

Effect of Quxie capsule in patients with colorectal cancer

A systematic review and meta-analysis

Suqin Zhang, MD^{a,*}, Peng Lian, MD^b, Tao Huang, MS^c, Jianhua Zhou, BS^a

Abstract

Objective: To investigate whether the Quxie capsule can decrease relapse, metastasis, and symptoms, as well as alleviate the side effects in colorectal cancer (CRC) patients.

Methods: A comprehensive literature search of multiple databases was performed. Two reviewers independently selected trials that assessed the relapse-metastasis rate, degree of symptoms, and side effects of Quxie capsule for CRC. The meta-analysis was performed using Review Manager 5.3.

Results: This meta-analysis included 6 studies, with a total of 408 cases. The quality of the included studies was generally low, with only 1 trial of high quality. A statistically significant difference was observed in the relapse-metastasis rate between the Quxie capsule and control groups after 2-years follow-up ($n = 185$, relative risk (RR) = 0.13, 95% confidence interval (CI) 0.04–0.46; $P = .002$). The Quxie capsule was found to reduce the traditional Chinese medicine symptom score as compared to the control ($n = 208$, weighted mean differences (WMD) = -4.15 , 95% CI -7.30 to -1.00 ; $P = .010$), while it showed no significant improvement in the Karnofsky Performance Status score ($n = 138$, WMD = 5.05; 95% CI -2.95 to 13.04; $P = .22$). There was no difference in adverse events between the 2 groups ($P = .66$).

Conclusion: This systematic review and meta-analysis showed no clear superiority of Quxie capsule for CRC patients receiving chemotherapy. The effect of Quxie capsule in CRC patients should be examined by high quality, large sample size, multi-center RCTs, with longer follow-up.

Abbreviations: AEs = adverse events, CI = confidence interval, CRC = colorectal cancer, KPS = Karnofsky Performance Status, RR = relative risk, TCM = traditional Chinese medicine, WMD = weighted mean differences.

Keywords: colorectal cancer, meta-analysis, Quxie capsule, relapse-metastasis rate, systematic review

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^a Department of Traditional Chinese Medicine, Shanghai Eighth People's Hospital,

^b Department of Colorectal Surgery, Fudan University Shanghai Cancer Center,

^c Department of Gastrointestinal Surgery, Shanghai Eighth People's Hospital, Shanghai, China.

* Correspondence: Suqin Zhang, Department of Traditional Chinese Medicine, Shanghai Eighth People's Hospital, Shanghai, China (e-mail: zhangsuqin2013@163.com).

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1. Introduction

Colorectal cancer (CRC), including colon and rectal cancers, is one of the most common types of cancer worldwide.^[1] CRC has the third highest incidence (10.2% of the total cases) and second highest mortality (8.2% of the total cancer deaths) among all cancers.^[2] In general, decrease in CRC mortality rates has been observed in numerous countries worldwide, which is most likely attributed to CRC screening, reduced prevalence of risk factors, and/or improved treatments. However, the mortality rates continue to increase in countries that have limited resources and increasing incidence.^[3]

Surgical resection of the primary tumor is the standard treatment for CRC in both early and advanced stages. Traditionally, in metastatic or advanced colorectal malignant disease, resection of the primary tumor was advocated as a mainstay of effective palliation. Approximately 15% of CRC patients present as a surgical emergency in the United States.^[4] Meanwhile, population-based studies have shown that 25% to 30% of patients diagnosed with CRC develop liver metastases during the course of their disease.^[5] Nevertheless, the primary goal is palliation in patients with metastatic disease who are unable to undergo surgery, with a focus on symptomatic control and maintenance of quality of life.^[6] Chemotherapy and radiotherapy remain the main treatments for metastatic and local late-stage CRC; while side effects and resistance to

chemotherapy or radiotherapy are the primary limitations that necessitate the search for alternative treatments.^[7,8]

Complementary and alternative medicine is commonly used for treatment of cancer patients. Data from the 2002 National Health Interview Survey (n=31,044) found that 62% of US adults reported using at least 1 type of complementary and alternative medicine in a year.^[9] Recent evidence indicates that traditional Chinese medicine (TCM) might be a promising complementary and alternative therapy for patients with CRC to prevent tumorigenesis, minimize toxicity of chemotherapy or radiotherapy, reinforce the treatment effect, improve quality of life, and revert multi-drug resistance.^[10-12] The formula for Quxie capsule was developed by Zhong-zi LI, a TCM doctor in the Ming dynasty, which was subsequently improved by Yu-fei Yang and used for more than a decade.^[13] The composition of Quxie capsule is as follows: *Croton tiglium*, *Evodia rutaecarpa*, *Rhizoma zingiberis*, *Cinnamomum cassia* Presl, *Radix aconiti*, *Pinellia ternata*, and *Pericarpium Citri Reticulatae*. A previous study found that Quxie capsule combined with chemotherapy reduces the risk of postoperative recurrence and metastasis in patients with stage II-III CRC.^[7] However, the effect of Quxie capsule has not been systemically reviewed as an adjuvant drug to decrease metastasis, relieve painful symptoms, and alleviate the side effects of CRC patients receiving chemotherapy.

Luo et al in 2006 reported that Quxie capsule reduced the relapse-metastasis rate in CRC patients after 2-year follow-up,^[14] while Yang in 2007 reported an adverse result.^[15] Therefore, a systematic review and meta-analysis were conducted to compare the relapse-metastasis rate, degree of painful symptoms, and side effects of CRC patients treated with chemotherapy combined with Quxie capsule or chemotherapy alone.

2. Methods

2.1. Databases and search strategy

Institutional Review Board approval was not required because this article is a meta-analysis. The data comes from published articles and does not require ethical approval.

The PubMed, EMBASE, Cochrane Central Register of Controlled Trials, ClinicalTrials.gov, China Academic Journals (CNKI) (including China Doctor/Master Dissertation Full Text Database and China Proceedings Conference Full Text Database), Chinese Science and Technology Journals (CQVIP), WanFang Database, and Chinese BioMedical Literature Database (CBM) were searched from their inception to December 2019. The keywords were related to colorectal cancer, and Quxie capsule. The English terms used were (colorectal cancer OR colorectal tumor OR colorectal carcinoma OR colorectal neoplasm OR CRC OR rectal cancer OR rectal tumor OR rectal carcinoma OR colon cancer OR colon tumor OR colon carcinoma) and (Quxie OR traditional Chinese medicine OR Chinese medicine OR Chinese herbs OR TCM). The reference lists of the retrieved articles were also reviewed to identify additional studies. Conference papers were manually searched. No language restrictions were imposed.

2.2. Selection criteria

The selection of studies for inclusion was independently conducted by 2 reviewers (Suqin Zhang and Peng Lian). They screened the abstracts of all identified potential studies. The full texts of all potentially relevant articles were then retrieved for comprehensive

assessment of inclusion criteria. Any disagreement was resolved by discussion or consensus with a third author.

The included studies met the following criteria:

1. randomized controlled trial (RCT) or non-RCT;
2. CRC patients undergoing chemotherapy, who were confirmed by cytology or pathology, with or without surgery;
3. intervention involving administration of Quxie capsule, and/or chemotherapy, radiotherapy, targeted therapy, and supportive care, as well as control;
4. outcomes measures were as follows: relapse-metastasis rate as primary outcome, and TCM symptom score, Karnofsky Performance Status (KPS) score, adverse events (AEs), and safety evaluation as secondary outcomes.

The TCM symptom score was used to guide the diagnosis and treatment of digestive diseases in TCM. The degree of fatigue and weakness, poor appetite, abdominal distention and pain, and abnormal stool were recorded as 0, 1, 2, 3 points, respectively. The higher the score, the more serious were the symptoms.^[16] The maximum KPS score was 100, which implied full functional capability to perform normal daily activities without clinical evidence (symptoms or signs) of disease, and the minimum score was zero, which implied death.^[17] When multiple articles using overlapping sample data were published, only the most recent study or research with sufficient information was selected.

Studies were excluded due to the following reasons:

1. did not meet the above criteria;
2. reviews, meeting abstracts, and cell/animal experiments;
3. did not enroll control treatment.

2.3. Data extraction

Data was independently extracted by 2 reviewers (Suqin Zhang and Peng Lian). All study characteristics and outcome data were independently extracted according to predefined criteria using standard data extraction forms. Any disagreement was resolved by discussion or consensus with a third author. Duplicate publications, missing data, changes in data, median data, and standard deviation were assessed by methods mentioned in the Cochrane Handbook.^[18]

2.4. Quality assessment

Selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), reporting bias (selective reporting), and other biases were evaluated according to the criteria of the Cochrane Handbook for Systematic Reviews of Interventions.^[18] Three potential bias judgments, low risk, high risk, and unclear risk, were determined for each trial. Any disagreements between the 2 reviewers were resolved by discussion with a third reviewer.

2.5. Statistical analysis

The Cochrane Collaboration software Review Manager 5.3 was used to perform the statistical analysis. Weighted mean differences (WMD) with 95% confidence interval (CI) were calculated for continuous data, and standardized mean differences were calculated for data measured in different ways by each trial.

Dichotomous data were expressed as relative risk (RR) or odds ratio with 95% CI. I^2 test was used to assess the heterogeneity of the data. If heterogeneity existed ($I^2 \geq 50\%$), a random-effects model was applied; otherwise, a fixed-effects model was applied. Statistically significant difference was considered as $P < .05$. We had originally planned to assess potential publication bias by funnel plots and Egger test, but were unable to do so because the number of studies included in the meta-analysis was fewer than 10, in which case the funnel plots and Egger test could yield misleading results and were not recommended.^[18]

3. Results

3.1. Search results and study characteristics

A total of 213 articles were retrieved by searching the databases. After screening the titles and abstracts to exclude the articles that

did not meet the inclusion criteria, a total of 6 studies were identified. Five trials were published in Chinese,^[14,15,19-21] and 1 in English.^[13] The flow diagram for study selection process is presented in Figure 1.

Five studies were RCTs, and 1 was non-RCT. The sample sizes of the trials ranged from 37 to 101. A total of 408 patients were enrolled in the studies, of which 202 patients participated in conventional therapy with Quxie capsule. Four trials enrolled postoperative patients with CRC,^[14,15,19,20] while 2 enrolled metastatic CRC patients,^[13,21] 1 study included patients with distant or local lymph node metastasis of CRC who could not undergo radical surgery.^[21] The administration duration of Quxie capsule ranged from 3 to 6 months, and the follow-up ranged from 12 weeks to 3 years. Table 1 shows the main characteristics of each trial included in the meta-analysis.

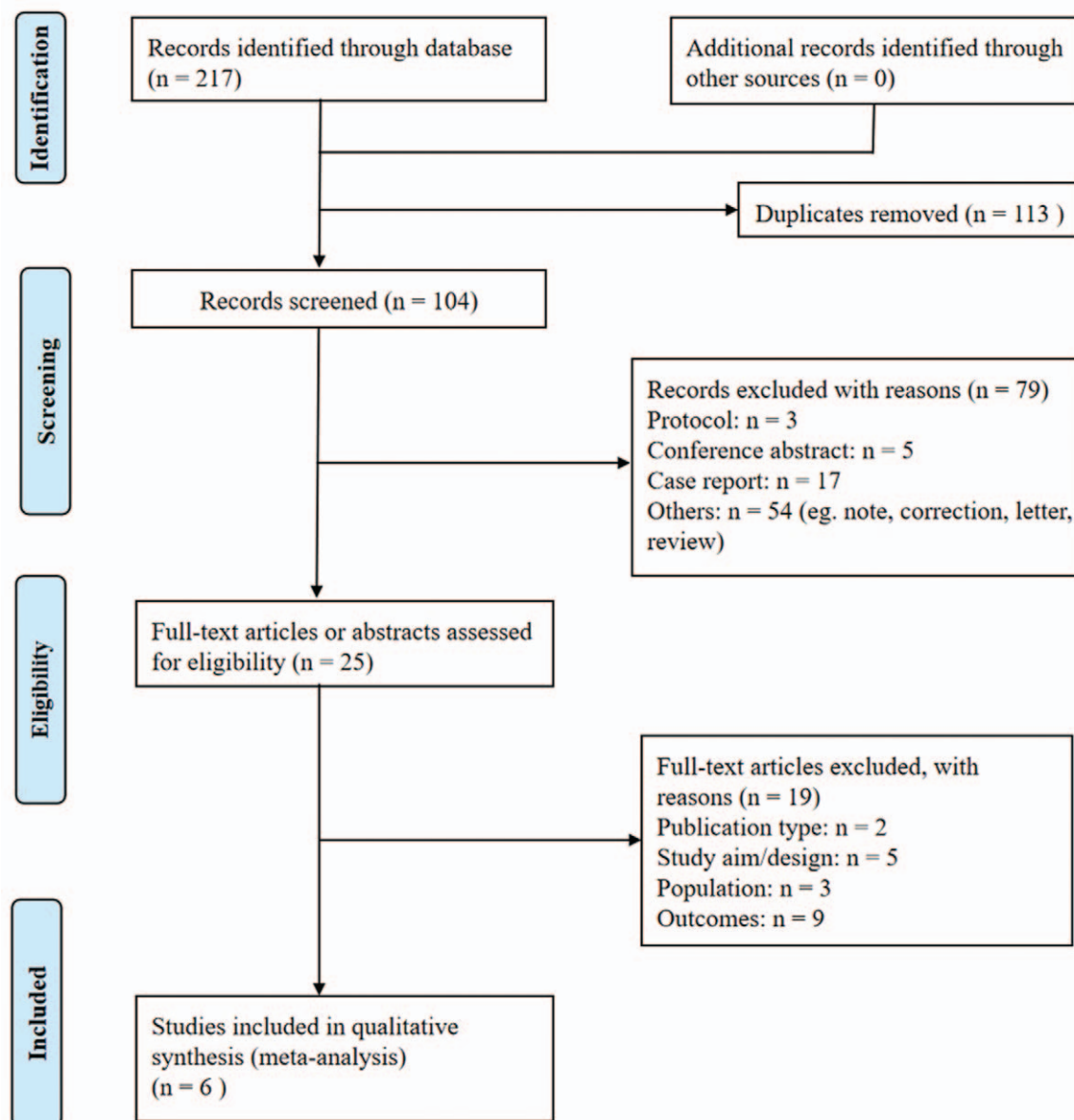


Figure 1. PRISMA flow diagram.

Table 1
Characteristics of the included studies.

Study	Patients	Treatment	Control	Administration of Quxie capsule	Sample size	Follow-up	Outcome
Zhang, 2018	Metastatic CRC, adenocarcinoma, at least one of the KRAS, NRAS, BRAF gene status, KPS score over 70	Conventional therapy (chemotherapy, radiotherapy, targeted therapy and best supportive care) combined with Quxie capsule	Conventional therapy combined with placebo	Orally administered at 50 mg/kg twice daily, day 1–20 in a 30-day course, with 3 courses of treatment	30/30	Every 3 months after 3 courses of treatment, follow up over than 1 year	Overall survival, progression-free survival, WBC, HGB, PLT, ALT, AST, Cr, AEs
Lei, 2017	Postoperative patients with CRC	Conventional therapy (chemotherapy, and targeted therapy), Fupiyichang Decoction, Fuzheng and Quxie capsule	Conventional therapy, and Fupiyichang Decoction	Orally initial dose 1# once daily, added 1# each week until 6# once daily, 12 weeks in a row, waited for 1 month then continued for 12 weeks	35/35	12 weeks	Scores of TCM symptom, CEA, IgA, IgG, clinical efficacy, AEs
Yang, 2015	Postoperative patients with CRC, II or III TNM stage, received chemotherapy	Chemotherapy combined with Quxie capsule for 6 months	Chemotherapy	Orally initial dose 1# once daily, added 1# each week until 6# once daily, 3 months in a row, waited for 1 month then continued for 3 months	48/48	6 months, 1, 2, and 3 years	Relapse-metastasis rate, relapse-metastasis time
Yang, 2008	Patients with distant or local lymph metastasis of CRC cannot undergo radical surgery	Conventional therapy (chemotherapy, targeted therapy and best supportive care) combined with Quxie capsule	Conventional therapy	Orally administered at 50 mg/kg twice daily, day 1–20 in a 30-day course, with 3 courses of treatment	18/19	NA	Fatality rate, survival time, median survival time, time to progression, quality of life, TCM symptom score, KPS, WBC, HGB, PLT, ALT, BUN, Cr, AEs
Yang, 2007	Postoperative patients with CRC in 2 years, II or III TNM stage	Ila: Quxie Capsule for 6 months Iib and Iii: chemotherapy, radiotherapy, Quxie capsule	Ila: Placebo for 6 months Iib and Iii: chemotherapy, radiotherapy, placebo	Orally initial dose 1# twice daily for 3 days, then added to 2# twice daily for 1 month, stop for 1 week, then continued for 6 months	23/21	6 months, 1, 2, and 3 years	Relapse-metastasis rate, scores of TCM symptom, KPS, CD3, CD4, CD8, CD4/CD8, NK, and B cell, AEs
Luo, 2006	Postoperative patients with CRC, B or C Dukes' stage, II or III TNM stage, received chemotherapy	Chemotherapy, and Quxie capsule	Chemotherapy, and Fuzheng capsule for 6 months	Orally initial dose 1# once daily, added 1# each week until 6# once daily, 3 months in a row, waited for 1 month then continued for 3 months	48/53	1, 2 and 3 years	Relapse-metastasis rate, AEs

AEs = adverse events, ALT = glutamic-pyruvic transaminase, AST = glutamicoxal acetic transaminase, BUN = blood urea nitrogen, CEA = carcino-embryonic antigen, Cr = creatinine, CRC = colorectal cancer, HGB = hemoglobin, KPS = Karnofsky Performance Status, PLT = platelet; TCM = traditional Chinese medicine, TNM = tumor-node-metastases, WBC = white blood cell count.

3.2. Quality assessment

The quality of the included studies was generally low, and only 1 trial was rated as high quality.^[13] Four trials described the special randomization method, of which 2 trials used the random sequence generation,^[20,21] while the other 2 used the block random seed produced by the seed generator of Statistics Analysis System (Proc Plan).^[13,15] Only Zhang et al reported that the random seed were sealed in a blind record as secret data, and all trial personnel, participants, and clinicians were blinded to treatment. Thus, the Zhang et al trial reported allocation concealment, blinding of participants and personnel, and blinding of outcome assessment.^[13] Only Yang et al adopted placebo to achieve patient blinding.^[15] The drop-out rate of 1

trial was >50% at 3-years follow-up, which was rated as high risk of attrition bias.^[15] Only 1 trial was registered in the peer-reviewed Chinese Clinical Trial Registry (No. ChiCTR-IOR-16009733) and was checked for no selective reporting.^[15] The other biases could not be excluded. The risk of bias is shown in Figures 2 and 3.

4. Main results

4.1. Relapse-metastasis rate

Three studies^[14,15,20] reported the relapse-metastasis rate during 1 to 3years follow-up. The results indicated a statistically

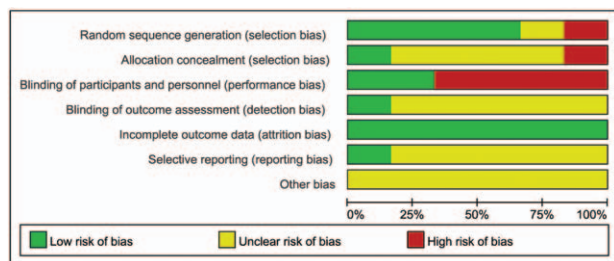


Figure 2. Risk of bias summary.

significant difference between the Quxie capsule and control groups in 2-years follow-up (3 studies, n=185, RR=0.13, 95% CI 0.04–0.46; P=.002), as compared to 1-year follow-up (3 studies, n=215, RR=0.19, 95% CI 0.03 to 1.01; P=.05), and 3-years follow-up (3 studies, n=159, RR=0.57, 95% CI 0.31–1.02; P=.06) (Fig. 4).

4.2. TCM symptom score

The TCM symptom score was reported in 3 studies.^[14,19,21] The Quxie capsule was shown to significantly reduce the TCM

symptom score as compared to the control (3 studies, n=208, WMD=-4.15; 95% CI -7.30 to -1.00; P=.010), with random-effects model (Chi²=11.32, P=.003; I²=82%) (Fig. 5).

4.3. KPS score

Only 2 studies^[14,21] reported the KPS score. The random-effects model was applied for analysis due to heterogeneity (Chi²=8.95, P=.003; I²=89%). The results indicated that the Quxie capsule had no superiority in improving the KPS score as compared to the control (2 studies, n=138, WMD=5.05; 95% CI -2.95 to 13.04; P=.22) (Fig. 6).

4.4. Adverse events

Complete adverse events were reported in 4 studies,^[13–15,19] and the random-effects model was applied for analysis because there was no heterogeneity (Chi²=5.22, P=.16; I²=42%). The results indicated no statistically significant difference in adverse events between the 2 groups (4 studies, n=257, RR=0.90; 95% CI 0.55–1.47; P=.66) (Fig. 7). The Quxie capsule was reported to cause minor gastrointestinal reaction, such as diarrhea and nausea.^[14,15,19,21]

4.5. Safety evaluation

Five out of the 6 studies evaluated safety with complete blood analysis, and liver and renal function tests.^[13–15,19,21] There was some degree of hematological toxicity or liver and renal function injury in the treatment group.^[13,21] Yang et al reported 1 case each in the treatment and control groups with minor abnormal liver function, both patients had a history of abnormal liver function during the previous chemotherapy.^[15] Lei et al reported 1 case of hematological toxicity, 1 case of liver function injury, and 2 cases of renal function injury in the treatment group, and 2 cases of hematological toxicity, 1 case of liver function injury, and 1 case of renal function injury in the control group.^[19] Luo et al reported 1 case with minor abnormal liver function in the treatment group.^[14]

5. Discussion

5.1. Limitations

This study had several limitations. The majority of trials included in the systematic review were not strictly designed. One trial enrolled experimental and control patients separately from 2 different hospitals.^[14] Only 2 trials conducted placebo-controlled study,^[13,15] only 1 conducted allocation concealment, blinding of participants and personnel, blinding of outcome assessment, and pre-registered the protocol,^[13] which may result in bias and overestimation of the efficacy of the treatment group, especially on the subjective outcomes. The follow-up duration for metastasis was not adequate. Second, heterogeneity was not assessed based on meta-regression analysis due to the small number of included studies, although there were variations among the studies in terms of administration of Quxie capsule, chemotherapy protocol, and duration of treatment, which may contribute to heterogeneity among the analyses such as the TCM symptom score and KPS score. Third, publication bias could not be excluded from this systematic review. Most of the findings presented in the included trials were positive results. Some

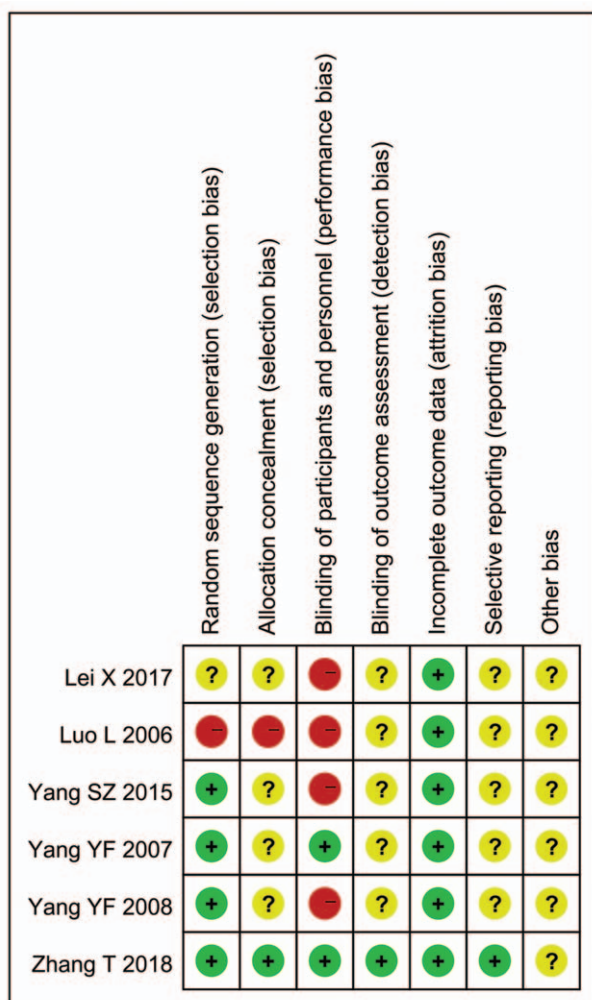


Figure 3. Risk of bias graph.

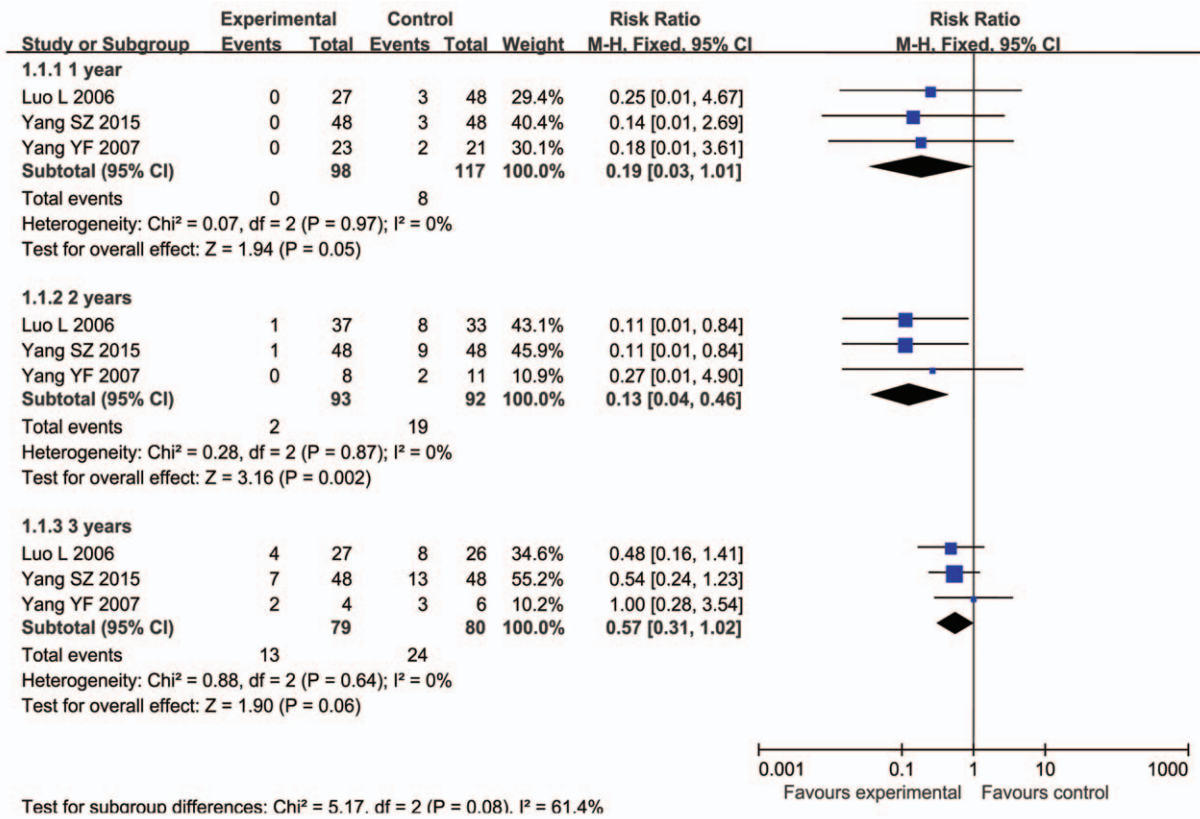


Figure 4. Comparison of the relapse-metastasis rate between the Quxie capsule and control groups.

negative results or outcomes may be unreported and therefore could not be included in the review.

5.2. The summary of this systematic review

To the best of our knowledge, this was the first study to systematically evaluate the relapse-metastasis rate, degree of

symptoms, and side effects of Quxie capsule on CRC patients. Six trials (including 408 patients) met the inclusion criteria. The meta-analysis showed that the Quxie capsule might decrease the relapse-metastasis rate in 2-years follow-up, and could relieve symptoms. However, the results showed no clear superiority of Quxie capsule to decrease the relapse-metastasis rate and relieve

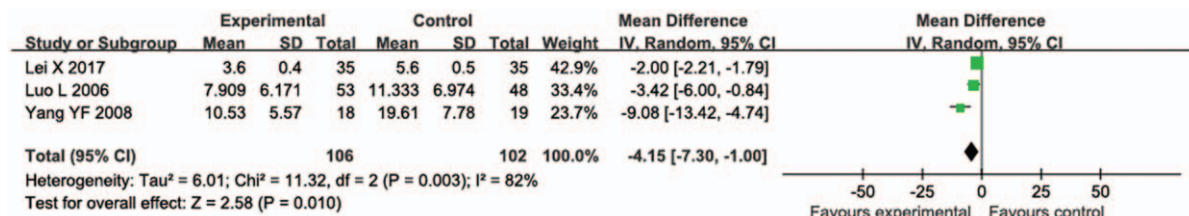


Figure 5. Comparison of the traditional Chinese medicine symptom score between the Quxie capsule and control groups.

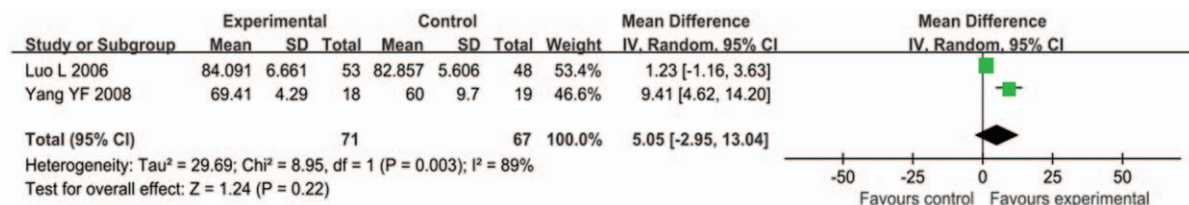


Figure 6. Comparison of the Karnofsky Performance Status score between the Quxie capsule and control groups.

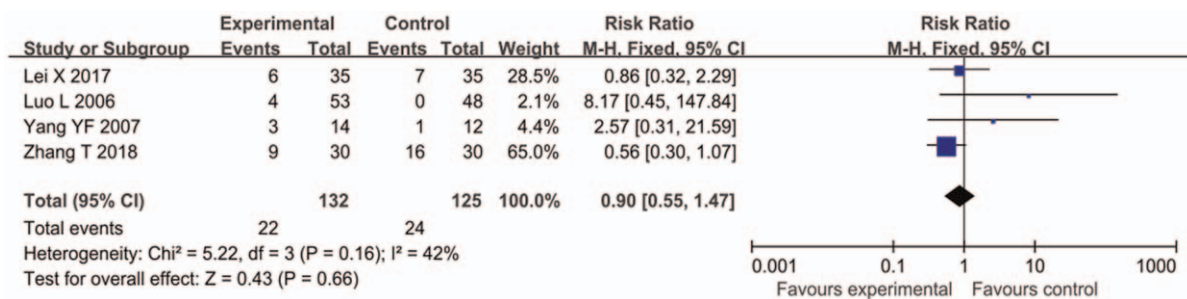


Figure 7. Comparison of the adverse events between the Quxie capsule and control groups.

symptoms based on the 5 clinical trials available. Five trials evaluated the safety based on complete blood analysis, and liver and renal function tests. The occasional minor abnormal functional injury indicated that the Quxie capsule could be safe. The adverse effects reported in the trials were not distinguished based on chemotherapy, radiotherapy, or Quxie capsule. The meta-analysis indicated no statistically significant difference in adverse effects between the 2 groups, suggesting that the Quxie capsule could not alleviate the side effects of CRC patients receiving chemotherapy. Although Quxie capsule is potentially safe, its efficacy for CRC remains uncertain.

5.3. Suggestions for future studies on Quxie capsule

The effect of Quxie capsule for decreasing metastasis, relieving symptoms, and alleviating the side effects in CRC patients should be confirmed by high quality, large sample size, multi-center RCTs, with longer follow-up. Second, the effect of Quxie capsule for improving the quality of life, including physical, and mental health, should be explored by employing recognized evaluation related to quality of life.

Quxie capsule is routinely used in advanced CRC treatment in Xiyuan Hospital in Beijing, China. The underlying mechanism of Quxie capsule in CRC was explored by the hospital team.^[22] The transcription factor forkhead box O1 (Foxo1) plays important roles in regulation of cell cycle, apoptosis, and immune response in various cancers. Quxie capsule treatment upregulated apoptotic proteins such as Fas, Bim, and cleaved Caspase-3 in tumor tissue as compared to the vehicle control group. Intriguingly, the ratios of Th1/Th2 and Th17/Treg cells and levels of T-bet protein (the key regulator of Th1 and Th2 cells) were higher, while the level of Foxp3 (the key regulator of Treg cells) was lower in Quxie capsule-treated mice as compared to vehicle control mice, revealing that Foxo1 upregulated T-bet, downregulated Foxp3, and induced a shift in immune balance. This shift could be critical in the anti-tumor efficacy of Quxie capsule.^[22] While this mechanism is focused on anti-proliferative activity, the effect of Quxie capsule on metastasis, and other aspects remains unknown. More basic studies should be conducted in the future.

6. Conclusions

This systematic review and meta-analysis showed no clear superiority of Quxie capsule for decreasing the relapse-metastasis rate, relieving symptoms, and alleviating the side effects of CRC patients receiving chemotherapy based on the 5 clinical trials available, although Quxie capsule seemed to be a safe treatment.

The effect of Quxie capsule for decreasing metastasis, relieving symptoms, and alleviating the side effects of CRC patients should be examined by high quality, large sample size, multi-center RCTs, with longer follow-up in the future.

Author contributions

Conceptualization: Suqin Zhang, Jianhua Zhou.

Investigation: Suqin Zhang, Peng Lian, Tao Huang.

Methodology: Suqin Zhang, Peng Lian, Tao Huang.

Writing – original draft: Suqin Zhang, Jianhua Zhou.

Writing – review & editing: Suqin Zhang, Jianhua Zhou.

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