

Herbs Against Human Papillomavirus

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Abstract

HPV-induced diseases are extremely common and carry substantial morbidity and mortality. Existing methods of prevention and treatment are still inadequate. In this article, the use of *Brassica oleracea* (broccoli, cabbage, etc.), indole-3-carbinol (I3C), and diindolylmethane (DIM) to prevent and treat HPV-related conditions is discussed. *Camellia sinensis* (green tea) leaf catechins including epigallocatechin (EGC) and epigallocatechin gallate (EGCG) and the approved botanical drug derived from them, sin catechins, are used to illustrate an example of a very effective herbal treatment for genital warts.

Other studies on herbal treatments for HPV-mediated diseases, including an immunostimulating formula including *Echinacea purpurea*; and a Chinese immune formula including *Astragalus membranaceus* (astragalus), *Platycodon grandiflorus* (balloon flower), *Angelica sinensis* (*dong quai*), *Wolfiporia cocos* (hoelen), *Ligustrum lucidum* (privet), *Glycyrrhiza uralensis* (Asian licorice), and other herbs, and topical *Periploca sepium* (silk vine) are discussed.

Introduction

Human papillomavirus (HPV), a nonenveloped DNA virus, is the most common sexually transmitted organism in the world.¹ Up to 43% of American women ages 14–59 have been shown to have cervical colonization with HPV and up to 7.5% of the general population in that same age range have been shown to have oropharyngeal colonization.^{2,3} There are > 150 types of HPV, but just a handful of high-risk types cause most of the cancer burden associated with this virus (see Known High-Risk Types of HPV). These cancers often have precancerous lesions that are detectable by screening tests, such as cervical and anorectal intraepithelial neoplasia detectable to the Papanicolaou smear or acetic-acid staining.

Types associated with most cases of anogenital warts and laryngeal papillomatosis are HPV6 and 11.⁴ Spread is via direct skin contact, mainly during sexual activity, but also vertically from mother to newborn. It must also be kept in mind when

assessing therapeutic research in this area that 70%–90% of HPV infections clear spontaneously.⁵

Condom use is still the most important way to prevent HPV, along with vaccination, against the main problem strains (types 6, 11, 16, and 18), but these are imperfect tools. It will take some time for the vaccine to come into widespread use, and there are still many infected people needing safe and effective treatment now. The vaccine is also hampered by lack of coverage for all oncogenic types. In this article, the efficacy and safety of herbal approaches to preventing and treating HPV infection are considered.

Of Brassicas, I3C, and DIM

All the brassica vegetables (*Brassica oleracea* varieties)—including broccoli, broccolini, Romanesco broccoli, cauliflower, cabbage, kale, Brussels sprouts, collard greens, and kohlrabi—contain compounds known as glucosinolates, including indoles. These sulfur-containing molecules exist as glycosides (bound to sugars) inside the plant cells. When the plants are cut or chewed, enzymes in the plants are released indiscriminately and they degrade the glycosides. This releases the aglycones of the glucosinolates, including the very important compound indole-3-carbinol (I3C; see Fig. 1) that is released from glucobrassicin. When I3C encounters stomach acid, this compound dimerizes quickly to diindolylmethane (DIM; see Fig. 1) and converts to a whole cascade of other metabolites (including indolocarbazole and 2-[indol-3-ylmethyl]-3,3'-diindolylmethane).

Brassica indoles are all potent anti-HPV molecules. They act in part by inducing cytochrome 1A1 (CYP1A1), primarily in the liver, which shifts estrogen metabolism toward 2-hydroxylation and away from 16 α - and 4-hydroxylation.⁶ This is beneficial because 2-hydroxyestrone suppresses HPV, while 16 α - and 4-hydroxyestrone promote it.⁷

The 2/16 α -hydroxyestrone ratio will increase in patients consuming an effective dose of brassica vegetables, or taking I3C or DIM, and could be considered a way to test and to ensure both sufficient dosing and patient follow-through (particularly

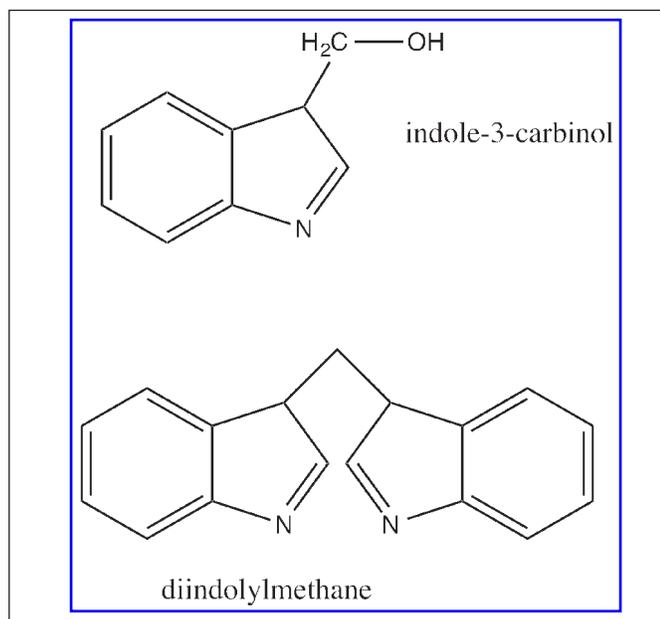


Figure 1. Indole-3-carbinol and diindolylmethane.

in patients who do not have clearing of their HPV-mediated disease).⁸ There is ample other evidence for other, more-direct anticancer mechanisms of these vegetables and compounds.⁹

Several clinical trials have been conducted showing efficacy for cabbage juice and I3C for treating patients with HPV-mediated diseases. Recurrent respiratory papillomatosis (RRP) is an HPV-induced disease that causes formation of large numbers of papillomas in the larynx that can obstruct breathing and usually requires frequent surgery to remove them.

In an early trial in patients with RLP, a higher 2/16 α -hydroxyestrone ratio was associated with less-severe RLP, and eating brassica vegetables improved the ratio and severity of RLP.¹⁰ An open trial assessed the effects of I3C in pills, 200 mg b.i.d., for adults and proportionally less based on weight for children, in patients with RLP.¹¹ Fully one-third of the subjects were completely cured, and another third had significant slowing of growth (and thus proportionally less need for surgery). The remaining third did not benefit. Improvement was associated with an increasing 2/16 α -hydroxyestrone ratio.

A long-term (average 4.8 years) follow-up trial followed 34 adults and children using the same I3C dosing.¹² Again, one-third of the cohort did not require any surgery during the trial, and just under one-third (30%) had significant reduction in papilloma growth. Just over one-third (36%) did not benefit. Adults generally responded better than children did. No one had worsening of the disease. Of 7 cured patients who stopped taking I3C, 4 had relapses. Both of these open trials showed no significant adverse effects.

One trial has evaluated I3C in patients with moderate-to-severe (stage 2 or 3) cervical intraepithelial neoplasia (CIN) associated with HPV infection.¹³ In this double-blinded randomized trial, affected women took I3C, 200 mg q.d. or b.i.d., or placebo for 12 weeks. No patient taking placebo reverted

to normal, while half of the women in both dose groups were cured as shown on repeat biopsy—a highly significant result favoring I3C. The 2/16 α -hydroxyestrone ratio increased in both groups who received I3C, compared to baseline, while the ratio decreased in the placebo group.

In comparison, a double-blinded clinical trial of DIM, 2 mg/kg/day, in 60 women with CIN (stage 2 or 3) failed to show that DIM was any different than placebo for regression of cervical lesions after 12 weeks of treatment.¹⁴ A larger randomized trial of 551 women found that DIM, 150 mg twice daily, failed to produce any better effect on CIN of any stage (but particularly stage 2 and 3) than placebo.¹⁵ An open trial of DIM, 150 mg b.i.d., did show that DIM also improved the urinary 2/16 α hydroxyestrone ratio in 14 women with thyroid disease.¹⁶

A randomized trial compared I3C 200 mg q.d. to b.i.d. dosing in women with high-grade vulvar intraepithelial neoplasia (VIN) for 6 months.¹⁷ While symptoms, such as itching and pain; lesion size and severity; and 2/16 α -hydroxyestrone ratio all improved significantly in both groups, compared to baseline (with no difference between the groups), repeat biopsy showed no improvement in grade of VIN in either group.

The optimal dose and dose-form for brassica vegetables or metabolites has not been determined. However, neither I3C nor DIM is likely the sole active constituent in brassica vegetables, given the array of beneficial acid-condensation products that are taken in from consuming these plants.¹⁸

However, given that the vast majority of clinical trials are on either whole vegetables or I3C, and that many metabolites form from these—not just DIM—it is unlikely that DIM is the optimal form to consume (though DIM may be a major final mediator in the body). There is evidence of synergy between indoles, such as I3C and nonindole compounds, in brassica vegetables.¹⁹ Glucosinolate levels vary in broccoli and other brassica vegetables depending on botanical variety, growing conditions, and postharvest processing.²⁰

The preponderance of clinical trial evidence suggests that patients with HPV-mediated diseases should eat 2–3 servings of brassica vegetables (including sprouts of the same) daily and/or take I3C 200 mg q.d.–b.i.d. I3C should be kept in the refrigerator to avoid degradation.²¹

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because acid is essential to the formation of active metabolites. While using DIM would circumvent this problem, as noted above, DIM was ineffective, compared to placebo, in two clinical trials for women with CIN, so DIM, therefore, would

not appear to be an acceptable alternative to I3C or brassica vegetables. This is one of many examples of areas where research on drug–herb interactions has failed to be conducted, in part, because of the excessive and likely misplaced concern about herbs interfering with drugs when the reverse is likely to be far more widespread.²²

Green Tea

Camellia sinensis (green tea) leaf contains large amounts of flavonoids known as catechins such as epigallocatechin (EGC) and epigallocatechin gallate (EGCG). This tea's many health benefits are beyond the scope of this article; here, the focus is solely on green tea's anti-HPV effects, particularly as the Food and Drug Administration (FDA) approved (in 2006) botanical drug sinecatechins. This is a combination of completely natural catechins (mostly EGCG at 55%) extracted from green tea and mixed in at much higher levels than present in the crude herb. The mechanism of action of green tea catechins against HPV is unknown, but they are unmistakably effective based on ample clinical research.

In a double-blinded trial, 503 patients with external genital warts were randomized to apply either 10% sinecatechins ointment, 15% sinecatechins ointment, or placebo three times daily for 16 weeks.²³ Approximately 50% of the patients in both sinecatechins groups had total clearance of their lesions, compared to 37% of the patients in the placebo group—a significant difference. Fully 78% of patients using either strength of sinecatechins had 50% or better lesion clearance. Of those who had complete clearance, 4%–6% had recurrence within 6 weeks in the sinecatechins groups. Sinecatechins ointment was very safe except for occasional irritation at the application site.

Another trial investigated oral versus topical sinecatechins versus both versus pure EGCG versus no treatment in 100 women with various degrees of CIN.²⁴ Topical ointment was applied twice a week. Patient who were given oral sinecatechins or pure EGCG ingested a 200-mg dose once daily. Treatment lasted 8–12 weeks in all cases. There was a significantly better response (resolution or reduction of cervical lesions) in the groups including a topical component (74% with just ointment, 75% with ointment plus capsules, compared to 50% in the oral sinecatechins group and 60% in the oral EGCG group). The overall response rate for all patients using sinecatechins was 69%, compared to just 10% in the untreated group—a significant difference.

Sinacatechins is safer and much better tolerated than imiquimod, podophyllin, or podofilox topical applications for treating genital warts.²⁵ Of course, podofilox and podophyllin are also natural products, being mixtures of lignans isolated from *Podophyllum pelatum* (mayapple). Both are effective for eliminating genital warts, but are much more likely to damage healthy skin (thus causing pain) and are contraindicated in pregnancy.²⁶

Empirically, the current author has found that green tea powder mixed into a cream base (which is vastly less expensive than sinecatechins) has been just as effective for treating external genital warts. Trials are urgently needed on crude green

Known High-Risk Types of HPV

HPV16 causes the majority of HPV-related cancer and 90% of oropharyngeal cancer^a

HPV18 is tied with HPV31 for being second most carcinogenic to the cervix^b

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HPV33

HPV35

HPV39

HPV45

HPV51

HPV52

HPV56

HPV58

^aGillison ML, Koch WM, Capone RB, et al. Evidence for a causal association between human papillomavirus and a subset of head and neck cancers. *J Natl Cancer Inst* 2000;92:709–720; ^bThomsen LT, Frederiksen K, Munk C, et al. Long-term risk of cervical intraepithelial neoplasia grade 3 or worse according to high-risk human papillomavirus genotype and semi-quantitative viral load among 33,288 women with normal cervical cytology. *Int J Cancer* 2014;December 4:e-pub ahead of print.

tea versus sinecatechins, as well as on the combination of I3C and green tea/sinacatechins, which are likely to work by very different mechanisms and thus should be synergistic.

Both I3C/brassica vegetables and green tea/sinacatechins also need to be studied for prevention of HPV infection and HPV-mediated diseases but are worth recommending in food forms for people at higher risk of such problems as a form of harm reduction (although vaccination and condom use are clearly the most important recommendations).

In one double-blinded, randomized trial, 98 women with low-grade CIN and persistent HPV infection, taking oral sinacatechins 800 mg q.d. or placebo were compared for 4 months.²⁷ Both groups had low rates (14%–17%) of complete clearance of lesions at the end of the study; the difference between the two groups was not significant. More patients (14%) in the sinacatechins group worsened than in the placebo group (7%). The treatment was very safe. Thus, oral sinacatechins alone are not effective for treating CIN. Topical sinacatechins should be studied for this problem.

Other Herbal Treatments Against HPV

A range of other herbs have been tested less rigorously for treating patients with HPV-mediated diseases. An open trial randomized 261 patients with anal warts to surgery alone or surgery plus a formula combining unspecified proportions and amounts of *Echinacea purpurea* aerial parts, *Uncaria* spp. (cat's claw) bark, *Tabebuia* spp. (*pau d'arco*) bark, papaya, grapefruit, and *Andrographis paniculata* (andrographis) aerial

Table 1. Base TCM Formula for Recurrent Respiratory Papillomatosis

Herb	Common names (Mandarin Chinese, Japanese, & English)	Part used
<i>Astragalus membranaceus</i>	Huáng qí, ōgi, astragalus	Root
<i>Platycodon grandiflorus</i>	Jié gēng, kikyō, balloon flower	Root
<i>Angelica sinensis</i>	Dāng guī, tōki, dong quai	Prepared root
<i>Crassostrea gigas</i>	Mǔ lì, borei, Pacific oyster	Shell
<i>Wolfiporia cocos</i>	Fú líng, bukuryō, hoelen	Sclerotium
<i>Carthamus tinctorius</i>	Hóng huā, kōkaa, safflower	Flower
<i>Ligustrum lucidum</i>	Nǚ zhēn zǐ, joteishi, privet	Fruit
<i>Glycyrrhiza uralensis</i>	Gān cǎo, kanzō, Asian licorice	Root
<i>Fritillaria cirrhosa</i>	Bèi mǔ, senbaimo, Sichuan fritillary	Bulb
<i>Prunus persica</i>	Táo rén, tōnin, peach	Seed

TCM, Traditional Chinese Medicine

Table 2. In Vitro Evidence of Anti-HPV Effects of Herbs

Herb or constituent	Results	Reference
<i>Hamamelis virginiana</i> (witch hazel) bark	In vitro inhibited HPV16 by tannins	a
<i>Ficus religiosa</i> (sacred fig) bark	Inhibited or induced apoptosis in cervical-cancer cells infected with HPV16 or HPV18	b
<i>Phyllanthus emblica</i> (Indian gooseberry) fruit	Inhibited carcinogenic gene expression by HPV16 & HPV18	c
Genistein	Induced immune benefits against HPV-induced cervical cancer in mice	d
<i>Bryophyllum pinnatum</i> (life plant, air plant) leaf	Inhibition of HPV18 transcription in cervical-cancer cells	e
<i>Pinellia pedatisecta</i> (fan-leaf Chinese green dragon) rhizome	Downregulation of HPV E6 protein in many cancer-cell lines	f

^aTheisen LL, Erdelmeier CA, Spoden GA, et al. Tannins from *Hamamelis virginiana* bark extract: Characterization and improvement of the antiviral efficacy against influenza A virus and human papillomavirus. PLoS One 2014;9:e88062; ^bChoudhari AS, Suryavanshi SA, Kaul-Ghanekar R. The aqueous extract of *Ficus religiosa* induces cell cycle arrest in human cervical cancer cell lines SiHa (HPV-16 positive) and apoptosis in HeLa (HPV-18 positive). PLoS One 2013;8:e70127; ^cMahata S, Pandey A, Shukla S, et al. Anticancer activity of *Phyllanthus emblica* Linn (Indian gooseberry): inhibition of transcription factor AP-1 and HPV gene expression in cervical cancer cells. Nutr Cancer 2013;65(suppl1):88–97; ^dGhaemi A, Soleimanjahi H, Razeghi S, et al. Genistein induces a protective immunomodulatory effect in a mouse model of cervical cancer. Iran J Immunol 2012;9:119–127; ^eMahata S, Maru S, Shukla S, et al. Anticancer property of *Bryophyllum pinnata* (Lam) Oken leaf on human cervical cancer cells. BMC Complement Altern Med 2012;12:15; ^fLi GL, Jiang W, Xia Q, et al. HPV E6 down-regulation and apoptosis induction of human cervical cancer cells by a novel lipid-soluble extract (PE) from *Pinellia pedatisecta* Schott in vitro. J Ethnopharmacol 2010;132:56–64.

HPV, human papilloma virus.

parts in 1 tablet form t.i.d. for 1 month postoperatively.²⁸ The trial volunteers were not overtly immunosuppressed. Recurrence was just over one quarter as much in the treated versus the control group (7% versus 27%)—a significant difference.

A double-blinded, placebo-controlled trial is warranted to determine if this herbal immunostimulating formula would truly reduce recurrence of anal warts postsurgically, but it looks promising. Other immune treatments should also be investigated for their activity in patients with HPV-mediated diseases.

Twenty patients with severe RRP (requiring many surgeries per year) were treated with traditional Chinese herbal decoctions in an attempt to reduce severity of the condition in one open trial in Japan.²⁹ A base immune-strengthening formula was

prescribed in each case (see Table 1), but practitioners determined the amounts and any additions specific to each patient's case based on Chinese medical energetic assessments. In each case the patients were instructed to take their medicinal decoctions three times per day. Two patients were dropped from the study when they developed squamous-cell carcinoma; 6 others dropped out voluntarily. The mean duration of Chinese herbal therapy was 43.3 months in the remaining 12 patients (9 children and 3 adults). Mean surgical frequency dropped from 2.46 times/year before therapy to 0.39 times/year after therapy—a significant difference. Clinical severity also declined significantly, compared to baseline. Two patients went into total remission. This provides preliminary support for individualized

Chinese herbal treatment of patients with RRP, but more work is needed to follow-up on these observations.

Periploca sepium (xiāng jiā pí, silk vine) root bark is a fairly toxic Chinese herb sometimes encountered as an adulterant of the similarly named *Eleutherococcus senticosus* (cì wǔ jiā, eleuthero) or *E. gracilistylus* (wǔ jiā pí, eleuthero).³⁰ Silk vine contains cardiac glycosides that can cause potentially fatal arrhythmias in overdose and triterpenoid saponins that can be immunosuppressive with long-term use.

Topically, two different preparations of silk vine were compared to podophyllotoxin to treat 81 patients with genital warts.³¹ Cure rates ranged from 43% to 63% with no significant differences between the groups. Adverse-effect rates were dramatically and significantly lower in the silk-vine groups than in the podophyllotoxin group (5%–7% versus 87%), and recurrence rates were significantly lower with silk vine versus podophyllotoxin as well (12%–14% versus 47%). There was some evidence of a direct anti-HPV effect of silk vine. Although systemic toxicity is still a concern, silk vine deserves more study as a topical treatment for genital warts.

Many other herbs have been assessed in vitro for inhibition of HPV (see Table 2). Trials are clearly needed to determine if these herbs are useful clinically.

Conclusion

HPV-mediated diseases are common with high morbidity and substantial mortality. Although preventive measures exist, they are still not sufficiently widely used. Conventional treatment methods all have drawbacks. This article has discussed briefly herbs that have been studied for inhibiting HPV, including one (sin catechins) already approved by the FDA and other national regulatory agencies as a botanical agent. While more research is warranted, the results presented here suggest that a range of herbs and medicinal foods have significant potential to prevent (in the case of brassica vegetables) and treat (in the case of green tea, immunostimulating Western and Chinese herbs, and silk vine) HPV-induced disease. ■

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