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# Efficacy and safety of Huaier granules combined with chemotherapy for gastric cancer
## A protocol for systematic review and meta-analysis

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## Abstract

**Background:** Huaier granules, the aqueous product of Huaier (*Trametes robiniophila Murr.*) extract, are a broad-spectrum anti-tumor drug and have been widely used for the treatment of gastric cancer (GC). The aim of this study is to systematically investigate the efficacy and safety of Huaier granules combined with chemotherapy in the treatment of GC.

**Methods:** Three English databases and four Chinese databases will be searched from its inception to July 2020. Two methodological trained researchers will select the qualified studies for data extraction independently. Cochrane Risk of Bias tool will be used to assess the risk of bias of included studies. The RevMan 5.2 and stata 14.0 software will be applied for statistical analyses. Statistical heterogeneity will be computed by Cochrane $X^2$ and $I^2$ 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 our systematic review will provide evidence to judge whether Huaier granules combined with chemotherapy is an effective intervention for patient with GC.

**OSF registration number:** 10.17605/OSF.IO/9BVJD.

**Abbreviations:** AEs = adverse events, CFDA = China Food and Drug Administration, ChiCTR = Chinese Clinical Trial Registry, CI = confidence interval, CNKI = China National Knowledge Infrastructure, CR = complete response, GC = gastric cancer, GRADE = Grading of Recommendations Assessment, Development and Evaluate system, MD = mean difference, OR = overall response, OS = overall survival rate, PFS = progression-free survival, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-analysis, PRISMA-P = Preferred Reporting Items for Systematic Reviews and Meta-analysis Protocols, QIR = quality of life improved rate, RCTs = randomized controlled trials, RR = risk ratio, Sino Med = China Biology Medicine Disc, SMD = standard mean difference, TCM = Traditional Chinese Medicine, VIP = Chinese Scientific Journals Database.

**Keywords:** gastric cancer, Huaier, protocol, systematic review and meta-analysis

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## 1. Introduction

Gastric cancer (GC) is the fifth most frequently diagnosed cancer and the third leading cause of cancer death around the world.[1,2] According to an epidemiological survey in 2018, there were 1,033,701 new cases of GC and 782,685 deaths related to GC worldwide.[3] As a standard treatment for GC, chemotherapy-based treatment has increased the cure rate of about 10% in the treatment of GC in the past few years.[4–6] However, the side effects and acquired drug resistance of chemotherapy restrict its application.[7,8]

Traditional Chinese medicine (TCM) has been effectively applied in treating malignant diseases for a long time in Eastern Asia.[9–11] Clinical studies have confirmed that the combination of chemotherapy and TCM can improve the therapeutic effect of GC.[12,13] Huaier granules, the aqueous product of Huaier (*Trametes robiniophila Murr.*), are one of the approved TCM by Chinese State Food and Drug Administration (SFDA) (Drug Approval Number: Z20000109). It has been used to treat liver cancer,[14,15] breast cancer,[16] lung cancer,[17] and gastrointestinal cancer.[18,19] Recent research has shown that Huaier granules can modulate innate immunity through the release of cytokines and the generation of reactive oxygen species and NO.[20]

Furthermore, it exerts anti-tumor responses by inducing cell cycle arrest at the G0/G1 checkpoint and inhibiting tumor angiogenesis.[21]

Recently, the using of Huaier granules combined with chemotherapy for treating GC has attracted increasing worldwide interest.[22–24] Although several epidemiologic studies were performed for its efficiency with gastric cancer, no consensus conclusion has been reached yet.[19] The efficacy and safety of Huaier granules combined with chemotherapy in the treatment for GC remain controversial. Hereby, we will systematically review current available randomized controlled trials (RCTs) to objective comment the efficacy and safety of Huaier granules during chemotherapy in patients with GC. It may provide more relevant information for clinician in clinical practice.

## 2. Methods and analysis

### 2.1. Study registration

This work has been registered at Open Science Framework (OSF, https://osf.io/), an open source project management that helps in the design of studies. The registration DOI of this study is 10.17605/OSF.IO/9BVJD. The protocol of our meta-analysis will be conducted followed the guideline of the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) recommendations.[25]

### 2.2. Eligibility criteria

**2.2.1. Study design.** Randomized controlled trials (RCTs) which used a combination of Huaier granules and chemotherapy as treatment measures will be eligible, while laboratory studies, qualitative studies, or observational study will be excluded in the research. There are no limitations on language and publication status.

**2.2.2. Types of participants.** We will include RCTs on participants who are diagnosed as GC. The race, sex, age, severity, and duration are not restricted.

**2.2.3. Types of interventions.** Interventions to be reviewed are Huaier granules combination with chemotherapy to treat the GC. The control intervention could be any management in patients with GC.

### 2.3. Outcomes

The primary outcomes of this review will focus on overall survival (OS) and progression-free survival (PFS). The secondary outcomes included overall response rate (ORR), disease control rate (DCR), quality of life improved rate (QIR), and adverse events.

### 2.4. Search strategy

To ascertain the relevant literature, 3 English databases including PubMed, Embase, Cochrane Library Central Register of Controlled Trials, and 4 Chinese databases including China National Knowledge Infrastructure (CNKI) database, Wanfang Data Knowledge Service Platform, Chinese Scientific Journal Database (VIP), China Biology Medicine Disc (Sino Med) will be searched from its inception to July 2020. In addition, Google scholar, Bing scholar, and Baidu scholar will be retrieved to find out other related literature. Moreover, the Chinese Clinical Trial Registry (ChiCTR) and ClinicalTrials.gov will also be searched. We will also search in OpenGrey.eu. website for potential gray literature. Two authors (DH and JX) will search and screen all the citations independently. An example of search strategy for PubMed database that combines MeSH terms and free words will be adopted. The search strategy was as follows:

#1 Search: ("Stomach Neoplasms"[Mesh]) OR (((((((((((((((((Neoplasm, Stomach[Title/Abstract]) OR (Stomach Neoplasm[Title/Abstract])) OR (Neoplasms, Stomach[Title/Abstract])) OR (Gastric Neoplasms[Title/Abstract])) OR (Gastric Neoplasm[Title/Abstract])) OR (Neoplasm, Gastric[Title/Abstract])) OR (Neoplasms, Gastric[Title/Abstract])) OR (Cancer of Stomach[Title/Abstract])) OR (Stomach Cancers[Title/Abstract])) OR (Gastric Cancer[Title/Abstract])) OR (Cancer, Gastric[Title/Abstract])) OR (Cancers, Gastric[Title/Abstract])) OR (Gastric Cancers[Title/Abstract])) OR (Stomach Cancer [Title/Abstract])) OR (Cancer, Stomach[Title/Abstract])) OR (Cancers, Stomach[Title/Abstract])) OR (Cancer of the Stomach [Title/Abstract])) OR (Gastric Cancer, Familial Diffuse[Title/Abstract]))

#2 Search: ("huaier" [Supplementary Concept]) OR (((((Trametes robiniophila Murr[Title/Abstract]) OR (Auricularia auricula[Title/Abstract])) OR (Jin Ke[Title/Abstract])) OR (Jinke [Title/Abstract])) OR (Jew Ear Parasitized Granula[Title/Abstract]))

#3 Search: ((((((((randomized controlled trial[Title/Abstract]) OR RCT[Title/Abstract]) OR random[Title/Abstract]) OR randomly[Title/Abstract]) OR random allocation[Title/Abstract]) OR allocation[Title/Abstract]) OR randomized control trial[Title/Abstract]) OR controlled clinical trial[Title/Abstract]) OR clinical trial[Title/Abstract]) OR clinical study[Title/Abstract]

#1 and #2 and #3

### 2.5. Selection of studies

The electronic citations extracted out from the above databases will be managed by EndNote X9.0 (Stanford, Connecticut, https://endnote.com). Two methodological trained investigators (DH and JX) will independently review all identified data based upon the exclusion and inclusion criteria and remove duplicate literature. Titles, abstracts, and full-text articles will be screened and data will be extracted independently by those reviewers. Any divergences between 2 investigators will be solved through discussion with another investigator (LY). We will note reasons for all excluded studies. A PRISMA flow chart (Fig. 1) will be drawn to present the whole process of study selection.[25]

### 2.6. Extraction and management of data

Two investigators (DH and JX) will extract relevant data independently with the standardized sheet recommended by the Cochrane Handbook of Systematic Reviews of Interventions. The data of those qualified articles will be export to Microsoft Excel, which includes the first author, published year, study location, study design, inclusion/exclusion criteria, pathological type, sample size, participants' baseline characteristics, intervention characteristics, control, outcome data, and adverse events. For articles with incomplete or uncertain data, the authors will be contacted for complete data whenever possible. If there is any dispute in the data extraction process, it will be submitted to a third researcher (LX) for processing.
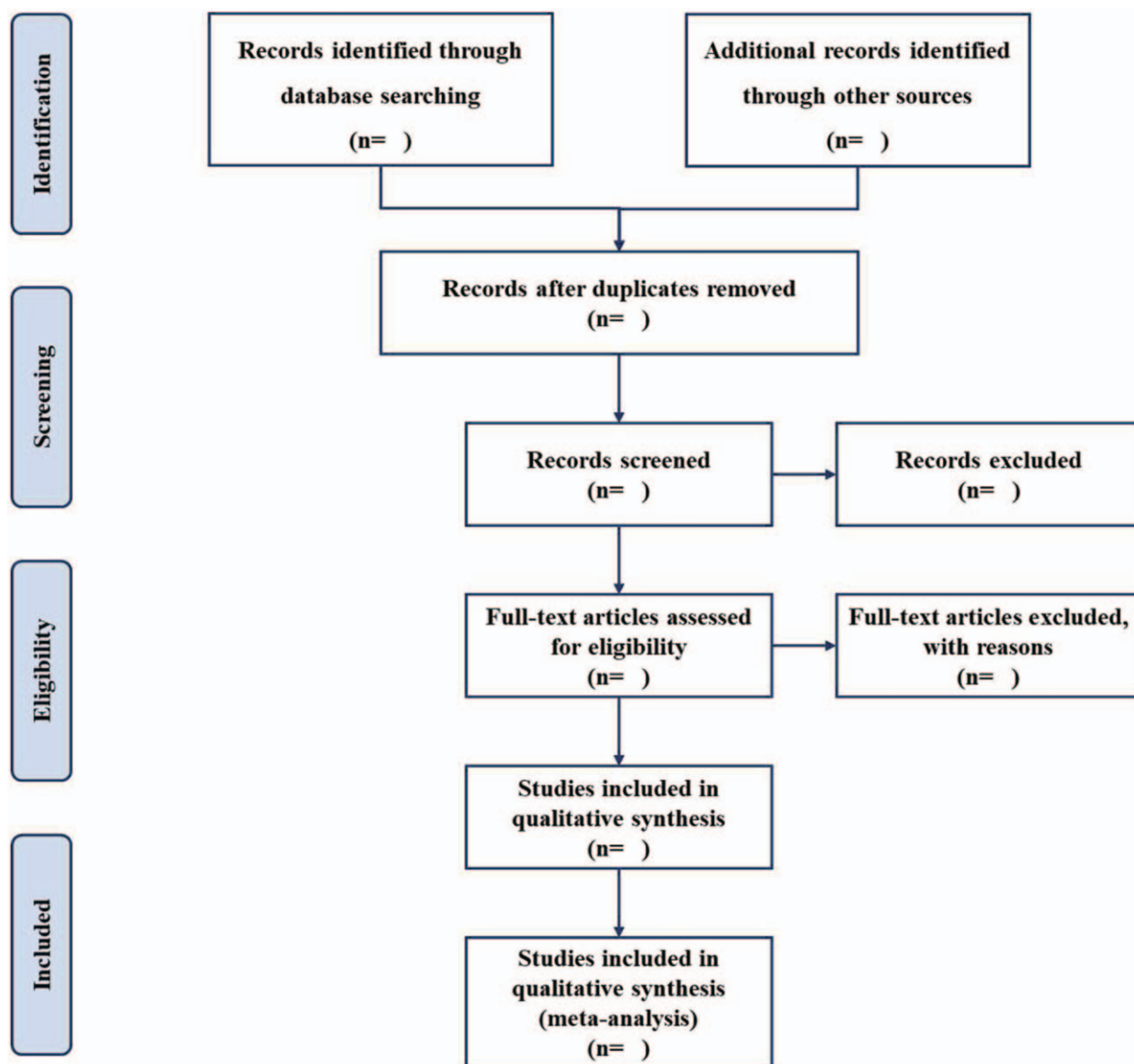
**Figure 1.** Flow chart of study selection.

### 2.7. Assessment of risk of bias in included studies

The Cochrane collaboration's tool, an established and reliable tool for assessing the risk of bias, will be used in studies evaluate the risk of bias for each study by two independent reviewers (DH and LY).[26] In this tool, the risk of bias of a trial is evaluated through 7 items, include random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), other bias. The assessment will be classified as "Low risk," "High risk," or "Unclear risk." Disagreements between the 2 reviewers will be resolved by discussion of all reviewers.

### 2.8. Synthesis of data

RevMan 5.2 (Cochrane, London, UK) and Stata 14.0 software (Stata Corporation, College Station, TX, USA) will be applied for statistical analyses. For dichotomous variables, the risk ratio (RR) will be applied to analyze. For continuous variables, a mean difference (MD) or a standard mean difference (SMD) will be used for analysis. 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. The confidence intervals (CI) for both dichotomous and continuous variables will be set to 95%.

### 2.9. Assessment of heterogeneity

Statistical heterogeneity will be computed by Cochrane $X^2$ and $I^2$ tests.[27] 75%, 50%, or 25% of $I^2$ statistics indicate high, medium, and low heterogeneity, respectively. The statistical heterogeneity is considered substantial when $P < .05$ and $I^2 > 50\%$ and the random-effect model will be applied to pool data. 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.[28] If there are enough researches, meta-regression will be performed to clarify the source of heterogeneity. If there is no significant heterogeneity ($P > .05$ and $I^2 < 50\%$), then the fixed-effect model will be used to calculate the effect size. 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.

### 2.10. Sensitivity analysis

To ensure the stability of the results, a sensitivity analysis will be performed for the outcomes. 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.

### 2.11. Assessment of reporting biases

The publication bias will be evaluated by funnel plots when >10 studies are included. Egg regression and Begger tests will be utilized to detect the funnel plot asymmetry.[29] $P < .05$ is considered to have publication bias. In the case of asymmetric funnel plot, subgroup analysis or sensitivity analysis will be performed to investigate possible causes.[30]

### 2.12. 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.[31] The quality of evidence will be assorted into "high," "moderate," "low," and "very low" quality.

### 2.13. Patient and public involvement

Patient and public were not involved in this study.

### 2.14. Ethics and dissemination

Ethical approval will not be required for this systematic review because the data used are not linked to individual patient. The results of this review will be disseminated by being published in a peer-reviewed journal.

## 3. Discussion

GC, a common cancer with high morbidity and mortality worldwide, requires continuous exploration for new treatment methods and concepts.[32] Huaier granule is a famous Chinese patent medicine for treating GC in clinical practice, and a series of clinical studies have been conducted on it.[33–35] However, there is no systematic review related to Huaier granules combined with chemotherapy for GC published. In this study, we will conduct systematic review and meta-analysis to provide more evidence on the effectiveness and safety for Huaier granules combined with chemotherapy. These findings may provide more guidance for clinicians in the treatment of GC.

### 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:** Lu Xiong.
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**Formal analysis:** Liangjun Yang, Lu Xiong.
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**Writing – original draft:** Daorui Hou, Jian Xiong.
**Writing – review & editing:** Daorui Hou, Jian Xiong, Liangjun Yang, Lu Xiong.

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