Efficacy of Herbal Medicine as an Adjunctive Therapy of Chemotherapy for Cervical Cancer: A Systematic Review and Meta-analysis

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This study aimed to evaluate the efficacy of herbal medicine (HM) combined with chemotherapy (CT) for cervical cancer. Ten electronic databases including Pubmed, Cochrane library, Embase, Korean databases, and Chinese medical databases were systematically searched up to October 2019. All randomized controlled trials with HM combined with CT to treat cervical cancer were included. A total of 21 trials were included for analysis. Compared to the control group, HM combined with CT group significantly increased tumor response (complete and partial response) (risk ratio [RR] = 1.24, 95% CI: 1.15-1.33, p < 0.00001) and Karnofsky performance score (standardized mean difference [SMD] = 1.71, 95% CI: 1.41-2.01, p < 0.00001). Also, HM combined with CT group remarkably reduced CT toxicity. In Conclusion, our study suggests that HM might be a potential option for cervical cancer to enhance curative efficacy and reduce CT toxicity.

keywords : Chemotherapy, Herbal medicine, Cervical cancer, Systematic review, Meta-analysis

Introduction

Cervical cancer is the fourth most common malignant tumor among women worldwide, with almost 0.6 million cases and 0.3 million deaths per year, and is a major public health problem affecting middle-aged women[1)]. Despite of advances in early screening methods, the incidence of cervical cancer is still high, particularly in some low- and middle-income countries[2)]. Despite of considerable advances in treatments for cervical cancer, the clinical application is limited by surgery-related complications, disease recurrence, and therapy-related side effects. It is well known that Chemotherapy (CT) is usually accompanied by adverse events, including hematologic and gastrointestinal toxicity[3,4)]. Conventional symptomatic therapy to reduce adverse events is commonly used, but the effect is not significant.

Herbal medicine (HM) has been widely used in cancer treatment for a long time because of its efficacy and low toxicity. In vitro and in vivo studies on cervical cancer indicated that crude extracts or bioactive compounds from HM inhibited proliferation and induced apoptosis[5)]. A meta-analysis of RCTs also suggested that HM improved quality of life in cancer patients[6)]. In addition, HM has a good effect on cancer symptoms and reducing side effects[7)]. Numerous studies have reported the effectiveness of HM as an adjuvant therapy for cancer[8)], but there is no systematic review and meta-analysis on the efficacy of HM in patients with cervical cancer.

This study aimed to observe the effect of HM combined with CT on tumor response, quality of life, and reduction of CT toxicity in patients with cervical cancer.

Material and Methods

1. Data sources and search strategy

The search was conducted in the following ten electronic databases to October 2019: Pubmed, Cochrane

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library, Embase, China National Knowledge Infrastructure (CNKI), Wanfang, Journal integration platform (VIP), Korean Medical Database (KMBASE), National Discovery for Science Leaders (NDSL), Oriental Medicine Advanced Searching Integrated System (OASIS), and Korean studies Information Service System (KISS). We also searched the references of all included studies by hand, the grey literature, dissertations, letters, government documents, research reports, conference proceedings and abstracts to avoid publication bias. 'Uterine cervical neoplasms' and 'Chinese herbal medicine' were the main keywords in our search strategy. The detailed search strategy is presented in supplementary 1.

2. Eligibility criteria

1) Types of studies

Only randomized controlled trials (RCTs) were eligible. Non-RCTs, quasi-RCTs, in vitro and animal studies were excluded.

2) Types of participants

Eligible studies included women with a clear diagnosis of cervical cancer confirmed by pathological sections. Also, all participants in the treatment and control groups were treated with CT. No restrictions were placed on age, ethnicity, degree of pain, surgery or disease duration.

3) Types of interventions

The patients in the treatment group were treated by HM combined with CT, while the control group was treated with only CT. Because there were the most studies using herbal medicine as adjuvant therapy for CT rather than monotherapy in a preliminary search. The included studies used HM in various forms such as decoctions, capsules, and tablets, except intravenous administration. Both monochemotherapy and polychemotherapy were included, and combination with radiotherapy was excluded.

4) Types of outcome measures

Tumor response and Karnofsky performance score (KPS) were the primary outcomes. CT toxicity was the secondary outcome.

3. Study selection and data extraction

Two reviewers (SYO and MSK) independently screened the articles according to the inclusion and exclusion criteria, and extracted the data based on standardized data collection form. When the two reviewers had disagreements during the process, they were resolved by consensus or inviting a third reviewer (JCJ). The following data were extracted: first author, year, sample size, patient characteristics, intervention details, outcomes.

4. Quality assessment

Two independent reviewers assessed methodological quality by using the Cochrane risk of bias tool (RoB) tool[9]. Disagreements between the two reviewers were resolved by discussion with a third reviewer (JCJ). The following items were used to assess the methodological quality of RCTs: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias.

5. Statistical analysis

The RevMan 5.3 software of the Cochrane Collaboration was used for data analysis. For dichotomous data, the risk ratio (RR) and 95% confidence interval (CI) were reported. For continuous variables, standardized mean difference (SMD) with 95% CI was reported. We used random effects model to estimate treatment effects. Heterogeneity was assessed using the I^2 statistic, and I^2 > 50% was assumed as high heterogeneity. P value <0.05 was considered statistically significant.

Results

A total of 3937 studies were identified through searching PubMed (n=159), Cochrane library (n=187), Embase (n=2074), CNKI (n=378), Wanfang database (n= 967), VIP (n=5), KISS (n= 55), Kmbase (n= 27), NDSL (n= 82), and OASIS (n= 3). The screening process is shown in Fig. 1. A total of 471 articles were excluded in screening the duplicates. After reviewing the titles and abstracts, 3404 studies were excluded additionally because they did not meet the criteria. The full texts of 62 studies were reviewed, and 21 studies[10-30] were finally included for this systematic review and meta-analysis.

1. Study characteristics

The included studies were all conducted in China and published in Chinese between 2014 and 2019. A total of 21 studies with 1647 patients were analyzed; 824 patients were in HM combined with CT group, and the other 823 patients were in CT alone group. The characteristics of the studies including sample size, age, duration, outcomes etc. were shown in Table 1. HM used in the included studies were Fuzhengguben decoction, BaZhen decoction, Modified RenShenYangRong decoction, and so on (supplementary 2).

2. Risk of Bias in Included Studies

The risk of bias in included studies is shown in Fig. 2. All studies were described as randomized, and 11 studies[10,14,18-22,25,26,29,30] used random number tables. None of the studies described the allocation concealment. All studies had high risk of bias in blinding of participants and personnel, because they did not use placebo in control group. All studies were unclear on blinding of outcome assessment and selective reporting outcome. Other bias was also evaluated as unclear in all studies due to insufficient information.

Table 1. Characteristics of included studies

Author, Year	Sample size (TG/CG)	Age (years)	FIGO CC stage (NO. of patients)	Duration	Intervention of TG	Intervention of CG	Outcomes
Chang et al. 2018[10]	84 (42/42)	TG: 48.75 ± 10.24 CG: 48.25 ± 10.13	TG: III, 26; IV, 16 CG: III, 25; IV, 17	4 weeks*3 courses	HM + Paclitaxel/ Cisplatin	Paclitaxel/ Cisplatin	1. Tumor response
Gong et al. 2018[11]	64 (32/32)	TG: 47.9 ± 2.4 CG: 48.2 ± 2.5	TG: I, 13; II, 12; III, 7 CG: I, 11; II, 13; III, 8	21 days*2 courses	HM + Paclitaxel/ Cisplatin	Paclitaxel/ Cisplatin	1. Tumor response
Han et al. 2016[12]	72 (36/36)	TG: 47.5 ± 12.4 CG: 49.1 ± 8.2	TG: I A, 7; I B, 15; II A, 10; II B, 4 CG: I A, 10; I B, 12; II A, 8; II B, 6	3 months	HM+ Cisplatin/ Irinotecan	Cisplatin/ Irinotecan	1. KPS
Jian et al. 2015[13]	41 (21/20)	TG: 52.38 ± 8.09 CG: 50.55 ± 9.81	TG: III A, 2; III B 3; IV A, 3; IV B, 13 CG: III A, 3; III B 4; IV A, 2; IV B, 11	CT: 21 days*2 courses HM: 8 weeks	HM+Cisplatin/ Docetaxel	Cisplatin/ Docetaxel	1. Tumor response 2. KPS 3. Chemotoxicity
Li et al. 2017[14]	60 (30/30)	TG: 33.3 ± 1.5 CG: 33.5 ± 1.7	TG: I, 17; II, 13 CG: I, 18; II, 12	CT: 5 days*2 courses HM: 10 days*2 courses	HM+ Cisplatin/ Fluouracil	Cisplatin/ Fluouracil	1. Chemotoxicity
Li et al. 2019[15]	61 (30/31)	TG: 47.53 ± 9.25 CG: 48.15 ± 9.34	TG: I B1, 10; I B2, 12; II A, 8 CG: I B1, 10; I B2, 12; II A, 9	21 days*5 courses	HM+ Cisplatin/ Docetaxel	Cisplatin/ Docetaxel	1. Tumor response 2. KPS 3. Chemotoxicity
Liu 2019[16]	100 (50/50)	TG: 54.11 ± 2.42 CG: 54.25 ± 2.47	TG: II B, 21; III, 19; IV, 10 CG: II B, 20; III, 20; IV, 10	8 weeks	HM+ Fluouracil/ Cyclophosphamide/ Pingyangmycin	Fluorouracil/ Cyclophosphamide/ Pingyangmycin	1. Tumor response
Nan et al. 2015[17]	60 (30/30)	TG: 48.8 ± 6.1 CG: 48.7 ± 6.3	TG: I, 5; II, 15; III, 10 CG: I, 6; II, 14; III, 10	4 weeks	HM+ Cisplatin + Irinotecan	Cisplatin+ Irinotecan	1. Chemotoxicity
Qin et al. 2016[18]	60 (30/30)	TG: 48.34 ± 5.35 CG: 50.45 ± 5.85	TG: II B, 18; III A, 5; III B, 7 CG: II B, 16; III A, 6; III B, 8	Not reported	HM+ Paclitaxel/ Irinotecan (Some patients combined Mitomycin/ Cisplatin/ 5-fluorouracil)	Paclitaxel/ Irinotecan (Some patients combined Mitomycin/ Cisplatin/ 5-fluorouracil)	1. Tumor response 2. KPS 3. Chemotoxicity
Sun et al. 2019[19]	116 (58/58)	TG: 55.46 ± 13.27 CG: 55.23 ± 13.12	TG: II B, 32; III A, 14; III B, 12 CG: II B, 33; III A, 12; III B, 13	CT: 21 days*1~2 courses HM:10 days*2 courses	HM+ Oxaliplatin/ Paclitaxel	Oxaliplatin/ Paclitaxel	1. Tumor response 2. KPS 3. Chemotoxicity
Wang 2014[20]	90 (45/45)	TG: 53.2 ± 7.5 CG: 53.5 ± 7.8	TG: II B, 25; III A, 9; III B 11 CG: II B, 27; III A, 8; III B 10	Unclear	HM + Paclitaxel/ Irinotecan	Paclitaxel/ Irinotecan	1. Tumor response 2. KPS 3. Chemotoxicity
Wen et al. 2019[21]	114 (57/57)	TG: 56.37 ± 7.93 CG: 55.49 ± 7.62	TG: II A, 19; II B, 20; III A 18 CG: II A, 19; II B, 21; III A 17	7 days*3 courses	HM+ Paclitaxel/ Cisplatin	Paclitaxel/ Cisplatin	1. Tumor response 2. Chemotoxicity
Wu 2017[22]	80 (40/40)	Total: 56.3 ± 7.2	II B 26, III A, 38, III B, 16	Unclear	HM+ Paclitaxel/ Irinotecan	Paclitaxel/ Irinotecan	1. Tumor response 2. Chemotoxicity
Xu et al. 2018[23]	90 (45/45)	TG: 53.3 ± 7.6 CG: 53.1 ± 7.4	TG: II B, 23; III A, 10; III B, 12 CG: II B, 24; III A, 10; III B, 11	Unclear	HM+ Paclitaxel / Irinotecan	Paclitaxel / Irinotecan	1. Tumor response 2. Chemotoxicity
Xu et al. 2019[24]	60 (30/30)	TG: 50.13 ± 14.26 CG: 50.27 ± 13.49	TG: I B1, 13; I B2, 10; II A, 5; II B, 2 CG: I B1, 14; I B2, 10; II A, 4; II B, 2	Unclear	HM+ Paclitaxel/ Irinotecan	Paclitaxel/ Irinotecan	1. Tumor response
Yang 2015[25]	80 (40/40)	TG: 58.7 ± 7.9 CG:59.4 ± 6.1	TG: I B, 7; II A, 5; II B, 19; III A, 5; III B, 4 CG: I B, 6; II A, 4; II B, 20; III A, 6; III B, 4	CT: 3 weeks* 3 courses HM: 9 weeks	HM+ Cisplatin/ Mitomycin/5-fluorouracil	Cisplatin/ Mitomycin /5-fluorouracil	1. Tumor response 2. Chemotoxicity
Yang 2017[26]	119 (60/59)	TG: 55.37 ± 12.82 CG: 54.86 ± 12.97	TG: II A, 18; II B, 30; III 12 CG: II A, 17; II B, 28; III 14	3 months	HM+ Oxaliplatin/ Paclitaxel	Oxaliplatin/ Paclitaxel	1. Tumor response
Yang et al. 2018[27]	62 (31/31)	TG: 48.24 ± 1.13 CG: 48.64 ± 1.33	TG: II B, 12; III A, 5; III B, 14 CG: II B, 10; III A, 3; III B, 18	CT: 5 days HM: 10 days	HM + Paclitaxel/ Cisplatin	Paclitaxel/ Cisplatin	1. Tumor response 2. Chemotoxicity
Zhang et al. 2015[28]	56 (28/28)	TG: 52.6 CG: 56.3	TG: III A, 12; III B, 8; IV, 8 CG: III A, 10; III B, 16; IV, 2	21 days*3 courses	HM+ Paclitaxel/ Cisplatin	Paclitaxel/ Cisplatin	1. Tumor response 2. Chemotoxicity
Zhu et al. 2019[29]	92 (46/46)	TG: 54.03 ± 7.12 CG: 53.29 ± 6.37	TG: II B, 31; III, 15 CG: II B, 32; III, 14	4 weeks*3 courses	HM+ Cisplatin/ Docetaxel	Cisplatin/ Docetaxel	1. Tumor response 2. Chemotoxicity
Zuo 2019[30]	86 (43/43)	TG: 46.53 ± 3.27 CG: 46.62 ± 3.87	TG: II B, 18; III A, 13; III B, 12 CG: II B, 17; III A, 15; III B, 11	21 days*2 courses	HM+ Paclitaxel/ Irinotecan	Paclitaxel/ Irinotecan	1. Tumor response 2. Chemotoxicity

CC, cervical cancer; TG, treatment group; CG, control group; HM, herbal medicine; CT, chemotherapy; AEs, adverse events; KPS, Karnofsky performance scale; NK, natural killer; ALT, alanine transaminase; AST, aspartate transaminase; BUN, blood urea nitrogen; Cr, creatinine; SCC-Ag, squamous cell carcinoma antigen; TSGF, tumor supplied group of factors; EORTC QLQ-C30, the European organisation for research and treatment of cancer quality of life questionnaire; VAS, visual analogue scale; SF-36, short form-3

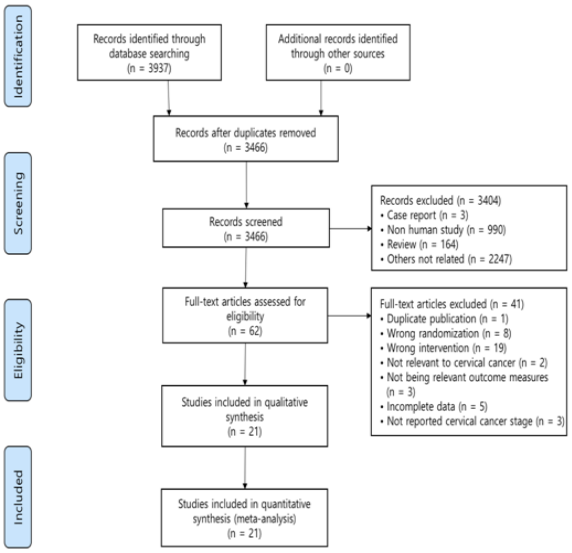


Fig. 1. Study flow diagram.

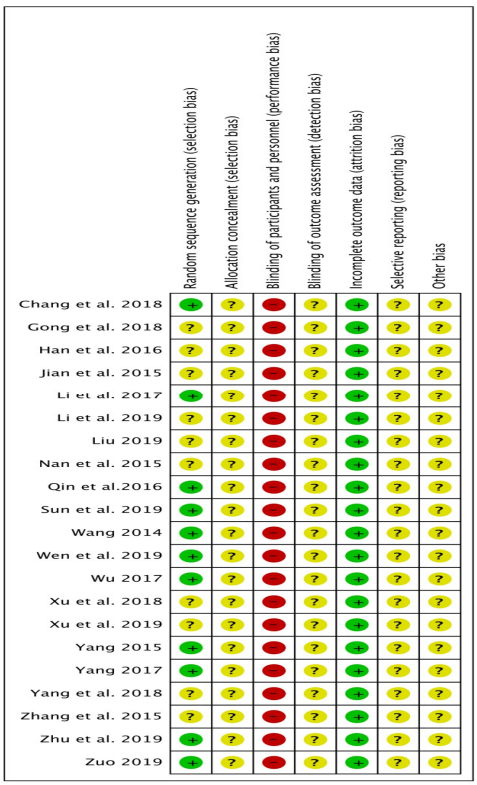


Fig. 2. Risk of bias summary.

3. Meta-analysis

1) Tumor response

18 studies[10,11,13,15,16,18-30] reported complete response (CR) or partial response (PR). As shown in Fig. 3, HM therapy combined with CT was associated with a significant increase in the number of patients who reported complete or partial response (RR = 1.24, 95% CI: 1.15-1.33, p < 0.00001, I^2 = 5%).

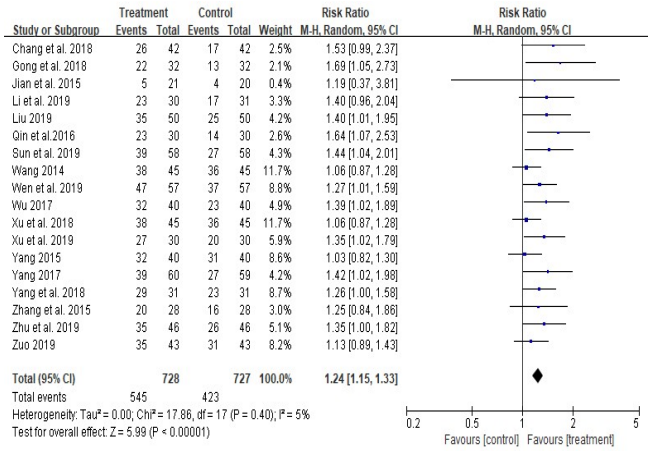
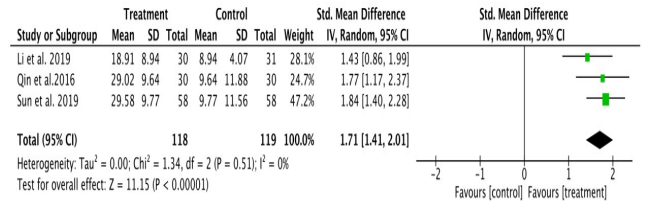


Fig. 3. The forest plot of tumor response of HM combined with CT versus CT alone. HM, herbal medicine; CT, chemotherapy; CR, complete response; PR, partial response.

2) Karnofsky performance score

KPS scores were reported as two types, the mean ± SD of KPS before and after treatment, and the number of patients who reported the improved or stable performance status based on KPS (ten-point cutoff). The value of KPS was recorded in three studies[15,18,19] with 237 patients. Meta-analysis reported that KPS score was significantly increased in HM combined with CT group compared with CT alone group (SMD = 1.71, 95% CI: 1.41-2.01, p < 0.00001, I^2 = 0%, Fig. 4A). The non-deterioration KPS was recorded in two studies[13,20] with 131 patients. The results of meta-analysis found that there was no significant difference between the two groups (RR = 1.12, 95% CI: 0.92 -1.38, p = 0.32, I^2 = 0%, Fig. 4B).

A



B

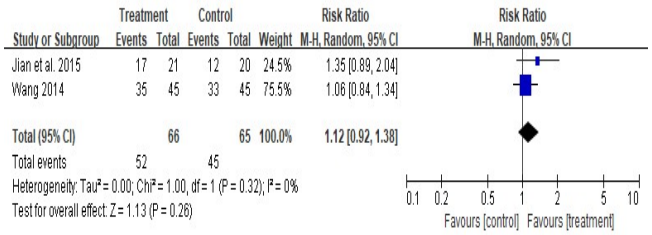


Fig. 4. The forest plot of KPS of HM combined with CT versus CT alone; outcomes: (A) mean ± SD of KPS; (B) number of patients with non-deterioration KPS. KPS, Karnofsky performance score; HM, herbal medicine; CT, chemotherapy.

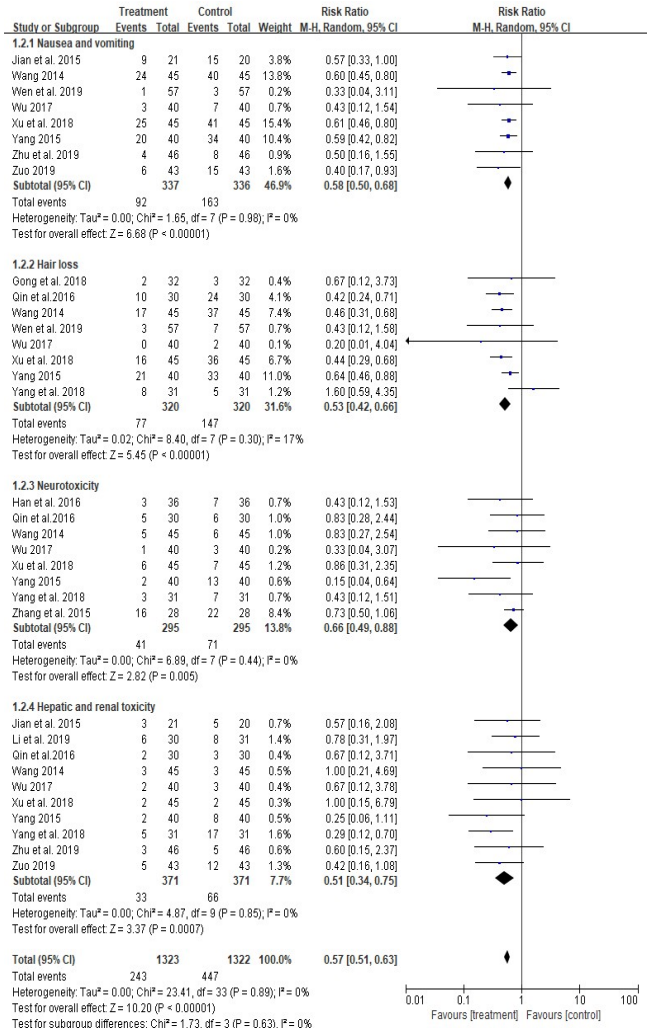


Fig. 5. The forest plot of CT toxicity (including nausea and vomiting, hair loss, neurotoxicity, hepatic and renal toxicity) of HM combined with CT versus CT alone. HM, herbal medicine; CT, chemotherapy.

3) CT Toxicity

Nausea and vomiting were recorded in eight studies[13,20-23,25,29,30]. Meta-analysis showed that the incidence of nausea and vomiting was significantly lower in HM combined with CT group than in CT alone group (RR = 0.58, 95% CI: 0.50-0.68, p < 0.00001, I^2 = 0%, Fig. 5 (1.2.1)). Hair loss was reported in eight studies[11,18,20-23,25,27]. Meta-analysis indicated that the incidence of hair loss was significantly lower in HM combined with CT group than in CT alone group (RR = 0.53, 95% CI: 0.42-0.66, p < 0.00001, I^2 = 17%, Fig. 5 (1.2.2)). Neurotoxicity was recorded in eight studies[12,18,20,22,23,25,27,28]. Meta-analysis found that the incidence of neurotoxicity was significantly lower in HM combined with CT group than in CT alone group (RR = 0.66, 95% CI: 0.49-0.88, p = 0.005, I^2 = 0%, Fig. 5 (1.2.3)). Hepatic and renal toxicity were recorded in eight studies[13,15,18,20,22,23,25,27,29,30]. The results of meta-analysis reported that the incidence of hepatic and renal toxicity were significantly lower in HM combined with CT group than in CT alone group (RR = 0.51, 95% CI: 0.34-0.75, p = 0.0007, I^2 = 0%, Fig. 5 (1.2.4)). Overall, the result showed that the incidence of CT toxicity was significantly lower in HM combined with CT group than in CT alone group (RR = 0.57, 95% CI: 0.51-0.63, p < 0.00001; I2 = 0%, Fig. 5).

Discussion

HM is a popular complementary and alternative therapy used for cancer patients because it can increase therapeutic effect and decrease side effects combined with CT. To our knowledge, this is the first systematic review and meta-analysis of RCTs on the efficacy of HM in cervical cancer. This meta-analysis evaluated the outcomes including tumor response, quality of life (KPS), and CT toxicity. A total of 21 studies were included in this review, involving 1647 patients (824 in HM combined with CT group, and 823 in CT alone group).

The results of meta-analysis found that the tumor response was significantly in favor of HM combined with CT. Astragalus membranaceus, Angelica sinensis, Paeonia lactiflora, Atractylodes macrocephala were the most frequently used herbs in the included studies. According to the reports, these herbs had immunomodulatory function and anti-tumor effects through some mechanisms[31-33]. The aqueous extract of Astragalus membranaceus could induce apoptosis of H22 tumor cells and had an inhibiting effect on tumor growth[34]. Polysaccharide from Astragalus membranaceus had potent immunomodulatory activity by stimulating macrophages and increase the level of cytokines including tumor necrosis factor-alpha (TNF-α) and granulocyte-macrophage colony-stimulating factor (GM-CSF)[35]. In addition, Wu et al. found that the combined therapy of Astragalus membranaceus and Angelica sinensis could attenuate cancer-related inflammation and had an inhibiting effect on tumor growth[36].

Both CT and radiotherapy have many side effects; therefore, it is necessary to find complementary and alternative approaches for reducing the side effects. In this meta-analysis, HM combined with CT significantly reduced side effects caused by CT, including nausea, vomiting, hair loss, neurotoxicity, hepatic and renal toxicity. HM usually comprises multiple herbs from natural origin. Acting of phytochemicals and herbal mixtures are multi-specific, so they attack multiple targets at the same time[37]. Multi-target therapies have been advocated to overcome resistance to

anti-cancer drugs. Especially, polypharmacology has more advantages than drug combination in reducing side effects and selectivity for cancer cells[38]. We hypothesize that these features of HM make it a good candidate for cervical cancer treatment.

The present study has some limitations. Firstly, although we conducted a comprehensive search, the included RCTs were only carried out in China. For this reason, the results might not be acceptable to other populations in other parts of the world. Secondly, the methodological qualities of included RCTs were generally poor. 11 RCTs reported having used "random number tables", while the other 10 RCTs only mentioned "randomization" and did not describe further details. The allocation concealment and blinding were not reported in all of included RCTs. In addition, most of them did not reported follow-up and drop-out rates; these methodological flaws might lead to potential biases, so the results should be interpreted with great caution. Thirdly, no placebo was used in all included RCTs. The characteristics of HM, like strong tastes and smells, can cause difficulty in making placebo, especially in decoctions. Also, we considered that it was due to clinical trial ethics on the treatment for cancer patients. This problem was considered as a high risk of bias in the blinding of participants and personnel. Fourthly, the long-term efficacy was not evaluated, because most of the studies did not give the data of long-term follow up. Lastly, none of the included studies reported responsible ethical committees have approved the experiments. Considering the importance of protecting the rights of patients, complementary and alternative medicine researchers must develop awareness of ethical issues.

Conclusion

In conclusion, our systematic review and meta-analysis results provide evidence for the efficacy of HM in cervical cancer treatment. HM might be an effective option to enhance curative efficacy and reduce chemotherapy toxicity. However, because the most of included studies had low quality, the results should be interpreted cautiously. To suggest stronger evidence for using HM in cervical cancer, high quality rigorous RCTs will be needed in the future.

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