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A systematic review on Chinese herbal treatment for radiotherapy-induced xerostomia in head and neck cancer patients

Running title: Review of Chinese herbs for xerostomia

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Abstract

**Background:** Over 80% of head and neck cancer patients suffer from radiotherapy-induced xerostomia (dry mouth). Xerostomia affects cancer patients’ quality of life, and xerostomia sometimes persists throughout the patients’ lifetime. This review aimed to evaluate the effectiveness and safety of Chinese herbs in relieving radiotherapy-induced xerostomia.

**Methods:** Systematic searches were conducted on 6 databases (English and Chinese). Studies published up till May 2017 were considered for inclusion.

**Results:** A final 14 RCTs (total 994 head and neck cancer patients undergoing radiotherapy) compared Chinese herbs with no herbs, were included in analysis. Very low to moderate quality of evidence found Chinese herbal treatment may relieve radiotherapy-induced xerostomia and other related complications (such as oral mucositis and loss of appetite) in head and neck cancer patients.

**Conclusion:** There is limited evidence that Chinese herbal treatment may relieve radiotherapy-induced xerostomia and other related complications in head and neck cancer patients.

**Word count:** 148 words

**Keywords:** Chinese herbal drugs; xerostomia; radiotherapy; head and neck neoplasms; meta-analysis
1. Introduction

Over 80% of head and neck cancer patients who have received radiotherapy suffer from radiotherapy-induced xerostomia (dry mouth) [1]. Xerostomia affects cancer patients’ quality of life by altering their taste which leads to loss of appetite [1], interrupting their sleep (due to the frequent need of drinking water) [2, 3] and makes routine activities such as chewing and swallowing a laborious task [1, 3]. Often, xerostomia persists well beyond radiotherapy and sometimes throughout the patients’ lifetime [3].

Pharmacologic treatment such as pilocarpine has been shown to transiently improve xerostomia symptoms [4, 5]. Moreover, pilocarpine causes some adverse effects such as sweating, headache, urinary frequency, and worsening cardiac and respiratory functions in patients with cardiovascular and respiratory diseases [4, 6]. Available non-pharmacologic interventions, namely oral lubricants/saliva substitutes are reported to provide only transient and partial relief for xerostomia symptoms [4].

Complementary therapy, such as acupuncture and Chinese herbal medicine, have been used variably in the management of radiotherapy-induced xerostomia. Guideline developers such as the National Comprehensive Cancer Network [7] and the Chinese Medical Association [8] have respectively included acupuncture and Chinese herbal medicine as part of the management recommendations. Controlled trials [9, 10] suggested that Chinese herbs can alleviate radiotherapy induced xerostomia, but to-date there is no systematic review to synthesise the findings of these trials to better
inform practice and direct future research. This systematic review aimed to evaluate the effectiveness and safety of Chinese herbs in relieving radiotherapy-induced xerostomia.

2. Methods

2.1 Literature search strategy

We performed a systematic search in May 2017 to identify studies using Chinese herbs to alleviate radiotherapy-induced xerostomia. The 6 databases – PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, AMED, CINAHL and China National Knowledge Infrastructure (CNKI) – and ongoing clinical trials (www.controlled-trials.com and clinicaltrials.gov) were searched from inception onwards. We contacted expert for guidance on review development and search terms. We did not contact any expert to identify additional trials that were potentially eligible. The following combination of MeSH terms and keywords were used: (‘xerostomia’ or ‘dry mouth’ or ‘asialia’ or ‘salivary gland hypofunction’ or ‘radioxerosomia’) and (‘drugs Chinese herbal’ or ‘Medicine Chinese Traditional’ or ‘plants medicinal’ or ‘plant extracts’ or ‘Chinese herbal medicine’ or ‘Chinese herbal drug’ or ‘Chinese drug plant’ or ‘medicinal plant’ or ‘plant preparation’ or ‘plant extract’ or ‘materia medica’) and (‘neoplasm’ or ‘tumor’ or ‘neoplasia’ or ‘cancer’). English and Chinese language journals were considered for this review.

2.2 Inclusion and exclusion criteria

Studies that satisfied the following criteria were included: i) randomized controlled trials, ii) Population: patients diagnosed with head and neck cancer, having received radiotherapy with/without chemotherapy, iii) Intervention: oral Chinese herbs either
alone or in combination with other treatment, iv) Outcome: severity of radiotherapy-induced xerostomia, evaluated by any means. We excluded the following types of studies: i) non-randomised controlled trials, animal studies and in-vitro studies, ii) studies that evaluated xerostomia caused by other conditions (e.g. Sjogren’s Syndrome), iii) Chinese herbs used to manage other cancer related symptoms and not xerostomia, iv) studies that were otherwise relevant but without including severity of radiotherapy-induced xerostomia as an outcome.

Primary outcomes were both acute (occur < 90 days after started radiotherapy) and late xerostomia effects (occur ≥ 90 days after radiotherapy started) [11]. Xerostomia may be evaluated using validated measurement scale (such as Toxicity Criteria of Radiation Therapy Oncology Group (RTOG), World Health Organization (WHO)), visual analog scale (VAS), measuring salivary flow or study participants subjective self-assessment of the treatment progress (i.e. improved, no change or worse than baseline). Secondary outcome was the effect of herbs on other radiotherapy’s adverse effects, study participants’ Quality of Life (QoL) or their tumour response following herbal treatment.

2.3 Data Extraction
Duplicated search results were first removed. Two authors independently screened through title and abstracts for relevant studies. Two authors screened the full text of the identified relevant studies, extracted data of the included studies and determined their risk of bias. The extracted data included: study characteristics, information relating to
the risks of bias and data for each outcome. The extracted data were cross-checked by another co-author for accuracy. Any disagreement was resolved by discussion. When there were two or more studies that were sufficiently similar in terms of patient characteristics, intervention, comparison and outcomes, meta-analysis was performed using the Review Manager (RevMan 5.3) software. Two authors rated the quality of evidence for each major outcome via the GRADE approach [12] using the online GRADEPRO platform. We displayed the quality of evidence using the “Summary of Findings” table [13].

3. Results

The search yielded a total of 1,202 studies as in Figure 1. Screening through title and abstracts shortlisted 28 studies. Though full text review included 20 eligible studies, however data from 5 studies were not included in the analysis. A final total of 15 studies were included for analysis.
Figure 1. Study flow diagram.

3.1 Included studies

Included studies were published between 2004 and 2016 and all evaluated herbs as an adjunctive treatment in alleviating the radiotherapy-induced xerostomia, except for 1 study [14] which compared the effect of 2 herbs in relieving the xerostomia (Ma 2012; Table 1). Thirteen studies recruited predominantly or solely patients with
nasopharyngeal (NPC) cancer and 2 studies did not specify the cancer type of the population. With regards to the staging of cancer, 4 studies [15-18] recruited Stage III and IV cancer patients (Hu 2011, Huang 2013, Wei 2009 and Yang 2014) and staging information had not been provided in the other studies. Across the included studies, only Huang 2013 [16] and Wei 2009 [17] used the same herbal intervention (i.e. Zhong Jie Feng). Study participants’ xerostomia was mainly assessed using the Visual Analog Scale (VAS; 4 studies) and the RTOG grading (4 studies) Table 1.

The included studies mostly used Mai Men Dong (Tuber Ophiopogonis Japonici; 11 studies), Dang Shen (Radix Codonopsis Pilosulae; 8 studies), Sheng Di Huang (Radix Rehmaniae; 7 studies) and Xuan Shen (Radix Scrophulariae Ningpoensis; 7 studies).
### Table 1. Characteristic of studies included in the systematic review.

<table>
<thead>
<tr>
<th>First author</th>
<th>Year of publication</th>
<th>Type of head and neck cancer</th>
<th>Cancer staging</th>
<th>Radiotherapy dose (Gy)</th>
<th>Intervention</th>
<th>Xerostomia assessment tool</th>
<th>Other outcome assessed</th>
<th>Adverse event from radiotherapy</th>
<th>QoL</th>
<th>Tumor Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hao, Q. 19</td>
<td>2016</td>
<td>Nasopharyngeal (NPC), oral, tongue, throat, sinus</td>
<td>Unspecified</td>
<td>60 - 68</td>
<td>Yu Nu Jian formula, OD taken from radiotherapy started till ended</td>
<td>Wang Zhong He and Guo Gao 2012 grading</td>
<td>Oral mucositis</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Hu, Y.R. 20</td>
<td>2004</td>
<td>NPC, tonsil, tongue</td>
<td>I-IV</td>
<td>36 - 70</td>
<td>Shen Qi Fang Hou formula, BD, taken from radiotherapy started till ended</td>
<td>Researcher own grading</td>
<td>Hardening of neck muscle</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Hu, X.M. 21</td>
<td>2011</td>
<td>NPC, oral, larynx, hypopharynx, nasal and sinus</td>
<td>III – IV</td>
<td>40 - 75</td>
<td>Yang Yin Jie Du Tang formula, BD during radiotherapy</td>
<td>Presence of xerostomia</td>
<td>Nausea and vomiting, fatigue, leukopenia, loss of appetite</td>
<td>√</td>
<td>√</td>
<td>---</td>
</tr>
<tr>
<td>Huang, D.N. 16</td>
<td>2013</td>
<td>NPC</td>
<td>III - IV</td>
<td>56-66</td>
<td>Zhong Jie Feng , OD, taken from 3 day pre-radiotherapy till radiotherapy ended</td>
<td>RTOG grading</td>
<td>Oral mucositis, dermatitis at neck</td>
<td>---</td>
<td>√</td>
<td>---</td>
</tr>
<tr>
<td>Jiang, Z.X. 21</td>
<td>2005</td>
<td>NPC, oral, tonsil, parotid, metastasis to neck (unknown origin)</td>
<td>Unspecified</td>
<td>60 - 70</td>
<td>Tian Men Dong, Mai Men Dong, Dang Shen, Sha Shen, Yuan Shen, Dan Sen, Sheng Di Huang, taken 60 ml TDS. Administration time was unspecified</td>
<td>Researcher own grading</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td>Jiang, Z.X. 22</td>
<td>2006</td>
<td>NPC, tonsil</td>
<td>Unspecified</td>
<td>60 - 70</td>
<td>Sheng Jin formula, TDS, taken from radiotherapy started till ended</td>
<td>Salivary flow (time needed to wet the filter paper)</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td>Li, H. 22</td>
<td>2009</td>
<td>NPC, oral</td>
<td>Unspecified</td>
<td>60 - 70</td>
<td>Xuan Mai Zeng Ye Hua Du</td>
<td>Salivary flow (time)</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Study</td>
<td>Year</td>
<td>Location</td>
<td>Grade</td>
<td>Duration</td>
<td>Treatment Details</td>
<td>Evaluation</td>
<td>Side Effects</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>10.</td>
<td>Wei, B. [17]</td>
<td>2009</td>
<td>NPC</td>
<td>III - IV</td>
<td>36 - 74</td>
<td>Zhong Jie Feng, OD, taken from 3 days pre-radiotherapy till radiotherapy ended</td>
<td>RTOG grading</td>
<td>Oral mucositis, leukopenia, loss of appetite</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Zhang, C.Y. [27] 2011 NPC I-IV 45 - 75 Qing Re Yang Yin formula, Jian Pi Yang Yin formula, Zi Shen Yang Yin formula were given based on Chinese medicine diagnosis. Taken from radiotherapy started for 6 months RTOG grading, VAS grading, presence of xerostomia


***All studies compared the effect between Chinese herbs and without Chinese herbs; except for Ma 2012 compared between 2 Chinese herbs (i.e. Qing Fei Yang Wei formula and Kang Fu Xin Ye)

OD = Once Daily, BD= Twice daily, TDS=Thrice daily

### Table 2. Study design of the included studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of participants</th>
<th>Study design</th>
<th>Study duration</th>
<th>Assessed time point of xerostomia</th>
<th>Intervention</th>
<th>Control treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Hao, Q. [19]</td>
<td>51 (27 CH, 24 control)</td>
<td>RCT</td>
<td>Whole RT course (49 days)</td>
<td>Week 2, 4, 6 during RT and post-RT</td>
<td>RT + Oral CH</td>
<td>RT</td>
</tr>
<tr>
<td>4. Huang, D.N. [16]</td>
<td>100 (50 CH, 50 control)</td>
<td>RCT</td>
<td>3 days pre-RT till RT ended</td>
<td>Post-RT</td>
<td>CT + RT + Oral CH</td>
<td>CT + RT</td>
</tr>
<tr>
<td>5. Jiang, Z.X.</td>
<td>108</td>
<td>RCT, placebo</td>
<td>6 months to 1 year</td>
<td>Post-RT</td>
<td>RT + Oral CH (during RT)</td>
<td>RT + Drink mineral</td>
</tr>
<tr>
<td>Study Number</td>
<td>Author/Surname</td>
<td>Year</td>
<td>Study Design</td>
<td>Course Duration</td>
<td>Treatment Details</td>
<td>Placebo (i.e. mineral water)</td>
</tr>
<tr>
<td>--------------</td>
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<td>-----------------------------</td>
</tr>
<tr>
<td>6</td>
<td>Jiang, Z.X.</td>
<td>(2005)</td>
<td>RCT, placebo control</td>
<td>Whole RT course</td>
<td>Pre-RT, at RT dose 20Gy, 40Gy, 60Gy</td>
<td>RT + Oral CH</td>
</tr>
<tr>
<td>7</td>
<td>Li, H.</td>
<td>(2006)</td>
<td>RCT, placebo control</td>
<td>Unspecified</td>
<td>Pre-RT, at RT dose 20Gy, 40Gy, 60Gy, 70Gy</td>
<td>RT + Oral CH (during RT)</td>
</tr>
<tr>
<td>8</td>
<td>Liu, Y.H.</td>
<td>(2007)</td>
<td>RCT</td>
<td>1 year</td>
<td>Pre-RT, post-RT, 1 year post-RT + Oral CH (for 30 days)</td>
<td>RT + Nursing intervention</td>
</tr>
<tr>
<td>9</td>
<td>Ma, X.Y.</td>
<td>(2008)</td>
<td>RCT</td>
<td>Whole RT course</td>
<td>Week 2, 4, 6 during RT and post-RT</td>
<td>RT + Oral CH</td>
</tr>
<tr>
<td>10</td>
<td>Wei, B.</td>
<td>(2009)</td>
<td>RCT</td>
<td>3 days pre-RT till RT ended</td>
<td>Post-RT</td>
<td>CT + RT + Oral CH</td>
</tr>
<tr>
<td>11</td>
<td>Wu, X.</td>
<td>(2010)</td>
<td>RCT</td>
<td>1st day RT till 30 days post-RT</td>
<td>RT dose 40Gy, 70Gy, 30 days post-RT</td>
<td>RT + Oral vitamin C 1g + Oral CH</td>
</tr>
<tr>
<td>12</td>
<td>Yang, H. Q.</td>
<td>(2011)</td>
<td>RCT</td>
<td>Unspecified</td>
<td>During RT</td>
<td>RT + Oral CH</td>
</tr>
<tr>
<td>13</td>
<td>Yin, L.H.</td>
<td>(2012)</td>
<td>RCT, placebo control</td>
<td>1st day RT till 28 days post-RT</td>
<td>Once weekly since started RT</td>
<td>RT + Oral CH</td>
</tr>
<tr>
<td>14</td>
<td>Zhang, C.Y.</td>
<td>(2013)</td>
<td>RCT</td>
<td>1st day RT till 6 months post-RT</td>
<td>Unspecified</td>
<td>RT + Oral CH</td>
</tr>
<tr>
<td>15</td>
<td>Zhang, Y.X.</td>
<td>(2014)</td>
<td>RCT</td>
<td>Whole RT course</td>
<td>Pre-RT, at RT dose 10Gy, 20Gy, 40Gy, 60Gy</td>
<td>RT + Oral CH</td>
</tr>
</tbody>
</table>

Placebo (i.e. mineral water) were used in 3 studies and blinding were unspecified in all the studies.

CH = Chinese herbal, CT = Chemotherapy, RCT=Randomised control trial, RT = Radiotherapy
3.2 Risk of bias among the included studies

All of the studies included in this review had at least one criterion with unclear or high risk of bias (Figure 2). As for performance bias, only Jiang 2006 scored low risk of bias while the remaining studies had high risk of bias (Figure 3).

Figure 2. Risk of bias graph: review authors’ assessment on each risk of bias item across all included studies (presented as percentage).

![Risk of bias graph](image)

Figure 3. Risk of bias summary: review authors’ assessment on each risk of bias item.
<table>
<thead>
<tr>
<th></th>
<th>Random sequence generation (selection bias)</th>
<th>Allocation concealment (selection bias)</th>
<th>Blinding of participants and personnel (performance bias)</th>
<th>Blinding of outcome assessment (detection bias)</th>
<th>Incomplete outcome data (attrition bias)</th>
<th>Selective reporting (reporting bias)</th>
<th>Other bias</th>
</tr>
</thead>
</table>
3.3 Analyses findings

Though all 20 included studies assessed xerostomia as the primary end-point, results of some studies were not included in the qualitative analysis for the following reasons: i). Unextractable or unsuitable data to be pooled: 2 studies [9, 29]; ii). The use of non-validated method of assessing salivary flow: 1 study [30]; iii). Head to head comparisons between 2 herbs: 1 study [14]; iv) secondary publication of earlier studies: 2 studies [10, 31].

Chinese herbs improved the salivary flow more than no herbs (MD -14.40, 95% CI -25.73, -3.07; $I^2$=71%, P=0.07, quality of evidence: moderate) based on data on 73 participants from 2 studies. As the heterogeneity was substantial, the results were analysed using random-effect model and the quality of evidence was downgraded for the same reason (Table 2). Fewer participants who received Chinese herbs had severe xerostomia post-radiotherapy (RR 0.42, 95% CI 0.32, 0.56; $I^2$=21%, P=0.28, quality of evidence: moderate) based on data on 404 participants from 6 studies (Table 2).

Table 3. Summary of findings for the main outcome.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Relative effect (95% CI)</th>
<th>No. of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salivary flow (time needed to wet the filter paper in seconds, assessed at 20Gy)</td>
<td>MD -14.40 (-25.73, -3.07)</td>
<td>73 (2 RCTs)</td>
<td>⧫⧫⧫◯ Moderate$^1$</td>
</tr>
<tr>
<td>Severe xerostomia different scales (during radiotherapy)</td>
<td>RR 0.60 (0.21 to 1.73)</td>
<td>115 (2 RCTs)</td>
<td>⧫⧫⧫◯◯◯ Very Low$^2$</td>
</tr>
<tr>
<td>Severe xerostomia different scales (post-radiotherapy)</td>
<td>RR 0.42 (0.32 to 0.56)</td>
<td>404 (6 RCTs)</td>
<td>⧫⧫⧫◯◯ Moderate$^3$</td>
</tr>
</tbody>
</table>
Severe oral mucositis different scales (post-radiotherapy) | RR 0.34 (0.25 to 0.45) | 431 (6 RCTs) | ⨁⨁⨁◯
---|---|---|---
Severe loss of appetite assessed with CTCAE grading (post-radiotherapy) | RR 0.17 (0.07 to 0.42) | 126 (2 RCTs) | ⨁⨁◯

CI: Confidence interval; MD: Mean difference; RR: Risk ratio
GRADE Working Group grade of evidence
High: It is very likely that the effect will be close to what was found in the research.
Moderate: It is likely that the effect will be close to what was found in the research, but there is a possibility that it will be substantially different.
Low: It is likely that the effect will be substantially different from what was found in the research, but the research provides an indication of what might be expected.
Very low: The anticipated effect is very uncertain and the research does not provide a reliable indication of what might be expected.

1 Quality of body evidence is downgraded due to substantial heterogeneity ($I^2 = 71\%$).
2 Quality of body evidence is downgraded due to imprecision (confidence interval included the null effect) and risk of bias (high risk of performance bias).
3 Quality of body evidence is downgraded due to risk of bias (high risk of performance bias).

4. Discussion
A final 14 studies (total 994 participants undergoing radiotherapy) compared Chinese herbs with no herbs, and 6 studies reported outcome data at similar assessment time-point and thus were suitable for meta-analysis. Though this review only included RCTs, the randomization method, measures to achieve allocation concealment and blinding of outcome assessment were not clearly stated in the studies. Consequently, all included studies had unclear risk of selection bias; and almost all had unclear risk of detection bias. Only Jiang (2006) scored low risk of performance bias as the xerostomia was assessed with salivary flow rate which was unaffected by the unblinded participants and personnel, while the remaining studies had high risk of bias.

The quality of evidence ranged from moderate to very low across the outcomes. The major factor that led to downgrading of quality of evidence was the risk of bias issues in the conduct of the study, in particular, unblinded participants and personnel, which was likely to
bias the assessment of subjective outcome (such as participants self-assessed absence/presence of xerostomia and grading their xerostomia severity using RTOG, VAS scale).

Chinese herbal medicine has been used in managing radiotherapy-induced complications, particularly xerostomia. Hospitals in China [32] and Taiwan [33] provide Chinese herbal to patients pre-, concurrent, and/or post-radiotherapy to prevent/reduce the side effects of xerostomia. The included studies mainly used Mai Men Dong (Tuber Ophiopogonis Japonici) in line with findings of an animal study of improved salivary secretion. The proposed mechanism of action is Mai Men Dong stimulates the transcellular fluid movement and secretion at secretory acinar cells [34]. Based on Chinese medicine concept, practitioners prescribe herb according to pattern differentiation (i.e. focusing certain pattern instead of a disease or a symptom) [32, 35]. Considering the differed characteristics of Chinese medicine than Western medicine, Liu et al have outlined the method in planning good quality Chinese medicine RCTs. For example, as herb are prescribed based on pattern differentiation, though it is difficult to blind the practitioners, detection bias can be minimized by blinding the outcome assessors and data analyzer [35].

The occurrence of radiation-induced xerostomia is multifactorial, depending on concurrent chronic conditions (e.g. Sjogren’s syndrome, sarcoidosis) [36], concurrent medicine [36], cancer staging [37], and radiation therapy (e.g. radiation dose, radiotherapy modalities) [1]. Though all included studies stated the total radiotherapy dose, we suggest that future studies on radiotherapy-induced xerostomia should describe the radiotherapy dose given to the major salivary gland (i.e. parotid gland) and types of radiotherapy modalities (e.g. Intensity-
modulated radiotherapy (IMRT), conventional radiotherapy). Patients who received lower radiotherapy dose to their major salivary glands (e.g. lower radiotherapy dose to the parotid gland, had parotid-sparing IMRT intervention), had less severe xerostomia [4, 38, 39].

Earlier reviews had: i). Focused on xerostomia resulting from non-cancer condition (e.g. Sjogren’s syndrome [40]; ii). Reviewed general management of radiotherapy-induced xerostomia [37, 42]. For example, Mercadante (2017) review on general management of radiotherapy-induced xerostomia was based on English databases and included one herbal study, i.e. Ameri et al (2016). Ameri et al (2016) examined the efficacy of the traditional Persian herbal and artificial saliva in relieving the xerostomia symptom [42]. Comparatively, this current review focused on radiotherapy-induced xerostomia, excluded studies using non-Chinese herbal medicine (e.g. Ameri 2016 [43]) and extended the searches to the Chinese database.

We searched for RCT at several electronic databases and included English and Chinese published studies. However, non-inclusion of the following studies may limit the scope of this review and generalizability of the pooled findings: i). Studies that used different measurement of xerostomia severity than other studies (such as assessing xerostomia using Uptake Rate and Excretion Rate [9]); ii). Studies with unextractable data/unsuitable data to be pooled; iii). Studies that used herbs that were not based on Chinese medicine concept (e.g. comparing ginger extract and placebo on post-radiotherapy head and neck cancer patients [44]. Another limitation of this review was hand searching for relevant symposia, conference proceedings was
not performed, although we believed that having searched the published literature extensively, 
the likelihood of having substantial additional evidence through hand-searching is low.

5. Conclusion
In conclusion, there is limited evidence that Chinese herbal treatment may relieve radiotherapy-
induced xerostomia and other related complications (such as oral mucositis and loss of 
appetite) in head and neck cancer patients.

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A systematic review on Chinese herbal treatment for radiotherapy-induced xerostomia in head and neck cancer patients

Highlights:

- A systematic review and meta-analysis of 14 randomised controlled trials.
- Chinese herbs were evaluated as an adjunct for head and neck cancer patients.
- Low-to-moderate quality evidence showing modest benefits in relieving xerostomia.

Character count with spaces for “Highlights”:

- 1\textsuperscript{st}: 75
- 2\textsuperscript{nd}: 79
- 3\textsuperscript{rd}: 83