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Review Article

# A REVIEW: ZINC AS AN ANTIVIRUS ALTERNATIVE TREATMENT FOR HERPES SIMPLEX VIRUS INFECTION

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**ABSTRACT**

This study aimed to review zinc's effectiveness as an antivirus in treating herpes simplex virus infection. The authors use international journals published from 2000-2022, and use search engines such as Google Scholar, PubMed, and Science Direct with the keywords "zinc and herpes simplex virus". The herpes simplex virus that often causes symptoms in humans are HSV type 1 and type 2. The lesions appear as vesicles which then rupture into ulcers. Zinc is one of the most abundant nutrients or metals in the human body besides iron. Studies about the effects of zinc on HSV have shown that it has the function of inhibiting the viral life cycle. HSV attaches to the host cells to replicate and synthesize new viral proteins. Zinc can inhibit this process by depositing on the surface of the virion and inactivating the enzymatic function which is required for the attachment to the host cell, disrupting the surface glycoprotein of the viral membrane so it could not adhere and carry out the next life cycle, it can also inhibit the function of DNA polymerase that works for viral replication in the host cell. This article showed that zinc has effectiveness as an antivirus against the herpes simplex virus, therefore, patients infected with HSV can be treated with zinc as an alternative to an antivirus drug.

**Keywords**: Herpes Simplex Virus (HSV), Zinc, Antivirus


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## INTRODUCTION

Herpes simplex virus (HSV) is a member of the human herpes virus (HHV) family, which is a double-stranded DNA virus [1]. This virus causes infection in humans; there are two types of HSV i.e. herpes simplex virus type 1 (HSV-1) and herpes simplex virus type 2 (HSV-2) [2, 3]. Commonly, HSV-1 causes lesions in the orofacial area or lesions 'above the belt (waist)', whereas HSV-2 causes lesions in the genital area or 'below the belt (waist)' [3]. This viral infection can cause primary, latent, and recurrent infections in individuals' lives [2, 3]. HSV is a virus that has an envelope with a round and regular shape [4]. This virus has a diameter between 120-200 mn [1, 4]. The virion has 3 main structures, namely nucleocapsid, envelope, and tegument [1, 4].

Primary oral mucosa infection is often subclinical, if symptomatic clinically presents as gingivostomatitis that appears as pinhead-sized vesicles which then rupture into red lesions [5]. These lesions will enlarge and develop into ulcerations covered by yellow fibrin [2, 3, 5]. Adjacent ulcerations may coalesce to form larger, shallower, and irregular ulcers [2, 3].

After primary infection, HSV will be latent in the ganglion nerve, which is reactivated due to several predisposing factors, such as decreased immune system [2, 5]. Activated HSV can cause recurrent herpes labialis (RHL) lesions and recurrent intraoral herpes (RIH) lesions [6]. HSV infection in immunocompromised individuals can be more widespread and more severe than in immunocompetent individuals [2, 7].

The peak prevalence of HSV 1 infection is in the fifth decade of life [8]. This viral infection is more common in lower socioeconomic groups than in higher socioeconomic groups. Approximately 3752 million people in the world have HSV type 1 infection, equivalent to a global prevalence of 66.6% in the age group 0-49 y [8, 9]. Different patterns are observed based on age, gender, and geographic area. Based on gender, women have a higher prevalence of HSV infection than men [10].

The goals of HSV infection management are pain control, supportive care, and definitive treatment [2, 6]. A group of antivirus drugs, such as acyclovir, is still the drug of choice for the definitive treatment of HSV infection [2, 6, 7, 11]. Acyclovir is converted by viral thymidine kinase into acyclovir monophosphate, which is then converted by host kinase enzymes to become acyclovir triphosphate (ACV-TP). ACV-TP inactivates HSV DNA polymerase which ultimately prevents viral DNA synthesis [1]. There are various studies regarding treatment options for HSV infection, one of which was using zinc[12]. Researchers have studied the effects of zinc on HSV for decades [12]. Zinc is an important micronutrient in human health, it affects almost every organ and cell of human body [12, 13]. It is an integral part of various enzymes, transcription factors, and 10% human protein [12, 13]. This article discusses the mechanism and effectiveness of zinc as an alternative antivirus treatment for herpes simplex virus infection.

## METHODS

This review article uses international journals published from 2000-2022. The author uses the keywords "zinc and herpes simplex virus" on the Google Scholar search engine, PubMed and Science Direct. The results obtained as many as 12 journals with this method, as shown in fig. 1.

The inclusion criteria were the original articles, in English, available in full paper, containing relevant bibliographies, specifically the topic of Zinc and HSV. Pre-Proof journals and journal are not related to the direct use of zinc against HSV were exlude.

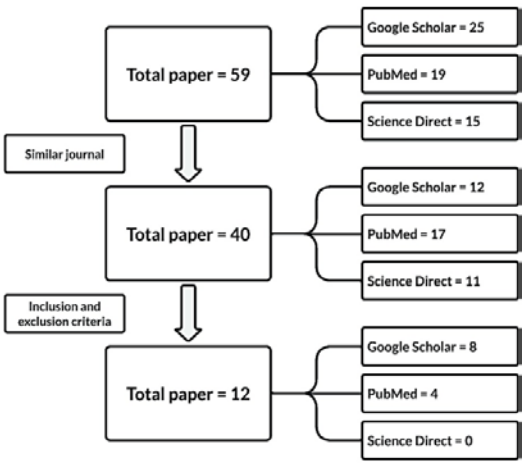


**Fig. 1: Method flowchart used in this review**

## LITERATURE REVIEW

### Zinc

Zinc has important functions in cellular processes such as DNA and RNA synthesis, growth, and development because zinc is a component of approximately 750 transcription factors and various enzymes [13]. Zinc is a micronutrient that plays a role in the body's metabolic processes, as much as 2-3 g of zinc contained in the human body [14]. Zinc can be found in the prostate gland, testes, semen, bones, teeth, hair, skin, liver, muscles, and leukocytes. Zinc is bound to proteins, both globulins, and albumins [12, 15–17]. Zinc intake in adults is around 6 to 15 mg/day or based on the RDA (Recommended Daily Allowances) recommendation of 0.2 mg/kg/day [12, 13]. Zinc is found in various foods such as seafood, liver, eggs, and meat. Zinc absorption is 20% of all food intake [12, 13].

Various functions of zinc that are beneficial for the human body can be seen in Fig.2. It has three basic roles as a catalyst, structural formation, and regulatory process [18]. First, zinc is a catalyst for more than 50 types of enzymes [18]. Alkaline phosphatase and CuZn superoxide dismutase are example enzyme that works by depending on zinc, mechanism of action will be reduced if zinc intake is low [18]. The second function is zinc as a structural constituent of various proteins and also plays a role in the process of cellulars such as transcription, adhesion, signal transduction, and differentiation or proliferation [14, 18]. The third, zinc functions, is the regulation of various gene expressions [14, 18].

Reduction of inflammatory cytokines in chronic inflammatory processes is one of the important roles of zinc [19]. Zinc can produce antioxidant enzymes for reducing oxidative stress [19]. In addition, zinc also shows benefits for diabetes mellitus, metabolic syndrome and atherosclerosis because it plays a role in insulin synthesis and protein, carbohydrate, and fat metabolism [14, 19].

Zinc is useful in the immune process. Epidemiological and clinical experience demonstrates the important role of zinc in host defense against immunologically mediated pathogens. Zinc can be a messenger for T cell receptors and IL 2 in the immune process [14]. In addition, zinc is required for B cell maturation and function [14, 20]. Zinc can improve the state of lymphopenia because it is associated with the process of lymphocyte development [20].

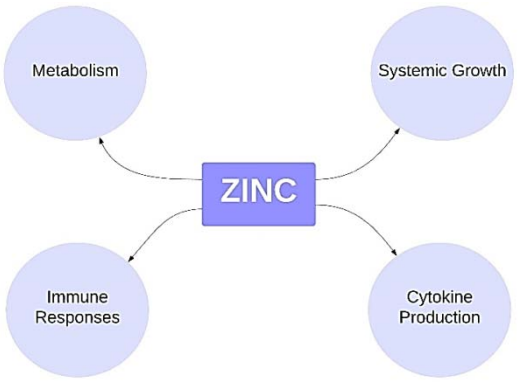


**Fig. 2: Function of zinc [13, 14, 19, 20]**

Zinc deficiency is very common as a result of various factors such as age, lifestyle and disease [14]. Zinc deficiency occurs in almost a quarter of the population in developing countries and a small proportion in developed countries [13]. Zinc status in a person greatly affects the risk of infection [14]. Immunocompromised, the elderly, and poor nutrition have a high risk of zinc deficiency so this group will be susceptible to various infectious diseases, cancer and other immune diseases [13, 20].

Zinc deficiency can cause a compromised immune system, which has been proven in animal studies that show thymic atrophy, lymphopenia, and impaired lymphocyte response [13]. The risk of infection increases in underdeveloped countries due to poor sanitation, public health status, and vaccination so zinc nutrition is very important in this group [13, 17]. Zinc deficiency affects cell-mediated immunity by reducing the phagocytic activity of macrophages and circulating T cells [13, 17]. Zinc serum is a biomarker to assess a person's zinc status. Salivary zinc levels in patients with RHL were found to be lower than healthy people [13, 17].

### Herpes simplex virus (HSV)

Human herpes virus (HHV) is a large family of herpesviridae and is a double-stranded DNA virus [1,4]. Based on its characteristics, herpesviridae is divided into three categories (subfamily), such as α-herpesvirinae, β-herpesvirinae and γ-herpesvirinae [1, 4]. α-herpesvirinae has a rapid cytocidal growth and lytic cycle [4]. It can be dormant or cause latent infection in nerve ganglia [3, 4]. The members of this group are varicella-zoster virus (VZV), herpes simplex virus types 1 (HSV-1), and herpes simplex virus type 2 (HSV-2) [3, 4]. The next group is β-herpesvirinae (cytomegalovirus group), this type has a slower replication cycle than the previous group [3, 4]. Lymphatic cells and glandular tissue are sites of latency for this type of virus. Members of this virus group include human cytomegalovirus (HCMV) and human herpesvirus types 6 and 7 (HHV-6 and HHV-7) [3, 4]. The last one is γ-herpesvirinae. This group of viruses replicates in mucosal cells and then becomes latent on B cells [3, 4]. Members of this group of viruses include the epstein barr virus and kaposi sarcoma herpes virus [3, 4].

The famous member of this family is the herpes simplex virus (HSV), which includes HSV type 1 (HSV-1 or HHV-1) and HSV type 2 (HSV-2 or HHV-2) [2]. The term herpes comes from an ancient Greek word meaning to creep or crawl, which seems to allude to a tendency to spread, latent infection, or recurrent infection [2]. These viruses cause primary infection and are latent in certain cell types in individuals' lives [1, 2]. When reactivation, the virus causes repeated infections which may or may not be symptomatic [1, 2]. Viruses are distributed in saliva or genital secretions and provide the way for infection in new hosts [1, 2].

Primary oral infections are often subclinical but may be symptomatic as in the case of viral-induced primary gingivostomatitis herpes simplex [6]. Reactivation of the latent form can lead to a variety of conditions. In immunocompromised subjects, infection with the herpes virus was more severe than in immunocompetent subjects [1, 3, 6].

The main structure of the virion consists of nucleocapsid, envelope, and tegument [3,4]. The viral DNA is in the capsid [4]. The shape of capsid is icosahedral [4]. The capsid has a shell with a diameter of 125 nm and a thickness of 15 nm [4]. The envelope contains about 11 glycoproteins, four of which play a role in the process of viral replication as part of the entry virus into the host cell, namely gD, gH, gL, and gB [3, 9, 4]. Between the envelope and capsid, there is protein material called tegument [4, 9]. This section contains various enzymes and transcription factors that are the virulence factors of HSV [4].

### HSV replication

HSV replicates in the nucleus of the host cell according to the basic pattern of viral DNA replication [1, 4, 9]. The general description of herpes simplex virus replication in primary infection includes adsorption and penetration into host cells, viral DNA replication, assembly of the nucleocapsid and viral envelope until a new virus is formed and causing latent infection and reactivation [1, 4, 9]. The HSV binds to receptors on the host cell membrane; then, fusion occurs between the viral envelope and the host cell membrane [1, 4, 9]. After fusion, the virus deposits its nucleocapsid and tegumentary proteins into the cytosol [1, 4, 9]. The function of one of the tegument proteins is to inactivate host cell protein synthesis by degrading host cell mRNA [1, 4, 9].

The nucleocapsid that is already in the cytosol is then transported into the nucleus and releases DNA contained therein [1, 4, 9]. Another task of the tegument protein is to activate cell RNA polymerase as an initial step in the gene transcription process and initiate further gene transcription [1, 4, 9]. Thymidine kinase, DNA

polymerase, and helicase are proteins needed in the viral replication process. These enzymes are widely used as targets of antivirus drugs (such as acyclovir) [1, 4, 9].

According to DNA viruses, the final gene codes for the virion's structural proteins and proteins involved in the assembly and maturation of viral progeny [1, 4, 9]. The newly synthesized envelope proteins accumulate on the nuclear membrane, and the nucleocapsid that has assembled in the nucleus acquires its envelope by budding [1, 4, 9]. The complete virus is then transported by the vacuole to the cell surface [1, 4, 9]. The next step is the formation of an envelope protein that covers the nucleus into a nucleocapsid by the budding process [1, 4, 9]. The complete virus moves to the cell surface to become a new virus that can infect other cells. During viral replication, many cellular synthetic pathways of the host cell are inactivated, ultimately leading to cell death [1, 4, 9].

**Antivirus as a treatment for HSV infections**

Supportive care and hydration are treatments for primary herpetic gingivostomatitis patients without immune disorders [2]. The main therapy for treating HSV infection is still using a group of antivirus drugs [6, 11]. One of the easily available and effective antivirus drugs for the treatment of primary viral infections is acyclovir [2, 6]. This antivirus drug works to inactivate the virus and reduce the release of new viruses [2, 6]. Viral DNA polymerase can be prevented by acyclovir [11]. The effective dose of acyclovir in children is 15 mg/kg five times a day [11]. Correct use of this drug will reduce pain in patients, progression of lesions, and incidence of hospitalization [2, 6].

Additional medications such as dyclonine hydrochloride spray, tetracaine hydrochloride, or nonsteroidal anti-inflammatory drugs (NSAIDs) may be used for faster pain relief [2]. Patients should also be instructed to limit contact with active lesions to prevent autoinoculation or spread to others [2].

Recurrent HSV infection often occurs due to precipitating factors such as sun exposure, so the use of sunscreen is highly recommended [1, 2]. In addition, the use of topical antivirus drugs such as 5% acyclovir cream and 3% penciclovir cream are still an option for the treatment of RHL [1, 2]. These drugs are best used at the onset of the lesion in a dose of three to six times a day [1, 2]. These drugs serve to reduce the duration of the lesion, its size, and pain in the patient [2, 9, 21]. In cases of HSV infection with frequent relapses or large lesions, treatment may be with systemic antivirus such as famciclovir or valaciclovir (500-1000 mg) [2, 22].

The use of acyclovir has several adverse effects, including malaise, nausea, vomiting, diarrhea, and headaches [23]. Administration of these antivirus drugs has various side effects, from mild to severe, including dizziness, fatigue, abdominal pain, alopecia, confusion, disseminated intravascular coagulation (DIC), anemia, and angioedema [23]. In the parenteral administration of acyclovir, acute kidney injury may occur, patient with history of chronic kidney disease are strongly discouraged from using this regimen [24]. Acyclovir is also known to decrease absolute neutrophil count and hemoglobin concentration in pediatric patients [11].

**Table 1: Effectiveness zinc on HSV**

| No | Author | Title | Publication year | Effect of zinc | References |
|---|---|---|---|---|---|
| 1 | Fani M *et al.* | Zinc sulfate in narrow range as an *in vitro* anti hsv 1 assay | 2019 | The treatment with 0.3 mm ZnSO4 strongly inhibited the replication of HSV progeny. | [27] |
| 2 | Mishra Y K *et al.* | Virostatic potential of micro-nano filopodia-like zno structures against herpes simplex virus-1 | 2011 | Zinc oxide nanomicrostructure efficiently traps virions unable to enter the target cell. | [28] |
| 3 | Antoine T *et al.* | Prophylactic, therapeutic and neutralizing effects of zinc oxide tetrapod structures against herpes simplex virus type-2 infection | 2012 | Zinc oxide tetrapod micro-nanostructures have the potential to stop the spread of the virus by blocking the entry of HSV into host cells and neutralizing virions. | [29] |
| 4 | Mahajan *et al.* | Herpes genitalis–topical zinc sulfate: an alternative therapeutic and modality | 2013 | Topical 4% ZnSO4 has been found to be an effective therapeutic modality not only for treatment but also for prolonging remissions in herpes genitalis. | [21] |
| 5 | Bourne N *et al.* | Efficacy and toxicity of zinc salts as candidate topical microbicides against vaginal herpes simplex virus type 2 infection | 2005 | Experimental zinc salt solutions applied to the vagina of rats are known to protect against HSV type 2 infection. | [30] |
| 6 | Ranjabar *et al.* | Comparative study of serum zinc concentration in recurrent herpes labialis patients and healthy individuals | 2020 | High levels of zinc significantly improve of healing recurrent herpes labialis. | [17] |
| 7 | Arens at al | Zinc salts inactivate clinical isolates of herpes simplex virus *in vitro* | 2000 | Zinc can prevent viral protein synthesis by inhibiting the function of the DNA polymerase enzyme. | [16] |
| 8 | Dugal N *et al.* | Zinc oxide tetrapods inhibit herpes simplex virus infection of cultured corneas | 2017 | Zinc oxide tetrapod-shaped nano and microstructures inhibited HSV infection of the cultured cells. | [31] |
| 9 | Khozeimeh F *et al.* | Comparative analysis of salivary zinc level in recurrent herpes labialis | 2012 | Prescribing zinc complement in low serum status has both treatment and preventive effects in RHL patients. | [32] |
| 10 | Altaei *et al.* | Treatment of herpes simplex by zinc sulphate | 2005 | Zinc sulfate can prevent virus attachment by interfering cell membrane surface glycoproteins. | [15] |
| 11 | Femiano *et al.* | Recurrent herpes labialis: a pilot study of the efficacy of zinc therapy | 2005 | Zinc has the capacity to inhibit the viral infection process through a cell-mediated immune response. | [12] |
| 12 | Mujayanto *et al.* | Topical application of 1% ZnSO4 on oral ulcers increases the number of macrophages in normal or diabetic conditions of wistar rats | 2016 | Zinc serves to regulate the process of proliferation, differentiation, and cell apoptosis. During the inflammatory phase, zinc supports the function of neutrophils and macrophages. | [33] |

**Zinc as an antivirus agent**

Zinc not only has a role in the prevention of infection for specific viruses but can also generate innate and acquired immune responses against viruses [13]. Various studies have been developed in this regard, Concentration of zinc required to function as an antivirus is much higher than the physiological concentration of zinc in plasma [13, 25].

Studies of zinc in various forms, such as creams, lozenges, and supplements show strong antivirus effects [13, 26]. Zinc with the right therapeutic dose will help in the treatment of chronic or acute viral infections so that it can reduce the symptoms [13, 26]. Zinc as antivirus can be categorized into two mechanisms as a treatment for viral infections and a supplement to increase response and immunity viruses in people with zinc deficiency [13, 26].

**Zinc effectiveness on HSV**

The virus can cause infectious diseases in humans and animals, one type of virus that can cause infection is HSV [22]. As previously explained that the treatment option for cases of HSV infection is to use antivirus drugs such as acyclovir and famciclovir [2]. The use of these drugs is known to be effective in suppressing viral replication and reducing recurrence, but on the other hand, these drugs also have various side effects and some sources state that there is resistance to this antivirus [23]. Because of this, various studies have been developed to look for alternative therapies that can be used for the treatment HSV infection. Several researchers have studied the impact of zinc on HSV, can be seen in table 1. These studies show that zinc does have the effect of inhibiting HSV infection.

**Zinc mechanism on HSV**

Various studies have shown that zinc has an antivirus effect against viruses such as HSV, rhinovirus, human immunodeficiency virus (HIV), severe acute respiratory syndrome virus (SARS CoV), respiratory syncytial virus (RSV), and human influenza virus [12, 13, 15]. Researchers have studied the effects of zinc on HSV, and these studies suggest the life cycle of the virus can be inhibited by zinc [13].

The mechanism of zinc in inhibiting HSV infection through various pathways. *In vitro* studies by Arens *et al.* (2000) confirmed zinc can prevent viral protein synthesis by inhibiting the function of the DNA polymerase enzyme so a virus cannot continue its replication process [16]. In addition, another study by Kumel G (1999) reported that the penetration of virions into host cells can be inhibited by zinc ions by interfering with the function of viral glycoproteins [25]. Electron micrographs showed zinc deposition on the virion surface, which appeared to inactivate the enzymatic function required for the process [16, 27].

HSV infect host cell by fuses through glycoproteins B, C, D, H, and L. Zinc can deposit on viral membrane glycoproteins and disrupt the function of these glycoproteins so the virus cannot penetrate [1, 16, 25]. Zinc ions can easily bind to viral surface glycoproteins and inactivate many viruses [1, 16, 25]. The accumulation of zinc on these surface glycoproteins depends on the concentration and incubation time [1, 16, 25].

Studies by Antoine *et al.* (2012), Dugal *et al.* (2017) and Mishra *et al.* (2011) explained the micro nanostructure of zinc oxide significantly blocked the entry of HSV into target cells [29–31]. In addition, zinc oxide also showed the ability to neutralize HSV virions [29–31]. The attachment of HSV virus to target cells requires negatively charged cell surface chemoreceptors and glycoproteins to interact ionically between that surround the positively charged virus and zinc oxide micro nanostructures can inhibit this process [29–31].

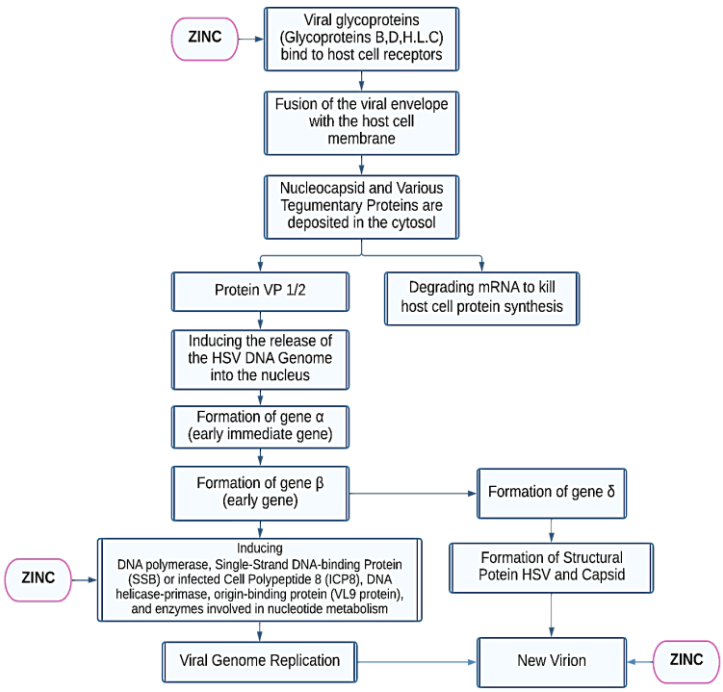


**Fig. 3: Mechanism of zinc in inhibiting HSV replication [12, 13, 15, 16, 25, 33]**

**Zinc as a treatment for oral HSV infection**

Topical zinc sulfate suspension is effective in the treatment of herpes simplex lesions. Zinc sulfate can reduce the duration of lesion so the pain caused by the lesion is shorter [15, 21]. A study by Altaei, T. (2005) showed a significant improvement in healing process with the use of 0.5% zinc sulfate [15]. The time required for patients treatment using 0.5% zinc sulfate suspension varied between 2-4 d while with placebo was 7-14 d; therefore, zinc sulfate participated in the healing process by re-epithelialization and repairing the tissue leading to healing the herpes simplex lesions in a short time [15]. No allergic skin reaction or toxic effects have been reported against zinc sulfate suspension usage and this probably encourages people to use it as a safe topical agent [15].

Ranjbar Z *et al.* (2020) compared serum zinc levels in healthy people with RHL patients [17]. The results showed that in healthy people serum zinc levels did not show a significant difference compared to patients with RHL [17]. However, from this study, it was found that serum zinc levels affect the duration of RHL healing. The higher of serum zinc level, the shorter of duration of healing. Therefore, zinc administration will be useful to reduce the duration of lesions in RHL [12, 17].

Femiano F *et al.* (2005) studied the effect of zinc sulfate on RHL and showed that systemic zinc sulfate appeared to reduce the number of episodes and speed up recovery time for herpes labialis [12]. RHL is a common recurrent infective ulcerative vesicle disease [12]. This study was conducted on 20 respondents who are often diagnosed with RHL [12]. Respondents were given 22.5 mg of zinc twice a day for 4 mo. The result is respondents experienced improvements in number of recurrences and duration of lesions [12]. RHL experienced by patients more than 6 times per year to only an average of 4 times per year. The duration of the lesion at relapse is about 8-12 d to only 7 d [12, 17].

Topical zinc application on ulcers will increase the bioavailability of zinc concentrations by about 1,000-3,000 mol/l [33]. Zinc has an important role in the wound healing process, such as assisting the process of cleaning necrotic tissue, inducing MMP (Matrix Metalloproteinases) to remove necrotic tissue, and facilitating the migration of keratinocytes in the re-epithelialization process [12, 33]. Zinc sulfate is recommended for the treatment of ulcers and in preventing recurrence because it has high absorption in the oral mucosa [12, 33]. In oral HSV infection, the application of 0.5% zinc oral suspension and 1% zinc gel is effective in reducing lesions and resulting pain [12, 33].

**Table 2: Zinc as a treatment for HSV oral infection**

| No | Author | Therapy | Dose | Results |
|---|---|---|---|---|
| 1 | Altaei, T. (2005) | Topical zinc sulfate 0.5% | 0.5% zinc sulfate suspension applied 3 times a day | Significant improvement in healing. The time required for treatment of patients with 0.5% zinc sulfate suspension varied between 2-4 d while the placebo was 7 to 14 d [15]. |
| 2 | Femiano F, Gombos F, Scully C. (2005). | Zinc sulfate tablets | 22.5 mg twice a day for 4 mo | Recurrence and period of RHL can be reduced by systemic zinc sulfate Recurrence of RHL 6 times/year decreases to 4 times/year also the healing period improves from 8-14 d to 6 d in the recurrence period [12]. |
| 3 | Mujayanto, R, Harijanti, K, Hernawan, I. (2016). | Topical zinc sulfate gel 1% | 1% zinc sulfate gel applied twice a day (morning and evening) | Decreasing perioral lesions and pain Application of ZnSO4 1% increases macrophage counts and clinically exhibits an early ulcus recovery in oral mucosa [33]. |

Macrophages play a role in the wound healing process, specifically to regulate the inflammatory process and angiogenesis [19]. Proliferation of macrophages is the result of a response to pathogens, inflammation, resolution, and tissue repair and it is a process of tissue hemostasis. Macrophages function also to secrete various inflammatory cytokines and growth factors, glucocorticoids, glucose, and lipid metabolism [19]. When inflammation occurs, macrophages will migrate from monocytes to the area around the ulcer within 2 d and will remain there for approximately 5 d [19, 33]. Macrophages will carry out their functions until the inflammation can be overcome. This process occurs in 3 to 5 d and is characterized by migration and increase of fibroblasts, proliferation of endothelial cells, and then the appearance of granulation tissue [19, 33]. Count of macrophages will increase with the application of 1% zinc sulfate and clinically demonstrated a faster healing process for ulcers in the oral mucosa [33].

## CONCLUSION

Zinc is known to be effective as an antivirus against HSV, which interferes with the function of viral polymerase, viral protein synthesis, and free viral inactivation. HSV infected people which was treated with zinc, could have a faster recovery time and fewer recurrences. Administration of zinc as an alternative treatment for HSV infection showed effectiveness in increasing healing significantly by shortening healing time and there was no mucosa allergic reaction or toxic effects. In addition, it can reduce the period of recurrence rate.

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Nil

## AUTHORS CONTRIBUTIONS

All authors have contributed equally.

## CONFLICT OF INTERESTS

There are no conflicts of interest.

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