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## **Adjuvant phytotherapy in the treatment of cervical cancer: a systematic review and meta-analysis**

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### **Short Title:**

Adjuvant phytotherapy for cervical cancer

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## **Abstract**

**Objective:** Clinical trials have investigated phytotherapy (PT) in the treatment of cervical cancer. This study aimed to assess the quality and data of current available trials, to compare the efficacy and safety of conventional therapies (CT) including surgical therapy, radiotherapy and chemotherapy with that of CT plus PT (CT-PT), and to identify herbs used commonly in clinical trials.

**Method:** 43 electronic databases were searched. The quality of eligible trials was assessed by Jadad's scale, and the Revman 5.0 software was used for data syntheses and analyses.

**Result:** (1) Of the 48 potential trials retrieved, 18 trials involving 1657 patients met the inclusion criteria, and two trials were graded as high-quality trials; (2) CT-PT achieved a higher 1-year survival rate (SR,  $P=0.0002$ ) and tumor remission rate (TRR,  $P<0.0001$ ) than CT alone; (3) PT showed therapeutic effects comparable to those of Western medications in diminishing vesical complications (VC,  $P<0.0001$ ) and rectal complications (RC,  $P=0.08$ ) caused by CT; (4) top 15 herbs used frequently to improve SR or TRR and to treat VC or RC in the retrieved trials were identified.

**Conclusion:** Adjuvant PT may improve the efficacy and safety of CT in clinical treatments of cervical cancer, although this result needs to be further verified by more high-quality trials.

**Keywords:** Phytotherapy—Cervical cancer—Systematic review—Meta-analysis

## Introduction

Cervical cancer is the most common malignant tumor threatening women especially those over 40 years old.<sup>1</sup> Worldwide deaths due to cervical cancer are about 0.25-million each year, and may increase 25% in the following ten years.<sup>2</sup> Current conventional therapies (CT) including surgical therapy, radiotherapy, chemotherapy, hormone therapy and others may be helpful to treat patients at the early-stage of cancer, but so far it is still very difficult to cure advanced-stage patients especially those with cancer relapse or metastasis. Moreover, CT may result in significant adverse effects such as about 16% patients who were treated with radiotherapy may develop rectal complications.<sup>3</sup> Searching for more effective and safer therapies to treat cervical cancer as well as other cancers is one of the important targets in oncologic studies.

Phytotherapy (PT) has been used to treat woman malignant tumors for thousands of years in China and some other countries. During the past decades, a number of clinical trials have been conducted to investigate the values of natural herbs in the treatment of cervical cancer. In present study we performed a systematic review and meta-analysis to (1) assess the quality and data of retrieved trials, (2) compare the therapeutic effects and adverse effects of CT plus PT (CT-PT) to those of CT alone in clinical treatments, (3) compare the effects of PT to those of Western medications (WM) in the treatment of vesical and rectal complications caused by CT, and (4) identify herbs used commonly in clinical trials. We hypothesized that the adjuvant PT might play a valuable role in the treatment of cervical cancer by increasing efficacy and safety of CT; and certain natural herbs and their effective components should become new reagents in future preclinical and clinical studies to overcome cervical cancer.

## Methods

### *Inclusion and exclusion criteria*

All randomized controlled trials (RCTs) and controlled clinical trials (CCTs)<sup>4</sup> that compared the effects and/or adverse events of CT-PT with those of CT alone were included. Meanwhile, all RCTs and CCTs that compared the effects of PT alone or PT plus WM (PT-WM) to WM alone in the treatment of vesical complications (VC) and rectal complications (RC) caused by CT were also included. Eligible participants were the women with clear diagnosis of cervical cancer confirmed by histopathological examinations.<sup>5</sup> There was no restriction on the stage and duration of cancer, or age and race of patients. In the treatment group, interventions included any treatment of CT-PT or PT alone or PT-WM at any dosage, while patients in control groups were treated with CT or WM alone. Trials in which patients received non-oral PT treatments such as injection and local use would be excluded. The outcome measurements were mainly based on the number/percentage of patients whose survival rate (SR) or tumor remission rate (TRR) was improved and VC or RC caused by CT was diminished.

#### *Searching strategy and database*

A search strategy was designed to retrieve all the literatures of relevant clinical trials by electronic searching and hand searching regardless of language and publication status. According to suggestions of the Cochrane Gynaecological Cancer Group and Cochrane Complementary Medicine Field,<sup>6,7</sup> keywords “cervical cancer”, “phytotherapy”, “clinical trials” and their synonyms such as cervical carcinoma, cervical tumor, uterine cancer, woman cancer, uterine bleeding, phytomedicine, plant medicine, plant drug, herbal therapy, herbal medicine, herbal preparation, Chinese medicine, Chinese herbal medicine, medical plant, etc. were applied during paper searching.

Forty-three electronic databases<sup>8-10</sup> including the Cochrane Central Register of Controlled Trials, MEDLINE, CINAHL, AMED, VIP Chinese Science and Technology Periodical Database, Wanfang Chinese Scientific Journal Database, CBMdisc, China National Knowledge Infrastructure, Traditional Chinese Medicine Database, Chinese Medical Current Contents, China Proceedings of Conference Databases, and China Doctorate/Master Dissertations Full Text Databases, etc. were searched. Meanwhile, other databases including WorldCat, MetaPress,

SpringerLink, Oxford Journals Online, Blackwell Synergy, ScienceDirect, ProQuest, and so on were also searched. The reference lists of retrieved papers were checked for finding any potential clinical trials matching the inclusion criteria. In addition, hand searching was carried out to explore newest papers or other publications in the libraries of Hong Kong Baptist University and Guangzhou University of Chinese Medicine until the latest copy available to June 2008.

#### *Data extraction and analysis*

According to the inclusion and exclusion criteria, full-text articles of eligible trials were retrieved and assessed by two independent reviewers (Min Xu and Chen Qi). Key information was extracted by one reviewer and confirmed by the other reviewer. Missing information was sought by contacting article authors. Meta-analyses were carried out using the Review Manager 5.0 (Cochrane software) to synthesize and analyze the data of individual trials. The statistical validity of combining various trials was assessed by examining the homogeneity in a Q-test (Mantel-Haenszel Chi-square test). Possible sources of heterogeneity were further assessed in subgroup analyses. Overall results of synthetic trials were calculated with a fixed-effect model, and the data were present as odd ratio (OR) and 95% confidence interval (95% CI). The methodological quality of included trials was assessed by Jadad's scale,<sup>11</sup> which assessed randomization, double-blinding and dropout rate of the trials by ranking them with 1-5 points. The trials scored with 1-2 points were considered as low-quality trials, whereas those scored with 3-5 points were considered as high-quality trials.

## **Results**

#### *Excluded and included trials*

The literature searching found 45 trials published in China and 3 trials published in Japan, Thailand and Germany. However, 30 trials of them were excluded as they did not meet the inclusion criteria including (1) inappropriate comparisons in the study design such as PT

compared to other PT (22 trials), and (2) unclear data reported in papers (8 trials). Finally, total 18 trials<sup>12-29</sup> involving 1657 patients were included for this systematic review and analysis (Table 1 and 2). 13 out of 18 trials reported the staging of cervical cancer,<sup>5</sup> among which 62.3% patients (834/1338 cases) classified as advanced stage (stage IIB and above). In addition, 10 out of 18 trials reported the histopathological types of cervical cancer, among which 96.0% patients (775/807 cases) were identified as squamous cell carcinoma, 3.6% patients (29/807 cases) were adenocarcinoma, and 0.4% patients (3/807 cases) were other types such as adenosquamous carcinoma. The other 8 trials did not provide patients' histopathological type although all participants had clear diagnosis confirmed by histopathological examinations.

### *Outcome measurement*

In the 18 included trials, SR was reported by 6 trials,<sup>12-17</sup> in which 1-, 2-, 3-, 5- and 10-year SR were reported by 4, 1, 2, 2 and 1 trials respectively (Table 3). TRR was also reported by 5 trials.<sup>17-21</sup> TRR was a percentage by calculating the number of patients whose tumor disappeared or reduced more than 50% after treatments. In these 10 included trials for SR and TRR analyses, 920 patients were involved, and 90.7% patients (834/920 cases) were classified as advanced stage of cervical cancer (stage IIB and above). Total 452 patients were treated with CT-PT, whereas 468 patients were treated with CT alone. In addition, the therapeutic effects of PT for diminishing VC or RC caused by CT were reported in 8 trials<sup>22-29</sup> and 386 patients in these trials were treated with PT alone or PT-WM, whereas 351 patients were treated with WM alone. Other endpoints were reported in the included trials such as patients' immune function, quality of life, adverse events occurred during treatments, etc., but these data were insufficient to conduct a meta-analysis.

### *Efficacy and safety assessment*

#### **(1) CT-PT vs. CT alone for improving SR and TRR**

Figure 1 (01) showed a meta-analysis on the 1-year SR of 427 patients involved by 4 included trials. The result of analysis using a fixed-effect model indicated that 1-year SR of 207

patients treated with CT was 83.1% (172/207 cases); whereas SR of 220 patients treated with CT-PT was 94.5% (208/220 cases), and was significantly higher than CT alone (OR=4.16; 95% CI: 1.97, 8.78; P=0.0002). No heterogeneity presented in data synthesis and analysis (P=0.41). Original data of included trials also indicated that the 2-, 3-, 5- and 10-year SR in patients treated with CT-PT were significantly higher than those in patients treated with CT alone (P<0.005 to P<0.05), although available data were insufficient to conduct a meta-analysis (Table 3).

Figure 1 (02) showed a meta-analysis using fixed-effect model on the TRR reported by 5 included trials in which 281 patients were involved. The result indicated that 99 out of 141 patients (70.2%) were significantly improved after CT treatments; whereas 122 out of 140 patients (87.1%) showed a significant improvement after CT-PT treatments, and the percentage was higher than CT alone (OR=5.12; 95% CI: 2.28, 11.50; P<0.0001). No heterogeneity presented in the data synthesis and analysis (P=0.37).

Besides SR and TRR, other endpoints were reported in the included trials such as immune function including CD4/CD8, T4/T8, NK cell, etc.,<sup>18,19</sup> radiotherapy dose,<sup>18</sup> vaginal bleeding,<sup>20</sup> quality of life<sup>19</sup> and adverse events occurred during treatments such as poor appetite, nausea, vomiting, stomachache, intestinal mucositis, diarrhea, low hemoglobin, low leucocytes or platelets, etc.<sup>16,19,20,21</sup> Basically, original data reported from most included trials indicated that CT-PT or PT alone was more effective and safer than CT or WM alone.

## (2) PT or PT-WM vs. WM alone for diminishing VC and RC

Figure 2 (01) showed a meta-analysis on the data of 4 included trials that compared PT or PT-WM to WM alone in diminishing VC. The result of analysis using a fixed-effect model indicated that 190 out of 232 patients (81.9%) were improved after treatments with WM alone; whereas 229 out of 243 patients (94.2%) treated with PT or PT-WM were improved, and the percentage was significantly higher than that of WM alone (OR=3.61; 95% CI: 1.92, 6.79; P<0.0001). No heterogeneity presented in the data synthesis and analysis (P=0.59).



There were 4 trials to compare PT or PT-WM with WM alone in diminishing RC. Except Song's study, original data from 3 other trials suggested that PT or PT-WM was more effective than WM alone in diminishing RC ( $P < 0.05$  and  $P < 0.01$ ), and a meta-analysis for these 4 trials also favored PT or PT-WM (OR=3.64; 95% CI: 0.77, 17.24;  $P = 0.01$ ). However, a significant heterogeneity presented in the meta-analysis ( $P < 0.0009$ ). Figure 2 (02) showed a sub-group meta-analysis using fixed-effect model for the data from 3 included trials<sup>27-29</sup> without Tian's data,<sup>26</sup> and the result indicated that 68 out of 94 patients (72.3%) showed a significant improvement after WM treatments; whereas 77 out of 93 patients (82.8%) treated by PT or PT-WM showed a significant improvement, and the percentage was higher than WM alone (OR=1.87; 95% CI: 0.92, 3.80;  $P = 0.08$ ). No heterogeneity presented in the data synthesis and analysis ( $P = 0.12$ ).

### *Herbal analysis*

In all 48 trials retrieved by literature searching (both included and excluded RCTs or CCTs), natural herbs were orally used in 18 trials to improve patients' SR or TRR and in 9 other trials to diminish VC or RC caused by CT. Among herbs reported in 18 trials for improving SR and TRR, top 10 herbs used frequently were Radix Astragali (44.4%), Radix Ginseng (25.9%), Radix Angelicae Sinensis (25.9%), Poria (22.2%), Radix Glycyrrhizae (22.2%), Curcumae (22.2%), Rhizoma Pinelliae (22.2%), Rhizoma Atractylodis Macrocephalae (18.5%), Semen Coicis (18.5%) and Herba Scutellariae Barbatae (18.5%). Whereas, among herbs reported in 9 other trials for treating VC or RC, top 10 herbs used frequently were Poria (40.9%), Radix Glycyrrhizae (40.9%), Radix Paeoniae Alba (31.8%), Radix Angelicae Sinensis (27.3%), Rhizoma Chuanxiong (27.3%), Rhizoma Atractylodis Macrocephalae (22.7%), Ramulus Cinnamomi (22.7%), Radix Ginseng (18.2%), Cortex Moutan (18.2%) and Pericarpium Citri Reticulatae (18.2%). Five herbs in them i.e. Poria, Radix Glycyrrhizae, Radix Angelicae Sinensis, Rhizoma Atractylodis Macrocephalae and Radix Ginseng were the same herbs identified above for improving SR and TRR (Figure 3).

### *Quality assessment*

The assessment by Jadad's scale showed that two included trials were classified as high-quality trials (scoring 3 points),<sup>14,17</sup> and the rest were low-quality trials (scoring 1-2 points) owing to poor descriptions on randomization, double-blind method and dropout rate.<sup>12,13,15,16,18-29</sup>

## Discussion

This is the first systematic review and meta-analysis to assess the efficacy and safety of PT as an adjuvant therapy of CT in the treatment of cervical cancer. The results indicated that adjuvant PT might be beneficial to treat patients with cervical cancer clinically. Our assessment was based on 18 included trials that were conducted during the past decades. The strengths of this review included acceptable standard and methodology, as well as considerable sample size, by which we could perform statistical analyses properly and obtain current evidence for the research target. Moreover, additional evidence on the efficacy of PT obtained from many observational trials generally supported the results of included RCTs and CCTs in our review even though they had been excluded before data syntheses.

Staging is a key prognostic indicator for estimating SR of cancer patients. It has been reported that acceptable SR of about 70~100% could be achieved by CT treatments in the patients at stage IA~IIA, but only 50~70% could be achieved for patients at stage IIB, and even less for those at stage III or above.<sup>30</sup> Data analyses in this study showed that an average 1-year SR of 94.5% was obtained after CT-PT treatments, which was significantly higher than that in patients treated by CT alone (83.1%,  $P=0.0002$ ). Among these two group patients, 90.7% of them were classified as stage IIB or above. It suggests that adjuvant PT should be valuable to improve patients' SR, even those at advanced stages of cervical cancer.

Varied TRR were reported in previous clinical studies with different CT treatments. For example, radiotherapy may achieve a complete remission in 75% of patients that is similar to the included trials of our study.<sup>31</sup> Our analysis in present study showed that CT-PT treatments might achieve a higher TRR (87.1%) than CT alone (70.2%). Clinical trials also indicated that

combinations of various CT might not only increase tumor remission rates but also increase adverse events,<sup>32</sup> whereas in included trials of this review patients treated by CT plus PT had a high TRR but was not associated with any increase of adverse effects.

So far plentiful evidence has been cumulated on the effects of PT to treat cancers. Clinical trials showed that *Rhizoma Curcumae* could significantly improve clinical conditions in 77.2% patients (210/272 cases) with cervical cancer at stage I~II or in 46.2% patients (43/93 cases) at stage III~IV.<sup>33</sup> In addition, certain natural herbs including *Radix Astragali*, *Radix Ginseng*, *Radix Angelicae Sinensis*, *Rhizoma Curcumae*, *Poria*, *Radix Glycyrrhizae*, *Herba Scutellariae Barbatae*, *Rhizoma Atractylodis Macrocephalae*, *Semen Coicis*, etc. had been examined their anti-cancer effects and mechanisms in previous studies. *In vivo* and *in vitro* experiments found these herbs may (1) inhibit proliferation of tumor cells or directly kill tumor cells through inducing apoptosis and cytotoxicity, (2) enhance immune functions via activating megalophages and stimulating cytokines such as TNF- $\alpha$ , (3) reduce impairments and side effects induced by CT and WM, and (4) improve body rehabilitation by regulating system functions, nutrition conditions, and others.<sup>34-42</sup> These findings might partly explain the reasons why PT could improve the efficacy of CT in the clinical treatment of cervical cancer.

VC is one major side effect of radical hysterectomy<sup>43</sup> as nerve, ligament, and blood supply in pelvis are readily to be damaged during operations. The complications commonly include dysuria, nocturia, hydronephrosis and so on. In addition, longstanding bladder dysfunction may result in asymptomatic chronic cystitis.<sup>44</sup> So far there is no special medication to solve these problems except for preventing recurrent infections; other aspects such as suprapubic pressure or abdominal straining have been applied in postoperative women, but long-term straining may result in the development of prolapse.<sup>45</sup> In this review the percentage of improved patients with VC after PT or PT-WM treatments achieved 94.2% that was obviously higher than WM treatments (81.9%). PT therefore should be recommended as a practical way to treat patients with VC resulted from CT. Furthermore, it was reported that radiotherapy could cause VC in 10% patients with cervical cancer,<sup>46</sup> so it is possible to treat these patients with PT as well.

Rectal damage and dysfunction is one of the most common complications of radiotherapy in patients, and transient symptoms may appear in all patients after receiving radiation. The acute rectal damage commonly causes diarrhea, mucus discharge, tenesmus, anal pain or incontinence, and rectal bleeding; whereas chronic rectal damage is characterized by obliterative enteritis with ulceration and fibrous induration in gut.<sup>47</sup> The effect of WM such as topical anti-inflammatory reagents and steroids is unsatisfactory.<sup>48</sup> In our analysis the percentage of improved patients after PT treatments was 82.8% that was higher than that of WM treatments (72.3%), although the difference was not significant statistically ( $P=0.08$ ). As PT was more favorable than or at least comparable to WM in diminishing RC, it should also be recommended as a valuable approach to treat RC in patients.

Exact mechanisms of natural herbs to improve rectal and vesical functions are still unclear. There is some evidence of pharmacological studies indicating some possible roles of herbs in protection of rectal and vesical functions. For example, Rhizoma Atractylodis Macrocephalae, Radix Paeoniae Alba, Radix Glycyrrhizae and Pericarpium Citri Reticulatae could inhibit the gastrointestinal motility and decrease defecation in diarrhea models.<sup>49,50</sup> Radix Paeoniae Alba and Radix Glycyrrhizae could protect intestines via depressing abnormal myoelectricity changes induced by CT such as cisplatin.<sup>51</sup> Radix Ginseng might also influence intestinal function via regulating nitric oxide, an inhibitory factor to smooth muscle of rectum.<sup>52</sup> Meanwhile, Poria, Radix Glycyrrhizae, Rhizoma Atractylodis Macrocephalae and Rhizoma Chuanxiong could increase the urine amount and shorten the latent period of urination in rats.<sup>53-55</sup>

Notable limits in study designs of retrieved clinical trials resulted in enhanced difficulties in our data analysis. For instance, diversity of sample sizes, staging classifications and histopathologic types of cancer patients in individual trials might partly increase the heterogeneity in data syntheses and analyses; inadequate descriptions on therapeutic details such as radiation or drug dose could potentially impair the comparisons between groups; although data from both RCTs and CCTs are valid for meta-analyses, insufficient randomization or blinding would also bring bias inevitably; certain outcomes as key endpoints including SR and TRR were not clearly reported in some trials; and data of long-term follow-up were insufficient to firmly prove the

effectiveness of natural herbs. Therefore, large sample size, long-term randomized controlled trials should be conducted to further verify the effects of PT in the treatment of cervical cancer.

In summary, our data from this review and analysis suggest that PT not only have therapeutic effects to improve SR and TRR of patients with cervical cancer, but also to diminish RC and VC caused by surgical therapy or radiotherapy. PT as an adjuvant therapy of CT should be valuable for the treatment of cervical cancer clinically. However, more clinical trials with high quality design should be conducted to further verify current evidence. Further clinical and pre-clinical studies that focus on the commonly used herbs identified in this study may also directly provide more valuable evidence of PT to treat cervical cancer.

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