Use of Complementary and Alternative Medicine for the Treatment of Genital Herpes

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KEY WORDS

▮ *COMPLEMENTARY AND ALTERNATIVE MEDICINE*
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SUMMARY

Conventional antiviral drugs have proven effectiveness for genital herpes; however, patients continue to use a variety of complementary and alternative medicine (CAM) treatments. Given that patients may be using these products, it is important that healthcare providers become familiar with the data regarding safety and efficacy. We have reviewed available scientific data on six commonly used treatments (echinacea, eleuthero, L-lysine, zinc, bee products and aloe). In addition, information about a number of other products is presented in tabular form. Currently, there are insufficient clinical data to be confident of the efficacy and safety of any of these products for the treatment of genital herpes. It is hoped that future clinical trials will be conducted with sufficient rigour to provide guidance to the patients using these products.

Introduction

COMPLEMENTARY AND ALTERNATIVE medicine (CAM) has been defined as 'a group of diverse medical and healthcare systems, practices and products that are not presently considered to be part of conventional medicine'.[1] These treatments are more likely to be used in conjunction with conventional therapies (complementary), but are sometimes used in lieu of them (alternative). Although CAM interventions can be categorized in a number of ways, five major classifications have been put forward by the National Institutes of Health: biologically based therapies; alternative medical systems; mind–body interventions; manipulative and body-based methods; and energy therapies.[1]

The current review focuses on biologically based CAM treatments (e.g. botanicals, dietary supplements), which are commonly used for the treatment of genital herpes. Individuals may seek treatment to reduce the duration, intensity, frequency and/or discomfort of outbreaks. Although safe and effective antiviral treatments are available, CAM is still utilized frequently by patients with genital herpes.[2]

When reviewing the data on CAM use, there are several caveats that apply to all products. The manner in which these products are regulated varies from country to country, but in a number of countries they are regulated differently and less stringently than other therapeutic products.[3] Evaluation of natural products is challenging given that they can contain multiple pharmacologically active constituents. One must also consider factors such as variations in plant parts used, local cultivating and processing conditions, extraction methods and product formulations.[3,4]

There are many biologically based treatments that have been used for the treatment of genital herpes, including several commercially marketed products that contain multiple biologicals. A critical review of the data on all biologicals and products is beyond the scope of the present manuscript. However, information about the products is available on proprietary web pages or internet sites devoted to CAM.[1,5] In addition, some books regarding the management of herpes provide information about CAM approaches.[6,7] In Table 1, we present a list of products reported to be used for the treatment of genital herpes for which there has been scientific evaluation of efficacy in the English-language literature based on *in vitro*, animal-model or human studies.[8–16] It should be noted that the data on some of these products did not support their efficacy, so inclusion in the table does not indicate that these are effective treatments. Common side-effects are presented in Table 2.[5,62] However, prior to using any treatment, patients and their care providers should review the potential for and typical signs of toxicity, other possible risks including the impact on the integrity of the genital epithelium, and consider whether a CAM product is contraindicated for a particular patient. This information can be obtained from reviews of natural products.[1,5,62] While numerous CAM products have been touted for genital herpes, six of the commonly used treatments listed in Table 1 were chosen for a more detailed review in this article, focusing on clinical evaluation of their efficacy.

Products

ECHINACEA

Preparations of echinacea come from the roots and aerial parts of coneflowers, which are members of the *Asteraceae*.[5] A recent US survey found echinacea to be the most popular biologically based CAM treatment.[63] Findings from *in vitro/in vivo* studies have suggested that various preparations of echinacea have anti-inflammatory,[64] antiviral[23] and immunomodulatory effects.[65]

In an *in vitro* study, *Viracea*, a product containing phytochemicals of *Echinacea purpurea*, had activity against herpes simplex virus (HSV)-2.[23] Another study found that echinacea extracts were active against HSV-1 only after exposure to light.[24] One published double-blind, placebo-controlled, cross-over study examined the efficacy of twice daily oral therapy with 800 mg of *Echinaforce*, a product containing an *Echinacea purpurea* extract (95% plant/5% root), for the treatment of genital herpes. The results failed to show a statistically significant benefit of *Echinaforce*; however, there was a 38% dropout rate, limiting the power to detect differences.[25] Currently, there is insufficient clinical evidence to support the use of echinacea in the treatment of herpes.

ELEUTHERO

Eleutherococcus senticosus (eleuthero/Siberian ginseng), originating primarily in Siberia and popular in China and Russia, is a member of the *Aaraliaceae*

Table 1: Complementary and alternative medicine treatments used for genital herpes

Common Names	Method of application	Selected references
Algae/seaweed	Oral or topical	8,9
Aloe vera	Topical	10–13
Astragalus	Oral	14
Butylated hydroxy-toluene (BHT)	Diet or oral	15,16
Bee products	Topical	17–21
Dragon's blood	Oral or topical	22
Echinacea	Oral	23–25
Eucalyptus oil	Topical	26
Eleuthero/Siberian ginseng	Oral	27,28
Garlic	Diet, oral or topical	29
Liquorice	Oral or topical	30
Lithium	Oral or topical	31–33
L-lysine	Diet or oral	34–41
Lemon balm/melissa	Oral or topical	42–44
Peppermint oil	Topical	45
Prunella vulgaris	Topical	46,47
Resveratrol	Diet or topical	48
St John's wort	Oral or topical	46
Tea tree oil	Topical	26
Vitamins	Diet, oral or topical	49
Zinc	Diet, oral or topical	50–61

Inclusion of a product in this table should not be interpreted as it being an effective treatment.

Table 2: Summary of possible side-effects of complementary and alternative medicine treatments used for genital herpes

Treatment	Possible side-effects
Echinacea (oral)	Rare, but may cause allergic reactions, mild GI effects, sore throat, tingling sensation and numbness of the tongue, mouth ulcers, headaches, dizziness, insomnia and disorientation.[5,62]
Eleuthero (oral)	Rare but more common when used in higher doses. It may cause slight drowsiness, insomnia, mastalgia and mood changes (anxiety, irritability, melancholy).[5,62]
L-lysine (oral)	Minimal with doses under 4000 mg/day.[62]
Zinc (topical)	Application to inflamed tissue can cause burning, stinging, itching or tingling; zinc oxide may cause skin discoloration with repeated application.[5]
Bee products (topical)	Dermatitis.[5,62]
Aloe vera (topical)	Rare but possible burning when applied to dermabraded skin, and redness or itching.[62]

GI, Gastrointestinal.

but differs from 'true' ginsengs from the same plant family.[62] Eleuthero root contains a number of active ingredients (e.g. eleutherosides) and is used because of beliefs in its health-promoting effects.[5]

An *in vitro* study found extract from the roots of eleuthero to inhibit replication of some viruses (e.g. influenza) but not HSV-1.[27] *Elegan*, a product for which the active ingredient was a pure standardized extract of eleuthero, was examined in a double-blind, placebo-controlled study of 93 men and women with HSV-2. More patients taking *Elegan* reported a reduction in severity, duration and frequency of outbreaks than those taking the placebo. However, the authors noted that more than 3 months of dosing were required before optimum effects were seen.[28] This would suggest that *Elegan* would be useful only for suppressive rather than episodic therapy. Additionally, it has been suggested that individuals under 40 years should not use this treatment,[62] which would eliminate many individuals with genital herpes.

L-LYSINE

L-lysine is an amino acid that is not naturally produced in the body. It can be acquired by eating certain foods (e.g. red meats and dairy) or taking supplements. In early *in vitro* studies, L-lysine had an inhibitory effect on HSV replication[34–36] but failed to prevent virus reactivation in ex-planted ganglia.[36] It has been proposed that L-lysine is antagonistic to another amino acid, arginine, which has a growth-supporting action on HSV.[34,35] Arginine also can be obtained through diet (e.g. chocolate and nuts). The antagonism between these two amino acids has led to the suggestion that individuals with herpes increase intake of foods high in L-lysine and reduce intake of arginine-rich foods or take L-lysine supplements.[35] The effects of L-lysine on HSV infections have been explored in a number of clinical studies;[37–41] however, interpretation is complicated by many factors. Study participants were frequently given both dietary recommendations and supplements, and the doses of L-lysine at play in both types of interventions varied widely across studies. In addition, some studies enrolled patients with only oral herpes, whereas others looked at both oral and genital herpes, and endpoints such as healing time or frequency of recurrences varied across studies.

Consequently, it is not surprising that the results of these studies are contradictory. While several have suggested that certain doses of L-lysine supplements are beneficial in reducing either the frequency of recurrences[38,40,41] or time to healing,[37,41] others did not find improved outcomes for one or both of those endpoints.[39,40] However, it is likely that dose is critical and chronic use may be necessary. The studies conducted to date do not provide sufficient information to address dosing and frequency of use.

ZINC

Zinc is found in many foods (e.g. meat, dairy, fish).[5] Oral zinc formulations are commonly believed to have antiviral activity[5] and to facilitate wound healing.[66] There is only anecdotal evidence for the use of oral zinc for the treatment of genital herpes.[50] Zinc has also been used topically.[5] A number of zinc salts have shown *in vitro* activity against HSV.[51,52] Further, in mouse models of genital HSV-2 infection, zinc salts provided protection when administered topically[52–54] but not when administered systemically.[52]

Clinically, there have been reports of beneficial effects using zinc sulphate solutions administered topically (0.25%/4%) or intravaginally with collagen sponges (40 mg).[55–57] However, recent studies in mice showed that intravaginal administration of concentrations of zinc that were active against HSV-2 infection resulted in disruption of the vaginal epithelium, raising important questions about safety.[53]

A series of studies were conducted with a topical formulation, *Herpigon* (3% zinc, 2% tannic acid, 30% urea).[58–61] The primary lesions of HSV-infected guinea

pigs healed faster when treated with *Herpigon* alone or in combination with an ultrasound massage (used to aid penetration of the ointment into infected cells).[58,59] When evaluated in humans, the investigators compared various combinations of *Herpigon* with ultrasound, *Herpigon* alone, ultrasound alone and placebo. The comparisons varied for men and women and for different outcomes. In general, it was reported that *Herpigon* with ultrasound reduced recurrences,[58,60,61] provided faster relief from itching,[61] and faster healing.[61] However, the use of an ultrasound machine is not a practical approach to treatment.

BEE PRODUCTS (I.E. HONEY, PROPOLIS)

Honey's medicinal qualities, specifically its use for wound healing, have been recognized since antiquity.[67] In a small, non-blinded, cross-over study comparing topical application of honey with aciclovir cream, patients with oral or genital herpes noted a significantly shorter duration of episodes and faster healing time when using the honey application compared with the aciclovir cream.[17]

Propolis is a sticky substance that bees produce from certain tree saps.[5] *In vitro* data have shown that propolis is both anti-bacterial and antiviral, including having activity against HSV.[18–20] In a randomized, blinded-investigator study (90 men/women), a greater number of individuals who used a propolis (3%) ointment as compared to those who used aciclovir or placebo ointments were healed after 10 days.[21] Given that preliminary findings appear promising, further examination of bee products is warranted.

ALOE VERA

Aloe vera is a member of the *Liliaceae*.[5] Topical aloe has been used for wounds such as cuts and burns owing to its perceived effectiveness in improving healing.[5,66] Aloe emodin, an anthraquinone prepared from aloe vera, was shown to inactivate HSV-2 *in vitro*.[10] In another study, acemannan (another ingredient in aloe), was reported to act synergistically with aciclovir against HSV *in vitro*.[11]

Two clinical trials that were conducted in Pakistan found that males with genital herpes who used a hydrophilic cream containing an aloe vera extract (0.5%) experienced a significantly shorter healing time and were more likely to have symptom resolution by 2 weeks compared to men using an aloe vera gel[12] or a topical placebo.[12,13] These findings suggest that the formulation was as important as, if not more so than, the active ingredient. There have been no follow-up studies and there are no clinical data on the use of aloe vera for the treatment of genital herpes among women.

Conclusions

This review highlights the data available on six commonly identified biologically based CAM treatments for genital herpes. Many of the studies reviewed here were conducted in the 1970s and 1980s, before the availability of aciclovir. For most of these natural treatments, there have been insufficient scientific data to make conclusive statements about their efficacy and safety.

Clinical trials on these products should be conducted with the same rigour (i.e. double-blind, placebo-controlled) that has been applied to conventional medications. Studies should evaluate optimum dosage, including concentration, method and frequency. Moreover, many CAM products contain natural ingredients with complex chemical components that can differ greatly by geographical locations and with purification and extraction procedures.[3,4] Thus, effective standardization is required if truly meaningful data are to be generated.

The recent experience with topical nonoxynol-9 suggests that rigorous evaluation of safety is required for products that will be applied frequently to the genital epithelium.[68] To date, CAM treatments have not been subjected to this kind of evaluation. This review has focused on treatment, but products with HSV antiviral activity may also have value as candidate microbicides.[69]

There is mounting evidence that genital herpes infection increases susceptibility to subsequent infection with HIV, particularly soon after initial HSV infection. This elevated risk is believed to be due to frequent HSV viral shedding in the genital tract.[70] That finding, combined with evidence that virus shedding is an important factor in genital herpes transmission,[70] strongly indicates that shedding should be included as an outcome variable in treatment studies. In addition, CAM clinical trials should include individuals who are taking oral antiviral medications to examine the effects of integrative approaches, particularly for those products used topically.

Since people use CAM approaches for a variety of reasons, healthcare providers need to be prepared to address CAM therapies with their patients. This includes taking the time to listen respectfully to the variety of reasons for use and to explore with patients varied aspects of treatment, including potential risks. To facilitate this dialogue, it may be necessary to have patients bring CAM products to clinic: some have similar names with different ingredients (e.g. *Herpigon* and *Herpagon*) and providers may need to see the labelling in order to render the most salient advice. Many patients learn about these products on the internet; thus, it also may be beneficial to aid them in becoming discriminating consumers of health information through educational websites such as *Health on the Net*.[71] In the end, the challenge for the provider is to help the patient balance the patient's perceptions that a particular treatment results in greater comfort, faster healing or fewer recurrences against the limited data regarding efficacy and safety, including the risk of increased shedding or damage to the genital epithelium. All of this will become easier to accomplish as clinical trials are conducted with the scientific rigour necessary to evaluate safety and efficacy.

Conflicts of Interest

No conflicts of interest were declared in relation to this article.

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