Systematic Review and Meta-Analysis

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Cardioprotective effect of Chinese herbal medicine for anthracycline-induced cardiotoxicity in cancer patients

A meta-analysis of prospective studies

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Abstract

Background: To assess the benefits and harmful effects of Chinese herbal medicine (CHM) formulations in preventing anthracyclines (ANT)-induced cardiotoxicity.

Method: The Cochrane Library, Pubmed and EMBASE databases were electronically searched for relevant randomized controlled trials (RCTs) published till December 2021 in English or Chinese-language, in addition to manual searches through the reference lists of the selected papers, and the Chinese Conference Papers Database. Data was extracted by 2 investigators independently.

Result: Seventeen RCTs reporting 11 different CHMs were included in this meta-analysis. The use of CHM reduced the occurrence of clinical heart failure (RR 0.48, 95% CI 0.39 to 0.60, $P < .01$) compared to the control group. Data on subclinical heart failure in terms of LVEF values showed that CHM reduced the occurrence of subclinical heart failure (RR 0.47, 95% CI 0.35 to 0.62, $P < .01$) as well.

Conclusion: CHM is an effective and safe cardioprotective intervention that can potentially prevent ANT-induced cardiotoxicity. However, due to the insufficient quality of the included trials, our results should be interpreted with cautious.

Abbreviations: ANT = anthracycline, CBM = Chinese BioMedical Database, CENTRAL = The Cochrane Central Register of Controlled Trials, CHM = Chinese herbal medicine, CI = confidence interval, CNKI = Chinese National Knowledge Infrastructure Database, CTCAE = Common Terminology Criteria for Adverse Events, cTNT = cardiac troponin T, FDA = Food and Drug Administration, LVEF = left ventricular ejection fraction, MUGA = radionuclide ventriculography, NYHA = New York Heart Association, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses, QoL = quality of life, RCT = randomized controlled trial, RevMan = Review Manager software, ROS = reactive oxygen species, RR = risk ratios, SMD = standard mean difference, TCM = traditional Chinese medicine.

Keywords: anthracycline, cancer, cardiotoxicity, Chinese herbal medicine, meta-analysis

1. Introduction

Anthracyclines (ANTs), such as doxorubicin, daunorubicin and epirubicin, are among the most effective antineoplastic antibiotics used in chemotherapy against lymphoma, sarcoma, breast cancer and pediatric leukemia. Their clinical use is however hampered by the high risk of cardiotoxicity, especially at high cumulative doses.[1,2] After the cardiac complications of daunorubicin were first reported in 1967,[3] it was confirmed as a common side effect of all ANTs in subsequent studies. Although the exact molecular basis for ANT-induced cardiotoxicity is still unknown, 1 widely accepted hypothesis is that iron mediated production of reactive oxygen species (ROS) results in myocardial oxidative stress.[4] However,

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The authors declare that they have no competing interests.

All data generated or analyzed during this study are included in this published article.

Ethical approval of this study was not necessary because this study was a meta-analysis and did not involve patient recruitment.

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Highlights

1. This is the first meta-analysis on the cardioprotective interventions of CHM during ANT chemotherapy to determine its role in preventing cardiotoxicity.
2. Our results indicate that CHM is an effective and safe cardioprotective intervention that can potentially prevent ANT-induced cardiotoxicity.

studies show limited protective effects of antioxidants or iron chelation on ANT-induced cardiotoxicity both in vivo and in vitro.[5,6] A recent study showed topoisomerase Top 2β as the key mediator of doxorubicin-induced cardiotoxicity, and that cardiomyocyte-specific deletion of Top2β protected the cells from DNA double-strand breaks and transcriptome changes triggered by this ANT, which result in defective mitochondrial biogenesis and ROS formation.[7]

ANT-induced cardiotoxicity is classified as early or late using 1 year as the cutoff, and both can eventually lead to irreversible heart failure, with a 60% 2-year mortality rate.[8,9] However, ANTs can improve survival rate in breast cancer by over 70% and that in childhood cancers by 75%.[10,11] Clinicians therefore have to strike a balance between effective chemotherapy and minimal risk of cardiac complications when using higher cumulative doses of ANTs.[12,13] Different cardioprotective agents have been studied to counter the cardiotoxic effects of routine ANTs.[14–19] A Cochrane meta-analysis on the current cardioprotective drugs show encouraging results with only dexrazoxane,[20] which is also the only drug among those studied that has been approved by Food and Drug Administration(FDA) for ANT-induced cardiotoxicity. However, it may have some undesirable side effects such as the potential risk of increased secondary malignancies.[21–23] Furthermore, dexrazoxane is not widely used due to its high costs, especially in the under-developed countries. Therefore, FDA has only approved its use for patients with metastatic breast cancer who need additional doxorubicin to control cancer spread, after they have received at least 300 mg/m²of doxorubicin.[24] Taken together, there is still no effective and safe strategy at present to prevent heart damage caused by ANTs.

Chinese herbal medicines (CHM) are an essential part of traditional Chinese medicine (TCM) that has been used in China for thousands of years, and are still an integral part of clinical medicine in China, Japan and Korea. Modern medical technologies have enabled CHM access in the form of capsules, tablets, decoctions or injections, and are now included in the national essential drugs list of China.

TCM follows a particular theoretical and methodological pathway for diagnosis and treatment. TCM regards illness as a Zheng (syndrome), the syndromes or diagnostic categories of TCM describe clinical patterns of both objective signs and subjective symptoms. The prescription of CHM diagnosis depends on making the correct TCM Zheng (syndrome) which is most similar to Western medicine diagnosis and disease classification. Although the term "ANT-induced cardiotoxicity" does not appear in historical TCM literature, the clinical syndromes of ANT-induced cardiotoxicity are palpitations, chest pain, short of breath which could be recognized and considered to be related to dysfunction of heart. According to TCM theory, that is both the heart Qi gradually deficiency which slows blood circulation. And the use of CHM could nourish the heart Qi and restore blood circulation. These fundamental theories and approaches of TCM, reflecting on the practice of CHM, determines contemporary scientific research in the field of ANT-induced cardiotoxicity symptoms.

CHM is often used in Chinese hospitals to manage the side effects of chemotherapy, and has been considered as a preventive measure against ANT-induced cardiotoxicity as well. Although different CHM formulations have documented cardioprotective effects,[25–41] evidence regarding their specific uses and potential side-effects in preventing ANT-induced cardiotoxicity still needs critical appraisal. We performed a meta-analysis on the cardioprotective interventions using CHM during ANT therapy. CHM defined in this review were either raw plant materials (plant seeds, berries, roots, leaves, bark and flowers), water or alcohol extracts of the raw plant materials, or herbal formulations in the form of capsules, tablets, decoctions or injections.

2. Methods

2.1. Search strategy

The Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2021) and MEDLINE (PubMed) databases were searched for studies published from January 1966 to December 2021, and the EMBASE database for publications between January 1980 and December 2021. The search strategies are described in Appendices 1–3. The Chinese BioMedical Database (CBM) (1979 to Dec 2021), Chinese National Knowledge Infrastructure Database (CNKI) (1979 to Dec 2021), and VIP Chinese Science and Technique Journals Database (1989–Dec 2021) were also searched for Chinese-language publications, and the search strategies have been described in Appendices 4–6. In addition, the reference lists of all short-listed papers and the Chinese Conference Papers Database (from inception to 2021) were searched manually. Finally, ongoing trials were searched through the National Research Register and www.controlled-trials.com., as well as by direct communication with pharmaceutical companies producing CHMs. The language of the publications was restricted to English and Chinese.

2.2. Selection criteria

2.2.1. Types of studies. Randomized controlled trials (RCTs) with correct randomization, allocation concealment and blinding of the trials were included, while Quasi-RCTs were excluded due to high risk of bias.

2.2.2. Types of participants. Cancer patients of both sexes and all age groups receiving ANT (doxorubicin, daunorubicin, or epirubicin) chemotherapy were included, and those receiving liposomal doxorubicin were excluded due to the extremely low cardiotoxicity of this formulation. In addition, the respective trials had excluded the patients with known heart diseases or multiple organ dysfunction.

2.2.3. Types of interventions. ANT chemotherapy with CHM, which included single herbs (including herb extracts), commercially available proprietary medicines, compound herbs or practitioner-prescribed herbal formulations (individualized treatment) were selected, and all dosage forms and routes of drug delivery were included. As controls, ANT chemotherapy with or without a placebo, and with conventional interventions were included. An important criterion was that the cumulative ANT dose, chemotherapy other than ANTs and radiotherapy should not be significantly different between the intervention and control groups.

2.3. Types of outcome measures

2.3.1. Primary outcomes. The primary outcome was clinical heart failure, which was evaluated according to the New York Heart Association (NYHA) Functional Classification[42] or Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 issued by the National Cancer Institute.[43]

2.3.2. Secondary outcomes. Secondary outcomes were subclinical heart failure, defined as reduction of left ventricular ejection fraction (LVEF) as measured by either radionuclide ventriculography (MUGA) or echocardiography, cardiac troponin T (cTNT) levels as the marker of early myocardial injury, quality of life (QoL) and other potential adverse effects e.g. diarrhea, leukopenia, nausea and vomiting. Since LVEF measured by echocardiography was more likely to be dependent on the operator, only studies where the echocardiography was performed by the same physician were selected.

2.4. Data collection and analysis

Two investigators (Wei H and Youyang S) independently scanned the titles, abstracts or both to screen for studies that met the inclusion criteria, and the full texts of the valid studies were retrieved and analyzed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[44] Any disagreements were resolved by consensus. The following data were extracted from each study: first author, year of publication, total number and number in comparison groups, sex, age, baseline characteristics, type of malignancy, single herb or compound herbs, dose, timing, route of delivery, outcomes and length of follow up and adverse effects. Any missing or unclear data was clarified by personal communication with the corresponding author.

2.5. Assessment of risk of bias in included studies

The random sequence generation, allocation concealment, incomplete outcome data, selective reporting and other bias were independently assessed for each study by the 2 authors (Wei H and Youyang S) based on the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Version 5.1.0).[45] Each domain was assessed as "low risk," "high risk," or "unclear risk" of bias and any disagreement was resolved by consensus.

2.6. Data analysis

Data was extracted using the Review Manager software (RevMan) and analyzed according to the guidelines of the Cochrane Handbook.[45] The dichotomous outcomes were presented as risk ratios (RR) and continuous outcomes as standard mean difference (SMD). All results were presented with the corresponding 95% confidence interval (CI). Heterogeneity was tested using the Chi^2 test with significance set at $P < .1$, and I^2 statistic was used to estimate the total variation across studies. $I^2 < 30\%$ was considered low level, 30% to 60% as moderate level, and higher than 60% as high level heterogeneity.[45] Subgroup analyses were conducted for parameters showing high level of heterogeneity across studies. Furthermore, a sensitivity analysis was conducted by removing 1 study at a time and recalculating the data of the others to estimate whether the overall results were significantly affected by any 1 study. A meta-analysis was performed for each cardioprotective parameter if 2 or more studies were sufficiently similar. Some of the parameters were reported in only 1 study, which precluded RR calculation, and thus fisher exact test was used instead.

3. Results

3.1. Study selection

We identified 4123 citations—4105 via electronic searches and 18 via manual-search. After excluding 1099 duplicates from the different databases, 3024 studies were assessed further. After scanning titles and abstracts, we excluded 2971 studies because they did not include the pertinent subjects, or were animal studies, reviews or case reports. Fifty-two studies, all of which were conducted in China and reported in Chinese language, were considered for full text screening, and 35 were excluded since they did not meet our selection criteria. Two of the excluded studies did not provide sufficient information, and our attempts to contact the authors were unsuccessful. Finally, 17 RCTs published between 2005–2021 were selected for the meta-analysis. The PRISMA flow diagram of our study selection is shown in Figure 1.

3.2. Study characteristics

The 17 RCTs included a total of 1978 patients—994 patients in the control group and 998 in the treatment group—and tested the effects of 11 different CHMs altogether.[25–41] The main characteristics of the studies are listed in Table 1.

3.3. Risk of bias in included studies

Although all included studies were RCTs, about 75% of the trials reported using the randomized sequence generation method, and 25% of the studies reported any allocation concealment. None of the studies reported whether the personnel or patients, or the outcome assessment were blinded to treatment. Over 50% of the studies reported the number of patients lost to follow up. The risk of bias is described and summarized in Figures 2 and 3.

3.4. Effect of interventions on outcomes

Not all data could be extracted from all studies. Some of the outcomes were therefore only presented as descriptive results. The RR, SMD, 95% CI and P values mentioned below were calculated in RevMan. Heterogeneity between studies were assessed using Cochran Q test.

3.5. Primary outcomes measurements

3.5.1. Clinical heart failure (CTCAE). CTCAE data for heart failure was available for 829 patients, 429 in the CHM group and 400 in the control group, from 12 RCTs. Clinical heart failure was reported in 85 (19.8%) patients in the CHM group and in 166 (41.5%) patients in the control group. Our meta-analysis showed that CHM significantly reduced the occurrence of clinical heart failure (RR 0.45, 95% CI 0.31 to 0.64, $P < .00001$), although moderate level heterogeneity was also detected ($P = .008$, $I^2 = 57\%$) (Fig. 4). To examine the possible sources of heterogeneity, we conducted a subgroup analysis based on the 2 types ANTs.

3.5.2. Doxorubicin plus CHM vs doxorubicin plus placebo. Nine trials with a total of 611 patients compared doxorubicin plus CHM (n = 313) with doxorubicin plus placebo (n = 298) for the risk of clinical heart failure. Forty-four (14.1%) patients in the CHM group and 108 (36.2%) in the control group showed heart failure, indicating that the use of CHM significantly reduced the occurrence of clinical heart failure (RR 0.43, 95% CI 0.32 to 0.58, $P < .00001$) (Fig. 5). No substantial heterogeneity was detected ($I^2 = 0\%$).

3.5.3. Epirubicin plus CHM vs Epirubicin plus placebo. Four trials with a total of 279 patients compared epirubicin plus CHM (n = 146) with epirubicin plus placebo (n = 133) for clinical heart failure. Forty-five (30.8%) patients in the CHM group and 70 (52.6%) in the control group had heart failure, again indicating significant cardioprotective effects of CHM (RR 0.55, 95% CI 0.30 to 1.00, $P = .05$) (Fig. 5), but with high level heterogeneity ($P = .05$, $I^2 = 74\%$).

We thus conducted a sensitivity analysis on these 4 RCTs by removing 1 study at a time and recalculating with the remaining,

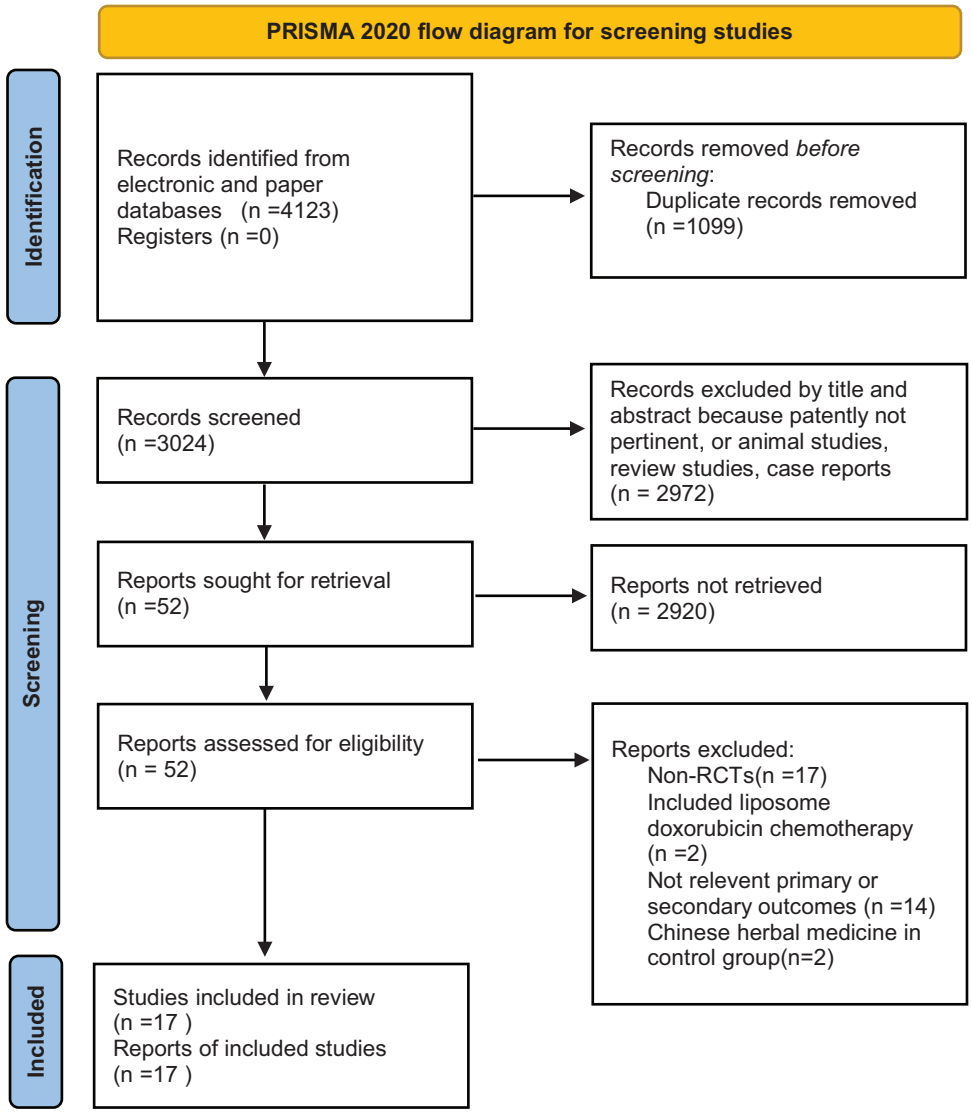

Figure 1. PRISMA 2020 flow diagram for screening studies.

in order to estimate whether the results were markedly affected by any 1 study. The trial conducted by Kong et al in 2013 had a higher number of patients suffering from ANT-induced clinical heart failure compared to the other 3 trials. After removing this trial and recalculating the results, we found that the use of CHM reduced the occurrence of clinical heart failure (RR 0.46, 95% CI 0.29 to 0.73, P = .001) (Fig. 6), with an acceptable low level of heterogeneity (P = .31, I^2= 14%).

3.6. Secondary outcomes measurements

3.6.1. Subclinical heart failure (LVEF). Data on subclinical heart failure with LVEF measurements was obtained from 12 trials with a total of 859 patients; 56 of the 438 patients (12.8%) in the CHM group and 114 of the 421 patients (27%) in the control group had subclinical heart failure. The meta-analysis showed that the use of CHM could reduce the occurrence of subclinical heart failure (RR 0.47, 95% CI 0.35 to 0.62, P < .00001) (Fig. 7), without substantial heterogeneity (I^2= 0%).

3.6.2. Cardiac troponin T (cTNT). The cTNT levels were reported in 9 trials involving 645 patients, and overall low levels were detected with no clinical significance in either groups. However, the meta-analysis showed that patients in CHM group had lower serum cTNT levels compared to the control group (SMD -2.43, 95% CI -3.42 to -1.43, P < .00001) (Fig. 8). Since high level of heterogeneity was detected (I^2= 96%), we again conducted a subgroup analysis based on the 2 ANTs to determine the sources of heterogeneity.

3.6.3. Doxorubicin plus CHM vs doxorubicin plus placebo. Six trials with a total of 453 patients compared the cTNT levels between the doxorubicin plus CHM and doxorubicin plus placebo groups, 3 of which used both doxorubicin and epirubicin. The meta-analysis showed that patients in CHM group had a lower serum cTNT level than control group (SMD -3.63, 95% CI -5.27 to -1.99, P < .0001) (Fig. 9), but a high level of heterogeneity was also detected (I^2= 98%). We conducted a sensitivity analysis, but still observed high heterogeneities that could not be explained.

3.6.4. Epirubicin plus CHM vs Epirubicin plus placebo. Six trials with a total of 406 patients compared epirubicin plus CHM with epirubicin plus placebo groups for serum cTNT levels, of which 3 used both doxorubicin and epirubicin. The meta-analysis showed that patients in the CHM group had lower serum cTNT levels than the control group (SMD –3.54, 95% CI –5.17 to –1.91, P < .0001) (Fig. 9), but with high levels

Table 1

The main characteristics of included studies.

Study	Year	Age (years)	Sex (female%)	Cancer type	Anthracycline type	Interventions	Sample size (n)		F/U (m)	Outcomes measurements	Cumulative Dose (mg/m²)
							Control	Treatment			
Zhang WWet al.[37]	2007	57.2 ± 24.2	44	Lung cancer 10 (12.5%)Gastric cancer 30 (37.5%)Colorectal cancer 15 (18.75%)Breast cancer 15 (18.75%)Liver cancer 10 (12.5%)	Doxorubicin	shenfu injection	40	40	4	CTCAELVEF	150–200
Yang SY et al[33]	2010	52 (35–67)	100	Breast cancer 96 (100%)	Epirubicin	shenfu injection	46	50	6	CTCAELVEFcTNT	N/A
Wang W et al[31]	2015	52 (38–67)	100	Breast cancer 70 (100%)	Epirubicin	Yiqi YangxinDecoction	35	35	6	LVEFcTNT	360
Zhuo XJ et al[40]	2018	55.63 ± 8.22	24	Lung cancer 19 (32%)Gastric cancer 22 (37%)Breast cancer 12 (20%)Lymphoma 7 (12%)	Doxorubicin	Danshen injection	30	30	N/A	CTCAEcTNT	N/A
Ren HJ et al[29]	2012	58 ± (36–70)	83	Breast cancer 48 (63%)Gastric cancer 6 (8%)Ovarian cancer 8 (11%)Lymphoma 14 (18%)	DoxorubicinEpirubicin	shenmai injection	36	40	N/A	CTCAE	N/A
Yang XL et al[35]	2011	35–60	100	Breast cancer 897 (100%)	Doxorubicin	shenmai injection	436	461	6	cTNT	300–360
Cheng HL et al[41]	2009	48 (30–72)	72	Breast cancer 48 (56%)Gastric cancer 13 (15%)Ovarian cancer 5 (6%)Lung cancer 5 (6%)nonHodgkin lymphoma15 (17%)	Doxorubicin	shenmai injection	41	45	1	CTCAELVEF	N/A
Zhang WH et al[34]	2021	47.5 ± 6.1	63	Breast cancer 18 (31%)Ovarian cancer 12 (20%)Lymphoma 29 (49%)	Doxorubicin	licorice soup	29	30	N/A	CTCAELVEF	250–550
Zhang Y et al[38]	2009	53 (36–70)	100	Breast cancer 119 (100%)	Doxorubicin	shengmai injection	62	57	4	LVEFcTNT	240
Liang H et al[26]	2013	43.25 ± 2.9	100	Breast cancer 62 (100%)	EpirubicinTherarubicin	Shenmaiyangxin Decoction	26	36	N/A	CTCAELVEFcTNT	N/A
Wang YA et al[32]	2010	32–68	74	Breast cancer 50 (62.5%)Gastric cancer 22 (27.5%)Lung cancer 8 (10%)	Doxorubicin	Fried Glycyrrhizae Decoction	38	42	N/A	CTCAE	N/A
Huang RH et al[39]	2019	45.2 ± 6.1	50	Breast cancer 18 (31%)Lymphoma 27 (47%)Lung cancer 8 (14%)Gastric cancer 3 (5%)Ovarian cancer 2 (3%)	Doxorubicin	Huanglian Ejiao Tang	28	30	N/A	CTCAELVEF	250–550
Kong JX et al[25]	2013	40 (20–63)	33	Breast cancer 33 (55%)nonHodgkin lymphoma 27 (45%)	EpirubicinTherarubicin	Astragalus injection	30	30	4	CTCAELVEFcTNT	N/A
Ning YL et al[28]	2008	58 (40–74)	17	Lung cancer N/ABreast cancer N/AGastric cancer N/ALymphoma N/A	Doxorubicin	Shenqifuzheng injection	26	28	6	CTCAELVEF	80–160
Wang QY et al[30]	2012	55.5 ± 14.5	57	Breast cancer 26 (43%)Lymphoma 7 (11%)Gastric cancer 15 (25%)Ovarian cancer 9 (15%)Cervical cancer 4 (6%)	DoxorubicinEpirubicin	Shenqifuzheng injection	31	30	6	CTCAELVEFcTNT	240–270
Yi SY et al[36]	2008	47 ± 4.9	100	Breast cancer 60 (100%)	Doxorubicin	Extract of Ginkgo Biloba (Egb761)	30	30	2.5	cTNT	200
Liu W et al[27]	2014	60.2 ± 9.7	77	Breast cancer 36 (60%)Lymphoma 1 (2%)Gastric cancer 18 (30%)Ovarian cancer 5 (8%)	N/A	Xinmailong Injection	30	30	6	LVEFcTNT	N/A

CTCAE = common terminology criteria for adverse events, cTnT = cardiac troponin T, F/U = follow-up, LVEF = left ventricular ejection fraction, N/A = no detailed information.

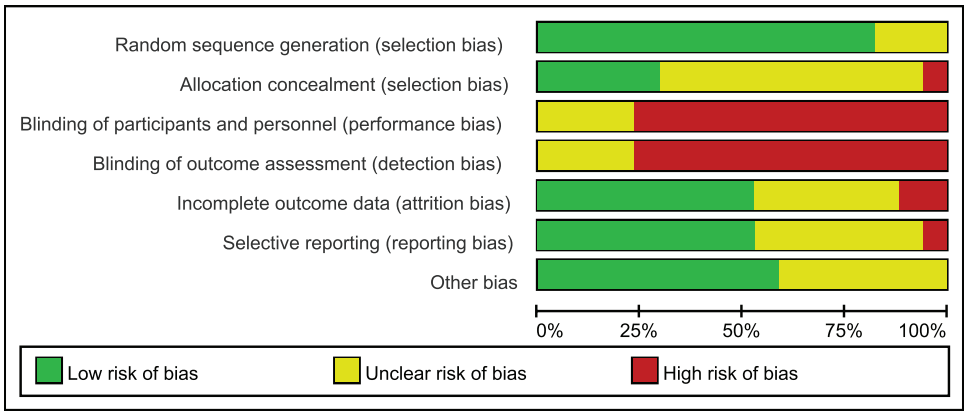

Figure 2. Risk of bias graph.

of heterogeneity (P = .05, I^2 = 97%). A sensitivity analysis however could not resolve the source of this heterogeneity.

3.6.5. Quality of life (QoL). Since only 1 trial (Ning et al 2008) evaluated QoL (through the FACT-P scale), we could not conduct a meta-analysis on this parameter because of the obvious heterogeneity. We therefore provided a descriptive result for this trial, which showed that CHM as an adjunctive therapy improved patients' QoL when compared to the control group.

3.6.6. Adverse effects. Only 2 trials (Wang et al 2012, Zhang et al 2007) reported adverse effects other than cardiotoxicity. Zhang et al reported thrombocytopenia and neutropenia according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0,[32] while Wang et al reported diarrhea, nausea and vomiting. However, the latter neither reported the number of patients suffering from these adverse effects, nor provided any references on the grading systems based on which the adverse effects were evaluated. Therefore, we excluded this trial for bias, and used descriptive conclusions for the Zhang et al trial. We analyzed only the severe or life threatening adverse effects that were grade 3 and 4, since all chemotherapies potentially cause adverse effects. Twelve out of 40 patients (30%) who received dexrazoxane and 13 of 40 (32.5%) patients in the control group developed neutropenia (RR 0.92, 95% CI 0.48 to 1.77, P = .81). Thrombocytopenia was reported in 4 patients (10%) in the dexrazoxane and 3 (7.5%) in the control groups (RR 1.37, 95% CI 0.29 to 6.56, P = .69).

4. Discussion

Cardiotoxicity is one of the most serious side effects in cancer patients receiving ANT chemotherapy. It can cause heart failure which reduces quality of life and even lead to premature death. ANT-induced risk of heart failure is dose-dependent, with estimated frequencies ranging from 5% at the cumulative doxorubicin dose of 400 mg/m^2, 16% at 500 mg/m^2, and 26% at 550 mg/m^2.[46] On the other hand, the efficacy of ANT chemotherapy is also proportional to its cumulative dose,[46] which creates a conundrum regarding its clinical use. However, there is still no consensus among clinicians on preventing ANT-induced cardiotoxicity. This study is the first meta-analysis of CHMs as potential cardioprotective agents during ANT chemotherapy.

This review included 17 RCTs conducted on 11 specific CHMs to evaluate their efficacy and safety in preventing ANT-induced cardiotoxicity in cancer patients. Our meta-analysis showed a statistically significant reduction in the incidence of cardiotoxicity, in terms of both clinical and subclinical heart failure, in patients that received CHM along with the ANT regimen. For clinical heart failure, moderate heterogeneity (I^2= 58%) was detected across the 12 RCTs that reported this parameter. These studies used 2 types of ANTs—doxorubicin and epirubicin—and the equimolar cardiotoxic dose ratio of doxorubicin to epirubicin is 1:1.7 to 2.0. The lower cardiotoxicity of the latter[47] could be the likely cause of heterogeneity. A subgroup meta-analysis based on the 2 ANTs showed a benefit of CHM use against both doxorubicin and epirubicin (RR 0.43, 95% CI 0.32 to 0.58, P < .00001, and RR 0.46, 95% CI 0.29 to 0.73, P = .001 respectively). There were no heterogeneity in the doxorubicin subgroup, while high level of heterogeneity (74%) was still present in the epirubicin subgroup. A sensitivity analysis showed extremely high morbidity in one RCT (Kong et al 2013), which reported clinical heart failure in 21 of 30 patients (70%) in the CHM and 22 of 30 patients (73.3%) in the control groups. On the contrary, epirubicin showed lower cardiotoxicity than doxorubicin.[48] After removing this RCT, the meta-analysis still showed a benefit of CHM use (RR 0.46, 95% CI 0.29 to 0.73, P = .001), with acceptably low levels of heterogeneity (I^2 = 14%).

Cardiac troponin T (cTNT) has proven to be a reliable biomarker of early myocardial injury, and a strong correlation has been observed between high dose ANT-chemotherapy and increased serum troponin levels. However, the patients in almost all RCTs included in our meta-analysis received low single dose ANTs, which explains the low, clinically insignificant levels of cTNT detected in their sera. Although our meta-analysis showed that patients in CHM group had a lower serum cTNT level than the control group (SMD –2.43, 95% CI –3.42 to –1.43, P < .00001), we also detected an unexplained high level of heterogeneity. For QoL, a meta-analysis was not possible since only 1 trial (Ning et al 2008) evaluated this parameter through the FACT-P scale. We therefore provided a descriptive result for this trial showing that CHM as an adjunctive therapy could improve QoL after chemotherapy compared to the control group. However, very few patients (28 in the CHM group, 22 in the control group) were included in this trial, which indicates risk of bias. Furthermore, only 2 trials reported noncardiac adverse effects. Wang et al 2012 reported diarrhea, nausea and vomiting, without reporting the number of patients or the grading system, which prompted us to exclude this trial for bias. Zhang et al 2007 reported thrombocytopenia and neutropenia, which were not significantly different between the CHM and control groups.

This review has several limitations that should be considered when drawing conclusions:

1. Several potential cardioprotective CHMs could not be included in this meta-analysis due to lack of RCTs. In addition, quasi-RCTs, nonrandomized studies and case reports that are available for some of the 11 included CHMs were also not included owing to a high risk of bias.
2. Although we searched both Chinese and English-language databases, almost all of the included trials were retrieved

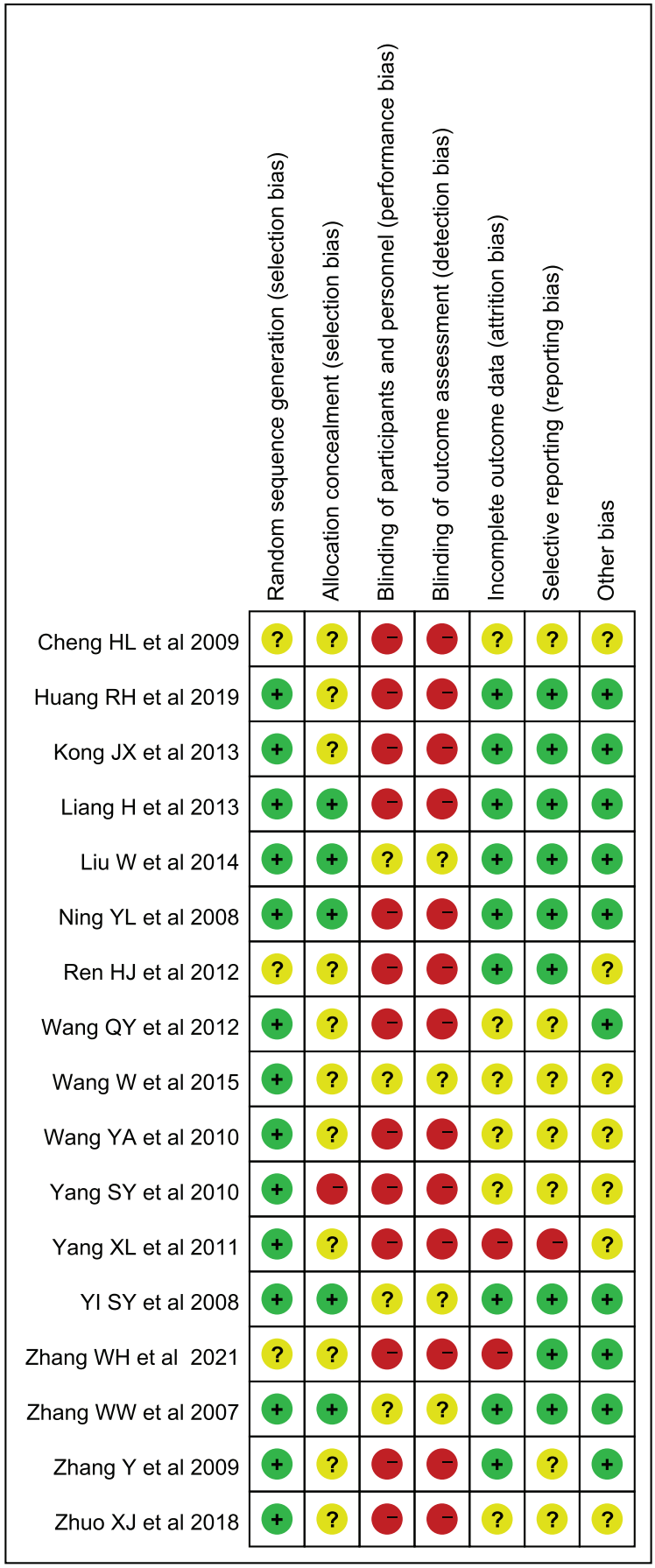

Figure 3. Risk of bias summary.

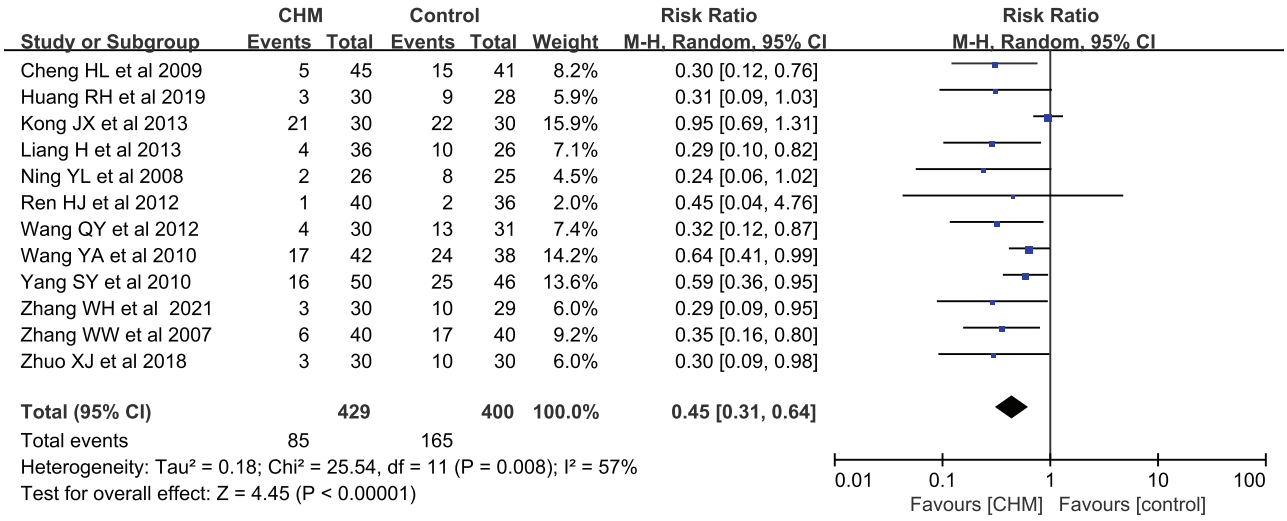

Figure 4. Forest plot: Clinical heart failure (CTCAE): (ANTs plus CHM vs ANTs plus placebo).

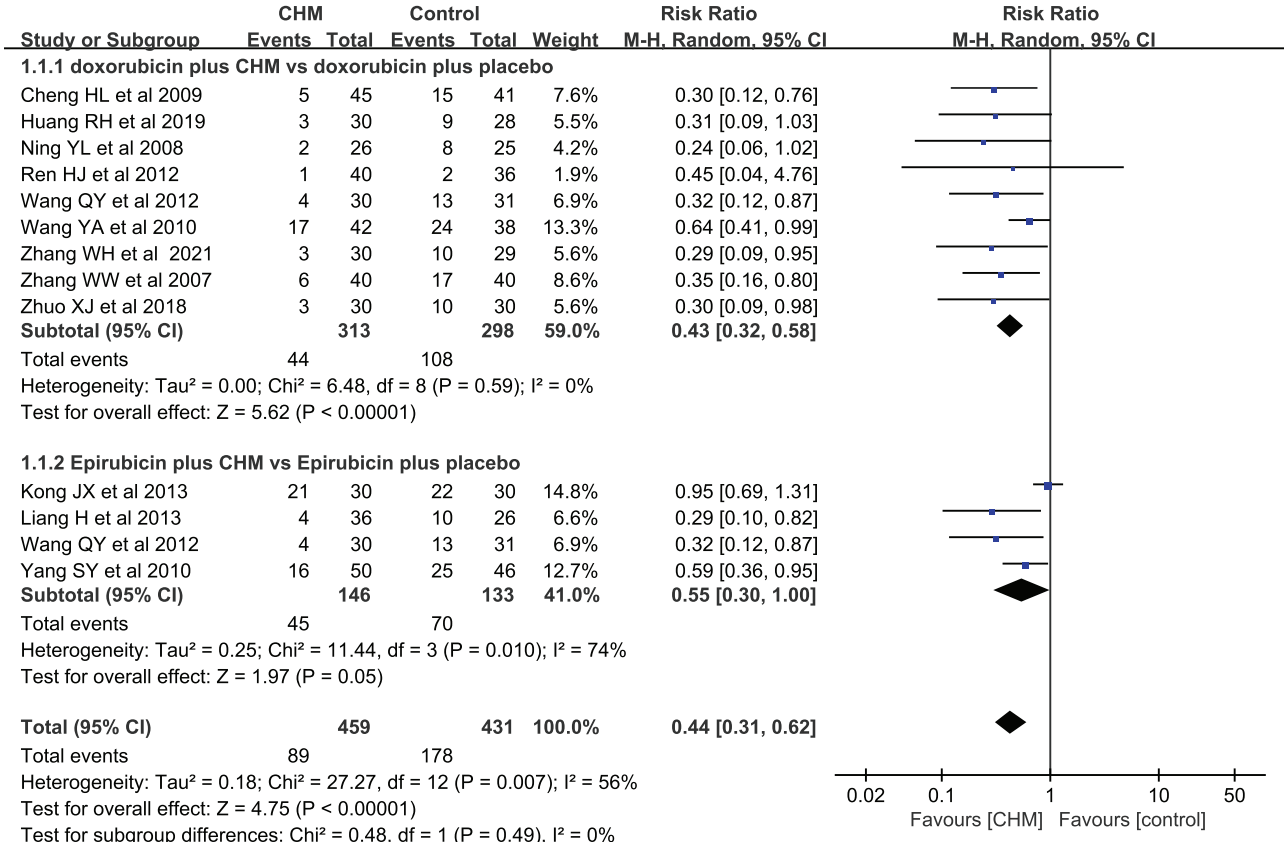

Figure 5. Forest plot of subgroup analysis: Clinical heart failure (CTCAE): (Doxorubicin/ Epirubicin plus CHM vs Doxorubicin/ Epirubicin plus placebo).

from Chinese-language literature, which may have potential selection bias and might have limited the external generalization of the evidence.

3. Some of included trials had only a few patients with short follow-up period. Furthermore, none of the trials compared the antitumor efficacy of ANT-chemotherapy of the CHM and control groups, and the potential effects of the CHM on tumor growth inhibition are unclear. This is a major limitation since a cardioprotective intervention ought to decrease ANT-induced cardiotoxicity without reducing the antitumor efficacy.
4. None of the RCTs reported whether the personnel or patients were blinded to the treatment and outcome assessment, which may have had potential performance and detection bias.
5. There was significant clinical heterogeneity due to CHM interventions and ANTs used in the included RCTs.

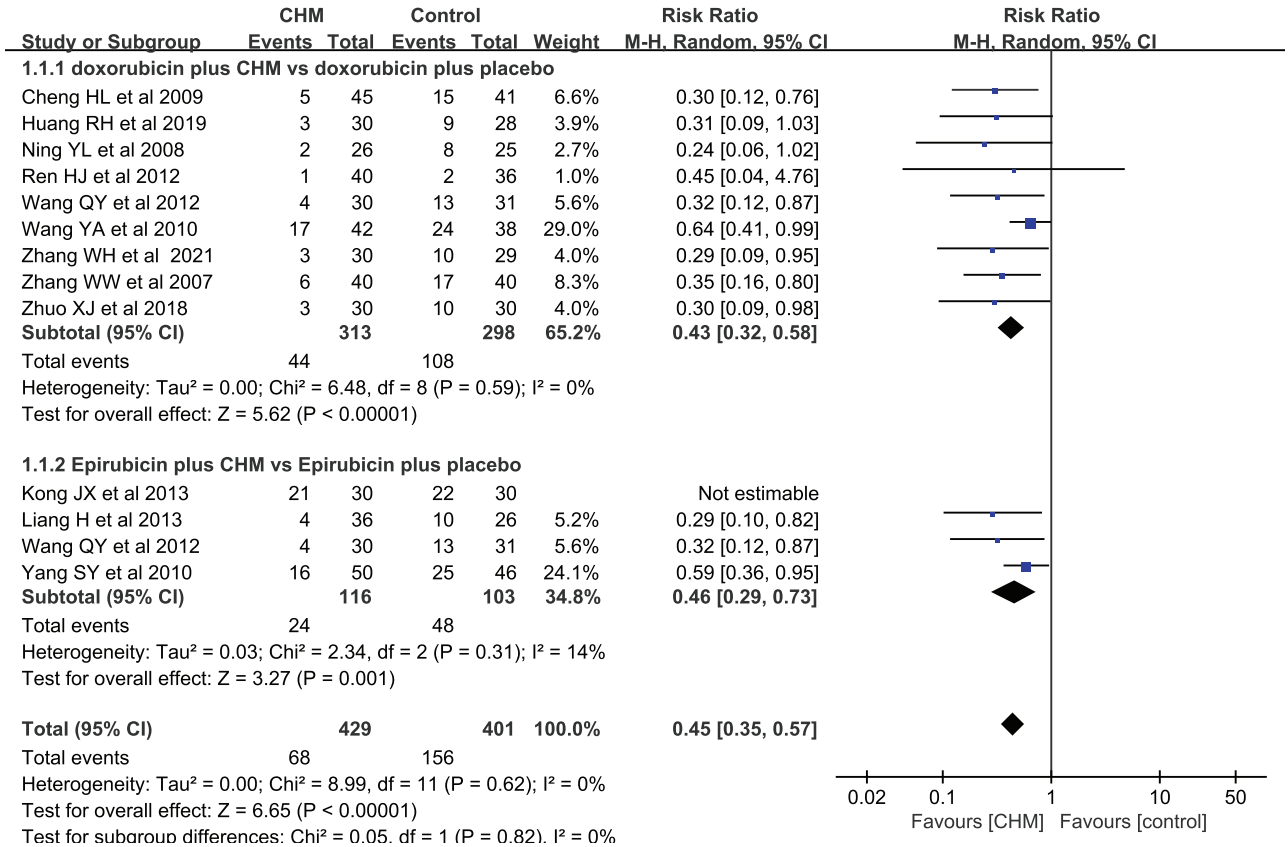

Figure 6. Forest plot of sensitive analysis: Clinical heart failure (CTCAE): (Epirubicin plus CHM vs Epirubicin plus placebo).

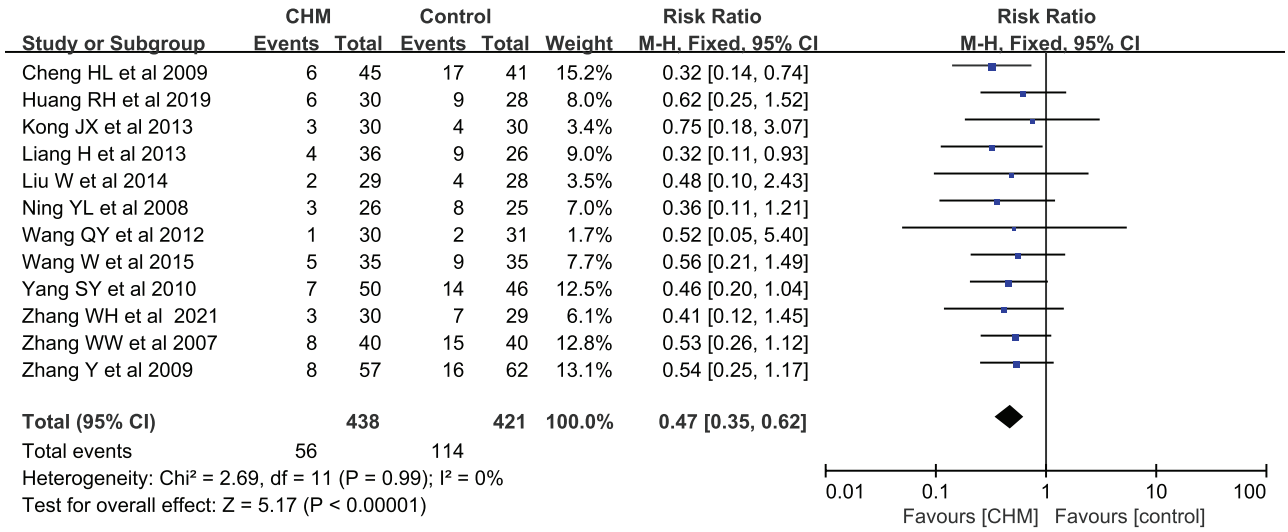

Figure 7. Forest plot: Subclinical heart failure (LVEF): (ANTs plus CHM vs ANTs plus placebo).

5. Conclusion

This is the first meta-analysis to be conducted on the cardioprotective interventions of CHM during ANT chemotherapy. CHM was effective and safe against ANT-induced cardiotoxicity, and may be considered as an adjuvant option to decrease heart damage among cancer patients receiving ANTs. However, due to the insufficient quality of the RCTs, our results should be interpreted with caution. Multicenter RCTs with larger cohorts and long follow-up duration are needed to evaluate whether CHM has any effect on the antitumor efficacy of ANT chemotherapy while decreasing heart damage.

Authors' contributions

SL participated in the design and coordination of the study. WH designed and drafted the manuscript, developed the search strategy, ran the search, and performed the data-extraction and risk of bias assessment. YN-Q and YY-S drafted all the figures and

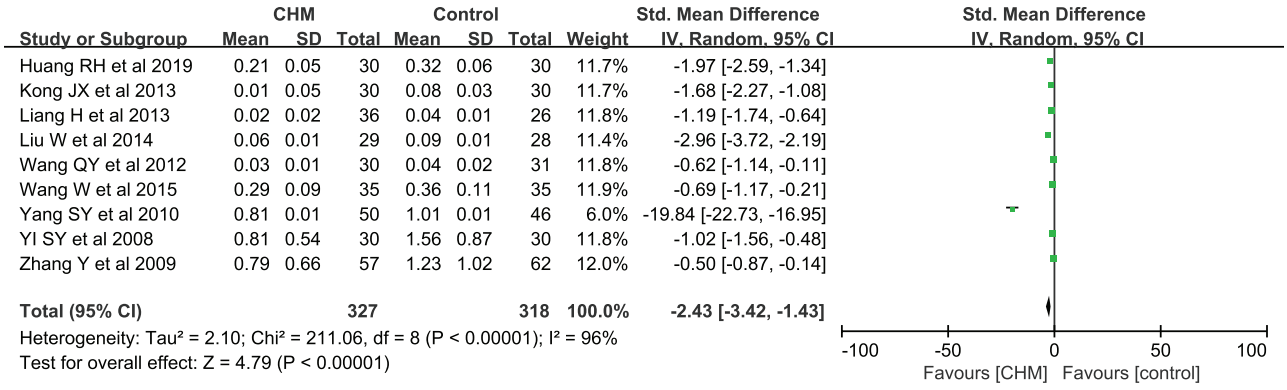

Figure 8. Forest plot: Cardiac troponin T (cTNT): (ANTs plus CHM vs ANTs plus placebo).

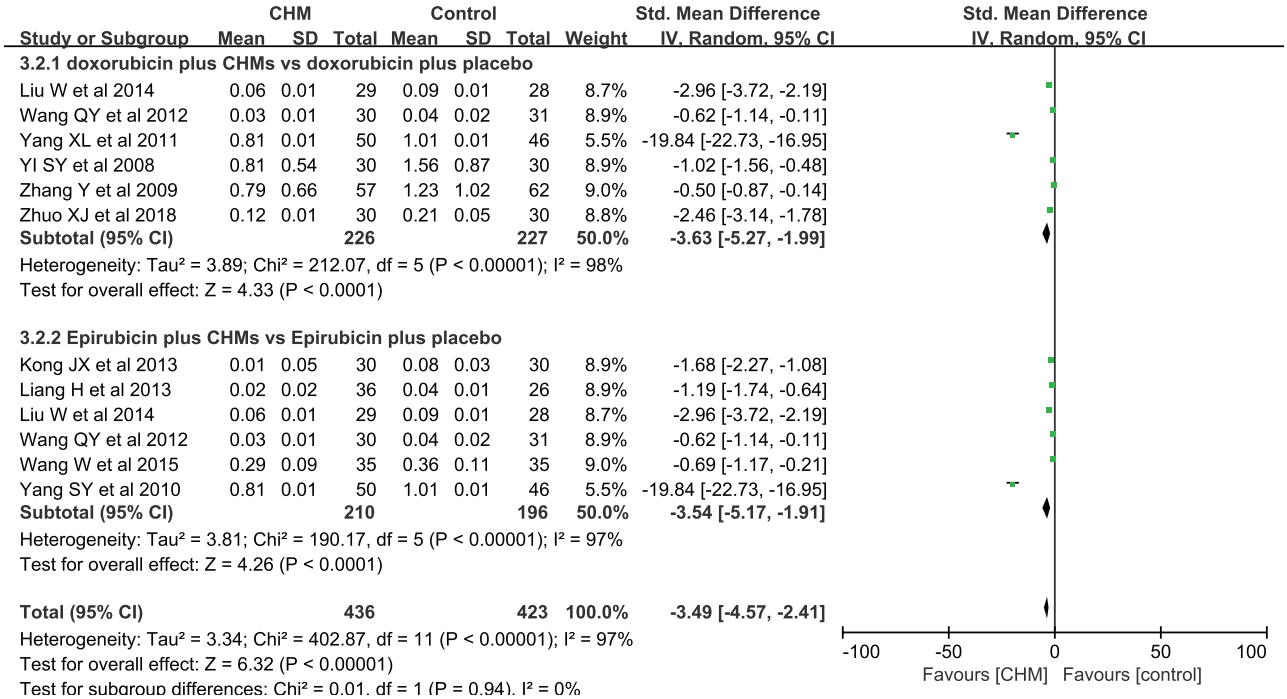

Figure 9. Forest plot of subgroup analysis: Cardiac troponin T (cTNT): (Doxorubicin/ Epirubicin plus CHM vs Doxorubicin/ Epirubicin plus placebo).

tables. CY-W and CP-S performed the data-extraction, risk of bias assessment, the data-analysis and the interpretation of the results. All authors critically reviewed and approved the final version.

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