



Pharmaceutical Platform

**The Roll of Acemannan in
Pharmaceutical Applications**

Scientific Review

OVERVIEW

Acemannan is a complex polysaccharide obtained from the inner gel of aloe vera leaves, it is considered the main functional component of Aloe vera and is largely responsible for the benefits Aloe vera offers.

Acemannan has been extensively studied and was pre-clinically and clinically shown to have many biological effects including anti-cancer, anti-inflammatory, antibacterial, antiviral and antioxidant.

Wound and burn management involve methods to enhance tissue regeneration and to minimize infection during the healing process. Acemannan Hydrogel exhibits multiple effects that are essential to the management and healing of wounds and burns including: macrophage activation, immunomodulatory effects, anti-inflammatory effects, hydration of the underlying tissues, pain relief, barrier against further contamination, promotion of cell proliferation and acceleration of skin wound closure.

Acemannan has been extensively studied in the last years and has been incorporated in many wound care products with excellent results. It has proven effectiveness in healing wounds (including oral wounds) and has the potential reduce radiation-induced skin reactions.

BACKGROUND

Aloe vera

Aloe vera is a plant widely used in the biomedical, pharmaceutical, food and cosmetic industries. There are at least 420 different plant species of Aloe. Aloe vera specifically refers to the *Aloe barbadensis* Miller plant, which is the most common form used in Aloe-based products (Rahman, Carter, & Bhattarai, 2017).

Aloe vera is considered a succulent species due to its thick fleshy leaves that help it to retain water (in the form of the famous gel) in hot, arid climate (Akev et al., 2015).

The transverse section of the leaf exhibiting three cells layers: the protective layer, middle layer and colorless inner layer (Sahu et al., 2013). The inner clear gel is thought to be responsible for the majority of the plant's therapeutic properties. Nearly 99% of this layer is water and the rest is made of glucomannans, amino acids, lipids, sterols, and vitamins (Rahman et al., 2017).

The plant leaves contain over 75 biologically active and naturally occurring compounds including polysaccharides, vitamins, minerals, enzymes, amino acids and natural sugars that work in association with other compounds of the human body to deliver numerous health benefits (Choi & Chung, 2003; Rahman et al., 2017). The bioactive components in the aloe vera have been reported to have antifungal, antiseptic, antiviral, antibacterial, antidiabetic, anti-inflammatory, antioxidant, immune-modulatory, gastro protective and wound healing properties.

Biologically active components in aloe vera may be labile, varied, or modified since the chemical composition of the aloe vera gel varies and depends on source, climate, region and the processing method (Choi & Chung, 2003; Klein AD, 1988).

Acemannan

Aloe is a rich source of polysaccharides (Choi & Chung, 2003) and these polysaccharides are responsible for the majority of the biological activities observed from the use of the Aloe vera plant (Hamman, 2008).

Acemannan is a predominant component polysaccharide of the Aloe vera gel. This polysaccharide constituted by acetyl-mannose unities united by β -(1,4) glycosidic bonds (Figure 1). It is a hydrophilic molecule with an average molecular weight of approximately 1-2 Million Daltons.

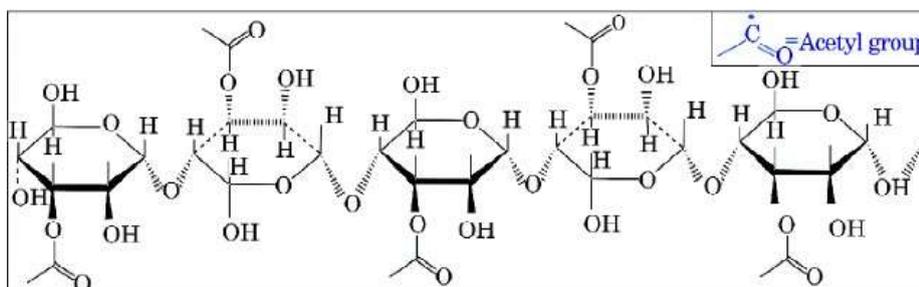


Figure 1: Basic molecular structure of acetylated mannan or Acemannan (Ray & Ghosh, 2014)

Acemannan is obtained from the inner gel of Aloe vera leaves and it is considered the main functional component of Aloe vera (Sahu et al., 2013).

As mentioned, biologically active components in Aloe vera may be labile, varied, or modified since the chemical composition of the aloe vera gel varies and that even within the same species, the plant depends on source, climate, region, and the processing method (Choi & Chung, 2003; Klein AD, 1988). It is also important to note that the processing steps can alter the properties of polysaccharides by affecting their original structure, which may bring some changes in the proposed physiological and pharmaceutical properties of these constituents (Rahman et al., 2017). This is why the manufacturing process is a key factor for obtaining an Extract that remain active, keeping all the beneficial properties of the plant.

Benefits of Acemannan

Acemannan has many nutritional qualities and is largely responsible for the benefits aloe vera offers (Ni, Turner, Yates, & Tizard, 2004). It has been extensively studied in the last 20 years and was shown to have many biological activities including anti-cancer, anti-inflammatory, antibacterial, antiviral, cell proliferation, immunomodulatory and wound healing effects. Acemannan has also been described as a unique antioxidant polysaccharide from aloe (Ray & Ghosh, 2014).

Anti-cancer

Acemannan and phenolic anthraquinones of the aloe vera gel are considered to be prophylactic against certain types of cancer and many chronic degenerative diseases being the potential antioxidants or pro-oxidants with unique DNA breakage preventing potential. Acemannan also prevent malignancy by its potential immune-stimulant activity (Ray & Ghosh, 2014). In a study on mice that had previously been implanted with murine sarcoma cells, Acemannan stimulates the synthesis and release of interleukin-1 (IL-1) and tumor necrosis factor from macrophages in mice, which in turn initiated an immune attack that resulted in necrosis and regression of the cancerous cells (Sahu et al., 2013).

Antiviral Activity

Acemannan have antiviral effects. It was shown to reduced herpes simplex infection in two cultured target cell lines, to have in vitro activity against HIV-1 and a dose dependent synergistic effect with AZT on HIV-infected cells (Kahlon JB et al., 1991; Sahu et al., 2013).

Antibacterial Activity

Aloe vera gel was bactericidal against *Pseudomonas aeruginosa* and Acemannan prevented it from adhering to human lung epithelial cells in a monolayer culture (Sahu et al., 2013). In in vitro study, material containing Acemannan with no other antimicrobial agents had limited effect on *E. coli* and *S. aureus* (Bidra AS, 2011).

Anti-inflammatory effect

The anti-inflammatory effect of aloe is a result of mannose-6-phosphate and Acemannan. These aloe vera constituents are thought to reduce inflammation caused by an increase in prostaglandin synthesis and an increase in the infiltration of leukocytes (Rahman et al., 2017).

Immunomodulatory activity

Glucomannan and Acemannan were proved to accelerate tissue regeneration, activate macrophages and stimulate the immune system (Rahman et al., 2017; Sahu et al., 2013). Acemannan was found to have immunomodulatory activity in various in vitro Immunomodulation Studies. It was reported to enhance nitric oxide and pro-inflammatory cytokines IL-6 and $TNF\alpha$ release in a mouse macrophage cell line exposed to Acemannan in combination with $IFN\gamma$ (Zhang L, 1996). In a separate study, nitric oxide release was also demonstrated when chicken macrophages were exposed to Acemannan (Karaca, Sharma, & Nordgren, 1995). This effect potentially could contribute to some of the antitumor and antimicrobial effects that have been observed with use of the compound (Ramamoorthy L, 1998). Acemannan was reported to activate macrophages; enhance cytokine release stem cell factors; stimulate interactions between macrophages, T-lymphocytes and B-lymphocytes; enhance the generation of cytotoxic T-lymphocytes; induced B- and T-lymphocyte activation and upregulate phagocytic activity (Choi & Chung, 2003; Thunyakitpisal, Ruangpornvisuti, Kengkwasing, Chokboribal, & Sangvanich, 2017). In addition,

investigators have reported on the functional maturation of immature dendritic cells when exposed to the compound (Lee et al., 2001).

ACEMANNANAND WOUND HEALING

Wound and burn management involve methods to enhance tissue regeneration and to minimize infection during the healing process. Acemannan Hydrogel exhibits multiple effects that are essential to the management and healing of wounds and burns including: macrophage activation, immunomodulatory effects, anti-inflammatory effects, hydration of the underlying tissues, pain relief, barrier against further contamination, promotion of cell proliferation and acceleration of skin wound closure.

In in- vivo study Acemannan was shown to significantly accelerate skin wound closure and cell proliferation. Acemannan activates AKT/mTOR signaling in skin primary fibroblasts and promotes their proliferation partly by inducing cyclin D1 expression at the translational level, leading to the promotion of cutaneous wound healing (Xing et al., 2014).

Beneficial effects of Acemannan on Radiation Dermatitis

Radiation therapy (RT) is a common treatment for cancer and nearly 50% of cancer patients receive RT at some point during the course of their illness (Leventhal J, 2017). One of the most common side effects of radiation is acute and/or chronic skin reaction (radiation dermatitis) that ranges from a mild rash to severe ulceration (Leventhal J, 2017; Salvo et al., 2010). Of those receiving RT, as many as 95% may experience some form of radiation dermatitis, or radiation-induced skin injury. While a reduced total dose of radiation and use of an advanced mode of radiation delivery may help to mitigate the severity of radiation effects on the skin, radiation dermatitis remains one of the most common side effects of RT (Leventhal J, 2017).

Skin reactions related to radiation therapy usually manifest within 1–4 weeks of radiation start, persist for the duration of radiation therapy, and may require 2–4 weeks to heal after completion of therapy (Salvo et al., 2010). Signs and symptoms of radiation dermatitis include: Red rash (erythema), itching, flaking or peeling skin (dry desquamation), blisters and wet peeling skin (moist desquamation), pigmentation changes, fibrosis or scarring of connective tissue, development of ulcers, pain, discomfort, burning, and general irritation. In some patients, these problems may restrict movement of an affected limb, impeding activities of daily living and lead to loss of independence and self-care ability (Bologna Jean , Jorizzo Joseph L.,; Salvo et al., 2010). The above symptoms of radiation dermatitis has a profound impact on the quality of patient's life, due to pain, discomfort and diminished aesthetic appearance. In addition, it may be the cause of premature interruption of radiation therapy, resulting in inadequate disease treatment (Salvo et al., 2010; Spalek, 2016).

A wide variety of topical, oral, and intravenous agents are used to prevent or to treat radiation-induced skin reactions. Types of treatments include: topical Steroids, washing practices (with soap and water), Biafine cream, oral enzymes, Amifostine, topical acid cream, Aloe Vera, hyaluronic acid–based compounds, sucralfate, calendula and wound dressings (include hydrocolloid or hydrogel dressings, soft silicone dressings, and silver-based dressings/ointments) (Chan et al., 2014; Fenig, 2001; Heggie S et al., 2002; Leventhal J, 2017; Olsen DL, Raub W Jr, Bradley C, Johnson M, Macias JL, Love V, 2001; Richardson, Smith, McIntyre, Thomas, & Pikington, 2005; Salvo et al., 2010; Zhang, & Shao, 2013). Even though radiation dermatitis is one of the most frequent side effects of RT, there is no gold standard in the prevention and management of this condition. Despite the high number of trials in this area, findings are conflicting and there is limited good, comparative research that provides definitive results suggesting the effectiveness of any single intervention for reducing radiation dermatitis (Chan et al., 2014; Leventhal J, 2017; Zhang et al., 2013).

Acemannan was found to reduce radiation-induced skin reactions in C3H mice. Wound dressing gel containing Acemannan was evaluated topically in a series of experiments on C3H mice receiving graded single doses of gamma irradiation to the right rear leg creating an acute radiation-induced skin reaction. The average peak skin reactions of the wound dressing gel-treated mice were lower than those of the untreated mice at all radiation doses tested (Figure 2). The authors conclusion was that wound dressing gel containing Acemannan, but not personal lubricating jelly or healing ointment, reduces acute radiation-induced skin reactions in C3H mice if applied daily for at least 2 weeks beginning immediately after irradiation (Roberts DB, 1995).

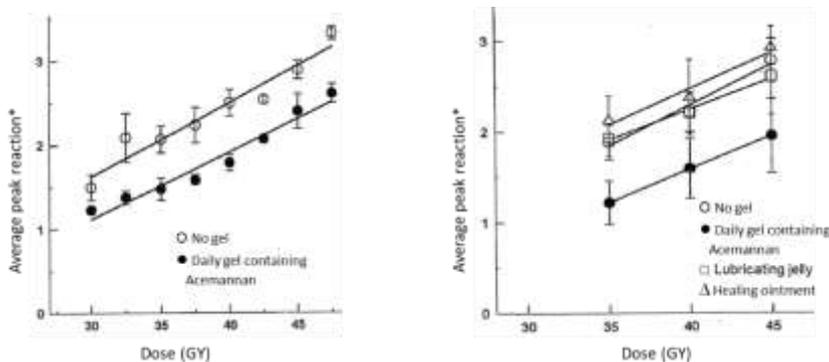


Figure 2: Acemannan Hydrogel reduces radiation-induced skin reactions in C3H mice [Skin reaction-scale of 0 (no visible reaction) to 3.5 (breakdown of the skin over the entire radiation field with severe exudation)] (data extracted from Roberts DB, 1995).

ACEMANNAN AND ORAL WOUND HEALING

In vitro study demonstrated gingival fibroblasts (GF) proliferation as well as significantly increased secretion of keratinocyte growth factor (KGF), vascular endothelial growth factor (VEGF) and Type I Collagen in Acemannan treated GF cells. In an *in vivo* study conducted by the same group, it was showed that wound healing of animals receiving Carbopol containing 0.5% Acemannan(w/w) was significantly better than that of the other treatments groups. These findings suggest that Acemannan plays a significant role in the oral wound healing process via the induction of fibroblast proliferation and stimulation of KGF-1, VEGF, and type I collagen expressions (Jettanacheawchankit et al., 2009).

Beneficial effects of Acemannan on Alveolar Osteitis

Alveolar osteitis (AO), also known as dry socket, is the most common complication occurring after the extraction or surgical removal of a permanent tooth. The condition has generally been characterized by delayed healing associated with blood clot that fails to form or is lost from the socket (Poor, Hall, & Poor, 2002). This leaves an empty socket and accompanied by exposure of the underlying bone. AO occurs within 1 to 5 days after extraction and results in severe pain in and around the extraction site that is not easily relieved by analgesics. This condition occur 3% to 4% after routine dental extractions and 1% to 45% after extraction of the mandibular third molars (Kaya, Yapici, Savaş, & Güngörmüş, 2011; Poor et al., 2002).

AO can be a burden for both patients and surgeons. This painful condition and the increase in recovery period results in repeated practice/hospital visits as 45% of patients who develop AO typically require multiple postoperative visits in order to manage this condition. This translates into costs in terms of the clinic time required to manage the patient's symptoms (Kaya et al., 2011; Kolokythas, Olech, & Miloro, 2010; Poor et al., 2002).

There are multiple approaches to the prevention of AO. Original treatments involved topical antibiotics mixed with cortisone gel. Later treatments involved nonsteroidal anti-inflammatory drugs before and after surgery, clot stabilizers both alone and mixed with antibiotics, topical antibacterial rinses, and, most recently, polylactic acid surgical dressing. Unfortunately, none of these techniques have eliminated the risk of AO (Poor et al., 2002). Curettage and irrigation alone will be insufficient, and it is equally important to use dressing to the extraction socket to fill the gap in the socket, prevent the accumulation of debris, relieve the pain, disinfect the alveoli, promote healing as quickly as possible and prevent malodor emanating from the empty socket (Kaya et al., 2011).

Acemannan has positive effects in the management of alveolar osteitis. In a clinical study that evaluated the effects of SaliCept patch (Acemannan hydrogel), Alvogyl and low-level laser therapy in the management of AO it was shown that Acemannan is an acceptable alternative to Alvogyl as a dressing for the management of AO (Kaya et al., 2011). In this study, the differences in the changes in the clinical signs and symptoms between the SaliCept patch and the control group were statistically significant on the third day after treatment (Figure 3). The intensity of pain decreased more rapidly in the SaliCept patch group than in the control group (Figure 4).

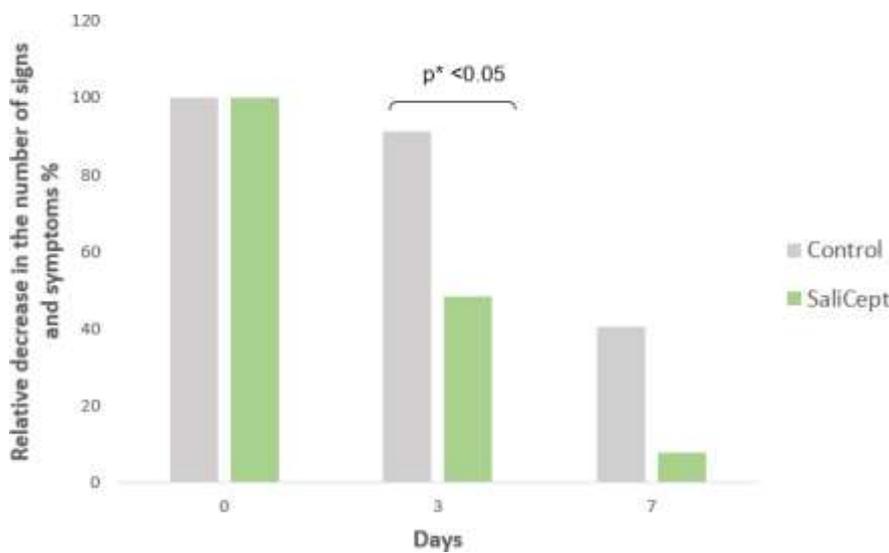


Figure 3: Acemannan Hydrogel reduced clinical signs and symptoms of AO (data extracted from Kaya et al., 2011)

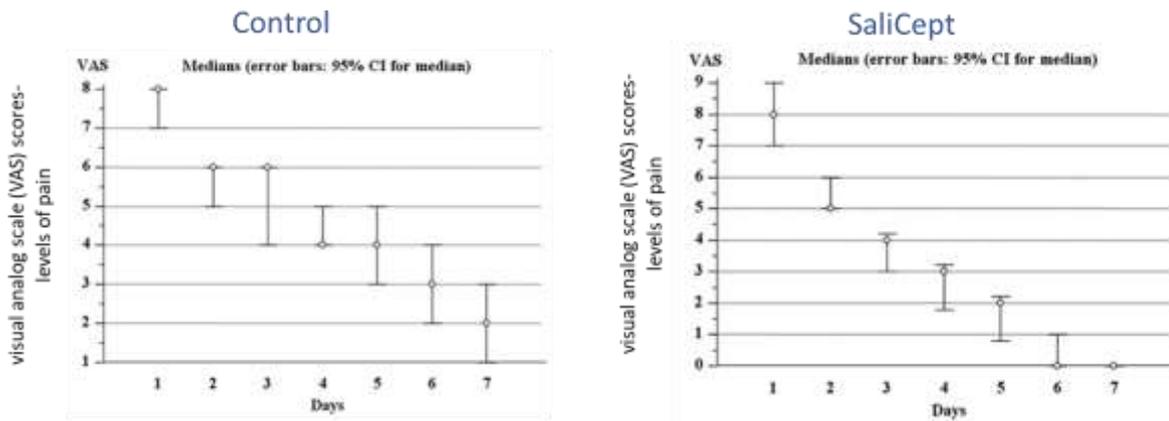


Figure 4: Acemannan Hydrogel significantly decreased the intensity of pain (data extracted from Kaya et al., 2011)

Acemannan Hydrogel has a big advantage as a treatment because of its positive effect on inflammation and the wound healing process. Acute pain is a symptom of injury, with the severity of pain reaching its peak during the inflammatory phase. Promoting wound healing will provide faster pain relief, and a treatment method that combines a strong anti-inflammatory effect with pain relief and contributes to early tissue repair would be considered a successful method to treat AO (Kaya et al., 2011).

In a different study, Poor et al. compared the incidence of AO in patients treated with either clindamycin-soaked Gelfoam (Pharmacia and Upjohn Co) or SaliCept (AcemannanHydrogel Patches). A retrospective evaluation was performed of the records of 587 patients (1,031 sockets) whose extraction sites had been treated with clindamycin-soaked Gelfoam. A prospective trial was conducted in which 607 patients (1,064 sockets) had 2 SaliCept Patches placed immediately after extraction. The study results suggest that the SaliCept Patch significantly reduces the incidence of AO compared with clindamycin-soaked Gelfoam (Figure 5). Further benefits of the use of the SaliCept Patch can be a significant reduction in the cost of the materials and in the time involved in management of the symptoms of AO (Poor et al., 2002).

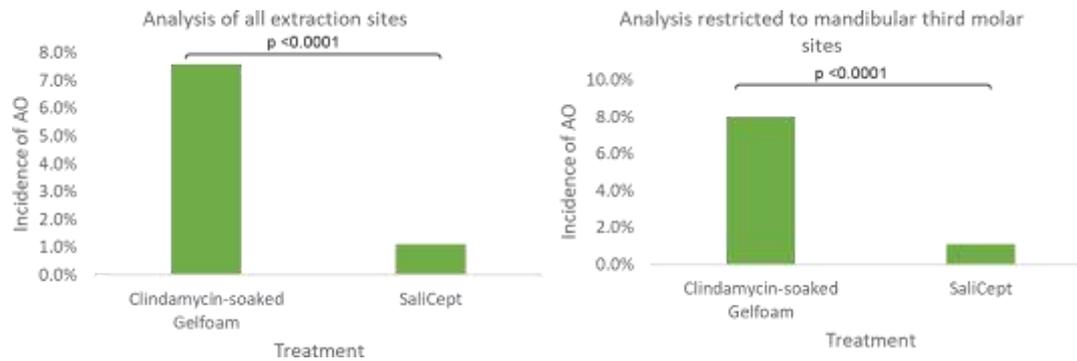


Figure 5: Acemannan Hydrogel significantly reduced the incidence of AO (data extracted from Poor et al., 2002)

Beneficial effects of Acemannan on Aphthous stomatitis

Recurrent aphthous stomatitis (RAS) or Recurrent aphthous ulceration (RAU) is one of the most common painful oral mucosal conditions seen among patients. These present as recurrent, multiple, small, round, or ovoid ulcers, with circumscribed margins, having yellow or gray floors and are surrounded by erythematous haloes, present first in childhood or adolescence (L Preeti, KT Magesh, K Rajkumar, 2011). The disease may be clinically characterized into three types (minor, major and herpetiform), of which the most common by far is minor aphthous ulceration.

RAU can affect up to 25% of the general population, in women, people under the age of 40 years, nonsmokers and those of high socio-economic status being more commonly affected. The etiology of recurrent oral ulceration remains unknown (Porter, Al-Johani, Fedele, & Moles, 2009). However, associations have been reported between RAU and immunological disorders and other predisposing factors including hormonal imbalance, bacterial infection, and sensitivity to certain diets.

Currently, there is no curative management of RAU available. The aims of treatment are the reduction of pain and inflammation, as well as promoting

healing, but do not include preventing the recurrence of the ulcers. Antimicrobial agents, topical analgesics, immunosuppressive agents, anti-inflammatory agents, and laser therapy have all been used to treat RAU. Usually, the treatment of choice for these lesions is topical steroid application. Because of the possible adverse effects from steroid treatment and the potential for the development of secondary oral candidiasis from long-term steroid use, herbal medicines have been advocated as an alternate form of treatment (Bhalang, Thunyakitpisal, & Rungsirisatean, 2013).

Acemannan was shown to be safe and effective in the treatment of oral aphthous ulceration. Acemannan reduced recurrent aphthous ulcer size significantly more than control in a controlled, randomized, double-blind clinical study (Figure 6) (Bhalang et al., 2013). While it was less effective comparable to that of 0.1% triamcinolone acetonide, Acemannan might be suitable for patients who wish to avoid the use of steroid medication. The author suggested that the effectiveness of Acemannan in the treatment of RAU that was observed in this study could be mediated through anti-inflammatory effects, wound healing promotion, and immunomodulation (Bhalang et al., 2013).

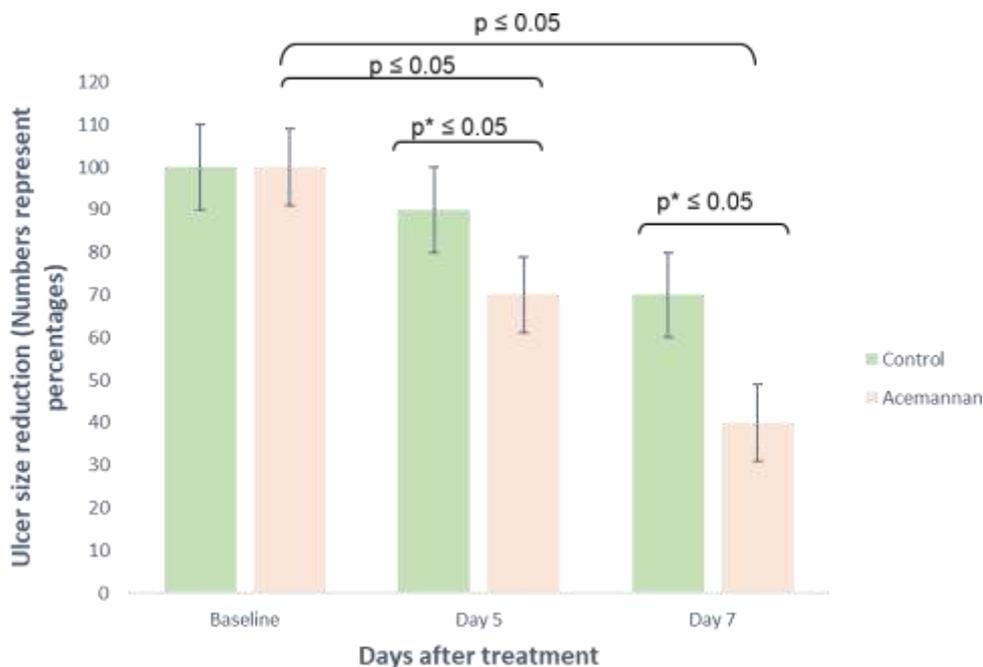


Figure 6: Acemannan Hydrogel significantly reduced aphthous ulcer size. At days 5 and 7, the reduction of ulcer size by Acemannan was significantly different from that of control ($p \leq 0.05$). Acemannan significantly reduced the ulcer size when compared to baseline ($p \leq 0.05$) while no significant reduction of ulcer size was found in the control group (data extracted from Bhalang et al., 2013).

Porter et al. conducted a clinical study to determine the safety and the efficacy of HybenX (Epien Medical Inc.) and Salicept (Carrington Laboratories Inc.) to reduce the symptoms and duration of RAU. Both treatments reduce the painful symptoms of RAU and gave rise to few adverse side effects all were unlikely to be related to the treatment devices (Porter et al., 2009).

In a different clinical study, it was shown that Acemannan hydrogel and freeze-dried Acemannan hydrogel significantly reduced the healing time in the treatment of RAU when compared to Orabase-Plain (Figure 7) (Plemons, J.M., Rees, T.D., Binnie, 1994).

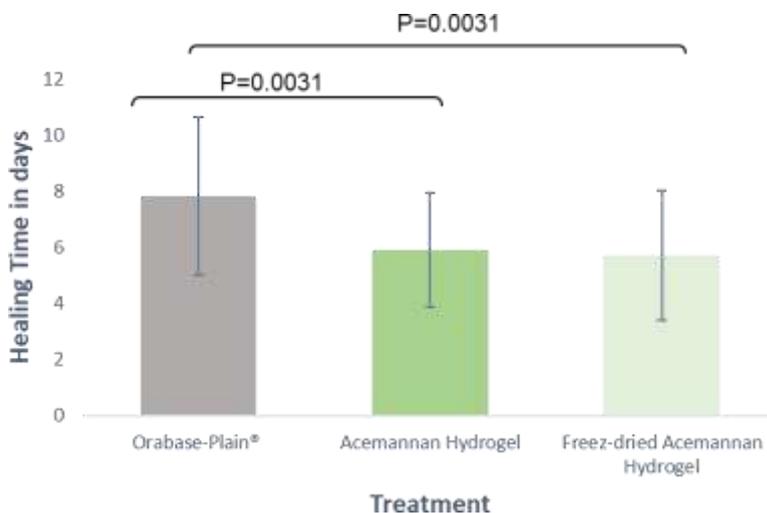


Figure 7: Acemannan Hydrogel significantly reduced the healing time of RAU (Data extracted from Plemons et al., 1994)

Beneficial effects of Acemannan on Dental pulp and Vital pulp therapy

Vital pulp therapy (VPT) is defined as a treatment which aims to preserve and maintain pulp tissue that has been compromised but not destroyed by caries,

trauma, or restorative procedures in a healthy state. VPT preserves the vitality of the remaining pulp, promotes new dentin formation (a mineralized bridge) to cover the exposed pulp and is essential for long-term tooth survival (Ghoddusi, Forghani, & Parisay, 2013; Songsiripradubboon et al., 2017).

Acemannan is biocompatible with dental pulp and it stimulates dentin regeneration in teeth with reversible pulpitis. In *in-vivo* and *in-vitro* study, Acemannan increased deciduous dental pulp cells (DDPCs) proliferation, growth factor and ECM synthesis, differentiation and induced mineralized bridge formation in inflamed pulp tissue. Furthermore, the effectiveness of Acemannan on dentin regeneration is comparable with that of MTA and it can be a less expensive alternative natural material for VPT of primary teeth (Songsiripradubboon et al., 2017).

In a different study that reveals the effect of Acemannan on dentin formation both *in vitro* and *in vivo*, Jittapiromsak et al. concluded that Acemannan accelerates new dentin formation via pulp cell proliferation, differentiation into odontoblast-like cells, upregulation of BMP-2 and DSP expression, and mineral deposition. In this study, Acemannan was superior to Calcium hydroxide (Ca(OH)₂), a recommended material for direct pulp capping. The results obtained from the Ca(OH)₂-treated group were poor. All samples revealed incomplete hard dentin bridge formation, with moderate to severe inflammation and dystrophic calcification of the pulp tissue (Jittapiromsak, Sahawat, Banlunara, Sangvanich, & Thunyakitpisal, 2010).

In Summary, Acemannan has been extensively studied in the last years and is an ingredient that has been incorporated in many wound care products with excellent results. It has proven effectiveness in healing wounds (including oral wounds) and has the potential to reduce radiation-induced skin reactions.

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