INPLASY PROTOCOL

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All of the authors declare that they have no known conflicts of interest.

Xiangshaliujun Decoction for functional dyspepsia: A Protocol for systematic review and meta-analysis of randomized controlled trials

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Review question / Objective: **The primary objective is to assess the efficacy and safety of Xiangshaliujun Decoction for the treatment of people with functional dyspepsia.**
Condition being studied: **Functional dyspepsia. Traditional Chinese medicine.**
Information sources: **The electronic databases such as The Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, EMBASE, China National Knowledge Infrastructure(CNKI), WanFang, Chinese Scientific Journals Database (VIP) and China Biology Medicine disc (CBMdisc)will be searched from establishment of the database until September 2019.In addition, we also manually searched additional relevant studies. There is no restriction on the language of publication. Searchers will be rerun prior to the final analysis. If any information is missing at the end of data extraction process, we will contact the authors of the trials to recover the specific information.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 08 September 2020 and was last updated on 08 September 2020 (registration number INPLASY202090033).

INTRODUCTION

Review question / Objective: **The primary objective is to assess the efficacy and safety of Xiangshaliujun Decoction for the treatment of people with functional dyspepsia.**

Condition being studied: **Functional dyspepsia. Traditional Chinese medicine.**

METHODS

Search strategy: **The electronic databases such as The Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, EMBASE, China National Knowledge**

Infrastructure(CNKI), WanFang, Chinese Scientific Journals Database (VIP) and China Biology Medicine disc (CBMdisc)will be searched from establishment of the database until September 2019.In addition, we also manually searched additional relevant studies. There is no restriction on the language of publication. Searchers will be rerun prior to the final analysis. We use the PubMed search strategy for example: #1 "Dyspepsia"[Mesh] #2functional dyspepsia[Title/Abstract]) OR functional dyspepsia[Title/Abstract] #3 #1 OR #2 #4 (((((Xiangsha Liujunzi Decoction[Title/Abstract]) OR Xiangshaliujunzi decoction[Title/Abstract]) OR Modified Decoction of Cyperus-Amomum with Six Noble Ingredients[Title/Abstract]) OR Xiangsha Liujunzi Tang[Title/Abstract]) OR Xiangsha Liujunzi[Title/Abstract]) OR XiangshaLiujunzi[Title/Abstract] #5 #3 AND #4.

Participant or population: Inclusion: (1) people with functional dyspepsia according to Romel,II,III or IV diagnostic criteria; (2) both genders; (3) age ≥18 years old. Exclusion: Patients with other types of diseases, such as severe cardiac dysfunction, severe hepatic dysfunction, severe kidney dysfunction, endocrine disease, cholecystitis, pancreatitis, and peptic ulcer.

Intervention: We will include studies assessing the effects of any form of Xiangshaliujunzi Decoction including oral preparations, decoctions, injections, powders, teas, tablets, capsules, suppositories, extracts, lotions, and fresh or dried plants. We will also include the studies must have an experimental group receiving Xiangshaliujunzi Decoction alone or Xiangshaliujunzi Decoction combined with acid suppression agents, prokinetics agents, PPIs, H. Pylori eradication, and Histamine 2-receptor antagonists (H2RAs). In addition, we will include the studies involving comparison between Xiangshaliujunzi Decocotion and placebo. There are no limitation on dosage, frequency or duration of the treatment.

Comparator: The control group should employ conventional pharmacotherapy, including but not limited to: acid suppression agents, prokinetic agents, PPIs, H. Pylori eradication, H2RAs or placebo of Chinese herbal medicine.

Study designs to be included: Only randomized controlled trials (RCTs) reporting clinical assessment will be included. Quasi-RCTs, parallel assignment, cross-over trials, cluster-randomized trials, and other study designs will be excluded. We will include studies reported as full text in academic journal and published dissertation. Language restriction are not applied during study selection.

Eligibility criteria: (1)Type of study: Only randomized controlled trials (RCTs) reporting clinical assessment will be included. Quasi-RCTs, parallel assignment, cross-over trials, cluster-randomized trials, and other study designs will be excluded. We will include studies reported as full text in academic journal and published dissertation. Language restriction are not applied during study selection. (2)Type of participants: Patients (aged 18 years or over) with FD according to Rome I,II,III or IV diagnostic criteria will be included, without the limitation of gender. Patients with other diseases, such as severe cardiac dysfunction, severe hepatic dysfunction, severe kidney dysfunction, endocrine disease, cholecystitis, pancreatitis, and peptic ulcer were excluded. (3) Type of interventions We will include studies assessing the effects of any form of Xiangshaliujun Decoction including oral preparations, decoctions, injections, powders, teas, tablets, capsules, suppositories, extracts, lotions, and fresh or dried plants. We will also include the studies with experimental group receiving Xiangshaliujun Decoction alone or Xiangshaliujun Decoction combined with acid suppression agents, prokinetics agents, PPIs, H. Pylori eradication, and Histamine 2-receptor antagonists (H2RAs). In addition, we will include the studies involving comparison between Xiangshaliujun Decoction and placebo. There was no limitation on dosage,

frequency or duration of the treatment. (4)Type of control: The control group should employ conventional pharmacotherapy, including but not limited to: acid suppression agents, prokinetic agents, PPIs, H. Pylori eradication, H2RAs or placebo of Chinese herbal medicine. (5)Outcomes measures: The primary outcomes will include Postprandial discomfort severity scale (PDSS) and Nepean Dyspepsia Index (NDI). The secondary outcomes will include Medical Outcome Study Short Form Health Survey (SF-36), Symptom scores, Functional Digestive Disorder Quality of Life questionnaire (FDDQL, adverse events and effective rate.

Information sources: The electronic databases such as The Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, EMBASE, China National Knowledge Infrastructure(CNKI), WanFang, Chinese Scientific Journals Database (VIP) and China Biology Medicine disc (CBMdisc)will be searched from establishment of the database until September 2019.In addition, we also manually searched additional relevant studies. There is no restriction on the language of publication. Searchers will be rerun prior to the final analysis. If any information is missing at the end of data extraction process, we will contact the authors of the trials to recover the specific information.

Main outcome(s): (1) Postprandial discomfort severity scale (PDSS). (2) Nepean Dyspepsia Index (NDI).

Additional outcome(s): (1) Medical Outcome Study Short Form Health Survey (SF-36). (2) Symptom scores. (3) Functional Digestive Disorder Quality of Life questionnaire (FDDQL). (4) Adverse events. (5) Effective rate, inefficient rate.

Data management: We will import all retrieved results into NoteExpress 3.2.0. Duplicate data from different databases will be identified first. Two reviewers independently will screen the remaining titles and abstracts to select potential trials, and then review full texts for eligible trials according to the criteria described above. We will include researches irrespective of whether outcomes data are reported in a 'usable' way. We will document reasons for the exclusion of ineligible researches that may have reasonably been expected to have been included in the review in a 'Characteristics of excluded studies' table. We will collate multiple reports of the same research so that each research, rather than each report, is the unit of interest in the review.The selection process will be detailed sufficiently to complete a PRISMA flow chart. We will use a standard data collection form for study characteristics and outcome data, which was piloted on five studies. Four review authors will divide into 2 group and extract the following study characteristics from included studies.Any disagreements will be resolved through discussion or by consultation with a third review author.

Quality assessment / Risk of bias analysis: We will summarize the 'Risk of bias' judgments across different studies for each of the domains listed. We will present a 'Risk of bias' summary figure and a 'Risk of bias' graph to illustrate these findings.

Strategy of data synthesis: We will undertake meta-analysis only if we consider that the participants, interventions, comparisons, and outcome assessment are similar enough to ensure that an answer would be clinically meaningful. Otherwise, we will present a qualitative synthesis to describe the results across the included studies. We will use a fixed-effect model in the meta-analysis if heterogeneity do not exist. When inconsistency is noted, causes of heterogeneity will be detected first by subgroup analysis. If this do not occur, a random-effects model will be applied. Results obtained by the random-effects model will be interpreted with caution. We will categorize global symptoms of dyspepsia as overall symptom improvement. We will calculate the relative risk reduction (RR) and 95% CIs. For dichotomous outcomes, we will use the

Mantel-Haenszel method. For continuous outcomes, we will use the inverse variance method. We will record global symptom score at pre- and post-treatment as well as mean and standard deviation of change scores from baseline in each group, if the information is available. We will also calculate the mean and standard deviation of change scores from baseline if only pre- and post-treatment scores are reported. We will calculate the MD and 95% CIs as the summary statistic for symptom scores for studies that used the same scales. We will calculate the SMD and 95% CIs between two groups if different scales are used in the primary studies. However, we will not combine final value and change scores as SMD, and will report them separately. We will use Review Manager 5 software to perform analyses (Review Manager 2014).

Subgroup analysis: Subgroup analysis will be based on possible factors that may lead to heterogeneity, such as treatment duration, intervention. We will assess differences between subgroups with the I2 statistic to test for subgroup interactions.

Sensibility analysis: We will conduct sensitivity analysis depending on study characteristics identified during the review process. Studies using individual symptom improvement as the outcome will be excluded in the sensitivity analysis. Studies with significant clinical heterogeneity will be excluded from the sensitivity analysis. Pre-specified sensitivity analyses such as fixed-effect model analysis, outcomes expressed as odds ratios(OR) versus relative risks(RR) will be included.

Language: There is no restriction on the language of publication. Searchers will be rerun prior to the final analysis.

Country(ies) involved: China.

Keywords: Xiangshaliujn Decoction; Functional dyspepsia; Traditional Chinese Medicine; Systematic review.

Dissemination plans: Once the results are registered, we will publish the protocol and research results in journal articles.

Contributions of each author:

Author 1 - Ning Dai - The author conceived and designed this protocol. Ning Dai is also responsible for extracting data and statistical analysis, as well as writing review.

Author 2 - Yfei Xu - The author is responsible for screening the remaining titles and abstracts to select potential trials, and then reviewing full texts for eligible trials according to the criteria described above, as well as assessing risk of bias.

Author 3 - Ruixue Hu - The author is responsible for searching databases and assessing risk of bias.

Author 4 - Xuejiao Wang - The author is responsible for designing the protocol, searching databases and exacting data and editing review.

Author 5 - Botan Li - The author is responsible for screening the remaining titles and abstracts to select potential trials, and then reviewing full texts for eligible trials according to the criteria described above, as well as assessing risk of bias.

Author 6 - Feng Li - The author designed this protocol and provided financial support. He is also responsible for dealing with disagreements and editing review.