SYSTEMATIC REVIEWS

Chinese herbal formula shen-ling-bai-zhu-san to treat chronic gastritis: Clinical evidence and potential mechanisms

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Abstract

BACKGROUND

Chronic gastritis (CG) is an inflammatory disease of the gastric mucosa. Shen-ling-bai-zhu san (SLBZS), a traditional Chinese medicine formula, is widely used for treating CG. Nevertheless, its effects are currently unclear.

AIM

To determine the clinical evidence and potential mechanisms of SLBZS for the treatment of CG.

METHODS

We systematically searched 3 English (PubMed, Embase, Medline) and 4 Chinese databases (Cochrane Library Central Register of Controlled Trials, China National Knowledge Infrastructure database, Wanfang Data Knowledge Service Platform, and the VIP information resource integration service platform) without language or publication bias restriction. Qualified studies were selected according to pre-set inclusion and exclusion criteria. RevMan 5.3 software was used for meta-analysis and literature quality assessment, Stata 14.0 software was used for sensitivity analysis, GRADE profiler 3.6 was used to evaluate the quality of evidence. And then, network pharmacology analysis was applied to primary research the mechanisms of action of SLBZS on CG.

RESULTS

Fourteen studies were finally included, covering 1335 participants. Meta-analysis indicated that: (1) SLBZS was superior to conventional therapies [risk ratio (RR): 1.29, 95% confidence interval (CI): 1.21 to 1.37, $P < 0.00001$]; (2) SLBZS was better

than conventional therapies [RR: 0.24, 95% confidence interval (95%CI): 0.11 to 0.55, P = 0.0007] in terms of recurrence rate and reversal of *Helicobacter pylori* positivity (RR: 1.20, 95%CI: 1.11 to 1.30, P < 0.00001); and (3) The safety of SLBZS for CG remains unclear. According to the GRADE method, the quality of evidence was not high. Besides, SNZJS might treat CG by acting on related targets and pathways such as EGFR tyrosine kinase inhibitor resistance, the PI3K-Akt signaling pathway, and others.

CONCLUSION
SLBZS might be useful in treating CG, but long-term effects and specific clinical mechanisms of it maintain unclear. More samples and high-quality clinical experiments should be assessed and verified in the next step.

Key Words: Chronic gastritis; Shen-ling-bai-zhu-san; Chinese herbal formula; Systematic review; Network pharmacology

Core Tip: A 2012 clinical practice guideline recommended Shenling Baizhu Powder for the Pattern of Spleen and Stomach Deficiency chronic gastritis (CG). The 2020 clinical guideline did not recommended Shen-ling-bai-zhu san (SLBZS), possibly because of inadequate clinical evidence and pharmacological mechanisms. We designed our study to focus on evidence of efficacy and potential mechanisms. Our study showed that SLBZS might be useful in treating CG; however, its long-term effects and mechanisms of action are unclear. Due to the poor quality of the evidence, more samples and high-quality clinical studies should be tested.

INTRODUCTION

Chronic gastritis (CG) is a set of inflammatory diseases of the gastric mucosa[1] and is one of the common diseases of the digestive system. The disease often relapses, accompanied by symptoms that severely affect the quality of life. Chronic atrophic gastritis is associated with intestinal metaplasia and intraepithelial neoplasia, increasing gastric cancer risk. Globally, on average, more than 50% of people may have CG at any given moment[2]. A pathological study of 8892 patients in China found that atrophic gastritis, intestinal metaplasia, and dysplasia were prevalent, occurring in 25.8%, 23.6%, and 7.3% of the population, respectively[3].

The treatment of CG with gastric mucosal repair consists of antacids, antacids, and gastric mucosal protective agents[4-7]. Nevertheless, the efficacy of triple or quadruple therapy is not ideal, and there are frequent side effects[8]. For these reasons, complementary and alternative medicine therapies such as acupuncture[9-12], moxibustion[13,14], and Chinese herbal formulas[15,16] are sought as alternative therapies.

The Chinese herb formula Shenling Baizhu Powder, also known as Shen-ling-bai-zhu-san (SLBZS), is a widely used prescription for digestive tract disease in China derived from the classic herb monograph "*Taipinghuiminhejijufang*" written in the Song dynasty[17]. Ten commonly used herbs constitute SLBZS; these include Baizhu (*Atractylodes macrocephala* Koidz), Fuling (*Smilax glabra* Roxb), Yiyiren [*Coix lacryma-jobi var*. ma-yuen (Rom.Caill.) Stapf], Renshen (*Panax ginseng* C.A.Mey), Shanyao (*Dioscorea oppositifolia* L), Baibiandou (*Lablab purpureus subsp*. purpureus), Lianzi (*Nelumbo nucifera Gaertn*), Sharen (*Amomum villosum* Lour), Jiegeng (*Platycodon grandiflorus*) and Gancao (*Glycyrrhiza uralensis* Fisch. ex DC). In China, clinical studies suggested that SLBZS treats CG[18,19] with efficacy. Nevertheless, mechanistic studies based on animal experiments are lacking.

Furthermore, a 2012 Clinical practice guideline[20] recommended Shenling Baizhu Powder for the Pattern of Spleen and Stomach Deficiency CG. The pathogenesis can be summarized as the stomach failing to be nourished because of splenic and gastric qi deficiency and disturbance of qi movement. A 2020 clinical guideline did not recommend SLBZS, possibly because of inadequate clinical evidence and pharmacological mechanisms[21]. Efficacy evidence and potential mechanistic studies are required.

Table 1 Search strategy

Number	Search terms
1	Mesh descriptor (Medicine, Traditional) explode all trees
2	(Medicine, Chinese Traditional*): ti,ab,kw
3	Mesh descriptor(Drugs, Chinese Herbal) explode all trees,
4	((Chinese Drugs, Plant*) or (Chinese Herbal Drugs*) or (Herbal Drugs, Chinese*) or (Plant Extracts, Chinese*) or (Chinese Plant Extracts*) or(Extracts, Chinese Plant*)): ti,ab,kw
5	Mesh descriptor (shen-ling-bai-zhu) explode all trees
6	((shen-ling-bai-zhu powder*) or (shen-ling-bai-zhu formula*) or (shen-ling-bai-zhu decoction*) or (shen-ling-bai-zhu decoction*) or (Shen-ling-bai-zhu powder*) or (Shen-ling-bai-zhu formula*) or (Shen-ling-bai-zhu formula*)): ti,ab,kw
7	Or 1-6
8	Mesh descriptor: (Chronic gastritis) explode all trees
9	((Chronic gastritis*) or (Digestive System Diseases*) or (Gastrointestinal Diseases*) or (Gastroenteritis*) or (Gastritis*) or (Chronic, gastritis*)): ti, ab, kw
10	Or 8-9
11	Mesh descriptor: (randomized controlled trials) explode all trees
12	(random*) or (randomly*) or (allocation*) or (random allocation*) or (placebo*) or (double blind*) or (clinical trials*) or (randomized control trial*) or (RCT*) or (controlled clinical trials*): ti, ab, kw
13	Or: 11-12
14	7 and 10 and 13

MATERIALS AND METHODS

Study registration
We registered this review and meta-analysis at the PROSPERO website (https://www.crd.york.ac.uk/PROSPERO/#recordDetails), an international prospective system review registration website. The registration number was CRD42020212979. We conducted the study based on the details of this protocol.

Database search
Our investigators independently searched PubMed, Embase, Medline, Cochrane Library Central Register of Controlled Trials, China National Knowledge Infrastructure database, Wanfang Data Knowledge Service Platform, and the VIP information resource integration service platform from their inception to November 2021. There were no limitations on language or publication status. They also searched conference articles and clinical registries for possible related trials.

Search terms
We adopted a search strategy that combined medical subject headings and free words. Two authors (YS, MFL) searched and screened all citations independently. The search strategy was as follows (Table 1): The search strategy followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement[22].

Inclusion criteria
Randomized controlled trials (RCTs) or quasi-RCTs that reported the effects of SLBZS on CG were included.

Participants: Studies that evaluated patients with a diagnosis of CG were included. For example, we used diagnostic criteria from the standardized consensus on the diagnosis of CG from the Branch of Spleen and Stomach Diseases of the Chinese Society of Traditional Chinese Medicine, China, that depends on endoscopy and pathological examinations[23]. We excluded studies that included CG patients complicated with hypertension, diabetes, heart disease, or severe allergic diseases. There was no restriction on the setting of interest or other population characteristics.

Interventions: SLBZ powder was the primary prescription, regardless of its dosage form, dosage, or course of treatment. If there were other medications, formulas, or traditional Chinese medicine (TCM) therapies (such as acupuncture, moxibustion, and ear-acupressure) in the treatment group, the control groups must also receive these therapies.

Comparisons: Western medicine, active control, and placebo were acceptable. If SLBZ + western medicine was applied in the experimental group, western medicine in the control group must be consistent.

Outcome measures: We considered efficacy outcomes as primary outcome measures, including effectiveness, recurrence rate, symptom score, *Helicobacter pylori* (*H. pylori*) eradication, and quality-of-life assessment. Secondary outcome measures were adverse events directly related to CG.

Exclusion criteria

The exclusion criteria were as follows: (1) The study was not an RCT, *e.g.*, retrospective study, cross-sectional study, observational study, case study, animal study, or others; (2) for multiple reports or repeated publications from the same study, we retained the one with a more significant number of details; (3) diagnostic criteria were not reported in trials, disease not CG; and (4) studies or trials used SLBZS as a part of complex interventions; for example, SLBZS decoction plus another herbal medicine formula *vs* acupuncture therapies. Western medicine is inconsistent in two groups.

Study selection and data extraction

According to our study registration protocol, two reviewers (WJ, QJL) independently performed trial searches, study selection, and raw data extraction. A third reviewer (JZ) checked the extracted data. We resolved conflicts through consensus.

Risk of bias assessment

According to the Cochrane Handbook details[24], we performed the risk of bias assessment analysis using the Cochrane collaborative bias risk tool in Review Manager 5.3 software. We resolved conflicts by consultation with a third investigator (WWH).

Statistical analysis

We used Review Manager 5.3 and Stata 14.0 software for statistical analysis. We calculated 95% confidence interval (CI) and mean difference for continuous variables and 95%CI and risk ratio (RR) for dichotomous variables. Differences with $P < 0.05$ were statistically significant. We determined the heterogeneity of data using Cochrane χ^2 and I^2 tests. We used a fixed-effect model if there was no significant heterogeneity; otherwise, we used a random-effect model. We conducted subgroup analyses to explore the source of heterogeneity. We determined publication bias by examining funnel plots and Egger's tests for more than ten trials. We used sensitivity analysis to explore the stability of the results. GRADE profiler 3.6 software was applied to evaluate the quality of evidence.

Mechanisms of network pharmacology of SLBZD to treat CG

Collection and screening of pharmacodynamic components in TCM System Pharmacology Database and analysis platform (TCMSP, HTTP://ibts.hkbu.edu.hk/LSP/tcmsp.php) in ginseng, atractylodes, poria cocos, yam, white hyacinth bean, lotus seed, coix seed, amomum fruit, radix platycodi, radix glycyrrhizae as keyword query filter chemical composition. The database contains about 500 drugs listed in the Chinese Pharmacopoeia, providing absorption, distribution, metabolism and excretion, ingredient data, and target and disease information. Oral bioavailability (OB) and drug-like properties (DL) are essential indexes determining whether a compound can be developed into a drug. Based on the relevant literature, OB and DL were set to > 30% and > 0.18, respectively, and the screened compounds were used as candidate ingredients[25,26].

Target prediction of pharmacodynamic components, the simplified molecular Linear Input specification (Simles) number, and Mol structure of each candidate component were retrieved using PubChem. We arranged candidate target genes using PharmMapper online (http://Lilab-ecust.cn/pharmmapper/index.html) and Swiss target prediction (HTTP://www.swisstargetprediction.ch/), and we arranged the standbys in an Excel form.

Prediction of disease Targets Genes associated with CG was identified by searching for "Chronic Gastritis" in GeneCards (http://www.genecards.org/).

Network construction and analysis

SLBZ Powder's candidate components and target genes were screened and imported into Cytoscape 3.7.2 software using Excel to obtain a component-target network diagram. The predicted disease candidate targets were imported into the online protein interaction (String) database, the species organism was set as human (*Homo sapiens*), and the PPI map was obtained. The PPI map was imported into Cytoscape 3.7.2 software. The potential targets of Shenlingbaizhu Powder in chronic gastritis can be obtained by merging the component-target network diagram and disease target PPI diagram using Merge software, which can be imported into the online String database the interaction map of potential targets.

Functional mechanism analysis of potential targets GO enrichment analysis, and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment annotation analysis of potential target genes were performed using the R package clusterProfiler.

Table 2 Excluded 11 studies after reading the full text	
Reason	Ref. (*n* = 11)
Intervention combined with other decoction (*n* = 3)	**Li GS**. Observation on the curative effect of Shenling Baizhu Powder and Taohong Siwu Decoction in treating chronic gastritis. *Zhongyi Linchuang Zazhi* 2007; **19** (10): 260-261
	Yang Y. Shenlingbaizhu san and zhaqupingwei powder combined with western medicine in the treatment of chronic gastritis randomized parraler controlled study. *Shiyong Zhongyi Neike Zazhi* 2013; **27** (10): 40-41
	Yang SX. Clinical study on the treatment of Chronic functional diarrhea with Shenling Baizhu Powder and Lizhong Decoction. *Yatai Chuantong Yixue* 2017; **30** (13): 145-146
Intervention combined with other decoction, no diagnostic criteria (*n* = 2)	**Jin JZ**. Shenling Baizhu Powder and Zuojin pill to treat chronic gastritis. *Shiyong Zhongyi Neike Zazhi* 2011; **27** (11): 752
	Gao CZ, Yang SM. Observation on curative effect of cefaclor combined with Shenlingbaizhu granule and Muxiang Shunqi pill in treating chronic gastritis. *Zhonghua Yixue Chuangxin Zazhi* 2012; **9** (22): 127-128
No diagnostic criteria (*n* = 1)	**Shi ZR**. Clinical observation on 8 cases of chronic gastritis treated by Shenling Baizhu Powder. *Neimenggu Zhongyi Zazhi* 2014 [DOI :10.16040/j.cnki.cn15 -1101.2014.07.024]
Not CG(*n* = 1)	**Zhang WW**. Clinical observation on 96 cases of spleen deficiency and stomachache treated with Shenling Baizhu Powder. *Zhongguo Minzuyixue Yu Minzuyaoxue* 2013; **9** (12): 80
Intervention combined with acupuncture (*n* = 3)	**Yang FX**. Acupuncture combined with Shenling Baizhu Powder to treat chronic gastritis with spleen deficiency and dampness. *Kouqiang Yixue Dianzi Zazhi* 2015; **6** (13): 140-143.
	Wu XR. 30 cases of chronic gastritis with spleen deficiency and dampness treated by acupuncture combined with Shenling Baizhu Powder. *Guangming Zhongyi* 2015; **30** (5): 1018-1020
	Wu CY. Analysis of curative effect of acupuncture combined with Shenling Baizhu Powder on chronic gastritis with spleen deficiency and dampness. *Jixu Yixue Jiaoyu Zazhi* 2019; **33** (10): 161-162
Intervention combined with other decoction, WM are inconsistent in two groups (*n* = 1)	**Yan Z**. Clinical study of cefaclor combined with Shenling Baizhu granule and Muxiang Shunqi pill in treating chronic gastritis. *Yatai Chuantong Yixue* 2015; **11** (18): 106-107

RESULTS

Database search results

We retrieved 335 trials from 6 databases. When duplicate records were deleted, 177 remained. We excluded 152 studies by reading the title and abstract of the papers, including seven repeatedly published studies, ninety-five reports on the SLBZS experience of experienced TCM doctors, four retrospective studies, seventeen observation studies, one case report, and twenty-eight studies of diseases that were not CG. We read the full texts of the remaining 25 records. We deleted 11 records because of exclusion criteria (Table 2).

Finally, we included 14 studies in our review (flowchart of database search and study identification is shown in Figure 1).

Study characteristics

There were 14 Chinese-language RCTs, comprising 1335 participants aged 15-68 years[27-40], published between 2008 and 2020. Interventions in these studies were SLBZS *vs* conventional medicine or SLBZS + conventional medicine *vs* conventional medicine. In conventional medicine therapy, there were four methods, including monotherapy in four trials[27,33,34,37], combined therapy in one study[36], triple therapy in seven studies[28,31,32,35,38-40] and two trials of quadruple therapy[29,30]. There were various treatment durations, including 4, 5, 8, and 12 wk.

Total effectiveness was the primary outcome measure in all trials. All trials reported balanced baseline characteristics. Five trials (36%) recorded adverse events[29,31,34,36,38], and three studies reported recurrence rates[34,38,40]. Two studies reported participant withdrawal information[31,34]. No study reported influence on the quality of life as an outcome measure. Characteristics of included studies are shown in Table 3.

Risk of bias assessment

(1) Fourteen trials were consistent at baseline, and all tests referred to RCTs, three studies[28,39,40] mentioned randomization using the "random number table" method; (2) all studies not reported "distribution hidden" method; (3) the "blinding method" was not reported in any study, two studies[31,34] reported "No cases withdrawal and dropped-out," and three studies[34,38,40] reported "recurrence rate"; (4) selective reporting may come out in studies that there were too few indicators were noted; and (5) we considered some support from pharmaceutical companies that the ethics committee would not approve as other bias. If herbs were offered free by pharmaceutical companies, bias might taint the results. Two studies[34,36] reported that an ethics committee approved the study, suggesting a low bias level. For another 12 studies, we could not determine the effects of other potential sources of bias

Table 3 Characteristics of included studies

Ref.	Study design	Sample size (E/C)	Gender (E/C) and age (yr)	Duration	Interventions		Period	Outcome measure	Balance report of baseline
					Control group	Experimental group			
Yun[27], 2014	RCT	48 (24/24)	(13/11) (10/14); (34.96 ± 11.39)/(34.08 ± 12.82)	Not mentioned	Rabeprazole enteric-coated capsule	Rabeprazole enteric-coated capsule + SLBZD	4 wk	Effective rate	P > 0.05
Chen et al[28], 2014	RCT	79 (40/39)	(24/16) (23/16); (42.6 ± 13.1)/43.5 ± 13.4	6-17 mo/6-19 mo	Triple therapy (clarithromycin sustained-release tablets + rabeprazole sodium capsule + metronidazole tablets)	Triple therapy + SLBZD	4 wk	Effective rate	P > 0.05
Chen et al[29], 2018	RCT	60 (30/30)	(14/16) (15/15); (55.45 ± 6.55)/(55.46 ± 6.44)	3-12 mo	Quadruple therapy (rabeprazole sodium capsule + amoxicillin + clarithromycin sustained-release tablets + biskal-citrate)	Quadruple therapy + SLBZD	8 wk	Effective rate; H. Pylori eradication; adverse event	P > 0.05
Du[30], 2017	RCT	48 (26/22)	(14/12) (12/10); (40.7 ± 6.1)/(41.2 ± 6.6)	7 mo-9 years/6 mo-8 years	Quadruple therapy (amoxicillin clavulanic potassium chewable tablets + metronidazole + omeprazole + compound bismuth aluminate capsule)	SLBZD	5 wk	Effective rate	P > 0.05
Gu[31], 2017	RCT	98 (49/49)	Not mentioned; 19-58	Not mentioned	Triple therapy (omeprazole + clarithromycin + amoxicillin)	Triple therapy + SLBZD	4 wk	Effective rate; H. Pylori eradication rate; adverse event	P > 0.05
Li et al [32], 2020	RCT	66 (33/33)	(19/14) (18/15); (58.54 ± 4.65)/(58.62 ± 4.57)	4-17 years/4-18 years	Triple therapy (mosapride tablet + polyzyme tablets + lansoprazole tablets)	Triple therapy + SLBZD	12 wk	Effective rate	P > 0.05
Tang [33], 2014	RCT	60 (30/30)	(16/14) (17/13); (22-46)/(23-52)	Not mentioned	Omeprazole enteric-coated capsules	Omeprazole Enteric-coated Capsules + SLBZD	8 wk	Effective rate	P > 0.05
Xia[34], 2015	RCT	300 (150/150)	Not mentioned; 18-85	Not mentioned	Omeprazole enteric-coated capsules	SLBZD	8 wk	Effective rate; recurrence rate; adverse event	P > 0.05
Xu et al [35], 2018	RCT	60 (30/30)	(17/13) (16/14); (55.6 ± 16.4)/(56.8 ± 14.9)	4-20 years/4-19 years	Triple therapy (mosapride tablet + polyzyme tablets + lansoprazole tablets)	Triple therapy+SLBZD	12 wk	Effective rate	P > 0.05
Zhang et al[36], 2020	RCT	68 (34/34)	(15/19) (17/17); (44.8 ± 5.0)/(45.2 ± 5.4)	1-12 years/2-14 years	Combination therapy (omeprazole + compound bismuth aluminate granules)	Combination therapy + SLBZD	8 wk	Effective rate; adverse events	P > 0.05
Zhao and Lin [37], 2010	RCT	80 (40/40)	(37/3) (38/2); (46.2 ± 6.7)/(44.2 ± 5.7)	2-7 years/2-8 years	No alcohol, famotidine	No alcohol, famotidine + SLBZD	4 wk	Effective rate;	P > 0.05
Zheng [38], 2014	RCT	92 (46/46)	(28/18) (30/16); (34 ± 5.34)/(33 ± 5.76)	5 mo-6 years/7 mo-6 years	Triple therapy (amoxicillin dispersion tablet + omeprazole enteric-coated capsules + clarithromycin tablet)	SLBZD	4 wk	Effective rate; adverse events; recurrence rate	P > 0.05
Zhuang et al[39], 2019	RCT	106 (53/53)	(65/41); (46.20 ± 8.75)	1-11 years	Triple therapy (omeprazole enteric-coated tablets + clarithromycin dispersible tablets+amoxil capsule)	Triple therapy + SLBZD	4 wk	Effective rate; H. Pylori's negative conversion rate	P > 0.05
Zou[40], 2015	RCT	170 (85/85)	(86/84); (40.9 ± 11.1)	Not mentioned	Triple therapy (amoxicillin + clarithromycin + omeprazole)	Triple therapy + SLBZD	8 wk	Effective rate; H. Pylori's negative	P > 0.05

	conversion rate; recurrence rate

RCT: Randomized controlled trial; *H. Pylori*: *Helicobacter pylori*; SLBZS: Shen-ling-bai-zhu san.
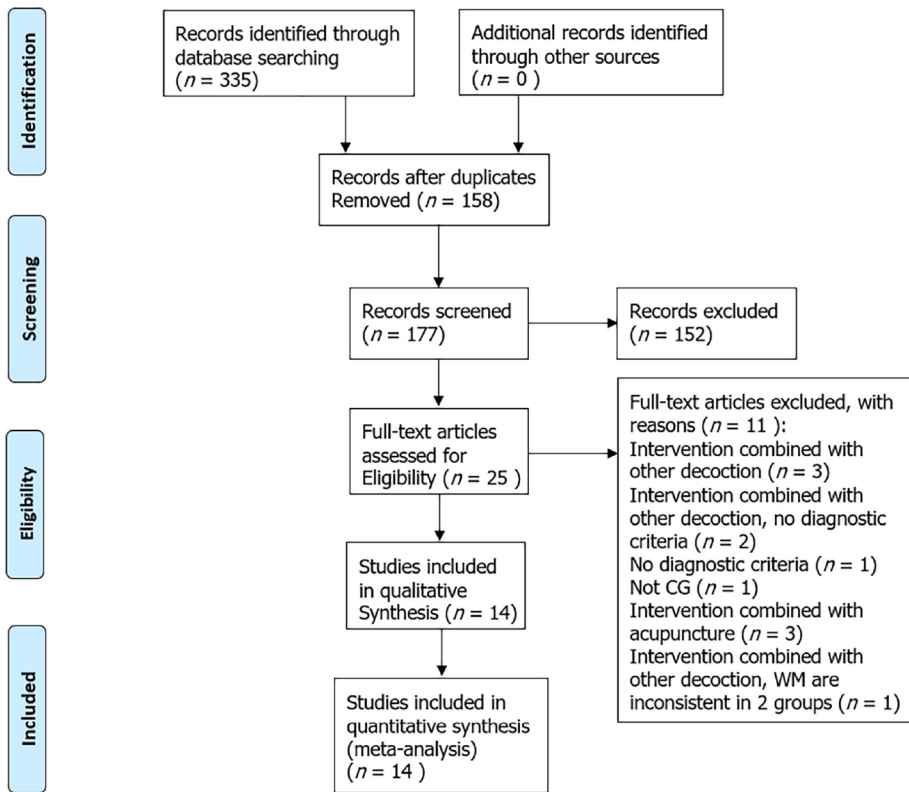
DOI: 10.3748/wjg.v28.i33.4890 **Copyright** ©The Author(s) 2022.

Figure 1 Flowchart of database searching and study identification.

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Figure 2 Risk of bias summary.

because there were no reports of herbs' sources. Details are displayed in Table 4. The included studies were therefore classified as low quality (Figure 2).

Evaluation of outcome measures

Total effectiveness: Total effectiveness is a composite endpoint composed of improved symptoms and

Table 4 Methodological quality details of all included studies

Ref.	Baseline	Randomization	Allocation concealment	Blind method	Withdrawal or dropped-out	Follow up	Protocol and registration	Ethics committee approved
Yun[27], 2014	Comparability	Random	NR	NR	NR	NR	NR	NR
Chen *et al* [28], 2014	Comparability	Random number table	NR	NR	NR	NR	NR	NR
Chen *et al* [29], 2018	Comparability	Random	NR	NR	NR	NR	NR	NR
Du[30], 2017	Comparability	Random	NR	NR	NR	NR	NR	NR
Gu[31], 2017	Comparability	Random	NR	NR	No cases withdrawal and dropped-out	NR	NR	Approved
Li *et al*[32], 2020	Comparability	Random	NR	NR	NR	NR	NR	Approved
Tang[33], 2014	Comparability	Random	NR	NR	NR	NR	NR	NR
Xia[34], 2015	Comparability	Random	NR	NR	No cases withdrawal and dropped-out	Recurrence rate	NR	Approved
Xu *et al* [35], 2018	Comparability	Random	NR	NR	NR	NR	NR	NR
Zhang *et al* [36], 2020	Comparability	Random	NR	NR	NR	NR	NR	NR
Zhao and Lin[37], 2010	Comparability	Random	NR	NR	NR	NR	NR	NR
Zheng[38], 2014	Comparability	Random	NR	NR	NR	Recurrence rate	NR	NR
Zhuang *et al*[39], 2019	Comparability	Random number table	NR	NR	NR	NR	NR	NR
Zou[40], 2015	Comparability	Random number table	NR	NR	NR	Recurrence rate	NR	NR

NR: Not Reported.

gastroscopy. The results fall into three categories: Obviously effective, effective, and invalid, according to clinical Research on New Chinese Medicines[41]. The details are as follows. Clinical cure: Epigastric pain and symptoms disappeared, gastroscopy returned to normal, *i.e.*, gastric mucosa repair, the disappearance of active inflammation, and mild chronic inflammation; Obviously effective: Epigastric pain and symptoms disappear or diminish. Gastroscopy showed significant improvement; that is, gastric mucosa was nearly normal, active inflammation was gone, and there was less chronic inflammation; Effective: Relief of epigastric pain and other symptoms. Gastroscopy showed reduced gastric mucosal lesions; that is, gastric mucosa was essentially normal, active inflammation was gone, and less chronic inflammation; and Invalid: no improvement or aggravation of clinical symptoms and signs. Gastroscopy showed no change. There were slight differences in this outcome's composition in various studies due to the non-uniform efficacy assessment criteria. All 14 RCTs compared the total effectiveness rate of SLBZS in patients with CG. SLBZS was superior to conventional therapies (RR: 1.29, 95%CI: 1.22 to 1.37, $P < 0.00001$) (Figure 3A). Heterogeneity in the total effectiveness was very small ($P = 0.91$, $I^2 = 0\%$).

We created subgroups based on the duration of treatment (4, 5, 8, or 12 wk) (Supplementary Table 1), comparison type (SLBZS *vs* conventional medicine or SLBZS + conventional medicine *vs* conventional medicine alone) (Supplementary Table 2), and intervention method (monotherapy, combined therapy, triple therapy, or quadruple therapy) (Supplementary Table 3). These subgroup analyses showed that the effectiveness rate of SLBZS did not differ based on the duration of treatment, combination with other medications, or intervention method (all $P > 0.05$) (Table 5).

Table 5 Subgroup analysis of total effectiveness

Subgroup method (total effective rate)	Items	Number of comparisons	Results (risk ratio, 95%CI)	P value for overall effect	I²	P value for subgroup difference
Course of treatment	All comparisons	14	1.29 (1.22,1.37)	< 0.00001	0%	
Supplementary Table 1	4 wk	5	1.27 (1.17,1.37)	< 0.00001	0%	
	5 wk	1	1.45 (1.04, 2.03)	0.03	NA	0.58
	8 wk	5	1.28 (1.16, 1.40)	0.02	0%	
	12 wk	2	1.44 (1.19, 1.74)	0.0002	0%	
Comparison type	All comparisons	14	1.23 (1.14, 1.32)	< 0.00001	47%	
Supplementary Table 2	SLBZS *vs* CM	3	1.23 (1.10, 1.38)	0.0003	0%	0.93
	SLBZS + CM *vs* CM	11	1.23 (1.11, 1.35)	< 0.0001	57%	
Intervention method	All comparisons	14	1.29 (1.22, 1.37)	< 0.0001	0%	
Supplementary Table 3	Monotherapy	4	1.25 (1.12, 1.40)	< 0.0001	5%	
	Combined therapy	1	1.41 (1.08, 1.84)	0.01	NA	0.82
	Triple therapy	7	1.30 (1.21,1.40)	< 0.0001	0%	
	Quadruple therapy	2	1.35 (1.11, 1.64)	0.003	0%	

NA: Not available; CM: Conventional medicine; SLBZS: Shen-ling-bai-zhu san.

Table 6 Adverse events

Study	Experiment group	Control group
Zhang, 2020	Diarrhea (2/34)	Dizziness (2/34) and dry mouth (1/34)
Chen, 2018	Headache (1/30), diarrhea (1/30), nausea (1/30)	Headache (2/30), diarrhea (1/30), nausea (2/30), constipation (1/30), rash (1/30)
Zheng, 2014	None	Headache and rash (17.39%)

Recurrence rate: Three studies reported recurrence rate[34,38,40]. Pooled raw data showed that SLBZS was better than conventional therapies (RR: 0.24, 95%CI: 0.11 to 0.55, *P* = 0.0007, Figure 3B).

HP negative conversion rate: Four trials noted the reversal rate for *Helicobacter pylori* (*H. pylori*) positivity[29,31,39,40]. Meta-analysis showed that SLBZS was superior to conventional therapies (RR: 1.20, 95%CI: 1.11 to 1.30, *P* < 0.00001, Figure 3C).

Other results

One trial compared the time required for symptom improvement in patients with CG[38]. The experimental group was superior to the control group regarding effects on epigastric stagnation, abdominal distension, belching, acid regurgitation, and nausea (*P* < 0.05).

There were no reports of significant responses or improvement in the quality-of-life data in these studies. One study reported the Questionnaire for Comprehensive Quality of Life Assessment responses pre- and post-treatment in two groups[36]. After two consecutive months of treatment, scores in all dimensions improved, and the treatment group's score was significantly higher than that of the treatment group (*P* < 0.05).

Publication bias

Funnel plots showed the publication bias of the effectiveness rate (Figure 4A). The funnel plot of the effective rate was symmetric, suggesting no significant publication bias. Egger's test results agreed with the funnel plots (*P* = 0.005 and 0.000, respectively).

Adverse events

Of the 14 studies, nine RCTs did not mention adverse events[27,28,30,32,33,35,36,39,40]. Two studies

Table 7 GRADE evidence for the effect of Shen-ling-bai-zhu san

No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	RQLQ	Control	Relative (95%CI)	Absolute	Quality	Importance
Quality assessment							**Summary of findings**					**Importance**
							No of patients		**Effect**		**Quality**	
Effective rate												
14	Randomized trials	Serious[1]	Serious[2]	Serious[3]	No serious imprecision[4]	None	595/670 (88.8%)	459/665 (69%)	RR 1.45 (1.22 to 1.37)	200 more per 1000 (from 152 more to 255 fewer)	Very low	Critical
								0.676		196 more per 1000 (from 149 fewer to 250 more)		
Recurrence rate												
3	Randomized trials	Serious[1]	Serious[2]	Serious[3]	No serious imprecision[4]	None	7/281 (2.5%)	31/281 (11%)	RR 0.24 (0.11 to 0.55)	84 fewer per 1000 (from 50 fewer to 98 fewer)	Very low	Important
								0.177		135 fewer per 1000 (from 58 fewer to 158 fewer)		
HP negative conversion rate												
4	Randomized trials	No serious limitations[1]	Very serious[2]	No serious indirections[3]	No serious imprecision[4]	None	207/217 (95.4%)	170/270 (78.3%)	RR 1.2 (1.11 to 1.3)	157 more per 1000 (from 86 more to 135 more)	Moderate	Important
								0.815		163 more per 1000 (from 90 more to 244 more)		

[1]Randomized controlled trial design method is not reported.

[2]The risk of bias assessment is mostly "unclear risk" because there are not enough details in articles.

[3]Studies come from China.

[4]There is significant heterogeneity between studies.

mentioned no prominent adverse events[34,29]. Three trials reported adverse events (Table 6); however, no study commented on methods used to manage these events.
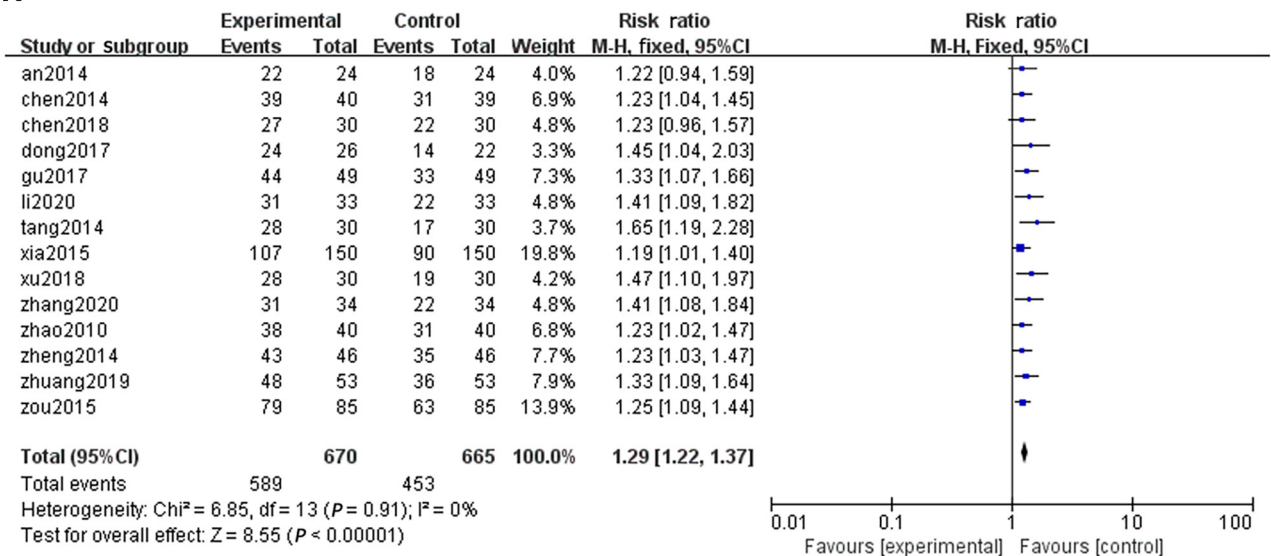
GRADE evidence for the effect of SLBZD

GRADE results of SLBZD is shown in (Table 7). However, the quality of evidence was very low or moderate because of the poor methodological quality.
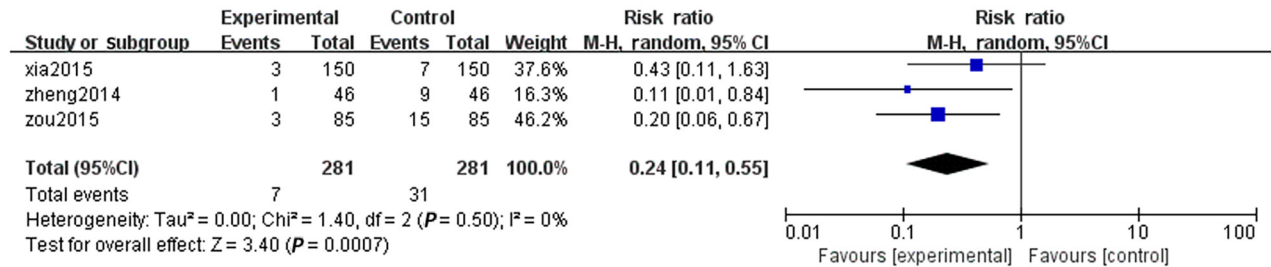
Network pharmacology results of SLBZS

Composition and targets of SCBZS: According to the OB > 30% and DL > 0.18 standard screening, we screened 189 ingredients, including seven in Baizhu (*Atractylodes macrocephala* Koidz), 15 in Fuling (Smilax glabra Roxb), 9 in Yiyiren [*Coix lacryma-jobi var.* ma-yuen (Rom.Caill.) Stapf], 22 in Renshen (*Panax ginseng* C.A.Mey), 15 in Shanyao (*Dioscorea oppositifolia* L), one in Baibiandou (*Lablab purpureus* subsp. purpureus), 11 in Lianzi (*Nelumbo nucifera* Gaertn.), 92 in Gancao (*Glycyrrhiza uralensis* Fisch. ex
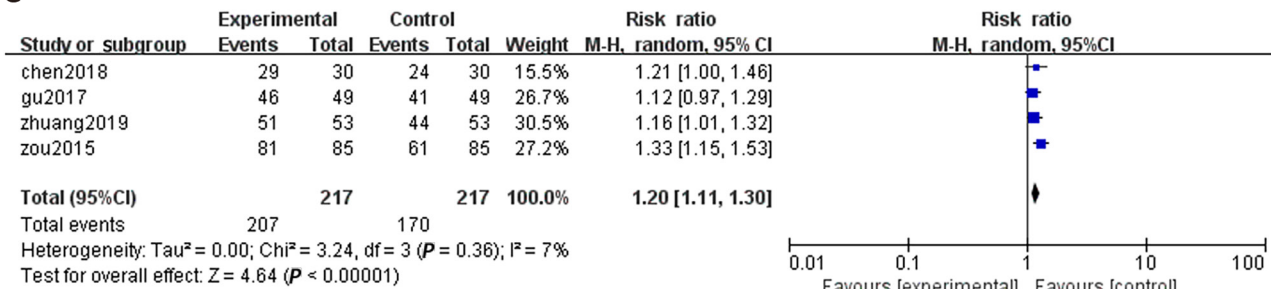
A

| Study or subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk ratio M-H, fixed, 95%CI
an2014	22	24	18	24	4.0%	1.22 [0.94, 1.59]
chen2014	39	40	31	39	6.9%	1.23 [1.04, 1.45]
chen2018	27	30	22	30	4.8%	1.23 [0.96, 1.57]
dong2017	24	26	14	22	3.3%	1.45 [1.04, 2.03]
gu2017	44	49	33	49	7.3%	1.33 [1.07, 1.66]
li2020	31	33	22	33	4.8%	1.41 [1.09, 1.82]
tang2014	28	30	17	30	3.7%	1.65 [1.19, 2.28]
xia2015	107	150	90	150	19.8%	1.19 [1.01, 1.40]
xu2018	28	30	19	30	4.2%	1.47 [1.10, 1.97]
zhang2020	31	34	22	34	4.8%	1.41 [1.08, 1.84]
zhao2010	38	40	31	40	6.8%	1.23 [1.02, 1.47]
zheng2014	43	46	35	46	7.7%	1.23 [1.03, 1.47]
zhuang2019	48	53	36	53	7.9%	1.33 [1.09, 1.64]
zou2015	79	85	63	85	13.9%	1.25 [1.09, 1.44]
Total (95%CI)		670		665	100.0%	1.29 [1.22, 1.37]
Total events	589		453			

Heterogeneity: Chi² = 6.85, df = 13 (*P* = 0.91); I² = 0%
Test for overall effect: Z = 8.55 (*P* < 0.00001)

B

Study or subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk ratio M-H, random, 95%CI
xia2015	3	150	7	150	37.6%	0.43 [0.11, 1.63]
zheng2014	1	46	9	46	16.3%	0.11 [0.01, 0.84]
zou2015	3	85	15	85	46.2%	0.20 [0.06, 0.67]
Total (95%CI)		281		281	100.0%	0.24 [0.11, 0.55]
Total events	7		31			

Heterogeneity: Tau² = 0.00; Chi² = 1.40, df = 2 (*P* = 0.50); I² = 0%
Test for overall effect: Z = 3.40 (*P* = 0.0007)

C

Study or subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk ratio M-H, random, 95%CI
chen2018	29	30	24	30	15.5%	1.21 [1.00, 1.46]
gu2017	46	49	41	49	26.7%	1.12 [0.97, 1.29]
zhuang2019	51	53	44	53	30.5%	1.16 [1.01, 1.32]
zou2015	81	85	61	85	27.2%	1.33 [1.15, 1.53]
Total (95%CI)		217		217	100.0%	1.20 [1.11, 1.30]
Total events	207		170			

Heterogeneity: Tau² = 0.00; Chi² = 3.24, df = 3 (*P* = 0.36); I² = 7%
Test for overall effect: Z = 4.64 (*P* < 0.00001)

Figure 3 Forest plot. A: Forest plot for total effectiveness; B: Forest plot for recurrence rate; C: Forest plot for the reversal rate of Helicobacter pylori positivity. 95%CI: 95% confidence interval.

DC), ten in Sharen (*Amomum villosum* Lour.), and seven in Jiegeng (*Platycodon grandiflorus*). The repeated components and components with no target were deleted, leaving 158 candidate components. Each candidate component's top 15 target genes were selected, and duplicated genes were identified, with 693 candidate target genes.

PPI network: The component-target network diagram of Shen-ling-bai-zhu Powder visually shows the interaction between pharmacodynamic components and target genes of Shen-ling-bai-zhu Powder (Figure 4B). The network contains 851 nodes with 2445 sides, among which 158 nodes represent candidate ingredients and 693 nodes represent candidate target genes related to drug candidate ingredients. The average number of neighborhood nodes was 5.561. There were 300 nodes and 3325 edges in the disease target interaction network, and the average number of neighborhood nodes in the network was 34.635. A total of 35 potential targets of SLBZS on chronic gastritis can be obtained by analyzing the component-target and disease target interaction networks. Figure 4C visually shows the interaction relationship between potential targets.

GO enrichment analysis and KEGG pathway enrichment analysis: The results of GO analysis showed that in the BP category, differentially expressed genes were concentrated in the regulation of reactive oxygen species metabolic process, response to oxidative stress, cellular response to chemical stress, and

B
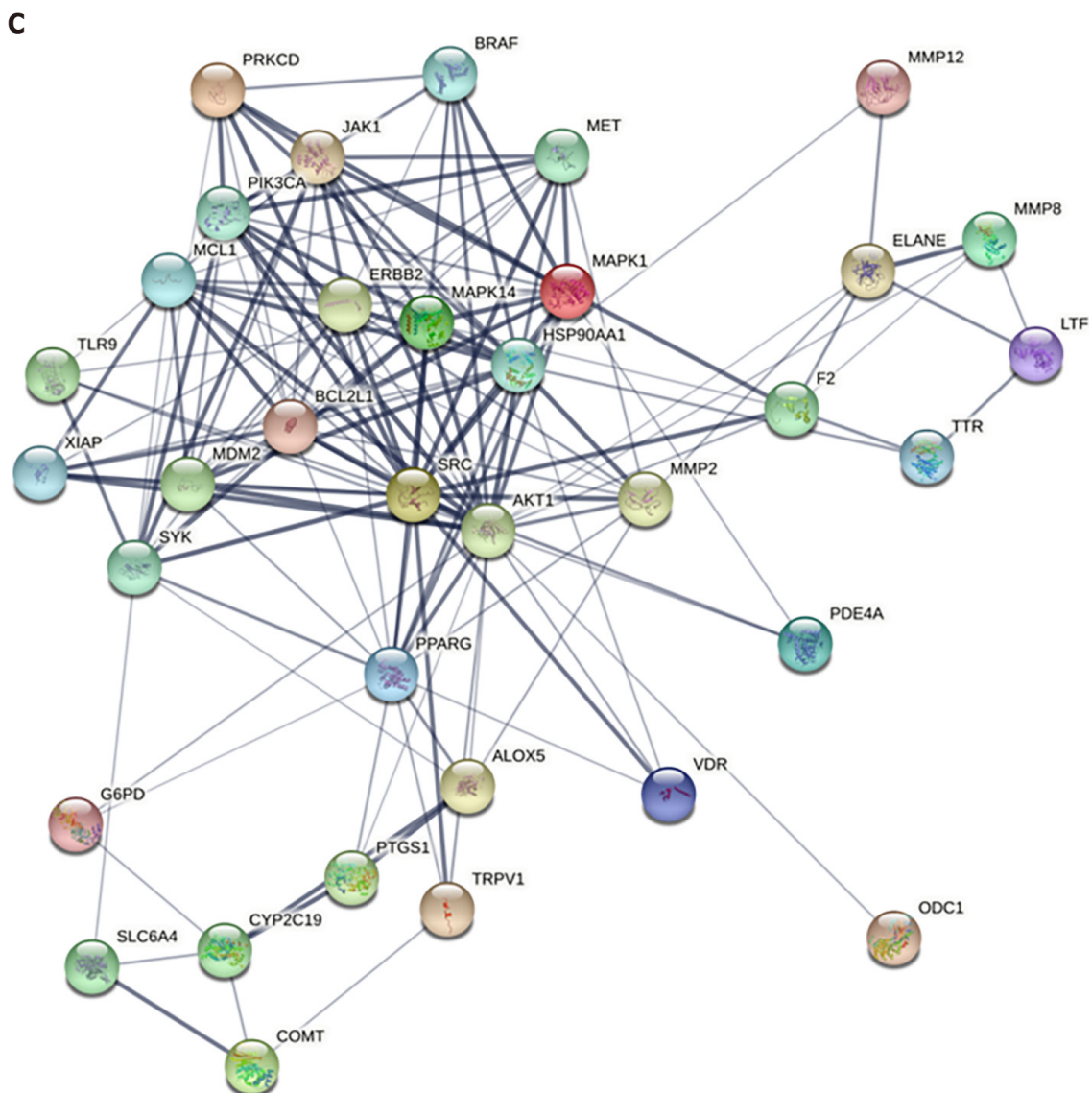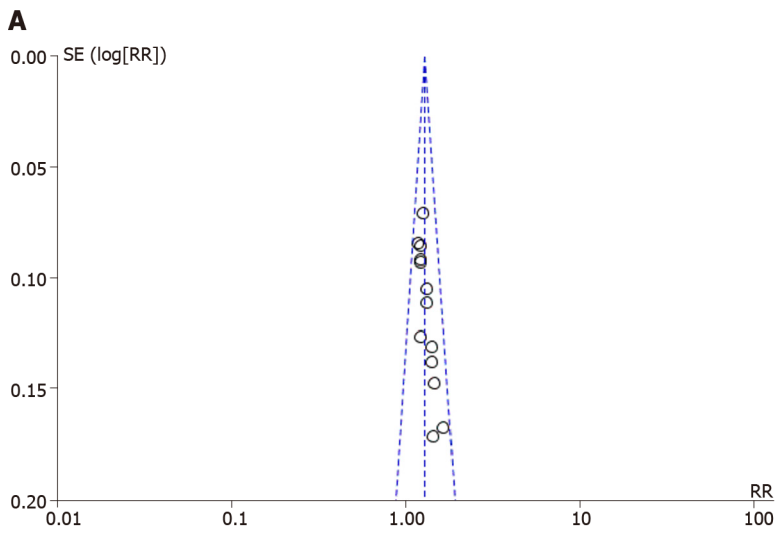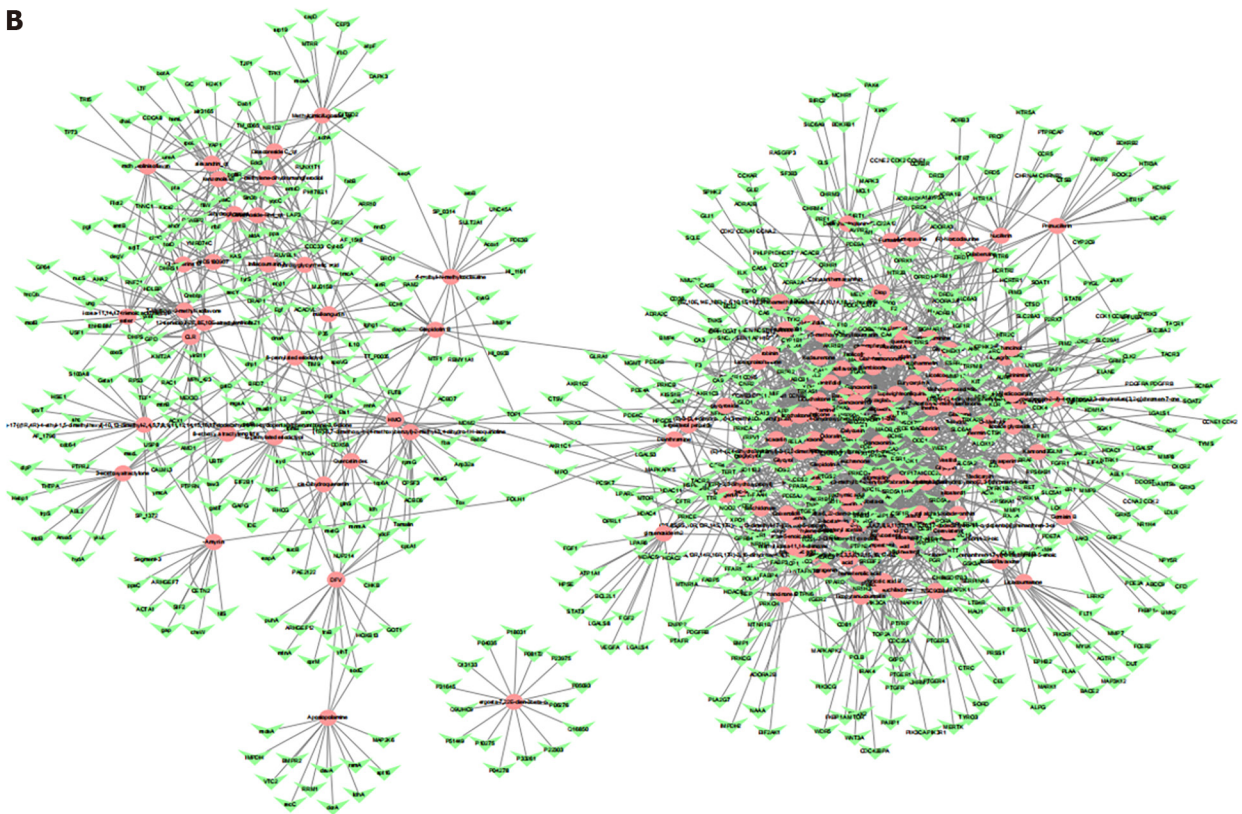
Figure 4 Funnel plot and network. A: Funnel plot of total effectiveness rate; B: Network plot of the active compounds of Shen-ling-bai-zhu san (SLBZS) target and chronic gastritis (CG) target; C: SLBZS-CG target protein interaction network.

others. Differentially expressed genes are enriched in vesicle lumen, cytoplasmic vesicle lumen, and secretory granule lumen in the CC category. Differentially expressed genes are enriched in tyrosine kinase activity, protein serine/threonine kinase activity, and phosphatase binding (Figure 5A). KEGG pathway analysis results showed that the differentially expressed genes involved EGFR tyrosine kinase inhibitor resistance and the PI3K-Akt signaling pathway (Figure 5B, Figure 6).

DISCUSSION

Effectiveness and safety of a formula used for CG treatment were evaluated by us. We also summarized the possible pharmacological mechanisms based on collecting as many medical records as possible. Before our study, at least two systematic reviews[42,43] focused on the efficacy of Chinese herbal medicine formulas as CG treatments. However, neither of these reviews included SLBZS as an experimental intervention, and there are no animal studies of SLBZS for CG.

Analysis of the 14 RCTs suggested that SLBZS reverses *H. pylori* seropositivity and recurrence rates in patients with CG more so than in western medicine. SLBZS formula treats CG based on the current evidence. There were insignificant heterogeneity and publication bias. The safety is not yet established. The study designs were not rigorous, and the GRADE assessment presented moderate and low quality. Therefore, large numbers of rigorously designed RCTs are required to obtain conclusive evidence for the effect and safety of SLBZS for CG.

CG is a common digestive system disorder characterized by an inflammatory condition of the gastric mucosa. CG also leads to mental and psychological disorders like interpersonal sensitivity and depression[44]. On the one hand, studies demonstrated that the link between gut flora and depression is strong[45-47], and gut peptides are essential regulators of microbiota-gut-brain signaling in health and stress-related psychiatric illnesses[45]. On the other hand, intestinal flora can be transformed by TCM compounds[48]. Chinese medicine can regulate the composition and metabolism of intestinal flora and regulate intestinal flora by affecting the secretion of brain-gut peptide and monoamine neurotransmitters, thus improving depression behavior[47-49]. Hence, the anti-inflammatory effect of regulating gut microbiota could represent a complementary and alternative direction for CG with depression symptoms.
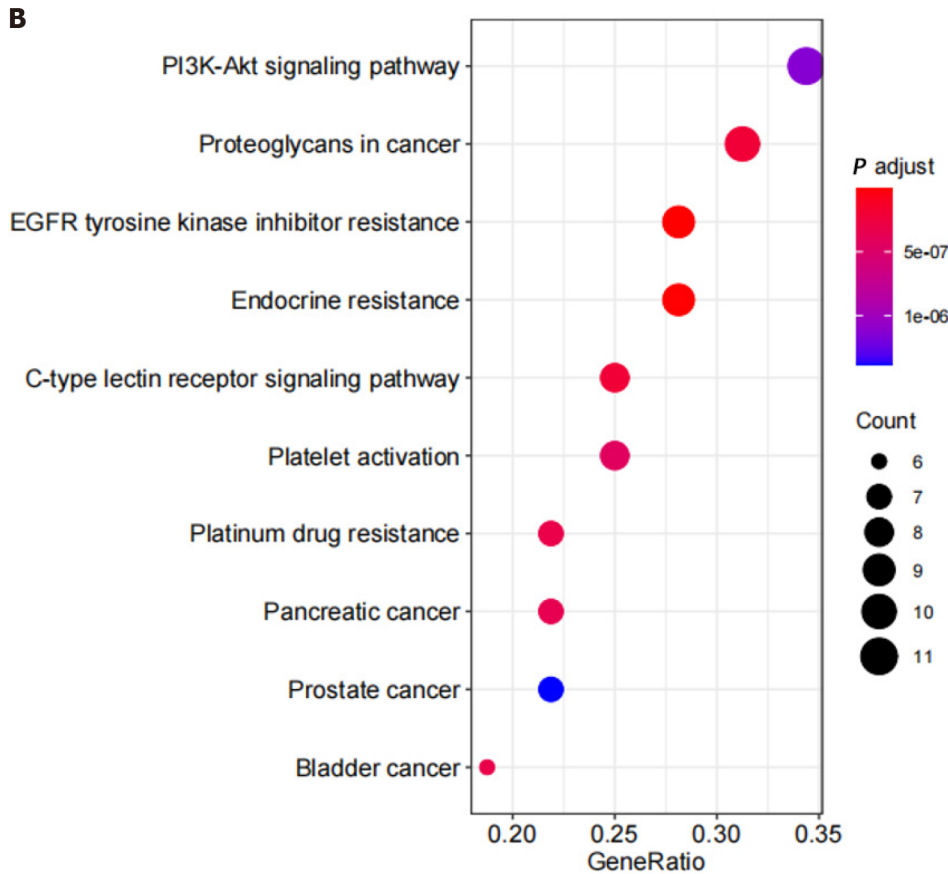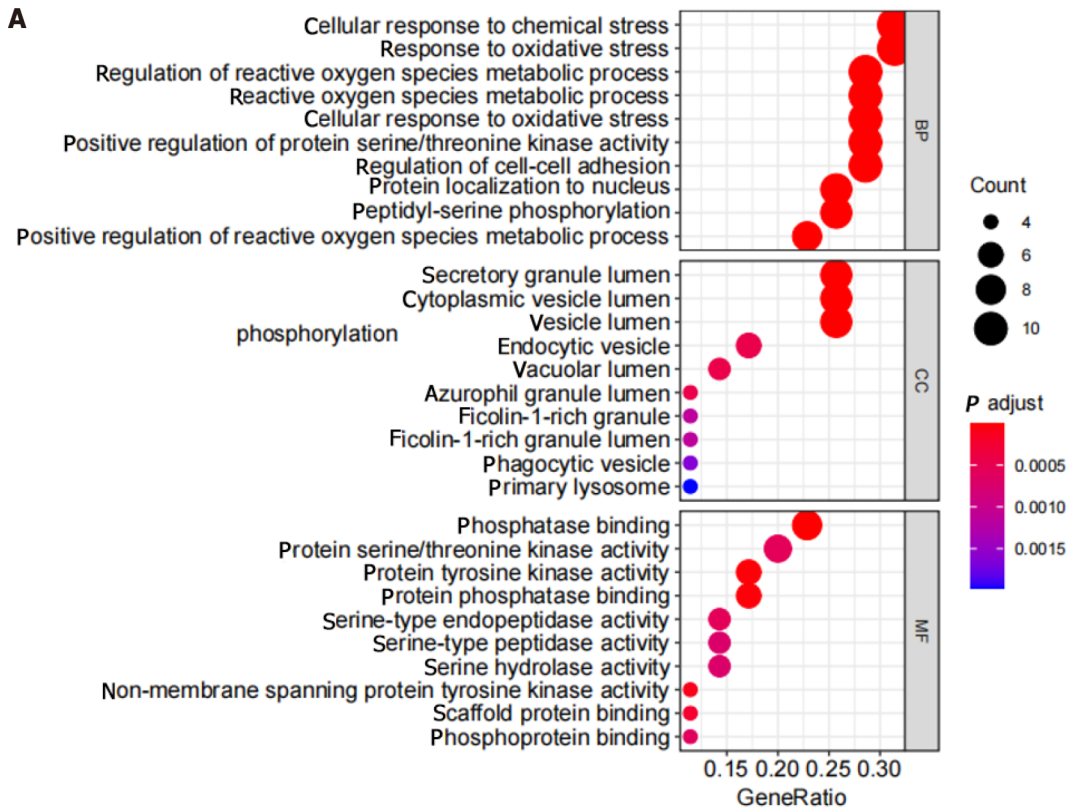
DOI: 10.3748/wjg.v28.i33.4890 **Copyright** ©The Author(s) 2022.

Figure 5 GO analysis and Kyoto Encyclopedia of Genes and Genomes enrichment analysis. A: GO analysis of the critical targets of Shen-ling-bai-zhu san (SLBZS) in treatment for chronic gastritis (CG); B: Kyoto Encyclopedia of Genes and Genomes enrichment analysis of the critical targets of SLBZS in treatment for CG.

Main pharmacological mechanisms

According to a study based on Chinese Medicine theory[50], the mechanism of TCM in treating CG is related to neuroprotective mechanisms, immune protective mechanisms, endocrine protective mechanisms, and other factors. A rat study showed that *Xiangshaliujunzi* decoction improved chronic atrophic gastritis symptoms by activating the TLR2, TLR4/MAPK/NF-κB/iNOS/NO signal pathway [51]. SLBZD reduced intestinal adenoma formation in adenomatous polyposis coli multiple intestinal neoplasia mice by suppressing hypoxia-inducible factor 1α-induced CD4 + CD25 + forkhead box P3 regulatory T cells[19]. Nevertheless, the mechanisms of SLBZS in CG have not been clarified.

In the present study, based on the network pharmacology analysis of drug and disease targets, a collateral relationship revealed the mechanism of SLBZS in the treatment of CG. First, we identified candidate target genes of SLBZS. Then, a protein interaction data network was generated, from which we obtained 36 related protein targets. The most protein targets included SRC, MAPK14, PPARG, and ERBB2. Critical GO entries were included regulation of reactive oxygen species metabolic process, response to oxidative stress, cellular response to chemical stress, protein tyrosine kinase activity, protein serine/threonine kinase activity, phosphatase binding, and others. Key signal pathways were identified in the KEGG enrichment analysis, primarily in EGFR tyrosine kinase inhibitor resistance, the PI3K-Akt signaling pathway, and others.

A study found that alterations in gastric cell stress-adaptive mechanisms due to *H. pylori* appear crucial during chronic infection[52]; therefore, response to oxidative stress of SLBZS to improve CG symptoms may determine the mechanism. In a future study, we will combine chemical analysis with network pharmacology to study the pharmacological effects of complex formulations comprehensively. The candidate target proteins and the formula's active ingredients are predicted by analyzing the corresponding networks. The chemical ingredients may be fully identified through experiments to confirm their presence in the formula. Therefore, further animal and clinical experiments are needed for research and exploration.

Limitations

This study had many limitations: (1) Only small sample sizes Chinese-language RCTs were included, and there were some defects in research design that resulted in the low or moderate quality of evidence; (2) most studies had design flaws like it focused only on results without illustrating a specific implementation of the random method, blind method, and follow-up reporting; (3) despite using validated documents supporting effectiveness assessment criteria, our non-uniform efficacy evaluation approach might influence outcomes and results. It might be challenging to employ the same effectiveness assessment criteria for each trial, as these criteria varied with each update; (4) adverse effects and recurrence rates information is rare reported; (5) the dosage of SLBZS has not been standardized and unified, and therefore the reasonable dosage was difficult to determined; (6) the pharmacology mechanism is unclear, especially the specific analysis of active ingredients and side effects; and (7) conflicts of interest of study investigators or funders may influence the risk of bias due to missing results. None of our included studies clearly reported their Chinese herbal sources, particularly whether pharmaceutical companies provided support. It is difficult to determine whether there were conflicts of interest. Presentation of herb sources in future studies could help determine bias.

CONCLUSION

This meta-analysis included 14 RCTs and summarized the clinical efficacy and potential mechanisms of the Chinese herbal formula SLBZS in treating CG. However, the methodological quality of the studies was not high, the risk of relapses and adverse reactions was underreported, and related mechanisms lacked validation; therefore, rigorous RCTs and basic science studies should be designed further to determine a definitive association between SLBZS and CG.
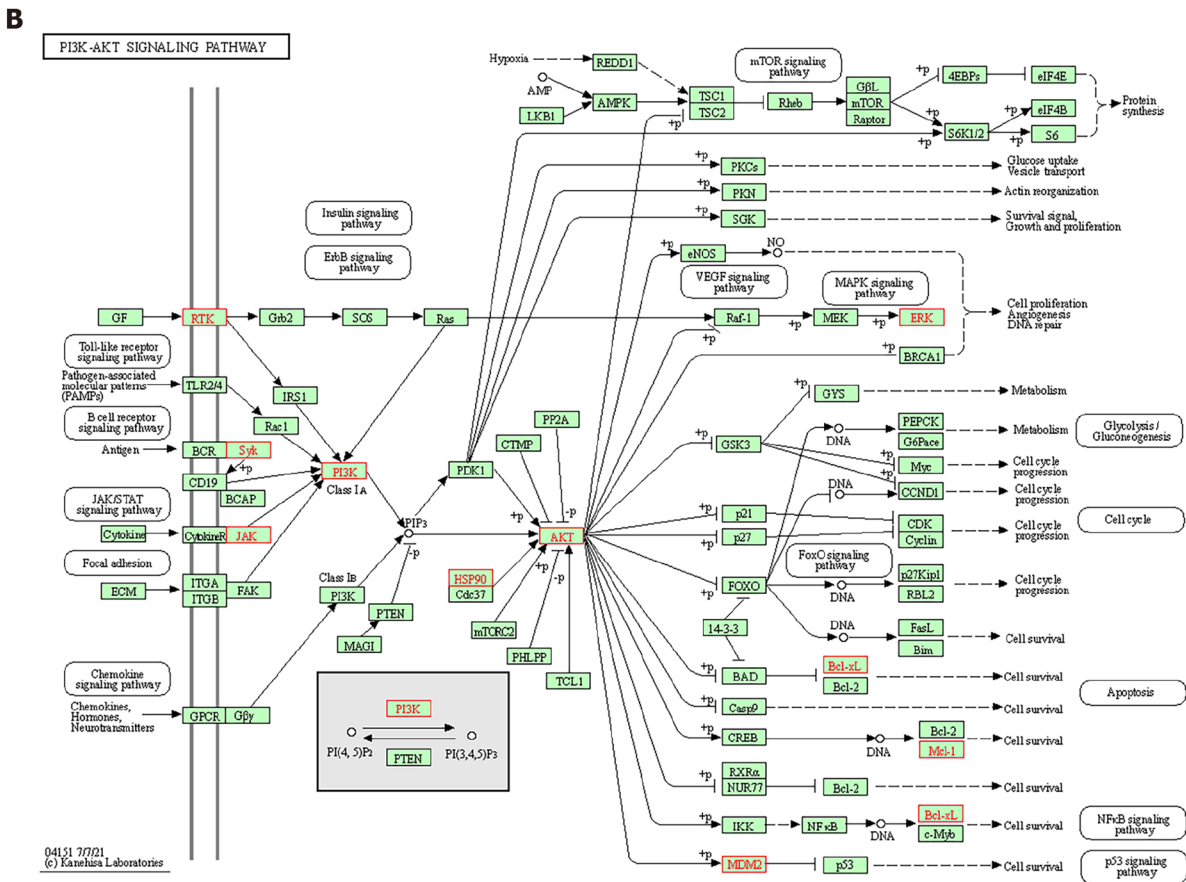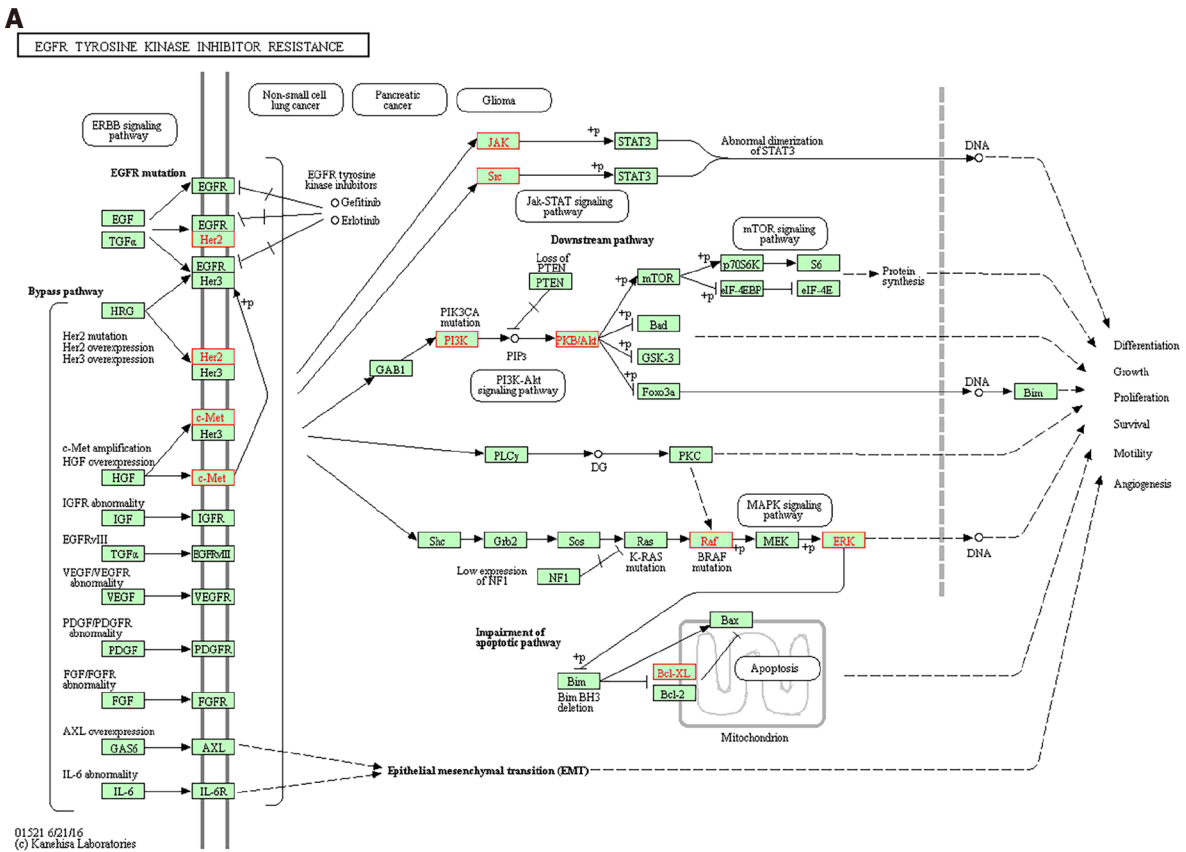
Figure 6 Schematic diagram. A: Schematic diagram of main Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway, EGFR tyrosine kinase inhibitor resistance; B: Schematic diagram of the main KEGG pathways, PI3K-AKT signaling pathway, arrows represent activation effect, T-arrows represent inhibition effect, and segments show activation or inhibition effects.

ARTICLE HIGHLIGHTS

Research background

The effects and safety of Shen-ling-bai-zhu san (SLBZS) are currently unclear.

Research motivation

A 2012 clinical practice guideline recommended SLBZ Powder for the Pattern of Spleen and Stomach Deficiency CG. The 2020 clinical guideline did not recommend SLBZS, possibly because of inadequate clinical evidence and pharmacological mechanisms. We designed our study to focus on evidence of efficacy and potential mechanisms. This controversy needed clarified.

Research objectives

To determine the clinical evidence and potential mechanisms of SLBZS for the treatment of CG.

Research methods

Evidence-based meta-analysis and network pharmacology methods.

Research results

Fourteen articles were eventually included, covering 1335 participants. SLBZS might treat CG by acting on related targets and pathways such as EGFR tyrosine kinase inhibitor resistance, the PI3K-Akt signaling pathway, and others.

Research conclusions

SLBZS might be useful in treating CG, but its long-term effects and specific clinical mechanisms keep unclear.

Research perspectives

More samples and high-quality clinical studies should be tested and verified in the next step.

FOOTNOTES

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