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Efficacy and Safety of Traditional Chinese Medicines as a Complementary Therapy Combined With Chemotherapy in the Treatment of Gastric Cancer: An Overview of Systematic Reviews and Meta-Analyses

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Abstract

Background: In China, traditional Chinese medicines (TCMs), as a complementary therapy combined with chemotherapy, is widely used in the treatment of gastric cancer (GC). In order to systematically evaluate and synthesize existing evidence to provide a scientific basis for the efficacy and safety of this complementary therapy, we present an overview of systematic reviews (SRs) and meta-analyses (MAs) on the topic of TCMs as a complementary therapy in combination with chemotherapy for the treatment of GC. **Methods:** SRs/MAs on TCMs combined with chemotherapy for GC were comprehensively searched in 8 databases. Methodological quality, risk of bias, reporting quality, and quality of evidence were assessed using the Assessment of Multiple Systematic Reviews 2 (AMSTAR-2), the Risk of Bias in Systematic (ROBIS) scale, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 (PRISMA 2020), as well as the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system. **Results:** Thirteen published SRs/MAs were included in our study. In terms of methodology, all SRs/MAs were considered to be of very low quality. Only 3 SRs/MAs has been assessed as low risk of bias. None of the SRs/MAs has been fully reported on the checklist. A total of 97 outcome indicators extracted from the included SRs/MAs were evaluated, and only 1 item was assessed as high quality. **Conclusions:** TCMs may be an effective and safe complementary therapy in combination with chemotherapy for the treatment of GC. However, this conclusion must be treated with caution as the quality of the evidence provided by SRs/MAs is generally low.

Keywords

traditional Chinese medicines, complementary therapies, gastric cancer, Systematic Reviews and Meta-Analyses, overview

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Introduction

Gastric cancer (GC) is a prevalent malignancy of the digestive system. It is the fifth most common cancer and the third leading cause of cancer-related mortality on a global scale, and the risk factors for it include Helicobacter pylori infection, Epstein-Barr virus infection, age, high salt intake, and a diet low in fruits and vegetables, among others.[1,2] The initial symptoms and signs of GC are often unremarkable. Despite the rapid advancements in gastroscopic technology, the diagnosis rate of early-stage GC remains low, most GCs are diagnosed only at advanced stages, which also leads to a poor prognosis and high mortality, making it a thorny issue to confront for clinicians.[3-5] In clinical practice, chemotherapy is the first-line treatment for a large number of patients with GC, barring those who are diagnosed early and can undergo radical surgery.[6,7] Despite the global acknowledgment of chemotherapy's efficacy in treating GC, no matter which chemotherapy regimen is used, it has suboptimal efficacy and excessive adverse effects in the clinical setting, posing challenges that conventional treatment methods struggle to address.[8,9] Even the emerging combination of immunotherapy, radiotherapy, and chemotherapy has not completely solved the issue of suboptimal efficacy and excessive adverse reactions in treatment.

Furthermore, the addition of these 2 therapies may lead to new adverse reactions.[10,11] It will make patients unable to obtain the ideal antitumor effect and seriously affect their medical compliance, thus leading to a serious detrimental effect on survival, quality of life, and even the outcome of treatment failure. Not only that, severe adverse reactions will directly reduce the quality of life of patients, which is extremely unfavorable for weak patients with GC. In addition, poor efficacy and excessive adverse reactions can also lead to the decline in patients' self-care abilities, damage to their dignity, and incur more treatment costs, causing great damage to their psychological and social levels. Therefore, there is an urgent need to find a new complementary therapy that can be combined with chemotherapy for the treatment of GC patients.

In ancient times, Chinese doctors had a clear understanding of tumor disease, which was called "Zhongyang," and the use of traditional Chinese medicines (TCMs) under the guidance of syndrome differentiation and treatment theory was an effective treatment plan at that time.[12] With the progress of related research, the clinical value of TCMs has been more and more recognized worldwide. There are many studies reporting that many TCMs can enhance the antitumor therapeutic effect by inhibiting proliferative, proapoptotic, antimetastatic, antiangiogenic, modulating immune responses, reversing chemoresistance; and they can also reduce the adverse reactions caused by chemotherapeutic agents through multiple pathways.[13-15] In practice, because of the high efficacy and safety, TCMs have also been recognized by many clinicians and patients as a complementary therapy combined with chemotherapy, and the positive effects provided by them are gratifying.[16] Therefore, the application of TCMs in this field deserves to be further explored to achieve better efficacy and fewer adverse effects in patients treated with chemotherapy for GC.

Nowadays, there are many systematic reviews (SRs)/meta-analyses (MAs) to evaluate the benefits of TCMs as complementary therapies in combination with chemotherapy for patients with GC. SR/MA is considered the gold standard for assessing the efficacy of clinical interventions. It can guide physicians' clinical decisions and is also an important basis for researchers to conduct relevant studies or develop guidelines. However, the quality of these studies has not been assessed, which may mislead physicians and researchers into making practical decisions. The overview of SRs/MAs in this study is a new approach that combines multiple SRs/MAs to assess their quality and various findings, addressing inconsistencies between them, to determine the effects resulting from interventions. The purpose of this study is to objectively and comprehensively evaluate the scientific quality of SRs/MAs of TCMs as a complementary therapy combined with chemotherapy for GC, and to provide evidence for the application of this treatment in clinical practice.

Methods

This research was conducted according to the Cochrane Handbook and some high quality articles with scientific research methodologies.[17-19] This overview protocol has been registered with the PROSPERO website (CRD42023423046).

Eligibility Criteria

Inclusion criteria

Type of research. SRs/MAs were based on randomized controlled trials (RCTs) about TCMs as a complementary therapy combined with chemotherapy for GC, and the language involved is limited to English and Chinese.

Types of participants. The participants were patients diagnosed with GC according to any national or international criteria without distinction of stage, age, sex, race, or nationality.[20,21]

Type of intervention. The control group received chemotherapy alone, while the intervention group received the same chemotherapy regimen combined with TCMs (including TCM formula, Chinese patent medicine, and TCM injection).

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Table 1. The Search Strategy of PubMed.

Query	Search term
#1	"TCM" OR "traditional Chinese medicine" OR "Chinese medicine" OR "Chinese herb" OR "traditional medicine"
#2	Stomach Neoplasms [Mesh]
#3	"Neoplasm, Stomach" OR "Stomach Neoplasm" OR "Neoplasms, Stomach" OR "Gastric Neoplasms" OR "Gastric Neoplasm" OR "Neoplasm, Gastric" OR "Neoplasms, Gastric" OR "Cancer of Stomach" OR "Stomach Cancers" OR "Gastric Cancer" OR "Cancer, Gastric" OR "Cancers, Gastric" OR "Gastric Cancers" OR "Stomach Cancer" OR "Cancer, Stomach" OR "Cancers, Stomach" OR "Cancer of the Stomach" OR "Gastric Cancer, Familial Diffuse"
#4	#2 OR #3
#5	Meta-Analysis as Topic [Mesh]
#6	"Systematic review" OR "meta-analysis" OR "meta analysis" OR "meta-analyses" OR "Review, Systematic"
#7	#5 OR #6
#8	#1 AND #4 AND #7

Types of outcomes. The following are the outcome measures: clinical objective response rate (ORR, including complete response and partial response of the tumor), disease control rate (DCR, including complete response, partial response, and stability of the tumor), Karnofsky performance score (KPS) and improvement rate of KPS, quality of life improved rate (QIR), pain relief rate (PRR), overall survival time, 1-year survival rate, 3-year survival rate, incidence of myelosuppression, incidence of leucopenia, incidence of anemia, incidence of thrombocytopenia, incidence of neutropenia, incidence of hepatorenal toxicity, incidence of hepatotoxicity, incidence of renal toxicity, incidence of neurotoxicity, incidence of gastrointestinal reaction, incidence of diarrhea, incidence of nausea and vomiting, incidence of hand-foot syndrome, incidence of oral mucositis, incidence of alopecia.

Exclusion Criteria. (1) Network meta-analyses, SRs without MAs, narrative reviews, conference abstracts, editorials, case reports, dissertations, and replication studies; (2) Publication with missing information; (3) Animal experiments; (4) Other traditional drugs not clearly defined as TCMs were used in the intervention group.

Publication Search Strategy

Two researchers independently searched a total of 8 literature databases, including PubMed, Cochrane Library, Embase, Web of Science, Wanfang Database, VIP Journal Database, China National Knowledge Infrastructure (CNKI), Chinese Biomedical Literature Database (CBM). We used the search method of Medical Subject Headings (MeSH) terms or keywords combined with free words to search. The keywords included "traditional Chinese medicine," "gastric cancer," "systematic review," and "meta-analysis." The specific search strategy was adjusted according to different databases. And the search time range was from database establishment to June 28, 2023. The search strategy of PubMed is shown in Table 1. Search strategies for other databases are described in "Supplemental Materials."

Publications Screening and Data Extraction

Publications screening and data extraction were performed independently by 2 researchers. The Publications to be screened were imported into NoteExpress software for literature management to remove duplicate studies and then preliminarily screened by browsing the title, abstract, and key words of the publication according to the established criteria. Finally, the full text was scanned to identify the included publications. At the same time, we also reviewed the references in the retrieved publications to avoid omissions. After identifying the included publications, we extracted the following data from them: first author, publication year, country, number of included RCTs, therapeutic measures for intervention groups and control groups, RCT quality assessment tool, and main conclusions.

Quality Evaluation of SRs/MAs

Two researchers independently assessed the methodological quality, risk of bias, report quality, and evidence quality of the included SRs/MAs, and any disagreements were left to the third researcher to resolve.

Assessment of methodological quality. We assessed the methodological quality of the included SRs/MAs using Assessment System for Evaluating Methodological Quality-2 (AMSTAR-2), an internationally recognized systematic methodological quality assessment tool.[22] The tool contains 7 key items (2, 4, 7, 9, 11, 13, and 15). Each item was categorized as "no," "partially yes," or "yes" depending on their adherence to the criteria. The overall methodological quality was classified into 4 levels: high, medium, low, or very low.

Assessment of risk of bias. This overview used the Risk of Bias in Systematic Reviews (ROBIS) scale to assess the risk of bias for inclusion in SRs/MAs.[23] The evaluation was conducted in 3 phases, each consisting of one or more key items, which were rated as "yes," "partial yes," "partial no," "no," and "no information" according to the corresponding criteria, and the risk of bias in each phase was rated as "low," "high," and "unclear."

Assessment of reporting quality. The quality of each SR/MA report included was assessed by the list of Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 (PRISMA 2020). This list consists of 27 items, each rated "yes," "partial yes," and "no" according to the corresponding criteria, focusing on reporting methods and outcomes for the inclusion of SRs/MAs.[24]

Assessment of quality of evidence. The quality of evidence for each SR/MA outcome was assessed by the Grading of Recommendations Assessment, Development, and Evaluation (GRADE).[25] According to the criteria, 5 aspects will lead to a decrease in the quality of evidence, including risk of bias, inconsistency, indirectness, imprecision, and publication bias. RCTs were initially considered to be high-quality studies. During the evaluation, if any of the above problems were identified, the quality of the evidence in the publicationwas reduced. Ultimately, evidence quality ratings were determined as "high," "medium," "low," or "very low." The evidence with no degradation factor is rated as high quality, while the evidence with one degradation factor is rated as medium quality, 2 degradation factors are rated as low quality, and more than 3 (including 3) degradation factors are rated as extremely low quality.

Data Synthesis

Narrative descriptions were given for the included SRs/MAs. Dichotomous variables were expressed as risk ratios (RR), odds ratios (OR), or hazard ratios (HR) with 95% confidence intervals (CI), while continuous variables were expressed as mean differences (MD) with 95% CI. In addition, the results of the AMSTAR-2, ROBIS, PRISMA 2020, and GRADE assessments are shown in the tables.

Network of SRs/MAs and RCTs

We collated the included SRs/MAs and the RCTs included in these SRs/MAs, established the network relationships between them, and completed the visualization using Cytoscape software.

Results

Results on Publication Search and Selection

A total of 157 publications were obtained from 8 databases, of which 67 were duplicates. After removing duplicates, the remaining 90 publications were preliminarily screened by reading titles and abstracts, and a total of 71 publications were excluded as unqualified according to the established inclusion and exclusion criteria. Subsequently, the remaining 19 publications were read in full, and it was found that 2 publications did not use chemotherapy at the time of intervention,[26,27] and the studies included in the 4 publications were not RCTs.[28-31] Finally, we identified 13 SRs/MAs for inclusion in our study.[32-44] The process of study selection is shown in Figure 1.

Description of Included SRs/MAs

The characteristics of the 13 SRs/MAs included in the overview are shown in Table 2. These publicationswere published between 2013 and 2022, and all were published by Chinese researchers. Among them, 6 are in English,[32-37] and the remaining 7 are in Chinese.[38-44] The number of RCTs included in these SRs/MAs ranged from 6 to 40, with a minimum sample size of 608 and a maximum sample size of 3098. In terms of therapeutic measures, the control group was treated with chemotherapy regimens commonly used for GC, while the intervention group received TCMs in addition to the same chemotherapy regimen. TCMs included 3 types: TCM formula,[32,35,36,38-44] Chinese patent medicine,[32,34-40,42,43] and TCM injection.[33-35,37,38,40] About quality evaluation scales, 12 SRs/MAs[32-39,41-44] used the Cochrane criteria for risk of bias assessment of included RCTs, and 1 SR/MA[40] used the Jadad scale. All SRs/MAs were subjected to meta-analysis and all reported positive results.

Methodological Quality Assessment

We conducted a methodological assessment of the included SRs/MAs using AMSTAR-2, and the specific results are shown in Table 3. All 13 SRs/MAs included were rated as very low quality due to multiple deficiencies in critical and non-critical items. The reasons for the reduction of methodological quality mainly come from the following items: item 2 (only 1 SR/MA[32] had a registered study protocol), item4 (only 2 SRs/MAs[33,38] were adequately searched for the literatures), item 7 (only 1 SR/MA[37] provided a list of excluded articles), and item 10 (none of the SRs/MAs provided a list of funding for RCTs). Among them, item 2, item 4, and item 7 were key items, which directly led to the reduction of the methodological quality of these SRs/MAs.

Risk of Bias of the Included SRs/MAs

The assessment details of SRs/MAs are shown in Table 4 and Figure 2. Regarding the results of the ROBIS assessment, both phase 1 (assessing relevance) and domain 1 (study eligibility criteria) of phase 2 rated all SRs/MAs as having low risk of bias. Nine of the SRs/MAs[32,33,36-39,41,43,44] were rated as low risk in domain 2 (identification and selection of studies), 10 SRs/MAs[32,34-39,41-44] were rated as low

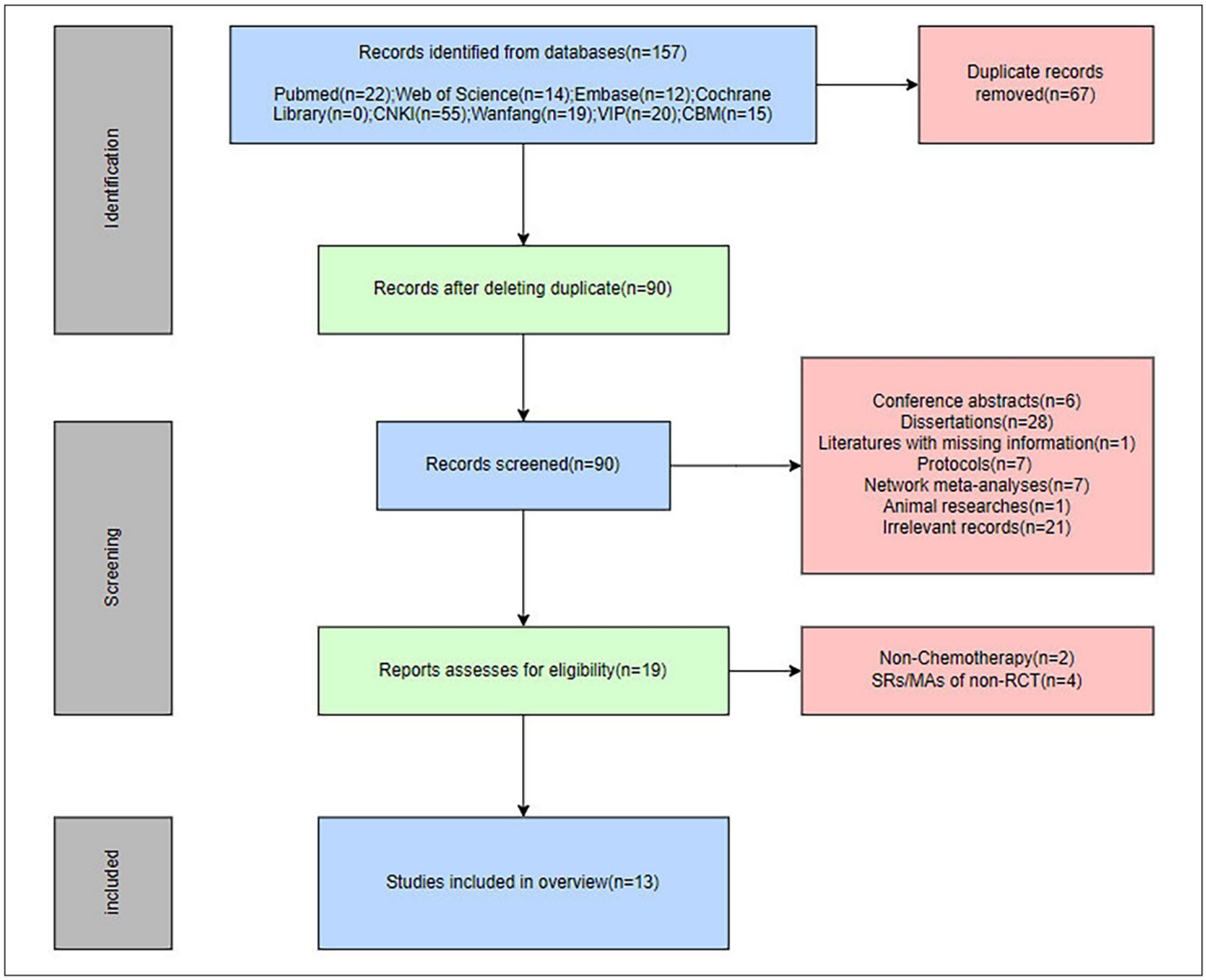

Figure 1. The flowchart of the screening process.

risk in domain 3 (collection and study appraisal), and 6 SRs/MAs[33,35,36,38,42,43] were rated as low risk in domain 4 (synthesis and findings). In phase 3 (risk of bias in the review), only 6 SRs/MAs[32,36-38,42,43] had a low risk of bias.

Report Quality

We used the PRISMA 2020 checklist to evaluate the report quality of SRs/MAs, details of which are provided in Table 5. The 13 included SRs/MAs were fully reported in the title, abstract, introduction, and discussion sections, but there were non-negligible defects in other sections. Some items had a response rate less than 50%, and some even had a response rate of 0%, which was the main reason for the reporting defect. In terms of method, item 7 had a response rate of 0%, none of the SRs/MAs could provide a complete search strategy; item 15 had a response rate of 0%, no SR/MA could provide a certainty assessment. In the results section, item 16 (b) response rate was 7.69%, only 1 SR/MA[37] provided a detailed exclusion list; item 20 (d) response rate was 46.15%, 6 SRs/MAs[32-35,43,44] presented the results of the sensitivity analysis; and item 22 response rate was 0%, none of the SRs/MAs had certainty of evidence. In the other information section, only 1 SR/MA[32] registered the study protocol, but it did not describe or explain whether there were any changes or modifications to the information of registration content or the protocol. The response rate of item 24 (a, b, c) was 7.69%, 7.69%, and 0%, respectively. Moreover, the response rate of item 26 was 46.15%, only 6 SRs/MAs declared the conflict of interest of the authors.

Evidence Quality of the Included SRs/MAs

GRADE specific assessment details are shown in Table 6. In this study, there are 97 outcomes included in 13 SRs/MAs

Table 2. Characteristics of the Included SRs/Mas.

Author and Country	Trials (Samples)	Participant	Intervention group	Control group	Main TCM type	Quality assessment	Main results
Tan et al,[32] China	40 (3029)	Advanced GC	TCM + oxaliplatin-based chemotherapy	Oxaliplatin-based chemotherapy	Formula, Chinese patent medicine	Cochrane Criteria	Overall, CHM has a positive effect on improving oxaliplatin-based chemotherapy for AGC, which can improve short-term efficacy and reduce the incidence of AEs.
Zhang et al,[33] China	12 (853)	Advanced GC	TCM + Conventional chemotherapy	Conventional chemotherapy	TCM injection	Cochrane Criteria	Our study still provided helpful information for clinical practice that Cinobufacini injection could enhance the efficacy of other treatments in AGC patients, reduce the side-effects induced by chemotherapy, and help to relieve cancer pain, which might be helpful for clinical medication.
Sun et al,[34] China	27 (1939)	Advanced GC	TCM + Conventional chemotherapy	Conventional chemotherapy	Chinese patent medicine, TCM injection	Cochrane Criteria	In summary, this meta-analysis indicated that cinobufotalin and chemotherapy combined therapy was effective in treating advanced GC. Clinical application of cinobufotalin not only evidently improved the therapeutic effects of chemotherapy but also effectively alleviated most of the side effects caused by chemotherapy.
Zhang et al,[35] China	10 (761)	GC	TCM + Conventional chemotherapy	Conventional chemotherapy	Formula, TCM injection, Chinese patent medicine	Cochrane Criteria	In conclusion, traditional Chinese medicine combined with chemotherapy can improve the treatment efficiency and survival rate of patients with gastric cancer and reduce the incidence of nausea and vomiting after chemotherapy.
Chen et al,[36] China	26 (3098)	GC	TCM + Conventional chemotherapy	Conventional chemotherapy	Formula, Chinese patent medicine	Cochrane Criteria	Traditional Chinese medicine Jianpi Bushen therapy combined with chemotherapy in the treatment of gastric cancer may really enhance the immunity of patients to improve the clinical efficacy and safety.
Li et al,[37] China	14 (1109)	GC	TCM + paclitaxel-based chemotherapy	paclitaxel-based chemotherapy	TCM injection, Chinese patent medicine	Cochrane Criteria	The results indicate that paclitaxel + TCM is more effective and safer.
Qiao et al,[38] China	20 (1735)	Advanced GC	TCM + Conventional chemotherapy	Conventional chemotherapy	Formula, TCM injections, Chinese patent medicine	Cochrane Criteria	In conclusion, Fuzheng Sanjie method of traditional Chinese medicine adjuvant chemotherapy may be better and safer than simple chemotherapy, and has certain clinical promotion and application value, but the evidence is weak.
Liang et al,[39] China	6 (608)	GC	TCM + Conventional chemotherapy	Conventional chemotherapy	Formula, Chinese patent medicine	Cochrane Criteria	Traditional Chinese medicine combined with chemotherapy based on invigorating spleen and supplementing qi is superior to chemotherapy alone in improving the quality of life and inhibiting tumor metastasis, but it cannot significantly improve the survival rate.
Xu et al,[40] China	15 (1052)	GC undergoing gastrectomy	TCM + Conventional chemotherapy	Conventional chemotherapy	Formula, TCM injection, Chinese patent medicine	Jadad	This study shows that traditional Chinese medicine combined with chemotherapy is better than chemotherapy alone in the side effects and survival time of postoperative patients with gastric cancer, suggesting that traditional Chinese medicine combined with chemotherapy is better than chemotherapy alone, which provides some evidence for clinical treatment.
Chen et al,[41] China	21 (1728)	Advanced GC	TCM + Conventional chemotherapy	Conventional chemotherapy	Formula	Cochrane Criteria	Traditional Chinese medicine compound combined with chemotherapy is more helpful to improve the clinical symptoms and tumor conditions of elderly patients with gastric cancer, improve the quality of life, and reduce the occurrence of gastrointestinal reactions.
Wang et al,[42] China	18 (1477)	Locally advanced GC undergoing gastrectomy	TCM + Conventional chemotherapy	Conventional chemotherapy	Formula, Chinese patent medicine	Cochrane Criteria	Traditional Chinese medicine combined with postoperative adjuvant chemotherapy is superior to chemotherapy alone in the prevention and treatment of postoperative recurrence and metastasis of LAGC, and has higher safety. Although the above conclusions are of low quality and the supporting evidence is relatively weak, clinicians should be cautious when applying the conclusions of this study in combination with clinical practice.
Wu et al,[43] China	23 (1339)	Advanced GC	TCM + FOLFOX chemotherapy	FOLFOX chemotherapy	Formula, Chinese patent medicine	Cochrane Criteria	In conclusion, TCM decoction combined with chemotherapy can benefit patients with advanced gastric cancer from multiple aspects
Zhao et al,[44] China	19 (1654)	Advanced GC	TCM + Conventional chemotherapy	Conventional chemotherapy	Formula	Cochrane Criteria	The results showed that the traditional Chinese medicine decoction combined with chemotherapy can effectively improve the clinical efficacy, and the safety is good, has the effect of reducing toxicity, increasing the efficacy, and has certain guiding significance for the clinical treatment of advanced gastric cancer.

Table 3. Result of the AMSTAR-2 Assessments.

Author	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Q15	Q16	Overall quality
Tan et al[32]	Y	Y	N	PY	Y	Y	N	Y	Y	N	Y	Y	Y	Y	Y	Y	VL
Zhang et al[33]	Y	PY	N	Y	Y	Y	N	Y	Y	N	Y	Y	Y	Y	Y	Y	VL
Sun et al[34]	Y	PY	N	PY	N	Y	N	Y	Y	N	Y	Y	N	Y	Y	Y	VL
Zhang et al[35]	Y	PY	Y	PY	N	Y	N	Y	Y	N	Y	Y	Y	Y	Y	Y	VL
Chen et al[36]	Y	PY	Y	PY	Y	Y	N	Y	Y	N	Y	Y	Y	Y	Y	Y	VL
Li et al[37]	Y	PY	Y	PY	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	VL
Qiao et al[38]	Y	PY	Y	Y	Y	Y	N	PY	Y	N	Y	Y	Y	Y	Y	N	VL
Liang et al[39]	Y	PY	N	PY	Y	Y	N	PY	Y	N	Y	Y	Y	Y	N	N	VL
Xu et al[40]	Y	PY	N	PY	N	Y	N	PY	Y	N	Y	Y	Y	Y	N	N	VL
Chen et al[41]	Y	PY	N	PY	Y	Y	N	Y	Y	N	Y	Y	N	Y	Y	N	VL
Wang et al[42]	Y	PY	N	PY	N	Y	N	Y	Y	N	Y	Y	Y	Y	Y	N	VL
Wu et al[43]	Y	PY	Y	PY	Y	Y	N	Y	Y	N	Y	Y	Y	Y	Y	N	VL
Zhao et al[44]	Y	PY	Y	PY	Y	Y	N	Y	Y	N	Y	Y	Y	Y	Y	N	VL

Abbreviations: Y, yes; PY, partially yes; N, no; VL, very low.

evaluated according to the GRADE guideline. We found that 1 item was rated as high quality, 23 items were rated as moderate quality, 43 items were rated as low quality, and the remaining 30 items were rated as very low quality. Among the downgrading factors, risk of bias (n=82) was the most common downgrading factor, followed by imprecision (n=52), publication bias (n=41), inconsistency (n=27), and indirectness (n=0).

SRs/MAs Outcomes of Intervention

In this overview, we have summarized and provided a narrative description of the outcomes for the quantitative evaluation of SRs/MAs. Complete information can be found in Table 7.

Effectiveness Assessment

In terms of clinical remission and control of the tumor, ORR was reported in 5 SRs/MAs[32-34,37,41] (evidence quality: 3 moderate, 2 low), and the meta-analysis of these 5 showed that TCMs in combination with chemotherapy had a more significant therapeutic effect than chemotherapy alone and could significantly improve patients' ORR. Additionally, 8 SRs/MAs[32-36,38,43,44] reported DCR (evidence quality: 1 high, 4 moderate, 3 low), all of these studies demonstrated that the efficacy of TCMs combined with chemotherapy was considerably superior to that of chemotherapy alone, which might greatly increase patients' DCR. Seven SRs/MAs reported KPS (evidence quality: 1moderate, 2 low, 4 very low), of which 5 were KPS improvement rate[33,36,37,41,43] and 2 were the score,[34,42] all showed that TCMs combined with chemotherapy could improve KPS more than chemotherapy alone. Two SRs/MAs[34,39] reported the QIR (evidence quality: 1 moderate, 1 very low), which showed that TCMs combined with chemotherapy could significantly improve the quality of life of patients. Four SRs/MAs[33,34,38,39] reported overall survival time (evidence quality: 3 low, 1 very low), only 1 showed TCMs combined with chemotherapy can improve in overall survival time. Besides, 2 SRs/MAs[35,40] reported 1-year survival rate and 3-year survival rate (evidence quality: 3 low, 1 very low), they all proved that TCMs combined with chemotherapy is more effective. Two SRs/MAs[33,34] reported PRR (evidence quality: 2 low), both of which showed that the combination of TCMs and chemotherapy could increase PRR in patients.

Safety Assessment

The reported adverse reactions of the included SRs/MAs were very comprehensive and diverse. In the hematology section, there are 3 SRs/MAs reported incidence of myelosuppression, 9 SRs/MAs reported incidence of leucopenia, 6 SRs/MAs reported incidence of anemia, 5 SRs/MAs reported incidence of thrombocytopenia, and 2 SRs/MAs reported incidence of neutropenia. In the digestive system section, 3 SRs/MAs reported incidence of gastrointestinal reaction, 10 SRs/MAs reported incidence of nausea and vomiting, 5 SRs/MAs reported incidence of diarrhea. In terms of liver and kidney toxicity, 1 SR/MA reported incidence of hepatorenal toxicity, 4 SRs/MAs reported incidence of hepatotoxicity, 3 SRs/MAs reported incidence of renal toxicity. In other areas, 7 SRs/MAs reported incidence of neurotoxicity, 3 SRs/MAs reported incidence of hand-foot syndrome, 2 SRs/MAs reported incidence of oral mucositis, 1 SR/MA reported incidence of alopecia. There are many contradictions among these results, and the level of quality is generally poor, but some results are worth noting that the addition of TCMs could reduce incidence of leucopenia[32-34,36-38,40,42,43] (evidence quality: 4 moderate, 1 low, 4 very low), incidence of gastrointestinal reaction[32,34,36] (evidence quality: 1 moderate, 2 low), incidence of nausea and vomiting[32-35,37,38,40-43] (evidence quality: 1 moderate, 5 low, 4 very low), and incidence of hand-foot syndrome[33,34,36] (evidence quality: 1 moderate, 2 low).

Table 4. Results of the ROBIS Assessments.

			Tan et al[32]	Zhang et al[33]	Sun et al[34]	Zhang et al[35]	Chen et al[36]	Li et al[37]	Qiao et al[38]	Liang et al[39]	Xu et al[40]	Chen et al[41]	Wang et al[42]	Wu et al[43]	Zhao et al[44]
Phase 1	Assessing relevance	Q1	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	The risk		Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Phase 2	Domain 1: Study eligibility criteria	Q1	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
		Q2	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
		Q3	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
		Q4	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
		Q5	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	The risk		Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
	Domain 2: Identification and selection of studies	Q1	PY	Y	PY	PY	PY	PY	PY	PY	PY	PY	PY	PY	PY
		Q2	PY	Y	PY	PY	PY	PY	PY	PY	PY	PY	PY	PY	PY
		Q3	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
		Q4	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
		Q5	Y	Y	N	N	Y	Y	Y	Y	N	Y	N	Y	Y
	The risk		Low	Low	High	High	Low	Low	Low	Low	High	Low	High	Low	Low
	Domain 3: Collection and study appraisal	Q1	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
		Q2	Y	PN	PN	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
		Q3	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
		Q4	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y
		Q5	PY	Y	PY	Y	PY	PY	PY	PY	PY	PY	PY	PY	PY
	The risk		Low	High	High	Low	Low	Low	Low	Low	High	Low	Low	Low	Low
	Domain 4: Synthesis and findings	Q1	PN	PY	PN	Y	PY	PN	PY	PN	PN	PN	PY	PY	PN
		Q2	Y	PY	PY	PY	PY	PY	PY	PY	PY	PY	PY	PY	PY
		Q3	Y	Y	Y	Y	PY	Y	Y	Y	Y	PY	Y	Y	Y
		Q4	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
		Q5	Y	Y	Y	Y	Y	Y	PY	PY	PY	Y	PY	PY	Y
		Q6	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	The risk		High	Low	High	Low	Low	High	Low	HIGH	High	High	Low	Low	High
Phase 3	Risk of bias in the review	Q1	Y	N	N	N	Y	Y	Y	N	N	Y	N	Y	N
		Q2	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
		Q3	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	The risk		Low	High	High	High	Low	Low	Low	High	High	Low	High	Low	High

Abbreviations: Y, yes; PY, partially yes; PN, partially no.

Network Relationships Between SRs/MAs and RCTs

The relationships between the SRs/MAs and the RCTs are shown in Figure 3. This network graph has 238 nodes and 250 edges, representing the 13 SRs/MAs included as well as the 225 RCTs included in these SRs/MAs. Because the number of nodes and edges is relatively similar, there were not too many identical RCTs included in different SRs/MAs. It shows the original researches that can support us in carrying out this overview are relatively sufficient, and there are no significant limitations due to the inclusion of a large number of similar studies.

Discussion

As one of the main treatment methods for GC, chemotherapy is of great significance for the health and quality of life for patients with GC. However, there are still nonnegligible problems associated with either one of the related chemotherapy regimens, mainly in poor efficacy and significant adverse reactions.[45,46] In China, TCMs are widely used in combination with chemotherapy in the treatment of GC to achieve more significant efficacy and fewer adverse reactions for patients.[47,48] The number of SRs/MAs of TCMs combined with chemotherapy for GC has been increasing in recent years. However, currently, there is no

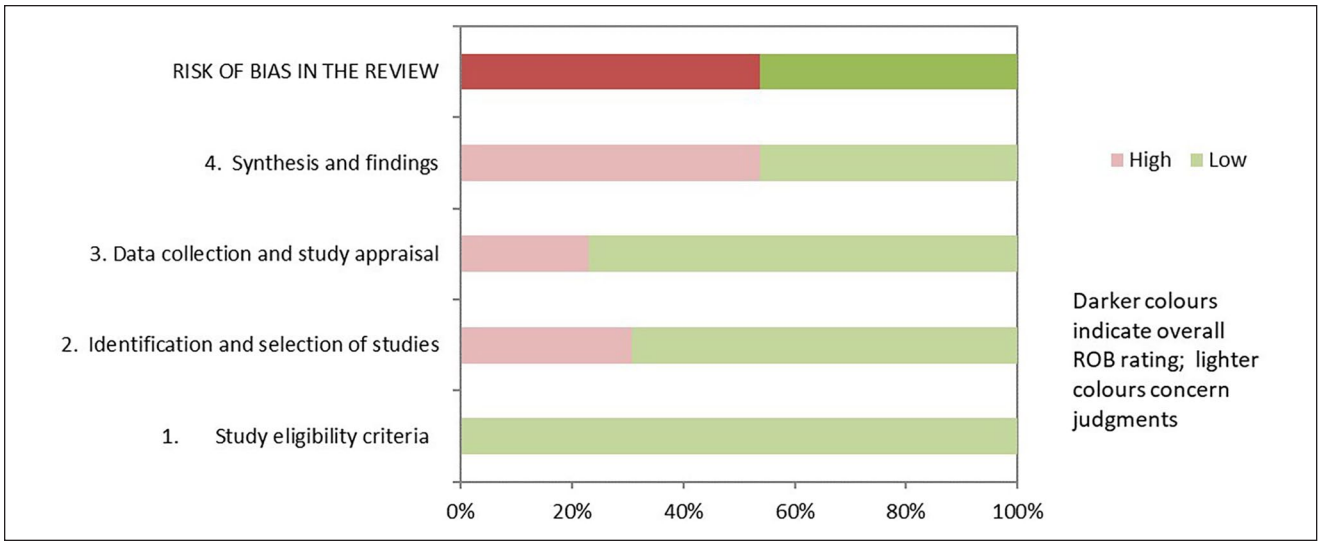

Figure 2. Results of the ROBIS assessments.

research to integrate them for a comprehensive and systematic review. Therefore, it is necessary to conduct research on this topic. To our knowledge, this study is the first to provide evidence on the efficacy and safety of TCMs as a complementary therapy combined with chemotherapy in the treatment of GC through a comprehensive systematic evaluation of existing SRs/MAs which based on RCTs.

Quality Issues of the Included SRs/MAs

According to the specific circumstances assessed by AMSTAR-2, the main reasons for the low methodological quality of the included publications come from 4 aspects: protocol registration (completion rate 1/13), adequate search of the literatures (completion rate 2/13), exclusion list (completion rate 1/13), and funding sources (completion rate 0/13). First, it is important to register research protocols after researchers have identified the research topic, which can help to increase transparency in the research process and minimize selective reporting bias, improve the rigor and credibility of research reports.[49] Apparently, the included SRs/MAs are deficient in this regard. Similarly, the vast majority of SRs/MAs did not provide an exclusion list of the literature, which also makes the transparency of the studies impaired, and there may be situations in which the studies cannot be replicated, leading to decreased reliability of these studies. Most SRs/MAs are insufficient in the retrieval of RCTs, which may lead to missing RCTs that meet the inclusion criteria, increase the risk of bias in research, and may lead to some deviations in the results. Therefore, a more perfect retrieval strategy should be developed to ensure the reliability of the results. In addition, there are no studies reporting the funding sources of the included RCTs, which may also increase the bias in reporting of clinical trials, as commercially funded research results may be biased by the interest of supporting relevant agencies.

According to the results of the ROBIS assessment, only 6 SRs/MAs were found to have a low risk of bias, while the main reasons leading to high risk of bias were inadequate assessment of publication bias in phase 2 and inadequate interpretation of risk of bias in phase 3.

In terms of reporting quality, after PRISMA 2020 evaluation, the results of which are more similar to those of AMSTAR-2. The 13 SRs/MAs included have considerable shortfalls in reporting on study protocol registration, literature search, exclusion lists and RCTs' funding sources. In addition, all SRs/MAs' assessments of the quality of outcome evidence are missing, which can reduce the support for their conclusions. And more than half of SRs/MAs did not conduct sensitivity analysis, which is not conducive to ensuring the stability of the judgment assessment. The aforementioned defects will lead to a decrease in the credibility of the research results and conclusions, and cannot provide strong support for their views.

Regarding evidence quality, the evaluation of 97 results included show that only 1 result is of high quality, 23 results are of medium quality, and the rest are of low or very low quality. The overall quality of evidence is not satisfactory. The most important factor leading to the reduction of quality is the risk of bias (82/97). The main problem is that the included RCTs had methodological defects, most of them did not clearly describe the methods of the random sequence generation method, the allocation concealment method, or the blinding method, which are also common defects of related studies.[50] Other factors contributing to the degradation of the quality of evidence were imprecision (52/97), publication bias (41/97), inconsistency (27/92), while reasons for these issues included insufficient size of included RCTs, lack of publication bias assessment, unjustified study design leading to high heterogeneity in relevant outcome measures.

Table 5. Results of the PRISMA 2020 Checklist.

Section/Topic		Items	Tan et al[32]	Zhang et al[33]	Sun et al[34]	Zhang et al[35]	Chen et al[36]	Li et al[37]	Qiao et al[38]	Liang et al[39]	Xu et al[40]	Chen et al[41]	Wang et al[42]	Wu et al[43]	Zhao et al[44]	Number of Yes or Partially Yes(%)
Title	Title	Q1	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100%
Abstract	Abstract	Q2	PY	PY	PY	PY	PY	PY	PY	PY	PY	PY	PY	PY	PY	100%
Introduction	Rationale	Q3	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100%
	Objectives	Q4	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100%
Methods	Eligibility criteria	Q5	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100%
	Information sources	Q6	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	92.31%
	Search strategy	Q7	N	N	N	N	N	N	N	N	N	N	N	N	N	0%
	Selection process	Q8	Y	Y	N	N	Y	Y	Y	Y	N	Y	N	Y	Y	69.23%
	Data collection process	Q9	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100%
	Data items	Q10 (a)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100%
		Q10 (b)	PY	PY	PY	PY	PY	PY	PY	PY	PY	PY	PY	PY	PY	100%
	Study risk of biasassessment	Q11	Y	Y	N	Y	N	Y	N	Y	N	Y	Y	Y	Y	69.23%
	Effect measures	Q12	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100%
	Synthesis methods	Q13 (a)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100%
		Q13 (b)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100%
		Q13 (c)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100%
		Q13 (d)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100%
		Q13 (e)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100%
		Q13 (f)	Y	Y	Y	Y	N	N	N	Y	N	N	N	Y	Y	53.85%
	Reporting bias assessment	Q14	Y	Y	N	Y	Y	Y	N	Y	N	Y	Y	Y	N	69.23%
	Certainty assessment	Q15	N	N	N	N	N	N	N	N	N	N	N	N	N	0%
Results	Study selection	Q16 (a)	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	92.31%
		Q16 (b)	N	N	N	N	N	Y	N	N	N	N	N	N	N	7.69%
	Study characteristics	Q17	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100%
	Risk of bias in studies	Q18	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	92.31%
	Results of individual studies	Q19 (a)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100%
		Q19 (b)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100%
	Results of syntheses	Q20 (a)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100%
		Q20 (b)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100%
		Q20 (c)	Y	Y	Y	Y	N	Y	N	N	N	Y	Y	Y	Y	69.23%
		Q20 (d)	Y	Y	Y	Y	N	N	N	N	N	N	N	Y	Y	46.15%
	Reporting biases	Q21	Y	Y	N	Y	N	Y	N	Y	N	Y	Y	Y	Y	69.23%
	Certainty of evidence	Q22	N	N	N	N	N	N	N	N	N	N	N	N	N	0%
Discussion	Discussion	Q23 (a)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100%
		Q23 (b)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100%
		Q23 (c)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100%
		Q23 (d)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100%
Other information	Registration and protocol	Q24 (a)	Y	N	N	N	N	N	N	N	N	N	N	N	N	7.69%
		Q24 (b)	Y	N	N	N	N	N	N	N	N	N	N	N	N	7.69%
		Q24 (c)	N	N	N	N	N	N	N	N	N	N	N	N	N	0%
	Support	Q25	Y	Y	Y	Y	Y	Y	N	Y	N	N	Y	Y	Y	76.92%
	Competing interests	Q26	Y	Y	Y	Y	Y	Y	N	N	N	N	N	N	N	46.15%
	Availability of data, code, and other materials	Q27	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100%

Abbreviations: Y, yes; PY, partially yes; N, no.

Regarding the Efficacy and Safety of Traditional Chinese Medicine as a Complementary Therapy in Combination With Chemotherapy for Gastric Cancer

According to the results of our study, the reports of ORR and DCR all show that the effect of TCMs combined with chemotherapy is more therapeutic than chemotherapy alone, and more than half of them have high or moderate quality of evidence, which also indicates that these results are quite valuable, further supporting the conclusion that TCMs as a complementary therapy combined with chemotherapy can improve antitumor efficacy. In terms of patient quality of life, whether the KPS or the QIR or the PRR, and the effect of the intervention group is better than that of the control group, indicating that the addition of TCMs can indeed enable patients to obtain a higher quality of life, which is beneficial for the treatment of patients with GC. However, the quality of

Table 6. Results of Certainty of Quality.

Author	Outcomes	Limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Quality
Tan et al[32]	Objective response rate (ORR)	−1 A	0	0	0	0	Moderate
	Disease control rate (DCR)	−1 A	0	0	0	0	Moderate
	Incidence of myelosuppression	−1 A	0	0	−1 C	0	Low
	Incidence of leucopenia	−1 A	0	0	0	0	Moderate
	Incidence of anemia	−1 A	0	0	−1 C	0	Low
	Incidence of thrombocytopenia	−1 A	0	0	0	0	Moderate
	Incidence of gastrointestinal reaction	−1 A	0	0	0	0	Moderate
	Incidence of diarrhea	−1 A	0	0	−1 C	0	LOW
	Incidence of nausea and vomiting	−1 A	−1 B	0	0	0	Low
	Incidence of hepatorenal toxicity	−1 A	0	0	−1 C	0	Low
	Incidence of hepatotoxicity	−1 A	0	0	0	0	Moderate
	Incidence of renal toxicity	−1 A	0	0	−1 C	0	Low
	Incidence of neurotoxicity	−1 A	0	0	0	0	Moderate
Zhang et al[33]	Objective response rate (ORR)	−1 A	0	0	0	−1 D	Low
	Disease control rate (DCR)	−1 A	0	0	0	−1 D	Low
	Overall Survival Time	−1 A	0	0	−1 C	0	Low
	Improvement rate of KPS	−1 A	0	0	−1 C	−1 D	Very low
	Incidence of leucopenia	−1 A	−1 B	0	−1 C	0	Very low
	Incidence of nausea and vomiting	−1 A	−1 B	0	−1 C	0	Very low
	Incidence of hand-foot syndrome	−1 A	0	0	−1 C	0	Low
	Pain relief rate (PRR)	−1 A	0	0	−1 C	0	Low
	Incidence of anemia	−1 A	0	0	−1 C	0	Low
	Incidence of diarrhea	−1 A	0	0	−1 C	−1 D	Very low
	Incidence of neurotoxicity	−1 A	−1 B	0	−1 C	0	Very low
	Incidence of oral mucositis	−1 A	−1 B	0	−1 C	0	Very low
Sun et al[34]	Objective response rate (ORR)	−1 A	0	0	0	0	Moderate
	Disease control rate (DCR)	−1 A	0	0	0	0	Moderate
	Overall survival time	−1 A	0	0	−1 C	0	Low
	Score of KPS	−1 A	−1 B	0	−1 C	0	Very low
	Quality of life improved rate (QIR)	−1 A	0	0	0	0	Moderate
	Pain relief rate (PRR)	−1 A	0	0	−1 C	0	Low
	Incidence of nausea and vomiting	−1 A	−1 B	0	0	0	Low
	Incidence of diarrhea	−1 A	0	0	0	0	Moderate
	Incidence of leucopenia	−1 A	0	0	0	0	Moderate
	Incidence of thrombocytopenia	−1 A	0	0	−1 C	0	Low
	Incidence of hepatotoxicity	−1 A	−1 B	0	−1 C	0	Very low
	Incidence of renal toxicity	−1 A	0	0	−1 C	0	Low
	Incidence of oral mucositis	−1 A	−1 B	0	−1 C	0	Very low
	Incidence of alopecia	−1 A	0	0	−1 C	0	Low
	Incidence of hand-foot syndrome	−1 A	0	0	0	0	Moderate
	Incidence of anemia	−1 A	0	0	0	0	Moderate
	Incidence of gastrointestinal reaction	−1 A	−1 B	0	0	0	Low
	Incidence of neurotoxicity	−1 A	0	0	0	0	Moderate
	Incidence of neutropenia	−1 A	0	0	−1 C	0	Low
	Incidence of myelosuppression	−1 A	−1 B	0	−1 C	0	Very low
Zhang et al[35]	Disease control rate (DCR)	−1 A	0	0	0	0	Moderate
	1-year survival rate	−1 A	0	0	−1 C	0	Low
	3-year survival rate	−1 A	0	0	−1 C	0	Low
	Incidence of nausea and vomiting	−1 A	0	0	0	0	Moderate
Chen et al[36]	Disease control rate (DCR)	0	0	0	0	0	High
	Improvement rate of KPS	0	0	0	0	−1 D	Moderate
	Incidence of leucopenia	0	0	0	0	−1 D	Moderate
	Incidence of thrombocytopenia	0	0	0	0	−1 D	Moderate
	Incidence of anemia	0	−1 B	0	0	−1 D	Low
	Incidence of gastrointestinal reaction	0	−1 B	0	0	−1 D	Low
	Incidence of neurotoxicity	0	0	0	−1 C	−1 D	Low
	Incidence of hand-foot syndrome	0	0	0	−1 C	−1 D	Low

(continued)

Table 6. (continued)

Author	Outcomes	Limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Quality
	Incidence of myelosuppression	0	0	0	−1 C	−1 D	Low
Li et al[37]	Objective response rate (ORR)	−1 A	0	0	0	−1 D	Low
	Improvement rate of KPS	−1 A	0	0	−1 C	0	Low
	Incidence of neutropenia	−1 A	−1 B	0	−1 C	0	Very low
	Incidence of leucopenia	−1 A	−1 B	0	−1 C	0	Very low
	Incidence of anemia	−1 A	0	0	−1 C	0	Low
	Incidence of thrombocytopenia	−1 A	0	0	−1 C	0	Low
	Incidence of nausea and vomiting	−1 A	−1 B	0	−1 C	0	Very low
	Incidence of hepatotoxicity	−1 A	0	0	−1 C	0	Low
	Incidence of neurotoxicity	−1 A	0	0	−1 C	0	Low
Qiao et al[38]	Disease control rate (DCR)	0	0	0	0	−1 D	Moderate
	Overall survival time	0	−1 B	0	0	−1 D	Low
	Incidence of nausea and vomiting	0	−1 B	0	0	−1 D	Low
	Incidence of leucopenia	0	0	0	0	−1 D	Moderate
Liang et al[39]	Quality of life improved rate (QIR)	−1 A	−1 B	0	−1 C	0	Very low
	Overall survival time	−1 A	0	0	−1 C	−1 D	Very low
Xu et al[40]	1-year survival rate	−1 A	0	0	0	−1 D	Low
	3-year survival rate	−1 A	0	0	−1 C	−1 D	Very low
	Incidence of leucopenia	−1 A	0	0	0	−1 D	Low
	Incidence of nausea and vomiting	−1 A	0	0	0	−1 D	Low
Chen et al[41]	Objective response rate (ORR)	−1 A	0	0	0	0	Moderate
	Improvement rate of KPS	−1 A	−1 B	0	0	−1 D	Very low
	Incidence of nausea and vomiting	−1 A	−1 B	0	0	−1 D	Very low
Wang et al[42]	Score of KPS	−1 A	−1 B	0	0	−1 D	Very low
	Incidence of leucopenia	−1 A	−1 B	0	−1 C	−1 D	Very low
	Incidence of anemia	−1 A	−1 B	0	−1 C	−1 D	Very low
	Incidence of thrombocytopenia	−1 A	0	0	−1 C	−1 D	Very low
	Incidence of hepatotoxicity	−1 A	0	0	−1 C	−1 D	Very low
	Incidence of renal toxicity	−1 A	0	0	−1 C	−1 D	Very low
	Incidence of nausea and vomiting	−1 A	0	0	−1 C	−1 D	Very low
	Incidence of diarrhea	−1 A	−1 B	0	−1 C	−1 D	Very low
	Incidence of neurotoxicity	−1 A	0	0	−1 C	−1 D	Very low
Wu et al[43]	Disease control rate (DCR)	−1 A	0	0	0	−1 D	Low
	Improvement rate of KPS	−1 A	0	0	0	−1 D	Low
	Incidence of nausea and vomiting	−1 A	0	0	0	−1 D	Low
	Incidence of diarrhea	−1 A	0	0	−1 C	−1 D	Very low
	Incidence of leucopenia	−1 A	−1 B	0	0	−1 D	Very low
	Incidence of neurotoxicity	−1 A	0	0	−1 C	−1 D	Very low
Zhao et al[44]	Disease control rate (DCR)	0	−1 B	0	0	−1 D	Low
	Incidence of adverse reactions (Mainly including gastrointestinal reaction and myelosuppression)	0	0	0	−1 C	−1 D	Low

A, The included studies have a large bias in methodology such as randomization, allocation concealment, and blinding. B, The confidence interval overlaps less or the *I*2 value of the combined results was larger. C, The sample size from the included studies does not meet the optimal sample size or the 95% confidence interval crosses the invalid line. D, The funnel chart is asymmetry.

outcome evidence in this area is relatively poor compared to that in antitumor, so the support for the combination of TCMs and chemotherapy in improving the survival quality of GC patients is somewhat weakened. On survival time, because many results showed that TCMs combined with chemotherapy cannot confer longer survival than chemotherapy alone, and the quality of available evidence on the outcomes of TCMs combined with chemotherapy improving patient survival time was low, we cannot be sure of the conclusion that the addition of TCMs can prolong patient survival time.

Although these SRs/MAs reported results on various adverse reactions, due to inconsistencies in some of the results and insufficient evidence quality, we can only make the judgment that the treatment plan of TCMs combined with chemotherapy has advantages in only some aspects. It can reduce the occurrence of leucopenia, gastrointestinal reactions, nausea and vomiting, and hand-foot syndrome, but it cannot seem to be helpful for myelosuppression, anemia, thrombocytopenia, neutropenia, hepatotoxicity, renal toxicity, neurotoxicity, oral mucositis, or alopecia.

Table 7. Summary of Evidence.

Author	Outcomes	Studies (Participants)	Heterogeneity (%)	Relative effect (95% CI)	*P*-value	Quality
Tan et al[32]	Objective response rate (ORR)	40 (3029)	0	RR = 1.35 (1.25, 1.45)	<.001	Moderate
	Disease control rate (DCR)	40 (3029)	0	RR = 1.12 (1.08, 1.16)	<.001	Moderate
	Incidence of myelosuppression	11 (819)	0	RR = 0.50 (0.41, 0.61)	<.001	Low
	Incidence of leucopenia	23 (1717)	0	RR = 0.54 (0.48, 0.61)	<.001	Moderate
	Incidence of anemia	14 (926)	3.25	RR = 0.77 (0.64, 0.92)	<.001	Low
	Incidence of thrombocytopenia	21 (1484)	0	RR = 0.57 (0.47, 0.70)	<.001	Moderate
	Incidence of gastrointestinal reaction	14 (1017)	11	RR = 0.55 (0.47, 0.64)	<.001	Moderate
	Incidence of diarrhea	9 (620)	0	RR = 0.54 (0.42, 0.69)	<.001	Low
	Incidence of nausea and vomiting	20 (1506)	39.16	RR = 0.61 (0.51, 0.73)	<.001	Low
	Incidence of hepatorenal toxicity	9 (779)	0	RR = 0.71 (0.56, 0.89)	<.001	Low
	Incidence of hepatotoxicity	20 (1374)	23.38	RR = 0.65 (0.52, 0.81)	<.001	Moderate
	Incidence of renal toxicity	12 (802)	0	RR = 0.55, (0.40, 0.77)	<.001	Low
	Incidence of neurotoxicity	27 (1980)	0	RR = 0.70 (0.61, 0.80)	<.001	Moderate
Zhang et al[33]	Objective response rate (ORR)	12 (853)	0	RR = 1.28 (1.10-1.48)	.001	Low
	Disease control rate (DCR)	11 (796)	9	RR = 1.12 (1.04-1.20)	.003	Low
	Overall Survival Time	2 (205)	0	HR = 0.94 (0.75-1.18)	.59	Low
	Improvement rate of KPS	6 (NR)	0	RR = 1.83 (1.40-2.39)	<.001	Very low
	Incidence of leucopenia	6 (NR)	50	RR = 0.76 (0.58-0.99)	.04	Very low
	Incidence of nausea and vomiting	5 (NR)	47	RR = 0.68 (0.53-0.86)	.001	Very low
	Incidence of hand-foot syndrome	3 (NR)	0	RR = 0.55 (0.33-0.91)	.02	Low
	Pain relief rate (PRR)	2 (NR)	0	RR = 1.81 (1.30-2.54)	<.001	Low
	Incidence of anemia	3 (NR)	0	RR = 0.79 (0.58-1.08)	.14	Low
	Incidence of diarrhea	5 (NR)	0	RR = 0.77 (0.52-1.15)	.21	Very low
	Incidence of neurotoxicity	3 (NR)	91	RR = 0.57 (0.23-1.43)	.23	Very low
	Incidence of oral mucositis	2 (NR)	88	RR = 0.37 (0.04-3.47)	.39	Very low
Sun et al[34]	Objective response rate (ORR)	26 (1898)	0	OR = 1.88 (1.54-2.31)	<.001	Moderate
	Disease control rate (DCR)	25 (1841)	0	OR = 2.05 (1.63-2.58)	<.001	Moderate
	Overall Survival Time	3 (366)	0	OR = 1.43 (0.89-2.30)	.14	Low
	Score of KPS	3 (180)	79	MD = 7.00 (2.25-11.75)	.004	Very low
	Quality of life improved rate (QIR)	12 (947)	5	OR = 2.39 (1.81-3.15)	<.001	Moderate
	Pain relief rate (PRR)	3 (201)	32	OR = 4.06 (2.24-7.35)	<.001	Low
	Incidence of nausea and vomiting	NR (889)	37	OR = 0.55 (0.41-0.74)	<.001	Low
	Incidence of diarrhea	NR (774)	0	OR = 0.65 (0.46-0.90)	.01	Moderate
	Incidence of leucopenia	NR (849)	34	OR = 0.62 (0.47-0.82)	<.001	Moderate
	Incidence of thrombocytopenia	NR (356)	0	OR = 0.69 (0.44-1.11)	.13	Low
	Incidence of hepatotoxicity	NR (386)	56	OR = 0.53 (0.24-1.16)	.11	Very low
	Incidence of renal toxicity	NR (224)	0	OR = 0.56 (0.16-1.95)	.36	Low
	Incidence of oral mucositis	NR (468)	64	OR = 0.62 (0.28-1.34)	.22	Very low
	Incidence of alopecia	NR (263)	0	OR = 0.61 (0.24-1.56)	.3	Low
	Incidence of hand-foot syndrome	NR (690)	0	OR = 0.57 (0.41-0.79)	<.001	Moderate
	Incidence of anemia	NR (583)	0	OR = 0.69 (0.48-0.99)	.05	Moderate
	Incidence of gastrointestinal reaction	NR (572)	57	OR = 0.56 (0.32-1.00)	.05	Low
	Incidence of neurotoxicity	NR (528)	0	OR = 0.32 (0.20-0.50)	<.001	Moderate
	Incidence of neutropenia	NR (110)	0	OR = 0.45 (0.14-1.42)	.17	Low
	Incidence of myelosuppression	NR (184)	80	OR = 0.38 (0.08-1.84)	.23	Very low
Zhang et al[35]	Disease control rate (DCR)	9 (664)	0	OR = 1.96 (1.39, 2.78)	<.001	Moderate
	1-year survival rate	4 (311)	0	OR = 3.25 (1.90, 5.54)	<.001	Low
	3-year survival rate	4 (311)	0	OR = 1.71 (1.06, 2.78)	.03	Low
	Incidence of nausea and vomiting	10 (760)	0	OR = 0.47 (0.34, 0.64)	<.001	Moderate
Chen et al[36]	Disease control rate (DCR)	8 (890)	0	OR = 1.44 (1.09, 1.90)	.01	High
	Improvement rate of KPS	10 (1011)	0	OR = 2.86, (2.11, 3.86)	<.001	Moderate
	Incidence of leucopenia	15 (2218)	6	OR = 0.21 (0.16, 0.26)	<.001	Moderate
	Incidence of thrombocytopenia	9 (1173)	29	OR = 0.30 (0.19, 0.48)	<.001	Moderate
	Incidence of anemia	7 (648)	54	OR = 0.33 (0.19, 0.59)	<.001	Low
	Incidence of gastrointestinal reaction	12 (1919)	37	OR = 0.31 (0.24, 0.40)	<.001	Low
	Incidence of neurotoxicity	5 (356)	0	OR = 0.33, (0.20, 0.55)	<.001	Low

(continued)

Table 7. (continued)

Author	Outcomes	Studies (Participants)	Heterogeneity (%)	Relative effect (95% CI)	*P*-value	Quality
	Incidence of hand-foot syndrome	5 (495)	0	OR = 0.31 (0.21, 0.45)	<.001	Low
	Incidence of myelosuppression	3 (196)	0	OR = 0.31 (0.17, 0.56)	<.001	Low
Li et al[37]	Objective response rate (ORR)	13 (948)	12	RR = 1.39 (1.24, 1.57)	<.001	Low
	Improvement rate of KPS	4 (246)	0	RR = 1.53 (1.19, 1.96)	<.001	Low
	Incidence of neutropenia	5 (392)	44	RR = 0.68 (0.55, 0.84)	<.001	Very low
	Incidence of leucopenia	4 (292)	40	RR = 0.69 (0.54, 0.90)	.006	Very low
	Incidence of anemia	5 (373)	0	RR = 0.65 (0.40, 1.04)	.07	Low
	Incidence of thrombocytopenia	6 (414)	32	RR = 0.66 (0.46, 0.96)	.03	Low
	Incidence of nausea and vomiting	8 (562)	85	RR = 0.50 (0.32, 0.80)	.004	Very low
	Incidence of hepatotoxicity	3 (260)	0	RR = 0.63 (0.33, 1.20)	.16	Low
	Incidence of neurotoxicity	3 (188)	0	RR = 0.64 (0.26, 1.55)	.32	Low
Qiao et al[38]	Disease control rate (DCR)	19 (1673)	26	RR = 1.77 (1.12, 1.22)	<.001	Moderate
	Overall survival time	6 (469)	50	RR = 0.57 (0.44, 0.73)	<.001	Low
	Incidence of nausea and vomiting	14 (1228)	48	RR = 0.49 (0.41, 0.57)	<.001	Low
	Incidence of leucopenia	14 (1228)	34	RR = 0.49 (0.44, 0.55)	<.001	Moderate
Liang et al[39]	Quality of life improved rate (QIR)	3 (360)	83	OR = 12.88 (2.30, 71.99)	.004	Very low
	Overall survival time	2 (188)	0	OR = 1.80 (0.98, 3.28)	.06	Very low
Xu et al[40]	1-year survival rate	4 (399)	0	OR = 2.17 (1.15, 4.08)	.02	Low
	3-year survival rate	4 (407)	0	OR = 2.26 (1.51, 3.99)	<.001	Very low
	Incidence of leucopenia	10 (666)	0	OR = 0.16 (0.11, 0.23)	<.001	Low
	Incidence of nausea and vomiting	10 (728)	9	OR = 0.20 (0.14, 0.28)	<.001	Low
Chen et al[41]	Objective response rate (ORR)	17 (1447)	0	OR = 1.90 (1.53, 2.36)	<.001	Moderate
	Improvement rate of KPS	9 (869)	53	OR = 2.35 (1.77, 3.13)	<.001	Very low
	Incidence of nausea and vomiting	11 (958)	56	OR = 0.29 (0.19, 0.45)	<.001	Very low
Wang et al[42]	Score of KPS	6 (455)	74	MD = 7.24 (5.17, 9.31)	<.001	Very low
	Incidence of leucopenia	6 (404)	79	RR = 0.64 (0.46, 0.89)	.007	Very low
	Incidence of anemia	5 (344)	83	RR = 0.60 (0.39, 0.93)	.02	Very low
	Incidence of thrombocytopenia	5 (347)	34	RR = 0.72 (0.54, 0.97)	.03	Very low
	Incidence of hepatotoxicity	5 (359)	0	RR = 0.69 (0.29, 1.64)	.41	Very low
	Incidence of renal toxicity	5 (359)	0	RR = 0.59 (0.18, 2.00)	.4	Very low
	Incidence of nausea and vomiting	4 (267)	0	RR = 0.54 (0.41, 0.70)	<.001	Very low
	Incidence of diarrhea	4 (267)	38	RR = 0.61 (0.39, 0.95)	.03	Very low
	Incidence of neurotoxicity	3 (207)	0	RR = 0.47 (0.21, 1.06)	.07	Very low
Wu et al[43]	Disease control rate (DCR)	15 (797)	0	OR = 1.67 (1.24, 2.26)	<.001	Low
	Improvement rate of KPS	8 (466)	0	OR = 4.75 (2.87, 7.86)	<.001	Low
	Incidence of nausea and vomiting	10 (640)	0	OR = 0.33 (0.22, 0.48)	<.001	Low
	Incidence of diarrhea	8 (389)	0	OR = 0.30 (0.19, 0.48)	<.001	Very low
	Incidence of leucopenia	12 (679)	41	OR = 0.52 (0.36, 0.74)	<.001	Very low
	Incidence of neurotoxicity	9 (437)	19	OR = 0.48 (0.31, 0.75)	.001	Very low
Zhao et al[44]	Disease control rate (DCR)	13 (1215)	45	RR = 1.51 (1.34, 1.70)	<.001	Low
	Incidence of adverse reactions (Mainly including gastrointestinal reaction and myelosuppression)	5 (505)	12	RR = 0.51 (0.38, 0.69)	<.001	Low

Abbreviations: NR, not report.

Overall, narrative analysis indicates that TCMs is an effective complementary treatment for GC chemotherapy patients, which can enhance disease control and relief, improve patients' quality of life, and reduce the occurrence of some adverse reactions. However, the overall poor quality of the included SRs/MAs may hinder its use as a scientific guide for clinical practice, so it is still necessary to be cautious when recommending TCMs as complementary therapy combined with chemotherapy for GC. In this current situation, medication can be guided based on Chinese medicine theories with a long history, such as syndrome differentiation and corresponding prescriptions, to ensure efficacy and safety.

Implications for Future Practice and Research

As an important means of Chinese medicine in the treatment of GC, TCMs has the characteristics of multiple targets, significant efficacy and few adverse reactions; TCM formula, Chinese patent medicine and TCM injection all have played a positive role in the treatment process.[51,52] At present, the

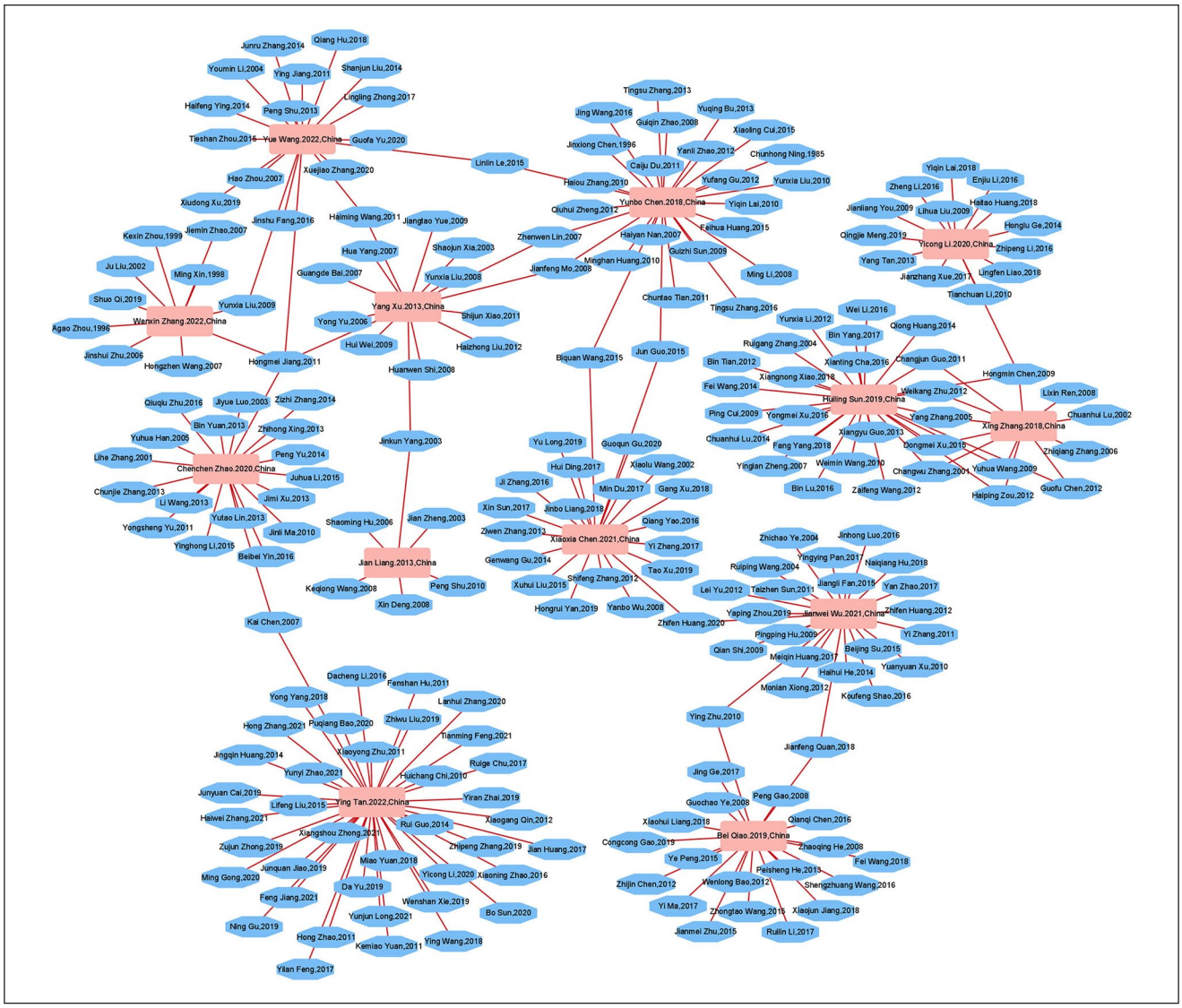

Figure 3. Network diagram incorporating SRs/MAs with RCTs.

anti-tumor mechanism of TCMs cannot be fully revealed, but there are many studies have reported multiple molecules and several pathways involved in the treatment of GC by TCMs.[53-55] In clinical practice, we also found that the regimens of TCMs combined with chemotherapy were superior to chemotherapy alone both in terms of efficacy in treating tumors, as well as in the incidence of adverse reactions. Patients could achieve better clinical remission and survival for the control of the disease, higher quality of life and dignity of life, fewer adverse reactions, a relatively better treatment experience with TCM treatment, and this aspect was also confirmed by a large number of studies.[56,57] Therefore, we expect that TCMs can be more widely and standardized used with chemotherapy for GC, which also requires a large number of SRs/MAs with the highest evidence-based level on this issue to support it. However, the quality of available relevant studies is unsatisfactory, leading to an inability to robustly support the widespread and standardized combination of TCMs into the chemotherapeutic treatment of GC, which requires a higher quality and level of relevant SRs/MAs in the future. We strongly recommend that future SRs/MAs be refined and improved on multiple fronts. Before the start of the SRs/MAs, researchers should register or publish the study protocol in advance to minimize the risk of bias, make the study transparent, and ensure the reliability of the results. In order to increase the reproducibility of the study and reduce the publication bias, researchers should comprehensively search the literature as much as possible, including the gray literature, provide a complete search strategy list of each electronic database, a list of excluded literatures, and the funding source of the RCTs. Moreover, researchers should also conduct sensitivity analysis during the course of the study to improve the reliability of

the study. For the high risk of bias in SRs/MAs, investigators should provide reasonable explanations to ensure the quality of conclusion. Furthermore, conducting a complete publication bias assessment will also improve the accuracy of meta-analysis results. In addition, more high-quality RCTs with good design, rigorous implementation and complete reporting are the cornerstone of research in this topic, which can well avoid the risk of bias.[58] It cannot be ignored that TCMs have the characteristics of a large variety of drugs and formulas as well as a flexible type of preparation, the difference of them may cause different results. Only a few of the SRs/MAs we included tried to solve this problem, which is far from enough. So, we suggest that future researchers can adopt more standardized medication regimens and more meticulous grouping studies when conducting RCTs and SRs/MAs, in order to more specifically study the effects of TCMs as complementary therapy in GC chemotherapy. Besides, the current indicators for efficacy evaluation are mostly focused on the rate of clinical control and remission, and we suggest that increased attention be paid to more objective and quantitative indicators such as tumor markers and biochemical indicators in subsequent studies to better investigate the underlying mechanisms of TCMs in the treatment process and to make clinical research more scientific.

Strengths and Limitations

Our study is the first to evaluate SRs/MAs based on RCTs which regarding TCMs as complementary therapy in combine with chemotherapy for GC according to AMSTAR-2, ROBIS, PRISMA 2020, and GRADE. It can give clinicians helpful advice on developing treatment options. This study also revealed obvious limitations and defect of current SRs/MAs and RCTs, which can help guide the design and conduct of future high-quality clinical research. However, at the same time, the overview has certain limitations because the assessment is subjective. Although our assessments were assessed and reviewed by 2 independent assessors, it is possible that the assessors had their own personal judgments and cognitive biases for each factor and thus the results may have bias. And we found that many of the included SRs/MAs were of poor quality, which might result in reduced confidence in the final conclusions.

Conclusion

TCMs may be an effective and safe complementary therapy in combination with chemotherapy for the treatment of GC, especially in enhancing control and remission of tumors. However, due to the generally poor quality of the existing SRs/MAs and RCTs, which reduce the reliability of the conclusions, physicians should treat these findings with caution in the clinical treatment process. And in order to provide convincing evidence for relevant researchers and clinicians, more high-quality clinical studies of TCMs as a complementary therapy in combine with chemotherapy for GC should be conducted, and the quality of relevant SRs/MAs should be improved.

Author Contributions

Weijian Xie designed the study. Weijian Xie, Meiqi Lu, Yunsong Zhang contributed to the publications search and data extraction. Weijian Xie and Shijun Wang performed data assessment. Weijian Xie, Yunsong Zhang, Meiqi Lu, and Shijun Wang wrote sections of the manuscript. Jingyun Tang and Xiaolin Zhu helped with manuscript revision. All authors reviewed the manuscript. All authors read and approved the final version of the manuscript. Weijian Xie is the first author. Both Meiqi Lu and Shijun Wang are the leaders of this study, and they jointly played a guiding and coordinating role in the research process. Meiqi Lu and Shijun Wang are both corresponding authors.

Data Availability Statement

The original contributions presented in the study are included in the article/supplementary materials. Further inquiries can be directed to the corresponding author.

Declaration of Conflicting Interests

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Trial Registration Number

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Supplemental Material

Supplemental material for this article is available online.

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