REVIEW ARTICLE

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Effect of Acemannan/Aloe Vera on Bone Regeneration Specially in the Oral and Maxillofacial Region: A Literature Review

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Abstract

Background and Aim: With the advances in technology, the use of natural materials has broadened. Acemannan is the main polysaccharide in aloe vera plant. It is a natural and biocompatible polymer with low toxicity. The acemannan monomers include mannose, glucose and galactose. Due to its biological properties, acemannan could be useful in bone regeneration. The aim of this study was to investigate the effect of acemannan/aloe vera on bone regeneration and extraction socket healing.

Materials and Methods: In this review article, an electronic search was conducted in PubMed and Scopus from 1996 to June 2022. Relevant data based on clinical indications were extracted. Twenty original articles, including 4 in vitro studies, 8 animal, and 8 human studies were reviewed. The inclusion criterion was articles that directly and originally evaluated the correlation of bone regeneration and acemannan/aloe vera.

Results: Over 30 studies were found in this field by database searching. According to the results, the proposed items could be categorized into 3 major groups of animals, human, and in vitro studies. Animal studies were divided into two groups of bone defect regeneration and extraction socket healing. Also, human studies were divided into two groups of bone defect regeneration and sinus floor elevation/guided bone regeneration surgeries. All studies reported positive effect of Acemannan/aloe vera on bone healing and regeneration.

Conclusion: Acemannan/aloe vera may be considered as a bioactive molecule due to induction and acceleration of bone formation.

Key Words: Acemannan; Aloe vera; Bone Regeneration; Tissue Engineering

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Introduction

Bone tissue, with its self-repairing properties, is under constant remodeling. However, it does not have the ability to reconstruct large defects that occur due to periodontal disease, tumors, accidents, or congenital anomalies [1].

In some situations, such as maxillofacial and orthopedic surgeries, more bone is required than the regenerative capacity of the existing tissue. For example, in bone regeneration for dental implant placement, or in osteoporosis where the tissue does not have the innate potential to regenerate, a supportive measure

is necessary to increase the treatment success [2].

Tissue engineering with the aim of repairing or reconstructing bone, has made significant progress so far, in such a way that it has the ability to replace the lost tissues and damaged organs, including bone, cartilage and skin [3]. Generally, presence of three basic factors is necessary for tissue engineering namely biomaterial scaffold, living cells, and growth factors [4].

In cases with inadequate bone mass, several periodontal regeneration strategies such as guided tissue regeneration with bone grafting and growth factor applications have been suggested in an attempt to regain bone and periodontal tissue [5-8].

Due to the limitations of preparation and use of autografts, allografts and xenografts, natural materials have received more attention in the recent years. Biocompatible materials have shown good performance in tissue reconstruction [4]. Acemannan is a natural polysaccharide and the main active ingredient of aloe vera gel [9].

Aloe vera

Nowadays, people are turning to traditional and holistic medicine with herbal products for prevention and treatment of diseases. Thus, medicinal herbs are increasingly used in almost every health field [10]. Aloe vera (*Aloe barbadensis* Miller) is a plant with spear-shaped and cactus-like leaves, that grows in dry climates [11].

Chemical composition of aloe vera gel

The aloe vera leaves contain a transparent and semi-solid gel [7]. This gel is made of various compounds including polysaccharides and sugars (72%), minerals (16%), proteins and lipids (11%), and phenolic compounds (1%) [12].

In total, 99-99.5% of aloe vera plant is water and only 0.5-1.0% of it is solid material, which has more than 75 different compounds. These compounds include polysaccharides (acemannan), anthraquinones (aloe emodin, emodin and chrysophanol), chromones (aloesin and aloesone), coumarins (esculetin and umbelliferone), anthranols (aloin A, aloin B, aloinoside A, aloinoside B and aloesaponol), pyrans and pyrones (aloenin), naphthalene derivatives (plicataloside) and flavonoids (isovitexin)[13].

Procurement of acemannan

To isolate acemannan from aloe vera gel, fresh aloe vera leaves are often procured as a raw material from botanical stores. Many experiments have been carried out in order to extract acemannan.

There are four methods to extract acemannan: (I) chromatography by size exclusion, (II) chromatography by size exclusion and sedimentation with cetyltrimethylammonium bromide (CTAB) and ethanol, (III) chromatography by size exclusion, and hollow-fiber ultrafiltration and ethanolic sedimentation, and (IV) direct sedimentation with CTAB and ethanol. Darzi et al. [14] showed that the sedimentation method with CTAB could be effective in reducing the costs and time. Powdered aloe vera is best used for tissue engineering applications and is often mixed with biodegradable polymers.

Other methods of extracting acemannan from aloe vera include homogenization and centrifugation. Gas chromatography-mass spectrometry and 13C NMR spectroscopy are also used to assess the monosaccharide and polysaccharide composition. The acemannan concentration obtained with this method is 0.2% [8,15–18].

Biochemistry and biological applications of acemannan

Acemannan is the main polysaccharide of aloe vera found in the inner leaf of aloe plant. The approximate chemical structure of acemannan is 1 β-(1, 4)-linked glucose, 31 β-(1, 4)-linked mannoses and 1 α-(1, 6)-linked galactoses [11]. According to previous studies, acemannan can cause differentiation and proliferation of bone marrow stromal cells with growth factor activation in vitro. In animal models, dentin repair and periodontal ligament reconstruction have been performed using aloe vera. In

clinical usage of acemannan, it was shown that it enhanced the healing of oral aphthous ulcers and prevented alveolar bone osteitis [6,9]. Acemannan can play a role in bone regeneration by stimulating the proliferation of bone marrow stem cells and expression of growth factors [19,20]. Due to the bioactive properties of acemannan, and induction of soft and hard tissue regeneration, this polysaccharide could be a candidate for periodontal tissue reconstruction [18].

The aim of this review study was to investigate the effect of acemannan/aloe vera on bone regeneration and extraction socket healing.

Materials and Methods

To evaluate the association between acemannan/aloe vera gel and bone regeneration, 3 steps were undertaken.

An electronic search was conducted in PubMed and Scopus for articles published from 1996 to June 2022 (Figure 1).

Inclusion criterion:

All articles that directly and originally evaluated the correlation between bone regeneration and acemannan/aloe vera.

Exclusion criteria:

1. Retracted articles
2. Review articles

Step 1. Appropriate terms were extracted from articles, books, and "MeSH" database in "PubMed and Scopus". These terms included:

1.Bone regeneration/reconstruction and acemannan

2.Bone regeneration/reconstruction and aloe vera

Step 2. The terms were searched separately. In this step, 23 articles for "bone regeneration/ reconstruction and aloe vera", and 9 articles for "bone regeneration/reconstruction and acemannan" were found.

Step 3. Abstracts were reviewed and articles were selected based on the inclusion and exclusion criteria. In this step, 20 relevant articles were selected.

The main keywords used included Acemannan, aloe vera, animal, bone regeneration, in vitro, in vivo, and tissue engineering.

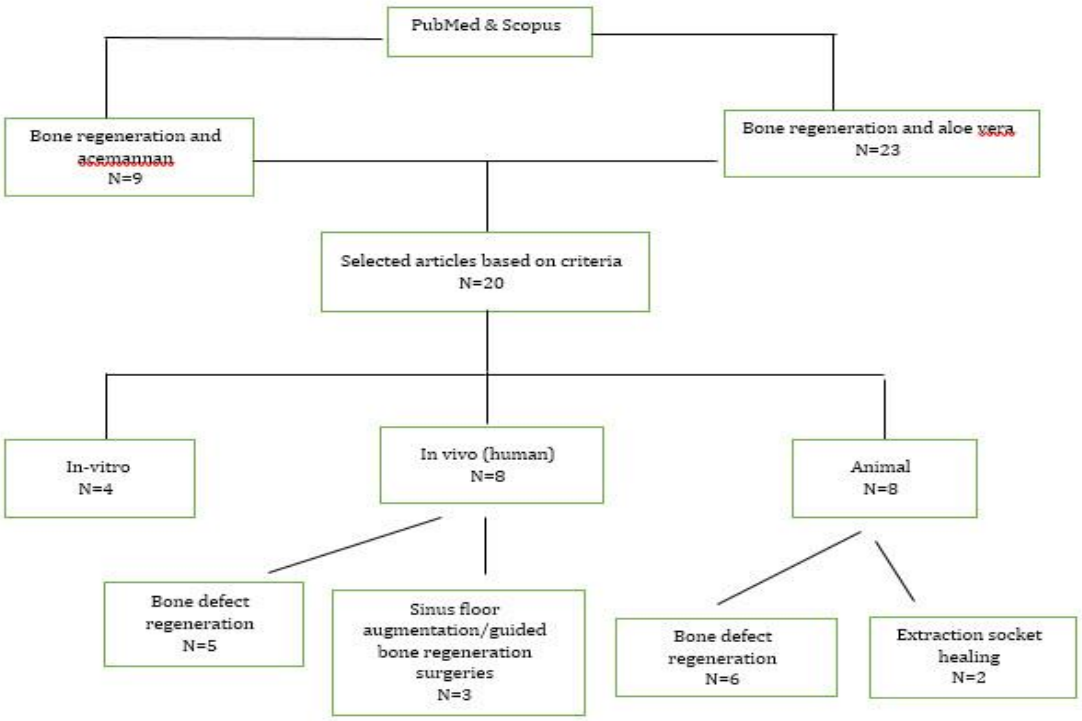

Figure 1. Overview of the search strategy

Results

The results were divided into 3 groups: in vitro, in vivo (human) and animal studies.

In vitro studies

Four in vitro studies on the effect of acemannan on a series of processes and production of materials such as cells or proteins in animals and humans were evaluated. Some of these studies assessed the effect of acemannan on the activity of numerous cytokines including interleukin-6 and tumor necrosis factor-α [21], poly 3-hydroxybutyrate-co-3-hydroxyvalerate [22], alkaline phosphatase activity, and production of bone morphogenetic protein-2 [17] and effect of aloe vera on osteoblast-like cells [23]. More explanation of in vitro studies is provided in Table 1.

Animal studies:

According to Table 2, animal studies were divided into 2 parts. In the first part, 6 animal studies were reviewed about bone defect regeneration. These studies investigated the effect of acemannan or aloe vera gel, alone or together with other herbal or chemical substances (such as collagen sponge, and Moringa oleifera hydrogel) on regeneration of femur, skull and tibia bones in animals such as rats, dogs and rabbits [9,18,24-27]. In the second part, 2 animal studies were reviewed about extraction socket healing. These studies investigated the effect of acemannan sponge or aloe vera gel, alone or in comparison with other materials in rats [28,29].

In vivo (human) studies:

In vivo studies were divided into 2 parts. The first part included 3 articles about sinus floor augmentation and guided bone regeneration surgeries. Studies in this part investigated the effect of acemannan sponge on bone augmentation for dental implant placement [20,30,31]. The second part included 5 articles on the effect of acemannan sponge or aloe vera gel, alone or in comparison with other materials on oral bone defect regeneration [6,32-35]. More explanation of in vivo studies is provided in Table 3.

Table 1. Summary of the results of reviewed in vitro studies

Author(s)	Population	Material	Conclusion
Zhang and Tizard 1996 [21]	Mouse macrophage cell line (RAW 264.7 cells)	Acemannan	Acemannan can activate macrophages and affect nitric oxide and cytokine production.
Tahmasebi et al. 2019 [22]	Human-induced pluripotent stem cells	Aloe vera gel and nanofibrous scaffold	Nanofibrous scaffold biocompatibility was significantly improved when combined with aloe vera gel.
Jittapiromsak et al. 2010 [17]	24 male Sprague Dawley rats' upper first molars and primary human dental pulp cells	Acemannan	Acemannan significantly induced alkaline phosphatase activity and production of BMP-2, which could induce bone formation.
Rasoulian et al. 2018 [23]	Human osteosarcoma cell line (MG-63)	Aloe vera gel	Osteoblast-like cells were exposed to aloe vera, followed by analysis of cell viability, lactate dehydrogenase release, and intracellular reactive oxygen species production. The results showed enhancement of cell biocompatibility.

Table2. Summary of the results of reviewed animal studies

Author(s)	Population	Material	Application	Conclusion
Elsheshtawy et al. 2021 [28]	32 adult male Albino rats	Aloe vera gel compared with methylpredniso-lone and silver nanoparticle gel	Lower right first molar socket healing	silver nanoparticle gel resulted in better socket healing at early periods as compared with aloe vera gel. The bone formation in aloe vera group improved significantly at day 14. At day 7, the socket was filled with osteoid tissue and this result was better than methylprednisolone treated group.
Pachimalla et al. 2020 [27]	8 males rabbits	Acemannan and Moringa oleifera hydro gel	Using the coated implants in tibia and femur	After using the implant with a hydrophilic surface, new bone was formed and the bone-to-implant contact increased. In the new bone-implant contact, there was no necrosis and inflammation.
Banerjee and Bose 2019 [26]	15 males Sprague-Dawley rats	Acemannan with hydroxyapatite coated titanium implants	Bone defect in the distal of femur	The results demonstrated improved osteoid formation and osseointegration from 34% in the control hydroxyapatite group to ~49% with the incorporation of acemannan in doped coatings.
Soares et al. 2018 [25]	75 Rattus norvegicus	Aloe vera gel and human dental pulp cells	Tibia bone defect	Bone regeneration in non-critical defects increased by using aloe vera extract with mesenchymal stem cells ($p<0.05$).
Godoy et al. 2018 [9]	35 female Sprague Dawley rats	Acemannan	Calvarial defect	Bone volume and density of tissue minerals increased histologically in the groups treated with acemannan compared to the control group ($p<0.05$).
Al-Hijazi et al. 2015 [24]	15 male Swiss rats	Aloe vera gel	Femur bone defect	Aloe vera significantly increased osteogenic cell proliferation, expression of BMP-7 and maturation of newly formed bone.
Boonyagul et al. 2013 [29]	53 male Sprague Dawley rats	Acemannan sponges	Incisor socket healing	Proliferation of bone marrow stem cells, expression of growth factors and acceleration of cavity healing occurred in presence of acemannan sponge ($p<0.05$).
Chantrawaratit et al. 2013 [18]	4 mongrel dogs	Acemannan sponges	Premolar class II furcation defect	Alkaline phosphatase activity, periodontal regeneration and mineral deposition in class II furcation defects increased by using acemannan sponge ($p< 0.05$).

Table 3. Summary of the results of reviewed in vivo studies

Author(s)	Population	Study type	Material	Application	Conclusion
Deesricharoen kiat et al. 2021 [20]	20 patients older than 20 years	Randomized clinical trial	Acemannan as a supplement to deproteinized bovine bone xenograft	Guided bone regeneration in the anterior maxilla	Acemannan had a favorable effect on dimensional stability in early stages of recovery after guided bone regeneration, but at 6 months, it did not have statistically significant differences with the xenograft.
Trinh et al. 2020 [31]	a 57-year-old female patient	Case report	Acemannan sponge	Sinus lift surgery	The histological results showed new bone formation after using acemannan sponge in sinus lift surgery. It also showed an increase in alveolar bone height on CBCT images 6 months after the operation.
Le Van et al. 2020 [34]	9 male and 13 female patients aged 18-45 years	Randomized clinical trial	Acemannan sponge	Periapical defect after apical surgery (22 anterior teeth)	The results of using acemannan sponge in apical surgery showed that the acemannan groups had a higher recovery rate than the control group. Therefore, this bone-inducing biomaterial can cause early healing of bone defects.
Trinh et al. 2019 [30]	30 patients aged 40 to 60 years	Randomized clinical trial	Acemannan sponge	Indirect sinus augmentation	At 3 and 6 months after sinus surgery, acemannan sponges caused more bone formation around the implant than the control group without graft.
Kurian et al. 2018 (33)	90 patients mean age oof 41 years	Randomized clinical trial	Aloe vera gel compared with 1% metformin	Bone defects in chronic periodontitis patients	Aloe vera gel significantly decreased pocket depth, increased adhesion and improved bone regeneration. But the results of using 1% metformin gel were significantly better than aloe vera gel.
Ipshita et al. 2018 [32]	90 patients	Randomized clinical trial	Aloe vera gel compared with 1% alendronate	Mandibular class II furcation defects in patients with chronic periodontitis as an adjunct to scaling and root planing	The use of alendronate and aloe vera gel compared to the placebo group led to improvement of clinical and radiographic parameters. However, the reduction of defect depth in alendronate group was significantly better than aloe vera.
Jansisyanont et al. 2015 [6]	99 volunteers (18–24 years old)	Randomized clinical trial	Acemannan sponge	Mandibular third molar socket healing	Based on the results, acemannan sponge, as a safe biological material, increased bone density in the tooth socket 3 months after surgery.
Poor et al. 2002 [35]	1,194 patients (587 in the Gel foam group (261 males and 326 females) and 607 in the SaliCept Patch group (273 males and 334 females). Age ranged from 9 to 89 years.	Retrospective and prospective clinical study	Acemannan patch compared with clindamycin Gel foam	Bone defect	The results showed that 78 of 975 sites (8.0%) in the Gelfoam group developed alveolar osteitis, whereas only 11 of 958 sites (1.1%) in the SaliCept group developed alveolar osteitis (p=0.0001).

Discussion

The purpose of tissue engineering is to regenerate the lost tissues with the help of chemistry, histology, cell biology, and immunology science for effective tissue regeneration. So far, various techniques and materials have been used for bone regeneration, such as autografts, allografts, and xenografts, each having advantages and disadvantages. The main disadvantages include limited access to the donor site, difficulty in obtaining sufficient amounts of bone, rapid absorption, risk of rejection by the immune system, and low osteogenic potential. With the advancement of technology, the use of plants in many fields has increased. Studies have also been conducted on the use of plant extracts in medical sciences or as a substitute for bone regeneration materials [8].

Aloe vera is among such plants. This cactus-shaped plant is filled with a transparent semi-solid gel. Totally, 72% of aloe vera gel is composed of polysaccharides and sugars. Also, this gel contains minerals, proteins, and lipids. One of the important constituents of aloe vera is a polysaccharide called acemannan [7,11,13].

Today, aloe vera is widely used in food industry and medicine. Also, it has medicinal properties such as anti-inflammatory, antibacterial, and antiseptic effects. It has also been used in treatment of skin injuries, cancer, and diabetes. The positive effect of acemannan, the main polysaccharide extracted from aloe vera, on expression of growth factors, stimulation of bone and periodontal ligament regeneration, and proliferation and differentiation of osteoblasts has been reported as well [19].

In the recent years, due to its potential to promote tissue regeneration because of its polysaccharides, like acemannan, the use of aloe vera in tissue engineering has gained increasing popularity, and several experiments have been done; some of them will be discussed below.

In this literature review, 20 original articles (4 in vitro, 8 ex-vivo, and 8 in vivo studies) were reviewed in two aspects (bone defect healing and extraction socket healing) to investigate the correlation between acemannan/aloe vera and bone regeneration. All studies showed positive effect of acemannan/aloe vera on bone formation. Some studies that used aloe vera extract reported its osteogenic properties probably due to the presence of acemannan polysaccharide in the aloe vera gel [24,25, 28,32].

In some studies, acemannan was used with other materials. Pachimalla et al. [27], used acemannan with moringa oleifera hydrogel. In a study by Banerjee and Bose [26], better results were obtained by adding acemannan to hydroxyapatite-coated titanium implants. The results of these two studies were in line with each other and indicated higher efficacy by adding acemannan to biomaterials compared with acemannan alone. Also, in a series of studies, acemannan was compared with some chemicals; but the results showed lower effectiveness of acemannan. Ipshita et al. [32], used aloe vera compared with 1% Alendronate. Kurian et al. [33] showed significantly better results by using 1% metformin gel than aloe vera gel. Elsheshtawy et al. [28] compared aloe vera with silver nanoparticles and methylprednisolone. But in a study by Poor et al, [35] acemannan was compared with clindamycin-soaked gel-foam, and the results suggested that acemannan SaliCept patch was significantly more effective.

In the present review study, four in vitro studies were also reviewed. The results were all consistent with each other and indicated the optimal efficacy of aloe vera in bone regeneration [17,21-23].

The mechanism of action of acemannan in bone regeneration and extraction socket healing is still under investigation. But it is deduced from the studies that it could probably be through adjustment of the expression of

alkaline phosphatase, vascular endothelial growth factor, bone morphogenetic protein 2, type I collagen, bone sialophosphoprotein, and osteopontin. Increased vascular endothelial growth factor secretion induces angiogenesis and osteoblast differentiation. Alkaline phosphatase is considered as an initial marker of osteoblast differentiation and induces mineralization.

Another mechanism is that acemannan/aloe vera has anti-inflammatory properties which stimulate osteogenesis due to the immunomodulatory function, which can regulate and reduce the inflammatory phase before bone formation by expressing inflammatory mediators such as interleukins 6 and 8. Acemannan sponge can also remain in the body for several weeks due to its three-dimensional and interconnected structure. By absorbing blood and serum, this sponge provides a basis for blood clot formation and becomes a temporary scaffold that is a reservoir for growth factors and facilitates cell attachment and extracellular matrix deposition [6,18,20,25,29,32,34].

Despite the challenges and the fundamental need for further research, our current understanding of the interaction of aloe vera and cells suggests that aloe vera and its important polysaccharide, acemannan, hold a promising future for improving bone regeneration outcomes. Also, our general review of the articles supposed that there is probably no difference in results between aloe vera and acemannan in osteogenic properties.

Conclusion

In summary, acemannan as a natural medical compound extracted from aloe vera gel, is a bioactive molecule due to inducing and accelerating bone formation and may serve as an acceptable alternative to bone augmentation materials for management of pathological bone defects.

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Conflicts of interest

There is no conflict of interests.

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