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Efficacy and safety of Simiao decoction in the treatment of cervical HPV infection: A systematic review and meta-analysis of randomized clinical trials

Lin Qiu [a,1], Ying Chen [b,c,1], Jue Wang [a,1], Lili Yu [a,**], Qibiao Wu [a,c,d,e,*], Hui Mo [a,c,***]

[a] Faculty of Chinese Medicine, State Key Laboratory of Quality Research in Chinese Medicines, Macau University of Science and Technology, Taipa, Macao, China
[b] School of Health Economics and Management, Nanjing University of Chinese Medicine, China
[c] Mo Hui's Inheritance Workshop by National Renowned TCM Doctors, Macao, China
[d] Macau University of Science and Technology Zhuhai MUST Science and Technology Research Institute, Hengqin, Zhuhai, China
[e] Guangdong-Hong Kong-Macao Joint Laboratory for Contaminants Exposure and Health, Guangdong University of Technology, Guangzhou, Guangdong, China

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ABSTRACT

Background: Persistent HPV infection can easily lead to the occurrence and development of cervical cancer and its precancerous lesions. Many studies have shown that Simiao Decoction may be effective in treating HPV infection, but the efficacy and safety of Simiao Decoction for HPV infection have never been systematically evaluated.

Purpose: To evaluate the efficacy and safety of Simiao Decoction in the treatment of cervical HPV infection.

Study design: A systematic review and meta-analysis of all randomized clinical trials (RCTs) comparing Simiao Decoction versus conventional treatment.

Materials and methods: Seven databases were searched from their inception until May 14, 2023. All the RCTs comparing the efficacy and safety of Simiao Decoction versus conventional treatment were selected. Analyses were performed using Review Manager 5.3. HPV negative conversion rate (NCR) was defined as the primary endpoint, and treatment response rate (TRR), and adverse reaction (AR) were defined as the secondary endpoints. The quality of each endpoint was

Abbreviations: AR, Adverse Reaction; CIs, Confidence Intervals; CNKI, China National Knowledge Infrastructure Database; GRADE, Grading of Recommendations, Assessment, Development and Evaluations; HPV, Human Papillomavirus; MD, Mean Difference; NCR, Negative Conversion Rate; OR, Odds Ratio; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses; RCT, Randomized Controlled Trial; RD, Risk Difference; RR, Risk Ratio; SMD, Standardized Mean Difference; TCM, Traditional Chinese medicine; TRR, treatment response rate; TSA, Trial Sequential Analysis; VIP, VIP-Database; WMD, Weighted Mean Difference.

* Corresponding author. Faculty of Chinese Medicine, State Key Laboratory of Quality Research in Chinese Medicines, Macau University of Science and Technology, Taipa, Macao, China.

** Corresponding author. Faculty of Chinese Medicine, State Key Laboratory of Quality Research in Chinese Medicines, Macau University of Science and Technology, Taipa, Macao, China.

*** Corresponding author. Faculty of Chinese Medicine, State Key Laboratory of Quality Research in Chinese Medicines, Macau University of Science and Technology, Taipa, Macao, China.

E-mail addresses: llyu@must.edu.mo (L. Yu), qbwu@must.edu.mo (Q. Wu), hmo@must.edu.mo (H. Mo).

[1] Co-first author contributed equally.

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assessed by The Grading of Recommendations, Assessment, Development and Evaluations (GRADE) system.
Results: Ten RCTs recruiting 799 patients with HPV infection were included. The results showed that compared with conventional treatment, Simiao Decoction improved NCR (RR = 1.45, 95 % CI 1.31, 1.61, $P < 0.00001$), TRR (RR = 1.24, 95%CI 1.15, 1.33, $P < 0.000\ 01$), while it did not increase AR (RR = 0.79, 95%CI 0.46, 1.33, $P = 0.37$). Most results were robust and the quality of evidence was moderate.
Conclusion: Simiao Decoction is safer and more effective than conventional treatment for HPV infection. However, the efficacy and safety of Simiao Decoction should be further assessed by more high-quality RCTs with the outcome of HPV viral load and long-term follow-ups.

1. Introduction

Cervical cancer is one of the three major malignant tumors that endanger women's health, and an estimation presented that about 311,000 women die each year due to cervical cancer [1]. Most cervical cancer cases are caused by persistent infection of human papillomavirus (HPV) [2,3]. Studies have reported that the HPV-positive rate in cervical cancer reaches 91.7 %, and the genital HPV-positive rate in sexually active women is 38 % [4,5]. Although most people can clear the virus on their own within 8–10 months, 5 %–10 % [6]of patients still have persistent HPV infection.

At present, there are no specific drugs to treat cervical HPV infection [7]. For cervical lesions caused by HPV infection, clinical treatment methods mainly include cryotherapy, carbon dioxide laser, surgical excision, and so on. HPV infections that do not cause cervical lesions are often treated with topical drugs, such as interferon, which is the most common type. However, long-term use of interferon will bring adverse reactions such as low blood pressure, headache, and fever to patients [8]. Besides, HPV often does not turn negative after using topical drugs.

Traditional Chinese medicine (TCM) is a commonly used complementary therapy for HPV infection in China and many countries. Some clinical studies have shown that TCM is effective for cervical HPV infection and has obvious advantages such as fewer adverse reactions and low drug resistance [9–12]. As one of the commonly used TCM formulae, Simiao Decoction has shown a good curative effect in the treatment of cervical HPV infection [13–16]. However, the efficacy and safety of Simiao Decoction for HPV infection have never been systematically evaluated. Therefore, all eligible RCTs were included in this study to systematically assess the effects of Simiao Decoction as an adjuvant treatment to conventional treatment for patients with HPV infection.

2. Methods

This study was performed in accordance with Preferred Reported Items for Systematic Review and Meta-analysis (PRISMA) guidelines [17]. We searched seven databases from their inception until May 14, 2023, and all RCTs that compared Simiao Decoction versus clinical conventional treatment for the treatment of HPV infection were selected. Revman V.5.3. was used for data synthesis and data analyses.

2.1. Types of studies

RCTs that compared Simiao Decoction vs. conventional treatment were selected and evaluated for inclusion in this research. Non-randomized controlled trials, empirical findings, animal experiments, case reports and reviews were excluded.

2.2. Types of participants

2.2.1. Inclusion criteria

The RCTs included in this study should meet the following criteria.

(a) All participants were diagnosed with cervical HPV infection, HPV (+). Age, sex, and race were not the limit of the inclusion criteria.
(b) The intervention measures in the experimental group were Simiao Decoction or Simiao Decoction combined with conventional treatment, and the intervention measure in the control group was conventional treatment.
(c) Conventional treatment was defined as topical drugs, such as interferon, metronidazole, Baofukang suppository, Kangfu gel, etc.
(d) The minimum duration of treatment for all patients was 4 weeks.
(e) The results of these studies should include at least one of the following indicators: HPV negative conversion rate (NCR); treatment response rate (TRR), and adverse reaction (AR).

2.2.2. Exclusion criteria

Studies were excluded if they met one of the following criteria.

(a) The participants were not HPV-infected.

(b) The study was not an RCT. Besides, empirical findings and animal experiments should be excluded.
(c) The result of TCT or electronic colposcopy biopsy showed: CIN II or III, carcinoma in situ, invasive carcinoma.
(d) Patients had HPV infection in other sites besides the cervix uterus.
(e) The intervention in the experimental group was not Simiao decoction.
(f) The interventions included physical, chemical, surgical treatments, or other TCM decoctions.
(g) Patients suffered from genetic or immune diseases.

2.3. Types of interventions

The experimental group was treated with Simiao Decoction or Simiao Decoction combined with conventional treatment. The control group was only treated with conventional treatment. In our study, conventional treatment was defined as topical drugs, which was identical in both groups. Conventional treatment included Recombinant Human Interferon α2b gel, metronidazole, Baofukang suppository, Kangfu gel, etc.

2.4. Types of outcome measures

The primary outcome was HPV negative conversion rate (NCR). Treatment response rate (TRR) and adverse reaction (AR) were the secondary outcomes. NCR was defined as when the HPV detecting test is negative after a patient finishes a course of treatment. TRR was calculated based on the improvement of clinical symptoms. As for AR, it included any discomfort for patients when accepting treatment, such as vaginal discomfort, abdominal pain, anorexia, low blood pressure, headache, fever, and so on. NCR and TRR were used to assess the clinical effectiveness of a periodic treatment, while AR was used to evaluate the safety of a treatment.

2.5. Information sources

Two independent reviewers searched Pubmed, Embase, Cochrane Library, International Clinical Trials Registry, Wanfang Database, CNKI, and VIP Chinese Science databases. Besides, they searched the International Registry of Clinical Trials for correlative RCTs and performed a conventional search to identify potential studies that were not included in the electronic databases. The last search date was May 14, 2023.

2.6. Search strategy

The Chinese databases were searched by the following terms: [‘Renrutouliubingdu (human papillomavirus)’ OR ‘HPV’ AND [‘Simiaotang’ (Simiao Decoction) OR] AND [‘LinChuangDuiZhaoYanJiu (Control clinical trials)’ OR ‘SuiJiDuiZhaoYanJiu (Randomized controlled trials)’ OR ‘SuiJiDuiZhao (Randomized controlled)’ OR ‘SuiJi (Randomized)’] (Table 1.).

The English databases were searched by the following terms : ((human papillomavirus [Title/Abstract] OR HPV [Title/Abstract] OR Alphapapillomavirus [Title/Abstract] OR Beta papillomavirus [Title/Abstract] OR Gammapapillomavirus [Title/Abstract] OR Mupapillomavirus [Title/Abstract] OR Nupapillomavirus [Title/Abstract]) AND (Simiaotang [Title/Abstract]) OR Simiao Decoction [Title/Abstract] AND (RCT [Title/Abstract] OR Randomized Controlled Trial [Title/Abstract] OR ‘Control clinical trials’ [Title/Abstract] OR ‘Randomized controlled’ [Title/Abstract] OR ‘Randomized’ [Title/Abstract] OR ‘Random’ [Title/Abstract] OR ‘Trials’ [Title/Abstract]) (Table 2.).

There are no restrictions on language or publication. Furthermore, references from all relevant articles were reviewed to identify potentially eligible studies.

2.7. Study selection

All candidate articles were screened by two independent reviewers (Lin Qiu and Ying Chen) according to the titles and abstracts.

Table 1
Search strategy used in Chinese databases.

Number		Search Items
1	Related to disease	Renrutouliubingdu (human papillomavirus)
2		HPV
3		1 or 2
4	Related to intervention	Simiaotang (Simiao-Decoction)
5	Related to study design	SuiJiDuiZhaoYanJiu (RCTs)
6		LinChuangDuiZhaoYanJiu (Control clinical trials)
7		SuiJiDuiZhao (Randomized controlled)
8		SuiJi (Randomized)
9		5 or 6-8
10		3 and 4 and 9

Notes: **HPV,** human papillomavirus; **RCT**, Randomized controlled trial.

Table 2
Search strategy used in English databases.

Number		Search Items
1	Related to disease	human papillomavirus
2		HPV
3		Alphapapillomavirus
4		Betapapillomavirus
5		Gammapapillomavirus
6		Mupapillomavirus
7		Nupapillomavirus
8		1 or 2–7
9	Related to disease	Simiao-Decoction
10		Simiaotang
11		9 or 10
12	Related to study design	Randomized controlled trials
13		Control clinical trails
14		Randomized controlled
15		Randomized
16		Random
17		Trials
18		RCT
19		12 or 13–18
20		8 and 11 and 19

Notes: **HPV,** human papillomavirus; **RCT**, Randomized controlled trial.

Besides, the full text was retrieved for further assessment based on the inclusion and exclusion criteria. If any inclusion disagreements arose, a third reviewer (Qi-Biao Wu) would join in a discussion to solve them.

2.8. Data extraction

Two independent reviewers (Lin Qiuand Ying Chen) extracted the data and the following information from RCTs: author name, Jadad's score, publication year, sample number, intervention method, control method, outcome measures, treatment duration, etc.

2.9. Risk-of-bias in individual trials

The risk-of-bias and the methodological quality of all included RCTs were appraised by two independent reviewers (Lin Qiu and Ying Chen) using the Cochrane Risk-of-Bias tool and Jadad's scale. Each trial was assessed for bias in accordance with the following items: random sequence generation, concealment of allocation, blinding method, incomplete outcome data, selective reporting, and other bias sources. For the above points, the risk of bias was classified as low risk (+), high risk (−), and unclear (?). Jadad's scores ranged from 0 to 7, 0–3 is considered low quality, and 4–7 is considered high quality. The dispute of the risk of bias was discussed with a third reviewer (Qi-Biao Wu) until the three examiners reached a consensus.

2.10. Summary measures and data synthesis

All meta-analysis data were processed using Revman software (Revman V.5.3). Continuous data were presented by standardized mean difference (SMD) or weighted mean difference (WMD) with 95 % confidence intervals (CIs), while dichotomous data were presented by risk ratio (RR), risk difference (RD), or odds ratio (OR) with a 95 % CI. Statistical heterogeneity was evaluated by Chi^2 and I^2 tests. The random-effects model was applied when $I^2 > 50$ %, while the fixed-effects model was applied when $I^2 < 50$ % [18,19].

2.11. Risk-of-bias across trials

When the number of trials included in a meta-analysis was more than 10, the potential bias of all trials was estimated by funnel plots and Egger's test [20,21].

2.12. Quality of evidence

The quality of evidence for each outcome was assessed through the Grades of Recommendations, Assessment, Development and Evaluations (GRADE) approach [22] by two independent reviewers (Lin Qiu and Ying Chen). A third reviewer (Qibiao Wu) would solve the disagreements regarding downgrades or upgrades. The quality of evidence was rated as "high", "moderate", "low" or "very low" according to the following domains: (I) limitation of the study design (if most domains had unclear bias risk, the evidence was downgraded by one level. If there were poor quality trials with poor robustness, the evidence was downgraded by two levels; (II) inconsistency (statistical heterogeneity with poor robustness after removing the trials with underestimated ADRs or overestimated efficacy); (III) indirection (the patients, interventions, outcomes or comparisons of the study did not meet the objectives of this study);

(IV) imprecision (the number of events for each outcome was less than 300); and (V) publication bias (reporting bias and results with poor robustness). Except for Domain I, the evidence for Domains II-IV was rated down by one level.

2.13. Additional analysis

The robustness of the results of the meta-analysis was assessed by Trial sequential analysis (TSA), subgroup analysis, and sensitivity analysis [23].

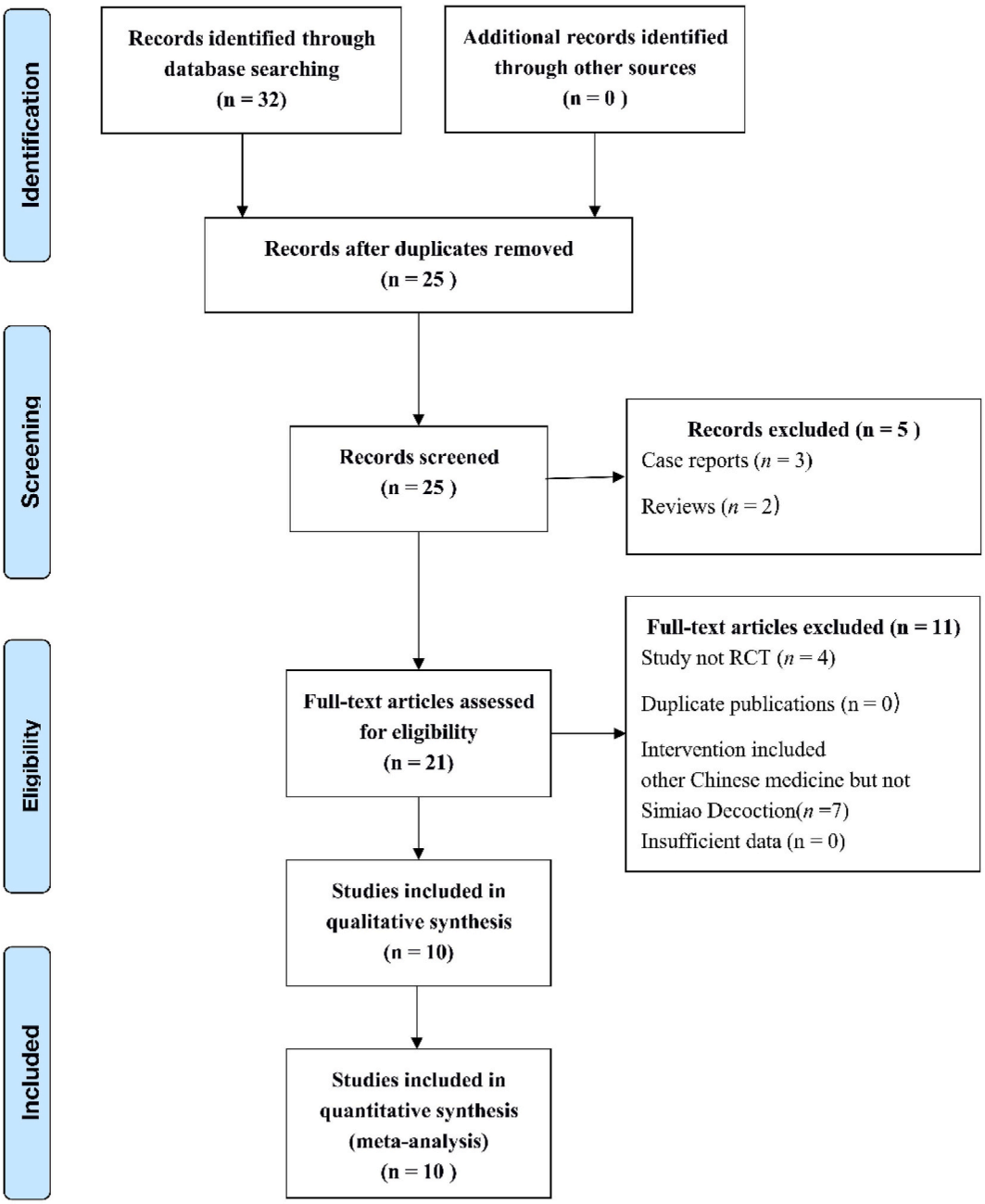

Fig. 1. PRISMA diagram of searching.
Notes: **PRISMA**, Preferred Reporting Items for Systematic Reviews and Meta-Analyses**; RCT**, randomized controlled trial.

3. Results

3.1. Study selection

There were 32 articles retrieved, of which 7 articles were obtained from CNKI, 16 articles were obtained from the Wanfang database, and 9 articles were obtained from VIP, all of which were published in Chinese. After excluding duplicate literature, 24 articles were included based on the screening of the titles. 4 papers did not meet the inclusion and exclusion criteria and were excluded after reading the abstracts, 11 papers were excluded by further screening the full texts, and a total of 10 papers were finally included [13–16,24–29] (Fig. 1).

3.2. Study characteristics

799 participants were recruited in 10 RCTs which were all published in Chinese from 2015 to 2022 [13–16,24–29]. There were 400 and 399 participants in the control and experimental groups. The ages of the participants varied from 26 to 51 years old and all of them were diagnosed with cervical HPV infection.

All included RCTs compared Simiao Decoction or Simiao Decoction plus conventional treatment vs. conventional treatment alone for HPV. The participants in the control group only received conventional treatment, such as Recombinant Human Interferon α2b gel and Baofukang Suppository, while participants in the experimental group were treated by Simiao Decoction or Simiao Decoction combined with conventional treatment.

The characteristics of all included trials are presented in Table 3.

3.3. Methodological quality

As shown in Table 4, Figs. 2 and 3, methodological quality and the risk of bias of all included RCTs were assessed and presented according to the Cochrane Risk of Bias Assessment Tool and the Jadad's scale [31]. When the methodological quality was assessed by Jadad score, there were 3 RCTs [15,16,28] who scored 3 out of 7, while 7 RCTs scored 4 [13,14,24–27,29] out of 7. In all trials, the blinding of participants, personnel, and outcome assessment were unclear. In some trials, the concealment of allocation was unclear. The data were complete in all included trials.

3.4. Outcome measures

The characteristics of all enrolled trials are presented in Table 5.

3.4.1. HPV negative conversion rate (NCR)

All ten articles explored the influence of the different interventions on the NCR of HPV. There were 799 subjects in total, including 400 in the control group and 399 in the intervention group. The pooled data showed that compared with the control group, the NCR in the intervention group was significantly higher (RR = 1.45, 95%CI = 1.31 -1.61, Z = 7.11, $P < 0.00001$). No significant heterogeneity was found in this outcome ($I^2 = 14$ %, P = 0.32), and a fixed-effects model was applied to combine the trials (Fig. 4.).

3.4.2. Treatment response rate (TRR)

Nine articles investigated the effect of Simiao Decoction treatment or conventional treatment on the TRR. The results showed that, compared with conventional treatment, Simiao Decoction significantly improved the TRR (RR = 1.24, 95%CI = 1.15–1.33, Z = 5.84, $P < 0.000\,01$). There was statistical homogeneity for the above outcome, ($I^2 = 0$ %, $P = 0.93$), and a fixed-effects model was applied to combine the trials (Fig. 5.).

Table 3
Principal characteristics of RCTs in meta-analysis.

Reference	Design	Jadad's score	Sample size (T/C)	Outcome measures	Treatment group		Control group
					Intervention	Treatment course	
Zhu, 2015[16]	RCT	3	30/30	**NCR, TRR, AR**	**SMD**	4 weeks	**CT**
Meng, 2021[26]	RCT	4	34/34	**NCR**	**SMD + CT**	3 months	**CT**
Liu, 2019[25]	RCT	4	42/42	**NCR, TRR, AR**	**SMD + CT**	3 months	**CT**
Xie, 2018[28]	RCT	3	44/44	**NCR, TRR**	**SMD + CT**	30 days	**CT**
Wang, 2016[14]	RCT	4	51/51	**NCR, TRR, AR**	**SMD + CT**	4 weeks	**CT**
Si et al., 2019[27]	RCT	4	60/60	**NCR, TRR, AR**	**SMD + CT**	30 days	**CT**
Zheng, 2016[29]	RCT	4	31/32	**NCR, TRR**	**SMD**	4 weeks	**CT**
Yuan, 2015[15]	RCT	3	24/24	**NCR, TRR, AR**	**SMD**	4 weeks	**CT**
Cheng et al., 2015[24]	RCT	4	43/43	**NCR, TRR**	**SMD**	4 weeks	**CT**
Wang et al., 2022[30]	RCT	4	40/40	**NCR, TRR, AR**	**SMD + CT**	6 weeks	**CT**

Notes: **AR**, Adverse reaction; **CT**, Conventional treatment; **NCR**, Negative conversion rate of HPV; **RCT**, Randomized controlled trial; **SMD**, Simiao Decoction; **T/C,** Treatment group/Control group; **TRR,** Treatment response rate.

Table 4
Methodologic quality of the included trials assessed using the Cochrane"risk of bias"tool.

Reference	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Zhu, 2015[16]	+	?	?	?	+	+	+
Meng. 2021 [26]	+	?	?	?	+	+	+
Liu, 2019[25]	+	?	?	?	+	+	+
Xie, 2018[28]	+	?	?	?	+	+	+
Wang, 2016 [14]	+	?	?	?	+	+	+
Si et al., 2019 [27]	+	?	?	?	+	+	+
Zheng., 2016 [29]	+	?	?	?	+	+	+
Yuan, 2015 [15]	+	?	?	?	+	+	+
Cheng et al., 2015[24]	+	?	?	?	+	+	+
Wang et al., 2022[30]	+	?	?	?	+	+	+

Notes: + = low risk of bias; **?** = unclear risk of bias; **-** = high risk of bias.

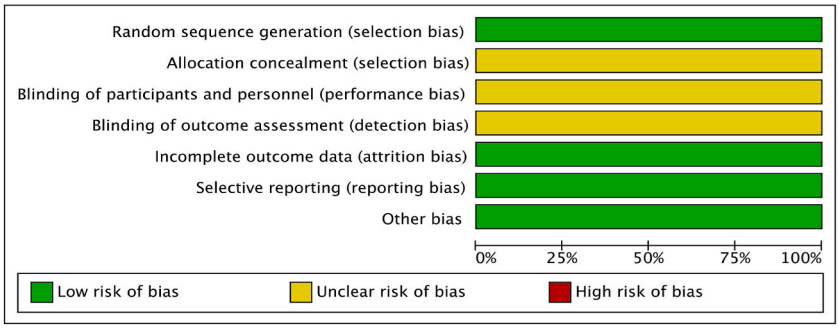

Fig. 2. Risk of bias graph.

3.4.3. Adverse reactions (AR)

Seven RCTs investigated and reported adverse reactions of Simiao Decoction or conventional treatment of HPV and 3 of them indicated that there were no side effects in either the treatment group or the control group. The results demonstrated that Simiao Decoction treatment did not make an increment in the rate of adverse reaction (RR = 0.79, 95 % CI = 0.46–1.33, $P = 0.37$). There was statistical homogeneity for this outcome ($I^2 = 0$ %, $P = 0.87$), and a fixed-effects model was applied to combine the trials (Fig. 6.).

3.4.4. Publication bias

The funnel plots of NCR (Fig. 7) and Egger's test (P = 0.035) showed a potential publication bias in the small trials.

3.4.5. Subgroup and sensitivity analysis

Generally, all included RCTs had a good homogeneity.

As for the primary outcome NCR, the pooled data demonstrated that Simiao Decoction significantly increased NCR (RR = 1.45, 95%CI = 1.31 -1.61, $P < 0.00001$). The results were similar when the subgroup and sensitivity analyses were conducted based on the number of participants (≥40 in each group) (RR = 1.42, 95 % CI = 1.26–1.59, $P < 0.00001$), treatment course (≤30 days) (RR = 1.43, 95 % CI = 1.27–1.61, $P < 0.00001$), quality of the study (Jadad score ≥4) (RR = 1.43, 95 % CI = 1.28–1.60, $P < 0.00001$), or publication date (≥5years) (RR = 1.45, 95 % CI = 1.25–1.69, $P < 0.00001$).

Regarding TRR, the subgroup and sensitivity analyses were conducted according to the number of participants (≥40 in each group), treatment course (≤30 days), quality of the study (Jadad score ≥4), or publication date (≥5 years), the results were similar.

For the incidence of adverse reactions, subgroup, and sensitivity analyses were not possible because of the limited amount of included trials.

Trial Sequential Analysis of NCR showed that Simiao Decoction plus conventional treatment was more effective than conventional treatment alone, and the cumulated sample size of all included studies has reached the required information size (RIS). (Fig. 8).

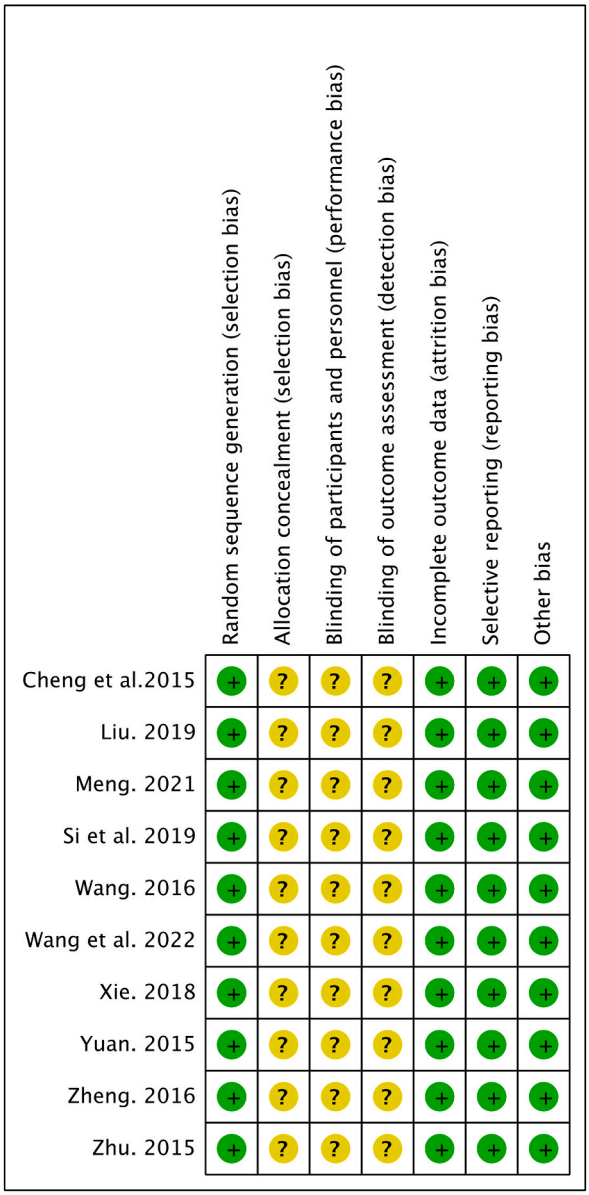

Fig. 3. Risk of bias summary.

3.4.6. Quality of evidence

In all trials, the quality of evidence was downgraded by one level because of the unclear risk of method bias in some trials. Egger's test ($p = 0.035$) of the NCR demonstrated that there was no obvious publication bias, and the evidence was not downgraded. No outcome was eligible for an upgrade. Consequently, the quality of evidence was moderate for the NCR, TRR, and AR scores (Table 6.).

4. Discussion

With a size of about 55 nm, the human papillomavirus (HPV) is a non-enveloped double-stranded DNA virus [32]. HPV is a host - and tissue-specific virus, it often infects epithelial cells through unclean sexual intercourse and damaged skin and mucous membranes, resulting in abnormal proliferation of human skin and mucous membranes [33]. Nowadays, more than 100 HPV genotypes have been found, which can be divided into 3 categories according to the virus's carcinogenic ability: low-risk HPV, including HPV6, 11, 40, 42, 43, 44, 54, 61, 70,72, mainly causing benign genital warts, cervical intraepithelial neoplasm (CIN); high-risk HPV, including HPV16, 18, 31, 33, 35, 39, 43, 51, 52, 56, 58, 59, 68, 73, 82, mainly causing cervical CIN II, CIN III, and cervical cancer. HPV16 and 18 are the most common; HPV26, 53, and 66 are possibly carcinogenic [34].

With economic development and social progress, people's lifestyles have changed, and the HPV-positive rate of women has

Table 5
Summary of the meta-analysis.

Outcome or subgroup		No. of Studies	Participants	Statistical method	Effect size	*p*
NCR		10	799	RR (fixed), 95 % CI	1.45 [1.31, 1.61]	<0.00001*
				OR (fixed), 95 % CI	3.29 [2.38, 4.54]	<0.00001*
				RD (fixed), 95 % CI	0.24 [0.18, 0.30]	<0.00001*
	the number of participants (≥ 40 in each group)	6	560	RR (fixed), 95 % CI	1.42 [1.26, 1.59]	<0.00001*
				OR (fixed), 95 % CI	3.15 [2.15, 4.62]	<0.00001*
				RD (fixed), 95 % CI	0.23 [0.16, 0.31]	<0.00001*
	treatment course (≤ 30 days)	7	567	RR (fixed), 95 % CI	1.43 [1.27, 1.61]	<0.00001*
				OR (fixed), 95 % CI	3.18 [2.19, 4.64]	<0.00001*
				RD (fixed), 95 % CI	0.24 [0.17, 0.31]	<0.00001*
	Jadad score ≥ 4	7	603	RR (fixed), 95 % CI	1.43 [1.28, 1.60]	<0.00001*
				OR (fixed), 95 % CI	3.39 [2.31, 4.97]	<0.00001*
				RD (fixed), 95 % CI	0.23 [0.17, 0.30]	<0.00001*
	publication date (≥ 5 years)	5	359	RR (fixed), 95 % CI	1.45 [1.25, 1.69]	<0.00001*
				OR (fixed), 95 % CI	3.36 [2.09, 5.41]	<0.00001*
				RD (fixed), 95 % CI	0.25 [0.16, 0.34]	<0.00001*
TRR		9	731	RR (fixed), 95 % CI	1.24 [1.15, 1.33]	<0.00001*
				OR (fixed), 95 % CI	3.39 [2.24, 5.12]	<0.00001*
				RD (fixed), 95 % CI	0.17 [0.12, 0.23]	<0.00001*
	the number of participants (≥ 40 in each group	6	560	RR (fixed), 95 % CI	1.24 [1.14, 1.34]	<0.00001*
				OR (fixed), 95 % CI	3.35 [2.10, 5.37]	<0.00001*
				RD (fixed), 95 % CI	0.17 [0.11, 0.23]	<0.00001*
	treatment course (≤ 30 days)	7	567	RR (fixed), 95 % CI	1.26 [1.16, 1.37]	<0.00001*
				OR (fixed), 95 % CI	3.66 [2.02, 6.65]	<0.00001*
				RD (fixed), 95 % CI	0.18 [0.12, 0.25]	<0.00001*
	Jadad score ≥ 4	6	535	RR (fixed), 95 % CI	1.22 [1.16, 1.37]	<0.00001*
				OR (fixed), 95 % CI	3.47 [2.10, 5.74]	<0.00001*
				RD (fixed), 95 % CI	1.16 [1.10, 1.23]	<0.00001*
	publication date (≥ 5 years)	5	359	RR (fixed), 95 % CI	1.25 [1.13, 1.39]	<0.0001*
				OR (fixed), 95 % CI	1.16 [1.10, 1.23]	<0.0001*
				RD (fixed), 95 % CI	0.18 [0.10, 0.26]	<0.0001*
AD		4	576	RR (fixed), 95 % CI	0.79 [0.46, 1.33]	0.37
				OR (fixed), 95 % CI	0.76 [0.42, 1.38]	0.37
				RD (fixed), 95 % CI	−0.02 [-0.06, 0.02]	0.36

*Favours treatment group with statistical significance.
NOTES: **AD**, Adverse Reaction; **CI,** confidence intervals; **NCR**, Negative Conversion Rate Of HPV; **OR,** odds ratio; **RD,** risk difference; **RR,** relative ratio **TRR**, Treatment Respond Rate.

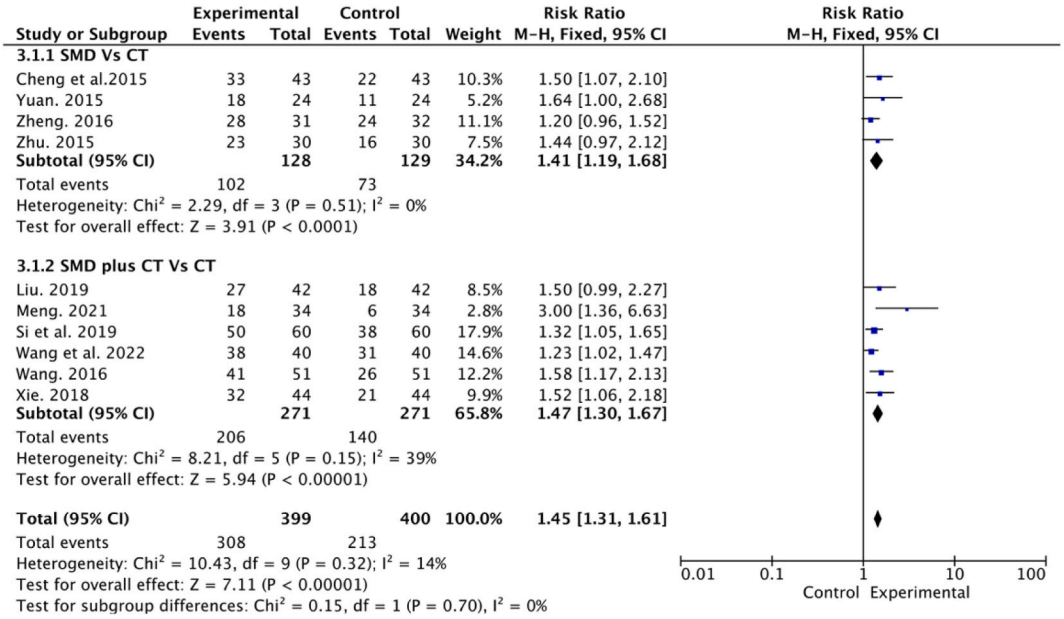

Fig. 4. Forest plot for NCR.
Notes: **CT**, Conventional treatment; **NCR**, Negative conversion rate of HPV; **SMD**, Simiao Decoction.

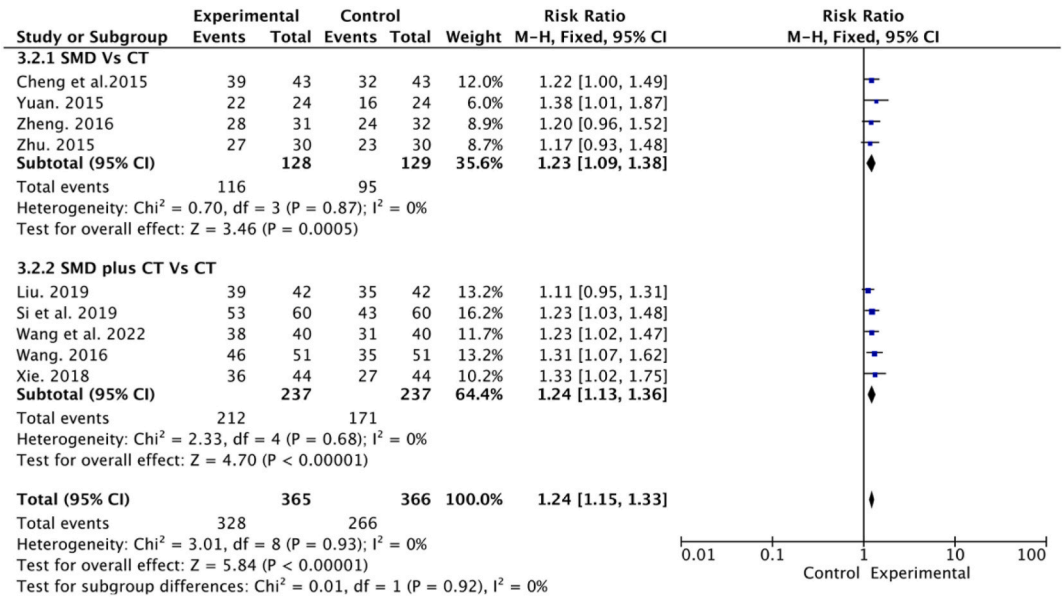

Fig. 5. Forest plot for TRR.
Notes: **CT**, Conventional treatment; **SMD**, Simiao Decoction; **TRR,** Treatment response rate.

increased [35,36]. Currently, there is no specific drug for the treatment of HPV infection. The most common clinical method is a vaginal external drug, such as recombinant human interferon α2b [37], which can effectively prevent and treat HPV infection, and have the effect of preventing and treating tumorigenesis, because of decreasing the replication of the virus in cells by inducing a variety of antiviral proteins and enhance natural killer (NK) cell activity and other immunoregulatory effects [38]. In China, TCM is also

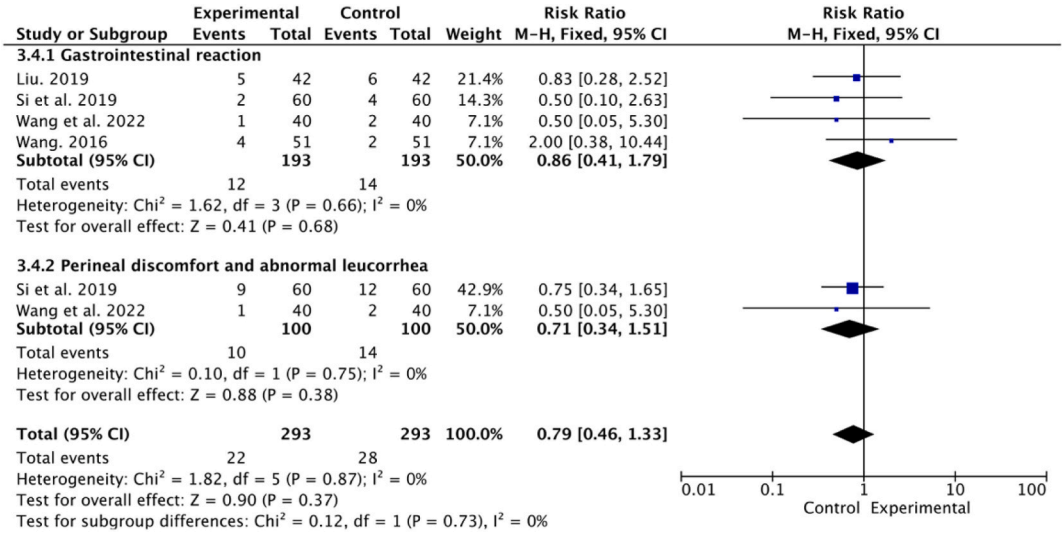

Fig. 6. Forest plot for AR.
Notes: **AR**, Adverse reaction; **CT**, Conventional treatment; **SMD**, Simiao Decoction.

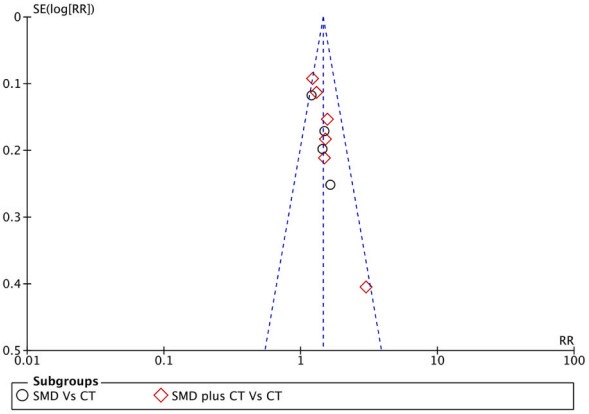

Fig. 7. Funnel plot for NCR.
Notes: **CT**, Conventional treatment; **NCR**, Negative conversion rate of HPV; **SMD**, Simiao Decoction.

commonly used to treat HPV infection, and its curative effect on HPV infection has also been confirmed in some clinical observations [39,30].

However external use of drugs is prone to cause adverse reactions and drug resistance [40,41], while oral TCM decoction has the advantages of low drug resistance, low price, and few adverse reactions by removing the HPV virus and improving immunity in patients [42–45].

Simiao Decoction came from Zhang Bingcheng's 'Fang Cheng Bian Du' in the Qing Dynasty, and it is mainly composed of Cortex Phellodendr, Coixin, Atractylodes, and Achyranthes-Huai. Pharmacological studies have shown that Cortex Phellodendri can enhance the phagocytic ability of phagocytes, thereby enhancing immunity. At the same time, the berberine of PhellodendronPhellodendri can inhibit the production of interleukin-1 and necrosis factor and has an anti-inflammatory effect [46–48]. Coixin, the active substance of Coix seed, can inhibit inflammatory proliferation, thereby alleviating inflammatory response [49,50]. Atractylodes can enhance the function of red blood cells, which also has the effect of antioxidant and anti-inflammatory. Moreover, Atractylodes can regulate immunity, which can enhance the body's non-specific immunity [51–53]. Achyranthes-Huai has an active effect on T cells, which has the effect of regulating immunity and anti-inflammatory [48,54].

At present, increasing clinical reports have shown that Simiao Decoction has a satisfactory effect on the treatment of cervical HPV infection. This study is the first systematic review and meta-analysis to evaluate the efficacy and safety of Simiao Decoction for HPV infection. In this study, 10 RCTs recruiting 799 patients with HPV infection were included. Trial sequential analysis of the primary outcome NCR revealed that Simaio Decoction plus conventional treatment was significantly superior to conventional treatment alone, the result of this meta-analysis provided some useful evidence for the combined use of Simaio Decoction and conventional treatment in

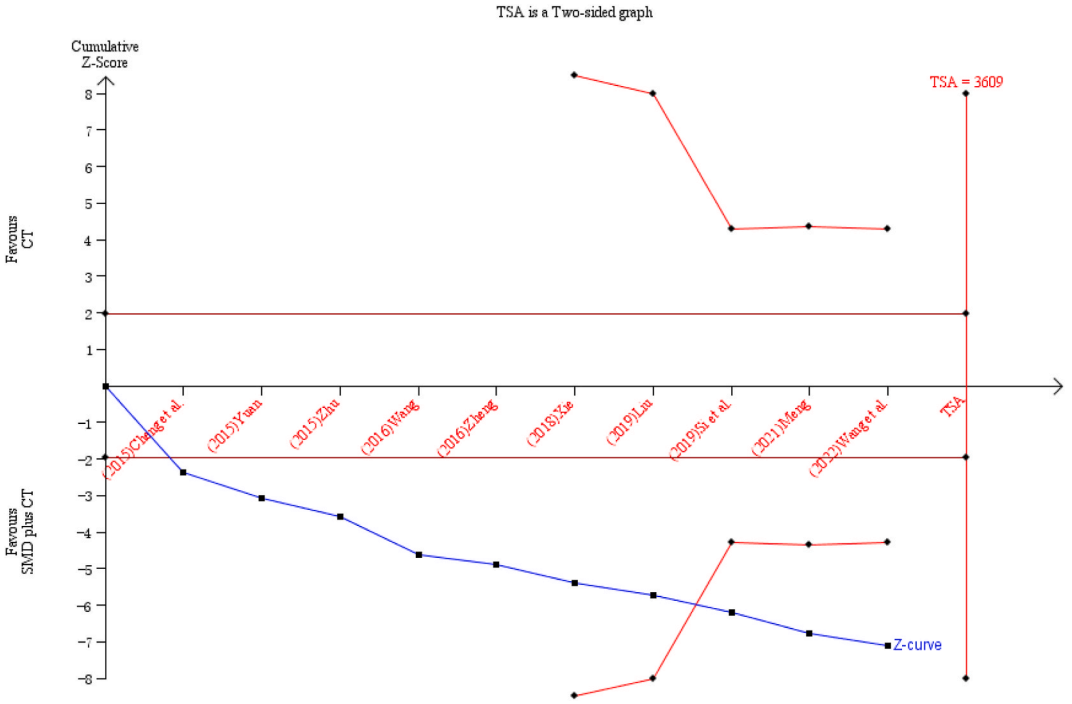

Fig. 8. TSA for NCR.
Notes: **CT,** Conventional treatment; **NCR,** Negative Conversion Rate of HPV; **SMD,** Simiao Decoction; **TSA,** Trial Sequential Analysis.

Table 6
Evidence GRADE profile.

Outcome (No. of trials)	Quality assessment					Treatments for cervical HPV infection		Clinical efficacy and safety		Quality
	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	SMD + CT Or SMD	CT	Relative ratio (95 % CI)	Adverse reactions	
NCR (10)	Serious[a]	No	No	No	None[b]	308/399 (77.2 %)	213/400 (53.3 %)	1.45 [1.31, 1.61]	240 more per 1000 (from 165 more to 325 more)	⊕⊕⊕O Moderate
TRR (9)	Serious[a]	No	No	No	None[b]	328/365 (89.9 %)	266/366 (72.7 %)	1.24 [1.15, 1.33]	174 more per 1000 (from 109 more to 240 more)	⊕⊕⊕O Moderate
AR (4)	Serious[a]	No	No	No	None[b]	22/293 (7.5 %)	28/293 (9.6 %)	Not estimable	20 more per 1000 (from 20 more to 60 more)	⊕⊕⊕O Moderate

Notes: **AR:** Adverse reaction; **NCR:** HPV negative conversion rate; **TRR:** Treatment Response Rate.
[a] Most trials had an unclear risk of methodological bias. Evidence was downgraded by one level.
[b] There was no publication bias. The results were robust. Therefore, the evidence was not downgraded.

the treatment of HPV.

HPV negative conversion rate (NCR) and treatment response rate (TRR) directly indicate the clinical effect of HPV treatment. Compared with conventional topical drugs, the results of this meta-analysis showed that Simiao Decoction significantly improved the HPV negative conversion rate ($P < 0.00001$) and increased the treatment response rate ($P < 0.000\ 01$). Subgroup and sensitivity analyses showed that the results were robust. On the other hand, the result of adverse reactions indicated that Simiao Decoction was safe because it did not increase the side effects for patients ($P = 0.37$). Only 1 RCT reported the HPV viral load of patients after treatment, so the meta-analysis of HPV viral load could not be conducted. There must be more relevant studies to observe this HPV viral load in the future because it can objectively quantify the curative effect after medication.

This study provides some evidence for the clinical application of Simiao Decoction for the treatment of HPV infection. However, the following limitations still exist in this study: (a) Only 1 RCT indicated the specific technique for HPV detecting in inclusion criteria, so it is hard to show detailed diagnostic criteria in our inclusion criteria. (b) The included trials had some potential risk of bias, such as publication bias. (c) Most of the included trials had a relatively small sample size; (d) Subgroup and sensitivity analyses could not be conducted for each endpoint due to the limited number of included trials. (e) HPV viral load can objectively quantify the curative effect after medication, but only 1 RCT reported this endpoint of patients after treatment.

5. Conclusion

Based on the current evidence, Simiao Decoction was more effective and safer than conventional treatment for the treatment of cervical HPV infection. It could effectively increase the negative conversion rate of HPV and treatment response rate while it did not increase adverse reactions. However, the efficacy and safety of Simiao Decoction should be further assessed by more high-quality RCTs with the outcome of HPV viral load and long-term follow-ups.

Data availability statement

Data will be made available on request.

CRediT authorship contribution statement

Lin Qiu: Conceptualization, Investigation, Methodology, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing, Data curation. **Ying Chen:** Investigation, Methodology, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Jue Wang:** Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Lili Yu:** Supervision, Validation, Writing – review & editing. **Qibiao Wu:** Conceptualization, Investigation, Methodology, Supervision, Validation, Visualization, Writing – review & editing. **Hui Mo:** Supervision, Validation, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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