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Keywords: Cardiotoxicity after chemotherapy, Shenmai injection, Meta-analysis, Breast cancer

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Shenmai injection in treating chemotherapy-related cardiotoxicity of breast cancer: a systematic review and meta-analysis

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Abstract

Shenmai injection (SMI) is an established treatment for cardiac diseases, and we performed to evaluate the efficacy of SMI combined with chemotherapy drugs for the treatment of chemotherapy-induced cardiotoxicity. The primary outcome was abnormal ECG, LVEF and E/A. The secondary outcomes included myocardial injury biomarkers (CK, CK-MB, and cTnI) and lipid peroxide markers (SOD, GSH, and MAD). Studies indicated that SMI combined with chemotherapy drugs has advantages over chemotherapy drugs alone in reducing the incidence of abnormal ECG (ST-T: RR = 0.613, 95% CI [0.437, 0.862], p = 0.005; extrasystole: RR = 0.527, 95% CI [0.349, 0.798], p = 0.002). Myocardial injury biomarkers in the experimental group were lower than those in the control group (CK: SMD = –2.614, 95% CI [–3.156, –2.071], p = 0.000; CK-MB: SMD = –6.882, 95% CI [–8.982, –4.782], p = 0.000; cTnI: SMD = –3.610, 95% CI [–4.949, –2.271], p = 0.000). Ultrasonic cardiogram analysis showed that the experimental group had a higher LVEF and E/A than the control group (LVEF: SMD = 1.572, 95% CI [1.176, 1.969], p = 0.000; E/A: SMD = 0.280, 95% CI [0.153, 0.407], p = 0.000). Lipid peroxide meta-analysis showed that the experimental group had higher SOD and GSH levels (SOD: WMD = 39.783, 95% CI (32.524, 47.042), p = 0.000; GSH: WMD = 32.960, 95% CI [26.055, 39.865], p = 0.000), and lower MDA (WMD = –4.962, 95% CI [–6.041, –3.883], p = 0.000). SMI is effective in reducing cardiac injury and the incidence of cardiotoxicity.

Keywords: Cardiotoxicity after chemotherapy; Shenmai injection; Meta-analysis; Breast cancer
INTRODUCTION

In breast epithelium, breast cancer is a malignant tumor. It is a hormone-dependent disease and one of the most malignant tumors in females [1]. Apart from surgical removal of malignant tissue, chemotherapy remains an important means of anti-tumor treatment. Anthracyclines, taxanes, and molecular targeted drugs, such as trastuzumab, are common chemotherapy drugs. For instance, the anthracyclines (such as doxorubicin (DOX) and epirubicin) are the cornerstone drugs for breast cancer adjuvant chemotherapy, which can significantly improve the survival of breast cancer patients [2]. Furthermore, the 10-year mortality rate of patients with breast cancer decreases by 10% [3].

With the massive use of chemotherapeutic drugs, the problem of adverse drug reactions has gradually become prominent. Chemotherapy drugs can cause toxic side effects, such as hair loss, bone marrow suppression, and gastrointestinal reactions. However, cardiotoxicity is the most serious side effect of chemotherapy drugs, and the damage is often progressive and irreversible. The main manifestations of cardiotoxicity associated with anthracycline and trastuzumab treatment are symptomatic congestive heart failure (CHF) and an asymptomatic left ventricular ejection fraction (LVEF) decline [4]. In recent years, a series of novel studies have shown that low-dose anthracyclines can cause cardiotoxicity. Before the maximum cumulative dose of anthracyclines was used, a considerable proportion of cardiac damage was observed with DOX; for example, when the cumulative dose was still 50 mg/m², left ventricular systolic and diastolic dysfunction could already be observed. Therefore, clinicians should pay close attention to the cardiotoxicity caused by chemotherapy—its prevention and treatment are the basis for ensuring chemotherapy benefit to patients.

At present, the commonly used clinical strategies to reduce the cardiotoxicity of anthracyclines entails: 1) assessing the risk of cardiotoxicity before treatment with cardiotoxic drugs; 2) appropriately adjust the dosage or regimen as appropriate; 3) strengthen monitoring of cardiac function; and 4) adopt other formulations (such as liposome formulations). A large amount of
evidence-based medical evidence indicates that dextroproimine (DZR) is the only drug that can effectively prevent cardiotoxicity caused by anthracyclines and reduce the incidence of cardiotoxicity during chemotherapy [5]. However, they are also considerably more expensive.

As an important means of adjuvant treatment of tumors, traditional Chinese medicine (TCM) plays an increasingly significant role in the treatment of malignant tumor complications. Shenmai injection (SMI), a patented TCM, was extracted from Panax ginseng C.A.Mey [Araliaceae] and Ophiopogon japonicus (Thunb.) Ker Gawl [Asparagaceae]. Its commonly used in the treatment of cardiovascular disease and to control cardiac toxicity caused by DOX treatment. In vitro studies have also shown that SMI prevents chemotherapy-induced cardiotoxicity [6-8].
METHODS

This meta-analysis conducted in accordance with the Meta-analysis of Observational Studies in Epidemiology (MOOSE) recommendations [9], Cochrane Handbook for Systematic Reviews of Interventions [10], and the Preferred Reporting Items for Systematic Meta-Analysis (PRISMA) reporting guidelines [11]. The study was registered with the International Prospective Register of Systematic Reviews (PROSPERO: CRD42021258134).

Search Strategies

Databases, including the Cochrane Library, PubMed, EMBASE, China National Knowledge Infrastructure (CNKI), Chinese Biomedical Database (CBM), VIP Information Resource Integration Service Platform, and WanFang Data Information Site, were searched from January 1st, 2000 to May 27, 2021. The search terms used included amongst others: “breast cancer,” “breast neoplasms,” “cardiotoxicity,” “cardiac toxicity,” “shenmai injection,” and “shenmai,” (see Supplementary Materials 2 for a comprehensive list of the search strategies).

Inclusion and Exclusion Criteria

Type of Study

Our study used randomized controlled trials (RCTs), regardless of blinding, that combined SMI with chemotherapy as an adjuvant treatment for breast cancer patients. To minimize publication
bias, the language was also not restricted.

Subjects Investigated

Inclusion criteria were as follows: (1) breast cancer patients diagnosed by postoperative pathology slices; (2) patients who had normal heart, liver, and kidney functions before treatment and no obvious complications according to the Karnofsky score; and (3) only studies that used the breast cancer drugs of interest. Age, sex, case source, disease course, tumor classification, and chemotherapy cycles were not restricted.

Exclusion Criteria

Exclusion criteria included: (1) non-RCT studies; (2) duplicated results for publications; (3) inconsistent baseline information (age, sex, case source, disease course, tumor classification, and chemotherapy cycle); (4) systematic reviews, important data reports, and case reports; or the author did not respond when contacted to request access to incomplete datasets present in articles; (5) inclusion criteria were not met for therapeutic measures; and (6) animal studies.
**Intervention**

The chemotherapy regimen in the experimental group included SMI combined with conventional cytotoxic drugs, such as cyclophosphamide (CTX), pirarubicin (THP), fluorouracil (5-Fu), epirubicin (EPI), adriamycin (ADM), etc. (dosage, duration, frequency, and course of treatment). For controls, only conventional cytotoxic drugs were included (dosage, duration, frequency, and course of treatment). The age, sex, and other baseline conditions of the study participants were well matched.

**Outcome Indicators**

Statistical analysis of the following indicators after treatment: (1) incidence of cardiac dysfunction (ECG and Holter), (2) LVEF, and (3) E/A; (4) incidence of decreased cardiac biomarkers (creatine kinase [CK], CK-MB, and cardiac troponin I [cTnI]); and (5) incidence of lipid peroxide (superoxide dismutase [SOD], glutathione [GSH], and malondialdehyde [MAD]).

**Data Extraction**

Two reviewers conducted independent searches based on search strategies and preliminarily excluded studies based on independent topics and abstracts based on search results. Full-text methodological screening of potentially eligible articles for inclusion, and contact authors when information was incomplete. The studies were then cross-validated by two reviewers. Any disagreement on the conclusions of the two reviewers was resolved through discussion. If such disagreement cannot be resolved through discussion, a third party shall make final judgments and
arbitration. Extracted included author names, year of publication, sample size, TNM stage, intervention, duration of treatment, and observations.

**Quality Evaluation**

Two authors independently assessed the risk of bias of the included studies according to the 'Risk of bias' assessment tool in the Cochrane Handbook for Systematic Reviews. The risk assessment consists of seven items: (1) random sequence generation; (2) allocation concealment; (3) blinding of participants and personnel; (4) blinding of the outcome assessment; (5) incomplete outcome data; (6) selective reporting; and (7) other bias. According to the evaluation criteria, these items were assessed as having "high risk of bias", "low risk of bias" or "unclear risk of bias" unclear bias risk.

**Data Analysis**

Statistical analyses were carried out according to guidelines from the Cochrane Handbook for Systematic Review of Interventions version 6.0. For the choice of effect size, if the index of the included study was a binary variable, the efficacy analysis statistic was expressed by relative risk (RR) and by its confidence interval (CI). Continuous variation was represented by weighted or standard mean differences (WMD or SMD) and 95% CI. For homogeneity testing, the degree of variation in the results of various original studies was examined to verify the homogeneity of the experiment. For meta-analyses, based on the results of heterogeneity tests, $P \geq 0.1$ and $I^2 < 50$ indicate that the results have good agreement and that the fixed effect model (FEM) may be used.
< 0.1 and $I^2 \geq 50$ suggest that the heterogeneity of the results cannot be ignored. If the included study was still clinically relevant, a random-effects model (REM) was used. For sensitivity analyses, in meta-analyses in which combined factors with multiple outcomes, possible abnormal studies were excluded prior to revaluation. Results were compared with those of meta-analyses prior to exclusion to determine the extent to which excluded studies would affect pooled effect sizes and whether these meta-analyses were stable. If there was a small difference between the two results, then the sensitivity of the results was low, and the results were stable, indicating high credibility. Subgroup analyses were performed for some of the indicators with high heterogeneity. For events where quantitative synthesis was not possible and events with very low incidence, qualitative assessment was based on description. In this study, Stata 16.0 software was used to conduct meta-analysis, sensitivity analysis, subgroup analysis, and to draw a sensitivity analysis chart.

**Publication Bias**

Publication bias occurs when positive data in a statistically significant similar research paper is more likely to be published in a journal. This situation is difficult to control. The funnel plot method is often used to detect the publication bias with Stata 16.0 software. Egger’s test was performed to detect the publication bias in the outcome measures with $\geq 6$ included studies or $I^2 \geq 30\%$ and a funnel plot was drawn. If large publication bias was found in a study index, the exact cause should be identified. If the cause of the bias cannot be found, the stability of the current results should be evaluated using the trim and filling method.
RESULTS

Search Results

A total of 270 articles [Cochrane Library (n = 3), PubMed (n = 0), Embase (n = 5), Web of science (n = 4), CBM (n = 66), CNKI (n = 69), Wanfang Data (n = 80), and VIP (n = 43)] were retrieved, of which 158 studies were excluded because of duplicated publications. The titles and abstracts of the remaining 112 articles were screened, and 97 articles were excluded because of obvious ineligibility (57 irrelevant studies, 24 animal experiments, and 16 reviews). A further 15 articles were excluded after a full-text review, 1 of which was duplicate data, 1 did not meet the inclusion criteria (1 study with no relevant data, which used the shenmai decoction, Yangxin). Finally, 13 articles were included in the meta-analysis. The screening process is summarized in the PRISMA flow diagram (Figure 1).
Figure 1 PRISMA 2009 Flow Diagram

Study Characteristics

In total, 13 RCTs (Yang et al., 2008 [12]; Liu et al., 2014 [14]; Yu et al., 2015 [15]; Fang et al., 2017 [18]; Li et al., 2014 [13]; Pan et al., 2016 [16]; Yao et al., 2016 [17]; Zhang et al., 2020 [23]; Yuan et al., 2017 [19]; Tang, 2021 [24]; Chen et al., 2017 [20]; Chen et al., 2018 [21]; Bu et al., 2018 [22]) involving 1,891 patients (950 in the experimental group and 941 in the control group).
were included in this review. The characteristics of these studies are summarized in Table 1. The quality control description of SMI in these studies is shown in Table 2.

Table 1 Characteristics of the included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Study type</th>
<th>Sample size</th>
<th>Age (years)</th>
<th>Disease stage</th>
<th>Intervention</th>
<th>Treatment/Control Ratio</th>
<th>Treatment</th>
<th>Chemotherapy plan</th>
<th>Dosage</th>
<th>Duration of treatment</th>
<th>Outcomes</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yang 2008</td>
<td>Prospective research</td>
<td>897 (461/436)</td>
<td>47.5</td>
<td>-</td>
<td>CAF (CTX+ADM+5-FU)</td>
<td>50 mL</td>
<td>3 weeks / cycle, 6 cycles, continue treatment for 5 days after chemotherapy</td>
<td>ECG, LDH, CK-MB, cTnT</td>
<td>Not mentioned</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liu 2014</td>
<td>RCT</td>
<td>42 (22/20)</td>
<td>50.18±7.06</td>
<td>IV</td>
<td>CAF (CTX+ADM+5-FU)</td>
<td>100 mL</td>
<td>21 days / cycle, 4 cycles</td>
<td>LVEF, cTnT, ECG</td>
<td>Not mentioned</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Li 2014</td>
<td>RCT</td>
<td>80 (40/40)</td>
<td>47.9±3.3</td>
<td>I-III</td>
<td>THP</td>
<td>50 mL</td>
<td>Once every 3 weeks</td>
<td>CK, CK-MB, cTnT, cTnl, ECG</td>
<td>Not mentioned</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yu 2015</td>
<td>RCT</td>
<td>120 (30/30/30/30)</td>
<td>45.2</td>
<td>I-III</td>
<td>CAF (CTX+ADM+5-FU)</td>
<td>50 mL</td>
<td>3 weeks / cycle, 4 cycles</td>
<td>ECG, LVEF, BNP, cTnT</td>
<td>Not mentioned</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pan 2016</td>
<td>RCT</td>
<td>80 (40/40)</td>
<td>42.28±0.15</td>
<td>I-III</td>
<td>CEF (CTX+EPI+5-FU)</td>
<td>50 mL</td>
<td>Use for 7 days, 21 days / cycle, 6 cycles, continue treatment for 1 week after chemotherapy</td>
<td>LVEF, E/A, cTnl, CK, CK-MB, SOD, GSH, MDA</td>
<td>Not mentioned</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yue 2016</td>
<td>RCT</td>
<td>98 (49/49)</td>
<td>-</td>
<td>I-III</td>
<td>CEF (CTX+EPI+5-FU)</td>
<td>60 mL</td>
<td>Use for 7 days, 21 days / cycle, 6 cycles, continue treatment for 1 week after chemotherapy</td>
<td>LVEF, E/A, cTnl, CK, CK-MB, SOD, GSH, MDA</td>
<td>Not mentioned</td>
<td></td>
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</tr>
<tr>
<td>Fang 2017</td>
<td>RCT</td>
<td>63 (31/32)</td>
<td>43.1±10.2</td>
<td>II-III</td>
<td>DXT+CTX+ADM ± DZR</td>
<td>60–100 mL</td>
<td>4 cycles</td>
<td>LVEF, BNP, cTnI</td>
<td>Not mentioned</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yan 2017</td>
<td>RCT</td>
<td>98 (42/56)</td>
<td>64.8±5.5</td>
<td>III-IV</td>
<td>CAF (CTX+ADM+5-FU)</td>
<td>50 mL</td>
<td>21 days / cycle, 4 cycles</td>
<td>LVEF, E/A, cTnl, CK</td>
<td>Not mentioned</td>
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<td></td>
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</tr>
<tr>
<td>Chen 2017</td>
<td>Retrospective study</td>
<td>36 (17/19)</td>
<td>54±8</td>
<td>I-IV</td>
<td>Trastuzumab</td>
<td>40 mL</td>
<td>Once every 3 weeks, 15 times total</td>
<td>LVEF</td>
<td>Not mentioned</td>
<td></td>
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</tr>
<tr>
<td>Bu 2018</td>
<td>Prospective research</td>
<td>83 (41/42)</td>
<td>45.12±4.05</td>
<td>I-III</td>
<td>CEF (CTX+EPI+5-FU)</td>
<td>50 mL</td>
<td>1 week / cycle, 6 cycles</td>
<td>LVEF, E/A, cTnl, CK, CK-MB, SOD, PCT, MDA</td>
<td>Not mentioned</td>
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</tr>
<tr>
<td>Chen 2018</td>
<td>RCT</td>
<td>80 (45/45)</td>
<td>46.08±4.30</td>
<td>I-III</td>
<td>CEF (CTX+EPI+5-FU)</td>
<td>50 mL</td>
<td>1 week / cycle, 6 cycles</td>
<td>IL-6, TNF-α, PCT, cTnl, CK, CK-MB, SOD, GSH, MDA</td>
<td>Not mentioned</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zhang 2020</td>
<td>RCT</td>
<td>110 (55/55)</td>
<td>42.33±0.31</td>
<td>I-III</td>
<td>CEF (CTX+EPI+5-FU)</td>
<td>50 mL</td>
<td>Use for 7 days, 21 days / cycle, 6 cycles</td>
<td>LVEF, E/A, cTnl, CK, CK-MB, SOD, GSH, MDA</td>
<td>Not mentioned</td>
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</tbody>
</table>
continue treatment for 1 week after chemotherapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Source</th>
<th>Species, concentration</th>
<th>Quality control reported? (Y/N)</th>
<th>Chemical analysis reported? (Y/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Ophiopogon japonicus (Thunb.) Ker Gawl. [Asparagaceae]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fang 2017</td>
<td></td>
<td>Ophiopogon japonicus (Thunb.) Ker Gawl. [Asparagaceae]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Li 2014</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Zhang 2020</td>
<td></td>
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<td></td>
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<tr>
<td>Yuan 2017</td>
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<td></td>
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<tr>
<td>Chen 2017</td>
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</tr>
<tr>
<td>Tang 2021</td>
<td></td>
<td></td>
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<tr>
<td>Yu 2015</td>
<td></td>
<td></td>
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<tr>
<td>Yao 2016</td>
<td></td>
<td>Ophiopogon japonicus (Thunb.) Ker Gawl. [Asparagaceae]</td>
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<tr>
<td>Chen 2018</td>
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<tr>
<td>Bu 2018</td>
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</tr>
<tr>
<td>Tips: All species had been fully validated by using <a href="http://mpns.kew.org/mpns-portal/?_ga=1.111763972.1427522246.1459077346">http://mpns.kew.org/mpns-portal/?_ga=1.111763972.1427522246.1459077346</a>. Chinese National Medicine Permission Number = NMPN.</td>
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</tbody>
</table>
Risk of Bias in Included Studies

Of those included, 10 studies mentioned randomized allocation, while 7 studies explained the specific allocation methods (Liu et al., 2014 [14]; Li et al., 2014 [13]; Pan et al., 2016 [16]; Yao et al., 2016 [17]; Zhang et al., 2020 [23]; Tang et al., 2021 [24]; Chen et al., 2018 [21]). Risk of bias in the included randomized controlled trials in Table 3. In any of these studies, there was no information on allocation concealment, blinding, or evaluator blinding. The quality assessment is shown in Figure 2.

Table 3 Risk of bias in the included randomized controlled trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Study type</th>
<th>Randomization</th>
<th>Allocation Concealment</th>
<th>Patients Blinding</th>
<th>Assessor Blinding</th>
<th>Incomplete Outcome Data Addressed</th>
<th>Selective Outcome Reporting</th>
<th>Other Bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yang 2008 [12]</td>
<td>Prospective research</td>
<td>Low</td>
<td>Unclear</td>
<td>High</td>
<td>Unclear</td>
<td>Low</td>
<td>Low</td>
<td>Unclear</td>
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<tr>
<td>Liu 2014 [14]</td>
<td>RCT</td>
<td>Unclear</td>
<td>Unclear</td>
<td>High</td>
<td>Unclear</td>
<td>Low</td>
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<tr>
<td>Li 2014 [13]</td>
<td>RCT</td>
<td>Low</td>
<td>Unclear</td>
<td>High</td>
<td>Unclear</td>
<td>Low</td>
<td>Low</td>
<td>Unclear</td>
</tr>
<tr>
<td>Pan 2016 [16]</td>
<td>RCT</td>
<td>Unclear</td>
<td>Unclear</td>
<td>High</td>
<td>Unclear</td>
<td>Low</td>
<td>Low</td>
<td>Unclear</td>
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<tr>
<td>Yao 2016 [17]</td>
<td>RCT</td>
<td>Low</td>
<td>Unclear</td>
<td>High</td>
<td>Unclear</td>
<td>Low</td>
<td>Low</td>
<td>Unclear</td>
</tr>
<tr>
<td>Fang 2017 [18]</td>
<td>RCT</td>
<td>Unclear</td>
<td>Unclear</td>
<td>High</td>
<td>Unclear</td>
<td>Low</td>
<td>Low</td>
<td>Unclear</td>
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<tr>
<td>Yuan 2017 [19]</td>
<td>RCT</td>
<td>Low</td>
<td>Unclear</td>
<td>High</td>
<td>Unclear</td>
<td>Low</td>
<td>Low</td>
<td>Unclear</td>
</tr>
<tr>
<td>Reference</td>
<td>Study Design</td>
<td>Bias</td>
<td>Randomization</td>
<td>Confounders</td>
<td>Withdrawals</td>
<td>Attrition</td>
<td>Follow-up</td>
<td></td>
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<tr>
<td>Chen 2017</td>
<td>Retrospective study</td>
<td>Low</td>
<td>Unclear</td>
<td>High</td>
<td>Unclear</td>
<td>Low</td>
<td>Low</td>
<td>Unclear</td>
</tr>
<tr>
<td>Bu 2018</td>
<td>Prospective research</td>
<td>Unclear</td>
<td>Unclear</td>
<td>High</td>
<td>Unclear</td>
<td>Low</td>
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<tr>
<td>Chen 2018</td>
<td>RCT</td>
<td>Low</td>
<td>Unclear</td>
<td>High</td>
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<td>Zhang 2020</td>
<td>RCT</td>
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<td>Unclear</td>
<td>Low</td>
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<tr>
<td>Tang 2021</td>
<td>RCT</td>
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<td>Unclear</td>
<td>High</td>
<td>Unclear</td>
<td>Low</td>
<td>Low</td>
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</tr>
</tbody>
</table>
Outcome Measures

Incidence of abnormal ECG

Four studies (Li et al., 2014 [13]; Liu et al., 2014 [14]; Yang et al., 2008 [12]; Yu et al., 2015 [15]) were incorporated into the analysis for abnormal ECG. After testing for heterogeneity ($I^2 = 80.4\%$, $p < 0.01$, Figure 3, Supplementary Figure 1), an REM was employed. Furthermore, we conducted Egger’s ($p = 0.172$) and Begger’s ($p = 0.308$) tests to verify that there was no publication bias (Supplementary Figures 2 and 3). To determine the cause of the high heterogeneity, we divided the ECG index into ST-T changes and extrasystole for further analysis.
Figure 3 Forest plot of abnormal ECGs

ST-T changes and Extrasystole

We also conducted an ECG analysis according to the specific ECG performance. Meta-analysis of the ST-T changes indicated a significant trend toward reducing the incidence of ST-T changes between the experimental and control groups \( \text{RR} = 0.613, 95\% \text{ CI} (0.437, 0.862), p = 0.005, I^2 = 12\% \). Compared with the control group, the premature beats in the experimental group increased significantly \( \text{RR} = 0.527, 95\% \text{ CI} [0.349, 0.798], p = 0.002, I^2 = 0\% \). (Figures 4, Supplementary Figures 4 and 7). Furthermore, we conducted Egger’s \( p = 0.373 \) and Begger’s \( p = 0.089 \) tests to verify that there was no publication bias (Supplementary Figures 5–6 and 8–9).
Figure 4 Forest plot of ST-T changes and extrasystole

_Ultrasonic Cardiogram_

_LVEF_

Nine studies (Liu et al., 2014 [13], Pan et al., 2016 [16]; Yao et al., 2016 [17]; Chen et al., 2017 [20]; Yuan et al., 2017 [19]; Fang et al., 2017 [18]; Bu et al., 2018 [22]; Zhang et al., 2020 [23]; Tang et al., 2021 [24]) were included in the analysis of LVEF. After testing for heterogeneity ($I^2 = 93.6\%$, $p < 0.01$, Figure 5, Supplementary)
Figure 10), an REM was employed. We conducted Egger’s (p = 0.125) and Begger’s (p = 0.754) tests to verify that there was no publication bias (Supplementary Figures 12–13). Given the high heterogeneity, a subgroup analysis of the LVEF data was performed.

Subgroup analysis of LVEF

Subgroup analysis of LVEF was performed according to the SMI dosage. Meta-analysis of the 50–60 mL SMI subgroup showed a significant trend towards improvement in LVEF between the experimental and control groups [SMD = 1.93, 95% CI (1.73, 2.15), p = 0.000]. Compared with the control group, there was no significant increase in LVEF in the experimental group (p > 0.01). (Figure 6, Supplementary Figure 11).

Figure 5 Forest plot of LVEF
E/A

A total of six studies (Pan et al., 2016 [16]; Yao et al., 2016 [17]; Yuan et al., 2017 [19]; Bu et al., 2018 [22]; Zhang et al., 2020 [23]; Tang et al., 2021 [24]) were included in the analysis of E/A. After testing for heterogeneity ($I^2 = 98\%$, $p < 0.01$, Figure 7, Supplementary Figure 14), an REM was employed. We conducted Egger’s ($p = 0.037$) and Begger’s ($p = 1.000$) verify that there was no publication bias (Supplementary Figures 16–17). Given the high degree of heterogeneity, a subgroup analysis of the E/A data was performed.

Subgroup analysis of E/A

We also performed E/A subgroup analyses based on chemotherapy strategies. Meta-analysis of the CEF (CTX + EPI + 5-FU) subgroup indicated a significant trend toward improvement in E/A between the experimental and control groups (WMD = 0.342, 95% CI [0.3223, 0.362], $p = 0.000$, $I^2 = 0\%$). (Figure 8, Supplementary Figure 15).
Figure 7 Forest plot of E/A

Figure 8 Subgroup analysis of E/A
Cardiac Biomarkers

CK

Eight studies (Li et al., 2014 [13]; Pan et al., 2016 [16]; Yao et al., 2016 [17]; Yuan et al., 2017 [19]; Chen et al., 2018 [21]; Bu et al., 2018 [22]; Zhang et al., 2020 [23]; Tang et al., 2021 [24]) were incorporated into the analysis of CK. After testing for heterogeneity ($I^2 = 86.7\%, p < 0.01$, Figure 9), an REM was employed. We conducted Egger’s ($p = 0.01$) and Begger’s ($p = 0.035$) tests to verify that there was no publication bias (Supplementary Figures 21–22). Given the high degree of heterogeneity, a sensitivity analysis was performed on CK data. By excluding one trial each time in a row and re-analysing the remaining trials, we observed that the results for CK were very similar, meaning that the results were stable (Supplementary Figure 19). The heterogeneity was potentially caused by the difference between the indicators measures of each study. At the same time, we conducted a meta-regression analysis, and the results showed that the heterogeneity between studies were independent of the six classification variables ($p > 0.05$ for all, Supplementary Figure 20). Therefore, we adopted an REM. Meta-analysis showed that the experimental group was superior to the control group in reducing CK ($SMD = -2.614$, 95% CI $[-3.156, -2.071]$, $p = 0.000$) (Figure 9, Supplementary Figure 18).
CK-MB

CK-MB data were available in seven studies (Li et al., 2014 [13]; Pan et al., 2016 [16]; Yao et al., 2016 [17]; Yuan et al., 2017 [19]; Chen et al., 2018 [21]; Bu et al., 2018 [22]; Zhang et al., 2020 [23]; Tang et al., 2021 [24]) involving 635 participants. Given the high heterogeneity ($I^2 = 96.8\%$, $p < 0.01$, Figure 10), sensitivity analysis and meta-regression of the CK data were performed. We conducted Egger’s ($p = 0.000$) and Beggar’s ($p = 0.133$) tests to assess publication bias (Supplementary Figures 26–27). Sensitivity analysis showed that excluding any trial and performing a meta-analysis on the remaining trials delivered stable results (Supplementary Figure 24). Meta-regression showed that heterogeneity between groups were independent of the five classifications (Supplementary Figure 25). Therefore, we adopted an REM. Meta-analysis showed that the experimental group was superior to the control group in reducing CK-MB [SMD = −6.882, 95% CI (−8.982, −4.782), $p = 0.000$]. (Figure 10, Supplementary Figure 23)
cTnI
cTnI data were available in eight studies (Li et al., 2014 [13]; Pan et al., 2016 [16]; Yao et al., 2016 [17]; Yuan et al., 2017 [19]; Fang et al., 2017 [18]; Chen et al., 2018 [21]; Bu et al., 2018 [22]; Zhang et al., 2020 [23]; Tang et al., 2021 [24]) involving 702 participants. Sensitivity analyses showed that any trials were excluded each time and the remaining trials were meta-analysed with stable results (Supplementary Figure 29). Meta-regression showed that heterogeneity between groups were independent of the 5 classifications (Supplementary Figures 30). As a result, we adopted an REM. Meta-analysis showed that the experimental group was superior to the control group in reducing cTnI [SMD =−3.610, 95% CI (−4.949, −2.271), p = 0.000] (Figure 11, Supplementary Figure 28). We conducted Egger’s (p = 0.000) and Begger’s (p = 0.019) tests to assess publication bias (Supplementary Figures 31–32).

Figure 11 Forest plot of cTnI
Lipid Peroxide

SOD

SOD data were available in five studies (Pan et al., 2016 [16]; Yao et al., 2016 [17]; Chen et al., 2018 [21]; Bu et al., 2018 [22]; Zhang et al., 2020 [23]) involving 461 participants. Given the high heterogeneity ($I^2 = 91.6\%$, $p < 0.01$, Figure 12), sensitivity analysis and meta-regression analysis were performed; but the cause of heterogeneity could not be determined (Supplementary Figure 34-35). Therefore, we adopted an REM. Meta-analysis showed that the experimental group was superior to the control group in reducing superoxide dismutase (WMD = 39.783, 95% CI [32.524, 47.042], $p = 0.000$) (Figure 13, Supplementary Figure 33). We conducted Egger’s ($p = 0.257$) and Begger’s ($p = 0.806$) tests to assess publication bias (Supplementary Figures 36–37).

![Figure 12 Forest plot of SOD](image)

**Figure 12 Forest plot of SOD**

GSH

GSH data were available in five studies (Pan et al., 2016 [16]; Yao et al., 2016 [17]; Chen et al., 2018 [21]; Zhang
et al., 2020 [23]) involving 378 participants. To determine the cause of the high heterogeneity ($I^2 = 70.5\%, p < 0.05$, Figure 13), sensitivity analysis and meta-regression analysis were performed; however, the source of the heterogeneity could not be identified (Supplementary Figure 39-40). Therefore, we adopted an REM. Meta-analysis showed that the experimental group was better than the control group in reducing GSH (WMD = 32.960, 95% CI [26.055, 39.865], $p = 0.000$). (Figure 13, Supplementary Figure 38). We conducted Egger’s ($p = 0.943$) and Begger’s ($p = 1.000$) tests to assess publication bias (Supplementary Figures 41–42).

![Figure 13 Forest plot of GSH](image)

**MDA**

MDA data were available in five studies (Pan et al., 2016 [16]; Yao et al., 2016 [17]; Chen et al., 2018 [21]; Bu et al., 2018 [22]; Zhang et al., 2020 [23]) involving 461 participants. Given the high heterogeneity ($I^2 = 86.0\%$, $p < 0.01$, Figure 14), sensitivity analysis and meta-regression analysis were performed; but the source of heterogeneity could not be determined (Supplementary Figure 44-45). Meta-analysis showed that the experimental group
performed better in reducing MAD than the control group (WMD = $-4.962$, 95% CI $[-6.041, -3.883]$, $p = 0.000$) (Figure 14, Supplementary Figure 43). We conducted Egger’s ($p = 0.865$) and Beggar’s ($p = 0.806$) tests to assess publication bias (Supplementary Figures 46–47).

**DISCUSSION**

In 2012, About 1.67 million women worldwide have been diagnosed with breast cancer, making it the second most common cancer [25]. In 2018, women with breast cancer who had access to appropriate treatment faced a very different situation: about 90% chance of being cured, and there were countless treatment options available [26]. The core of the improvement in prognosis is the use of three systemic treatment modalities: chemotherapy, endocrine therapy, and targeted therapy. Chemotherapy is the most effective treatment for breast cancer at various periods of breast cancer [27]. Unfortunately, further progress is needed in reducing treatment-related costs and avoiding unnecessary toxicity, which is ultimately detrimental to patients who need treatment. SMI is a TCM
compound designed to prevent or treat heart disease. According to the basic theory of TCM, these compounds work by strengthening the healthy qi ("vitality" or "energy") to eliminate pathogens. Therefore, it has been widely used as an adjuvant treatment in China [28-32]. This study systematically reviews the efficacy of ginsengmai injection in combination with chemotherapy in the treatment of chemotherapy-induced cardiotoxicity (CIC), thus providing an evidence-based medical basis for the treatment of CIC by integrated traditional Chinese and Western medicine. This meta-analysis included 13 studies, with a total of 1,891 participants who met the inclusion criteria.

The main findings are summarized as follows.

*Incidence of abnormal electrocardiography.* ECG plays a vital role in cardiotoxicity monitoring. Studies have shown that ECG changes occur earlier in cancer patients treated with anthracyclines than those observed on echocardiography [33]. ECG changes are a signal of early myocardial damage, and there is a significant advantage to reduce the incidence of abnormal ECG in patients with breast cancer receiving SMI combined with chemotherapy drugs compared with chemotherapy drugs alone. Due to the high heterogeneity of the included studies, further analysis of ST-T alterations and premature beats was performed. The benefit of SMI for patients was observed in all analyses, with low heterogeneity. Hence, we speculate that the different manifestations of abnormal ECGs are a potential source of heterogeneity.

*LVEF.* The LVEF levels were significantly lower in patients treated with SMI than in the control group. In the subgroup analysis according to the SMI dosage, significant differences in LVEF were observed between the experimental and control groups treated with 50–60 mL SMI/time. We propose that dosage may be a key factor of SMI efficacy as the majority of patients achieved the LVEF goal on this stage. Therefore, adjuvant treatment with 50–60 mL SMI/time should be considered. However, due to the poor methodological quality of these trials, the reliability of the conclusions should be assessed in prospective studies.

*Myocardial Injury Biomarkers.* Meta-analysis revealed a significant improvement in myocardial injury
biomarkers (CK, CK-MB, and cTnI) for SMI combined with chemotherapy drugs against chemotherapy drugs alone. This further illustrates the important role of combined SMI in reducing chemotherapy-induced cardiotoxicity. However, due to the major differences between studies, such as measurement methods, operation methods, and outcome indicator units, the reliability of these indicators has been reduced. Therefore, more randomized controlled studies are needed to confirm this.

**Lipid Peroxide.** Lipid peroxide is a common indicator of oxidative stress, including SOD, GSH, and MDA. Among them, MDA is one of the main metabolites of lipid peroxidation, which can aggravate oxidative damage [34]. SOD is an oxygen free radical scavenging enzyme that has the function of anti-aging and reducing toxic side-effects [35]. GSH is an important antioxidant and free radical scavenger, which can enhance the body's immunity, remove the toxic products produced by chemotherapy drugs, and repair and protect damaged cells [36]. This study showed that the levels of SOD and GSH were significantly higher, whereas the MDA level was significantly lower in the SMI treatment group compared to the control group. This showed that SMI can effectively improve oxidative stress and protect the myocardial tissue. However, due to the lack of large case-control studies, the heterogeneity between the studies was high. Therefore, more clinical trials and basic studies are needed to confirm the relevant effects and mechanisms of lipid peroxides on cardiotoxicity.

**ETHICS APPROVAL AND CONSENT TO PARTICIPATE**

Not applicable.

**CONSENT FOR PUBLICATION**

All authors gave their consent for publication.
AVAILABILITY OF DATA AND MATERIALS

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

AUTHOR CONTRIBUTIONS

MF initiated this study and participated in its design; MF and HH performed study selection, data extraction, and data analysis. MF drafted the manuscript. CY supervised all the aspects of the study. All authors contributed to the manuscript and approved the submitted version.

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CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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SUPPLEMENTARY MATERIAL

The supplementary material for this article is available online.

REFERENCES


improves doxorubicin cardiotoxicity via miR-30a/Beclin 1. Biomed Pharmacother. 2021 Apr 23;139:111582. doi:

SB. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of
Observational Studies in Epidemiology (MOOSE) group. JAMA. 2000 Apr 19;283(15):2008-12. doi:

www.training.cochrane.org/handbook.

Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015:
elaboration and explanation. BMJ. 2015 Jan 2;350:g7647. doi: 10.1136/bmj.g7647. Erratum in: BMJ. 2016 Jul
21;354:i4086. PMID: 25555855.

[12] Yang X. The clinical observation of Shenmai injection to CAF chemotherapy caused myocardium toxicity of
Xinjiang Uygur women with breast cancer. Xinjiang Medical University Thesis. 2008.


[14] Liu Q, Zhang X, Cheng X, et al. Clinical Observation of Cardiac Toxicity Induced by FAC Regimen in


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