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RESEARCH ARTICLE

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Traditional Chinese medicines and capecitabine-based chemotherapy for colorectal cancer treatment: A meta-analysis

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Abstract

This meta-analysis was conducted to evaluate the efficacy and safety of the addition of Traditional Chinese Medicine (TCMs) to capecitabine-based regimens for colorectal cancer (CRC) in term of tumor. The eight electronic databases including Cochrane Library, PubMed, Web of Science (WOS), Excerpt Medica Database (Embase), Chinese Biomedical Literature Database (CBM), China National Knowledge Infrastructure (CNKI), Chinese Science and Technology Journals (CQVIP), and Wanfang Database were systematically searched for eligible studies from their inception to March 2021. Thirty-nine randomized controlled trials were involved in this study, and all the data were analyzed by Review Manager 5.3 (Nordic Cochran Centre, Copenhagen, Denmark) and R 4.0.5 software. The meta-analyses suggested that TCMs in combination with capecitabine-based regimens increased objective response rate (ORR) in the palliative treatment of CRC (risk ratio [RR], 1.35 [1.17, 1.55], $I^2 = 0\%$), disease control rate (DCR) (RR, 1.22 [1.12, 1.32], $I^2 = 3\%$), and quality of life (QOL) (RR, 1.71 [1.44, 2.03], $I^2 = 0\%$), with decreased risks of myelosuppression, anemia, thrombocytopenia, liver/renal dysfunction, neurotoxicity, nausea/vomiting, neutropenia, diarrhea, leukopenia, improved the peripheral lymphocyte, reduced the expression of tumor markers, and related factors. Further sensitivity analysis of specific plant-based TCMs found that dangshen, fuling, and gancao had significantly higher contributions to the results of the RR. The results show that capecitabine-based chemotherapy combined with TCM in the treatment of CRC increases the efficiency of ORR and DCR, reduces chemotherapeutic agents-associated adverse reactions, and improves their life quality as compared with chemotherapy alone, but further randomized and large sample of studies are needed.

KEYWORDS
capecitabine, colorectal cancer, meta-analysis, traditional Chinese medicine

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1 | INTRODUCTION

Globally, the incidence of colorectal cancer (CRC) ranks third among all cancers, second in mortality,[1] and cancer cases and deaths represent 10% of all cancer cases and deaths.[2] Despite radiotherapy and chemotherapy is the main treatment method nowadays, the outcome of advanced CRC remains poor due to tumor recurrence and metastasis and drug resistance. For patients who cannot tolerate surgery, the goal is to minimize the tumor and control its further spread and growth.[3,4]

Current first-line chemotherapy approach to treating CRC is fluoropyrimidine (5-FU)[5] or multidrug combination regimen including oxaliplant (OX), irinotecan (IRI), and carbapitabine (CAP). However, the adverse drug reactions during chemotherapy have not been effectively solved, and the treatment outcomes are often unsatisfactory.[6] As a predrug of fluorouracine, capecitabine achieves similar efficacy after oral administration. The incidence of adverse reactions with the capecitabine modified XELIRI (CAP+ IRI) protocol was significantly reduced.[7] However, capecitabine still produces adverse reactions such as hand-foot syndrome, myelosuppression, liver/renal dysfunction, and gastrointestinal reactions during patients.[8]

Traditional Chinese Medicines (TCM) has been widely used in China for the supplementary treatment of cancer, including colorectal cancer (CRC).[9,10] As an adjuvant therapy, TCM reduces the side effects of cancer reagents and increases the chemotherapeutic efficacy.[11] However, its substantial evidence is inefficient to prove whether the TCM combined capitabine-based regimen is more effective than capitabine alone.

In this study a systematic review and meta-analysis is performed to compare the clinical efficacy and safety between the capecitabine-based chemotherapy combined with TCM and capecitabine alone in the treatment of CRC. At the same time, the frequencies of combined TCMs are further analyzed to determine which combination methods are efficient to improve objective response rates (ORR) and reduce adverse effects, which will provide evidences for the clinical applications of TCM combinations with capitabine-based regimen in treating CRC.

2 | MATERIALS AND METHODS

The protocol for this systematic review was registered on INPLASY (Unique ID number) and was available in full on the inplasy.com (https://doi.org/10.37766/inplasy2021.3.0095) and was performed in accordance with the PreferredReporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

2.1 | Eligibility criteria and outcome measures

According to the PICOS acronym,[12] the inclusion criteria were as follows: Participants (P): All included cases must be confirmed to be CRC after histopathological examination. No restriction on gender, race, or nation was found. Patients with non-primary CRC or other tumors were excluded.

Intervention (I): The random clinical trials (RCTs) with TCMs combined with capecitabine-based chemotherapy were included. No restrictions were in the types of TCM.

Comparison (C): In the control groups, the patients with CRC were treated with the capitabine-based regime.

Outcomes (O): efficacy and safety of TCM.

Study design (S): RCTs.

Exclusion criteria: (i) no capecitabine-based chemotherapy and (ii) non RCTs and (iii) with incomplete outcomes and (iv) lack in sufficient data. Primary outcomes included three efficacy measurements: short- and long-term clinical efficacy, and adverse drug reactions (ADRs) according to world health organization (WHO) criteria and response evaluation criteria in solid tumors (RECIST). (I) Short-term clinical efficacy: the short-term tumor response included complete response (CR), partial response (PR), response rates in stable disease (SD), response rates in progressive disease (PD), ORR, and disease control rate (DCR). ORR was defined as the sum of CR and PR, and DCR was the sum of CR, PR, and SD; (II) Long-term clinical efficacy: 1–5 year overall survival rate (OS); (III) quality of life (QOL), QOL is considered to be improved when Karnofsky performance status (KPS) score is higher than 10 points after treated. Secondary outcomes included ADRs, peripheral blood lymphocytes, tumor markers and related cytokines, transfer rate, and time to progress (TTP). According to WHO

recommendations for grading of acute and subacute toxicity or NCI common terminology criteria for adverse events (CTCAE), ADRs are evaluated by testing hematotoxicity (neutropenia, anemia, thrombocytopenia, and leukopenia), gastrointestinal reaction (nausea and vomiting, diarrhea), liver/renal dysfunction, neurotoxicity, myelosuppression, and hand-foot syndrome. T-lymphocyte subsets such as the proportion of $CD3^+$, CD4+, and $CD8^+$ T cells, the ratio of $CD4^+/CD8^+$ T cells, and the proportion of natural killer cells (NK cells) are measured. Tumor markers and related factors tested include CEA, CA199, CA125, CA724, and TNF-α.

2.2 | Search strategy and study selection

Literature search in both international (Cochrane Library, PubMed, EMBASE, and Web of Science) and Chinese (CBM, CNKI, CQVIP, and Wanfang Database) databases will be systematically searched for eligible studies from their inception to March 2021, were independently conducted by two researchers (Hui-zhong Jiang and Ya-li Jiang). The retrieved keywords included TCM, CRC, capecitabine, and ADRs. The titles and abstracts were independently screened and then full texts of relevant publications for eligibility were read. Any discrepancy was discussed with a third researcher (Dong-xin Tang). In addition, the references listed in original reports and previous reviews were reviewed, and manually selected for other available publications.

2.3 | Data extraction

The following study and participant characteristics were extracted, including first author, year of publication, sample size, type of medications, mean age of participants, cancer staging system (TNM stage), Karnofsky performance status (KPS), TCM intervention (dosage and duration), drug delivery, capecitabine regimen (dose and cycles), and outcome measurements. Any disagreement was resolved by consensus.

2.4 | Quality assessment and evidence level

The quality of studies were assessed by Cochrane risk of bias tool Review Manager 5.3 (Nordic Cochran aa). The review criteria cover seven areas included random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, other sources of bias. The included studies were evaluated to three degrees including low, unclear, and high risk of bias.

2.5 | Statistical Analyses

Statistical analyses were performed using Review Manager 5.3 and R 4.0.5 software. The outcomes were mainly represented by risk ratio (RR) and standardized mean difference (SMD) with its 95% CIs. A two-tailed $p < 0.05$ is considered to be statistically significant. Cochrane's Q-test and I^2 statistics were used to assess heterogeneity between studies; $p \leq 0.1$ or $I^2 > 50\%$ indicates statistical heterogeneity. A fixed-effects model was used to calculate the outcomes when statistical heterogeneity was absent. Otherwise, the random-effects model was used according to the DerSimonian and Laird method. Studies with zero events were included to avoid overestimation of effect.[13] When the same outcome was reported by more than 10 studies, publication bias was tested using funnel plots, Egger's regression test, and Begg's rank test. Sensitivity analysis was conducted to explore an individual study's influence on the pooled results by deleting one single study each time from pooled analysis.

Subgroup analyses were carried out based on the methods of the TCM administration. Meanwhile, only the TCMs with significant tumor responses were included in our analyses. Pooled ORRs were calculated for each group of studies that contained the same TCM. The same pairs of TCMs in three or more studies were identified. The pooled RRs were calculated. They were listed in descending order and any significant was highlighted.

3 | RESULTS

3.1 | Literature search and study characteristics

A total of 313 articles were initially identified. After screening the titles and abstracts, 119 articles were retrieved for full-text review. Finally, 39 studies[14–52] with 1384 patients in the TCM combined with capecitabine group and 1367 patients in the capecitabine group were included for meta-analyses (Figure 1). All the 39 studies were RCTs, and the characteristics are summarized in Table 1. All the 39 studies were conducted in China. Thirty-five studies used the oral TCM, two studies used external TCM, and two studies used commercially available TCM injections (Table 1).

3.2 | Methodological bias of the included studies

In 39 trials, the methods of random allocation were described clearly in only 18 trials.[14,15,16,22,26,30,37,38,39,40,42,44,45,47,48,49,50,52] This indicated that there was selectivity bias in the included

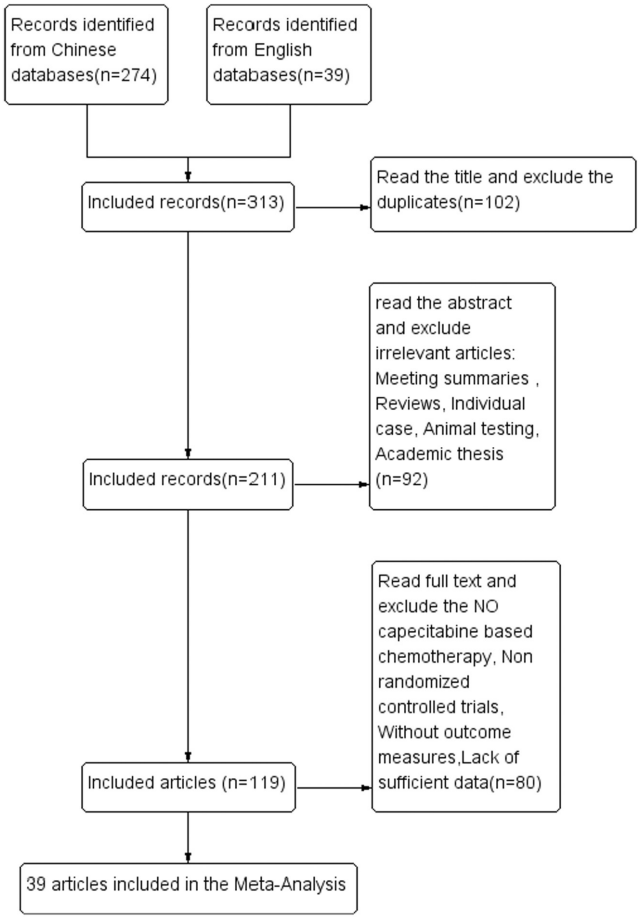

FIGURE 1 The flow charts of included studies.

studies. The random allocation concealment was unclear. Not all the included studies were described as blinding to patients and doctor. Therefore, it indicated that there were selective bias and implementation bias. All data were complete and selective report did not appear in all of the studies. Other bias was not clear. Characteristics and quality of all included studies are presented in Figure 2.

3.3 | Tumor response

According to the WHO[53] or RECIST[54] guidelines, 14 trials[18,21,24,27,30,31,32,34,37,38,39,40,41,43] containing 997 and 12[18,21,24,27,30–32,37–40,43] trials containing 837 cases evaluated ORR and DCR, respectively (Figure 3A,B). Cochran's χ^2 test and I^2 statistic showed no heterogeneity (ORR, $I^2 = 0\%$; DCR, $I^2 = 3\%$). Therefore, the data both using an FEM were synthesized. Compared with capecitabine alone, TCMs in combination with capecitabine significantly increased ORR (RR, 1.35 [1.45–1.88], $p < 0.00001$) and DCR (RR, 1.22 [1.12, 1.32], $p < 0.00001$).

Two groups were divided for meta-analyses to evaluate ORR: non-oral group (2 studies) and oral group (12 studies). The non-oral group has different ways (e.g., Kang'ai injection, and enema TCM) were tested in two studies ($n = 122$). Significant improvement in ORR (RR, 1.13 [0.80, 1.60], $I^2 = 0\%$) was found in the non-oral group. Twelve studies ($n = 875$) were included in the oral group, including decoctions, capsules, or tablets. The pooled ORR showed significant improvement in the oral group (RR, 1.39 [1.19, 1.61], $I^2 = 0\%$).

One study and 11 studies were included to evaluate the DCR in the non-oral and oral groups. Similarly, compared with capecitabine alone, the combined treatment significantly improved the pooled DCR in the non-oral and oral groups ($n = 62$, RR, 1.07 [0.80, 1.41]; $n = 775$, RR, 1.23 [1.13, 1.34], $I^2 = 9\%$), respectively.

3.4 | Quality of life

The quality of life (QOL) changes on KPS were reported as two types of data in the included studies, the number of patients[21,23,33,34,36,38,42,43,45] who reported the improved or stable performance status based on KPS (10-point cutoff) and the mean ± SD of KPS before and after treatment.[14,15,19,23,24,26,27,29,31,32,35,40,42,46,47,49,50,52] The results showed that compared with capitabine alone, the combined treatment significantly increased the number of improved patients based on KPS (RR, 1.71 [1.44, 2.03]; $p < 0.0001$, $I^2 = 0\%$) (Figure 4A), and elevated KPS (SMD, 0.79 [0.51, 1.08]; $p < 0.0001$, $I^2 = 82\%$) (Figure 4B). Taken together, the KPS in TCM combined with capecitabine group was significantly improved compared with the control group.

3.5 | Overall survival rate

Four trials[15,21,27,33] with 303 patients reported the 1-year survival rate. The meta-analysis showed significant difference between these two treatment groups (RR, 1.18 [1.04, 1.35]; $p = 0.0126$, $I^2 = 0\%$; Figure 5A). Three trials[15,21,33] reported the 2-year survival rate and indicated no statistically significant difference between the two treatment groups (RR, 1.48 [0.90, 2.43]; $p = 0.1205$, $I^2 = 54\%$) (Figure 5B). Heterogeneity was present after one study (Ding, p. 2017)[21] was removed (RR, 1.89 [1.22, 2.94], $p = 0.0047$, $I^2 = 3\%$). These results showed that TCM combined with capecitabine improved 1-year/2-year survival rate of CRC patients as compared with capitabine alone.

3.6 | Adverse drug reactions

Twenty-one trials[16–18,21,22,24–26,29,31–34,36,38–40,42,43,48–50] with 1663 cases reported the ADRs (Table 2; Figure S1).Some

TABLE 1 Characteristics of randomized controlled trials of TCMs combined with capecitabine-based regiments for CRC

First author (year)	Design	Sample size T/C; Age T/C	TNM (T/C); KPS	TCM intervention; Dosage and duration	Drug delivery	Capecitabine (Cap.) Regimen; Dose, Cycles (T/C)	Outcome measures
Zhao 2017[14]	RCT	30/30; (54.1 ± 4.9)/ (53.3 ± 5.6)	II-III(all); NR	Changningyin, 150 ml, bid, 21 days/ cycle, for 2 cycles	Orally	XELOX: Ox. 130 mg/m^2, ivgtt, d1, capecitabine 1250 mg/m^2, bid, po, 21 days/cycle (all)	O2
Shi 2018[15]	RCT	48/48; (57.26 ± 7.24)/ (59.31 ± 7.97)	II: 7/5, III: 32/35, IV: 9/8; KPS > 60	Erlingyiren decoction, bid, 1 month/cycle, for 3 cycles	Orally	XELOX:Ox. 130 mg/m^2, ivgtt, d1, capecitabine 1250 mg/m^2, bid, po, d1-d14, 21 days/cycle, for 4 cycles (all)	O2, 5
Chen[16]	RCT	48/48; (61.07 ± 8.64)/ (60.86 ± 8.57)	II: 40/41, III: 8/7; NR	Erlingyiren decoction, 300 ml, bid, continue for 2 weeks, stop for 1 week, 3 weeks/cycle, for 3 cycles	Orally	XELOX: Ox. 130 mg/m^2, ivgtt, d1, capecitabine 1000 mg/m^2, bid, po, d1-d14, 21 days/cycle, for 3 cycles (all)	O4, 5, 6
Gu[17]	RCT	28/28; (56.5 ± 1.4)/ (56.4 ± 1.3)	NR; NR	Erlingyiren decoction, 300 ml, bid, d1-d14, 3 weeks/cycle	orally	XELOX: Ox. 130 mg/m^2, ivgtt, day 1, capecitabine 1000 mg/m^2, bid, po, d1-d14, 21 days/cycle (all)	O4, 5, 6
Zhang[18]	RCT	30/30; (67 ± 11)/(63 ± 13)	IV (all); KPS ≥70	Jianpijiedufang, 200 ml, bid, 21 days/cycle, for 2 cycles	Orally	Capecitabine 1000 mg/m^2, bid, po, continue for 2 weeks, stop for 1 week, 3 weeks/cycle, for 2 cycles (all)	O1, 4
Cui[19]	RCT	20/20; 18–70	IV (all); KPS ≥60	Jianpiquyufang, 200 ml, bid, for 8 weeks	Orally	Xeloda+CPT-11: Xeloda 1000 mg/m^2, bid, for 14 days, CPT-11 60 mg/m2, ivgtt for d1, d8, d15, 4 weeks/cycle, for 2 cycles(all)	O2
Sun[20]	RCT	29/29; (54.6 ± 4.8)/ (56.0 ± 4.6)	NR;NR	Jianpiziyin decoction, 300 ml, tid, for 14 days	Orally	XELOX: Ox. 130 mg/m^2, 3 hours ivgtt, capecitabine 1000 mg/m^2, bid, po, d1-d14 (all)	O6
Ding[21]	RCT	32/30; (35–76)/(37–78)	III-IV (all); KPS > 70	Kang'ai injection, 40 ml, ivgtt, qd, d1-d14, 21 days/cycle	Injection	XELOX: capecitabine 1000 mg/m^2, bid, 0.5 h p.c. po, d1-d14, Ox. 130 mg/m^2, 2 h ivgtt, d1, 21 days/cycle (all)	O1, 2, 4
Min[22]	RCT	41/41; (59.05 ± 6.42)/ (59.89 ± 6.71)	III (29), IV (12)/III (30), IV (11)	Shiyiwei Shenqi Capsules, 5 pills, tid	Orally	XELOX: capecitabine 1250 mg/m^2, bid, d1-d14, Ox. 130 mg/m^2, 6 hs ivgtt, d1, 3 weeks/cycle, for 6 cycles (all)	O4, 6
Pan[23]	RCT	32/32; (58.7 ± 3.2)/ (59.2 ± 3.3)	II (13), III (19)/II (12), III (20); KPS ≥60	Silingsan, 300 ml, bid, po, 3 weeks/ cycle, for 4 cycles	Orally	XELOX: Ox. 130 mg/m^2, 2 h ivgtt, d1, capecitabine 1000 mg /m^2, bid, 3 weeks/cycle, for 4 cycles (all)	O2, 5, 6
Yue[24]	RCT	37/39; (51.65 ± 12.15)/ (51.86 ± 12.05)	IV (all); KPS ≥60	Tongtai decoction 150 ml, bid	Orally	XELIRI: irinoteca 100/m^2, ivgtt, d1-d14, capecitabine, po, bid, 21 days/cycle, for 2 cycles (all)	O1, 2, 4, 6

TABLE 1 (Continued)

First author (year)	Design	Sample size T/C; Age T/C	TNM (T/C); KPS	TCM intervention; Dosage and duration	Drug delivery	Capecitabine (Cap.) Regimen; Dose, Cycles (T/C)	Outcome measures
Zhou[25]	RCT	60/60; (57.9 ± 9.8)/(58.2 ± 9.6)	NR; NR	TCM, bid, 1 h p.c. d1-d14, 21 days/cycle	Orally	Capecitabine 2000 mg/m^2, bid, 0.5 h p.c. treatmeat for 2 weeks, stop 1 week (all)	O4, 5
Gu[26]	RCT	60/60; (53.62 ± 6.74)	II (47), III (73); KPS ≥70	Xiaoaiping injection, p.r., qd, 2 weeks/cycle, for 4 weeks	Enema	XELOX: Ox.130 mg/m^2, 2 h ivgtt, d1, capecitabine 1000 mg/m^2, po, bid, d1-d14, 21 days/cycle, for 2 cycles (all)	O2, 4
Xiao[27]	RCT	30/30; 37–74/39–72	NR; KPS ≥60	Guiqiliujun decoction, bid, 21 days/cycle, for 2 cycles	Orally	XELOX: Ox.130 mg /m^2, 3 h ivgtt, d1, capecitabine 1000 mg /m^2, po, d1-d14, 21 days/cycle, for 2 cycles (all)	O1, 2, 3, 5, 8
Bin[28]	RCT	40/36; NR	NR; KPS ≥70	Zhenxiang capsules, 6 pills, tid, 0.5 h p.c.	Orally	Capecitabine 2500 mg/m^2, po, d1-d14, 21 days/cycle, for 2 cycles (all)	O5
Yao[29]	RCT	21/21; (62.45 ± 9.64)/(57.5 ± 10.35)	IV (all); KPS > 60	TCM, bid, po, for 6 cycles	Orally	XELOX: Ox.1350 mg/m^2, d1, 2 h ivgtt, capecitabine 1000 mg/m^2, po, d1-d14, 21 days/cycle, for 2 cycles (all)	O2, 4, 6
Guo[30]	RCT	45/45; (55.1 ± 6.1)	III (52), IV (28); KPS > 60	Fuzhengxiaoji decoction, bid or tid, d1, 14 days/cycle, for 3 cycles	Orally	Ox. 85 mg/m^2, ivgtt, d1, capecitabine 1000 mg/m^2, po, d1-d14, 21 days/cycle, for 2 cycles (all)	O1, 5, 6
Chen[31]	RCT	28/28; 34–73	III (32), IV (24); KPS ≥60	Shenyi capsules, 20 mg, bid, 6 weeks/cycle, for 2 cycles	Orally	Capecitabine 2000 mg/m^2, po, d1-d14, 0.5 h p.c. Ox. 85 mg/m^2, 2 h ivgtt, 21 days/cycle, for 4 cycles (all)	O1, 2, 4, 5
Liu[32]	RCT	40/40; (61.28 ± 5.05)/(61.85 ± 4.93)	IV (all); KPS > 60	Shengxuefang, bid, for 6 weeks	Orally	XELOX: Ox.130 mg/m^2, ivgtt, d1, capecitabine 1000 mg/m^2, po, bid, d1-d14, 21 days/cycle (all)	O1, 2, 4, 5
Yao[33]	RCT	45/40; 68–80	NR; KPS ≥70	TCM, bid, 0.5 h p.c. d3, 14 days/cycle	Orally	XELOX: capecitabine 1000 mg/m^2, po, bid, d1-d14, Ox. 130 mg/m^2, ivgtt, d1, 28 days/cycle, for 4 cycles (all)	O2, 3, 4
Li[34]	RCT	30/30; 48–69	NR; NR	TCM, 300 ml, pr, 30 min-1 h, p.r.	enema	Capecitabine 1.5 g, po, bid, d1-d14, 21 days/cycle (all)	O1, 2, 4
Zhou[35]	RCT	27/26; (59.19 ± 6.83)/(58.50 ± 7.62)	IV (all); KPS ≥60	TCM, 90 ml, bid, p.c. for 4 cycles	Orally	XELOX: Ox. 130 mg/m^2, ivgtt, d1, capecitabine 1000 mg/m^2, bid, d1-d14, 4 weeks/cycle, for 4 cycles (all)	O2, 5, 6
Jiao[36]	RCT	45/45; 55–78/45–75	IV (all); NR	Zibu decoction, 100 ml, bid	orally	Capecitabine 1250 mg/m^2, po, bid, d1-d14, 21 days/cycle (all)	O2, 4
Liu[37]	RCT	23/22; (56 ± 12)/(59 ± 11)	NR; KPS > 90	Fuzheng shengbai orally liquid, 20 ml, tid, for 3 months	Orally	Capecitabine 1250 mg/m^2, bid, for 14 days, Ox. 130 mg/m^2, d1, 21 days/cycle, for 4 cycles (all)	O1

(Continues)

TABLE 1 (Continued)

First author (year)	Design	Sample size T/C; Age T/C	TNM (T/C); KPS	TCM intervention; Dosage and duration	Drug delivery	Capecitabine (Cap.) Regimen; Dose, Cycles (T/C)	Outcome measures
Dong[38]	RCT	64/58; (76 ± 5.27)/(57.76 ± 4.38)	NR; KPS ≥60	Fufang tengligen preparation, 500 ml, bid	Orally	Irinoteca 180 mg/m^2, ivgtt, d1, capecitabine 1000 mg/m^2, po, bid, d1-d14, 3 weeks/cycle, for 4 cycles (all)	O1, 2, 4, 5
Sun[39]	RCT	18/18; 38–72	NR; KPS ≥60	Pebenyiyang decoction, 200 ml, po, bid	orally	CapeOx: capecitabine 1250 mg/m^2, po, bid, d1-d14, Ox. 130 mg/m^2, 2 hours ivgtt, 21 days/cycle (all)	O1, 4
Xu[40]	RCT	43/43; (59.24 ± 6.45)/(58.87 ± 7.21)	NR; KPS ≥60	Shengxue decoction, 200 mL, qd, for 6 weeks	Orally	Xelox: Ox. 130 mg/m^2, ivgtt, d1, capecitabine 1000 mg/m^2, po, bid, d1-d14, 21 days/cycles, for 2 cycles (all)	O1, 2, 4, 5
Xu[41]	RCT	50/50; (72.3 ± 5.9)	II (25), III (75); NR	TCM, bid, for 2 cycles	orally	Ox. 130 mg/m^2, d1, 3 h ivgtt, capecitabine 1000 mg/m^2, po, bid, d1-d14, 21 days/cycle, for 2 cycles (all)	O1, 7, 8
Ding[42]	RCT	35/35; (47.5 ± 8.6)/(48.2 ± 7.5)	II (13), III (22)/II (15), III (20); KPS ≥60	Aidi injection 100 ml, ivgtt, qd, d1-d7, d15-d21	Injection	XELOX: Ox. 130 mg/m^2, 3 h ivgtt, d1, capecitabine 1000 mg/m^2, po, bid, d1-d14, 21 days/cycle, for 3 cycles (all)	O2, 4
Xie[43]	RCT	32/32; 58.35 ± 1.32	II-III (all); KPS ≥60	Boerning capsules, 0.6 g, tid, for 4 weeks	Orally	XELOX: Ox. 130 mg/m^2, 2 hours ivgtt, d1, capecitabine 1000 mg/m^2, po, bid, d1-d14, 21 days/cycle, for 4 cycles (all)	O1, 2, 4, 5
Ma[44]	RCT	23/23; (53.28 ± 4.62)/(53.37 ± 4.83)	II (4), III (19); KPS: 76.23 ± 7.93	Buqiyichangfang, bid	Orally	Ox. 130 mg/m^2, capecitabine 1250 mg/m^2, bid, d1-d14, 3 weeks/cycle, for 6 cycles (all)	O5, 6
Bian[45]	RCT	20/20; 59.2	II (15), III (23), IV (2); NR	Gubenyiliufang, qd, for 3 weeks	orally	Capecitabine 1250 mg/m^2, bid, po, 3 weeks/cycle, for 4 cycles (all)	O2, 5, 6
Li[46]	RCT	40/40; (63.51 ± 5.63)/(62.47 ± 5.71)	II-IV (all); KPS ≥60	Jianpi Fuzheng Recipe, 300 ml, bid, 3 weeks/cycle, for 2 cycles	Orally	Ox. 130 mg/m^2, 2 hours ivgtt, d1, capecitabine, 1000 mg/m^2, po, bid, d1-d14, 3 weeks/cycle, for 2 cycles (all)	O2, 5
Xie[47]	RCT	30/30; (65.7 ± 3.5)/(65.2 ± 2.8)	NR; NR	Jianpiyiqi, 300 ml, bid	Orally	Capecitabine 2000 mg/m^2, bid, 0.5 h p.c. d1-d14, 21 days/cycle (all)	O2, 5
Qi[48]	RCT	30/30; (54.1 ± 5.1)/(54.3 ± 5.8)	II-III (all); NR	Ningchangyin, po, bid	Orally	XELOX: Ox. 130 mg/m^2, 2 h ivgtt, d1, capecitabine 1250 mg/m^2, po, bid, d1-d14, 21 days/cycle, for 4 cycles (all)	O4
Zhou[49]	RCT	30/30; (53.63 ± 7.78)/(55.53 ± 8.12)	II-III (all); KPS ≥60	Sanmiao granules, tid, 21 days/cycle, for 3 cycles	Orally	XELOX: capecitabine 1.25 g/m^2, 14 days/cycle, Ox. 85 mg/m^2, 2 hours ivgtt, for 3 weeks (all)	O2, 4, 5

TABLE 1 (Continued)

First author (year)	Design	Sample size T/C; Age T/C	TNM (T/C); KPS	TCM intervention; Dosage and duration	Drug delivery	Capecitabine (Cap.) Regimen; Dose, Cycles (T/C)	Outcome measures
Wu[50]	RCT	40/40; (47.52 ± 5.11)/(48.03 ± 6.29)	II (8), III (13), IV (19)/II (7), III (12), IV (21); KPS ≥60	Prunella vulgaris tablets, 6 pills, bid, 3 weeks/cycle, for 2 cycles	orally	XELOX: Ox. 130 mg/m^2, 2 hours ivgtt, d1, capecitabine 800–1000 mg/m^2, po, bid, d1-d14, 21 days/cycle, for 2 cycles (all)	O2, 4, 6
Xiao[51]	RCT	30/30; NR	II-III (all); NR	Tonifying Qi and nourishing Yin prescription, 150 ml, bid, p.c. for 2 weeks	Orally	XELOX: Ox. 130 mg/m^2, 2 h ivgtt, d1, capecitabine 800–1000 mg/m^2, po, bid, d1-d14, 21 days/cycle, for 2 cycles (all)	O6
Xiao[52]	RCT	30/30; 60–71	II (18), III (42); NR	Yiqi Yangyin Huatan Recipe, 150 ml, bid, 0.5 h p.c.	Orally	XELOX: Ox. 130 mg/m^2, 2 h ivgtt, d1, capecitabine 800–1000 mg/m^2, po, bid, d1-d14, 21 days/cycle, for 2 cycles (all)	O2,5

Abbreviations: bid, twice per day; C, control group; d, day; ID, intravenous drip; ivgtt, injection venosa gutta; KPS, Karnofsky Performance Status; N, number; NR, not reported; O: outcomes, O1: tumor response including the objective response rate (ORR), and disease control rate (DCR); O2: quality of life (QOL), O3: Overall Survival rate (OS); O4: adverse drug reactions (ADRs); O5: the levels of peripheral blood lymphocytes; O6: tumor markers and related factors; O7:transfer rate,O8: time to progress (TTP); Ox., oxaliplatin; p.c., post cibum; po, per os; pr, per rectum; qd, once per day; T, treatment group; TCM, traditional Chinese medicine; tid, thrice per day; TNM, Tumor Node Metastasis ("T" for tumor, denotes the extent of invasion of the intestinal wall, "N" for lymphatic node, the amount of lymphatic node involvement, and "M" for the metastasis); Xel/Cap., capecitabine; XELOX, Ox. + capecitabine; XELIRI, irinoteca + capecitabine.

studies described gastrointestinal reactions and hematological toxicity, but did not distinguish them in detail. Significant heterogeneity in gastrointestinal reaction ($I^2 = 90\%$), nausea/vomiting ($I^2 = 58\%$), hand-foot syndrome ($I^2 = 93\%$), and hematological toxicity ($I^2 = 97\%$). The results also showed that TCM combined with capecitabine-based chemotherapy had lower risks of neutropenia (RR, 0.67 [0.54, 0.85], $p = 0.0006$), thrombocytopenia (RR, 0.76 [0.58, 0.99], $p = 0.0409$), leukopenia (RR, 0.70 [0.60, 0.82], $p < 0.0001$), nausea/vomiting (RR, 0.67 [0.50, 0.88], $p = 0.0049$), diarrhea (RR, 0.61 [0.49, 0.74], $p < 0.0001$), liver/renal dysfunction (RR, 0.64 [0.47, 0.86], $p = 0.0025$), myelosuppression (RR, 0.67 [0.54, 0.82], $p < 0.0001$), anemia (RR, 0.69 [0.52, 0.92], $p = 0.012$), neurotoxicity (RR, 0.79 [0.64, 0.98], $p = 0.0344$) than those of chemotherapy alone. There were no significant differences in RR values and their 95% CI of gastrointestinal reaction (RR, 0.75 [0.50, 1.14], $p = 0.18$), hand-foot syndrome (RR, 0.62 [0.23, 1.67], $p = 0.3449$), hematological toxicity (RR, 0.62 [0.09, 4.26], $p = 0.6244$) between the two groups.

3.7 | The levels of peripheral blood lymphocytes

Twenty trials[15–17,23,25,27,30–32,35,38,40,43–47,49,52] with 1465 cases reported the levels of peripheral blood lymphocytes (Table 3; Figure S2). There was statistical heterogeneity in $CD3^+$ T cells ($I^2 = 93\%$), $CD4^+$ T cells ($I^2 = 91\%$), $CD8^+$ T cells ($I^2 = 97\%$), $CD4^+/CD8^+$ T cells ratio ($I^2 = 92\%$), and excluded medium heterogeneity in NK cells ($I^2 = 45\%$). Therefore, the data of $CD3^+$ T cells, $CD4^+$ T cells, $CD8^+$ T cells, and $CD4^+/CD8^+$ T cells ratio and the NK cells were calculated by using a FEM. The meta-analysis results showed that TCM plus capecitabine-based chemotherapy improved the $CD3^+$ T cells (RR, 1.47 [0.96, 1.98], $p < 0.0001$), $CD4^+$ T cells (RR, 1.70 [1.27, 2.13], $p < 0.0001$), $CD4^+/CD8^+$ T cells ratio (RR, 1.47 [1.05, 1.89], $p < 0.0001$), and NK cells (RR, 0.87 [0.69, 1.06], $p < 0.0001$) compared with those of chemotherapy alone. No significant differences were found in RR values and their 95% CI of $CD8^+$ T cells (RR, −0.22 [−0.99, 0.54], $p = 0.565$) between the two groups.

3.8 | Tumor markers and related factors

Thirteen trials[15–17,23,25,27,28,30–32,35,38,40,43–47,49,52] with 843 cases reported the tumor markers and related factors (Table 4 and Figure S3). In the studies, result showed that there was a significant difference in the level of CEA, CA199, and CA125 between the two groups, and the TCM with chemotherapy group was found to have lower CEA, CA199, and CA125 (RR, −1.83 [−2.69, −0.96], $I^2 = 96\%$, $p < 0.0001$; −0.86 [−1.32, −0.40], $I^2 = 81\%$, $p = 0.0003$; −1.73 [−3.14,

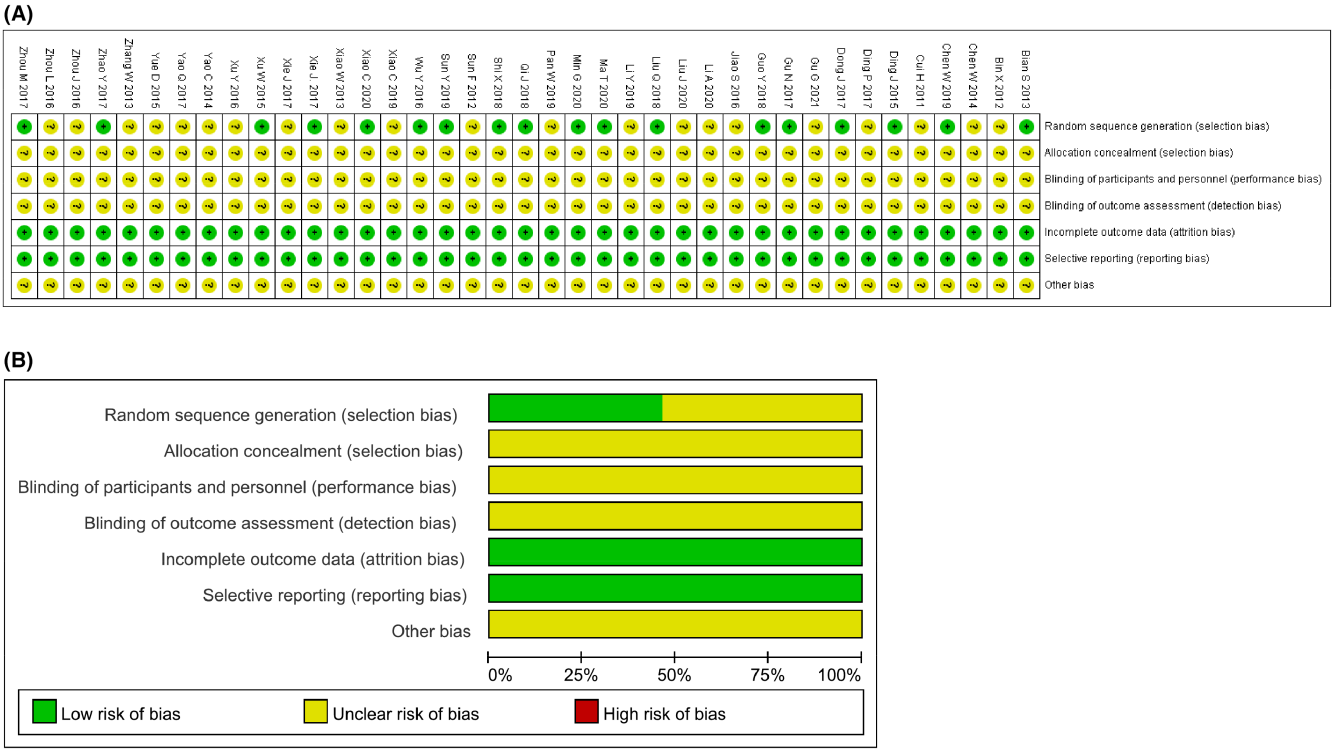

FIGURE 2 Risk of methodological bias of the included studies. (A) Risk of bias summary: review authors' judgments about each risk of bias item for each included study. (B) Risk of bias graph: review authors' judgment about each risk of bias item presented as percentages across all included studies.

−0.32], $I^2 = 96\%$, $p = 0.0162$). But about CA724 and TNF-α, the result indicated no statistical differences between the two groups (RR, −2.39 [−7.14, 2.36], $I^2 = 99\%$, $p = 0.3246$; RR, 0.13 [−2.65, 2.91], $I^2 = 98\%$, $p = 0.9262$).

3.9 | Transfer rate and TTP

Of the 39 trials, only two studies[15,41]reported the tumor transfer rate, and no significant difference was found between the two groups(RR, 0.55 [0.29, 1.03], $I^2 = 0\%$, $p = 0.0647$) (Figure 6A). And three trials[25,27,41] reported TTP (RR, 1.33 [0.05, 2.60], $I^2 = 95\%$, $p = 0.0419$), with a significant difference between the two groups (Figure 6B).

3.10 | Publication bias analysis

More than 10 studies reported the same outcomes, including ORR, DCR, KPS, thrombocytopenia, liver/renaldysfunction, neurotoxicity, nausea/vomiting, diarrhea, leukopenia, $CD3^+$ T cells, $CD4^+$ T cells, $CD8^+$ T cells, $CD4^+/CD8^+$ T cells ratio, and CEA. Publication bias was tested using funnel plots (Figure 7) and Egger's regression test (Figure 8). Other publication bias is shown in the previous tables (Tables 2 and Table 3).

3.11 | Sensitivity analysis

Thirty-nine trials were included for sensitivity analysis, excluding the poor/over/ underestimated trials. The result demonstrated that except for CA724, TNF-α, and transfer rate, no heterogeneities were found in other parameters tested (Table 5 and Figures S4 and S5). Although excluding the trials,[16,17,22,24,29,30,35,45,50,51] heterogeneity was also found in CEA (Table 5).

3.12 | The effects of multi-ingredient TCM in the oral administration group

The multi-ingredient TCM formulae had similarity in their main ingredients and functional approximation. In order to identify the most comparable subgroups of studies and potential synergistic effects, a series of planned sensitivity analyses were made. Only the TCMs with significant ORR results have been reported in our analyses. In Table 6, all significant RR results (excluding those with heterogeneity >30%) were ranked in order according to descending RR.

Level 1: Single TCM. Sixty ingredients in the formulae have been included in this review. Among them, there are 11 ingredients that have been used in three or more formulae. The Chinese name in pin yin of each ingredient was used to represent the TCMs. According to their

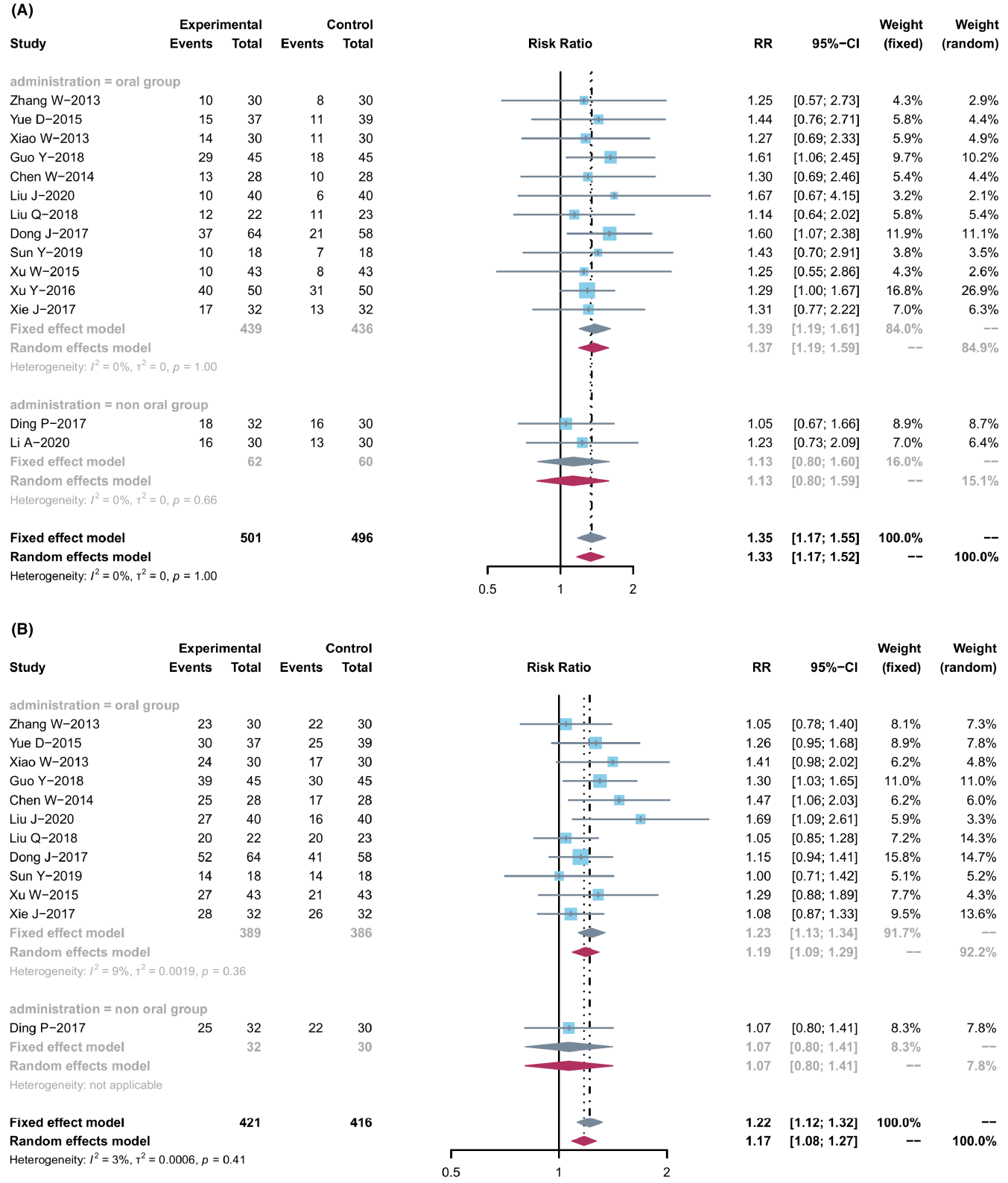

FIGURE 3 Tumor response. (A) Forest plot displaying the results of the meta-analysis for ORR. (B) Forest plot displaying the results of the meta-analysis for DCR.

frequency in the formulae, TCMs were listed as follows: Huangqi (n = 8), baizhu (n = 8), dangshen (n = 5), jixueteng (n = 4), fuling (n = 4), gancao (n = 4), yiyiren (n = 3), sheshecao (n = 3), banxia (n = 3), taizishen (n = 3), and nvzhenzi (n = 3). Then, the RR values were calculated, which are listed in descending order in Table 2. The

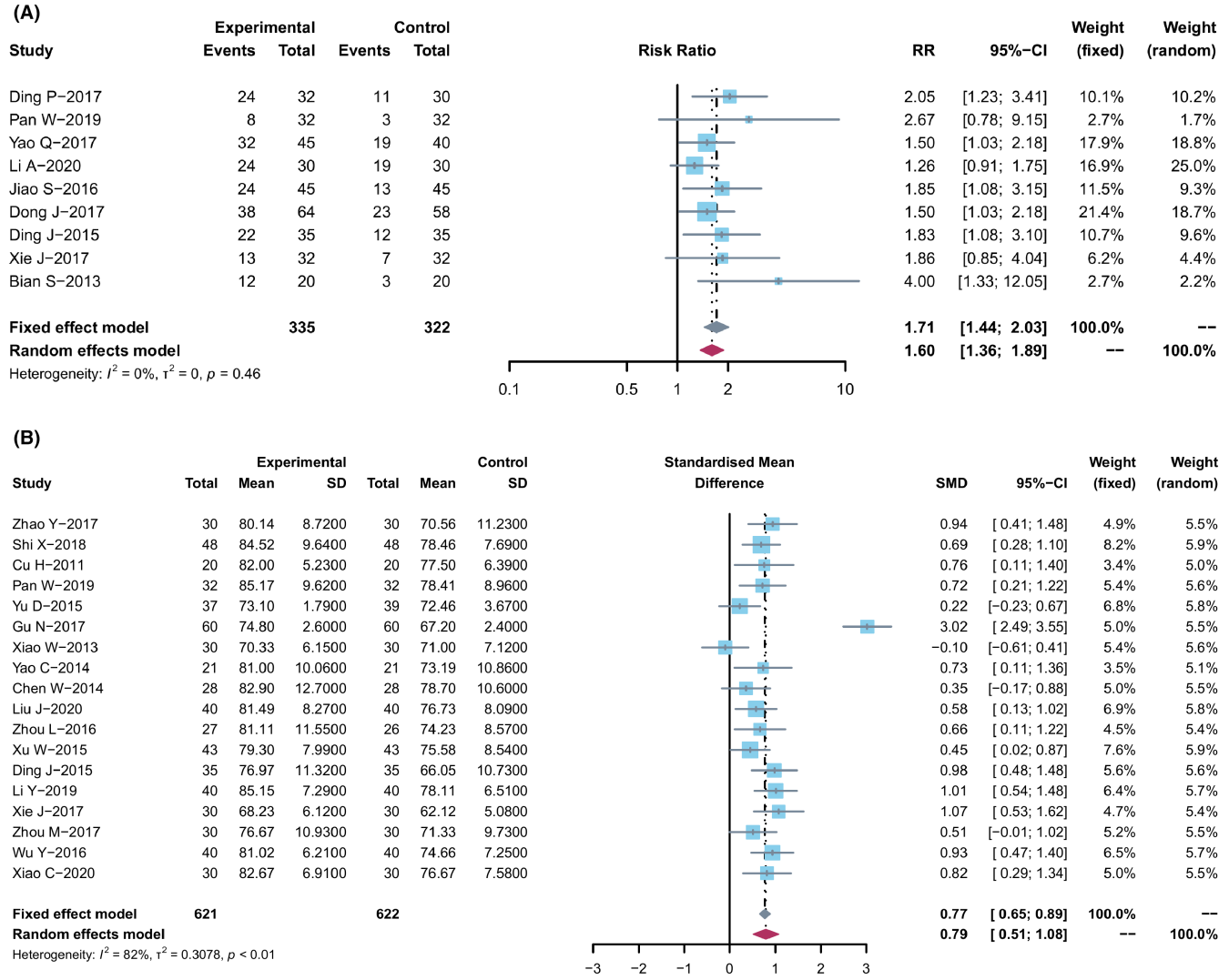

FIGURE 4 Quality of life. (A) Forest plot displaying the results of the meta-analysis for KPS according to number of patients. (B) Forest plot displaying the results of the meta-analysis for KPS according to mean ± SD.

pooled RR values were divided into two groups. The RR values in the first group were equal to or greater than the total pool. In the second group, the RR values were less than the total pool.

The first group included eight TCMs: yiyiren (n = 3), fuling (n = 4), gancao (n = 4), baizhu (n = 8), sheshecao (n = 3), dangshen (n = 5), banxia (n = 3), and nvzhenzi (n = 3). In the second group there were only three TCMs, huangqi (RR, 1.3767 [1.1082, 1.7103]), taizishen (RR, 1.3636 [0.8420, 2.2086]), and jixueteng (RR, 1.3439 [0.9411, 1.9189]), which had a lower value than the total pool (RR, 1.3881 [1.1932, 1.6148]) (Table 6).

Level 2: Combinations of two TCMs. Compared with the total pool, at this level, the RR values of 14 pairs including baizhu+yiyiren (n = 3), baizhu+dangshen(n = 4), baizhu+fuling (n = 4), baizhu+gancao(n = 4), dangshen+gancao (n = 4), fuling+gancao (n = 4), huangqi+sheshecao (n = 3), baizhu+sheshecao (n = 3), huangqi+banxia (n = 3), huangqi+baizhu (n = 6), banxia+baizhu (n = 3), baizhu+jixueteng (n = 3), huangqi+nvzhenzi (n = 3), huangqi+dangshen (n = 3) were equal to or greater. Three pairs were lower than the total pool (baizhu+taizishen, huangqi+taizishen, huangqi+jixueteng) (Table 6).

Level 3: Combinations of 3 TCMs. At this level, there were two significant pairs from level 2 that were combined with other TCMs that showed significant RRs compared with single TCM group. At this level, the RR values of all pairs including dangshen+fuling+gancao (n = 4), huangqi+banxia+baizhu (n = 3) were greater than the total pool (Table 6).

Levels 4 to 7: Combinations of 4 to 7 TCMs. There were no combinations of 4, 5, 6 TCMs, and there was one combination of 7 which showed an RR equal to the pool:

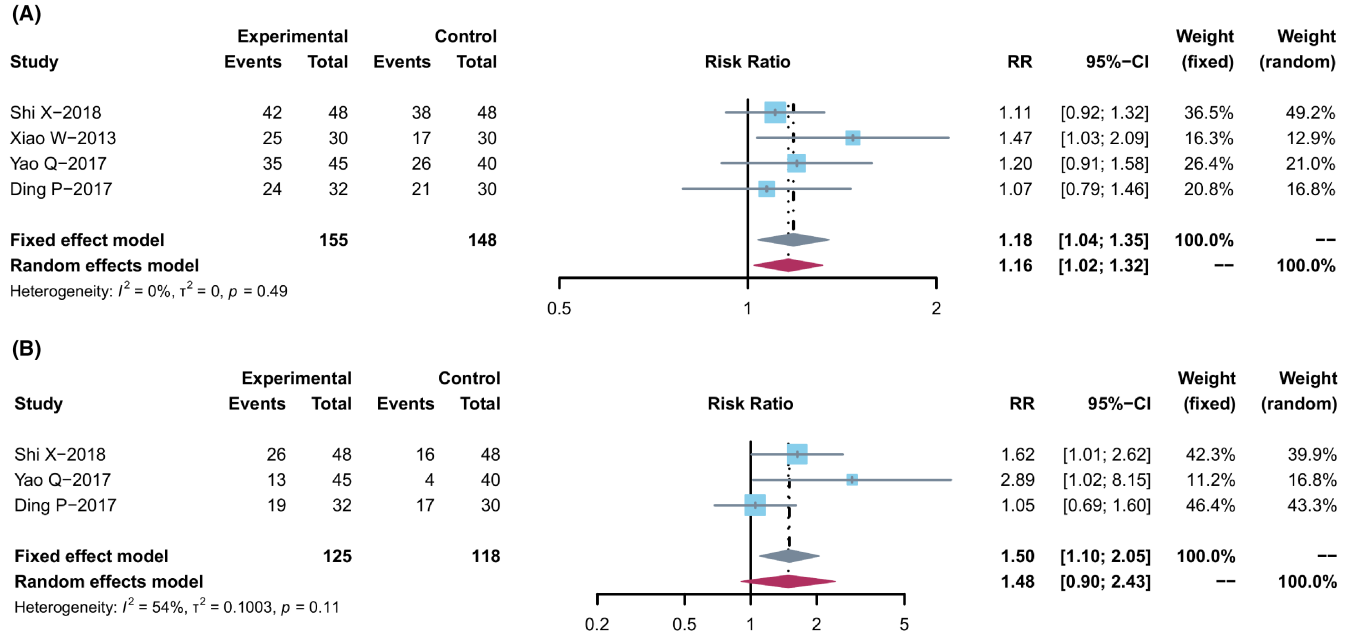

FIGURE 5 Overall survival rate. (A) Forest plot displaying the results of the meta-analysis for 1-year survival rate. (B) Forest plot displaying the results of the meta-analysis for 2-year survival rate.

TABLE 2 Meta-analysis results of ADRs

Outcomes	Trials	Experimental group (Events/Total)	Control l group (Events/Total)	SM	RR,95% CI	I^2 (%)	p	PB
Myelosuppression	9	81/302	121/300	FEM	0.67 (0.54, 0.82)	0	<0.0001	No
Gastrointestinal reaction	8	81/288	121/286	REM	0.75 (0.50, 1.14)	90	0.18	Unclear
Anemia	5	49/217	71/213	FEM	0.69 (0.52, 0.92)	0	0.012	Unclear
Thrombocytopenia	10	70/431	92/428	FEM	0.76 (0.58, 0.99)	0	0.0409	No
Liver/Renal dysfunction	11	52/446	83/442	REM	0.64 (0.47, 0.86)	0	0.0025	No
Neurotoxicity	13	94/432	119/429	FEM	0.79 (0.64, 0.98)	0	0.0344	No
Nausea/vomiting	12	111/447	169/443	REM	0.67 (0.50, 0.88)	58	0.0049	Yes
Neutropenia	3	53/139	77/133	FEM	0.67 (0.54, 0.85)	25	0.0006	Unclear
Hand-foot syndrome	8	64/281	90/276	REM	0.62 (0.23, 1.67)	93	0.3449	Unclear
Diarrhea	12	93/452	151/443	FEM	0.61 (0.49, 0.74)	0	<0.0001	No
Leukopenia	11	133/435	189/432	FEM	0.70 (0.60, 0.82)	32	<0.0001	Yes
Hematological toxicity	3	40/88	53/88	REM	0.62 (0.09, 4.26)	97	0.6244	Unclear

Note: Forest of all results are in Figure S1.

Abbreviations: CI, confidence interval; FEM, fixed-effects model; PB, Publication bias; REM, random-effects model; RR, relative ratio; SM, statistical method.

TABLE 3 Meta-analysis results of the levels of peripheral blood lymphocytes

Outcomes	Trials	SM	SMD, 95% CI	I^2 (%)	p	PB
$CD3^+$ T cells	16	REM	1.47 (0.96, 1.98)	93	<0.0001	Yes
$CD4^+$ T cells	17	REM	1.70 (1.27, 2.13)	91	<0.0001	Yes
$CD8^+$ T cells	15	REM	−0.22 (−0.99, 0.54)	97	0.565	No
$CD4^+/CD8^+$ T cells ratio	19	REM	1.47 (1.05, 1.89)	92	<0.0001	Yes
NK cells	7	FEM	0.87 (0.69, 1.06)	45	<0.0001	Unclear

Note: Forest of all results are in Figure S2.

Abbreviations: CI, confidence interval; FEM, fixed-effects model; PB, Publication bias; REM, random-effects model; SM, statistical method; SMD, standardized mean difference.

TABLE 4 Meta-analysis results of tumor markers and related factors

Outcomes	Trials	SM	SMD, 95% CI	I^2 (%)	*p*	PB
CEA	12	REM	−1.83 (−2.69, −0.96)	96	<0.0001	Yes
CA199	7	REM	−0.86 (−1.32, −0.40)	81	0.0003	Unclear
CA125	4	REM	−1.73 (−3.14, −0.32)	96	0.0162	Unclear
CA724	2	REM	−2.39 (−7.14, 2.36)	99	0.3246	Unclear
TNF-α	2	REM	0.13 (−2.65, 2.91)	98	0.9262	Unclear

Note: Forest of all results are in Figure S3.

Abbreviations: CI, confidence interval; FEM, fixed-effects model; PB, Publication bias; REM, random-effects model; SM, statistical method; SMD, standardized mean difference.

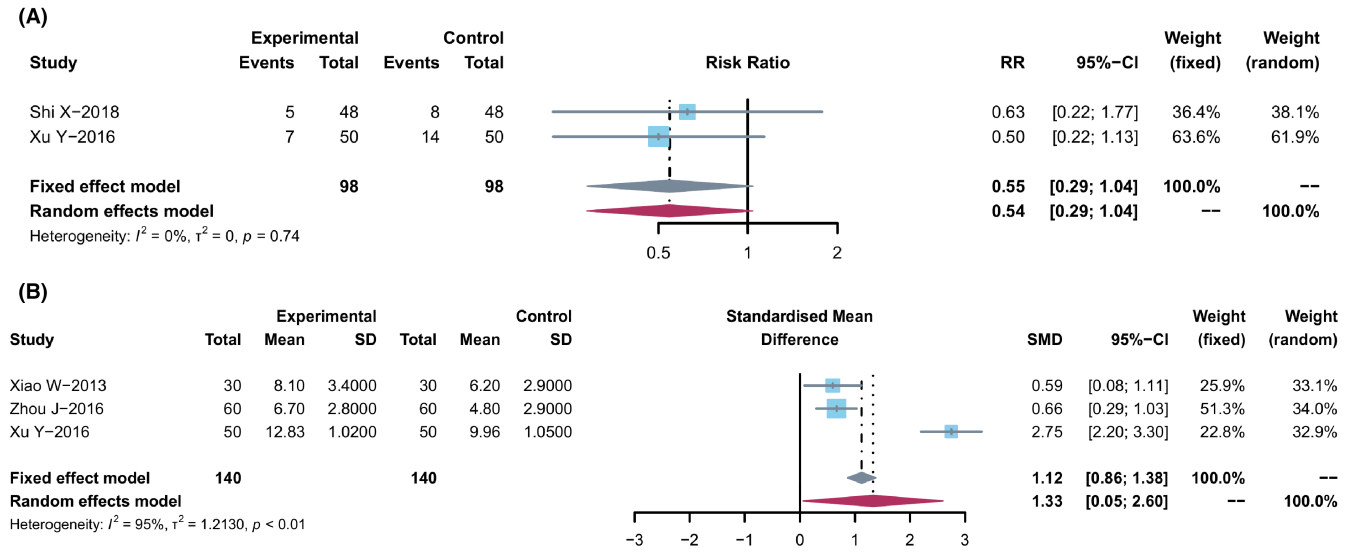

FIGURE 6 Transfer rate and TTP. (A) Forest plot displaying the results of the meta-analysis for transfer rate. (B) Forest plot displaying the results of the meta-analysis for TTP.

huangqi+banxia+baizhu+sheshecao+dangshen+fuling+gancao (n = 2) (Table 6).

3.13 | TCMs potential synergistic effects selection

Compared with TCM alone, 10 TCM pairs showed higher RR values and potential synergistic effects in group 1, including baizhu+yiyiren (n = 3), baizhu+dangshen (n = 4), baizhu+fuling (n = 4), baizhu+gancao (n = 4), dangshen+gancao (n = 4), fuling+gancao (n = 4), huangqi+sheshecao (n = 3), baizhu+sheshecao (n = 3), huangqi+banxia (n = 3), huangqi+nvzhenzi (n = 3), while the RR values of two combinations in levels 3–7 with were lower than the level 1, such as huangqi+banxia+baizhu (n = 3), huangqi+banxia+baizhu+sheshecao+ dangshen+fuling+gancao (n = 2). In all levels, dangshen, fuling, and gancao showed significant ORRs equal or higher than the totalpool at each level.

4 | DISCUSSION

TCM's essential components are being studied constantly, and more and more research has proven that TCM may assist with tumor treatment.[55,56] Capecitabine, a 5-FU prodrug, is an effective first-line therapy for CRC due to its ease of use and low frequency of ADRs.[57] Though oxaliplatin- or 5-FU-based chemotherapy combined with TCM was shown to be more effective than TCM alone in two studies,[58,59] the efficiency of capecitabine-based chemotherapy combined with TCM in CRC is yet unknown.

Thirty-nine studies including 2751 patients were included in meta-analyses to evaluate the therapeutic CRC regimen capitabine-based coupled with TCMs clinical effectiveness and ADRs. As a consequence, capecitabine-based chemotherapy regimens were shown to be more effective when combined with TCM. The ORR and DCR of the oral TCM or non-oral group (e.g., injection, enema) were shown to be substantially greater than those utilizing capitabine alone, as a consequence of which we exhibited. Improving immunological function and overall well-being

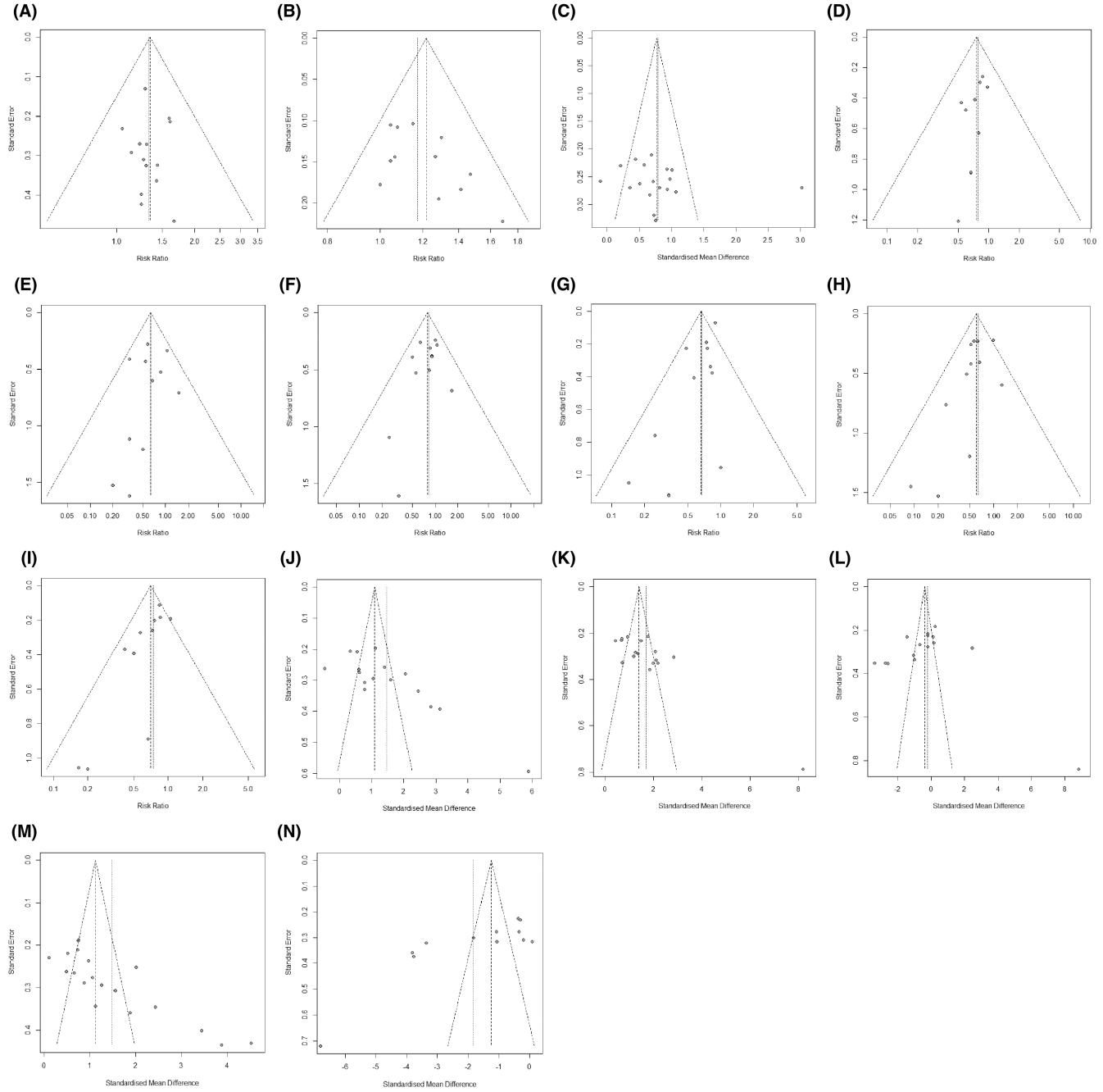

FIGURE 7 Funnel plots displaying the results of the meta-analysis for Publication bias analysis. (A) ORR. (B) DCR. (C) KPS (mean ± SD). (D) Thrombocytopenia. (E) Liver/Renal dysfunction. (F) Neurotoxicity. (G) Nausea/Vomiting. (H) Diarrhea. (I) Leukopenia. (J) $CD3^+$ T cells. (K) $CD4^+$ T cells. (L) $CD8^+$ T cells. (M) $CD4^+/CD8^+$ T cells. (N) CEA.

is critical for cancer patients undergoing treatment. We compared the QOL and the number of peripheral blood lymphocytes in each group as part of our research. According to the findings, combining capecitabine-based chemotherapy with TCM improved $CD3^+$ T cells, $CD4^+$ T cells, $CD4^+/CD8^+$ T cells ratio, and NK cells, as well as overall QOL. In addition, it has the potential to decrease tumor marker expression levels (CEA, CA199, and CA125). This will assist the patient's immune system, allowing him or her to fight off tumor recurrence and metastasis in the future. T-lymphocyte expression is linked to poor prognosis and tumor metastasis,[60] such as $CD3^+$,[61] $CD4^+$,[62] $CD4^+/CD8^+$ T cell ratio,[63] and NK cells,[64] increasing immune function to inhibit tumor growth.[65] An important clinical biomarker for gastrointestinal malignancies is a cell surface glycoprotein called carcinoembryonic antigen (CEA)[66]. There has been an increase in CEA overexpression in 90% of gastrointestinal cancers, including CRC tumor recurrence

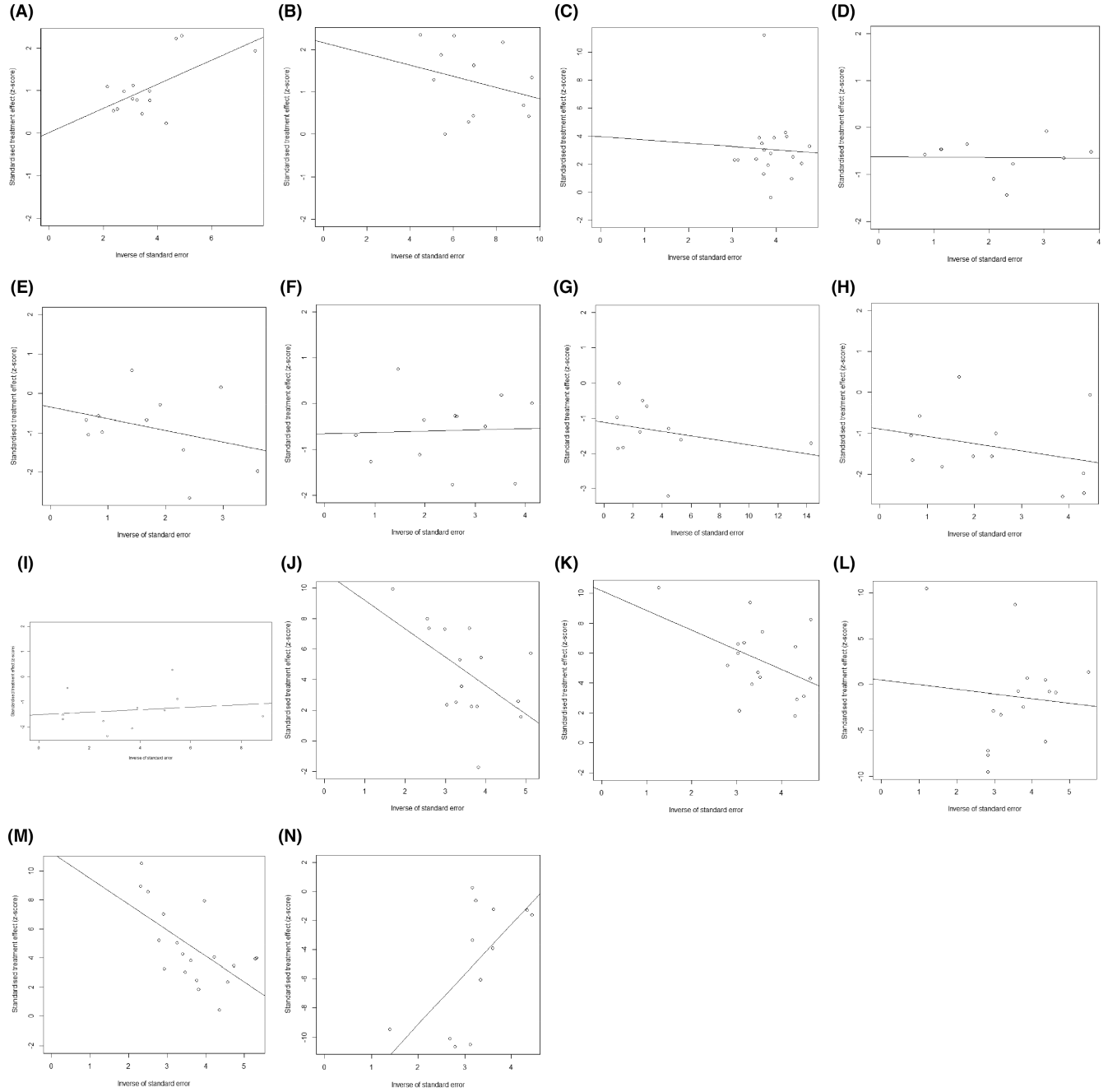

FIGURE 8 Egger's analysis for Publication bias analysis. (A) ORR. (B) DCR. (C) KPS (mean ± SD). (D) Thrombocytopenia. (E) Liver/Renal dysfunction. (F) Neurotoxicity. (G) Nausea/Vomiting. (H) Diarrhea. (I) Leukopenia. (J) $CD3^+$ T cells. (K) $CD4^+$ T cells. (L) $CD8^+$ T cells. (M) $CD4^+/CD8^+$ T cells. (N) CEA.

is predicted by an increase in postoperative CA125 and CA199 levels, and this information is critical for the diagnosis of digestive system cancer.[67,68]

TCMs used orally or intravenously showed promise in the treatment of CRC. Specific plant-based TCMs were further analyzed and shown to have substantially greater contributions to the RR value, including yiyiren, fuling, gancao, baizhu, sheshecao, dangshen, banxia, and nvzhenzi. Dangshen, fuling, and gancao all contributed considerably more to the RR value than the others at all levels. Capecitabine-based chemotherapy for CRC may benefit from the addition of TCMs.

5 | CONCLUSION

Our research found that the combination of TCM and capecitabine-based chemotherapy was more effective than the capecitabine-only regimen. Additionally, it has the potential to decrease adverse responses in patients,

TABLE 5 Sensitivity analysis by excluding the poor/over/underestimated trials

Outcomes	Trials	SM	RR/SMD, 95% CI	I^2 (%)	Excluded trials (Reference number)	Trials	SM	RR/SMD, 95% CI	I^2 (%)
(a)									
ORR	14	FEM	1.35 (1.17, 1.55)	0	1[39]	13	FEM	1.31 (1.13, 1.52)	0
DCR	12	FEM	1.22 (1.12, 1.32)	3	1[32]	11	FEM	1.19 (1.09, 1.29)	0
KPS(number)	9	FEM	1.71 (1.44, 2.03)	0	1[34]	8	FEM	1.80 (1.49, 2.18)	0
KPS(mean ± SD)	18	REM	0.79 (0.51, 1.08)	82	1[26]	17	REM	0.65 (0.53, 0.77)	33
1-year Survival rate	4	FEM	1.18 (1.04, 1.35)	0	1[27]	3	FEM	1.13 (0.98, 1.30)	0
2-year Survival rate	3	REM	1.48 (0.90, 2.43)	54	1[21]	2	FEM	1.89 (1.22, 2.94)	3
b)									
Myelosuppression	9	FEM	0.67 (0.54, 0.82)	0	1[21]	8	FEM	0.72 (0.58, 0.88)	0
Gastrointestinal reaction	8	REM	0.75 (0.50, 1.14)	90	1[31]	7	FEM	0.71 (0.59, 0.85)	32
Anemia	5	FEM	0.69 (0.52, 0.92)	0	1[38]	4	FEM	0.76 (0.57, 1.03)	0
Thrombocytopenia	10	FEM	0.76 (0.58, 0.99)	0	1[24]	9	FEM	0.72 (0.54, 0.97)	0
Liver/Renal dysfunction	11	REM	0.64 (0.47, 0.86)	0	1[24]	10	FEM	0.56 (0.40, 0.79)	0
Neurotoxicity	13	FEM	0.79 (0.64, 0.98)	0	1[25]	12	FEM	0.84 (0.67, 1.05)	0
Nausea/Vomiting	12	REM	0.67 (0.50, 0.88)	58	1[15]	11	FEM	0.70 (0.59, 0.84)	41
Neutropenia	3	FEM	0.67 (0.54, 0.85)	25	1[40]	2	FEM	0.56 (0.37, 0.85)	0
Hand-foot Syndrome	8	REM	0.62 (0.23, 1.67)	93	1[16]	7	FEM	0.58 (0.40, 0.82)	0
Diarrhea	12	FEM	0.61 (0.49, 0.74)	0	4[16,29,38,44]	8	FEM	0.55 (0.43, 0.70)	0
Leukopenia	11	FEM	0.70 (0.60, 0.82)	32	1[33]	10	FEM	0.73 (0.63, 0.86)	18
Hematological toxicity	3	REM	0.62 (0.09, 4.26)	97	1[31]	2	FEM	0.48 (0.27, 0.86)	0
c)									
$CD3^+$ T cells	16	REM	1.47 (0.96, 1.98)	93	12[15,16,17,23,31,43,44,47,49,52]	4	FEM	1.26 (1.01, 1.50)	0
$CD4^+$ T cells	17	REM	1.70 (1.27, 2.13)	91	8[16,28,30,32,40,43,45,47]	9	FEM	1.74 (1.56, 1.93)	32
$CD8^+$ T cells	15	REM	−0.22 (−0.99, 0.54)	97	8[15,23,30,44,45,46,47,52]	7	FEM	−0.06 (−0.23, 0.11)	40
$CD4^+/CD8^+$ T cells ratio	19	REM	1.47 (1.05, 1.89)	92	13[15,16,23,25,27,28,35,38,40,43,46,49,52]	6	FEM	1.24 (1.01, 1.48)	17
NK cells	7	FEM	0.87 (0.69, 1.06)	45	1[49]	6	FEM	0.80 (0.61, 0.99)	5
d)									
CEA	12	REM	−1.83 (−2.69, −0.96)	96	10[16,17,22,24,29,30,35,45,50,51]	2	REM	−1.45 (−2.19, −0.71)	67
CA199	7	REM	−0.86 (−1.32, −0.40)	81	3[17,44,45]	4	FEM	−0.63 (−0.86, −0.39)	48
CA125	4	REM	−1.73 (−3.14, −0.32)	96	2[22,35]	2	FEM	−1.23 (−1.58, −0.88)	45
CA724	2	REM	−2.39 (−7.14, 2.36)	99	2[22,35]	0	NO	NO	NO
TNF-α	2	REM	0.13 (−2.65, 2.91)	98	2[20,44]	0	NO	NO	NO
e)									
Transfer rate	2	FEM	0.55 (0.29, 1.03)	0	2[15,41]	0	NO	NO	NO
TTP	3	REM	1.33 (0.05, 2.60)	95	1[41]	2	FEM	0.64 (0.34, 0.94)	0

Abbreviations: CI, confidence interval; FEM, fixed-effects model; ORs, odds ratios; Over or Under, over or underestimated trial which the result had significant difference and was beneficial to TCMs use; Poor trial (Poor) that had at least one domain being considered as high risk of bias; SM, statistical method; SMD, standardized mean difference.

TABLE 6 Effects of specific orally administered TCMs on tumor response: single TCMs and combinations

Level	Traditional Chinese medicine	RR	95% CI	No. of Studies, References	No. Part	I^2 (%)
1	Yiyiren	1.5682	1.2038, 2.0428	3[24,30,38]	288	0.0
1	Fuling	1.5195	1.1890, 1.9419	4[27,30,38,39]	298	0.0
1	Gancao	1.5195	1.1890, 1.9419	4[27,30,38,39]	262	0.0
1	Baizhu	1.4720	1.1948, 1.8136	8[18,24,28,30,32,38,39,40]	600	0.0
1	Sheshecao	1.4705	1.0849, 1.9932	3[24,28,30]	226	0.0
1	Dangshen	1.4602	1.1655, 1.8294	5[28,30,37,38,39]	307	0.0
1	Banxia	1.4324	1.0436, 1.9661	3[18,28,30]	200	0.0
1	Nvzhenzi	1.3954	1.0500, 1.8545	3[30,37,43]	189	0.0
1	Huangqi	1.3767	1.1082, 1.7103	8[18,24,28,30,32,37,40,43]	551	0.0
1	Taizishen	1.3636	0.8420, 2.2086	3[18,32,40]	226	0.0
1	Jixueteng	1.3439	0.9411, 1.9189	4[24,32,37,40]	287	0.0
2	Baizhu+yiyiren	1.5682	1.2038, 2.0428	3[24,30,38]	258	0.0
2	Baizhu+dangshen	1.5195	1.1890, 1.9419	4[28,30,38,39]	278	0.0
2	Baizhu+fuling	1.5195	1.1890, 1.9419	4[28,30,38,39]	278	0.0
2	Baizhu+gancao	1.5195	1.1890, 1.9419	4[28,30,38,39]	278	0.0
2	Dangshen+gancao	1.5195	1.1890, 1.9419	4[28,30,38,39]	278	0.0
2	Fuling+gancao	1.5195	1.1890, 1.9419	4[28,30,38,39]	298	0.0
2	Huangqi+sheshecao	1.4705	1.0849, 1.9932	3[24,28,30]	216	0.0
2	Baizhu+sheshecao	1.4705	1.0849, 1.9932	3[24,28,30]	216	0.0
2	Huangqi+banxia	1.4324	1.0436, 1.9661	3[18,28,30]	200	0.0
2	Huangqi+baizhu	1.4324	1.1048, 1.8572	6[18,24,28,30,32,40]	442	0.0
2	Banxia+baizhu	1.4324	1.0436, 1.9661	3[18,28,30]	200	0.0
2	Baizhu+jixueteng	1.4324	0.9202, 2.2296	3[24,32,40]	242	0.0
2	Huangqi+nvzhenzi	1.3954	1.0500, 1.8545	3[30,37,43]	189	0.0
2	Huangqi+dangshen	1.3902	1.0350, 1.8672	3[28,30,37]	185	0.0
2	Baizhu+taizishen	1.3636	0.8420, 2.2086	3[18,32,40]	226	0.0
2	Huangqi+taizishen	1.3636	0.8420, 2.2086	3[18,32,40]	226	0.0
2	Huangqi+jixueteng	1.3439	0.9411, 1.9189	4[24,32,37,40]	287	0.0
3	Dangshen+fuling+gancao	1.5195	1.1890, 1.9419	4[28,30,38,39]	298	0.0
3	Huangqi+banxia+baizhu	1.4324	1.0436, 1.9661	3[18,28,30]	200	0.0
7	h + b + b + s + d + f + gancao	1.4828	1.0506, 2.0927	2[28,30]	140	0.0

Abbreviations: 95% CI, 95% confidence interval; I^2%, measure of heterogeneity; RR, risk ratio for tumor response; No. Part., number of participants; 7.h + b + b + b + d + f(huangqi+banxia+baizhu+ sheshecao+dangshen+fuling).

enhance survival rates, and the body's capacity to fight off infection, lower tumor marker expression levels, and even slow tumor development. Specific TCMs may have the potential to improve the efficacy of capecitabine-based chemotherapy for CRC.

AUTHOR CONTRIBUTIONS

Hui-Zhong Jiang and Ya-Li Jiang conceived of and designed the study. They had full access to all data in the study and took responsibility for the integrity of the data, the accuracy of the data analysis, and the writing of the report. Yang Bing, Feng-Xi Long, Zhu Yang, and Dong-Xin Tang critically revised the report. Hui-Zhong Jiang and Ya-Li Jiang performed the statistical analyses. All the authors contributed to the data acquisition and analyses. The authors have reviewed and approved the final version of the manuscript.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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