Traditional Chinese medicine for human papillomavirus (HPV) infections: A systematic review

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1. Introduction

Human papillomavirus (HPV) infection, one of the most common sexually transmitted diseases, is detectable at least once in the lifetime of most sexually active people (1). According to a study on a large sample in China, HPV positive rate was 21.7% by hybrid capture II test (HCII) and 15.7% by multiplex polymerase chain reaction fluorescence testing (MPFT) method (2). The virus can be divided into two categories: low-risk types and high-risk types. In most cases, low-risk HPV infections resolve spontaneously due to human immune defense, taking HPV type 1, 2, 3, and 4 as examples. In very few cases, the infection persists and causes warts, benign papilloma, precancerous lesions, and even cancer. High-risk types, HPV 16 and 18 included, are known as a definite biological carcinogen for cancers of the cervix, vulva, vagina, penis, anus, and oropharynx. HPV infection was associated with 4.8% of cancers in 2008 globally, 86.9% of cases being cervical cancer (3). A recent study pointed out that HPV infection explained around 660,000 cases of cancer and 350 million genital warts (4). Genes E6 and E7 are the oncogenes of HPV, which modulate p53 and PDZ-domain proteins and target the retinoblastoma protein family (5). E6 and E7 proteins facilitate viral genome amplification in ways driving cell cycle entry, promoting basal cell proliferation, and causing neoplasia.

There are three HPV vaccines available on the global market, all being safe and effective. Bivalent and quadrivalent vaccines provide protection against
nearly 70% of HPV-associated cervical precancerous and cancerous problems, while the nine-valent vaccine protects against 90% (6). But controversy remains when it comes to the high cost, incomplete protection, nontherapeutic activity and unknown co-factors that influence the efficacy of vaccines. Listed below are the current therapies for cervical intraepithelial neoplasia with HPV infections: i) antiviral drugs like cidofovir, ii) immunoenhancers like interferon and imiquimod, iii) cytotoxic agents like 5-flurouracil (5-FU), iv) photodynamic therapy (PDT), v) therapeutic vaccines, and vi) ablative or excisional treatment (7). However, these approaches are expensive and of limited efficacy with side effects and safety concerns, which greatly restricts their application. Thus, traditional Chinese medicine gains increasing popularity to cover their limitations.

2. Mechanisms

The potential role of traditional Chinese medicine for HPV related diseases has been demonstrated by in vitro and in vivo experiments, which take a step further in the exploration of the underlying mechanism of its active components. Presented below (Table 1) is a brief outline of some recent research on the pharmacology of common Chinese medicine, whose findings can be summarized as follows.

### 2.1. Induce apoptosis

In 1999, Zheng et al. carried out an in vitro study to examine the effect of arsenic trioxide (As$_2$O$_3$), a widely used ingredient in the practice of traditional Chinese medicine, on HPV 16 DNA-immortalized human cervical epithelial cells (HCE16/3 cell line). As$_2$O$_3$ was discovered to increase apoptosis of HCE16/3 cells at a low concentration, which might have a connection with viral oncogene suppression (8). Another study revealed that butein, isolated from the stem extract of Rhus verniciflua, exhibited an inhibitory effect on MCF-7 human breast cancer cell line and human cervical carcinoma cell line HeLa. Butein treatment was found to reduce cell viability, induce apoptosis, and cause DNA damage compared with untreated cells (9).

### 2.2. Modulate gene transcription and protein synthesis

Pinellia extract fraction treatment notably decreased the mRNA expression and protein level of HPV E6 while increasing the mRNA and protein level of p53 in CaSkI and HeLa cervical cancer cells. The down-regulation of HPV E6 gene expression and up-regulation of the

<table>
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<th>Component, Year</th>
<th>Material</th>
<th>Methods</th>
<th>Mechanism of action</th>
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<tr>
<td>Arsenic trioxide (8), 1999</td>
<td>HCE16/3 cells</td>
<td>MTT assay, DNA-fragmentation assay, RT-PCR, flow cytometry, western blot</td>
<td>Decrease intestinal alkaline phosphatase level, repress oncogenes, reactivate p53 and p21, increase apoptosis</td>
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<td>Yigan Kang (12), 2006</td>
<td>HeLa cells, NOD-SCID mice</td>
<td>MTT assay, intestinal alkaline phosphatase activity assay, reversion frequency assay, semi-quantitative RT-PCR, flow cytometry, western blot, tumorigenicity testing</td>
<td>Decrease intestinal alkaline phosphatase level, repress oncogenes, reactivate p53 and p21, increase apoptosis</td>
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<tr>
<td>Baofukang (13), 2007</td>
<td>CaSkI and H8 cells</td>
<td>MTT assay, flow cytometry, RT-PCR</td>
<td>Inhibit cell proliferation, arrest cell cycle, down-regulate oncogene expression, increase apoptosis</td>
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<tr>
<td>Pinellia extract fraction (10), 2012</td>
<td>CaSkI and HeLa cells</td>
<td>RT-PCR, western blot</td>
<td>Down-regulate E6, up-regulate p53</td>
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<td>Youdujing (15), 2012</td>
<td>Cervical tissue of HPV infected patients</td>
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<td>Inhibit hTERT expression</td>
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<td>Tanshinone IIA (11), 2015</td>
<td>CaSkI, SiHa, HeLa, and C33a cells, athymic nude mice</td>
<td>MTT assay, DNA-binding dyes, flow cytometry, western blot, tumor xenograft, real-time PCR</td>
<td>Inhibit oncogene expression, arrest cell cycle, induce p53 and cause apoptosis</td>
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<td>Dehydrocostus lactone (16), 2015</td>
<td>HeLa and C33a cells</td>
<td>MTT assay, flow cytometry, transwell analysis, western blot</td>
<td>Inhibit cell proliferation, inhibit invasion, induce apoptosis, down-regulate phospho-Akt</td>
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<tr>
<td>Butein (9), 2016</td>
<td>MCF-7, HeLa, and ME180 cells</td>
<td>MTT assay, DNA ladder assay, flow cytometry, alkaline comet assay</td>
<td>Reduce cell viability, increase apoptosis, cause DNA damage</td>
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<td>Erhuang Powder (17), 2016</td>
<td>Vaginal lavage and cervical tissue of HPV infected CIN I patients</td>
<td>ELISA and immunohistochemistry assay</td>
<td>Regulate Th1/Th2 balance, increase IFN-γ and Tbet</td>
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</table>

**Abbreviations:** HPV, human papillomavirus; MTT, 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2-H-tetrazolium bromide; RT-PCR, reverse transcription polymerase chain reaction; hTERT, human telomerase reverse transcriptase; Akt, protein kinase B; CIN, cervical intraepithelial neoplasia; ELISA, enzyme-linked immunosorbent assay; IFN, interferon.
p53 gene was thought to be critical to the anti-tumor effect of Pinellia extract fraction (10). In examination of HPV positive CaSk i cells, the Tanshinone IIA, active component of Danshen (Salvia miltiorrhiza), was proven to repress the expression of viral oncoproteins like E6 and E7 genes, reactivate p53 gene, and modulate proteins like E6AP ubiquitin-protein ligase (E6AP), E2F1, and retinoblastoma protein (pRb). This research revealed that the apoptotic effect of Tanshinone IIA was p53-mediated with Bax, Bcl2, and caspase-3 involved (11). In another experiment with Yigan Kang, it was discovered that Yigan Kang down-regulated E6 and E7 oncoproteins while up-regulating p53 and p21 expression in the HeLa cervical cancer line (12). Studies of the Baofukang suppository reported reduction of HPV E6 and E7 mRNA along with inhibition of cell proliferation in the H8 immortalized cervical epithelial cell line, and the CaSk i and SiHa cervical cancer cell lines (13, 14). Highly expressed in most malignant tumors, human telomerase reverse transcriptase (hTERT) was detected to be down-regulated and deactivated after Youdujing treatment (15).

2.3. Regulate cell signal transduction pathways

As one of the traditional Chinese medicines for a broad range of diseases, dehydrocostus lactone could inhibit proliferation and invasion of HeLa (HPV 18 positive) and C33a (HPV negative) human cervical cancer cell lines associated with a reduced level of phospho-protein kinase B (Akt) phosphorylation in a time- or dose-dependent manner. These inhibitions were particularly enhanced combined with specific phosphatidylinositide 3-kinase (PI3K)/Akt inhibitors, which suggested that dehydrocostus lactone might give play to the anti-tumor role via the PI3K/Akt pathway (16).

2.4. Boost immunity

Tumor genesis is closely linked with immune function of the human body. Immunocompromised hosts are at a higher risk for developing HPV related diseases or malignancies. The anti-tumor activity relies mainly on cell immunity, where Th1 cells play an important role. In the study of the clinical effect of Erhuang Powder in HPV-infected cervical intraepithelial neoplasia (CIN) I patients, it was found that the level of interferon-γ (IFN-γ) in vaginal lavage was significantly higher after treatment accompanied by increased expression of T-bet in the cervical tissue, which indicated the regulation of Th1/Th2 balance and improvement of the cervical immune microenvironment (17).

3. Traditional Chinese Medicine

Since there have not been any clinically recommended pharmacological therapies for HPV related health problems, traditional Chinese medicine continues to be an alternative for reasons of efficacy, safety, low cost, and so on. Basic laboratory research has demonstrated the multi-target effectiveness of traditional Chinese medicine for HPV related diseases. Presented below (Table 2) is a brief outline of application of traditional Chinese medicine in HPV related diseases on the basis of clinical findings.

3.1. Internal treatment

Traditional Chinese doctors have treated cervical diseases based on the symptoms and signs since a long time ago. According to the theory formed in practice, Rhizoma Atractylodis, Cortex Phellodendri, Semen Coicis, and Poria have a beneficial effect on spleen function and fluid metabolism; Radix Astragali and Radix Angelicae Sinensis are prescribed to enhance immunity; Flos Lonicerae, Herba Hedyotidis Diffusa, Herba Scutellariae Barbarae, and Herba Lobeliae Chinensis are heat-clearing and detoxifying herbs which are capable of relieving genital itching and pain.

Modified Simiao Decoction, main components containing Radix Atractagali 20 g, Rhizoma Atractylodis 15 g, Cortex Phellodendri 15 g, Semen Coicis 30 g, Radix Angelicae Sinensis 15 g, Poria 15 g, Flos Lonicerae 15 g, Herba Hedyotidis Diffusa 30 g, Herba Scutellariae Barbarae 10 g, Herba Lobeliae Chinensis 10 g, Radix Glycyrrhizae 10 g, exhibited better improvement of clinical symptoms compared with the classic Chinese medicine formulation Baofukang in patients with cervical HPV infection (18). In addition, Modified Simiao Decoction had greater performance of virus clearance and a higher level of IFN-α and tumor necrosis factor-α (TNF-α) which confirmed its antiviral and immune-regulatory effect (19).

Yiqi Huashi Jiedu Decoction, composed of Radix Astragalii 15 g, Poria 20 g, Rhizoma Atractylodis Macrocephalae 15 g, Cortex Phellodendri 10 g, Rhizoma Cyrtomii 10 g, Fructus Amomi 10 g, Radix Angelicae Sinensis 10 g, Rhizoma Chuanxiong 10 g, Radix Gentianae 6 g, Radix Glycyrrhizae 6 g, was another classic formulation that had the power of activating blood circulation, dissipating blood stasis, eliminating necrotic tissues, promoting granulation, dissipate heat, and enhancing diuresis. Adding Fructus Tsoosendan and Rhizoma Corydalis for patients with abdominal pain, Cortex Magnoliales Officinalis for poor appetite, Semen Euryales for leukorrhaga, and Yi qi Huashi Jiedu Decoction showed higher clinical healing rate, better virus clearance, and less recurrence than routine western medical treatment in patients with HPV infection and cervicitis (20).

3.2. External treatment

Evidence has been accumulating on topical Chinese medicine effecting HPV related cervical infection.
### Table 2. The application of Traditional Chinese Medicine in HPV related diseases on the basis of clinical findings

<table>
<thead>
<tr>
<th>Experimental group, Year</th>
<th>Sample size</th>
<th>Control group</th>
<th>Sample size</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modified Simiao Decoction (38), 2013</td>
<td>44</td>
<td>Baofukang</td>
<td>42</td>
<td>Cervical HPV infection</td>
</tr>
<tr>
<td>Modified Simiao Decoction (39), 2015</td>
<td>43</td>
<td>Baofukang</td>
<td>43</td>
<td>Cervical HPV infection</td>
</tr>
<tr>
<td>Yiji Huashi Jiedu Decoction (20), 2015</td>
<td>49</td>
<td>Routine western medical treatment</td>
<td>49</td>
<td>Cervicitis with HPV infection</td>
</tr>
<tr>
<td>Baofukang (21), 2010</td>
<td>137</td>
<td>No</td>
<td>131</td>
<td>Cervicitis with HPV infection</td>
</tr>
<tr>
<td>Baofukang (22), 2013</td>
<td>113</td>
<td>IFN-α2b</td>
<td>143</td>
<td>CIN I, high risk type HPV infection</td>
</tr>
<tr>
<td>Radix Sophorae Flavescentis Ointment (23), 2013</td>
<td>120</td>
<td>No</td>
<td>103</td>
<td>Cervical HPV infection</td>
</tr>
<tr>
<td>ZMLS (24), 2007</td>
<td>94</td>
<td>IFN-α2a</td>
<td>92</td>
<td>Cervicitis, CIN I, HPV infection</td>
</tr>
<tr>
<td>Realgar (25), 2012</td>
<td>26</td>
<td>No</td>
<td>25</td>
<td>CIN I, HPV infection</td>
</tr>
<tr>
<td>Paiteling (26), 2011</td>
<td>80</td>
<td>No</td>
<td>40</td>
<td>CIN I/II, high risk type HPV infection</td>
</tr>
<tr>
<td>Zhai gel (27), 2012</td>
<td>32</td>
<td>No</td>
<td>30</td>
<td>High risk type HPV infection</td>
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<tr>
<td>Youdujing (28), 2012</td>
<td>35</td>
<td>Physiological saline</td>
<td>35</td>
<td>High risk type HPV infection</td>
</tr>
<tr>
<td>Chinese medicine (33), 2016</td>
<td>34</td>
<td>IFN-α2b, Levamisole</td>
<td>34</td>
<td>HPV infection</td>
</tr>
<tr>
<td>Fuheh Jiedu Decoction (34), 2014</td>
<td>40</td>
<td>Pure Chinese medicine/IFN-α</td>
<td>40/40</td>
<td>High risk type HPV infection</td>
</tr>
<tr>
<td>Chinese medicine and Baofukang (35), 2016</td>
<td>40</td>
<td>Baofukang</td>
<td>40</td>
<td>High risk type HPV infection</td>
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<tr>
<td>Qingre Fuheh (36), 2010</td>
<td>64</td>
<td>Water</td>
<td>64</td>
<td>High risk type HPV infection</td>
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<tr>
<td>Ezhiyou-N-CWS (37), 2009</td>
<td>30</td>
<td>No</td>
<td>30</td>
<td>High risk type HPV infection</td>
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<td>CO2 laser and Baofukang (38), 2016</td>
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<td>CO2 laser and polyacryl sulfonic aldehyde</td>
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<td>Microwave therapy and Baofukang (39), 2013</td>
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<td>Microwave</td>
<td>60</td>
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<td>Microwave therapy and Baofukang (40), 2009</td>
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<td>Microwave</td>
<td>279</td>
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<td>Electrocauterization and Baofukang (41), 2016</td>
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<td>Electrocauterization/Baofukang</td>
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<td>High risk type HPV infection</td>
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<tr>
<td>Baofukang and interferon (42), 2014</td>
<td>110</td>
<td>Baofukang/interferon</td>
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<td>Recombinant human IFN-α2b and Baofukang (43), 2016</td>
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<tr>
<td>Jiawei Jiani Decoction and XinFuNing (44), 2016</td>
<td>30</td>
<td>XinFuNing, recombinant human IFN-α2b</td>
<td>30</td>
<td>HPV infection</td>
</tr>
<tr>
<td>Xunxi No. 1 and radiotherapy (45), 2016</td>
<td>40</td>
<td>Radiotherapy</td>
<td>40</td>
<td>Cervical cancer with high risk type HPV infection</td>
</tr>
</tbody>
</table>

**Abbreviations**: HPV, human papillomavirus; IFN, interferon; TNF, tumor necrosis factor; LCT, liquid based cytology; HCII, hybrid capture II test; CIN, cervical intraepithelial neoplasia; ZMLS, Zhimiling suppository; TCT, thinprep cytologic test; hTERT, human telomerase reverse transcriptase; IL, interleukin; ISH, *in situ* hybridization.
As one of the representative drugs for external use, Baofukang suppository was reported to have a higher cure rate and effectiveness in a test group evaluated by gynecological examination, hybrid capture II test (HCII) and liquid based cytology (LCT). Rhizoma Curcumae and Borneolium are the main contents of Baofukang suppository. After a 3-month medication, it showed a 38% HPV negative rate and a 37% relative light units/cutoff (RLU/CO) ratio improvement rate (21). Comparison of Baofukang and IFN-α2b indicated that Baofukang reached a higher HPV negative rate and CIN I reversal rate (22). Radix Sophorae Flavescentis ointment is known as a heat-clearing and damp-drying drug whose antitumor and antivirus function has been gradually recognized in the application of hepatic and gastric carcinoma. Clinical study proved that it had a 36% viral conversion rate which was remarkably higher than the spontaneous regression rate of the blank control group (23). Zhimiling suppository (ZMLS) intravaginal suppository, ingredients including Cortex Phellodendri, Radix Sophorae Flavescentis, Catechu, and Borneolium, had a 93.6% efficacy rate versus 93.5% for the IFN-α2a treatment (24). It emphasized a similar clinical remission result for ZMLS which is more cost-effective. Verified by clinical trials, external application of realgar, 1 g each time every 3 days in the cervical surface of patients tested with HPV infection and CIN I pathological changes, yielded a 53% HPV negative rate and 50% CIN I reversal rate. (25). Paiteling, composed of Herba Hedyotidis Diffusae, Folium Isatidis, Fructus Cnidii, and Fructus Bruecae, had a cytotoxic effect for repressing proliferation of cancer cells and damaging the HPV pathogen which took effect in CIN I/II patients (26). Zibai gel, the active ingredient being Radix Arnebiae, Rhizoma Curcumae, Cortex Phellodendri, Flos Lonicerae, and Radix Sophorae Flavescentis, was found to reduce viral load, effectively relieve symptoms, and improve cytological and pathological results for cervical infected patients (27). Apart from the clinical effectiveness of Youdujing cream in cervical infected patients from etiological, cytological, and pathological levels (28), it was a popular choice for condyloma acuminatum as well. The active components of Youdujing include Fructus Bruecae, Rhizoma Curcumae, Raidx Arnebiae, and so on. To investigate the therapeutic effect of Youdujing in genital lesions, in vitro experiments were conducted showing the inhibition of HPV-DNA amplification (29,30).

As another form of traditional Chinese medicine, acupuncture is useful in treating a variety of dermatologic disorders, human papillomavirus warts included. As the research work goes further and becomes more detailed, increased importance has been attached to the neuro-immuno-modulation role of acupuncture in pathogenesis of dermatological HPV infections (31). There was a case report about the long-term therapy of traditional Chinese acupuncture clearing away a giant HPV wart that an HIV infected patient developed when cryotherapy failed (32).

3.3. Internal and external treatment

Various combinations of internal and external medicine, focusing on both the local lesion and whole body, have been used to treat HPV infection. Modern pharmacology of traditional Chinese medicine has demonstrated the power of those herbs. For instance, Folium Isatidis, Radix Isatidis, and Herba Portulacae are able to clear heat-toxin and eliminate dampness; Semen Persicae, Flos Carthami, and Rhizoma Cyperi can promote blood circulation and dissipate stasis; Concha Margarithfera, Concha Ostreae, and Spica Prunellae are capable of removing lumps and warts; Radix Astragali, Rhizoma Atractylodis Macrocephalae, and Poria strengthen the spleen and stomach; and Fructus Lycii, Radix Polygoni Multiflori, and Radix Rehmanniae are beneficial to the liver and kidney. Oral administration and fumigation of Chinese medicine has proven to have clinical value (33). Compared with pure external use of Chinese medicine or IFN-α, the combined use of oral decoction and topical powder received better clinical effects assessed by symptoms and signs in line with the decline of viral load (34). A decoction containing Poria 30 g, Rhizoma Dioscoreae Hypoglaucae 15 g, Radix Achyranthis Bidentatae 12 g, Semen Coicis 30 g, Radix Stephaniae Tetrandrae 10 g, Fructus Forsythiae 12 g, Radix Angelicae Dahuricae 10 g, Rhizoma Atractylodis Macrocephalae 10 g, Herba Violae 15 g, Cortex Phellodendri 12 g, Radix Glycyrrhizae 6 g, with Herba Hedyotidis Diffusae, Herba Patriciae, and Herba Portulacae for patients with excessive heat and toxin, Flos Carthami and Semen Persicae for genital drying, Fructus Kochiae and Cortex Dictamni for genital itching, exhibited significant improvement of cervicitis combined with intravaginal Baofukang suppository (35). According to the study, the associative action of internal treatment and external intervention yielded a notably higher level of IgG, IgA, and IgM (36).

3.4. Integrated medicine

Although western medicine is scientifically sound for treating HPV related health conditions and widely acknowledged for its fast onset, Chinese medicine has been well accepted due to its rich philosophical content. Integrated medicine complements each other. Ezhuyou-N-CWS, a combination of Nocardia rubra cell wall skeleton (N-CWS) and Chinese medicine Ezhuyou, which brought the potent adjuvant and antitumor activities of N-CWS to the broad spectrum of the anti-microorganism effect of Ezhuyou, inhibited the proliferation of HeLa cells in vitro and exhibited effective results in patients with cervical HPV infection (37). In patients with vaginal intraepithelial neoplasia and HPV infections after a cervical cancer operation, CO2 laser
combined with Baofukang suppository showed a superior curative effect compared to pure laser treatment (38). Both, retrospective and prospective studies confirmed the better clinical effect of microwave therapy combined with Baofukang in chronic HPV infected patients (39,40). The application of electrocauterization and Baofukang was also reported to have a better therapeutic effect (41). A clinical trial showed that the HPV negative rate was 92.8% in cervical infected patients after the combined use of Baofukang and IFN, higher than 61% in the IFN group and 59.1% in the Baofukang group (42). Moreover, further research pointed out this combination could regulate immune function measured by TNF-α and interleukin-6 (IL-6) level (43). For cervical HPV infected patients, Jiawei Jianpi Decoction plus recombinant IFN-α2b exhibited a higher effective rate and HPV negative rate and a lower symptoms score than the pure IFN group (44). Chinese medical intervention (Xunxi No.1) plus radiotherapy benefited cervical cancer patients, whose 5-year disease-free survival rate was higher and metastasis rate was much lower compared with a radiotherapy group (45).

4. Conclusion

Persistent infections of human papillomavirus (HPV) bring various health problems. HPV vaccines provide type-restricted and expensive protection for uninfected groups. Perfect treatments for HPV-associated benign or malignant diseases are not available at the moment. Chinese medicine emphasizes integrity and has fewer side effects. This systematic review summarized the clinical findings and laboratory research with the theme of the application of traditional Chinese medicine in HPV infection and related diseases. It explored the composition and mechanisms of some most frequently used prescriptions. To conclude, traditional Chinese medicine improves clinical index in the treatment of cervical cancer and genital warts as a result of its signal transduction pathways and body immune function.

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