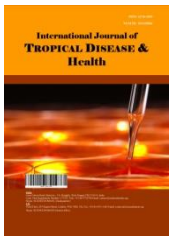

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Anti-Leishmanial Effect of Oral Zinc Sulfate in Acute Cutaneous Leishmaniasis: A Mini-review

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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ABSTRACT

Cutaneous Leishmaniasis (CL) is an endemic parasitic infection caused by various Leishmania species, with a specific predisposition of each species into a particular geographical area. Cutaneous lesions can either be a single, limited skin lesion or multiple, large, locally destructions skin lesions**.** Several therapies are proposed for CL, but severe side effects, high costs, and incomplete efficacy make researchers find replaceable therapies**.** Since the usage of zinc sulfate as a therapeutic agent has a long history in treating of various dermatological diseases, Zinc plays an essential role in the development and function of innate immunity cells (neutrophils and natural killer cells), which play significant roles in killing parasites. It also has a significant inhibitory effect on key enzymes involved in the carbohydrate metabolism and virulence of *L. major* and *L.tropica*. Therefore, its use as an oral therapy for CL might represent a significant addition to the armamentarium of anti-leishmanial medications. This review summarizes and discusses previous and recent findings regarding the therapeutic roles of oral zinc sulfate in cutaneous leishmaniasis therapy.

Keywords: Cutaneous leishmaniasis; zinc sulfate; cutaneous lesions; oral formulation; therapy.

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1. INTRODUCTION

Cutaneous leishmaniasis (CL) is an infection caused by Leishmania protozoa, are usually transmitted by biting various phlebotomine sand flies [1]. It is endemic in 88 countries, including; Sudan, Iraq, Iran, Brazil, Afghanistan, Peru, and Syria [1]. Epidemiologically, around 12 million people suffered from CL, with 1 - 1.5 million new cases each year. This disease is becoming a global health problem due to immigration and travel, leading to increased CL incidence [2].

Cutaneous lesions can either be a single, limited skin lesion or multiple, large, locally destructions skin lesions [3]. The disease presents as brownish, erythematous papules, which gradually enlarge and turn into nodules within six months. Subsequently, these nodules usually ulcerate from their center, and a brownish crust covers the infection area and ulcer [4]. Although CL is a self-healing disease, it may lead to a disfiguring of the scar and long-lasting stigmas, damaging underlying structures such as the ear, nose, or exposed skin sites that cause patients psychological distress [5].

Multiple treatment suggestions are available for cutaneous leishmaniasis [6]. Pentavalent antimonies are considered the first-line therapy. However, due to their severe side effects and consequences such as cardio-toxicity, kidney failure, pancreatitis, and leucopenia, high costs, increased cases of therapeutic failure, extended treatment duration, and new species emerging [7]. Considerable attempts are being made to find effective treatments that are more patient-acceptable and have fewer side effects.

Since zinc sulfate as a therapeutic agent has a long history in treating various dermatological diseases [8], its use as an oral therapy for CL might represent a significant addition to the armamentarium anti-leishmanial medications. In this mini-review, we will discuss the therapeutic roles of oral zinc sulfate in cutaneous leishmaniasis therapy.

2. ZINC SULFATE IN DERMATOLOGICAL DISEASES

Zinc as an element or in different forms of zinc salts, have been used as therapeutic modalities for centuries for several dermatological conditions, including infections (warts, leishmaniasis), inflammatory dermatoses (acne vulgaris, rosacea), pigmentary disorder (melasma), and neoplasias (basal cell carcinoma) [9].

3. MECHANISMS OF ACTION

3.1 Role of Zinc in Host Immunity

Zinc is an essential element and affects the multiple aspects of the immune system, it is involved in the normal development and function of cell-mediating innate immunity, neutrophils, and natural killer cells. Phagocytosis, intracellular killing, and cytokine production are affected by zinc deficiency [10,11]. Additionally, zinc deficiency also severely affected the growth and function of the acquired immune system cells (T and B cells) [12].

Interferon-γ (IFN-γ) and IL-12 play significant roles in killing parasites, viruses, and bacteria by macrophages-monocytes. The gene expression of IL-2 and IFN-γ (Th1 cytokines) are zinc-dependent [13]. Zinc induces isolated leukocytes to produce cytokines. It also induces the production of interleukin-1, interleukin-6, and tumor necrosis factor- α by monocytes [14]. Also, IL-2 is involved in the activation of NK and T-cytotoxic cells. IL-12 is generated by stimulated macrophages-monocytes and is zinc-dependent. Zinc deficiency adversely affects the secretion and functions of cytokines, the essential messengers of the immune system [13].

Furthermore, IFN-γ induces massive infiltration of macrophages and chemokine such as Monocyte Chemoattractant Protein-l (MCP-l) in the dermis of patients affected by CL. High levels of MCP-l expression are facilitated by the healing process in patients with self-healing CL. MCP-l and IFN-γ synergistically activate monocytes to clear intracellular parasites, whereas IL-4 abrogates the effect of MCP-l [15,16]. Predominant T helper (Th_l)-type cell responses are associated with IFN-γ-induced macrophage activation, indicating a network of pleiotropic cytokines, in which IL-12, produced by activated antigen-presenting cells (APC), such as macrophages and dendritic cells, shapes the essential response, and IFN-y and other cytokines also participate [17].

It has been reported that in CL, there is a depression of helper T cell function. Zinc sulfate showed a potent stimulatory effect on T-lymphocytes, which contributed to its immunomodulatory activity. Moreover, zinc is an essential component of thymulin, a thymic hormone involved in the maturation and

differentiation of T-cells [18]. Another possible site for the action of zinc is the macrophages. In CL, macrophages engulf Leishmania amastigotes which divide inside them [19]. Zinc is known to influence macrophage function [20].

3.2 Role of Zinc in Parasite Metabolism Pathway

Zinc sulfate has a significant inhibitory effect on key enzymes involved in the carbohydrate metabolism and virulence of *L. major* and *L.tropica* [20]. The Embden–Meyerhof pathway is one of the important pathways in carbohydrate metabolism. Zinc sulfate is reported to have an inhibitory effect on the key enzymes of this pathway [21]. The pentose phosphate pathway (PPP) is a fundamental component of cellular metabolism. The PPP is vital to maintain carbon homeostasis, to provide precursors for nucleotide and amino acid biosynthesis. Key enzymes of the hexose-monophosphate (pentose-phosphate) shunt and citric-acid cycle were all dose-dependently inhibited by zinc sulfate [20].

4. ANTI-LEISHMANIAL ACTIVITIES OF ZINC SULFATE

4.1 *In-vitro* Anti-leishmanial Effect of Zinc Sulfate

Zinc sulfate displayed potent *in-vitro* and *in-vivo* anti-leishmanial activities. Zinc sulfate has been reported to inhibit parasite growth and proliferation in a concentration-dependent manner [22]. One study showed that both strains *L. major* and *L.tropica* were sensitive to zinc sulfate, and their perspective LD50221.9 mg/ml were lower than the LD50of the pentavalent antimony compound (334.7 mg/ml) [22]. The same results were shown by another study conducted in Iran; the LD50 for zinc sulfate was 221.9 mg/mL, and the LD50 for pentavalent antimony compounds was 334.7 mg/mL [23].

4.2 *In vivo* Anti-leishmanial Effect of Zinc Sulfate

Zinc sulfate has been reported to exhibit potent *in-vivo* anti-leishmanial effects. One study showed that oral zinc sulfate was effective in treating mice infected with cutaneous leishmaniasis at the dose of 10 mg/kg/day for five days. It demonstrated the effectiveness of orally administered zinc sulfate against the lesions induced by inoculation of the leishmania parasite. In this model, the ED50 of zinc sulfate was reported as 59 mg/kg compared to 37.64 mg/kg of meglumine antimoniate in the same model [22]. In another study, 2mg/kg daily doses of oral zinc sulfate did not show any treatment effect on the growth of *L.major* in Balb/c mice [24].

4.3 Clinical Effect of Zinc Sulfate

Many reports also indicated the anti-leishmanial activity of zinc sulfate in humans (Table 1). Results of Sharique study indicated a probable therapeutic effect against CL of zinc sulfate in a dose range of 2.5± 10 mg/kg. The cure rates were 83.9% and 93.1%for 2.5 mg/kg and 5 mg/kg group, respectively, within the 45 days of follow-up. While, 10 mg/kg dose gave a cure rate of 96.9%. Although the results appear to be dose-dependent, the treatment groups' difference was not statistically significant [25].

According to the study of Yazapanh et al., oral zinc sulfate seemed to have little effect on CL; because only 9% of patients were cured after being treated with 10 mg/kg/day for 45 days [26]. The absence of any secretion and ulcerative lesions in our patients, 1.5 months after completion of treatment, favored the diagnosis of dry-type leishmaniasis compared with the study of Sharique et al., in which oral zinc sulfate gives excellent therapeutic results [25]. The possible difference in drug resistance of Leishmania species in Iran and Iraq might have accounted for the failure of treatment in this study [26].

Table 1. Clinical effect of oral zinc sulfate against cutaneous leishmaniasis

Dose	Duration of treatment	Number of patients	Cure rate	Reference
2.5 mg/kg	45 day	31	83.9%	
5 mg/kg	45 day	29	93.1%	25
10 mg/kg	45 day	32	96.9%	
10 mg/kg	45 day	31	9 %	26
10 mg/kg	45 day	26	30.2%	27
10 mg/kg	6 weeks	24	60%	28

Another study revealed the effectiveness of zinc sulfate in comparison to systemic meglumine antimoniate injections. Acceptable cure after completing 45 days of follow-up occurred in 30.2% of patients treated with 10mg/kg/day zinc sulfate, while it was 35.5% for the patient treated with antimoniates [27]. In another study, the cure rate of zinc sulfate10mg/kg/day was 60% within six weeks of therapy [28].

4.4 The Effect of Combination of Oral Zinc Sulfate and Oral Ketoconazole

The current standard treatment regimens for cutaneous leishmaniasis all involve mono-therapy. The use of combination therapy may improve efficacy, and if toxic drugs can be used at lower levels, improve tolerance [29]. Single therapies, using oral zinc sulfate or oral ketoconazole, have given a good satisfactory result, while the combination of both drugs gave a cure rate of 96%, [20] which was comparable with intra-lesional sodium stibogluconate with a cure rate reaching 94% with one or two injections [30].

5. CONCLUSION

Most studies showed that oral Zinc Sulfate was effective in treating cutaneous leishmaniasis. More research is required to determine its daily proper dose and concentration, duration, and possible side effects.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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