

Efficacy and safety of Xiaoaiping injection for breast cancer

A protocol for systematic review and meta-analysis

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Abstract

Background: Xiaoaiping injection, extracted from the Chinese herb *Marsdenia tenacissima* (Roxb.) Wight et Arn., is a broad-spectrum anti-tumor drug and has been widely used for the treatment of breast cancer in China. The aim of this study is to systematically investigate the efficacy and safety of Xiaoaiping injection for the treatment of breast cancer.

Methods: We will perform the comprehensive literature search in the following databases from their inception to August 2020 for data extraction: PubMed, the Cochrane Library, Embase, the China National Knowledge Infrastructure, Wanfang Database, Chinese Science and Technology Periodical Database, and Chinese Biomedical Literature Database. Cochrane Risk of Bias tool will be used to assess the risk of bias of included studies. The RevMan 5.4 and Stata 16.0 software will be applied for statistical analyses. Statistical heterogeneity will be computed by I² tests. Sensitivity analysis will be conducted to evaluate the stability of the results. The publication bias will be evaluated by funnel plots and Egger's test. The quality of evidence will be assessed by the GRADE system.

Results: The results of our research will be published in a peer-reviewed journal.

Conclusion: The conclusion of this study will provide evidence to show whether Xiaoaiping injection is an effective intervention for patient with breast cancer.

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Abbreviations: CI = confidence interval, GRADE = Grading of Recommendations Assessment, Development and Evaluate system, MD = mean difference, RCTs = randomized controlled trials, SMD = standard mean difference, TCM = Traditional Chinese Medicine.

Keywords: breast cancer, protocol, systematic review and meta-analysis, Xiaoaiping

1. Introduction

Breast cancer, ranking as the second-leading cause of cancer-related deaths in women, is one of the most common malignancy.^[1,2] In the past few years, the breast cancer incidence

rate increased slightly by 0.3% per year in America.^[3] In recent years, therapies for breast cancer have evolved rapidly, from chemotherapy and radiotherapy to targeted therapy and immunotherapy.^[4,5] However, these therapies also experience intractable issues, such as acquired resistance, low tumor response rates, and unaffordable medical expenses.^[6]

Traditional Chinese medicine (TCM) has been effectively applied in treating malignant diseases for thousands of years in Eastern Asia.^[7-9] Researches have shown that Chinese medicine combined with chemotherapy can significantly enhance tumor response and alleviate toxicity compared with chemotherapy alone.^[10] Xiaoaiping injection, mainly composed of the Chinese herb *Marsdenia tenacissima* (Roxb.) Wight et Arn., was approved by the China Food and Drug Administration (CFDA) for tumor treatment with approval number Z20025868. It has exhibited antitumor effects on various cancers such as ovarian cancer,^[11,12] esophageal cancer,^[13] gastric cancer,^[14] lung cancer,^[15,16] liver cancer,^[17,18] and breast cancer.^[19,20]

Studies have shown that Xiaoaiping injection can significantly reverse multidrug resistance of cancer,^[21] enhance efficacies of chemotherapy,^[20,22] and reduce the side effects induced by chemotherapy in breast cancer patients.^[19] However, there is still a lack of high-quality evidence to support the effectiveness and safety of Xiaoaiping injection on patients with breast cancer. In this work, we will perform a systematic review to evaluate the efficacy and safety of Xiaoaiping injection in the treatment of breast cancer and to provide a reference for clinical application.

DH and JX have contributed equally to this work and are co-first authors.

The authors declare that there is no competing interest in this research.

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The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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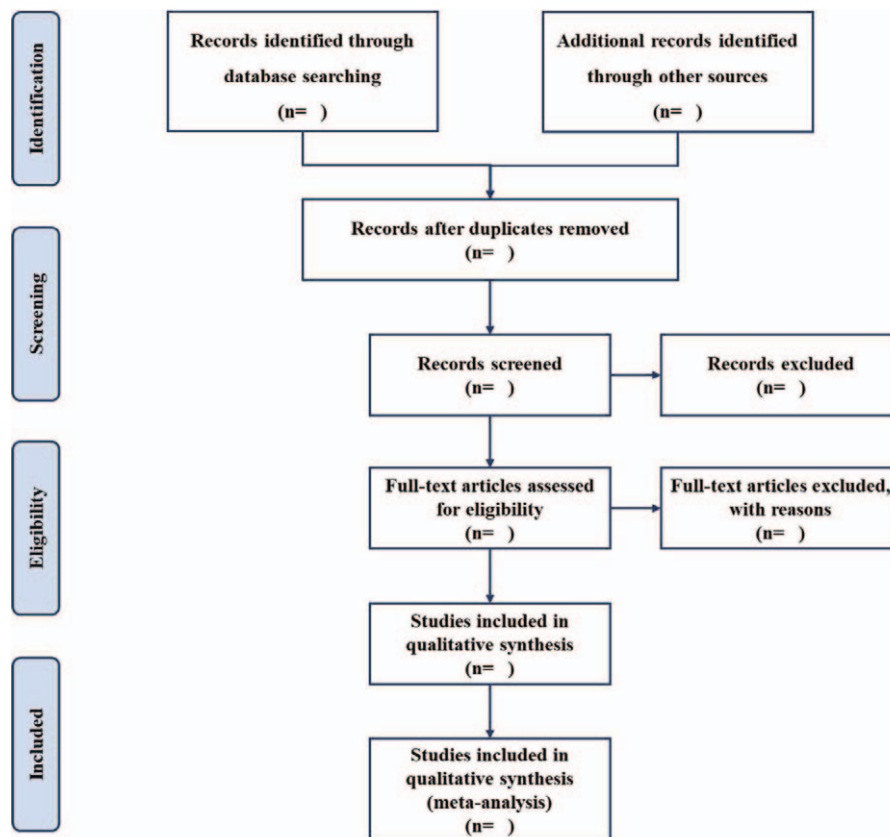


Figure 1. Flow chart of study selection.

sequence generation, allocation concealment, blinding of the participants and personnel, blinding of the outcome assessments, incomplete outcome data, selective reporting, and other sources of bias. The bias risk assessment is divided into 3 criteria: “Low risk,” “High risk,” or “Unclear risk.” Inconsistencies will be resolved by discussion within the group.

2.3.4. Synthesis of data. A meta-analysis will be carried through using RevMan 5.4 (The Cochrane Collaboration, Oxford, England) and Stata 16.0 software (Stata 16.0, College Station, TX). Dichotomous data will be reported as risk ratio (RR) with 95% confidence interval (CI), whereas continuous data will be reported as mean difference (MD) or standard mean difference (SMD) with 95% CI. MD will be used when the treatment outcome was measured by the same scale. SMD will be used when the treatment outcome was measured by different scales in different studies.

2.3.5. Assessment of heterogeneity. Statistical heterogeneity will be identified by I^2 statistics.^[25] Acceptable heterogeneity is considered if $I^2 \leq 50\%$ and a fixed-effect model will be applied. Otherwise, obvious heterogeneity is regarded if $I^2 > 50\%$, and a random-effect model will be utilized.

2.3.6. Subgroup analysis. In the case of high heterogeneity, we will conduct subgroup analysis according to the region of the studies, age, stage of the subjects, types of treatments, and different outcomes. We will evaluate the credibility of the subgroup analysis in term of the guidance.^[26] If quantitative synthesis is not appropriate due to substantial heterogeneity, then

systematic review will be conducted and the results will be displayed in tables and figures.

2.3.7. Sensitivity analysis. Sensitivity analysis will be conducted to identify the robustness of the result and detect whether there are any exceptional studies bringing about an evident heterogeneity. We will exclude each study included in the analysis one by one. Then we will reanalyze and compile the data and compare the difference between the reobtained effects and the original effects. If there is one or more very large study, we will repeat the analysis excluding them to determine how much they dominate the results.

2.3.8. Assessment of reporting bias. When there are sufficient studies available (normally over 10 studies), we will check the reporting bias using funnel plot and Egger regression test.^[27,28] $P < .05$ is considered to have publication bias.

2.3.9. Grading the quality of evidence. We will assess the quality of evidence using The Grading of Recommendations Assessment, Development and Evaluation (GRADE), a widely used tool in evaluating the quality of assessment.^[29] The quality of evidence will be rated as high, moderate, low, or very low.

2.4. Patient and public involvement

Patient and public were not involved in this study.

2.5. Ethics and dissemination

This systematic review will not require ethical approval because there are no data used in our study that are linked to individual

patient data. This systematic review will be disseminated through a peer-reviewed publication.

3. Discussion

Breast cancer is the most common malignancy in women. Xiaoaiping injection is a famous Chinese patent medicine for the treatment of breast cancer in clinical practice, and a series of clinical studies have been conducted on it.^{19,20} However, no systematic review related to Xiaoaiping injection for breast cancer has been published currently. In this study, we will conduct systematic review and meta-analysis to provide more evidence on the effectiveness and safety for it. These findings may provide helpful guidance for clinicians in the treatment of breast cancer.

3.1. Amendments

If amendments are needed, we will update our protocol to include any changes in the whole process of research.

Author contributions

Conceptualization: Daorui Hou, Lu Xiong.

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Writing – review & editing: Daorui Hou, Jian Xiong, Yahui Peng, Ya Li, Lu Xiong.

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