



# Bee products and the treatment of blister-like lesions around the mouth, skin and genitalia caused by herpes viruses—A systematic review



Karsten Münstedt

Ortenau Klinikum Offenburg und Gengenbach, Ebertplatz 12, 77654, Offenburg, Germany

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## ABSTRACT

**Objectives:** To assess the value of bee products with respect to antiviral efficacy against herpes viruses.

**Design:** A systematic review was done using the JUSTfind System of the Justus-Liebig-University Gießen and Scopus.

**Results:** Three trials on honey and 6 trials on propolis were conducted. Each trial provided evidence that these two bee products are interesting alternatives to acyclovir, especially propolis, which was found to be superior to acyclovir in 4 trials.

**Conclusions:** The evidence from these trials suggests that propolis is the best of all natural possibilities in the treatment of herpetic skin lesions, especially those related to HSV-1. Future studies should analyse if propolis could be an adjunct to treatment with acyclovir. For lesions in the oral cavity, honey could be an interesting alternative.

## 1. Introduction

There are eight known herpes viruses that affect human health: herpes simplex virus type 1 (HSV-1; oral herpes lesions), herpes simplex virus type 2 (HSV-2; genital herpes lesions), varicella zoster virus (VZV; chickenpox, shingles), Epstein-Barr virus (EBV; infectious mononucleosis), cytomegalovirus (CMV; CMV mononucleosis), human herpes virus 6 (HHV-6; roseola, mononucleosis syndromes), human herpes virus 7 (HHV-7; no human disease definitively linked) and human herpes virus 8 (HHV-8; suspected association with Kaposi's sarcoma).<sup>1</sup> The herpes simplex viruses and varicella zoster virus have the greatest clinical importance. They are briefly described.

Herpes simplex viruses are highly infectious, causing painful blister-like lesions around the mouth and genitalia, and the infections are essentially identical. Although it was previously believed that HSV-1 was primarily transmitted by oral-oral contact, causing orolabial herpes or 'cold sores' around the mouth, new estimates also consider HSV-1 an important cause of genital herpes, which was formerly regarded as the domain of HSV-2, transmitted almost entirely sexually through skin-to-skin contact. According to estimates from 2012, more than 3.7 billion people under the age of 50 are infected with HSV-1.<sup>2</sup> One hundred forty million people aged 15–49 years old suffer from genital herpes infection due to HSV-1, while 417 million people suffer from genital herpes infections due to HSV-2.<sup>2,3</sup> After an infection the viruses remain inactive in the deoxyribonucleic acid (DNA) of nerve ganglia. Triggered by

stress, dental procedures, infections and trauma, they reactivate from time to time, travel down the nerve and start an eruption. However, flare-ups become less severe over time.

Another important virus is the varicella zoster virus (VZV). It causes a painful skin rash with blisters (shingles) in a single, wide strip, either on one side of the body or on the face, and is a reactivation of the same virus that causes chickenpox at the initial infection. Although the rash usually heals within two to four weeks, some people develop ongoing nerve pain (postherpetic neuralgia), which can last for months or years.<sup>4</sup>

Conventional treatments of skin lesions that occur due to VZV and HSV include antiviral drugs, such as acyclovir. They have been found to shorten the length and intensity of outbreaks, reduce the frequency of flare-ups, and thus, reduce the transmission of the disease.<sup>5</sup> However, several natural remedies for disease prevention and treatment have been proposed. For HSV, these include L-lysine, *Melissa officinalis*, *Aloe vera*, topical zinc, adenosine monophosphate, *astragalus*, bee propolis, cat's claw, *echinacea*, elderberry, *Eleutherococcus*, kelp, sage-rhubarb cream, sandalwood, tea tree oil, vitamin C, witch hazel and others.<sup>6</sup> The question is whether or not these substances can be recommended; only the use of *Melissa officinalis*, tea tree oil, topical zinc, sage-rhubarb cream and vitamin C is supported by clinical trials.<sup>7–11</sup> However, in most cases there are trials that present only preliminary data, with few confirming trials, and generally no direct comparison to acyclovir, the accepted conventional treatment. In summary, most substances cannot

E-mail address: [karsten.muenstedt@ortenau-klinikum.de](mailto:karsten.muenstedt@ortenau-klinikum.de).

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be recommended. For VZV, extracts from echinacea, sage, rhubarb and *Melissa officinalis* are recommended by naturopaths<sup>12</sup> although there are no clinical trials which support such recommendations.

Although a recent systematic review and meta-analysis concluded that the data available for using propolis (bee glue) for treatment of oral, skin, and genital diseases are not conclusive because of low methodological qualities and small sample sizes, some newer trials on the subject were reported.<sup>13–16</sup> Therefore, we decided to undertake a new search of literature on the subject of herpetic skin lesions and the effects of propolis and other bee products, since an *in vitro* study showed that these could be as efficient as acyclovir and can be considered alternatives in the treatment of herpetic lesions.<sup>17</sup> Propolis and bee venom have also exhibited antiviral activity against the herpes simplex viruses in *in vitro* studies.<sup>18–20</sup> Furthermore, the antiviral mechanisms of propolis have been elucidated: it prevents the entrance of the virus into the cell, interacts with virus cell membranes and the conversion of viral envelopes and has a direct effect on free virions.<sup>21,22</sup>

## 2. Methods

This systematic review was carried out according to the recommendations of the PRISMA.

### 2.1. Data sources and searches

Articles were searched without any language restriction using the JUSTfind System of the Justus-Liebig-University Gießen, Germany, which comprises 337 databases from the EBSCO Discovery Service. Scopus was also used with the following search terms: “propolis” OR “honey” OR “royal jelly” OR “bee venom” AND “herpes” OR “herpetic” OR “shingles” AND “trial” OR “study”. This strategy revealed 65 documents.

Studies on any of the named bee products and herpes were selected. In a second step, the references listed in the retrieved studies, meta-analyses and systematic reviews were analysed in a similar fashion to capture documents that might not have been identified in the primary search.

### 2.2. Eligibility criteria

Eligible studies were randomized and non-randomized controlled clinical trials, including case-control studies. Studies were eligible if they were published as full papers in the English, German, French or Italian language. The publication date range included in the search was 01 January 2000 to 31 December 2018. The target population consisted of all types of patients who suffered from lesions caused by the viruses listed above.

### 2.3. Study selection

The full titles and abstracts of the articles retrieved in the initial search were assessed for adherence to the eligibility criteria. Duplicate articles and those that did not meet the eligibility criteria were removed. Afterwards, the full texts of the remaining articles were read and assessed for eligibility.

### 2.4. Data collection

Relevant data (title of the paper, authors' information, country in which the study was conducted, condition treated (HSV-1, HSV-2, HZV), study design, primary and secondary endpoints, results from primary assessment to last follow-up and side effects from all retrieved studies were extracted using a standardized data extraction form. Methodological quality of a clinical trial was assessed using the Jadad scale.<sup>23</sup>

**Table 1**

Results of the literature search on bee products and the treatment of herpes viruses.

	Propolis	Honey	Royal jelly	Bee venom
Records screened	82	34	2	4
Full-text articles assessed for eligibility	7	5	0	1
Articles included from assessed full-text articles	0	1	0	0
Articles included in the review	6	3	0	0

## 3. Results

Using the mentioned systems, we identified the studies shown in Table 1.

### 3.1. Honey and its effects on herpes viruses

Regarding honey, 3 trials were identified, the first of which analysed 16 patients with a history of recurrent attacks of herpetic lesions (8 labial and 8 genital) in a cross-over design and compared treatment with polyfloral honey and acyclovir cream.<sup>24</sup> In spite of the small number of patients, significant differences were found in favour of honey with respect to duration of attacks and healing time. Regarding the occurrence of crusts and pain duration, the data also spoke in favour of honey, although these differences were not statistically significant. Another cross-over study of 15 comparing kanuka honey with acyclovir found no statistically significant differences between honey and acyclovir treatments; however, the results showed an advantage regarding acceptability of the honey intervention.<sup>25</sup> Recently, a prospective randomized, double-blind, placebo-controlled trial was published comparing oral acyclovir alone to a combination of honey and oral acyclovir in 100 children with herpes simplex gingivostomatitis.<sup>26</sup> This study found significant differences with respect to earlier disappearance of herpetic oral lesions, eating difficulties and pain scores, favouring the combination of honey and acyclovir.<sup>26</sup> All reported trials speak in favour of using honey for the treatment of herpetic lesions. Currently, there is an ongoing trial comparing kanuka honey with acyclovir, with an intended sample size of 950 patients. This trial could give a reliable answer to the role of honey in treating herpetic oral lesions.<sup>27</sup>

### 3.2. Propolis and its effects on herpes viruses

The research revealed 6 randomized trials, which are summarized in Table 2. The studies show that propolis is superior to placebo and acyclovir in HSV-1, HSV-2, and HZV infection with respect to factors related to healing and pain. As shown by Holcová and Hladíková,<sup>15</sup> the optimal concentration of the propolis extract GH 2002 in an ointment is 0.5%. Propolis Extract ACF® was used at a concentration of 3% but there are published trials which support that this is the optimal concentration.

### 3.3. Other bee products and herpes viruses

There is some evidence that other bee products could ease symptoms associated with herpes viruses. This refers to postherpetic neuralgia, and there are 2 case reports that describe an improvement with bee venom.<sup>31,32</sup> Apart from these two reports no clinical evidence for the use of bee products for herpes virus-associated diseases was found.

## 4. Discussion

This systematic review shows that honey, and especially propolis, are interesting natural alternatives or adjuncts to standard therapies for herpes virus infections. This conclusion is based on 6 trials involving

**Table 2**  
Results of the literature search on propolis.

Study or subgroup	Type of virus	Jadad-Score	Intervention		Control		Effect on pain	Effect on healing
			Sample size propolis	Concen-tration propolis	Sample size	Type of control		
Vynograd <sup>28</sup>	HSV-2	2	30	3 % ointment	30	Acyclovir	–	**
					30	Placebo	**	**
Hoheisel <sup>29</sup>	HSV-1	5	33	3 % ointment	35	Placebo	**	**
Holcova <sup>15</sup>	HSV-1	4	50	0.5 % ointment	48	Propolis 0.1 %	–	–
					52	Propolis 1.0 %	–	**
						ointment		
						ointment		
Tomanova <sup>30</sup>	HZV	4	33	0.5 % ointment + oral	27	Placebo + oral	**	**
				acyclovir		acyclovir		
Arenberger <sup>14</sup>	HSV-1	4	189	0.5 % ointment	190	Acyclovir	**	**
Jautova <sup>16</sup>	HSV-1	5	200	0.5 % ointment	200	Acyclovir	**	**

\*\* = significant difference favouring the intervention arm.

propolis and 3 trials on honey, most of them with acceptable study designs. Apart from *in vitro* studies, which have demonstrated the antiviral activity of propolis, other clinical trials on the treatment of cutaneous warts and cervical lesions have reported that propolis can be considered as an effective antiviral mean because it also works against human papillary viruses.<sup>33–35</sup>

In comparison to other natural approaches, like *Melissa officinalis* (lemon balm), *Aloe vera*, L-lysine, zinc, or *Eleutherococcus*, the evidence regarding propolis is better. With respect to lemon balm, the trials that compare to a placebo show some effect,<sup>36</sup> but largely fail when tested against acyclovir.<sup>37</sup> Similarly, there is only evidence for *Aloe vera* extracts in trials with comparison to placebos.<sup>38,39</sup> Since acyclovir was found to be effective in a meta-analysis, from the perspective of a patient it seems important that he is treated with the most effective and safest means.<sup>5</sup> To the best of our knowledge there are no trials comparing *Aloe vera* to acyclovir. Similarly, there are no trials comparing zinc to acyclovir, only to placebo.<sup>11</sup> The results regarding L-lysine are conflicting. A review on the subject concluded that L-lysine may only be effective in disease prevention.<sup>40</sup> There is also some evidence with respect to vitamin C, while other natural substances originating from *Echinacea purpurea* or tea tree oil were found to be not effective.<sup>8–10,41</sup> One of the few effective natural combinations is a topical sage-rhubarb preparation, which proved to be as effective as acyclovir cream.<sup>7</sup> However, in spite of these promising results, there have not been further trials on the subject. To the best of our knowledge, only low-level laser therapy may be an alternative to propolis. For low-level laser therapy there is a systematic review which suggests that it may be regarded as a safe and effective treatment alternative for the management of recurrent herpes labialis.<sup>42</sup> However, several questions remain unanswered, including the following:

- Since only one study analysed the effectiveness of propolis against genital herpes, the evidence may be regarded as too scarce.
- Only one clinical trial assessed the value of propolis as an adjunct to treatment with acyclovir in HZV. It remains unclear whether a combination of acyclovir and propolis would be effective in infections with HSV-1 and HSV-2. Such an approach could provide some clinical benefit. Also, more evidence is needed regarding the use of propolis against HZV.
- It would also be interesting to know if and how propolis works in comparison or in combination with low-level laser therapy or honey.
- Finally, identifying the critical components of propolis regarding efficacy against herpes viruses has to be considered to be an important task. All studies presented in this review are based on the commercially produced extracts Propolis Extract ACF® and GH 2002.<sup>14–16,28–30</sup> Only a few details of the extraction processes have

been published.<sup>43</sup> Focusing on the relevant components of propolis could reduce the problems associated with propolis allergy.

With respect to honey, the current evidence is not sufficient, since the two trials performed had only a few numbers of patients. The trial on herpes simplex gingivostomatitis indicated significant improvements in patients who used honey, including earlier disappearance of herpetic oral lesions, less difficulty eating and lower pain scores.<sup>26</sup> This may be due to the antiviral properties of honey, or to its protective effects on the oral mucosa.<sup>17</sup> However, it could be also be a combination of both effects. Recent systematic reviews on radiation or chemotherapy-induced oral mucositis have shown an efficacy for honey.<sup>44,45</sup> Therefore, it is suggested that honey helps all kinds of oral wounds no matter whether they are due to radiation, chemotherapy, surgery or infections.<sup>46</sup>

In summary, this review provides some evidence that propolis can be a good alternative to the topical application of acyclovir in cases of HSV-1 infections. All other mentioned aspects deserve further study in the future.

## Conflict of interests

There are no conflicts of interest, except that KM is a hobby beekeeper

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