Hangeshashinto for preventing oral mucositis in patients receiving cancer treatment: protocol for a systematic review and meta-analysis

Yu-Ting Wang , Yifeng Ren, Chong Xiao, Hong Liu, Xi Fu, Feng-Ming You

ABSTRACT
Introduction Hangeshashinto has been employed for oral mucositis prevention in patients receiving cancer treatment, but the evidence has not been sufficiently robust to guide clinical decision-making. This study will therefore be undertaken to assess the effectiveness of Hangeshashinto for preventing oral mucositis in patients with cancer who are receiving treatment.

Methods and analysis The databases will include PubMed, Embase, the Cochrane Library, Chinese databases and Japanese databases. The literature will be searched from the databases’ inception until May 2021. Other sources, such as potential grey literature, reference lists from included studies and relevant systematic reviews and conference papers, will also be searched. The primary outcome is the incidence of mucositis of any severity, and the secondary outcomes are interruptions to cancer treatment, oral pain and nutritional status. The risk of bias of eligible studies will be assessed using the Cochrane Collaboration’s ‘risk of bias’ tool. Both the Q test and I² statistic will be performed to assess statistical heterogeneity. If I² >50%, sensitivity and subgroup analysis will be conducted. The quality of evidence will be rated according to the Grading of Recommendations, Assessment, Development and Evaluation approach. Egger’s test will be used to assess reporting bias.

Ethics and dissemination This systematic review will evaluate only published data; therefore, ethical approval is not required.

PROSPERO registration number CRD42020216145.

INTRODUCTION
Oral mucositis (OM), a frequent and painful toxicity for patients with cancer, is an inflammatory response of the epithelial mucosa to antineoplastic treatments. Approximately 20%–40% of patients receiving conventional chemotherapy will develop OM, and this percentage increases to 60%–85% in those treated with haematopoietic stem cell transplantation and to 90% in those with head and neck neoplasms treated with radio-plus chemotherapy.1

OM typically manifests as erythema or/and ulcerations, which may cause pain and difficulty eating, swallowing and talking.2 Severe OM increases the requirement for narcotics and enteral nutritional support (including feeding tube use or gastrostomy) and can lead to the interruption of cancer treatments, which compromises tumour control. Furthermore, the ulcer provides an access site for pathogens and may increase the risk of infection or sepsis for immunocompromised patients with cancer. These complications are associated with prolonged hospital stays, increased mortality and increased healthcare costs.3 4 Thus, there has been significant interest in the prevention and treatment of OM.

Despite strategic advances in understanding the molecular basis of OM over the past decade, treatment options are still limited to symptom control with topical agents and systemic pain medication.5 6 Currently, several interventions and prevention guidelines are available, but their effectiveness is uncertain. It is worth noting that palifermin, the recombinant human keratinocyte growth factor 1, is the only agent approved by both the US Food and Drug Administration and the European Medical Agency for preventing OM in patients receiving antineoplastic treatments.6 However, due to the high costs and possibility of stimulating cancer cell growth, palifermin is not widely used in the
clinic for OM management. Other therapies that are more feasible, affordable and accessible to the general public are in urgent demand.

Hangeshashinto (TJ-14), a Kampo medicine containing seven herbal extracts (pinellia tuber, coptis rhizome, scutellaria root, processed ginger, glycyrrhiza, ginseng and jujube), has been approved as a prescribed medicine in Japan and China.\textsuperscript{7,8} Recently, in vitro and in vivo experiments have revealed the underlying mechanisms by which TJ-14 improves OM, which is related to anti-inflammatory and antibacterial effect.\textsuperscript{14–16} The results of these studies suggest that TJ-14 may provide a cheap and effective alternative for preventing or minimising OM, but no systematic review so far has authenticated the correlation between TJ-14 use and OM. Therefore, the purpose of this systematic review is to provide a retrospective investigation of the current evidence regarding the effectiveness of the application of TJ-14 for preventing OM in patients receiving cancer treatments to guide clinical decisions.

Objectives
To assess the effectiveness of TJ-14 in preventing OM in patients who are receiving treatment for cancer.

METHODS AND ANALYSIS
This study will be performed in agreement with Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidelines\textsuperscript{17} using the Population, Intervention, Comparison, Outcomes and Study framework.\textsuperscript{18} The PRISMA-P checklist and the PRISMA flow chart for the primary literature selection process are shown in online supplemental checklist and figure.

Search strategy
A systematic electronic search will be conducted in the following databases: PubMed, Embase, Cochrane Library, Chinese databases (Chinese National Knowledge Infrastructure (CNKI) and Wan-Fang Database) and Japanese databases (Citation Information by Nii (CiNii) and Ichushi-web). The reference lists from eligible studies and relevant systematic reviews will be searched manually, and relevant conference proceedings will also be searched. Additionally, we plan to search OpenGrey.eu for potential grey literature to ensure completeness of the literature search.

The retrieval time will be set from the time of database inception to May 2021. The publication languages will be limited to English, Japanese or Chinese. The following terms will be used for the search: neoplasms, cancer, tumor, leukemia, lymphoma, radiotherapy, antineoplastic agents, oral mucositis, stomatitis, Hangeshashinto and TJ-14. The PubMed search strategy is shown in Table 1. The search strategies used for Embase, Cochrane Library, CNKI, Wan-Fang Database, CiNii and Ichushi-web are supplied in online supplemental search strategies.

Eligible criteria
Type of studies
All randomised controlled trials (RCTs) and quasi-RCTs published since the time of database inception to May 2021 will be included.

Type of participants
Patients receiving cancer treatments will be included.

Type of interventions and comparisons
All studies comparing TJ-14 with placebo, no treatment, usual care or any other approach to prevent OM induced by cancer treatments will be included in this study.

We will exclude studies of combination interventions for the prevention of OM because it may be difficult to attribute any effect expressed to a specific component of the intervention.

Table 1 Search strategy used in PubMed

<table>
<thead>
<tr>
<th>Number</th>
<th>Search terms</th>
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<tbody>
<tr>
<td>#1</td>
<td>(Neoplasms[mesh]) OR (Neoplas*[ti/ab]) OR (Tumor*[ti/ab]) OR (Tumour*[ti/ab]) OR (cancer*[ti/ab]) OR (Malignanc*[ti/ab]) OR (Malignant*[ti/ab])</td>
</tr>
<tr>
<td>#2</td>
<td>(Leukemia[mesh]) OR (Leukemias*[ti/ab]) OR (Leucocythaemia*[ti/ab]) OR (Leucocytosynthesis*[ti/ab])</td>
</tr>
<tr>
<td>#3</td>
<td>(Lymphoma[mesh]) OR (Lymphoma*[ti/ab]) OR (Germinoblast*[ti/ab]) OR (Reticulolymphosarcoma*[ti/ab])</td>
</tr>
<tr>
<td>#4</td>
<td>(Radiotherapy[mesh]) OR (Radiotherap*[ti/ab]) OR (Therap*[ti/ab]) OR (Treatment*[ti/ab]) AND (Radiation*[ti/ab])</td>
</tr>
<tr>
<td>#5</td>
<td>(Antineoplastic Agents[mesh]) OR (Antineoplastic*[ti/ab]) OR (Antitumor*[ti/ab]) OR (Cancer*[ti/ab]) AND (Agent*[ti/ab]) OR (Drug*[ti/ab])</td>
</tr>
<tr>
<td>#6</td>
<td>(Bone Marrow Transplantation[mesh]) OR (Bone Marrow*[ti/ab]) AND (Grafting*[ti/ab]) OR (Transplantation*[ti/ab])</td>
</tr>
<tr>
<td>#7</td>
<td>(Stomatitis[mesh]) OR (Stomatitides*[ti/ab]) OR (Oral Mucositis*[ti/ab]) OR (Mucositis, Oral*[ti/ab]) OR (Oromucositis*[ti/ab])</td>
</tr>
<tr>
<td>#8</td>
<td>(Hangeshashinto*[ti/ab]) OR (TJ-14*[ti/ab]) OR (Banxia Xie Xin*[ti/ab]) OR (Banxia xie xin*[ti/ab]) OR (Ban Xie Xie Xin*[ti/ab]) OR (Banha-Sasim-Tang*[ti/ab]) OR (Pinellia Heart-draining*[ti/ab]) OR (Pinellia Decoction for Draining the Heart*[ti/ab])</td>
</tr>
<tr>
<td>#9</td>
<td>(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7) AND #8</td>
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</table>
Types of outcome measures

Primary outcomes
The primary outcome is the incidence of OM of any severity. We are interested in both the presence/absence of OM, and also different levels of severity. Two of the most commonly used scales for OM are the WHO classification and National Cancer Institute Common Terminology Criteria for Adverse Events. It will be measured on a scale of 0–4 (none to severe) and be dichotomised as no mucositis versus any mucositis (0 vs 1+), mild versus moderate to severe mucositis (0–1 vs 2+), and mild to moderate versus severe mucositis (0–2 vs 3+).

Secondary outcomes
1. Interruptions to cancer treatment.
2. Oral pain: the Numeric Rating Scale and the Visual Analogue Scale will be used to evaluate oral pain.
3. Nutritional status: including bodyweight reduction, serum albumin levels, feeding tube or gastrostomy use.

Selection studies
Two review authors (YW and CX) will independently screen the titles and abstracts of studies retrieved from the electronic searches. We will obtain the full text of all studies that appear to meet the inclusion criteria for further review and assessment. Any disputes will be resolved through discussion or consultation with the third review author (YR) if we are unable to resolve disagreements. Excluded studies will be recorded along with the reasons for exclusion.

Data extraction and coding
Two review authors (YW and CX) will independently extract data from all included studies using a data extraction form, which will include the following information: the first author, the year of publication, study population, study design, the number of total and analysed patients, baseline analysis, blinding method, imputation method, interventions, controls, and primary and secondary outcomes. To investigate the characteristics of the TJ-14 effect, we will also extract data on sex, age, features of cancer (such as primary site, cancer stage, cancer type and duration from the first diagnosis), features of cancer treatments (such as form, dose and frequency), and control intervention details. We will contact the study authors for missing data. Any disagreement will be resolved through discussion or consultation with the third review author (YR) to achieve consensus if necessary.

Quality assessment
Two separate review authors (HL and XF) will independently assess the risk of bias for eligible studies using the Cochrane Collaboration’s risk of bias tool. Six major domains will be assessed for each trial, including random sequence generation, allocation concealment, blinding method, incomplete outcome data, selective reporting and other sources of bias. All studies will be categorised into three grades (low, high and unclear risk of bias). Any disagreement will be resolved through discussion and consultation with the third review author (F-MY) if necessary. RevMan V.5.3.5 will be used to generate the graphical presentation of the assessment of risk of bias.

Statistical analysis
To determine the distinctions between the intervention and control groups, OM incidence of any severity at the completion of cancer treatments and at the end of follow-up will be extracted as a primary outcome. The number of interruptions to cancer treatment, incidence of oral pain, nutrition status, adverse events, number of hospitalisation days and number of days intervention with analgesics will be included as secondary outcomes. The incidence of OM will be measured on a scale of 0–4 (none to severe) and be dichotomised as no mucositis versus any mucositis (0 vs 1+), mild versus moderate to severe mucositis (0–1 vs 2+), and mild to moderate versus severe mucositis (0–2 vs 3+). For dichotomous outcomes (eg, mucositis of any severity vs none), the Relative Risk (RR) with 95% CI will be used to express the effect of TJ-14 treatment. For continuous outcomes (eg, number of hospitalisation days), the Mean Deviation (MD) with 95% CI will be extracted and calculated as an effect estimate.

Both the Q test and I² statistic will be performed for the assessment of statistical heterogeneity. Values of I² equal to or greater than 50% will be considered to represent substantial heterogeneity, and values equal to or greater than 75% indicate considerable heterogeneity. We will explore the sources of heterogeneity by conducting subgroup analysis and sensitivity analysis. Funnel plots will be used for the assessment of reporting biases and Egger’s test will be performed to evaluate funnel plot asymmetry. The meta-analysis results will be displayed in a forest plot with 95% CIs. The Grading of Recommendations, Assessment, Development and Evaluation approach will be used to summarise the quality of the evidence for the obtained results. We will categorise the overall quality of evidence as high, moderate, low or very low.

Patient and public involvement
No patient and public involved.

DISCUSSION
OM is a significant complication of cancer therapy, affecting more than 75% of high-risk patients. TJ-14 has been widely used for prevention and treatment of OM, but the evidence has not been sufficiently robust to guide clinical decision-making. This systematic review and meta-analysis will provide an assessment of the current state of TJ-14 for OM. Conclusions drawn from this study may benefit patients with OM, clinicians and policymakers. The process of this review will comprise four sections: identification, study inclusion, data extraction and data synthesis. Two main potential limitations may affect the conclusions. First, we will retrieve data from...
only English-language, Japanese-language and Chinese-language databases, which could limit the available data or result in language bias. Second, the quality of original studies may be poor, limiting the ability to generate conclusions based on high confidence.

ETHICS AND DISSEMINATION
Ethical approval is not required since this review will only include published data which already received ethical approval prior to publication.

Acknowledgements
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Contributors
Conception and design—F-MY and YR. Administrative support—F-MY. Provision of study materials or patients—Y-TW, CX and YR. Collection and assembly of data—Y-TW, CX and YR. Data analysis and interpretation—HT, XF and F-MY. Manuscript writing—all authors. Final approval of manuscript—all authors.

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Competing interests
None declared.

Patient consent for publication
Not required.

Provenance and peer review
Not commissioned; externally peer reviewed.

Supplemental material
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REFERENCES
Reporting checklist for protocol of a systematic review and meta analysis.

Based on the PRISMA-P guidelines.

**Instructions to authors**

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-P reporting guidelines, and cite them as:


<table>
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<th>Reporting Item</th>
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<td>If registered, provide the name of the registry (such as PROSPERO) and registration number</td>
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<td>Authors</td>
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<tr>
<td>Authors</td>
<td>Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author</td>
</tr>
<tr>
<td>Contribution #3b</td>
<td>Describe contributions of protocol authors and identify the guarantor of the review</td>
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<td>Amendments #4</td>
<td>If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments</td>
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<td>Support Sources #5a</td>
<td>Indicate sources of financial or other support for the review</td>
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<td>Sponsor #5b</td>
<td>Provide name for the review funder and / or sponsor</td>
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<tr>
<td>Role of sponsor or funder #5c</td>
<td>Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol</td>
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<td>Introduction Rationale #6</td>
<td>Describe the rationale for the review in the context of what is already known</td>
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<tr>
<td>Objectives #7</td>
<td>Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)</td>
</tr>
<tr>
<td>Methods Eligibility criteria #8</td>
<td>Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review</td>
</tr>
<tr>
<td>Information sources #9</td>
<td>Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage</td>
</tr>
<tr>
<td>Search strategy #10</td>
<td>Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated</td>
</tr>
<tr>
<td>Study records - #11a</td>
<td>Describe the mechanism(s) that will be used to manage</td>
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**data management**

**Study records - selection process**

State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis) 10-11

**Study records - data collection process**

Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators 11

**Data items**

List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications 11

**Outcomes and prioritization**

List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale 9-10

**Risk of bias in individual studies**

Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis 11-12

**Data synthesis**

Describe criteria under which study data will be quantitatively synthesised 12

**Data synthesis**

If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I², Kendall’s τ) 12

**Data synthesis**

Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) 12-13

**Data synthesis**

If quantitative synthesis is not appropriate, describe the type of summary planned 12-13

**Meta-bias(es)**

Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies) 12-13
Confidence in cumulative evidence

12-13

Describe how the strength of the body of evidence will be assessed (such as GRADE)

The PRISMA-P elaboration and explanation paper is distributed under the terms of the Creative Commons Attribution License CC-BY. This checklist was completed on 26 April 2021 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai
PRISMA flow chart for the primary literature selection process

1. Identification
   - Records identified through database searching (n=)
   - Additional records identified through other sources (n=)

2. Screening
   - Records after duplicates removed (n=)
   - Records excluded by title and abstract (n=)

3. Eligibility
   - Records screened (n=)
   - Full-text articles assessed for eligibility (n=)
   - Full-text articles excluded with reasons (n=)
   - Studies included in qualitative synthesis (n=)

4. Included
   - Studies included in qualitative synthesis (meta-analysis) (n=)
Supplementary Search Strategies

**Embase**

#1: 'Stomatitis'/exp

#2: 'Stomatitis':ab,ti OR 'Stomatitides':ab,ti OR 'Oral Mucositis':ab,ti OR 'Oral Mucositides':ab,ti OR 'Mucositides, Oral':ab,ti OR 'Oromucositis':ab,ti

#3. #1 OR #2

#4: 'Hangeshashinto':ab,ti OR 'TJ-14':ab,ti OR 'Banxia Xiexin':ab,ti OR 'Banxiaxiexin ':ab,ti OR 'Ban Xia Xie Xin':ab,ti OR 'Banha-Sasim-Tang':ab,ti OR 'Pinellia Heart-draining':ab,ti OR 'Pinellia Decoction for Draining the Heart':ab,ti

# 5: #3 AND #4

**Cochrane Library**

#1: MeSH descriptor: [Stomatitis] explode all trees

#2: (Oral Mucositis): ti, ab, kw

#3: (Hangeshashinto): ti, ab, kw OR (TJ-14): ti, ab, kw OR (Banxia Xiexin): ti, ab, kw OR (Banha-Sasim-Tang): ti, ab, kw OR (Pinellia Heart-draining): ti, ab, kw OR ('Pinellia Decoction for Draining the Heart): ti, ab, kw

#4: #1 OR #2

#5: #3 AND #4

**CNKI/Wan-Fang Database**

Strategy in Chinese phonetic alphabet (ie., Pinyin):
SU=terms which refer to title, abstract or key word.

（SU=“banxiaxiexintang”） and (SU=“kouqiangnianmoyan” or SU=“kouqiangyan” or
SU=“kouqiangkuiyang” or SU=“kouyan”) and (SU=“suijiduizhaoshiyan” or
SU=“linchuangguancha” or SU=“suiji” or SU=“shiyian” or SU=“linchuangshiyan”)

SU=字段（题目、摘要或关键词）

（SU=“半夏泻心汤”） and (SU=“口腔黏膜炎” or SU=“口腔炎” or SU=“口腔溃疡”
or SU=“口炎”) and (SU=“随机对照试验” or SU=“临床观察” or SU=“随机” or SU=“试验” or SU=“临床试验”)

**CiNii and Ichushi-web Database**

Oral Mucositis AND Hangeshashinto (in Japanese)