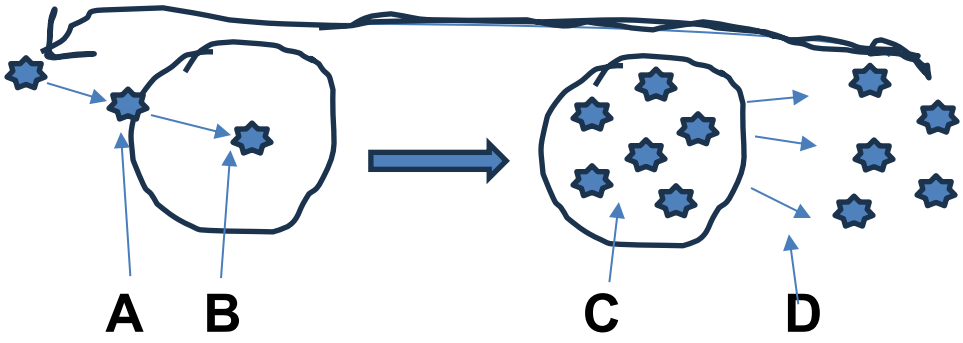
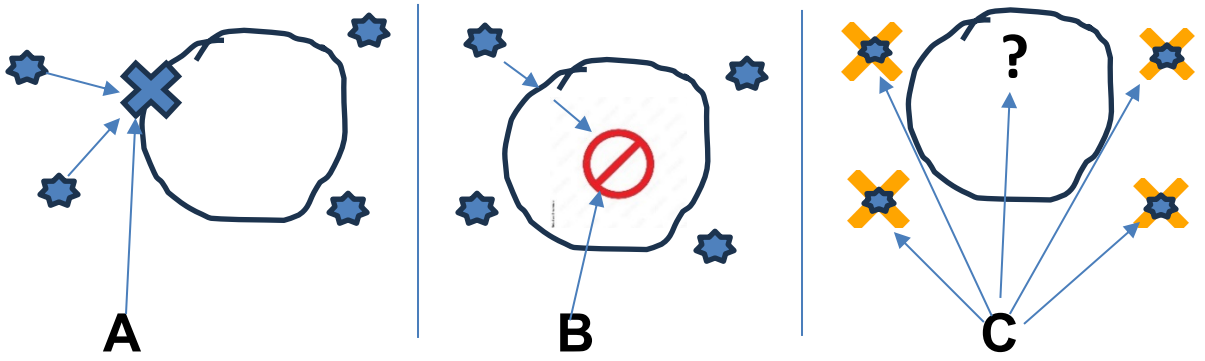
FOR THE HEALTHCARE PROFESSIONAL

Stages of Viral Infection



A- Viral Fusion to cell membrane
B- Viral Entry into cell
C- Viral Replication (intracellular)
D- Viral Exit from cell (exocytosis) newly formed virions are now able to infect more cells → repeat steps A, B, C & D, generating exponential replication

Therapeutic Viral Targeting



A- Docosanol – Extracellular effect - blocks viral fusion with cell membrane
Viral particles (virions) are not killed → potential to spread
B- Antiviral Medications (e.g., nucleoside analogues) - Intracellular effects

Block viral DNA replication ➡ block viral replication
Any remaining extracellular virions are not killed → potential to spread
C- Zap-H™ - Extracellular ((possible intracellular)- disrupts viral membrane together with immune system → virions are eradicated / killed

- **No Viral Fusion**
- **No Viral Entry or Replication**
- **No Viral progression to other cells**

UNDERSTANDING THE HERPES VIRUS

BACKGROUND ON THE COLD SORE VIRUS

Herpes Virus Replication

The enveloped virus first binds to and then enters a cell in the body. After viral entry, the virus replicates rapidly inside the host cell. The herpesvirus particles (virions) develop a protective outer envelope by taking a part of the host cell membrane as they exit the host cell – this process is called exocytosis. The greatly expanded number of viral particles that are released from the cell can now spread to other cells, repeating the replication process. In this way, the virions expand exponentially at a rapid pace.

The herpes virus is classified as a DNA virus and an enveloped virus. Viral DNA is stabilized by a shell of proteins called the capsid. Together the DNA and capsid are referred to as the nucleocapsid. The nucleocapsid is surrounded by the outer envelope. The virion consists of an outer envelope that surrounds the inner nucleocapsid.

The viral particle is always surrounded by this envelope except after it enters a cell, whereby the nuclear material, nucleocapsid, is released. The released nucleocapsid enters the host nucleus, wherein lies the host DNA. In the nucleus the viral DNA replicates by manipulating and utilizing host cell machinery for this process. After subsequent release from the nucleus, the newly formed nucleocapsid particles fuse with the host cell membrane. In a process referred to as exocytosis the newly formed and expanded nucleocapsid particles "bud off" from the host cell plasma membrane, incorporating a piece of the host cell membrane which forms the viral envelope. In this way, the viral envelope is acquired from the host cell plasma membrane. The viral envelope being formed from host cell membrane helps it evade the immune system – i.e., the immune system views this envelope as normal cellular tissue.

Why cold sores, also called fever blisters, may be difficult to treat.

The herpes HSV-1 virus is the main cause of cold sores/fever blisters on lips. A similar herpesvirus, HSV2, is the main cause of genital herpes, but either one of these 2 versions can cause oral cold sores. Herpesvirus owes its successful spread to its complexity, which has enabled it to effectively slow down the human immune system in several different ways. As discussed above, because the viral envelope is formed from the host cell membrane, it may not be viewed as foreign by the immune system.

Furthermore, glycoproteins of the herpesvirus envelope play a significant role in the early interactions, attachment, and entry of viral particles into the host cell. They modulate the immune system to maintain a presence in the infected host. They maintain a balance between preventing from being targeted and killed by the immune system,

while at the same time preventing host cell death, as their survival depends on host cell survival.

Further yet, herpesvirus has evolved a mechanism by which to remain dormant in the body for long periods of time, wherein it can linger in a hibernation state known as viral latency. The herpesvirus (HSV-1) has a predilection for neurons near the base of the brain, in an area called the trigeminal ganglion. The virus lies dormant within these nerve cells and can do so for months to many years, even 30 or more. It can be activated by numerous factors, and this may vary between individuals. Triggering factors include stress, lack of sleep, exposure to sun, cold wind, a cold, flu or other illness, a weak immune system, and changing hormone levels.

The cold sore early stage typically begins with a tingling sensation on the lip. Within 12-24 hours the early sore, a red bump, develops. It then may take 1-2-3 days to form a blister(s), i.e., the cold sore. The sore may build up and then excrete a highly infectious clear/yellow liquid, the so-called "weeping phase." The final phase is the formation of a scab, which can take 7-14 days to resolve, and up to several weeks in the immune compromised individual. Both the blister, and the subsequent scab that forms, can develop a microscopic biofilm, a shield that protects the virus from the local micro-environment. The protective biofilm challenges the body's immune system to fight the virus and can also hinder certain treatments. This is yet another mechanism by which the herpesvirus evades the immune system and makes it difficult to target.

Why cold sore treatments have limited effectiveness.

In addition to having developed methods by which to hide itself from the immune system, HSV1 infection therapies have had limited success for one main reason - current treatment methods do not target the virus directly. For example, many cold sore treatments focus on relieving the symptoms, namely itch, tingling and pain, where the effects are typically of temporary nature. Second, treatments are available that block viral entry into host cells, however there is no direct effect on HSV1, and the virions can survive. Third, treatments are available that prevent viral replication, but again the virions can survive. A common denominator for all these treatment methods is that they do not eradicate or kill the viral particles themselves.

The immune system is left to deal with the virus on its own, where the lesions and subsequent scab typically last anywhere from 7-14 days, and up to 3-4 weeks in some cases, especially in an individual with a compromised immune system. Whereas treatments that focus on relieving symptoms have no effect on cold sore duration, treatments that block viral entry and those that prevent replication can reduce the duration of a cold sore lesion.

There are limitations. For example, agents that block viral entry reduce the duration of a cold sore on average 18 hours. 1 ½ days of improvement is relatively minor improvement for a lesion that can last 7-14 days, and longer in the immune compromised individuals. Second, antiviral medications (e.g., nucleoside analogues)

can reduce duration of symptoms down to 4 days. However, there are some potential issues with antiviral medications.

A problem for both viral entry blocking agents and antiviral medications, is that treatment results are best when started within 24 hours but can be effective at 24-48 hours after onset of symptoms, i.e., the sensation of tingling of a small red discoloration along the lip line. After 2 days of symptoms, the viral particles have proliferated to the extent that further prevention becomes futile.

Antiviral medications are more effective in reducing duration of symptoms as compared to viral entry blocking agents. A problem with antiviral medications is that their overuse can lead to viral resistance to these medications, making the medications less effective, or even ineffective. The development of resistance is most common in immune compromised individuals who have a more difficult time eradiating cold sores, and thus more frequent use of the viral medications, which leads to development of resistance.

The Zap-H™ Benefit

Mechanism of action and what it means?

Combining the information from our lab studies and existing publications, it is thought that a key mechanism of action for Zap-H™ is the ability of its ingredients to disrupt the protective viral envelope. Once the viral envelope is disrupted, it exposes the herpesvirus internal components, which can then be targeted by the body's immune system. This gives the immune system the opportunity to eradicate the virus more effectively. Furthermore, because the immune system can now identify viral molecular targets that have been exposed, it allows the immune system to learn how to build protective measures against the virus. These learned protective measures help the body to prevent the frequency and severity of any potential future outbreaks.

What's a viral envelope and why do I care?

The viral envelope (also called viral membrane) protects the HSV viral DNA. Disrupting the viral envelope can lead to either direct killing of the virus by Zap-H™ or it can allow for the immune system to target and kill the HSV viral particles. It is well established that numerous fatty acids kill a wide variety of viruses, and this is accomplished by disrupting their viral envelopes, or membranes *.

* Reference - Thormar H, et al; Inactivation of enveloped viruses and killing of cells by fatty acids and monoglycerides. Antimicrob Agents Chemother. 1987;31(1):27-31. doi:10.1128/AAC.31.1.27.

Zap-H™ comprises such fatty acids that disrupt viral membranes. Furthermore, in-vitro (i.e., lab tests) testing with Zap-H™ has shown rapid killing of viral particles. In this way, Zap-H™ kills HSV viral particles by disrupting their envelopes.

Further yet, although numerous fatty acids/ oils can kill viruses, the combination of ingredients in Zap-H™ significantly enhances, i.e., synergizes, such viral killing. In this way, the combination of Zap-H™ ingredients is profoundly more effective than using such fatty acids/ oils alone.

Our laboratory studies demonstrate that the combination of ingredients in Zap-H™ is more effective than either ingredient used alone. Our hospital clinical study and human testing results are consistent with our laboratory testing, confirming that the combination of ingredients in Zap-H™ improves the antiviral features beyond using any of the ingredients alone.

While laboratory studies show viral envelope disruption and a viral killing feature by fatty acids, any clinical effect has not been evaluated by the FDA. However, the rapid in-vitro viral envelope disruption correlates with a rapid in-vivo effect (i.e. demonstrated with a double-blind, hospital clinical study showing a significant reduction in time for symptoms to disappear). In other words, our laboratory research testing in the past correlates highly with results obtained with the clinical use of Zap-H™.

Effective even at 5 days post onset of symptoms

Our clinical experience further shows that individuals using Zap-H™ anecdotally note that it is effective even if treatment application begins after the blisters have formed, i.e., at 5 days after onset of a cold sore (see also below on biofilm). This is a benefit over docosanol based products and prescription antiviral medications, which need to be started within 2 days of the onset of a cold sore, being ineffective once blisters form.

Generalized Antiviral Effect

Zap-H™ has also shown antiviral efficacy against other viruses that were tested in the lab. These pertain not only to herpesvirus, but also coronavirus, RSV (respiratory syncytial virus), influenza and Mpox viruses. The formulations need to be altered for specific viruses for best results - the same formula is not optimal for every virus. We do not advocate that the Zap-H™ formulation should be used to mitigate symptoms for these other viruses, but the lab results further confirm the general antiviral features of Zap-H™ ingredients.

Anti-inflammatory effect

Fatty acids can reduce inflammation in epithelial cells, as for example those lining the mammary glands. An anti-inflammatory feature of fatty acids in Zap-H™ can help reduce the swelling and symptoms of cold sores.

Zap-H™ & Biofilm

An additional benefit for Zap-H™ pertains to biofilm. Biofilm is a complex extracellular matrix that is formed by microorganisms which protects them from substances in their local micro-environment, and this includes antibiotics, antiviral agents, and some antiseptic agents.

In addition to plant oils having well established antiviral properties, fatty acids found in oils also have antimicrobial effects against numerous pathogenic bacteria that can cause disease. However, they do not kill beneficial bacteria, such as Bifidobacteria and Lactobacilli. Fatty acids are also known to have biofilm disrupting effects against numerous bacteria. Biofilm protects both bacteria and viruses hidden within such biofilm. With respect to viral particles embedded in biofilm, biofilm disruption would be beneficial to eradicate the associated virus particles.

Zap-H ™ cream was initially developed as an antibacterial biofilm disrupting technology, before it was found to have antiviral properties. The blend of Zap-H™ ingredients breaks down biofilm in multiple types of microorganisms. In-vitro lab testing at an independent top microbiology testing center demonstrates effects against mature biofilm organisms, including Gram positive Staph. aureus and Enterococcus; Gram negative Pseudomonas aeruginosa, E. coli, and Klebsiella pneumonia; and Candida fungal biofilm.

When open sores develop, bacteria infiltrate such open wounds, and form biofilm as a manner by which to protect themselves. Bacteria are known to reside within biofilm in the eschar (i.e., scab) above a wound bed, such as a scabbed cold sore lesion. Viruses are known to lodge within bacterial and fungal biofilms. In this respect, after a cold sore blister breaks and the scab forms the herpesvirus can exist in the bacterial biofilm of the cold sore eschar. Because Zap-H™ disrupts biofilm, this is yet an additional benefit as it can target viruses that may be present within biofilm located on open sores. Moreover, if one could breakdown biofilm (such as with Zap-H™), it would expose the encased viral particles, rendering them susceptible to topical viral envelope-disrupting agents, such as Zap-H™, and the body's immune response. In other words, Zap-H™ does both – it first disrupts the biofilm to expose the viral particles and subsequently dissolves the viral membranes thus allowing for the killing of the now-exposed viral particles by the immune system. This is correlated clinically by individuals where treatment of cold sores with Zap-H™ was started up to 5 days from symptom onset. At this stage the outbreak formed an eschar (i.e., scab). Nonetheless, subjects reported that their symptoms were resolved more quickly with Zap-H™ application, even at this relatively late stage in treatments, as compared to an untreated cold sore scabbed lesion.

Zap-H™ & Skin Absorption

A yet additional benefit for Zap-H™ is rapid skin absorption. Moreover, when an antiviral formulation is applied topically, in order to be effective, it needs to penetrate into the skin such that the active ingredients can actually reach the viral particles which are buried under the skin, and potentially within biofilm. Zap-H™ ingredients comprise a water-based formulation which has rapid skin penetration, and this enhances its clinical efficacy (i.e.., the active ingredients can actually reach and make contact with the viral particles). A further benefit is that a formulation that absorbs well does not leave a visible or irritating residue on the skin/ lip.

When we tested numerous over-the-counter (OTC) products, it was noted that most did not have good skin absorption properties. Docosanol, for example, has shown poor skin

permeation properties. In fact, the Product Monograph from a pharmaceutical company, the manufacturer/ distributor of a docosanol 10% cream, on November 26, 2013, specifically states “Dermal and gastrointestinal absorption of docosanol ..... is limited…...”. If a composition does not absorb through the skin, then one can imagine that there is limited ability for such a product to target a virus, which is lodged deep underneath the skin surface. Zap-H™, on the other hand, absorbs quickly, typically within 5-10 minutes. This is due to the presence of skin permeation enhancers in the Zap-H™ formula. Such rapid penetration through the skin and into the local tissues allows for the ingredients to reach the cells. Any viral particles that are either ready to enter a host cell, or those newly formed viral particles that have exited the cells can be targeted by the absorbed Zap-H™, which will disrupt the viral envelope, allowing the immune system to eradicate the virus.

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GENITAL HERPES

The genital herpesvirus (HSV2) is structurally very similar to the cold sore HSV1 virus particle. The viral envelopes are similar, as both are formed from the host cell wall. In this respect, because Zap-H™ targets the viral envelope, it theoretically would have effectiveness against the genital HSV2 viral envelope. (Clinical testing for genital herpes has not yet been performed.) At this time, we are not able to recommend Zap-H™ for use on HSV2 or genital herpes sores. The information provided herein is for healthcare professionals.

SHINGLES

Shingles rash is the reactivation of the chicken pox herpesvirus (Varicella Zoster, or Herpes Zoster - HZ) infection in adults. It can be very painful and debilitating. Zap-H™ has not been formally tested for shingles, however, because shingles is caused by a similar herpesvirus, with a similar viral envelope, anecdotal reports indicate that it may be effective in relieving pain symptoms of the shingles rash and reducing duration of the rash. Because no formal testing has been done for shingles, at this time we cannot recommend the use of Zap-H™ for application on shingles sores. This information is provided for healthcare professionals.

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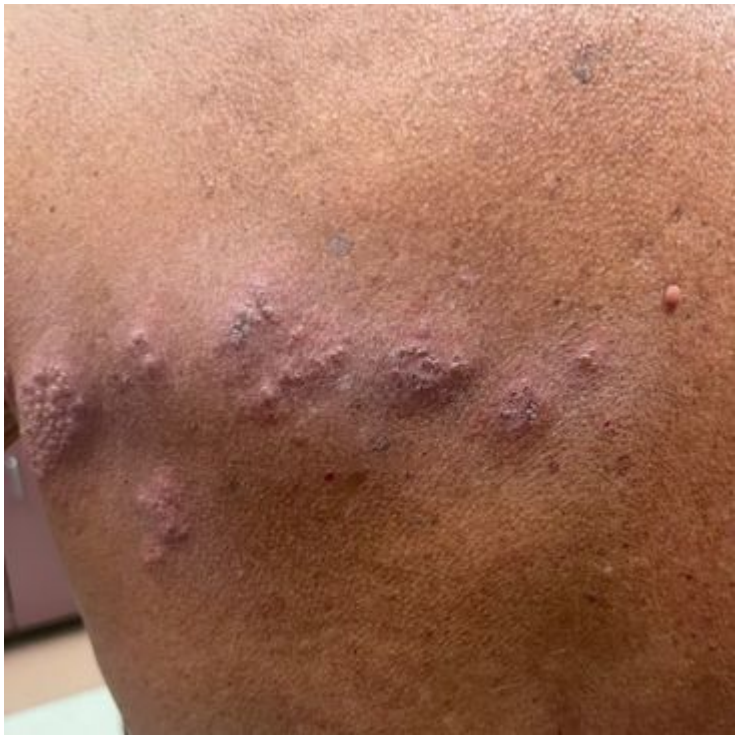
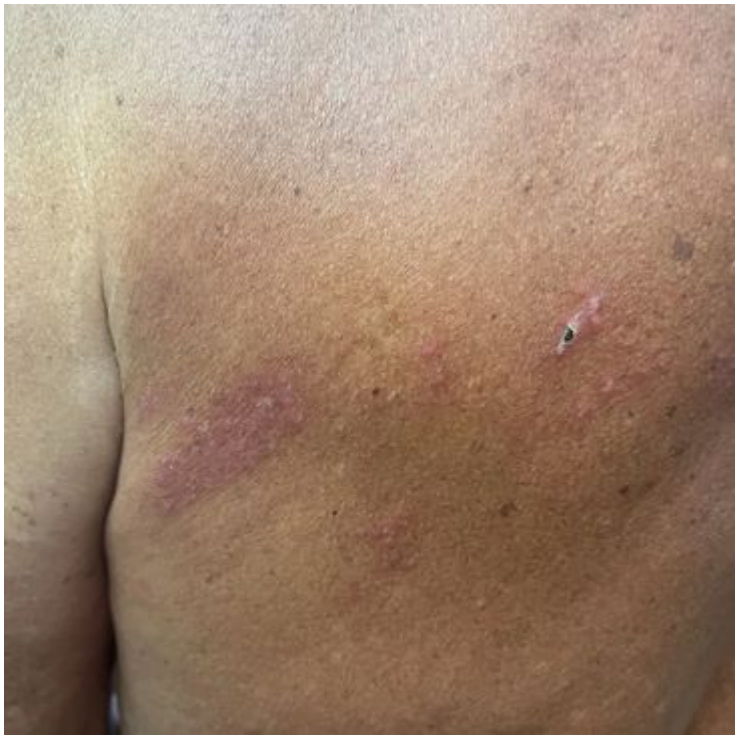


SHINGLES (CASE STUDY) BEFORE ZAP-H™
PHOTO: 68 year old, healthy male, unvaccinated for shingles. Day 4 of shingles outbreak. Symptoms of pain, itch and tingling.



SHINGLES (CASE STUDY) AFTER ZAP-H™

PHOTO: Day 6, after applying Zap-H™ on Day 4, 5 and 6. Painful symptoms were relieved more rapdily than the typical duration of 3-5 weeks.

Note. This is only one example, and it does not prove that Zap-H™ will have similar results for other subjects. We show this to highlight that Zap-H™ ingredients have a unique ability to potentially help the body's immune system to better deal with a viral skin infection. Zap-H™ does not cure any disease and has not been tested or approved by the FDA for use in treating symptoms associated with a shingles outbreak. This information is provided for healthcare professionals.