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CLINICAL EFFICACY OF A SPECIFIC TANNIN-RICH OSMOTICALLY ACTIVE SOLUTION FOR THE TREATMENT OF LABIAL HERPES

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ABSTRACT

Herpes Simplex Virus, responsible for Herpes simplex labialis, affects over 50% of the world population. After initial infection, the presence of a large amount of free virus particles in the lesion infects new healthy cells, recruiting the help of some specific proteolytic enzymes. Neutralizing the infectivity of the free virus particles may constitute one of the best treatment strategies. Hp-OR, a specifically formulated solution, was therefore prepared and tested for efficacy. 60 patients having visible lesions of herpes labialis were treated with Hp-OR in an open label, single arm, prospective, multi-centric, pilot clinical trial for a maximum period of 14 consecutive days. Product was applied topically on the lesion 3-4 times per day, up to complete lesion healing. The amount of virus in the lesion, size of the lesions, severity of pain, burning sensation, lesion healing parameters, and product tolerance were recorded. A very fast reduction in the amount of free virus particles and an accelerated healing time with concomitant reduction in herpes labialis symptoms were observed, while the topical mode of application prevented any side effects. Results demonstrate that neutralizing and eliminating the free virus particles from the open lesion is one of the best strategies to treat labial herpes.

Key Words: Clinical, Herpes Simplex Virus, Labial herpes, Tannins.

INTRODUCTION

Herpes simplex labialis (HSL) , commonly known as fever blisters, cold sores, oral herpes or herpes labialis, caused by herpes simplex virus type 1 (HSV-1), is one of the most common skin infections affecting human beings. After primary infection, usually through direct contact, the virus ascends the sensory nerve axon and remains latent in the various ganglia, including trigeminal, facial and vagus ganglia (Gershon *et al*., 2012). There is evidence that the latent infection also develops in the epithelial tissue of the lips (Wittek *et al*., 2010). The dormant virus awaits a trigger to get reactivated periodically, which may happen under various stress conditions, then starts migrating towards the surface. During the incubation period, which may vary from 2 to 10 days, the virus travels at an average speed of 1-2 mm per day (Petersen *et al*., 2010) and infects a few dermal or mucosal cells. The patient starts feeling some initial topical itching, irritation, tingling and pain at the site of infection. Following virus growth and initial cell lysis, a small vesicle erupts at the site, opens, and creates a small surface lesion. The fluid in the vesicle contains a large amount of free virus particles that are liberated into the lesion and in turn infect new host cells. New lesion continues developing for 4-6 days, while body defence mechanisms activate; and resolution can take up to 15-20 days. The main cause of lesion progression is the presence of free virus particles on the surface of the lesion, which continue generating new virus progeny and infecting new adjacent healthy cells during this period. Therefore an ideal treatment should neutralize the free virus particles present

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on the surface of the lesion and should also stimulate the lesion healing process.

In absence of a specific topical antiviral drug, nucleoside inhibitors, such as Zovirax, and neuraminidase inhibitors, such as Tamiflu, which are both intracellular virus growth inhibitors, are commonly used for topical application but they do not affect free virus particles in the open lesion (De Clercq, 2004). These intracellularly acting drugs are very effective in preventing the infection, particularly in patients experiencing minimum 3-6 episodes of HSL per year, but using preventive treatment in patients experiencing just 1 or 2 lesions a year may expose the patient to unwanted side effects of orally administered drugs and may lead to the possibility of developing a drug-resistant viral strain. Patients are also usually reluctant to use a preventive treatment and most patients start treating the lesion only when the HSL lesions are physically visible. Therefore the best method of treating HSL resides in neutralizing the free virus particles in the lesion and in simultaneously stimulating lesion healing.

Many antiviral compounds have been proposed for the treatment of HSL lesions, particularly those containing cyclovirs in different proportions (Chono *et al*., 2010), but although they showed some clinical efficacy in reducing the healing time (Cunningham *et al*., 2012) (McKeough *et al*., 2001), because of their intracellular mode of action they were logically found to be ineffective in many other independent clinical studies (Mc Carthy *et al*., 2012) (Femiano *et al.*, 2001) (Morrel *et al*., 2006).

Therefore, the aim of our research work was to find suitable topical antiviral agents associated with a mechanism capable of cleaning the lesion of free virus particles and other contaminants so as to stop viral progression and to accelerate lesion healing.

HSL is an enveloped DNA virus containing several proteins (glycoprotein) on its outer coat. When present in a lesion, viruses use these envelope proteins to attach to the cell membrane heparan receptors to enter the host cell. One of the possibilities to treat HSL infection was to block heparan receptors; however, blocking cellular receptors may influence cellular functions. Therefore, a second possibility was to neutralize the virus glycoproteins enabling virus attachment to the cellular heparan receptors. Recent scientific work also indicates that herpes virus recruits the help of some proteases (Matrix Metalloproteases – MMPs) as proteolytic enzymes to facilitate virus entry into the cells (Shrivastava, 2012) (Yang *et al*.,2004) (Hong *et al*.,2010), and MMP-inhibitors have already been suggested as potent future antiviral drugs (Supuran *et al*., 2003).

Taking into consideration the amount of free virus particles on herpes-infected surface and the different types and sub-types of virus surface glycoproteins and proteases involved in virus infection, it was practically impossible to find a drug which could simultaneously block all virus surface proteins, or other kinds of proteins, at once. Since the virus surface glycoproteins and the virus entry-enhancing proteases are protein in nature, our aim was to find a protein binding agent which can bind and neutralize simultaneously all the virus glycoproteins as well as the proteases so as to stop further viral infection.

Tannins are abundant in the plant kingdom and are known to bind with a wide range of protein molecules (Tarahovsky, 2008). The tannins' procyanidin (PCD) fraction contains big phenolic compounds with multiple structure units and may have selective protein binding properties (Zhang *et al*., 2006). This multiple structure of tannins confers them the capacity to form strong hydrogen bonds with various protein structures. Incubation of different plant PCDs with virus suspension or proteases, followed by calculation of virus titer in HSL-sensitive Vero cells, was retained as a model to verify tannin-protein binding. The selected plant PCDs were then added into an osmotically active, hypertonic solution as described in a patent by Shrivastava *et al*. to evacuate the bound virus particles from the HSL lesions. After initial selection of the best antiviral composition, a pilot clinical trial was conducted to verify the composition treatment efficacy on HSL.

MATERIALS AND METHODS

Test product preparation

131 known tannin-rich plants were selected and procyanidin-rich plant extracts were prepared using the method described by Giner-Chavez *et al*. In short, initial tannin-rich plant extract was obtained with an aqueous organic solvent containing 70% acetone and 30% water. The extracts were then successively passed through Sephadex LH-20 columns by progressively increasing the volume of methanol (60 x 88.5 cm), and the intended fractions were eluted to produce a dry solid. The product was identified by mass spectrometry. The extracts contained mainly procyanidin (epicatechin – catechin) B1, B2, B3 and C 1 fractions, between 60 and 80%, depending on the part of the plant used.

The proteases involved in enhancing herpes virus entry into the cells, virus surface glycoproteins, and specific procyanidins capable of binding with one or more of these proteins, were identified employing the methods previously described (Shrivastava, 2011).

In short, to identify the proteases involved in HSV infection, herpes virus-sensitive Vero cells were grown in 96-well tissue culture plates (Corning, USA) *in vitro* in a protease-free Dulbecco's Modified Eagle's Medium (DMEM) and infected with HSV to obtain 50% cell death ($TCID_{50}$). Proteases were then added into the culture medium, either individually or in association, to evaluate the effect on virus growth. Increase in virus growth indicated participation of the protease(s) in HSV infection. To evaluate the protein binding properties of PCDs, a fixed concentration of virus (TCID100) and/or proteases was pre-incubated with a specific procyanidin, and the

reduction in virus growth was evaluated and compared to the corresponding controls. A reduction in virus growth indicated virus or protease neutralization by the PCD. All the active PCDs were then associated in varying concentrations so as to obtain 100% inhibition of virus infection *in vitro*. The concentration of each PCD necessary to inactivate 100% virus growth in a single well (surface area 0.328 cm^2) of a 96-well culture plate was determined and the final association was designated as VB-HpOR-PCDs. The PCD association (0.80%) was incorporated into an osmotically active hypertonic solution (Shrivastava, 2005) containing glycerol (76.15%), honey (20.0%), water (2.95%), and xanthan gum (0.10%). This filmogen solution attracts hypotonic liquid from the inner parts of the lesion, thereby cleaning the lesion of contaminants. The solution was filled into 6ml plastic tubes with a canula and labelled Hp-OR.

Clinical Trial

Location

An open label, single arm, prospective, multicentric, pilot study was conducted by the Nexus Clinical Research Pvt Ltd in Mumbai, India, between 06-2009 and 12-2010.

Ethical aspects

This pilot study was conducted only after the approval of Institutional Review Board/ Independent Ethical committee agreed by the Indian Council of Medical research (ICMR) respecting GCP (Good Clinical Practice) and following Helsinki declaration guidelines. The investigative institute is authorized to conduct clinical trials and is regularly inspected by the regulatory authorities.

Informed Consent and Subject Information

Subjects were enrolled after the study's nature, purpose, possible benefits and reasonably anticipated risks had been explained to them, and an informed consent was obtained from each participant. Subjects were followed by the clinical research coordinator and the investigator throughout the study.

Due to the variability of HSL lesions and the aim of the study, instead of comparing the efficacy with a placebo group, it was decided to quantify the amount of virus in the lesions using Tzank test as well as the time required for healing as key parameters.

Inclusion and exclusion criteria

The main inclusion criteria were: 1. Participant presenting all clinical signs and symptoms of one or more open labial herpes infection(s), less than 48 hours old, and not treated with any systemic or topical therapy, 2. Male and female , belonging to the 18-65 age group, 3. Having no past or present history of immunosuppressive condition, 4. Having no history of adverse effects or allergies to any ingredient used in the product composition, 5. Presenting no evidence of any other dermatological disorder, 6. Absence of any severe disease (checked by analyzing haematological, blood biochemical, and urinary parameters), pregnancy (women) or AIDS, 7. Giving written consent and willing to follow the protocol as recommended.

It was decided to stop the treatment in case of any critical event, conformingly to the declaration of Helsinki/Tokyo/Venice and the law of December 20th, 1988, concerning the protection of volunteers for biomedical research.A total 82 subjects were screened for entry into the study, out of which 22 were rejected due to non-compliance with the inclusion criteria of the study.

Study design

Patients were asked to apply 3-4 drops of the test product directly onto the open labial herpes lesion, three times per day, up to complete healing or for a maximum period of 14 consecutive days.

Efficacy and safety evaluation

After recruitment, the medical history of patient was recorded in the observation file. Upon evaluation of the entire baseline parameters as per study protocol, each patient received the test product and symptom observation diary.

The key parameters studied were: improvement in the signs of oral herpes, changes in the patient symptoms, symptom severity scores at each visit using a 0 to 3 scale where 0 indicated no symptom, 1: mild symptoms, 2: moderate, and 3 : severe symptoms, to evaluate the severity of tingling, itching, burning and pain sensation, and clinical symptoms by the patient and by the investigator (just before first treatment on day 1, 2 hours after first treatment and on days 4, 7, 14). The rate of wound healing was determined by measuring the lesion size (length x width in cm^2) at each time point.

Tzanck test was performed to quantify the amount of free virus particles by collecting scrapings from the lesions, followed by haematoxylin and eosin staining and by quantifying the number of virus-infected multinucleated giant cells as described by Gupta et al. [21]. Herpes virus-infected cells transform into multinucleated syncytial giant cells with acantholytic nucleus.

Safety of the drug was assessed by evaluating the incidence of adverse events during the study. Standard blood biochemical and urine parameters were also analyzed before treatment and on day 14 to determine product safety.

Statistical methods used for data analysis

Clinical data were analyzed using SAS 9.1.3. statistical program. The statistical paired sample t-test, Wilcoxon Sign Rank tests were used to compare the laboratory parameter. The Wilcoxon Sign Rank test was

used when the normality assumption was false. Descriptive Statistics i.e. mean Standard Deviation (SD), minimum and maximum frequency distribution were used for the analysis of the demographic details, clinical evaluation, medical history, and laboratory parameters. If the P-value was greater than 0.05, the results were considered to be not significant.

RESULTS

Subjects and lesion distribution

A total 82 subjects were selected for initial screening in five different hospitals in the state of Maharashtra in India (Saraswati skin clinic - Beed, Lokmanya Care Hospital – Pune, Ushakiran Hospital – Pune, Skin Hospital – Latur, and Twacha Care Centre – Pune), out of which 22 were rejected due to non-compliance with the study's inclusion criteria. Among the 60 participants, 31 (51.67%) were men and 29 (48.33%) women, within the 25-64 age group (mean age 47.30 ± 10.63 years), with a mean body weight of 67.40 kg (± 9.13 kg), All subjects included were suffering from apparent HSL lesions. 33 patients had only outer labial lesions on the lips and skin, 16 had only inner lesions on the inner side of the lips or oral mucosa, while 11 had both outer and inner lesions in or around the oral cavity. Only one lesion in each patient, presenting a well-defined border and a quantifiable surface area (>0.5 cm^2 at study outset) was selected for treatment and corresponding observations.

Presence of HSL in the lesion

All the patients were positive for the presence of HSL virus-infected multinucleated cells at the start of the treatment and 2h after first treatment [Table 1]. Virus was not detected in only 2/60 (3.3%) lesions on day 4, and in 10/60 (16.6%) lesions on day 7, but all the lesions were virus-free on day 14.

Quantification of the number of virus particles present in the lesions [Table 2] show that there were above 750 (± 17.72) virus-infected cells in each lesion at the start of treatment. Just 2h after the first drug application, the quantity of free virus particles was diminished by 38% (465 ±10.82) indicating that the test product eliminates virus from the open lesions. The reduction in virus concentration inside the lesion was as much as 52% after 4 days of treatment, 70% after 7 days and 100% after 14 days of treatment. As increased liquid exudation was observed during the first 5-10 minutes following each product application, it can be postulated that the VB-HpOR-PCDs bind with the free virus particles while osmotic imbalance, which creates an outward flow of hypotonic liquid from the lesion, drains the conjugated virus particles from the lesion.

No virus was detected on day 14 as most of the lesions were healed. The mean size of the lesions which was 1.528 cm^2 on day 1, was reduced to 0.683 cm^2 on day 4 (- 55.3%) and only 0.193 cm^2 (- 87.4%) on day 7.

As the lesion healing process was rapid but the amount of scrapings collected from each lesion remained identical at each sampling, the samples do not reflect the real amount of virus particles, proportionately to the surface area of the lesion. The amount of virus proportionate to the surface area, as shown in Table 2, clearly indicates that the amount of virus-infected cells was considerably reduced right after the first application (-38%), with over 75% reduction after day 4, and 90% reduction after day 7. Virus growth stopped completely between days 7 and 14.

These results indicate that the test product eliminates free virus particles very rapidly, right after first application, although new virus particles, shedding from the pre-infected cells, probably continue entering into the lesion, and showing presence up to complete healing.

If we consider that nearly 20-30% new virus particles enter the lesion during the first 4-5 days, the free virus-eliminating properties of the test product are highly significant. These results also indicate that the test product does not affect intracellular virus reserves and does not influence already activated migrating virus in the nerve cells, or viruses in the phase of intracellular incubation.

Effect on the sensation of itching, burning and pain:

All patients were asked to score the intensity of itching, burning, pain sensation and other parameters on a 0 to 3 scale as shown in Table 3.

Most subjects (nearly 80%) had a severe to moderate sensation of itching, burning and/or pain, in and around the labial herpes lesion before the start of treatment. This sensation started diminishing only 2h after the first treatment application, but the improvement was initially mild to moderate. For all these symptoms, a clear improvement was seen from day 4 onwards, and most patients had only minor topical irritation on day 7. These results correspond to progressive lesion healing and reduction in virus particle amount observed in most patients. There were no signs of itching, burning or pain in any of the patients at the end of the study, indicating that the test product is highly effective not only in reducing the virus load but also in stopping those clinical signs of labial herpes, and in facilitating lesion healing.

Similar improvement was observed in other clinical symptoms of HSL such as lesion tenderness, soreness, swelling around the lesion, and blister oozing which diminished progressively within a week and disappeared in most patients during the second week of treatment (results not shown).

Side effects

As the results of the study indicate, the intensity of the HSL symptoms was progressively diminished in all patients over the course of the study, and as no patient complained about any undesirable topical effects, the product can be considered as completely safe for topical application on labial herpes lesions.

Table 1. Presence or absence of virus in the lesions as measured by Tzanck test (n=60)

		Day 1 Before treatment	**Day 1** 2h	**Day 4**	**Day 7**	**Day 14**
Virus	Absent	0	0	02	10	60
	Present	60	60	58	50	0

Size of the lesion and virus concentration

Table 2. Mean virus concentration per lesion as measured by quantifying the number of multinucleated virus infected giant cells and % change compared to before treatment values (± Standard deviation), the mean surface area of the lesions in cm^2, % change in lesion area compared to before treatment values and the relative concentration of free virus particles adjusted according to the mean surface of the lesions (n= 60) before treatment on the day 1, 2h after the 1st treatment and on days 4, 7, and 14 (mean ± SD)

Mean Values	**Day 1 Before treatment**	**Day 1 2h after first treatment**	**Day 4**	**Day 7**	**Day 14**
Mean number of virus infected cells per field	>750 *(± 17.72)*	465 *(±10.82)*	359 *(± 6.35)*	226 *(± 10.22)*	0
% change	*0*	*- 38%*	*- 52.13%*	*- 69.87%*	*-100%*
Surface area CM^2	1.528 *(± 0.72)*	1.528*(± 0.73)*	0.683 *(± 0.36)*	0.193 *(± 0.11)*	0
% change	*0%*	*0%*	*-55.3%*	*-87.37*	*-100%*
% change in virus concentration compared to the surface area of the lesion	0%	-38.0	-76.69	-91.18%	-100%

Table 3. Number of patients rating the sensation of itching, burning and pain on a scale of 0 to 3 (0 = no symptom, 1= mild, 2 = moderate, 3 = severe) at the start of treatment, 2h after 1st product application and on the days 4,7, and 14.

	Number of replies (n=60)				
Parameter : Itching sensation	**None**	**Mild**	**Moderate**	**Severe**	***p-value***
Day -1 before treatment	07	19	20	14	*0.0698*
+ 2h	07	39	19	13	*0.0460*
Day 4	10	27	14	09	*0.0033*
Day 7	22	20	18	0	*0.8187*
Day 14	56	04	0	0	*<.0001*
Parameter : Burning sensation					
Day -1 before treatment	05	09	20	26	*0.0003*
+ 2h	06	10	21	23	*0.0033*
Day 4	12	15	16	17	*0.8174*
Day 7	27	19	14	0	*0.1165*
Day 14	60	0	0	0	.
Parameter : Pain sensation					
Day -1 before treatment	12	26	14	08	*0.0074*
+ 2h	15	28	12	05	*0.0003*
Day 4	28	21	09	02	*<.0001*
Day 7	45	07	08	0	*<.0001*
Day 14	60	0	0	0	.

DISCUSSION

Despite being a pilot clinical trial, this study represents an important step towards the treatment of topical viral infections because this is the first time a completely new approach of targeting and neutralizing the real cause has been employed. HSL is caused by an enveloped DNA virus of the Herpesviradae family, comprising over 25 viruses among which eight are known to infect Man with various skin lesions such as HSL, Herpes keratitis, Eczema herpeticum, Varicella zoster, Herpes gladitorium, and others (Whitley, 2002). The common feature of all topical herpes virus infections is that, following initial infection, a large amount of free virus particles is present on the lesion's surface, which is the main cause of new host cell infection and morbidity.

Stopping virus growth and blocking virus entry therefore constitutes the most logical approach to stop the infection.

The HSV genome encodes a number of enzymes and at least 11 surface glycoproteins involved in virus cell attachment (gB, gC, gD, gH) and virus fusion with the host cell membrane (gB), while gC, gE, gI are considered to be involved in immune escape and other functions (Connolly *et al*., 2011). New research findings also indicate that the virus may use proteolytic enzymes to facilitate its growth inside the cells (Delboy *et al*., 2008). In absence of complete knowledge regarding virus–host cell membrane interaction and the involvement of multiple virus proteins along with some proteolytic enzymes (Yang *et al*., 2003), it is practically impossible to design a drug or a molecule capable of interfering with all these proteins at once. Currently there is no effective treatment for HSL as the interlukin and interferon inhibitors, antibodies, individual proteins, immunomodulators, and vaccines lack either efficacy or the required safety profile (Vanpouille *et al*., 2009). Neuraminidase inhibitors, such as Tamiflu, and nucleoside inhibitors, such as Zovirax, valacyclovir, penciclovir and famciclovir, are commonly used as first choice of treatment but all these drugs act intracellularly and cannot affect topically available free virus particles which are the primary cause of the disease symptoms (Kleymann, 2003). The new helicase-primase inhibitors directed to inhibit intracellular virus replication with low virus resistance and higher activity can only act on the virus growing inside the cell nucleus, but may not be of any use in neutralizing topically available viruses (Biswas *et al*., 2008) (Chono *et al*., 2010). Scientific literature also clearly indicates that topically applied antiviral drugs are hardly more effective than an excipient (Anonymous, 2009).

As the various protein structures on the HSL coat and the proteases are all proteins in nature, and since certain plant tannins have the capacity to bind with proteins, the aim of our research was to identify the tannins, or parts of tannins, possessing this protein-binding capability. However, the various proteins have different surface hydrophobicities and present variable specificities in their binding with diverse polymeric forms of polyphenols or PCDs (Granato *et al*., 2010). To find corresponding PCDs, initial *in vitro* tests were conducted to select a minimal number of plant PCDs capable of binding with all the key proteins involved in HSL infection. These PCDs were incorporated into a solution of glycerol which is a strongly hypertonic, osmotically active, solution capable of creating, almost instantly, an outward exudation of hypotonic liquid from the inner parts of the lesion, thereby cleaning mechanically the contaminants and virus-PCD conjugates from the lesion.

Untreated HSL lesions usually take between 2 and 3 weeks to heal, but the results of this study show that Hp-OR not only removes the free-floating HSL virus from the lesion but also accelerates lesion healing while lessening HSL symptoms, such as pain, burning and itching sensations. The amount of virus was reduced by as much as 38% just 2 hours after the first Hp-OR application and by 76% after 4 days of treatment. This activity would be related to the HSL–PCD binding and not to the presence of glycerol as glycerol is commonly used in many topical pharmaceuticals to treat various skin infections, but was not found to possess any antiviral activity. A recent study (Hayashi *et al*., 2010) indicates that some glycerol derivatives may reduce virus pathogenicity by interfering with virus cell attachment but this effect remains very limited. Absence of any additional therapeutic benefit in some clinical trials where polyethylene glycol (PEG) was associated with cyclovirs for the treatment of HSL (Spruance *et al.*, 1982) (Whitley, 2006) also confirms that glycerol alone has no effect on HSL lesions as virus, due to its very minute particle size, is not eliminated and continues degrading new host cells. The main role of glycerol involves cleaning the lesion and thereby accelerating the lesion healing process as described by Shrivastava *et al*. The dual mechanism of Hp-OR, i.e. the PCDs binding with the virus glycoproteins and thereby blocking HSL attachment to the host cell, coupled with the activity of glycerol to clean the wound, seems essential to treating HSL lesions. This mechanism of action is completely mechanical as there is no interaction between the ingredients of Hp-OR and the biological surface over which the product is applied; however, such a preparation can only be used to treat open lesions or the mucous membranes where skin keratinocyte barrier is either absent or damaged. This topical and mechanical mode of action of Hp-OR also helps prevent drug resistance, which is becoming one of the major problems in antiviral therapy (Mundinger *et al*., 2008).

Some traditional plant preparations are suggested for the treatment of HSL (Alvarez *et al*., 2009) but none of those plant preparations, with or without tannins, was found to be effective. This is comprehensible because the concentration of free virus particles on the lesion surface is very high and requires blocking the entire virus–host cell interaction in order to stop virus growth. Since tannin–virus glycoprotein or tannin–protease binding is highly specific, as our previous work on the binding of proteases and virus glycoproteins with PCDs has clearly proven (Shrivastava, 2011), it is unlikely that a non-specific tannin could act simultaneously on all these parameters at once.

Taking into consideration the progressive reduction in the mean amount of free virus particles in the lesion, and the concomitant reduction in the size of the lesions, the results indicate that nearly all the existing free virus particles were expelled from the lesion within 24-48h and that the product continued removing newly liberated free virus particles from the lesion. In absence of any modifications in other haematological, blood, biochemical or urinary parameters, or any reporting of side effects by participants, Hp-OR can be considered a very safe topical,

protease- and virus-inhibitor for the treatment of open HSL lesions.

Although Hp-OR is completely safe, non-irritant, and well tolerated by patients, the possibilities of occasional allergic reaction due to the presence of plant extracts cannot be excluded.

CONCLUSION

Neutralizing and eliminating the free virus particles from the open lesion is one of the best strategies to treat labial herpes.

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