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Acemannan, an Extracted Polysaccharide from *Aloe vera*: A Literature Review

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In this review, the composition, actions, and clinical applications of acemannan in medicine and its effectiveness as an adjunct in the treatment of diseases are presented. An electronic literature search was performed up to January 2014 for studies and research presenting data to validate the efficacy of acemannan. A total of 50 titles, abstracts and full-text studies were selected and reviewed. Acemannan has various medicinal properties like osteogenic, anti-inflammatory, and antibacterial, which accelerate healing of lesions. Also, acemannan is known to have antiviral and antitumor activities *in vivo* through activation of immune responses. It was concluded that *Aloe vera* has immense potential as a therapeutic agent. Even though the plant is a promising herb with various clinical applications in medicine and dentistry, more clinical research needs to be undertaken to validate and explain the action of acemannan in healing, so that it can be established in the field of medicine and a more precise understanding of the biological activities of these is required to develop *Aloe vera* as a pharmaceutical source.

Keywords: *Aloe vera*, Acemannan, Pharmacology.

1. Introduction

The inclusion of medicinal plants in alternative medicine has been increasing in our society because of the therapeutic properties of plants [1]. *Aloe vera* (*A.barbadensis* Miller) is a cactus-like plant that grows in dry climates. Currently, because of demand, it is cultivated in large quantities [2]. *A. vera* is used to produce two different products, each of which has a completely different composition and therapeutic properties, *A. vera* gel and the bitter yellow latex [3]. According to the International Aloe Scientific Council, aloe leaf can be processed into two types of juices for commercial use: the inner leaf juice and decolorized whole leaf juice [4]. *A. vera* juice is approximately 99% water [4] and the rest contains potentially 75 active constituents [5]. Aloes have been used therapeutically for centuries. Different properties are ascribed to the inner, colorless, leaf gel and to the exudates from the outer layers. The reasons for aloe gel efficacy are varied [6]. Polysaccharides are one of the gel constituents to which activity has been ascribed [6]. These polysaccharides can be acetylated, partially acetylated or not acetylated [7]. Acemannan, β-(1, 4)-acetylated polymannose is the major polysaccharide of *A. vera* gel. It has significant beneficial therapeutic effects [8] such as immune-stimulating [9], anti-neoplasic [10] and wound-healing actions [11]. Acemannan has been used for the management of wounds using protocols approved by the US Food and Drug Administration (FDA) for the past decade. In addition, FDA approval was recently obtained for the treatment of alveolar osteitis [12]. This mini review gives an overview of the present knowledge about the pharmacological potential of acemannan and related problems.

2. Biochemistry of acemannan

There is considerable discrepancy in the literature as to the structure of acemannan. Acemannan, a β-(1, 4)-linked polydispersed, highly acetylated mannan is found in the inner leaf gel of the aloe plant, where it is produced by a specialized cells called leucoplasts.

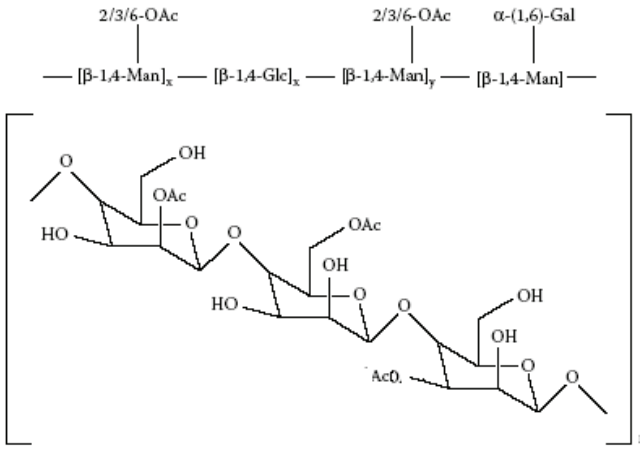

Figure 1: Structure of the mucopolysaccharide acemannan, extracted from *Aloe vera*.

Lobo *et al*. called acemannan aloeverose [12]. As a polysaccharide, acemannan is composed of mannose, glucose and galactose monomers. The approximate monosaccharide composition of acemannan is 31 β-(1, 4)-linked mannoses, 1 β-(1, 4)-linked glucose, and 1 α-(1, 6)-linked galactose [13, 14].

3. Procurement of acemannan

Given a variety of possible uses and applications of this polysaccharide, it was necessary that isolation studies were carried out to obtain acemannan for clinical trials [15]. Fresh whole *A. vera* leaves obtained from a botanicals shop were used as the raw material in most experiments. Several trials have been performed in the preparation and characterization of acemannan. Mabel Alonso *et al*. [15] studied the application of four processes for obtaining

acemannan; a) size exclusion chromatography (SEC) using Sepharose CL-4B matrix followed by ethanolic precipitation, b) size exclusion chromatography, ultrafiltration using hollow-fiber cartridges and ethanol precipitation, c) size exclusion chromatography, precipitation with cetyltrimethylammonium bromide (CTAB) and ethanolic precipitation, and d) direct precipitation with CTAB and ethanolic precipitation. For the extraction of the active substance a collection of 100 plant leaves was used, washed, decontaminated, and the pulp gel was homogenized in a domestic blender. Ethanol was added slowly, and the suspension was left with slow agitation and then centrifuged. Their results suggest that the precipitation procedure with CTAB simplifies the production process and diminishes the costs and operation time [15]. Acemannan has also been extracted from fresh extracted *A. vera* pulp gel by homogenization, centrifugation and ethanol precipitation. First, the skin is washed and removed from the leaves and the parenchyma is soaked for 30 minutes. Then, the parenchyma gels are blended using a homogenizer and centrifuged. The supernatant is collected and mixed with absolute ethanol at a 1:3 ratio and the precipitated white opaque particles are collected before further centrifugation and lyophilization. In all these investigations the molecular weight of acemannan was analyzed by HPLC. The monosaccharide composition and structure of the polysaccharide was determined by gas chromatography-mass spectrometry and ^{13}C NMR spectroscopy. The authors stated that the acemannan concentration obtained from this extraction method was 0.2% [8, 11, 16, 17, 18, 19, 20]. Other authors separated acemannan by silica gel TLC using an isocratic gradient elution technique; the yield was determined by HPTLC-photodensitometry. They found the proposed method to be simple and sensitive and that it could be used for the routine assay of acemannan in phytomedicines [12].

3.1 Commercial production

Use of aloe gel has become widespread and consequently a large industry has developed [6]. Given the deep understanding of the uptake, acemannan has received regulatory approval for several animal and human indications. Carrington Laboratories, one of the most important producers in the USA, manufacture Acemannan immunostimulant. This was approved as a prescription product for veterinarians to treat fibrosarcoma in dogs and cats [10]. Another product manufactured by Carrington is Salicept Patch, a freeze-dried pledget that contains Acemannan Hydrogel [21]. Carravet contains acemannan from *A. vera*. This was formulated for pain relief and the management of wounds for horses, dogs and cats. The gel is specially formulated to maintain the moist environment vital to wound healing and it can be used for all types of wounds, including radiation reactions. Pure acemannan of 10 and 100 mg is manufactured by Elicytil Oligotech, a biotech company specializing in carbohydrate engineering and production of glycoproducts for research, development and industrial applications [22]. Notwithstanding, the immunopotentiating activity of acemannan should not vary from that of the polysaccharide obtained by different processes, indicating that acemannan preparations with a mannose composition similar or superior to 75% conserve its immunopotentiating activity [15].

4. Clinical trials of acemannan

4.1 Clinical wound healing studies: Wound healing is considered to be composed of three overlapping events: inflammation, new tissue formation and matrix remodeling [23]. Existing evidence demonstrates that *A. vera* used in a variety of dosage forms might be effective in speeding up the wound healing process and tend to increase the rate of success of healing, when compared with conventional treatments [24]. The colorless gel that comes from the leaf parenchyma has been used to treat burns because, besides being a potent moisturizing agent, it helps in the healing process of skin lesions and alleviates pain [25]. The promotion of burn wound healing was shown in a study conducted with Guinea pigs. The authors claim that the *A. vera* gel extract permitted faster healing of the burn, and reestablishing the vascularity of the burn tissues. These effects might be due to several mechanisms, including an increasing collagen synthesis and rate of epithelization produced by acemannan [26]. For testing the efficacy of acemannan on bone formation, a number of tests have been used. During bone formation, osteoprogenitors migrate to the wound site, proliferate and differentiate into osteoblasts. Osteoblasts secrete local growth factors, extracellular matrix, and induce mineralization. Boonyagul *et al*. investigated the effects of acemannan on the healing of a tooth socket in a rat model. They concluded that acemannan significantly stimulated proliferation of bone marrow stem cells, expression of growth factors and mineralization, and then the acceleration of socket healing [16]. Periodontal disease is a common chronic infectious disease causing the destruction of the periodontium. Based on the bioactivity of acemannan in inducing hard tissue healing, it is a candidate for use in periodontal tissue regeneration. Chantawarit *et al*. evaluated the effect of acemannan on the regeneration of periodontium. Their results suggest that acemannan stimulates alkaline phosphatase activity, mineral deposition, and periodontal regeneration in class II furcation. The authors claim that acemannan is a bioactive molecule; however, the precise molecular mechanisms governing the effects of acemannan on cellular activity remain unknown [8]. Another study showed that acemannan stimulated dentin formation after intentional exposure of pulp in rats [17], and the inductive effects on hard tissue healing were evaluated by Sahawat *et al*. on the possible role for acemannan in cementum regeneration. They concluded that acemannan may be a possible therapeutic agent for cementum regeneration [18]. Jettanacheawchankit *et al*. investigated the effects of acemannan on the proliferation of gingival fibroblasts, expression of growth factors like vascular endothelial growth factor (VEGF), and keratinocyte growth factor (KGF-1). Their findings revealed that acemannan significantly induced gingival fibroblast proliferation, and synthesis of the growth factors that play an important role in new blood vessel formation [11]. Whole *A. vera* gel, which contains acemannan and other components, has been shown to accelerate wound healing in tissue delayed by acute radiation [27]. By increasing transforming growth factor beta 1 (TGF-β1) and fibroblast growth factor (FGF) production, wound contraction was accelerated significantly by *A. vera* gel orally administered. Acemannan has also been shown to be an agent that could reduce the severity of radiation-induced skin reactions. Roberts *et al*. concluded that acemannan induces secretion of several cytokines, including tumor necrosis factor (TNF) and interleukin-1 (IL-1), which is believed to regulate wound healing [28].

4.2 Immunomodulation studies: Acemannan is one of the polysaccharides that dramatically increase white blood cell, macrophage and T cell numbers. One mechanism by which aloe components may enhance wound healing is by activation of macrophages. Zhang *et al*. demonstrated that acemannan, in combination with interferon gamma, has an effect on the release of nitric oxide, interleukin-6 and tumor necrosis factor-α by macrophages [29]. Release of these cytokines stimulates an increase of up to 300% in the replication of fibroblasts in tissue culture and enhances macrophage phagocytosis [30]. Ramamoorthy *et al*. demonstrated that acemannan in the presence of interferon gamma induce apoptosis in RAW 264.7 cells [31]. Acemannan has also been demonstrated to have hematoaugmenting properties by

increasing peripheral and splenic blood cellularity in hematopoietic progenitors in mielosuppressed mice [32], and has been shown to upregulate function and generation of cytotoxic T-lymphocytes [33]. Lee *et al.* demonstrated that acemannan has immnunomodulatory activity also on dendritc cells by inducing maturation of these cells [34]. Acemannan thus exhibits multiple immunomodulatory effects which are important to the healing of wounds. This activity is attributed to the recognition of terminal mannose by macrophages as a foreign substance due to it being common on the polysaccharides and oligosaccharides produced by microorganisms. On the other hand, Karaca *et al.* affirm that very high concentrations of acemannan (200-2000 µg/mL) are required to achieve modest activation of macrophages and, therefore acemannan is either not a potent immunostimulatory molecule or trace amounts of a potent compound are present as a contaminant within acemannan preparations [35]. Pugh *et al.* affirm that acemannan exhibits weak NF-kappa B directed luciferase expression, which supports previous observations of the high concentration of acemannan to macrophage activation [36]. In summary, in most investigations, acemannan allows the production of cytokines, interleukin-6, interferon gamma and tumor necrosis factor, the release of nitric oxide, which in turn is related to receptors for mannose monosaccharide, and candicidal activity by phagocytes. It is also known that increasing the antigen expression on the cell surface is a consequence of the release of gamma interferon, allowing increased expression of the molecules of the major histocompatibility complex; in this case it would carry the Class I viruses on the surface of the cell and would ensure their recognition by cytotoxic T cells to be eliminated. Another mechanism implicated by acemannan is inhibition of opsonization, the production of specific antibodies and the induction of delayed hypersensitivity; all these are responsible for the immunomodulatory effect of Aloe [37].

4.3 Antimicrobial and antiviral activity: The activity of *A. vera* inner gel against both Gram-positive and Gram-negative bacteria has been demonstrated by several different methods. The common involvement of mannose in bacterial interaction with host cells suggests that mannans might interfere with bacterial binding. The structure suggests that it might block bacterial adherence to the host epithelium by binding to either bacterial or host sites. Azghani *et al.* measured the adherence of several different strains of *P. aeruginosa* to human lung epithelial cells and compared the effects in the presence and absence of acemannan. Addition of acemannan to the mixture of radiolabelled bacteria and cells inhibited bacterial binding to the lung cells, but the experiments indicate that acemannan is a relatively non-specific inhibitor of adherence and the effect is probably not related to the mannose-containing receptor on bacteria or host cells [38]. As an anti-fungal agent, it was demonstrated that short term exposure of macrophages to acemannan upregulates the phagocytosis and candidicidal activity [39]. As an antiviral agent, acemannan has also demonstrated antiviral activity *in vitro* against human immunodeficiency virus, Newcastle disease virus and influenza virus. In addition, acemannan has been shown to inhibit acquired immunodeficiency syndrome virus *in vitro*, and an injectable form has been found to be of benefit in feline immunodeficiency virus infected cats. Acemannan possesses antiviral activity by modifying glycosylation of both virally infected cells and glycoprotein coats of viruses, thus inhibiting virus replication and infectivity [40].

4.4 Anticancer activity: The major goal of cancer chemoprevention is to reduce the incidence of human cancer, either by inhibiting the process of carcinogenesis or by preventing high levels of carcinogen exposure [41]. Acemannan has been shown to have anticancer activity and it has been approval for treatment of fibrosarcoma in cats and dogs. Harris *et al.* in 1991 and King *et al.* in 1995 treated tumors with acemannan by intralesional and intraperitoneal routes of administration, demonstrating that acemannan immunostimulant may be an effective adjunct in combination with surgery and radiation therapy [42]. Liu *et al.* injected acemannan into mice, producing migration of macrophages to the peritoneal cavity. Peritoneal macrophages, when treated with acemannan *in vitro*, increased the expression of major histocompatibility complex II (MHC II) and enhanced endocytosis, phagocytosis, nitric oxide production, tumor necrosis factor-α (TNF-α) secretion and tumor cell cytotoxicity [43]. It is believed that acemannan exerts its antitumor activity through macrophage activation and the release of tumor necrosis factor (TNF), interleukin-1 (IL-1) and interferon gamma (IFN). Also the anticancer biological mechanism of acemannan may be exerted through pluripotent effector cells, such as macrophages [41].

4.5 Hypoglycemic activity: *A. vera* is a traditional remedy for diabetes mellitus in many parts of the world. Some evidence in humans and animals suggests that *A. vera* is able to alleviate chronic hyperglycemia and perturbed lipid profile that are characteristic of diabetes mellitus. Advanced type 2 diabetes mellitus needing insulin therapy is a common disease. Huseini *et al.* evaluated the efficacy and safety of aloe leaf gel in the treatment of type 2 diabetic patients resistant to oral synthetic anti-hyperglucemic drugs needing insulin. The only bioactive substance that was identified and quantified in the aloe gel used in this trial was acemannan. Acemannan lowered the blood levels of fasting glucose and glycosilated hemoglobin significantly without any significant effects on liver or kidney function tests. Considering the results of the trial, further clinical trials concerning the safety and efficacy of aloe gel in the treatment of patients with type 2 diabetes mellitus, as well as more studies addressing the bioactivities and mechanisms involved in the anti-hyperglycemic actions of acemannan seem necessary [44, 45].

5. Acemannan in dentistry

It has been reported that acemannan accelerates the healing of aphtous ulcers and reduces the pain associated with them [3]. Bhalang *et al.* elucidated the safety and effectiveness of acemannan in the treatment of oral aphtous ulceration. No subjects exhibited side effects to acemannan, which can be used for the treatment of oral aphtous ulceration, although the effectiveness was not comparable with that of 0.1% triamcinolone acetonide [46]. The SaliCept Patch is a freeze-dried pledget that contains acemannan Hydrogel (Carrington Laboratories). Preclinical studies have suggested that this extract promotes wound healing, augments reticuloendothelial function, regulates the immune response and acts as an inflammatory and antibacterial agent. Given the severe pain and subsequent anxiety of patients with alveolar osteitis, pain relief is the primary goal of treatment. Acemannan inhibits the inflammatory process and relieves pain by interfering with the arachidonic acid pathway by way of cyclooxygenase, concluding that acemannan in the form of SaliCept patch is an acceptable alternative to alvogyl as a dressing for the management of alveolar osteitis [47]. Due to its inherent viscosity, acemannan could be used as a denture adhesive. Tello *et al* manufactured a prototype acemannan denture adhesive formulation and evaluated pH changes, cytotoxicity to human fibroblasts and adhesive strength in dry and wet conditions. The denture adhesive formulations consisted of five combinations of 20 g/mL acemannan with varying concentrations of preservatives and two other formulations without

preservatives of 20 g/mL and 150 g/mL. They concluded that acemannan denture adhesive formulation 150:1, which was the most viscous formulation, was an effective herbal substitute for traditional denture adhesives [48].

6. Toxicology studies

In 2010, the National Toxicology Program released a technical report on *A. vera* that concluded that there was clear evidence of carcinogenic activity of a non-decolorized whole leaf extract of *A. vera* in male and female rats based upon increased incidence of adenomas and carcinomas of the large intestine [49]. In previous studies, aloe derivatives without the anthraquinone-containing latex were not associated with the adverse effects. Sehgal *et al*. tested *A. vera* gel by administering a single oral dose of 150 mg/kg; no evidence of aloe toxicity was found, nor any changes in behavior, body weight or organ weights. The differences in findings between this study and that of the National toxicology program are most likely due to the different *A. vera* juices tested [4]. Candidates for adverse reactions are the anthraquinones associated with the latex in whole leaf juice. In relation to acemannan, the Cosmetic Ingredient Review Expert Panel found that acemannan has no significant toxicity in mice, rats or dogs at maximum dose levels of 200, 50, and 50 mg/kg, respectively, administered intraperitoneally and intravenously at 4 day intervals over 30 days. In the diet of dog, doses of 1500 mg/kg a day, and doses up to 2000 mg/kg a day in mice had no observable toxic effect [7]. Jettanacheawchankit *et al*. affirm that acemannan at 16 mg/mL, the maximum concentration they used, was not toxic to gingival fibroblasts. These data corresponded with the study of Fogleman *et al*. that reported no significant toxicity in oral administration of acemannan to rats for 14 days and to dogs for 90 days at up to 1500 mg/kg per day [50].

7. Conclusion

The literature covered by the previous review contained case reports of the healing powers of acemannan. The pharmacological attributes of acemannan have been revalidated in modern science through various *in vivo* and *in vitro* studies. Many study findings have shown that acemannan is an acceptable alternative for the management of pathological conditions. However, more and better trial data are needed to define the clinical effectiveness of this popular herbal remedy more precisely. Research on standardized methodological quality is needed to identify if acemannan, individually or in combination, exhibits therapeutic properties, and to know the exact mechanisms by which it act.

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