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Research Progress and Network Pharmacological Analysis of Single Herb Improvement of Functional Dyspepsia by Jineijin Shanzha (Galli Gigerii Endothelium Corneum and Crataegi Fructus) Traditional Chinese Medicine Patch

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Abstract [**Objectives**] To investigate the efficacy and potential mechanism of the topical preparation Jineijin - Shanzha Patch (composed of Galli Gigerii Endothelium Corneum and Crataegi Fructus) in improving functional dyspepsia (FD) based on network pharmacology. [**Methods**] Firstly, we reviewed the existing research progress on each constituent drug of the Jineijin Shanzha Patch for FD improvement. Following this, identified overlapping genes were utilized to construct both a "Drug-Active Component-FD Target" network and a Protein-Protein Interaction (PPI) network specific to the patch. In addition, Gene Ontology (GO) analysis was carried out. [**Results**] We identified that the 13 herbs in the Jineijin Shanzha Patch are mainly used for food stagnation, qi stagnation, and spleen deficiency. Screening revealed 43 active patch components, 1 414 FD-related targets, and 284 shared targets between them. The PPI network analysis further identified the top 10 core targets from these shared targets. From the "Drug-Active Component-FD Target" network, we identified the core elements. These included the herbal components Vignae Semen (from Liushenqu), Crataegi Fructus, and Pseudostellariae Radix; the active components quercetin, genistein, and apigenin; and the key targets CASP3, BCL2, and CASP9. GO analysis of the 284 overlapping targets indicated that the Jineijin Shanzha Patch may exert its therapeutic effects via regulation of biological processes such as the response to lipopolysaccharide, response to bacterium-derived molecules, and regulation of the apoptotic signaling pathway. [**Conclusions**] The main active components of the Jineijin Shanzha Patch (quercetin, genistein, and apigenin) may improve FD by modulating signaling pathways such as the response to lipopolysaccharide, response to bacterium-derived molecules, and regulation of the apoptotic signaling pathway, thereby acting on key targets including CASP3, BCL2, and CASP9.

Key words Medicinal plant, Functional dyspepsia, Action mechanism, Network pharmacology

1 Introduction

Functional dyspepsia (FD) is a common clinical disorder, characterized primarily by symptoms such as epigastric pain, epigastric bloating, belching, postprandial fullness, early satiation, and postprandial discomfort. It can be subcategorized into two subtypes: epigastric pain syndrome (EPS) and postprandial distress syndrome (PDS)[1]. The reported prevalence of FD ranges from approximately 10% to 40% in Western countries and from 5% to 30% in Asian countries[2]. In addition, FD is highly prevalent among children of all age groups and significantly impacts patients' families and quality of life[3]. Modern medical research indicates that the etiology of FD is complex, with factors such as gastrointestinal dysmotility, abnormal gastric acid secretion, visceral hypersensitivity, psychological anxiety, and *Helicobacter pylori* infection being highly associated with its development[4]. In Traditional Chinese Medicine (TCM), FD is categorized under syndromes like "Pi Man" (fullness and stuffiness) and "Wei Wan Tong" (epigastric pain). TCM interventions have demonstrated notable advantages in treating FD, including significant efficacy, minimal side effects, and a lower recurrence rate upon long-term follow-up[5].

Components of Jineijin - Shanzha (Galli Gigerii Endothelium Corneum-Crataegi Fructus) Traditional Chinese Medicine Patch (hereinafter referred to as Jineijin Shanzha Patch) include Jineijin (Galli Gigerii Endothelium Corneum), Crataegi Fructus, Citri Reticulatae Pericarpium, Aucklandiae Radix, Liushenqu (Medicated Leaven), Citri Reticulatae Pericarpium Viride, Magnoliae Officinalis Cortex, Atractylodis Macrocephalae Rhizoma, Poria, Atractylodis Rhizoma, Pseudostellariae Radix, Amomi Fructus Rotundus, and Euodiae Fructus. Studies have shown that Crataegi Fructus, Citri Reticulatae Pericarpium, Aucklandiae Radix, Magnoliae Officinalis Cortex, Atractylodis Macrocephalae Rhizoma, Poria, and Pseudostellariae Radix are medicinal materials frequently used in the treatment of FD[6]. This patch exerts a health-promoting effect by aiding recovery from spleen-stomach discomfort, abdominal pain, and intestinal flatulence. Taking the Jineijin Shanzha Patch as an example, we first analyzed the TCM syndrome attributions and modern pharmacological research of each herbal component in the formula to clarify their association with FD. Then, we employed a network pharmacology approach to predict its potential active components, core targets, and action pathways. The aim was to provide a theoretical prediction and scientific basis for the efficacy mechanism of this topical TCM component formulation in improving FD.

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2 TCM syndrome and modern pharmacological basis of each medicinal material in the patch formulation

To systematically elucidate the association between the Jineijin

Shanzha Patch formulation and FD, this study first utilized the TCM Syndrome Association Database, SymMap, to retrieve and analyze the primary TCM syndromes and symptoms corresponding to the 13 herbal medicines in the patch. This information was then integrated with contemporary pharmacological research to establish a theoretical and material foundation for the subsequent network pharmacology analysis.

2.1 Jineijin (Galli Gigerii Endothelium Corneum) As an inexpensive and readily available medicinal and edible traditional Chinese medicine, Galli Gigerii Endothelium Corneum primarily comprises proteins, polysaccharides, amino acids, and trace elements. It is clinically used for promoting digestion and resolving food stagnation[7]. Research has shown that Galli Gigerii Endothelium Corneum markedly improves gastric emptying, intestinal propulsion, digestive enzyme activity, and raises serum gastrin, motilin, and ghrelin levels in rat models of FD, confirming its therapeutic potential[8]. Besides, SymMap analysis revealed its principal TCM syndrome associations are "indigestion", "food stagnation", and "gallbladder distension", linked to clinical manifestations like epigastric discomfort and flank pain (Fig. 1A). This alignment suggests that its traditional function of "eliminating stagnation" corresponds well to its modern pharmacological actions of stimulating GI motility and enhancing digestion.

2.2 Crataegi Fructus Crataegi Fructus contains active substances such as flavonoids, triterpenoids, organic acids, and sterols[9]. Modern pharmacological studies have shown that Crataegi Fructus extract has therapeutic effects on indigestion, significantly reducing gastric residual volume, increasing intestinal propulsion rate, dietary intake, and gastrointestinal hormone levels[10]. SymMap analysis indicates that the syndromes associated with Crataegi Fructus are mostly related to "blood stasis" and "stasis obstruction" (Fig. 1B). However, modern studies confirm its good digestive-promoting effects, suggesting that it primarily exerts the pharmacological activity of promoting digestion and resolving food stagnation in component formulations.

2.3 Citri Reticulatae Pericarpium Citri Reticulatae Pericarpium refers to the dried mature pericarp of *Citrus reticulata* Blanco and its cultivated varieties from the Rutaceae family, with the effect of regulating qi and fortifying the spleen[11]. Studies have found that hesperidin, the main active component of Citri Reticulatae Pericarpium, can modulate Drp1-mediated mitochondrial autophagy in ICC, thereby alleviating mitochondrial damage and promoting gastric motility in FD model rats[12]. Its SymMap syndrome network is highly associated with "spleen deficiency," "qi stagnation," and "phlegm excess" (Fig. 1C), confirming its traditional efficacy in regulating qi, fortifying the spleen, and improving gastrointestinal function in cases of spleen deficiency with qi stagnation.

2.4 Aucklandiae Radix Aucklandiae Radix, the dried root of *Aucklandia lappa* Decne. (Asteraceae), is traditionally employed to fortify the spleen and aid digestion[13]. In a study by Guo *et al.*[14], the methanol extract of Aucklandiae Radix was shown to influence gastric emptying and small intestinal motility, demonstrating antispasmodic activity within the gastrointestinal tract. SymMap analysis associates this herb mainly with patterns like "qi stagnation" and "food accumulation" (Fig. 1D). Its traditional function of "moving qi" aligns with modern pharmacological evidence supporting its role in modulating gastrointestinal motility and relieving spasms.

2.5 Medicated Leaven Medicated Leaven is fermented by mixing Polygonii Flaccidi Herba, Artemisiae Annuae Herba, Xanthii Fructus, Armeniacae Semen Amarum, and Vignae Semen, has the function of strengthening spleen and promoting digestion[15]. Studies indicate that Medicated Leaven after fermentation treatment can promote food hydrolysis, enhance gastrointestinal motility and intestinal content propulsion, thereby aiding in the treatment of gastrointestinal diseases[16]. SymMap analysis shows that the constituent herbs of Medicated Leaven have different emphases: Artemisiae Annuae Herba is associated with "summer-heat" and "dampness-heat" (Fig. 2A); Armeniacae Semen Amarum is linked to "phlegm excess" and "rebellious qi" (Fig. 2B); while Vignae Semen is closely related to "dampness-heat" and "wind-dampness-heat" (Fig. 2C). As a whole, Medicated Leaven primarily exerts the effect of promoting digestion and harmonizing the stomach in component formulations.

2.6 Citri Reticulatae Pericarpium Viride Citri Reticulatae Pericarpium Viride is the dried pericarp of the young or unripe fruit of *Citrus reticulata* Blanco and its cultivated varieties from the Rutaceae family. It can be used to treat food stagnation with qi stagnation, and abdominal distension and pain[17]. It has been reported that Citri Reticulatae Pericarpium Viride can coordinate and promote gastrointestinal function by affecting gastrointestinal smooth muscle[18]. Its SymMap syndrome network is closely centered around "food accumulation" and "qi stagnation" (Fig. 2D), which directly corresponds to the common symptoms of abdominal distension and pain in FD.

2.7 Magnoliae Officinalis Cortex Magnoliae Officinalis Cortex is the dried bark of *Magnolia officinalis* Rehder & E. Wilson from the Magnoliaceae family. It exhibits certain antispasmodic effects and can relieve gastrointestinal and bronchial spasms[19]. SymMap analysis indicates that Magnoliae Officinalis Cortex is associated with syndromes such as "food accumulation," "qi stagnation," and "phlegm-fluid retention" (Fig. 2E). Its effects of promoting qi flow, dispersing accumulation, descending qi, and relieving fullness contribute to alleviating abdominal distension symptoms in FD.

2.8 Atractylodis Macrocephalae Rhizoma Atractylodis Macrocephalae Rhizoma, as a traditional herbal medicine, possesses significant gastrointestinal motility-regulating effects and can alleviate abdominal pain induced by visceral hypersensitivity such as in irritable bowel syndrome[20]. Its SymMap syndrome network shows that Atractylodis Macrocephalae Rhizoma is highly

associated with "spleen deficiency," "qi deficiency," and "qi stagnation" (Fig. 2F), making it a key herb for treating FD caused by spleen-stomach weakness and impaired transportation and transformation.

2.9 Poria Poria is a medicinal fungus whose primary component, Poria polysaccharide, can regulate intestinal mucosal function to maintain intestinal homeostasis[21]. In the SymMap analysis, besides being associated with "spleen deficiency," Poria is also linked to syndromes such as "blood stasis" (Fig. 3A). This indicates that in addition to its effects of fortifying the spleen and promoting diuresis, it may also function through pathways like regulating microcirculation.

2.10 Atractylodis Rhizoma Atractylodis Rhizoma is the dried rhizome of *Atractylodes lancea* (Thunb.) DC. or *Atractylodes chinensis* (DC.) Koidz. from the Asteraceae family. Liu Fen *et al.*[22] found that the extract of Atractylodis Rhizoma can increase the expression of Toll-like receptor 4 (TLR4) in intestinal mucosal cells of rats with spleen deficiency syndrome, thereby enhancing intestinal immunity and helping to improve the pathological damage of gastric mucosa and gastrointestinal dysfunction caused by spleen deficiency. Its SymMap syndromes are closely related to "dampness obstructing the middle jiao" and "cold-dampness" (Fig. 3B), highlighting its effect of drying dampness and strengthening the spleen in treating gastrointestinal diseases due to dampness encumbering the spleen.

2.11 Pseudostellariae Radix Pseudostellariae Radix, as a traditional Chinese medicine with dual use as both medicine and food, is commonly employed in TCM for treating spleen deficiency syndrome. Xiao *et al.*[23] found that Pseudostellariae Radix and its main active component, polysaccharides, can reduce pro-inflammatory cytokine levels in rats with spleen deficiency syndrome, regulate the intestinal flora, and thereby alleviate spleen deficiency symptoms. SymMap analysis shows that Pseudostellariae Radix primarily corresponds to syndromes such as "spleen deficiency" and "qi-yin deficiency" (Fig. 3C), and its effect of replenishing qi and fortifying the spleen aligns with the fundamental pathogenesis of spleen-stomach weakness in FD.

2.12 Amomi Fructus Rotundus Amomi Fructus Rotundus is the dried mature fruit of *Amomum kravanh* Pierre ex Gagnep. from the Zingiberaceae family and is commonly used clinically to treat spleen and stomach discomfort[24]. It has been reported that the aqueous extract of Amomi Fructus Rotundus can inhibit the decrease in the number of interstitial cells of Cajal, enhance colonic contractility, normalize gastrointestinal motility, and further alleviate constipation symptoms in mice[25]. Its SymMap syndrome network is associated with "food accumulation" and "damp-turbidity obstructing the middle jiao" (Fig. 3D), reflecting its effects of resolving dampness, promoting qi movement, warming the middle jiao, and relieving vomiting.

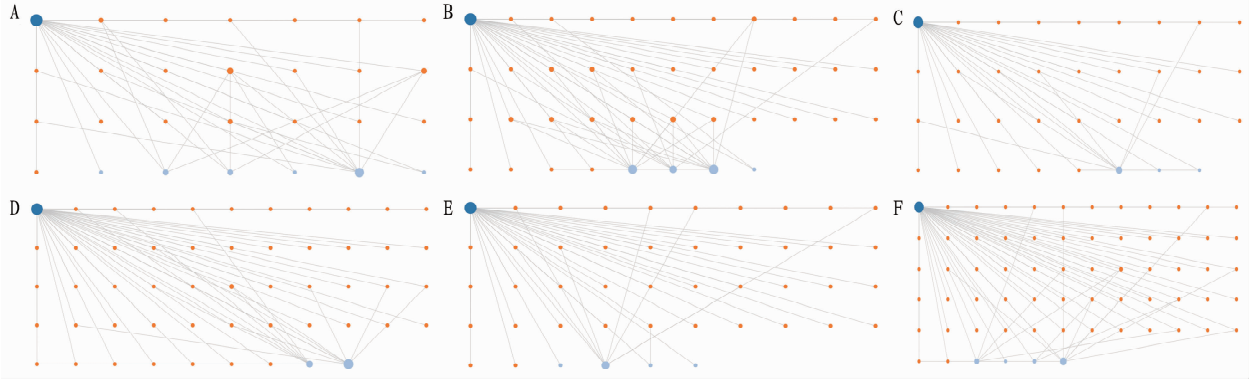
2.13 Euodiae Fructus Euodiae Fructus has a long history and is widely used in clinical practice. It was first recorded in the ancient Chinese medical classic *Shennong's Classic of Materia Medica*[26]. In clinical external applications, Euodiae Fructus is often employed to treat digestive system diseases, cardiovascular system diseases, neurological system diseases, *etc.* It can effectively treat conditions such as diarrhea, constipation, nausea and vomiting, postoperative gastrointestinal dysfunction, hypertension, insomnia, headache, and dizziness[27]. SymMap analysis indicates that Euodiae Fructus is associated with syndromes such as "cold-dampness," "qi stagnation," and "cold hernia" (Fig. 3E). Its effects of warming the middle jiao, dispersing cold, soothing the liver, and descending qi can be used to treat epigastric discomfort caused by cold congelation and qi stagnation.

2.14 Formula-based overall syndrome pattern analysis and its correlation with FD Based on the compiled results, the TCM symptoms associated with the Chinese herbs contained in the Jineijin Shanzha Patch are presented in Fig. 3F. In the word cloud, the font size of a term corresponds to its frequency, indicating a stronger association between the patch and that particular symptom. The word cloud reveals that the primary indications for this herbal patch include food stagnation, sluggish flow of qi, and deficiency of spleen, among others. In summary, a word cloud (Fig. 3F) was generated from the main TCM symptoms corresponding to the 13 herbs in the Jineijin Shanzha Patch. Terms such as "food stagnation," "sluggish flow of qi," and "deficiency of spleen" are the most prominent, constituting the core indications of this formula. Liu *et al.*[28], in their study on the distribution patterns of TCM syndromes in modern clinical literature of FD, pointed out that common FD syndromes include liver-stomach disharmony, spleen-stomach weakness, and dietary stagnation. The disease location involves the spleen, stomach, and liver, with disease nature involving qi stagnation, qi deficiency, and food stagnation. The comparison shows that the core indications of this patch's formula highly align with the major clinical syndromes of FD, supporting its rationale for treating FD from the perspective of TCM theory.

In a study reviewing modern clinical literature on FD, Liu *et al.*[28] investigated the distribution patterns of TCM syndromes and the standardization of syndrome differentiation. They identified the eight most frequently reported syndromes: liver-stomach disharmony, spleen-stomach weakness, cold-heat complex, dietary stagnation, liver depression-spleen deficiency, liver depression-qi stagnation, spleen-stomach deficiency-cold, and spleen-stomach dampness-heat. The analysis revealed that abdominal distension is a common symptom across these eight TCM syndromes associated with FD. Furthermore, these syndromes involve three primary disease locations: the spleen, stomach, and liver, with pathological factors including qi stagnation, qi deficiency, cold, heat, dampness, and food stagnation. Based on the network pharmacology analysis results, the main TCM symptoms corresponding to the herbal formula in the Jineijin Shanzha Patch align with the major clinical syndrome types of FD.

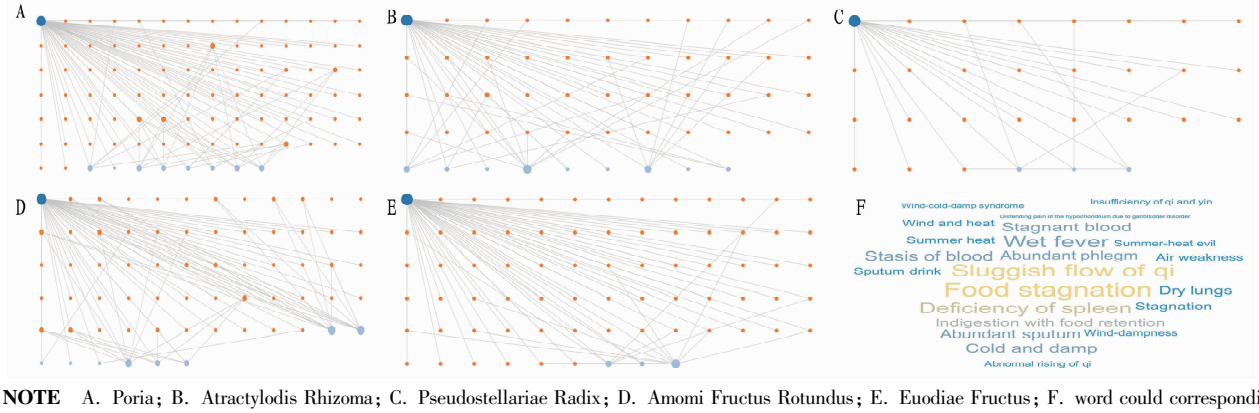
NOTE A. Galli Gigerii Endothelium Corneum; B. Crataegi Fructus; C. Citri Reticulatae Pericarpium; D. Aucklandiae Radix. The size of the node represents the strength of the correlation degree.

Fig. 1 Jineijin Shanzha Patch drug-syndrome-symptom correlation network



NOTE A. Medicated Leaven-Artemisiae Annuae Herba; B. Medicated Leaven-Armeniacae Semen Amarum; C. Medicated Leaven-Vignae Semen; D. Citri Reticulatae Pericarpium Viride; E. Magnoliae Officinalis Cortex; F. Atractylodis Macrocephalae Rhizoma.

Fig. 2 Jineijin Shanzha Patch drug-syndrome-symptom correlation network



NOTE A. Poria; B. Atractylodis Rhizoma; C. Pseudostellariae Radix; D. Amomi Fructus Rotundus; E. Euodiae Fructus; F. word could corresponding to TCM drugs.

Fig. 3 Jineijin Shanzha Patch drug-syndrome-symptom correlation network and TCM symptom word cloud

3 Prediction of efficacy mechanism based on network pharmacology

On the basis of clarifying the TCM syndromes of the formulation, we further used the network pharmacology method to predict the potential material basis and molecular mechanism of Jineijin Shanzha Patch to improve FD.

3.1 Screening of active components and targets To comprehensively acquire the pharmacologically active components in the patch, known components from the constituent herbs and their corresponding targets were collected using the herbal ingredients and targets database HIT 2.0 (Herbal Components' Targets Platform, http://www.badd-cao.net:2345/). Components were also retrieved from the TCMSP database (https://old.tcmsp-e.com/) and screened based on predictive parameters. Those with a drug-likeness (*DL*) value ≥ 0.18 were considered to have potential pharmacological activity. Besides, components with a topological polar surface area (*TPSA*) ≤140 Å^2 were selected as potentially effective active ingredients capable of penetrating skin or mucous membranes. Applying these screening criteria, a total of 43 potential active components derived from the main herbal components of Jineijin Shanzha Patch (Table 1) and their corresponding 49 targets were thereby identified.

Table 1 Potential active components of Jineijin Shanzha Patch formulation (*DL*≥0.18, *TPSA*≤140)

No.	Molecule name	*DL*	*TPSA*	Medicinal plant
1	Tumulosic Acid	0.81	77.76	Poria
2	Pachymic Acid	0.81	83.83	Poria
3	Betunolic Acid	0.78	54.37	Medicated Leaven-Vignae Semen
4	Taraxasterol	0.76	20.23	Aucklandiae Radix
5	Stigmasterol	0.76	20.23	Aucklandiae Radix
6	Oleanolic Acid	0.76	57.53	Crataegi Fructus
7	Schottenol	0.75	20.23	Pseudostellariae Radix
8	ursolic acid	0.75	57.53	Crataegi Fructus; Pseudostellariae Radix
9	Beta-Sitosterol	0.71	20.23	Crataegi Fructus; Medicated Leaven-Vignae Semen; Atractylodis Rhizoma; Atractylodis Macrocephalae Rhizoma; Pseudostellariae Radix
10	Nomilin	0.67	121.64	Citri Reticulatae Pericarpium
11	Evodiamine	0.64	39.34	Euodiae Fructus
12	Sitogluside	0.62	99.38	Pseudostellariae Radix
13	Rutaecarpine	0.60	50.68	Euodiae Fructus
14	Beta Carotene	0.58	0	Citri Reticulatae Pericarpium
15	Limonin	0.57	104.57	Citri Reticulatae Pericarpium; Euodiae Fructus
16	Vitamin E	0.55	29.46	Medicated Leaven-Armeniacae Semen Amarum; Medicated Leaven-Vignae Semen;
17	Liriodenine	0.53	48.42	Medicated Leaven-Xanthii Fructus
18	Lycorine	0.51	62.16	Citri Reticulatae Pericarpium Viride
19	Anonaine	0.47	30.49	Magnoliae Officinalis Cortex
20	Tangeretin	0.43	76.36	Citri Reticulatae Pericarpium; Citri Reticulatae Pericarpium Viride
21	Cynaropicrin	0.38	93.06	Aucklandiae Radix
22	1-Monolinolein	0.30	66.76	Pseudostellariae Radix
23	Rhamnetin	0.30	120.36	Medicated Leaven-Vignae Semen
24	Quercetin	0.28	131.36	Crataegi Fructus; Medicated Leaven-Armeniacae Semen Amarum
25	Epigallocatechin	0.27	130.61	Crataegi Fructus; Medicated Leaven-Artemisiae Annuae Herba
26	Luteolin	0.25	111.13	Atractylodis Rhizom; Atractylodis Macrocephalae Rhizoma; Pseudostellariae Radix
27	Acacetin	0.24	79.90	Medicated Leaven-Vignae Seme; Pseudostellariae Radix
28	Glycitein	0.24	79.90	Galli Gigerii Endothelium Corneum
29	Prunetin	0.24	79.90	Medicated Leaven-Armeniacae Semen Amarum
30	(−)-Epicatechin	0.24	110.38	Crataegi Fructus; Medicated Leaven-Artemisiae Annuae Herba; Atractylodis Macrocephalae Rhizoma
31	(+)-Catechin	0.24	110.38	Poria; Crataegi Fructus
32	Cianidanol	0.24	110.38	Crataegi Fructus; Medicated Leaven-Artemisiae Annuae Herba
33	Kaempferol	0.24	111.13	Crataegi Fructu; Medicated Leaven-Armeniacae Semen Amarum
34	Wogonin	0.23	79.90	Atractylodis Rhizoma
35	Apigenin	0.21	90.90	Medicated Leaven-Vignae Semen
36	Galangin	0.21	90.90	Medicated Leaven-Vignae Semen
37	Genistein	0.21	90.90	Galli Gigerii Endothelium Corneum
38	Pinocembrin	0.20	66.76	Medicated Leaven-Vignae Semen
39	Pyrene	0.19	0	Atractylodis Rhizom; Atractylodis Macrocephalae Rhizoma
40	Daidzein	0.19	70.67	Galli Gigerii Endothelium Corneum
41	Obovatol	0.18	49.69	Magnoliae Officinalis Cortex
42	Chrysin	0.18	70.67	Medicated Leaven-Vignae Semen
43	Adenosine	0.18	138.49	Galli Gigerii Endothelium Corneum

3.2 Disease target collection and intersection target acquisition Using "functional dyspepsia" as the keyword, a total of 3 472 FD-related targets were retrieved from the GeneCards database (https://www.genecards.org/). Targets with a "Relevance score" above the average value (1 414 in total) were screened to obtain disease targets with higher relevance to FD. These curated disease targets were then intersected with the 495 action targets corresponding to the active components from the main herbal components of Jineijin Shanzha Patch. This intersection yielded 284 potential gene targets that may act on FD (Fig. 4). Based on these intersecting targets, components lacking corresponding target relationships were subsequently filtered out.

3.3 "Drug-component-target" network construction and core node analysis The "Drug-component-target" network of Jineijin Shanzha Patch was constructed using Cytoscape software (version 3.10.3) as shown in Fig. 5. In this network, nodes denote the active components of the herbal formula and their corresponding targets, while edges represent the interaction relationships between them. Topological analysis was performed based on the established network. The importance of nodes within the network was evaluated using two metrics: degree (the number of connections a node has) and betweenness centrality (a measure of a node's influence in bridging other nodes). According to the topological analysis results, the network comprised a total of 338 nodes (284 targets, 43 components, and 11 medicinal herbs) and 833 edges. The network topology analysis revealed an average node degree of 4.9, with 76 nodes exhibiting a degree value greater than the average. The average betweenness centrality was 0.006 5, with 54 nodes exceeding this average value. Nodes meeting both screening criteria are listed in Table 2. The analysis suggests that Vignae Semen from the Medicated Leaven group, Crataegi Fructus, and Pseudostellariae Radix may constitute the core medicinal plants responsible for the pharmacological effects of Jineijin Shanzha Patch. Key bioactive components are likely quercetin, gen istein, and apigenin. The core action targets potentially include CASP3, BCL2, and CASP9. This indicates that, at the level of direct interactions, the patch may primarily exert its effects by acting on apoptosis-related targets via these core components.

Table 2 Key topology nodes of "Drug-component-target" network of Jineijin Shanzha Patch

No.	Node name	Node type	Degree value	Betweenness centrality	No.	Node name	Node type	Degree value	Betweenness centrality
1	Quercetin	Compound	149	0.422 4	27	NOS2	Target	10	0.013 0
2	Genistein	Compound	84	0.197 0	28	VEGFA	Target	10	0.024 3
3	Apigenin	Compound	81	0.166 9	29	Medicated Leaven-Vignae Semen	Medicinal plant	9	0.008 9
4	ursolic acid	Compound	63	0.108 1	30	AKT1	Target	9	0.010 2
5	Luteolin	Compound	60	0.087 6	31	Crataegi Fructus	Medicinal plant	9	0.010 4
6	Vitamin E	Compound	52	0.087 8	32	ICAM1	Target	9	0.012 1
7	Daidzein	Compound	46	0.084 3	33	MMP9	Target	9	0.013 0
8	Wogonin	Compound	37	0.039 1	34	Evodiamine	Compound	9	0.015 1
9	Kaempferol	Compound	36	0.040 3	35	Beta Carotene	Compound	8	0.007 1
10	Chrysin	Compound	24	0.026 2	36	TP53	Target	8	0.008 6
11	Acacetin	Compound	21	0.010 7	37	CYP1A2	Target	8	0.009 1
12	CASP3	Target	20	0.053 2	38	RELA	Target	8	0.009 3
13	(+)-Catechin	Compound	19	0.025 4	39	IL6	Target	8	0.009 7
14	Epigallocatechin	Compound	16	0.015 0	40	PPARG	Target	8	0.011 0
15	BCL2	Target	15	0.035 7	41	NFKBIA	Target	8	0.011 6
16	Galangin	Compound	14	0.016 9	42	MAPK1	Target	7	0.007 9
17	Beta-Sitosterol	Compound	13	0.011 1	43	CXCL8	Target	7	0.008 2
18	CASP9	Target	13	0.020 2	44	FASN	Target	7	0.009 5
19	BAX	Target	13	0.029 7	45	Pseudostellariae Radix	Medicinal plant	7	0.017 2
20	PTGS2	Target	13	0.035 5	46	Sitogluside	Compound	7	0.020 0
21	(−)-Epicatechin	Compound	12	0.010 7	47	FOS	Target	6	0.007 5
22	CDKN1A	Target	11	0.015 6	48	Cianidanol	Compound	5	0.006 6
23	JUN	Target	11	0.016 7	49	HIF1A	Target	5	0.007 5
24	TNF	Target	11	0.017 8	50	CYP3A4	Target	5	0.008 3
25	Rutaecarpine	Compound	10	0.010 5	51	PTGS1	Target	5	0.009 9
26	NFKB1	Target	10	0.011 8					

Modern studies have shown that quercetin can prevent gastritis and apoptosis induced by Helicobacter pylori infection by influencing the expression levels of p38MAPK, BCL-2, and BAX[29]. Genistein, also known as golden isoflavone, has been found to dose-dependently reduce the average contraction amplitude of gastrointestinal smooth muscle, helping to regulate gastrointestinal motility and alleviate spasmodic pain[30]. Apigenin, a type of flavonoid, can alleviate intestinal pathological damage, inhibit in-

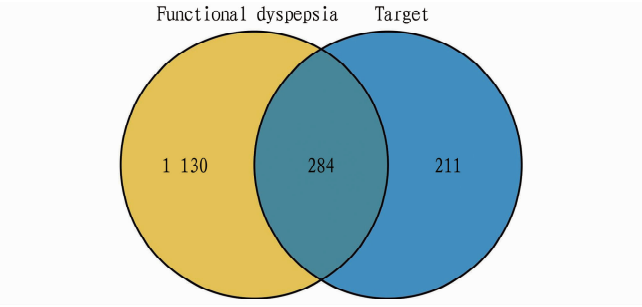
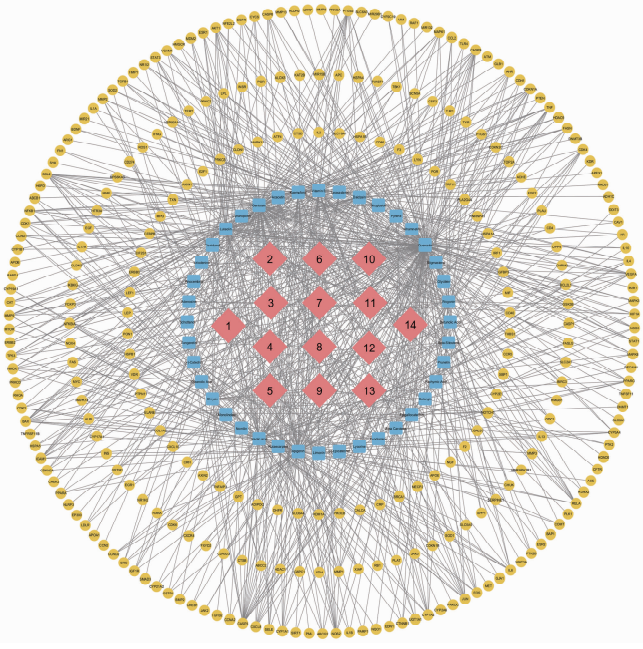


Fig. 4 Venn diagram of the intersection of Jineijin Shanzha Patch targets and disease target genes



NOTE Pink diamond represents drug; blue square denotes components; yellow circle represents targets; 1. Medicated Leaven-Artemisiae Annuae Herba; 2. Poria; 3. Galli Gigerii Endothelium Corneum; 4. Medicated Leaven-Xanthii Fructus; 5. Atractylodis Macrocephalae Rhizoma; 6. Medicated Leaven-Armeniacae Semen Amarum; 7. Aucklandiae Radix; 8. Citri Reticulatae Pericarpium; 9. Medicated Leaven-Vignae Semen; 10. Atractylodis Rhizoma; 11. Pseudostellariae Radix; 12. Crataegi Fructus; 13. Euodiae Fructus; 14. Citri Reticulatae Pericarpium Viride.

Fig. 5 "Drug-component-target" network of Jineijin Shanzha Patch

flammation, protect the intestinal barrier, and remodel disordered gut microbiota[31]. In addition, apigenin can improve high-fat diet-induced hepatic fat accumulation, hepatomegaly, and liver dysfunction by modulating liver metabolism and transcription, thereby reducing the metabolic burden on the digestive system caused by dietary imbalances at the source[32]. Current research indicates that the active ingredients in Jineijin Shanzha Patch may be beneficial in alleviating gastrointestinal inflammation, regulating symptoms related to intestinal dysfunction, and helping to correct metabolic disorders in the digestive system.

3.4 PPI network and Hub gene analysis The obtained 284 targets of the active components from Jineijin Shanzha Patch were imported into the STRING database. After removing single protein nodes with no interaction relationships, a PPI network was constructed to investigate the pharmacological mechanism of Jineijin Shanzha Patch in addressing FD at the protein interaction level. The resulting PPI network is shown in Fig. 6. This network comprises 281 protein nodes and 4 582 edges.

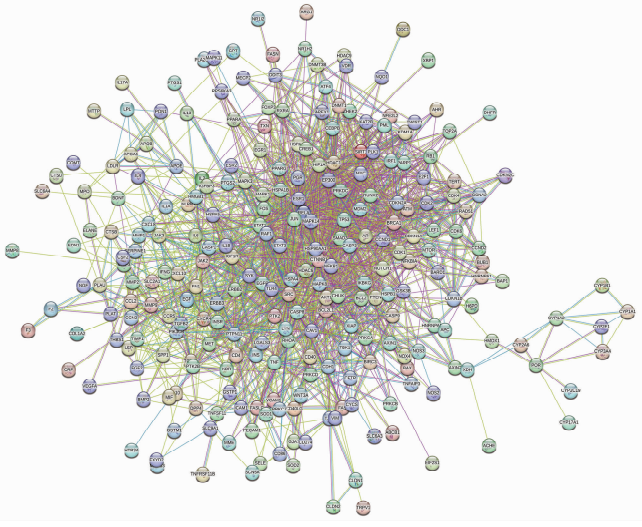


Fig. 6 PPI network of potential targets of Jineijin Shanzha Patch

We imported the constructed PPI network information into Cytoscape software, and analyzed the Hub gene targets using the MCC algorithm of the cytoHubba plugin. The core targets of Jineijin Shanzha Patch for regulating FD were thereby identified. As shown in Fig. 7, the top five hub gene targets of this patch are AKT1, NFKB1, STAT3, JUN, and IL6. These genes occupy pivotal regulatory positions within the PPI network. While they may not necessarily be the primary targets directly acted upon by the active compounds, they are likely key nodes in downstream signal transduction, playing a central role in integrating multi-target effects and regulating complex biological processes such as inflammation, cell survival, and proliferation. For instance, the AKT1 protein, a serine/threonine kinase, plays a significant role in maintaining intestinal epithelial barrier function[33]. The NFκB family can be activated by almost all immune receptors and plays a key role in regulating immune responses and inflammatory processes by coordinating the expression of pro-inflammatory cytokine genes[34]. Castaño-Rodríguez *et al.*[35] found that expression of NFKB1 was significantly upregulated in THP-1 cells infected with Helicobacter pylori. Signal transducer and activator of transcription 3 (STAT3) is a transcription factor widely involved in inflammatory responses[36]. The cytokine interleukin-6 (IL-6) can activate STAT3 signaling, thereby further promoting the development of chronic gastritis[36]. In addition, Wu *et al.*[37] demonstrated that activation of the IL-6/STAT3 pathway can induce damage to the intestinal mucosal barrier and exacerbate intestinal inflammation.

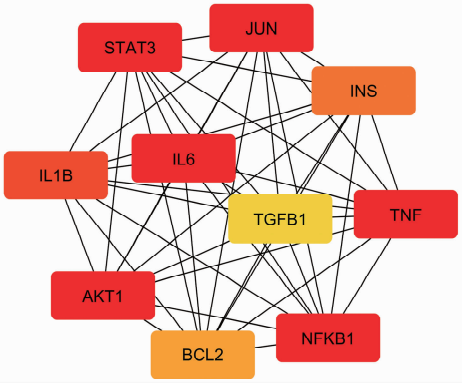
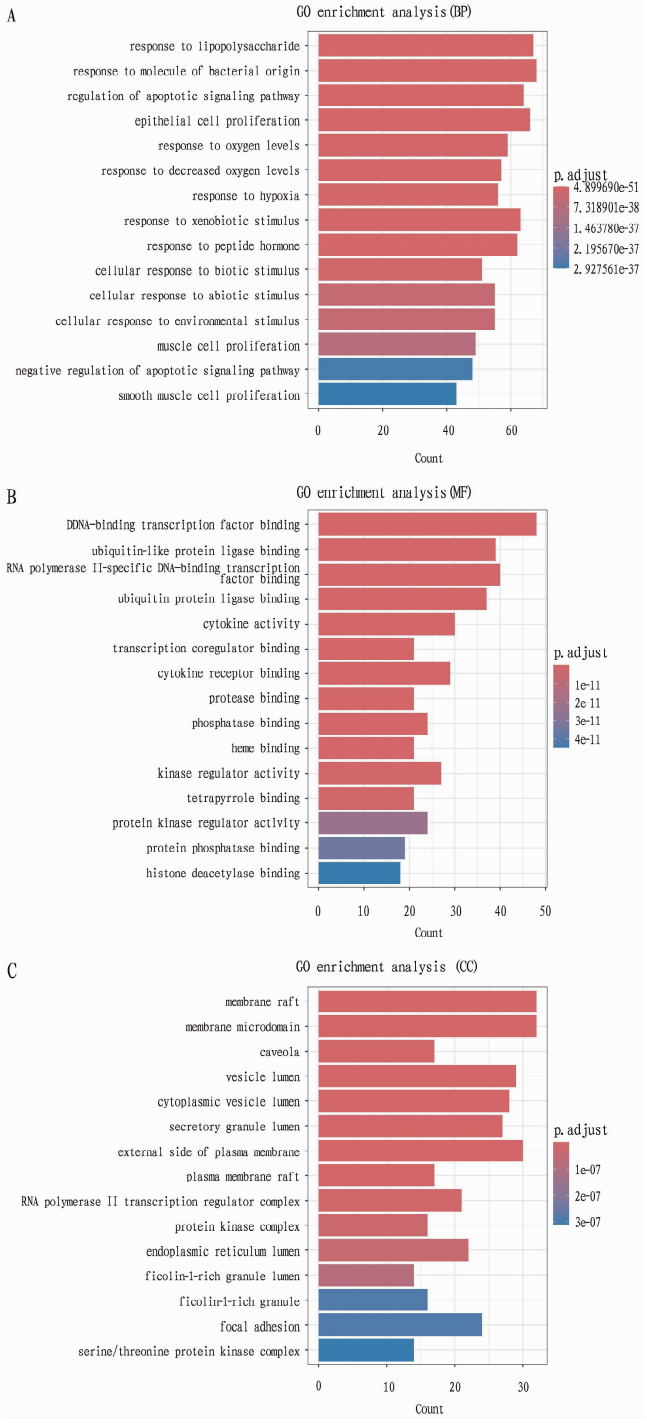


Fig. 7 PPI network Hub genes (top 10) screened based on MCC algorithm

3.5 GO functional enrichment analysis We input the coding gene information of the relevant targets associated with the Jineijin Shanzha Patch herbal formula into the DAVID database (https://davidbioinformatics.nih.gov/). Using Homo sapiens as the analysis species, we performed GO functional analysis under the condition of $P<0.01$. This screening yielded 1 001 GO terms, comprising 764 biological process (BP) terms, 160 molecular function (MF) terms, and 77 cellular component (CC) terms. We then imported the analysis results into the Hiplot biomedical data online visualization tool (https://hiplot.cn). Based on a comprehensive filter of the *P*-value, *Q*-value ($Q<0.05$), and the number of enriched genes, we selected the top 15 terms from each of the BP, MF, and CC categories to generate the bar charts shown in Fig. 8. The GO analysis results indicate that the active compounds of Jineijin Shanzha Patch may exert their effects by modulating biological processes such as the response to lipopolysaccharide, response to molecules of bacterial origin, regulation of apoptotic signaling pathways, epithelial cell proliferation, and response to oxygen levels. These actions are likely associated with cellular components including membrane rafts, membrane microdomains, caveolae, vesicle lumen, and cytoplasmic vesicle lumen. Furthermore, the compounds may influence specific molecular functions, such as sequence specific DNA binding transcription factor binding, ubiquitin-like protein ligase binding, RNA polymerase II-specific DNA-binding transcription factor binding, ubiquitin protein ligase binding, and cytokine activity.

4 Conclusions

Focusing on Jineijin Shanzha Patch, we integrated documented knowledge and network pharmacology to explore how this topical herbal preparation improves FD and its underlying mechanisms. The findings indicate that the patch's potential benefits may arise from active ingredients like quercetin, genistein, and apigenin present in its herbal components (*e.g.*, Vignae Semen, Crataegi Fructus, Pseudostellariae Radix). These compounds are predicted to interact with targets including CASP3, BCL2, and CASP9, leading to the alleviation of TCM syndromes like food accumulation, qi stagnation, and spleen deficiency. The TCM principle of applying herbal remedies externally to address internal disorders



NOTE A: BP enrichment result; B: MF enrichment result; C: CC enrichment result.

Fig. 8 GO analysis of active compound targets of Jineijin Shanzha Patch

offers advantages such as efficacy, good safety profile, and ease of use, which is especially relevant for treating children and chronic conditions[38]. However, the multi-target action mechanisms of complex herbal formulas and the scientific rationale behind transdermal herbal therapy require more extensive investigation and verification.

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