiao L Y. Neurotrophin signaling and visceral hypersensitivity [J]. Front Biol (Beijing), 2014, 9(3): 216-224.
[15] Chen D, Zhang Y, Yao C, et al. Increased levels of serum IL-17 and induced sputum neutrophil percentage are associated with severe early-onset asthma in adults [J]. Allergy Asthma Clin Immunol, 2021, 17(1): 64.
[16] Ma K, Cheng Z, Jiang H, et al. Expert Consensus on Ion Channel Drugs for Chronic Pain Treatment in China [J]. J Pain Res, 2024, 17: 953-963.
[17] Shen J, Gao Y, Deng Y, et al. Eucommia ulmoides extract regulates oxidative stress to maintain calcium homeostasis and improve diabetic osteoporosis [J]. Food Sci Nutr, 2024, 12(10): 8067-8083.