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***Aloe vera* as a new treatment modality for management of chemotherapy-induced oral mucositis in patients with acute leukemia: A review article**

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Abstract

Leukemia is the most common hematological malignancy in children, particularly acute lymphoblastic leukemia (ALL), which often requires high doses of methotrexate, increasing the risk of oral mucositis (OM). OM is a painful side effect that negatively affects children's quality of life and treatment adherence. Effective management is important and includes maintaining good oral hygiene, topical agents and pain relief. Recent advancements, such as cryotherapy, low-level laser therapy (LLLT), and natural substances like honey and olive oil, have shown promise in reducing the occurrence and grade of OM. Additionally, growth factors like palifermin are emerging as protective options for mucosal protection. Recently *Aloe vera* is one of the herbal agents known for its healing properties, has gained attention as a potential therapeutic agent for CIOM. *Aloe vera* possesses anti-inflammatory, antioxidant, and antimicrobial properties, which may help alleviate symptoms and promote healing of the oral mucosa. This reviews focus on the efficacy of *Aloe vera* and Recent advancements in managing CIOM in children.

Keywords: *Aloe vera*, leukemia, oral mucositis, chemotherapy, hematological cancer

Introduction

Acute Leukemias

Leukemi refers to the clonal proliferation and cessation of normal myeloid or lymphoid hematopoiesis. Acute leukemias account for 97% of all pediatric leukemia cases ^[1]. According to the National Cancer Institute at Cairo University, Egypt, the annual incidence is approximately four cases per 100,000 children ^[2]. Acute leukemia is the most prevalent malignancy in children, representing about one-fourth of all childhood cancers, with Acute Lymphoblastic Leukemia (ALL) making up roughly 75% of these cases. The peak incidence of ALL occurs between the ages of 2 and 5 years, and it is more frequently diagnosed in males than in females, with a male-to-female ratio of 1.2:1 among children aged 0–14 years in the USA ^[3].

The most frequently used medications in the treatment of pediatric Acute Lymphoblastic Leukemia (ALL) include methotrexate, steroids, L-asparaginase, vincristine, cyclophosphamide, adriamycin, and 6-mercaptopurine. These agents make varying levels of immunosuppression ^[5]. In managing ALL, high doses of methotrexate are administered during chemotherapy protocol, which significantly increases the risk of Oral Mucositis occurrence (OM) ^[2].

Definition of oral mucositis

OM is defined as inflammation of the oropharynx that result from cancer treatment.⁴ It typically develops 2 to 18 days after chemotherapy begins and affects nearly 80% of children undergoing hematopoietic stem cell transplantation and about 40% of those receiving standard chemotherapy ^[5].

Clinical presentation of oral mucositis

Mucositis presents as erythema, edema, or ulceration, which can vary from a mild burning

sensation to extensive, painful ulcers. This condition significantly impacts the patient's quality of life, hindering essential oral functions such as speech, swallowing saliva, and eating. Oral mucositis can lead to various complications, including difficulties in speech and swallowing, severe pain, and the risk of ulcerative infections. These infections may result in systemic complications, such as bacteremia or fungemia, posing a serious threat to the patient's life and often necessitating hospitalization, which can lead to increased healthcare costs [6].

Pathogenesis of oral mucositis

Oral mucositis is classified into five stages: initiation, signaling, amplification, ulceration, and healing, based on its progression and the clinical presentation of the patient. It develops when reactive oxygen species generate damage to the oral mucosa, leading to the activation of the transcription factor NF- κ B, which in turn increases the production of pro-inflammatory cytokines [7]. This process promotes ulceration, facilitating bacterial colonization and exacerbating the pathogenic response. In the early stages, oral mucositis manifests as localized or generalized erythema, accompanied by discomfort and a burning sensation during food intake. As the condition progresses, ulcerative and erosive lesions may emerge, often involving extensive necrosis and bleeding. Consequently, patients experience pain and dysphagia, which can restrict oral intake and affect verbal communication. These complications can lead to malnutrition and dehydration, significantly impacting quality of life. Furthermore, oral mucositis can disrupt the duration and intensity of antineoplastic treatment [8]. In severe cases, hospitalization may be necessary for enteral or parenteral nutritional support, and treatment may require dosage reductions or even cessation, adversely affecting cancer therapy and prognosis. Additionally, these patients are at heightened risk of sepsis due to opportunistic infections, which can be life-threatening in immunosuppressed individuals [8].

Evaluation of OM

The WHO scale is one of the most universally accepted scale for grading the severity of OM. It is a simple and easy-to-use scale that combines both subjective and objective measures [9].

Grades of oral mucositis according to WHO [9]

- **Grade 0:** No oral mucositis
- **Grade 1:** Erythema and soreness
- **Grade 2:** Ulcers, able to eat solids
- **Grade 3:** Ulcers, requires a liquid diet (Due to mucositis)
- **Grade 4:** Ulcers, alimentation not possible (Due to mucositis).

Current Prevention Methods for Mucositis

1. Preventive strategies for mucositis encompass pharmacological and non-pharmacological approaches:
2. **Pharmacological Interventions:** These include growth factors (e.g., palifermin), anti-inflammatory agents (e.g., benzydamine), and antimicrobial mouthwashes (e.g., chlorhexidine) [10]. While some agents like palifermin have shown efficacy, their use is often limited by cost and specific indications.
3. **Low-Level Laser Therapy (LLLT):** LLLT has demonstrated benefits in reducing mucositis severity and duration by promoting mucosal healing and reducing inflammation [11].

4. **Cryotherapy:** The application of ice chips during chemotherapy administration can reduce blood flow to the oral mucosa, limiting the exposure of mucosal cells to chemotherapeutic agents and thereby decreasing mucositis incidence [12].

5. **Nutritional Support:** Maintaining adequate nutrition and hydration is critical in managing mucositis, as malnutrition can exacerbate mucosal damage and impair healing [13].

Despite these interventions, there remains a need for more effective and accessible preventive measures, leading to increased interest in natural remedies like *Aloe vera*.

Aloe vera

Properties and Mechanisms of Action

Aloe vera (*Aloe barbadensis miller*) is a succulent plant with a long history of medicinal use. Its gel contains bioactive compounds such as polysaccharides (e.g., acemannan), glycoproteins, vitamins, and minerals, which contribute to its anti-inflammatory, antioxidant, and wound-healing properties [14].

Mechanisms Relevant to Mucositis Prevention

- **Anti-Inflammatory Effects:** *Aloe vera* modulates the production of pro-inflammatory cytokines, thereby reducing mucosal inflammation [15].
- **Antioxidant Activity:** The antioxidant components in *Aloe vera* neutralize reactive oxygen species (ROS) generated during chemotherapy, mitigating oxidative stress-induced mucosal damage [16].
- **Promotion of Mucosal Healing:** *Aloe vera* stimulates fibroblast proliferation and collagen synthesis, facilitating tissue repair and regeneration [17].

Evidence of *Aloe vera* in Preventing Chemotherapy-Induced Mucositis

Several studies have investigated the efficacy of *Aloe vera* in preventing or alleviating mucositis:

Clinical Trials

Behrouz *et al.* conducted a randomized controlled trial involving 60 patients undergoing chemotherapy. The intervention group received *Aloe vera* gel mouthwash, resulting in a significant reduction in mucositis severity compared to the control group, as assessed by the WHO Oral Toxicity Scale [15].

Seyedeyan *et al.* evaluated the effect of *Aloe vera* on oral mucositis in patients receiving head and neck cancer chemotherapy. Findings indicated that *Aloe vera* significantly decreased the incidence and duration of mucositis, enhancing patients' quality of life [19].

Preclinical Studies

Aljuffali *et al.* explored *Aloe vera*'s protective effects in a murine model of chemotherapy-induced mucositis. The study demonstrated that *Aloe vera* administration reduced histopathological damage and inflammatory markers in oral tissues [20].

Systematic Reviews and Meta-Analyses

Pallotta *et al.* reviewed multiple studies on natural agents for mucositis prevention and concluded that *Aloe vera* shows promise, although more high-quality randomized trials are needed to confirm its efficacy [21].

Comparative Efficacy of *Aloe vera* and Other Preventive Methods

When compared to standard preventive measures, *Aloe vera* exhibits comparable or superior efficacy in certain contexts:

Kouvelis *et al.* compared *Aloe vera* with LLLT in a study on oral mucositis and found that both interventions significantly reduced mucositis severity, with no significant difference between them. However, *Aloe vera* was noted for its ease of use and lower cost^[11].

Jacobi *et al.* highlighted that while cryotherapy is effective, its application can be uncomfortable for patients. In contrast, *Aloe vera* gel is well-tolerated and can be easily integrated into daily oral care routines^[12].

5. Safety and Side Effects

Aloe vera is generally considered safe when used topically or as a mouthwash. However, some patients may experience allergic reactions or oral irritation^[14]. It is essential to monitor patients for adverse effects, especially those with sensitivities to plant-based products.

Limitations of Current Research

Despite promising findings, several limitations exist:

Heterogeneity of Studies: Variations in study design, *Aloe vera* formulations, dosages, and administration protocols make it challenging to draw definitive conclusions^[14].

Sample Sizes: Many studies involve small sample sizes, limiting the generalizability of results.

Long-Term Outcomes: There is a lack of data on the long-term efficacy and safety of *Aloe vera* in mucositis prevention.

Future Directions

Future research should focus on:

- 1. Standardizing *Aloe vera* Preparations:** Establishing standardized formulations and dosages to ensure consistency across studies.
- 2. Large-Scale Randomized Trials:** Conducting multicenter trials with larger populations to validate efficacy and safety.
- 3. Mechanistic Studies:** Further elucidating the molecular mechanisms by which *Aloe vera* exerts its protective effects on mucosal tissues.

Conclusion

Aloe vera presents a promising natural alternative for the prevention of chemotherapy-induced mucositis, offering anti-inflammatory, antioxidant, and healing properties. While current evidence supports its potential benefits, further research is necessary to establish standardized protocols and confirm its efficacy in diverse patient populations. Integrating *Aloe vera* into mucositis prevention strategies could enhance patient comfort and adherence to cancer treatment regimens.

Conflict of Interest

Not available

Financial Support

Not available

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