

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

Jing Lin^{1,2,3,*}, Lanting Chen^{1,2,3,*}, Xuemin Qiu^{1,2,3}, Na Zhang^{1,2,3}, Qiting Guo⁴, Yan Wang^{1,2,3}, Mingyan Wang^{1,2,3}, Hans-Jürgen Guber⁵, Dajin Li^{1,2,3}, Ling Wang^{1,2,3,**}

¹Laboratory for Reproductive Immunology, Hospital & Institute of Obstetrics and Gynecology, IBS, Shanghai Medical College, Fudan University, Shanghai, China;

²Shanghai Key Laboratory of Female Reproductive Endocrine-related Diseases, Shanghai, China;

³The Academy of Integrative Medicine of Fudan University, Shanghai, China;

⁴Public Health of Zhejiang University, Hangzhou, China;

⁵Department of Pharmacy, Kepler University Clinic, Neuromed Campus, Linz, Austria.

Summary

Human papillomavirus (HPV) infections are common and generally harmless, but persistent infections can bring health problems like cancer and genital warts. For the uninfected group, HPV vaccines provide safe and effective protection, but they're type-restricted and expensive. For those infected, so far there have been a handful of treatments for HPV-associated benign or malignant diseases, traditional Chinese medicine being one of them. This systematic review focuses on the application of traditional Chinese medicine in HPV infection and related diseases on the basis of clinical findings. Moreover it covers compositions and mechanisms based on *in vitro* laboratory methods and animal models. Traditional Chinese medicine improves clinical index in the treatment of cervical cancer and genital warts; the mechanisms behind the effectiveness might be the regulation of cell apoptosis, viral gene transcription and translation, cell signal transduction pathways, and immune function.

Keywords: Traditional Chinese medicine, human papillomavirus (HPV), HPV infection, cervical cancer, genital warts

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

Released online in J-STAGE as advance publication May 6, 2017.

*These authors contributed equally to this work.

**Address correspondence to:

Dr. Ling Wang, Laboratory for Reproductive Immunology, Hospital & Institute of Obstetrics and Gynecology, IBS, Fudan University Shanghai Medical College, 413 Zhaozhou Road, Shanghai 200011, China.

E-mail: Dr.wangling@fudan.edu.cn

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-fluorouracil (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_2O_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_2O_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 1. The methodologies and findings of recent researches on Traditional Chinese Medicine for HPV infections

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

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 CaSki cells, the Tanshinone IIA, active component of Danshen (*Salvia miltiorrhiza*), was proven to repress the expression of viral oncogenes 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 oncogenes 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 CaSki 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 phosphatidylinositol 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; Faeces Troglodyterpri, Flos Lonicerae, Herba Hedyotidis Diffusae, Herba Scutellariae Barbatae, 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 Astragali 20 g, Rhizoma Atractylodis 15 g, Cortex Phellodendri 15 g, Semen Coicis 30 g, Radix Angelicae Sinensis 15 g, Poria 15 g, Faeces Troglodyterpri 10 g, Flos Lonicerae 15 g, Herba Hedyotidis Diffusae 30 g, Herba Scutellariae Barbatae 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 Astragali 15 g, Poria 20 g, Rhizoma Atractylodis Macrocephalae 15 g, Cortex Phellodendri 10g, Rhizoma Cyrtomii 10 g, Fructus Amomi 10 g, Radix Angelicae Sinensis 10 g, Rhizoma Chuanxiong 10 g, Radix Gentianae 6g, 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 Toosendan and Rhizoma Corydalis for patients with abdominal pain, Cortex Magnoliae Officinalis for poor appetite, Semen Euryales for leukorrhagia, and Yiqi 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

Experimental group, Year	Sample size	Control group	Sample size	Patients	Clinical index
Modified Simiao Decoction (18), 2013	44	Baofukang	42	Cervical HPV infection	Symptoms, HPV negative rate
Modified Simiao Decoction (19), 2015	43	Baofukang	43	Cervical HPV infection	Symptoms, histopathology, HPV negative rate, IFN- α , TNF- α
Yiqi Huashi Jiedu Decoction (20), 2015	49	Routine western medical treatment	49	Cervicitis with HPV infection	Symptoms, colposcopic observation, HPV negative rate
Baofukang (21), 2010	137	No	131	Cervicitis with HPV infection	LCT, HCII, colposcopic observation
Baofukang (22), 2013	113	IFN- α 2b	143	CIN I, high risk type HPV infection	LCT, colposcopic observation and biopsy, HCII, HPV negative rate
Radix Sophorae Flavescens Ointment (23), 2013	120	No	103	Cervical HPV infection	HPV negative rate
ZMLS (24), 2007	94	IFN- α 2a	92	Cervicitis, CIN I, HPV infection	Symptoms, HPV negative rate
Realgar (25), 2012	26	No	25	CIN I, HPV infection	TCT, HPV negative rate, colposcopic observation and biopsy
Paiteling (26), 2011	80	No	40	CIN I/II, high risk type HPV infection	TCT, HPV detection, colposcopic observation and biopsy
Zibai gel (27), 2012	32	No	30	High risk type HPV infection	Symptoms, HCII, LCT, colposcopic observation and biopsy
Youdujing (28), 2012	35	Physiological saline	35	High risk type HPV infection	HPV detection, colposcopic observation and biopsy, hTERT mRNA expression
Chinese medicine (33), 2016	34	IFN- α 2b, Levamisole	34	HPV infection	Flow cytometry, HPV detection
Fuzheng Jiedu Decoction (34), 2014	40	Pure Chinese medicine/IFN- α	40/40	High risk type HPV infection	Symptoms, HPV detection, IL-6 level
Chinese medicine and Baofukang (35), 2016	40	Baofukang	40	High risk type HPV infection	Gynecological examinations, HPV detection, HCII
Qingre Fuzheng (36), 2010	64	Water	64	High risk type HPV infection	HPV detection, LCT, biopsy, measure of IgA, IgG, IgM, C3, and C4
Ezhuyou-N-CWS (37), 2009	30	No	30	High risk type HPV infection	HPV detection, LCT, biopsy, levels of IgA, IgG, IgM, C3, and C4
CO ₂ laser and Baofukang (38), 2016	80	CO ₂ laser and polycresol sulfonic aldehyde	60	Intraepithelial neoplasia and high risk type HPV infection	HPV detection, TCT, colposcopic biopsy
Microwave therapy and Baofukang (39), 2013	121	Microwave	60	Chronic cervicitis with high risk type HPV infection	TCT, colposcopic observation, HPV detection
Microwave therapy and Baofukang (40), 2009	278	Microwave	279	Chronic cervicitis with HPV infection	Symptoms, colposcopic observation, HPV detection
Electrocauterization and Baofukang (41), 2016	47	Electrocauterization /Baofukang	56/43	High risk type HPV infection	Colposcopic observation, HCII, HPV detection
Baofukang and interferon (42), 2014	110	Baofukang/interferon	110/100	Cervical erosion and HPV infection	HPV detection, colposcopic observation and biopsy, cytology
Recombinant human IFN- α 2b and Baofukang (43), 2016	53	Baofukang	53	High risk type HPV infection	HPV detection, colposcopic observation and biopsy, levels of TNF- α and IL-6
Jiawei Jiapi Decoction and XinFuNing (44), 2016	30	XinFuNing, recombinant human IFN- α 2b	30	HPV infection	Symptoms, HPV detection
Xunxi No. 1 and radiotherapy (45), 2016	40	Radiotherapy	40	Cervical cancer with high risk type HPV infection	ISH for HPV16/18, 5-year disease-free survival, pelvic lymphnode metastasis

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 effectivity in a test group evaluated by gynecological examination, hybrid capture II test (HCII) and liquid based cytology (LCT). Rhizoma Curcumae and Borneolum 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- α 2b 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 antiviral 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 Borneolum, had a 93.6% efficacy rate versus 93.5% for the IFN- α 2a 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 Bruceae, 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 Bruceae, Rhizoma Curcumae, Radix 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 Margaritifera, 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 Patriniae, and Herba Portulacae for patients with excessive heat and toxin, Flos Carthami and Semen Persicae for genital drying, Fructus Kochiae and Cortex Dictamnii 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- α 2b 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 regulation in cell apoptosis, viral gene expression, cell signal transduction pathways and body immune function.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (grant no. 31571196 to Ling Wang), the Science and Technology Commission of Shanghai Municipality 2015 YIXUEYINGDAO project (grant no.15401932200 to Ling Wang), the FY2008 JSPS Postdoctoral Fellowship for Foreign Researchers (P08471 to Ling Wang), the National Natural Science Foundation of China (grant no. 30801502 to Ling Wang), the Shanghai Pujiang Program (grant no. 11PJ1401900 to Ling Wang), the National Natural Science Foundation of China (grant no. 81401171 to Xue-Min Qiu), the Development Project of Shanghai Peak Disciplines-Integrated Chinese and

Western Medicine (grant no. 20150407).

References

1. Park IU, Introcaso C, Dunne EF. Human papillomavirus and genital warts: A review of the evidence for the 2015 centers for disease control and prevention sexually transmitted diseases treatment guidelines. *Clin Infect Dis*. 2015; 61:S849-855.
2. Zeng Z, Austin RM, He X, Chen X, Guo X, Zheng B, Wu S, Yang H, Zhao C. Prevalence of high-risk human papillomavirus infection in China: Analysis of 671,163 human papillomavirus test results from China's largest college of American pathologists-certified laboratory. *Am J Clin Pathol*. 2016; 145:622-625.
3. Forman D, Martel CD, Lacey CJ, Soerjomataram I, Tieulent JL, Bruni L, Vignat J, Ferlay J, Bray F, Plummer M, Franceschi S. Global burden of human papillomavirus and related diseases. *Vaccine*. 2012; 30:12-23.
4. Denny L. Epidemiology and burden of disease associated with HPV infection. *Curr Obstet Gynecol Rep*. 2016; 5:189-195.
5. Doorbar J, Quint W, Banks L, Bravo IG, Stoler M, Broker TR, Stanley MA. The biology and life-cycle of human papillomaviruses. *Vaccine*. 2012; 30:55-70.
6. Angioli R, Lopez S, Aloisi A, Terranova C, Cicco CD, Scaletta G, Capriglione S, Miranda A, Luvero D, Ricciardi R, Montera R, Plotti F. Ten years of HPV vaccines: State of art and controversies. *Crit Rev Oncol Hematol*. 2016; 102:65-72.
7. Hampson L, Martin-Hirsch P, Hampson IN. An overview of early investigational drugs for the treatment of human papilloma virus infection and associated dysplasia. *Expert Opin Investig Drugs*. 2015; 24:1529-1537.
8. Zheng J, Deng YP, Lin C, Fu M, Xiao PG, Wu M. Arsenic trioxide induces apoptosis of HPV16 DNA-immortalized human cervical epithelial cells and selectively inhibits viral gene expression. *Int J Cancer*. 1999; 82:286-292.
9. Tong XQ, Lv W, Luo WQ, Lu WX, Li N. Treatment of human cervical cancer cells with butein leads to apoptosis and DNA damage. *Int J Clin Exp Med*. 2016; 9:11084-11089.
10. Li GL, Xia Q, Chen SH, Gui SQ, Xu CJ. Effects of Pinellia extract fraction on expressions of HPV16 and P53 genes in cervical cancer cell lines. *China J Tradit Chin Med Pharm*. 2012; 27:113-116. (in Chinese)
11. Munagala R, Aqil F, Jeyabalan J, Gupta RC. Tanshinone IIA inhibits viral oncogene expression leading to apoptosis and inhibition of cervical cancer. *Cancer Lett*. 2015; 356:536-546.
12. Deng WP, Chao MW, Lai WF, Sun C, Chung CY, Wu CC, Lin IH, Hwang JJ, Wu CH, Chiu WT, Chen CY, Redpath JL. Correction of malignant behavior of tumor cells by traditional Chinese herb medicine through a restoration of p53. *Cancer Lett*. 2006; 233:315-327.
13. Zhang XY, Bian ML, Fang Q, Chen QY, Chen ZH, Xu M. Study on the mechanism of the proliferative inhibition of Baofukang suppository on human papillomavirus *in vitro*. *J China-Japan Friendship Hosp*. 2007; 21:216-219+259. (in Chinese)
14. Shang YH, Bai LX, Wei LH. The molecular mechanism of Baofukang suppository as a potential inhibitor for cervical carcinoma cell. *Chin J Clin Obstet Gynecol*. 2003; 4:336-338+381. (in Chinese)

15. Xiao J, Wu J, Yu B, Xie HH. Therapeutic efficacy of Youdujing preparation in treating cervical high-risk human papilloma virus infection patients. *Chin J Integr Tradit West Med* 2012; 32:1212-1215. (in Chinese)
16. Jiang EP, Sun XW, Kang HX, Sun LP, An WF, Yao YH, Hu XR. Dehydrocostus Lactone inhibits proliferation, antiapoptosis, and invasion of cervical cancer cells through PI3K/Akt signaling pathway. *Int J Gynecol Cancer*. 2015; 25:1179-1186.
17. Xu YX, Yuan L. Improvement of cervical microenvironment and effect of Erhuang Powder on CIN I accompanied by human papillomavirus infection according to Th1/Th2 immune balance. *Liaoning J Tradit Chin Med*. 2016; 43:962-965+1118. (in Chinese)
18. Dou BF, Zhang JG, Liu B. Analysis on effect of Modified Simiao Decoction in treatment of cervical HPV infection. *Liaoning J Tradit Chin Med*. 2013; 40:1141-1142. (in Chinese)
19. Cheng JM, Tong Y, Chen SC, Zhang L. Clinical effect of modified Simiao Decoction in treating cervical HPV infection. *Pharm Clin Chin Mater Med*. 2015; 31:149-150. (in Chinese)
20. He JM, Huo DZ, Chen YM. Influence of Yiqi Huashi Jiedu Decoction on TCM symptom score and HPV turn rate of cervicitis with HPV infection. *Chin Arch Tradit Chin Med*. 2015; 33:2390-2392. (in Chinese)
21. Bian ML, Chen QY, Zhu J, Ma L, Hao M, Liu J, Chen Y. The efficacy of baofukang suppository for treatment of cervicitis combined with persistent HPV infection. *Chin J Pract Gynecol Obstet*. 2010; 26:383-385. (in Chinese)
22. Shen JJ, Liu ZH, Li J, Zhou YQ, Wang C, Wu RF. The clinical observation for Baofukang and interferon in promoting the regression of low-grade cervical intraepithelial neoplasia. *Chin J Clin Obstet Gynecol*. 2013; 14:509-512. (in Chinese)
23. Wang YH, Wang F, Li YQ. Clinical study on treatment of cervical HPV infection by Radix Sophorae Flavescens ointment. *Med J Natl Defending Forces Southwest China*. 2013; 23:189-191. (in Chinese)
24. Zhang Y, Wang XY, Ding ZY. Treatment of female patients with vaginal and cervical HPV infection. *Chin J Infect Chemother*. 2007; 7:293-294. (in Chinese)
25. Zhang MY. Clinical study on the interventive effect of realgar on the clearance of HPV and CIN. *J Clin Exp Med*. 2012; 11:580-581. (in Chinese)
26. Chen R, Zhao J, Liao QP. The clinical observation report of paiteling on treatment of CIN1/2. *Chin J Pract Gynecol Obstet*. 2011; 27:703-705. (in Chinese)
27. Ma XL, Xue XO, Li S, Wang Y, Xie W. Clinical study of Zibai gel on treatment of cervical high-risk human papillomavirus infection. *Chin J Inform TCM*. 2012; 19:9-12. (in Chinese)
28. Xiao J, Huang JL, Cai LE. Study of Youdujing in treating HR-HPV infected cervical lesions. *Guangdong Med J*. 2011; 32:2036-2039. (in Chinese)
29. Hou MJ, Fan RQ, Sun J, Xuan GW, Chi FH. Effect of Chinese medicine Youdujing for human papilloma virus DNA. *J Guangzhou Univ Tradit Chin Med*. 1998; 15:57-60. (in Chinese)
30. Feng Y, Deng YH, Xuan GW, Zhou D, Sun J, Yuan XH, Zhao RZ. Preparation and *in vitro* pharmacodynamics effect of the Youdujing cream. *Chin Hosp Pharm J*. 2004; 24:7-8. (in Chinese)
31. Ma C, Sivamani RK. Acupuncture as a treatment modality in dermatology: A systematic review. *J Altern Complement Med*. 2015; 21:520-529.
32. Ursini T, Polilli E, Congedo G, Tontodonati M, Masi FD, Mazzotta E, Parruti G, Pippa L. Complete healing of a giant wart in a severely immune-compromised patient with HIV infection treated with acupuncture. *Case Rep Dermatol*. 2011; 3:175-180.
33. Mai LX, Yang GZ, Yuan SH, Wang DN, Zhang T, Deng WC, Huang PJ. Effect of treatment by Chinese herbs for subclinical papillomavirus infection (SPI) and change of T cell subpopulation. *Liaoning J Tradit Chin Med*. 2016; 43:750-752. (in Chinese)
34. Ye LQ, Lou KL, Chen Y, Jiang Y. Clinical study of Chinese medicine intervention in treating cervical HR-HPV infection. *Acta Chin Med Pharm*. 2014; 42:79-82. (in Chinese)
35. Qin JL, Fu MX, Cheng JJ. Clinical effect of Chinese medicine and Baofukang in treating high-risk human papilloma virus. *Modern J Integr Tradit Chin West Med*. 2016; 25:1538-1540. (in Chinese)
36. Zhang PY, Wang XB, Xu X, Yang J, Yang HY. Study of intervention by traditional Chinese medicine for cervical precancerous lesion infected by high-risk HPV. *Liaoning J Tradit Chin Med*. 2010; 37:1191-1194. (in Chinese)
37. Chi Y, Li J. Ezhuyou-N-CWS carrier suppository for antagonizing HPV infection and preventing cervical cancer. *J Beijing Univ Tradit Chin Med*. 2009; 32:419-421. (in Chinese)
38. Wang Y, Su L, Kong WM, Wu YM, Duan W. Clinical study of CO2 laser combined with Baofukang suppository in the treatment of vaginal intraepithelial neoplasia with high risk HPV infection. *Oncol Prog*. 2016; 14:441-443+448. (in Chinese)
39. Zhao MJ, Wang SJ, Wei WH. Analysis of microwave therapy plus Baofukang in treating chronic cervicitis with high risk HPV infection. *Matern Child Health Care China*. 2013; 28:5730-5731. (in Chinese)
40. Yan LS, Yan JF. Clinical value of microwave therapy plus Baofukang in treating chronic cervicitis with HPV infection. *Matern Child Health Care China*. 2009; 24:4182-4183. (in Chinese)
41. Yu J, Yang HY, Zhang LJ, Zhang HP, Liu Y. Clinical study on the treatment of high risk HPV infection. *Chin J Nosocomiol*. 2016; 26:3069-3071. (in Chinese)
42. Xu JQ, Xu JG, Song XZ. Clinical observation of Baofukang combined with interferon in the treatment of cervical erosion complicated with HPV infection. *Chin Arch Tradit Chin Med*. 2014; 32:2028-2030. (in Chinese)
43. Li MX, Xue HY, Chen JP, Zhang XQ, Zhang YL. Effects of treatment efficacy and immune function of recombinant human interferon α -2b with Baofukang vaginal for patients combined with human papillomavirus infection. *Chin J Nosocomiol*. 2016; 26:3296-3298. (in Chinese)
44. Tang QJ, Guo SS, Wang ZZ. Clinical study of cervical HPV infection treated by Jiawei Jianpi Decoction combined with XinFuNing. *Shanghai J Tradit Chin Med*. 2016; 50:55-57. (in Chinese)
45. Xu X, Zhang B, Hao L, Gu J, Liu L, Wang X, Wu M, Zhang P, Cheng H. Combined use of Xunxi No. 1 and radiotherapy have clinical benefits in stage Ia-IIb cervical cancer patients with high-risk human papilloma virus infection. *Minerva Biotechnol*. 2014; 26:309-313. (in Chinese)

(Received March 8, 2017; Revised April 17, 2017; Accepted April 20, 2017)