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Review Article

# Chinese herbal injections in combination with radiotherapy for advanced pancreatic cancer: A systematic review and network meta-analysis

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ABSTRACT

*Background:* Advanced pancreatic cancer (APC) is a fatal disease with limited treatment options. This study aims to evaluate the effectiveness and safety of different Chinese herbal injections (CHIs) as adjuvants for radiotherapy (RT) in APC and compare their treatment potentials using network meta-analysis.

*Methods:* We systematically searched three English and four Chinese databases for randomized controlled trials (RCTs) from inception to July 25, 2023. The primary outcome was the objective response rate (ORR). Secondary outcomes included Karnofsky performance status (KPS) score, overall survival (OS), and adverse events (AEs). The treatment potentials of different CHIs were ranked using the surface under the cumulative ranking curve (SUCRA). The Cochrane RoB 2 tool and CINeMA were used for quality assessment and evidence grading.

*Results:* Eighteen RCTs involving 1199 patients were included. Five CHIs were evaluated. Compound Kushen injection (CKI) combined with RT significantly improved ORR compared to RT alone (RR 1.49, 95 % CrI 1.21–1.86). Kanglaite (KLT) plus RT (RR 1.58, 95 % CrI 1.20–2.16) and CKI plus RT (RR 1.49, 95 % CrI 1.16–1.95) were associated with improved KPS score compared to radiation monotherapy, with KLT+RT being the highest rank (SUCRA 72.28 %). Regarding AEs, CKI plus RT was the most favorable in reducing the incidence of leukopenia (SUCRA 90.37 %) and nausea/vomiting (SUCRA 85.79 %).

*Conclusions:* CKI may be the optimal choice of CHIs to combine with RT for APC as it may improve clinical response, quality of life, and reduce AEs. High-quality trials are necessary to establish a robust body of evidence.

*Protocol registration:* PROSPERO, CRD42023396828.

## 1. Introduction

Advanced pancreatic cancer (APC) is an extremely lethal disease, and the standard chemotherapy regimen FOLFIRINOX (5-fluorouracil, folinic acid, irinotecan and oxaliplatin) has yielded only modest improvements in patient outcomes.[1,2] Radiotherapy (RT) has been employed as a palliative treatment option, either alone or in combination with chemotherapy,[3] and recent advancements in radiation techniques offer new treatment possibilities.[4] However, RT can also lead to adverse effects.[5,6]

Chinese herbal injections (CHIs), derived from herbal extracts, have been explored as adjunctive therapies for various diseases, including cancer.[7] Data from cell culture, animal, and clinical studies suggest that CHIs may play an adjunctive and palliative role in managing pancreatic

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cancer.[8,9] Previous studies have indicated that CHIs, when combined with chemotherapy, may enhance clinical effectiveness, improve the quality of life (QoL), and reduce adverse events (AEs).[10,11] However, the evidence base from randomized controlled trials (RCTs) is inconclusive due to uncertain risk of bias, and there is a lack of systematic evaluation of CHIs in conjunction with RT for APC.

Among various CHIs with potential anti-cancer properties, compound Kushen injection (CKI) has been extensively studied in combination with RT for different cancer types.[12–17] These studies have consistently demonstrated the positive impact of CKI in combination with RT, resulting in improved treatment efficacy and reduced severity of radiation-induced side effects.[18–20] Notably, a recent network pharmacology study has shed light on the molecular mechanisms underlying CKI's effectiveness in treating pancreatic cancer, implicating the involvement of cell cycle, JAK-STAT, ErbB, PI3K-Akt, and mTOR signaling pathways, providing insights into the mechanisms operating in CKI.[21] However, the specific role of CKI as an adjunctive therapy for RT in the treatment of pancreatic cancer remains to be investigated.

This systematic review and network meta-analysis (NMA) aimed to evaluate the effectiveness and safety of different CHIs as adjuvants for RT in patients with APC. The specific role of CKI as an adjunctive therapy for RT in treating APC was also investigated and compared with other CHIs. The findings from this study could potentially enhance our understanding of the treatment potentials of CHIs and improve the management of pancreatic cancer patients.

## 2. Methods

The review protocol has been registered with PROSPERO (https://www.crd.york.ac.uk/prospero/, registration number: CRD42023396828). We reported the study in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension statement for NMA (see Supplementary File for the PRISMA checklist).[22]

### 2.1. Eligibility criteria

#### 2.1.1. Types of studies

RCTs were included, with no restrictions on language and publication year.

#### 2.1.2. Types of participants

Adult patients (above 18 years of age) diagnosed with APC through either histological or cytological findings. Patients who had not undergone invasive examinations were diagnosed based on symptoms, physical signs, imaging, and tumor markers. All patients were in locally advanced (IIb-III) or metastatic stage (IV) and were not considered candidates for surgery according to multidisciplinary discussions.

#### 2.1.3. Types of interventions

Any type of RT, including radiation alone or chemo-radiation, administered intravenously in combination with one of the specified CHIs, versus RT alone, were eligible. For patients with pancreatic cancer, radiation could be used alone or concurrently with gemcitabine- or fluoropyrimidine-based chemotherapy.[23] For patients not amenable to surgery, chemo-radiation was a conventional option for the management of locoregional pancreatic cancer, and radiation without chemotherapy was used in the metastatic setting for palliation of pain refractory to analgesic therapy.[23] The CHIs of interest included CKI, Aidi injection (AD), Huachansu injection (HCS), Tongguanteng injection (TGT), Yadanzi injection (YDZ), Shenqi Fuzheng injection (SQFZ), Polyporus umbellatus polysaccharide injection (PUP), Kangai injection (KA), Kanglaite injection (KLT), Astragalus polysaccharide injection (APS), and Shenmai injection (SM). All of these CHIs were indicated for adjuvant cancer management as per the inventory of Chinese patent drugs authorized by the National Healthcare Security Administration of the People's Republic of China (http://www.nhsa.gov.cn/). Studies that administered other traditional Chinese medicine (TCM) therapies, such as oral herbal formulae or acupuncture, were excluded.

#### 2.1.4. Types of outcome measures

*2.1.4.1. Primary outcome.* The primary outcome was the objective response rate (ORR), defined as the proportion of patients achieving complete response and partial response after treatment according to the criteria set by the World Health Organization[24] or RECIST guideline.[25]

*2.1.4.2. Secondary outcomes.* Secondary outcomes included improvement in QoL, 1-year and 2-year overall survival (OS) rates, and the incidence of AEs. QoL was assessed using the Karnofsky performance status (KPS) score, with an increase of more than 10 points after treatment indicating an improvement in QoL. OS was defined as the duration of survival until death from any cause. AEs included leukopenia and nausea/vomiting.

### 2.2. Search strategy

Seven databases, including MEDLINE (*via* PubMed), EMBASE (*via* embase.com), Cochrane Central Register of Controlled Trials, China National Knowledge Infrastructure (CNKI), SinoMed, Wanfang, and Chinese Scientific Journals Database (VIP), were searched from their inception to July 25, 2023. Medical subject headings, free-text words, and publication types were combined to create a specified search strategy for each database (see Supplementary File 2 for details).

### 2.3. Study selection

EndNote 20.0.1 was used to manage study records. Two authors (RTZ, YFX) independently scanned the titles and abstracts of all retrieved studies to exclude ineligible ones. They then read the full articles to determine the final studies to be included in the review. Disagreements were resolved through discussion or by consulting a third author (YRC).

### 2.4. Data extraction

Two authors (SBH, BBF) independently extracted raw data from the publications and resolved any disagreements by referring to a third author (YJM). The following characteristics were extracted from each included study: first author, publication year, sample size, follow-up duration, methodological quality, intervention regimens, mean/median age, sex, disease stage, response to treatment, OS, AEs, and QoL.

### 2.5. Risk of bias assessment

The revised Cochrane risk-of-bias tool for randomized trials (RoB 2) was used for quality assessment.[26] Two authors (RTZ, YJZ) independently evaluated the risk of bias for each study. The result of this assessment was verified by a third author (YJM).

### 2.6. Evidence grading

Two authors (YJM and YBH) independently rated the quality of the evidence using the Confidence in Network Meta-Analysis (CINeMA) tool (https://cinema.ispm.unibe.ch/). CINeMA is an online software developed on the basis of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach for evaluating confidence in the results from NMA.[27] Differences of opinion were settled through discussion or by consulting a third author (ZLL).

**Table 1**
Characteristics of the studies included in the NMA.

| Study | Sample size (M/F)<br>Age (Mean/Range)<br>TNM Stage | Intervention | Control | Outcomes |
|---|---|---|---|---|
| Cong and Qiao[35] | 60 (35/25)<br>A:65.7; B:65.6<br>III, IV | (A) CKI (20 ml qd 30d, $n$ = 30) + (B) | (B) RT (3D CRT 50 Gy/25#/5 w, $n$ = 30) | 1) ORR: A vs. B (RR 1.80 [0.68, 4.74])<br>2) Leukopenia: A vs. B (RR 0.43 [0.12, 1.50])<br>3) Nausea/vomiting: A vs. B (RR 0.50 [0.17, 1.48]) |
| Zhang et al.[36] | 120 (69/51)<br>A:64.3; B:65.1<br>III, IV | (A) CKI (30 ml qd 28d, $n$ = 60) + (B) | (B) RT (3D CRT 50–55 Gy/25–30#/5–6 w, $n$ = 60) | 1) ORR: A vs. B (RR 1.45 [0.74, 2.87])<br>2) Leukopenia: A vs. B (RR 0.67 [0.33, 1.36])<br>3) Nausea/vomiting: A vs. B (RR 0.43 [0.21, 0.86]) |
| Xu et al.[38] | 48 (31/17)<br>42–76<br>IIb, III | (A) CKI (20 ml qd 21d, $n$ = 24) + (B) | (B) RT (3D CRT 50 Gy/25#/5 w, $n$ = 24) | 1) ORR: A vs. B (RR 1.58 [1.01, 2.48])<br>2) QoL: A vs. B (RR 1.55 [0.93, 2.56])<br>3) Leukopenia: A vs. B (RR 0.36 [0.13, 0.98])<br>4) Nausea/vomiting: A vs. B (RR 0.90 [0.45, 1.81]) |
| Wang 2015a[37] | 65 (42/23)<br>A:57; B:55<br>IIb, III | (A) CKI (20 ml qd 21d, $n$ = 33) + (B) | (B) RT (Gamma Knife 36–50 Gy/8–12#/2–3 w, $n$ = 32) | 1) ORR: A vs. B (RR 1.70 [1.01, 2.84])<br>2) QoL: A vs. B (RR 1.49 [0.97, 2.29])<br>3) 1-year OS: A vs. B (RR 0.68 [0.39, 1.19]); 2-year OS: A vs. B (RR 0.69 [0.47, 1.01]) |
| Yuan et al.[41] | 62 (40/22)<br>32–78<br>IIb, III | (A) CKI (30 ml qd 21d, $n$ = 31) + (B) | (B) RT (Gamma Knife 35–45 Gy/8–12#, $n$ = 31) | 1) ORR: A vs. B (RR 1.56 [1.07, 2.29])<br>2) QoL: A vs. B (RR os1.44 [0.73, 2.88])<br>3) Leukopenia: A vs. B (RR 0.92 [0.50, 1.69])<br>4) Nausea/vomiting: A vs. B (RR 0.69 [0.35, 1.38]) |
| Zhang[39] | 63 (37/26)<br>A:55.9; B:55.2<br>III, IV | (A) CKI (30 ml qd 21d, $n$ = 32) + (B) | (B) RT (Gamma Knife 35–45 Gy/8–12#/2–3 w, $n$ = 31) | 1) ORR: A vs. B (RR 1.48 [1.03, 2.12])<br>2) QoL: A vs. B (RR 1.56 [0.96, 2.54])<br>3) Leukopenia: A vs. B (RR 0.48 [0.24, 0.97])<br>4) Nausea/vomiting: A vs. B (RR 0.79 [0.46, 1.35]) |
| Chen 2012[40] | 66 (35/31)<br>A:35–75; B:35–71<br>IIb, III, IV | (A) CKI (20 ml qd 28d-42d, $n$ = 36) + (B) | (B) RT (X-ray 40–60 Gy/20–30#/4–6 w, $n$ = 30) | 1) QoL: A vs. B (RR 1.83 [1.04, 3.24])<br>2) Leukopenia: A vs. B (RR 0.61 [0.33, 1.12]) |
| Wang 2015b[42] | 92 (55/37)<br>A:52.3; B:53.1<br>IIb, III | (A) KLT 100 ml qd 21d, $n$ = 46) + (B) | (B) RT (3D CRT 45–50 Gy/25#/5 $w$ + GEM 800 mg/m$^2$ d1,8,15/q28d*2, $n$ = 46) | 1) ORR: A vs. B (RR 1.62 [1.02, 2.60])<br>2) QoL: A vs. B (RR 1.62 [1.20, 2.20]) |
| Shu 2013[43] | 50 (30/20)<br>A:27–69; B:25–69<br>IIb, III | (A) KLT 100 ml qd 21d*2, $n$ = 25) + (B) | (B) RT (3D CRT 45–50 Gy/25#/5 $w$ + GEM 800 mg/m$^2$ d1,8,15/q28d*2, $n$ = 25) | 1) QoL: A vs. B (RR 1.53 [1.01, 2.31])<br>2) 1-year OS: A vs. B (RR 0.82 [0.41, 1.62]); 2-year OS: A vs. B (RR 0.83 [0.56, 1.25])<br>3) Leukopenia: A vs. B (RR 0.85 [0.61, 1.19])<br>4) Nausea/vomiting: A vs. B (RR 1.00 [0.56, 1.78]) |
| Cao 2012[45] | 56 (31/25)<br>44–73<br>IIb, III | (A) KLT (100 ml qd 21d*2, $n$ = 28) + (B) | (B) RT (3D CRT 45–50 Gy/25#/5 $w$ + GEM 800 mg/m$^2$ d1,8,15/q28d*2, $n$ = 28) | 1) 1-year OS: A vs. B (RR 0.85 [0.46, 1.56]); 2-year OS: A vs. B (RR 0.86 [0.60, 1.22]) |
| Shen 2012[46] | 50 (30/20)<br>A:56.0; B:54.8<br>IIb, III | (A) KLT (100 ml qd 21d*2, $n$ = 25) + (B) | (B) RT (3D CRT 45–50 Gy/25#/5 $w$ + GEM 800 mg/m$^2$ d1,8,15/q28d*2, $n$ = 25) | 1) ORR: A vs. B (RR 1.20 [0.64, 2.25])<br>2) 1-year OS: A vs. B (RR 0.82 [0.41, 1.62]); 2-year OS: A vs. B (RR 0.83 [0.56, 1.25])<br>3) Nausea/vomiting: A vs. B (RR 0.84 [0.58, 1.22]) |
| Zhu 2013[44] | 55 (31/24)<br>A:37–70; B:39–72<br>IIb, III | (A) KLT (200 ml qd 21d*2, $n$ = 28) + (B) | (B) RT (Gamma Knife 36–49 Gy/9–12#, $n$ = 27) | 1) ORR: A vs. B (RR 1.11 [0.84, 1.47])<br>2) QoL: A vs. B (RR 2.07 [1.00, 4.27]) |
| Xie 2020[49] | 102 (60/42)<br>A:53.5; B:52.3<br>III, IV | (A) SQFZ (250 ml qd 21d*2, $n$ = 51) + (B) | (B) RT (3D CRT 50–60 Gy/28#/5–6 $w$ + GEM 600–1000 mg/m$^2$ d1,8,15/q28d*3–6, $n$ = 51) | 1) ORR: A vs. B (RR 1.53 [0.99, 2.34])<br>2) Leukopenia: A vs. B (RR 0.68 [0.38, 1.23])<br>3) Nausea/vomiting: A vs. B (RR 0.65 [0.39, 1.10]) |
| Guo 2016[50] | 78 (41/37)<br>A:56.3; B:55.8<br>III, IV | (A) SQFZ (250 ml qd 21d*2, $n$ = 39) + (B) | (B) RT (3D CRT 50–60 Gy/28#/5–6 $w$ + GEM 600–1000 mg/m$^2$ d1,8,15/q28d*3–6, $n$ = 39) | 1) ORR: A vs. B (RR 1.40 [0.86, 2.29])<br>2) 1-year OS: A vs. B (RR 0.77 [0.56, 1.05]); 2-year OS: A vs. B (RR 0.92 [0.85, 1.01])<br>3) Leukopenia: A vs. B (RR 0.65 [0.35, 1.20])<br>4) Nausea/vomiting: A vs. B (RR 0.75 [0.41, 1.37]) |

(*continued on next page*)

**Table 1** (*continued*)

| Study | Sample size (M/F)<br>Age (Mean/Range)<br>TNM Stage | Intervention | Control | Outcomes |
|---|---|---|---|---|
| Liu 2011[47] | 32 (18/14)<br>66.5<br>III, IV | (A) SQFZ (250 ml qd 21d*2, $n$ = 17) + (B) | (B) RT (3D CRT 50–60 Gy/28#/5–6 $w$ + GEM 600–1000 mg/m$^2$ d1,8,15/q28d*3–6, $n$ = 15) | 1) ORR: A vs. B (RR 1.13 [0.56, 2.29])<br>2) 1-year OS: A vs. B (RR 0.88 [0.55, 1.40]); 2-year OS: A vs. B (RR 0.94 [0.84, 1.06])<br>3) Leukopenia: A vs. B (RR 0.76 [0.54, 1.06])<br>4) Nausea/vomiting: A vs. B (RR 0.76 [0.54, 1.06]) |
| Liu 2021[48] | 100 (56/44)<br>A:53.9; B:52.6<br>IIb, III | (A) SQFZ (250 ml qd, $n$ = 50) + (B) | (B) RT (RT + GEM 1000 mg/m$^2$, once a week, $n$ = 50) | 1) Nausea/vomiting: A vs. B (RR 0.50 [0.10, 2.61]) |
| Wang 2013[51] | 46 (25/21)<br>A:39–70; B:36–67<br>IIb, III | (A) KA (40 ml qd 21d, $n$ = 23) + (B) | (B) RT (SBRT 30–40 Gy/9–12#, $n$ = 23) | 1) ORR: A vs. B (RR 1.86 [0.91, 3.79])<br>2) QoL: A vs. B (RR 1.60 [0.93, 2.74]) |
| Zhang 2010[52] | 54 (36/18)<br>30–72<br>IIb, III | (A) SM (80 ml qd, $n$ = 27) + (B) | (B) RT (SBRT, $n$ = 27) | 1) ORR: A vs. B (RR 1.22 [0.89, 1.69])<br>2) QoL: A vs. B (RR 1.36 [0.77, 2.40]) |

Note: 3D CRT, 3D conformal radiotherapy; AEs, adverse events; CKI, compound Kushen injection; F, female; GEM, gemcitabine; KA, Kangai injection; KLT, Kanglaite injection; M, male; OS, overall survival; ORR, objective response rate; QoL, quality of life; RR, risk ratio; RT, radiotherapy; SBRT, stereotactic body radiation therapy; SM, Shenmai injection; SQFZ, Shenqi Fuzheng injection.

### 2.7. Statistical methods

Primary and secondary outcomes, including ORR, improvement rate of KPS score, 1-year, and 2-year OS rates, and the incidence rate of leukopenia and nausea/vomiting, were all binary outcomes. Therefore, the relative risk (RR) was used as the effect measure and corresponding 95 % credible intervals (CrIs) for RR estimates were calculated. Due to the heterogeneity of multiple interventions included, a random-effects model was used for NMA. The R package "BUGSnet"[28] was employed to perform a Bayesian NMA with the Markov chain Monte Carlo method. An uninformative prior distribution was set for four Markov chains to run iterative simulations (burn-in iterations = 50,000, iterations = 500,000, thinning factor = 1). Convergence was assessed using the potential scale reduction factor (PSRF), with a PSRF value close to 1 indicating convergence.[29] League tables were presented to display comparative effects between various comparisons within the treatment network. The surface under the cumulative ranking curve (SUCRA) values were calculated to estimate the ranking probabilities of multiple CHIs for different outcomes.

The fundamental assumptions underlying an NMA are those of similarity, transitivity, and consistency.[30] The similarity or homogeneity assumption typically pertains to direct comparisons, and it is met when the true treatment effects of two interventions are similar across studies in a standard pairwise meta-analysis.[30] Heterogeneity arises when there is variation in the true treatment effect. We conducted a standard pairwise meta-analysis using the R package "meta".[31] Heterogeneity was assessed using the chi-squared test, where a low $P$ value (<0.10) indicates evidence of heterogeneity in treatment effects.[32] We computed the $I^2$ statistic to quantify heterogeneity in each direct comparison. We interpreted the $I^2$ statistic using the following criteria: 0 % to 40 % may not be of significant concern; 30 % to 60 % could indicate moderate heterogeneity; 50 % to 90 % suggests substantial heterogeneity; 75 % to 100 % indicates considerable heterogeneity.[32] When there is no significant heterogeneity, we adopt a fixed-effects model; otherwise, we used a random-effects model. The transitivity assumption is relevant to indirect comparisons.[33] We established inclusion criteria with the transitivity assumption in mind, ensuring that individuals meeting the predetermined criteria were equally eligible to be randomized to any of the included interventions examined in this review, making them 'jointly randomizable'.[34] We also extracted important clinical and methodological characteristics from each included study to evaluate whether there were significant imbalances in potential effect modifiers across the planned comparisons, beyond the treatments under examination. The consistency assumption is applicable to mixed comparisons that involve both direct and indirect comparisons.[33] Since no closed loops were observed in the treatment network, there was no testing for inconsistency between direct and indirect evidence in this NMA.

Due to the small number of studies included for multiple comparisons, we were unable to perform any subgroup or sensitivity analysis. Publication bias was evaluated with the comparison-adjusted funnel plot using STATA.

## 3. Results

### 3.1. Study characteristics

A total of 1883 records were retrieved. After de-duplication, 1150 were screened for their titles and abstracts to exclude irrelevant studies. Eighty-five studies remained for full-text screening, from which 18 trials were eventually considered eligible. The detailed flow diagram of the study selection process is presented in Fig. 1.

The 18 included RCTs were all conducted in China between 2010 and 2021, involving 1199 patients, of whom 59 % were male. The RT approaches used included 3D conformal radiotherapy, stereotactic body radiation therapy, and conventional X-ray radiation (see Table 1 for detailed regimens). Five different CHIs were evaluated, with 7 RCTs for CKI,[35–41] 5 RCTs for KLT,[42–46] 4 RCTs for SQFZ,[47–50] 1 RCT for KA,[51] and 1 RCT for SM.[52] The network plot for each outcome is displayed in Supplementary File 3. Detailed pharmacological features for the included CHIs are provided in Supplementary File 4.

### 3.2. Risk of bias assessment

For the randomization process, the study by Xie et al.[49] assigned groups based on treatment methods (high risk of bias), while two studies[43, 46] used tables of random numbers and sealed envelopes (low risk of bias). The remaining studies did not provide sufficient information about their randomization methods (some concerns). Only one study used a single-blind method.[51] No registration information and prespecified study protocols were found for any of the included studies. Thus, in terms of overall bias, one study[49] was rated as high-risk-of-bias,

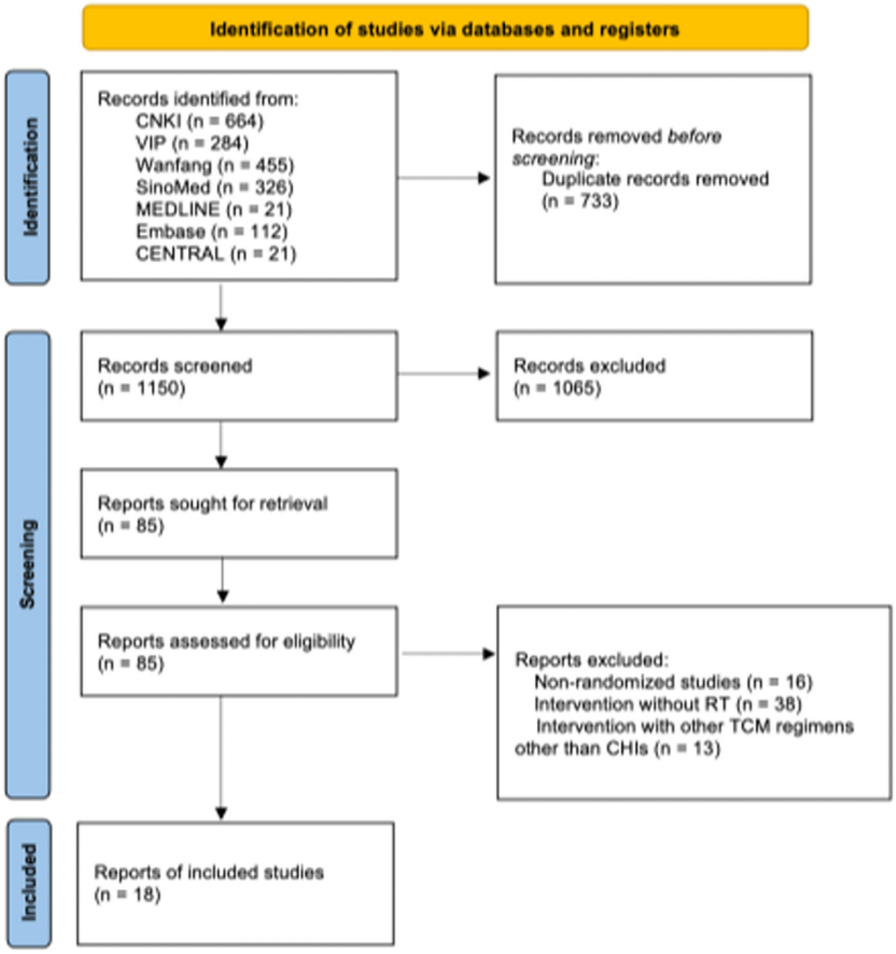


**Fig. 1.** Flow diagram of the study selection process. Note: CENTRAL, Cochrane Central Register of Controlled Trials; CHIs, Chinese herbal injections; CNKI, China National Knowledge Infrastructure; n, number; RT, radiotherapy; TCM, traditional Chinese medicine; VIP, Chinese Scientific Journals Database.

while the others were all rated as having some concerns (Supplementary File 5).

### 3.3. Pair-wise meta-analysis

#### 3.3.1. Overall response rate

Pairwise meta-analysis revealed that the combination of CHI+RT was significantly more favorable compared to RT alone in terms of improving ORR (RR=1.45, 95 % CI 1.27–1.64). There was no significant heterogeneity observed ($P$ = 0.91, $I^2$ = 0 %). Among the five CHIs, CKI+RT (RR=1.57, 95 % CI 1.28–1.92), KLT+RT (RR=1.31, 95 % CI 1.02–1.68), and SQFZ+RT (RR=1.41, 95 % CI 1.05–1.89) were all significantly more effective than RT alone. Detailed results can be found in Supplement 6, A.

#### 3.3.2. Quality of life

In general, the combination of CHI+RT demonstrated a significant advantage over RT alone in enhancing QoL (RR=1.58, 95 % CI 1.36–1.85, $I^2$=0 %). Specifically, CKI+RT (5 studies, RR=1.57, 95 % CI 1.24–1.99, $I^2$ = 0 %) and KLT+RT (3 studies, RR=1.65, 95 % CI 1.29–2.10, $I^2$ = 0 %) displayed significant statistical differences (see Supplement 6, B).

#### 3.3.3. Overall survival

Regarding the survival rate, the results of pairwise meta-analysis indicated that CHI+RT had an overall beneficial effect on improving the 1-year (RR=0.79, 95 % CI 0.64–0.97, $I^2$ = 0 %) and 2-year OS rates (RR=0.85, 95 % CI 0.76–0.96, $I^2$ = 34 %). However, none of the CHIs demonstrated significant differences within their respective subgroups (see Supplement 6, C and D).

#### 3.3.4. Adverse events

When considering safety evaluation, the combination of CHI+RT was significantly beneficial in reducing the incidence of leukopenia (RR=0.66, 95 % CI 0.55–0.80, $I^2$ = 0 %) and nausea/vomiting (RR=0.71, 95 % CI 0.59–0.86, $I^2$ = 0 %). Notably, CKI+RT (for leukopenia, RR=0.60, 95 % CI 0.44–0.81, $I^2$ = 0 %; for nausea/vomiting, RR=0.64, 95 % CI 0.47–0.88, $I^2$ = 0 %) and SQFZ+RT (for leukopenia, RR=0.69, 95 % CI 0.51–0.95, $I^2$ = 0 %; for nausea/vomiting, RR=0.70, 95 % CI 0.52–0.94, $I^2$ = 0 %) exhibited significant differences in reducing AEs (see Supplement 6, E and F).

### 3.4. Network meta-analysis

#### 3.4.1. Overall response rate and quality of life

Fourteen RCTs reported the ORR for five types of CHIs (Supplement 3, A). Combining CKI with RT showed a superior ORR compared to RT alone (RR=1.49, 95 % CrI 1.21–1.86). Other comparisons between interventions did not reveal statistically significant differences (Fig. 2A). According to SUCRA values, KA+RT (78.99 %) might be the best option regarding the response rate, followed by CKI+RT (75.17 %), which ranked second (Fig. 3). The SUCRA plot is provided in Supplement 7.

A total of 10 RCTs reported the improvement rate of KPS score (Supplement 3, B). CKI+RT (1.49, 95 % CrI 1.16–1.95) and KLT+RT

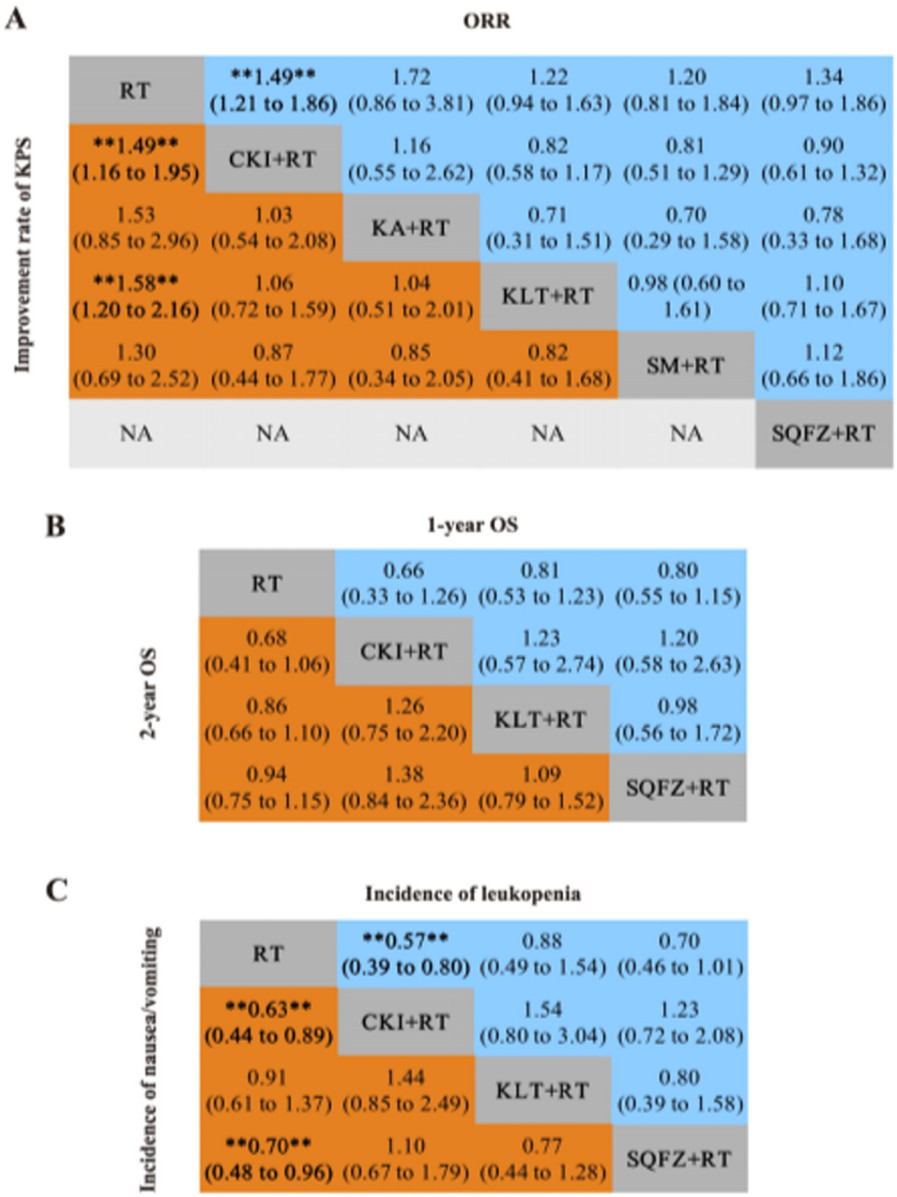


**Fig. 2.** League tables of NMA estimates for each outcome. (A) ORR (upper right half) and improvement rate of KPS (lower left half). (B) 1-year OS rate (upper right half) and 2-year OS rate (lower left half). (C) Incidence of leukopenia (upper right half) and nausea/vomiting (left lower half). Note: CKI, compound Kushen injection; KA, Kangai injection; KLT, Kanglaite injection; NA, not available; OS, overall survival; RT, radiotherapy; SM, Shenmai injection; SQFZ, Shenqi Fuzheng injection. Each cell represents the RR between the treatment on the right versus the treatment on the left. For ORR and KPS improvement rate, an RR greater than 1 indicates that the treatment on the right is superior. In the case of OS and AEs, an RR smaller than 1 suggests that the treatment on the right is better. Cells with bold font and asterisks indicate a statistically significant difference. For example, in the first row of Fig. 2A, the first blue cell signifies that CKI+RT significantly outperformed RT in improving ORR (RR=1.49, 95 % CrI 1.21–1.86).

(RR=1.58, 95 % CrI 1.20–2.16) demonstrated statistically significant improvements in KPS score compared to RT alone (Fig. 2A), with KLT+RT potentially being the optimal treatment (SUCRA 72.28 %). We also compared the effectiveness between the interventions using SUCRA values regarding ORR and KPS together, suggesting that CKI+RT and KA+RT might be prominent choices considering both clinical response and QoL (Supplement 8, A).

### 3.4.2. Overall survival

Only 6 studies reported 1-year and 2-year OS rates involving 3 CHIs (Supplement 3, C). However, no significant differences were found between any of the comparisons in the treatment network (Fig. 2B). The SUCRA values indicated that CKI+RT (76.70 % for 1-year OS, 89.52 % for 2- year OS) might be better in improving long-term survival (Fig. 3).

### 3.4.3. Adverse events

Regarding safety outcomes, 10 RCTs reported incidence of leukopenia (Supplement 3, D), and 11 studies reported the incidence of nausea/vomiting (Fig. S1E). CKI+RT showed statistical differences in reducing both leukopenia (0.57, 95 % CrI 0.39–0.80) and nausea/vomiting (RR=0.63, 95 % CrI 0.44–0.89) when compared to RT alone (Fig. 2C). SQFZ+RT could also relieve nausea/vomiting (RR=0.70, 95 % CrI 0.48–0.96). Based on SUCRA values, CKI+RT ranked first in both reducing leukopenia and nausea/vomiting (Fig. 3). We also displayed 3D plot considering SUCRA values of ORR and AEs together, suggesting that

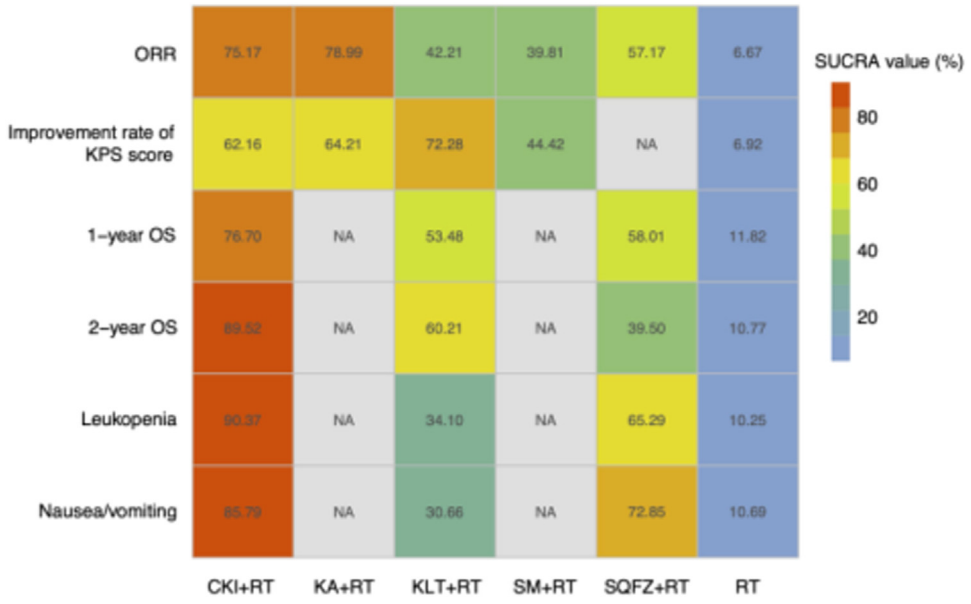


**Fig. 3.** Rank-heat plot. Note: CKI, compound Kushen injection; KA, Kangai injection; KLT, Kanglaite injection; NA, not available; OS, overall survival; RT, radiotherapy; SQFZ, Shenqi Fuzheng injection; SM, Shenmai injection. The numbers represent SUCRA values. A higher SUCRA value indicates improved ORR, enhanced KPS, extended OS, and reduced incidence of leukopenia and nausea/vomiting.

CKI+RT may be the optimal choice in improving clinical response and reducing AEs simultaneously (Supplement 8, B).

### *3.5. Publication bias*

Comparison-adjusted funnel plots for each outcome are presented in Supplement 9. The zero line (red) represents the null hypothesis that the study-specific effect sizes do not differ from the pooled effect estimates. As shown in the funnel plots, the regression line (blue) for each outcome did not comply with the zero line, indicating potential bias resulting from reporting bias and small-study effects in our findings.

### *3.6. Evidence grading*

Grading of confidence in evidence is provided in Supplementary File 9. Due to the overall low-quality of reporting in the primary studies, within-study bias was all rated as “some concerns”. With no closed loop of evidence, the incoherence test between direct and indirect evidence was not available, thus “some concerns” was suggested. Moreover, reporting bias was indicated by the comparison-adjusted funnel plots (Supplement 8). Finally, after downgrading for these main reasons, the confidence rating was generally very low.

## 4. Discussion

### *4.1. Summary of the main findings*

In this systematic review, we included 18 RCTs involving 5 different CHIs and 1199 patients. We assessed the effects of combining these CHIs with RT for the treatment of APC. The results of pairwise meta-analysis indicated that the use of CHI in conjunction with RT was generally beneficial in improving clinical response, enhancing QoL, and reducing treatment-related AEs compared to RT alone. Moreover, no heterogeneity was observed in direct comparisons. The NMA results, as indicated by the SUCRA values, suggested that the combination of CKI with RT may be the most promising option. However, it is important to note that statistical significance was only observed for certain herbal interventions, such as CKI+RT, KLT+RT, and SQFZ+RT, when compared to RT alone in the pairwise meta-analysis. This aligns with the results from NMA, where only CKI plus RT showed statistical significance for improving ORR, enhancing QoL, and reducing AEs simultaneously, when compared to RT alone. In addition, KLT+RT exhibited a statistically significant difference in QoL improvement, and SQFZ+RT significantly reduced the incidence of nausea/vomiting. This necessitates a cautious interpretation of the overall results. Additionally, it is essential to recognize that the comparisons between CHIs were exclusively based on indirect comparisons, and the statistical test did not achieve significance when comparing the different herbal injections. This highlights the need for a careful interpretation of these findings, considering the limitations of indirect comparisons (see Section 4.5 for details).

Concerning the three assumptions essential for conducting a NMA, we observed no indications of significant variations in important effect modifiers, including age, sex, TNM stage, and treatment duration, among the comparisons (see Table 1). The participants exhibited sufficient similarity to meet the transitivity assumption for the NMA, meaning that there were no systematic distinctions between the available comparisons aside from the treatments under evaluation. Nonetheless, several comparisons were constrained by having only one or two studies, and the absence of data prevented us from examining the distribution of prior treatments among these comparisons. Thus, the possibility of intransitivity seems to be unlikely even if it could not be totally excluded. Regarding homogeneity and consistency, we identified no significant heterogeneity in direct comparisons within the pairwise meta-analysis. However, the lack of direct comparisons involving different CHIs did not allow us to assess consistency between direct and indirect evidence.

### *4.2. Comparison with previous studies*

This is the first NMA to specifically assess the clinical benefits and safety of different CHIs when combined with RT for APC patients. While previous systematic reviews[10,11] have explored the combined effects of CHIs with chemotherapy in pancreatic cancer treatment, our findings focus on CHIs combined with RT align with and support previous studies. These findings suggest that CHIs are compatible with diverse anti-cancer therapies and have the potential to enhance clinical response, improve QoL, and mitigate treatment-related toxicities to some extent. However, it is important to be cautious in interpreting these results due to the overall low quality of available evidence.

### 4.3. Role of CHIs as adjuvants in RT and their anticancer mechanisms

There has been ongoing interest in naturally occurring radioprotectors due to their lower toxicity and high efficacy.[53] Our findings underscore CKI as a potential optimal choice in terms of clinical response, QoL improvement, and reduced side effects when combined with RT for pancreatic cancer treatment. Several studies support the potential of CKI as an adjunctive therapy in radiation treatment. For instance, oxymatrine, an extract derived from *Sophora flavescens* Aiton (a primary herbal ingredient in CKI) was found to expedite hematological recovery and improve survival rates following irradiation-induced injury by activating the MAPK signaling pathway.[18] Matrine, another essential alkaloid component found in *Sophora flavescens* Aiton, has been shown to inhibit pancreatic cancer cell migration and invasion through the ROS/NF-$\kappa$B/MMPs pathway.[54] Additionally, matrine may down-regulate STAT3 expression to suppress KRAS-driven pancreatic cancer growth.[55] CKI has also demonstrated potential in alleviating gastrointestinal mucositis induced by RT, reducing inflammation, and apoptosis in the intestinal mucosa.[19] Furthermore, CKI has been studied in the context of radiation-induced skin injury, where it protected the skin and mitigated radiation injury by regulating Bim protein expression.[20] These findings complement our research results, which indicate that CKI, particularly compounds derived from *Sophora flavescens* like matrine and oxymatrine, play a crucial role in enhancing treatment efficacy and reducing side effects in radiation therapy for APC.

The other four CHIs included in our NMA also exhibited their respective potentials for the treatment of APC. KLT has been found to downregulate key signaling pathways like PI3K/Akt/mTOR, indicating its role in inhibiting cell survival, proliferation, and cancer cell progression.[56] Additionally, unsaponifiable matter in KLT was investigated for its anti-pancreatic cancer effects, targeting key genes and modulating pathways related to cell cycle, apoptosis, and signaling.[57] Moreover, KLT has shown a protective effect against RT-induced mucositis in head and neck cancer patients, leading to a low incidence of severe mucositis and favorable patient outcomes during RT.[58] These findings collectively suggest that KLT holds promise as an adjuvant therapy in pancreatic cancer treatment and also demonstrates potential in reducing the side effects of RT, highlighting its multifaceted role in improving cancer patient care. In the context of radiation-induced brain injury, SQFZ has been found to effectively mitigate the adverse effects of cranial radiation therapy by inhibiting the NF-$\kappa$B signaling pathway and microglial activation.[59] SQFZ has also exhibited promising results in alleviating cancer-related fatigue in mouse models, a debilitating condition commonly experienced by cancer patients.[60] KA, another traditional herbal injection, has shown promise in various medical applications. A network pharmacology study identified quercetin as a key compound in KA, and *in vitro* experiments validated its potential to suppress cancer cell proliferation by inhibiting the PI3K/AKT pathway, confirming the network pharmacology predictions.[61] Moreover, in the treatment of malignant pleural effusion, KA in combination with thermotherapy has been shown to significantly improve clinical effects and QoL.[62] Additionally, KA was found to exhibit anti-proliferative effects on cancer cells, which could inhibit cell proliferation through the IL-6/STAT3 pathway, leading to G1 phase arrest and modulation of key cell cycle regulators.[63] SM, a well-established TCM preparation, has gained recognition for its therapeutic potential in various aspects of cancer treatment. SM was investigated for its potential anti-angiogenic effects, and protopanaxadiol-type ginsenoside was identified as a key bioactive component with a notable anti-angiogenic impact on tumor vasculature.[64] Additionally, SM's role in enhancing antitumor immunity in combination with programmed death-1 inhibitors was also explored, showing that SM could reprogram the tumor immune microenvironment by promoting natural killer (NK) cell infiltration and revitalizing the cytotoxic activity of NK and T cells.[65]

### 4.4. Implications for clinical practice and further research

Pancreatic cancer is a highly lethal disease with limited curative treatment options. Traditional medicine is currently gaining attention due to its therapeutic and palliative role in cancer management. While TCM is widely used in China and other Asian countries, the lack of high-level evidence on its effectiveness has raised concerns among TCM practitioners and researchers.[66] Given the overall low-quality of current evidence, clinical decisions regarding the use of these CHIs for patients with APC should be made cautiously. Additional efforts are needed to properly design and conduct future trials to detect clinically significant effects and minimize the risk of bias. CHIs play multifaceted roles in cancer therapy, including anti-angiogenic properties, immune modulation, enhancement of chemotherapeutic drug delivery and cytotoxicity. These findings underscore the potential of CHIs as valuable complements to conventional cancer treatments, offering novel strategies to enhance the efficacy and safety of cancer therapy. While the empirical evidence of their efficacy is mounting, there is a pressing need for in-depth mechanistic studies to elucidate the precise molecular and cellular mechanisms underlying their effects. Understanding these mechanisms is crucial for optimizing their use, improving treatment outcomes, and potentially identifying new targets for innovative cancer therapies.

### 4.5. Strengths and limitations

This study possesses several strengths. Firstly, it stands out as the first NMA to comprehensively evaluate the effectiveness and safety of different types of CHIs combined with RT for the treatment of APC. Secondly, we employed the CINeMA tool to evaluate the confidence of evidence derived from the NMA results, providing a comprehensive overview of the available body of evidence. Thirdly, our study integrated clinical evidence that CKI may serve as an adjunctive therapy in radiation treatment for pancreatic cancer. Lastly, the rank-heat plot was used to visualize the ranking probabilities of the interventions, facilitating the quick identification of the most effective and safest treatment options. This enhances the interpretability of our results and aids clinicians in making informed decisions.

There are several limitations to this study. First and foremost, it is important to acknowledge that the comparisons between herbal injections were based solely on indirect comparisons. The number of included studies was relatively small. No closed loops were observed in the treatment network. This absence of closed loops means that the evaluation for incoherence between direct and indirect evidence was unavailable. The indirect comparison may lead to either an overestimation or underestimation of the results, without a clear bias towards either direction when compared to the results of the head-to-head randomised trials.[67] Additionally, the optimal ranking of a particular treatment, such as CKI, was determined through indirect comparison, and the statistical test did not yield significant results when comparing different herbal injections. This introduces the possibility of overestimation and other limitations that should be approached with caution. The conclusions drawn from NMA should be subjected to scrutiny, considering the various aspects of the methodology and results. The study's limitations can indeed impact the reliability of its rankings and conclusions. To fully understand the findings and conclusions, it is crucial to consider the geometry and strength of the network, evaluate factors such as heterogeneity, consistency, and transitivity, and not focus solely on the numeric ranking of treatments.[68] Second, the risk-of-bias assessment results indicated poor reporting and conducting quality of the primary studies, and comparison-adjusted funnel plots suggested that publication bias may exist, thus the overall picture of the evidence could be biased. Third, we overlooked the interactive (synergistic and antagonistic) effects of integrative therapies, which is certainly beyond the scope and capacity of our systematic review. On the one hand, interactions may occur be-

tween TCM and western medicine. On the other hand, synergistic effects may happen in the combination of multiple herbal substances. These interactive effects should be further explored in future studies that focus on pharmacological features and treatment targets of the CHIs. Furthermore, it is essential to acknowledge the limitations inherent in the scope of application of CHIs since all the studies included in this review were conducted in China, and the patient populations consisted solely of Chinese individuals. This specific focus may introduce a degree of selection bias to the results, making it crucial to interpret the findings within this context. It is worth noting that the Russian Federation approved the clinical trial of KLT in 2002, and KLT has been available in the Russian market since 2005.[69] In the United States, the Food and Drug Administration authorized a clinical trial of KLT in 2001, and a phase II study was completed in 2014.[9] However, despite these international developments, the clinical application of CHIs remains relatively limited beyond China, with a notable absence of large-scale, international multicenter studies. Consequently, it is imperative to recognize that the conclusions drawn from the results presented here may not be universally applicable on a global scale.

### 4.6. Conclusions

This NMA provided evidence regarding the use of various CHIs in combination with RT for the treatment of APC, indicating that CKI may be the most favorable option for improving clinical response, enhancing quality of life, and reducing AEs simultaneously. However, it is crucial to recognize that the findings are inconclusive due to indirect comparisons and the overall low quality of evidence. This highlights the urgent need for large-scale, meticulously designed, and well-reported clinical trials.

## CRediT authorship contribution statement

**Yun-Ru Chen:** Conceptualization, Methodology, Software, Formal analysis, Writing – original draft. **Ruo-Tong Zhao:** Investigation, Resources. **Yi-Fang Xu:** Validation, Data curation, Visualization. **Shao-Bo Hu:** Validation, Data curation, Visualization. **Xue-Hui Wang:** Validation. **Bing-Bing Fan:** Validation, Data curation, Visualization. **Yan-Ji Zhou:** Validation. **Yu-Bei Huang:** Writing – review & editing. **Nicola Robinson:** Conceptualization, Writing – review & editing. **Jian-Ping Liu:** Supervision. **Zhao-Lan Liu:** Project administration, Funding acquisition.

## Conflict of interests

The authors declare that they have no conflicts of interest.

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## Ethical statement

Not applicable.

## Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.imr.2023.101004.

Supplement 1. PRISMA-NMA checklist.
Supplement 2. Search strategy for each database.
Supplement 3. Network plot for each outcome.
Supplement 4. Detailed information of the included CHIs.
Supplement 5. Risk of bias assessment by RoB 2.0.
Supplement 6. Pairwise meta-analysis.
Supplement 7. SUCRA plots.
Supplement 8. 3D plot based on SUCRA values.
Supplement 9. Comparison-adjusted funnel plots.
Supplement 10. Evidence grading by CINeMA tool.

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