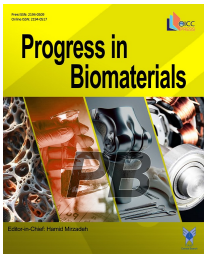

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Acemannan from Aloe Vera: A Promising Biological Agent for Osteoinductive Applications in Guided Bone Regeneration

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Abstract:

Aim: This systematic review investigates the osteoconductive properties of acemannan, a principal polysaccharide derived from Aloe vera, in the context of guided bone regeneration (GBR). With the growing interest in biological agents for bone healing, this study aims to elucidate the role of acemannan in enhancing bone regeneration outcomes.

Materials and methods: A comprehensive search was conducted across multiple electronic databases such as Embase, PubMed, Scopus, Web of Science, and Google Scholar for studies published between 2000 and 2023. Two independent researchers screened the literature, removing duplicates and irrelevant articles to focus on experimental studies, case reports, and clinical trials that specifically examined the effects of acemannan on bone regeneration.

Results and discussion: From an initial pool of 185 studies retrieved, 16 eligible articles were selected for review, comprising nine experimental studies, four clinical trials, and two case reports/case series. The findings indicate that A. vera and acemannan promote osteogenic differentiation, reduce inflammation, and enhance bone healing, making them promising agents for dental and orthopedic applications.

Conclusion: This review highlights the potential of acemannan and Aloe vera as effective biological agents in bone regeneration strategies. The evidence suggests that acemannan promotes osteogenic differentiation, reduces inflammation, and improves overall bone healing outcomes. Further research is warranted to explore its applications in clinical settings, particularly in enhancing GBR techniques.

Keywords: Acemannan; *Aloe vera*; Bone regeneration; Tissue engineering; Guided bone regeneration

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Introduction

There are some common reasons for maxillofacial bone loss, such as ageing, cancer, trauma, tooth loss, and periodontal disease (Wang et al., 2023). Horizontal and vertical bone loss in the region of an implant can cause considerable clinical problems, so augmentation before implant treatment would be necessary (Al-Fakeh et al., 2022).

Guided bone regeneration (GBR), split-crest surgery, and distraction osteogenesis can be used to achieve the desired repair in bone structures (Milinkovic and Cordaro, 2014). GBR, the most widely used of all the methods, is used in almost 40% of patients with bone disorders (Abtahi et al., 2023). GBR, a surgical technique, utilizes a barrier membrane that influences the growth of new bone tissue (Kim and Ku, 2020). GBR is generally used in implant treatments,

resulting in sufficient bone structures to support the implant (Kim and Ku, 2020). The procedure begins with a small incision in the soft tissue; a space should be created for the barrier membrane and bone graft materials, and the process ends with tissue suturing (Kim et al., 2023). Bone materials perform the role of scaffolds and guide osteocytes and osteoblasts to the region of the bone defect, resulting in new bone formation (Saito et al., 2021). Autografts, xenografts, allografts, and alloplasts are commonly used materials for bone regeneration (Ferraz, 2023). Currently, autografts are considered the "gold standard" due to their ideal properties, including osteogenesis, osteoinductivity, and osteoconductivity (Garcia-Gareta et al., 2015).

However, they require a donor site, which can lead to increased patient morbidity (Baldwin et al., 2019). Consequently, xenografts, allografts, and alloplastic materials have emerged as alternatives (Ferraz, 2023). Despite their advantages, allografts and xenografts raise concerns related to religious beliefs and the potential transmission of diseases (Bucchi et al., 2019). Given the widespread application of these techniques, research aimed at enhancing osteoinductivity and osteoconductivity is increasingly significant (Garcia-Garcia et al., 2023). A substantial body of research focuses on the use of biological agents in combination with xenografts, including growth factors (Mijiritsky et al., 2022), bioactive coatings (Tao et al., 2020), and platelet-rich fibrin (Kargarpour et al., 2021; Egierska et al., 2023) (Table 4). Hydrogels fabricated from natural polymers like alginate and hyaluronic acid have been developed as porous scaffolds for bone fillers in orthopedic applications (Jamnezhad et al., 2020). Growth factors accelerate bone regeneration by stimulating and regulating cell behaviors, such as migration, proliferation, adhesion, and differentiation (Safari et al., 2021). Numerous growth factors have been introduced and utilized in treatments, with ongoing investigations to deepen our understanding of bone regeneration at the molecular level (Safari et al., 2021). However, concerns about their cost and safety in clinical applications remain significant (Niu et al., 2019). Natural components are also interesting because they are inexpensive and non-invasive (Rao et al., 2019). Studies on plant extracts indicate their effectiveness in bone healing through processes involving both osteoconductivity and osteoinductivity (Toosi and Behravan, 2020). Notably, A. vera, belonging to the Liliaceae family (Darzi et al., 2021), exhibits various therapeutic activities such as anti-inflammatory, antifungal, antibacterial, antiviral, and hypoglycemic effects (Nasiri et al., 2021; Poorkazemi et al., 2022). Chemically, Aloe vera gel contains over 75 bioactive compounds, including polysaccharides (e.g., acemannan), glycoproteins, anthraquinones, enzymes, and minerals. The β-(1 − 4)-acetylated polymannose compound Acemannan, which is extracted from Aloe vera, shows immunomodulatory effects and induces strong bone growth in both laboratory and animal studies by substantially increasing bone surface area, volume, and mineral density. It stimulates the secretion of type I collagen, BMP-2, and VEGF, and upregulates key osteogenic markers including alkaline phosphatase, osteopontin, bone sialoprotein, and osteocalcin in bone marrow stem cells. Mechanistically, acemannan triggers the TLR5/NF-κB signaling pathway, which is crucial for osteoblast proliferation and bone matrix formation (Amirian et al., 2015; Godoy et al., 2018; Kaparakou et al., 2021; Kargarpour et al., 2021; Tao et al., 2020; ZadehGharaboghaz et al., 2020). This interest is not limited to bone. Other natural polymers, such as chitosan and its derivatives, are also being investigated for soft tissue applications like wound healing, where they are fabricated into porous, antibacterial dressings using techniques like freeze-drying (Raisi et al., 2020). Similarly, natural gums like tragacanthin are combined with chitosan to create bionanocomposite scaffolds (Liang et al., 2022).

In dentistry, Aloe vera has been used to treat conditions such as aphthous stomatitis (Shi et al., 2020), oral submucous fibrosis (Dalai et al., 2023), oral lichen planus (Andabak-Rogulj et al., 2023), and bone regeneration (Rasoulian et al., 2019). Research has identified several active ingredients in the gel of Aloe vera leaves, including acemannan, saponin, aloe emodin, aloe mannans, aloe rids, sterols, amino acids, aloin, and vitamins (Hamman, 2008). Acemannan, the main polysaccharide of A. vera, promotes the synthesis of the extracellular matrix, stimulates growth factors, and enhances cell proliferation and mineralization in various tissues, including the periodontal ligament, the dental pulp, and stromal cells of the bone marrow (Boonyagul et al., 2014; Thant et al., 2023). Additionally, acemannan is believed to possess osteoinductive properties that accelerate the formation of new cementum, periodontal ligament, and alveolar bone (Chantarawaratit et al., 2014). Acemannan has different biomedical applications, such as wound healing, tissue engineering, immune enhancement, and antitumor activity (Abu-Seida and Heba, 2023; Bai et al., 2023; Turner et al., 2004). Acemannan also contributes to bone regeneration by various mechanisms, including stimulating cell proliferation and differentiation, enhancing extracellular matrix formation and mineralization, supporting bone growth and density, promoting wound healing and tissue regeneration, and acting as an osteoinductive agent (Bai et al., 2023; Godoy et al., 2018) (Fig. 2).

This systematic review evaluates the effects of acemannan on bone regeneration, emphasizing its chemical properties, molecular mechanisms, and clinical applicability.

Materials and methods

Study design and registration

This systematic review was conducted per the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (Moher et al., 2010) to ensure methodological rigor and transparency. Before data extraction and analysis, the study protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under CRD420251025746.

Search strategy

To investigate the effects of acemannan on bone regeneration, we searched electronic databases, including Embase, PubMed, Scopus, Web of Science, and Google Scholar for eligible studies published from 2000 to 2023. The complete search strategy is detailed in Table 1, outlining the spe-

cific search terms and criteria used across these databases. No language restrictions were applied during the search to ensure a comprehensive retrieval of relevant literature.

Study selection and inclusion criteria

Two researchers independently reviewed all identified studies. All citations were imported into reference management software. Duplicate studies were removed after irrelevant studies were eliminated based on the titles and abstracts. The full texts of the remaining studies were then assessed, and only experimental studies, case reports, and clinical trials that evaluated the effect of acemannan or A. vera extracts on bone regeneration were included in this review. In case of uncertainty, a third researcher resolved the issues.

Data extraction

A standardized data extraction form was developed for data collection from each study. Data, including author name, year of publication, country, study type, objective of the study, participants, mean age, duration of follow-up, intervention, outcome measures, key findings, adjustments, and conclusions, were extracted by two independent researchers.

Quality assessment and risk of bias evaluation

To ensure the methodological rigor and validity of the included studies, a comprehensive quality assessment was performed using the Joanna Briggs Institute (JBI) Critical Appraisal Tools. The following checklists were applied based on the study design:

- Randomized Controlled Trials (RCTs): These were evaluated using the JBI Checklist for RCTs, assessing randomization, blinding, allocation concealment, dropout rates, and statistical analysis. This evaluation was utilized to determine internal validity and risk of bias for each clinical trial.

- Case Series Studies: Appraised with the JBI Checklist for Case Series, focusing on clarity of inclusion criteria, consecutive recruitment, outcome measurement, and follow-up completeness. This appraisal focused on the methodological quality and the extent to which the study minimized the potential for bias in its conclusions.

Two independent reviewers conducted the assessments, resolving discrepancies through discussion or consultation with a third reviewer. Studies that met $\geq 70\%$ of the quality criteria were included, while those with a high risk of bias or insufficient methodological details were excluded. This structured quality appraisal was critical for determining the strength of the evidence provided by each study and explaining the significance of this review's findings. Supplementary Material (Table S1) provides the full quality assessment results for transparency.

Results and discussion

In this systematic review, 185 studies were retrieved from various electronic databases. After applying specific inclusion criteria and removing duplicates, reviews, retracted

Table 1. The whole search strategy across electronic databases.

Search engine	Search strategy
PubMed N=17	((“acemannan”[Title/Abstract]) OR (“aloe vera”[Title/Abstract])) AND ((“bone regeneration”[Title/Abstract]) OR (“socket preservation”[Title/Abstract]) OR (“alveolar ridge preservation”[Title/Abstract]) OR (bone augmentation [Title/Abstract]) OR (lateral ridge augmentation [Title/Abstract]) OR (horizontal ridge augmentation [Title/Abstract])) AND (“2000”[Date - Publication]: “2024”[Date - Publication])
Scopus N=22	(TITLE-ABS-KEY (aloe vera) OR TITLE-ABS-KEY (acemannan)) AND (TITLE-ABS-KEY (bone AND regeneration) OR TITLE-ABS-KEY (bone AND augmentation) OR TITLE-ABS-KEY (socket AND preservation) OR TITLE-ABS-KEY (alveolar AND ridge AND preservation) OR TITLE-ABS-KEY (lateral AND ridge AND augmentation) OR TITLE-ABS-KEY (horizontal AND ridge AND augmentation)) AND PUBYEAR >1999
Embase N=17	(’acemannan’: ti, ab, kw OR ’aloe vera’: ti, ab, kw) AND (’alveolar ridge preservation’: ti, ab, kw OR ’bone regeneration’: ti, ab, kw OR ’bone augmentation’: ti, ab, kw OR ’lateral ridge augmentation’: ti, ab, kw OR ’horizontal ridge augmentation’: ti, ab, kw) AND [2000 – 2024]/py
Web of science N=29	(TI=(acemannan) OR AB=(acemannan) OR TI=(aloe vera) OR AB=(aloe vera)) AND (TI=(bone regeneration) OR AB=(bone regeneration) OR TI=(alveolar ridge preservation) OR AB=(alveolar ridge preservation) OR TI=(bone augmentation) OR AB=(bone augmentation) OR TI=(socket preservation) OR AB=(socket preservation) OR TI=(alveolar ridge augmentation) OR AB=(alveolar ridge augmentation) OR TI=(lateral ridge augmentation) OR AB=(lateral ridge augmentation) OR TI=(horizontal ridge augmentation) OR AB=(horizontal ridge augmentation)) AND PY=(2000 – 2024)
Google scholar N=100	acemannan “bone regeneration” OR “socket preservation” OR ”bone augmentation” OR “alveolar ridge preservation” OR “alveolar ridge augmentation”

articles, book chapters, and other non-eligible documents, 16 studies were deemed suitable for inclusion. Figure 1 demonstrates the flow diagram of article selection. The included studies included nine experimental studies, four clinical trials, and three case reports/series. A detailed summary of the characteristics, interventions, and key findings from these studies is presented in Table 2. These studies originated from multiple countries, including Japan, Iran, Thailand, Vietnam, Belgium, Brazil, Portugal, Egypt, India, and Sweden (Table 2). The studies can be categorized into two primary groups: Those investigating the effects of A. vera on bone repair and those examining the bone regeneration features of acemannan, the main polysaccharide of A. vera.

Preclinical evidence from in vitro and animal studies

Teymori et al. incorporated A. vera extract into polycaprolactone (PCL) scaffold to evaluate its osteoconductive effect on adipose-derived mesenchymal stem cells (ADSCs). The viability assay indicated no toxic effects. Alizarin Red staining revealed that A. vera promoted osteogenic differentiation of ADSCs, confirmed by increased expression of osteogenic markers such as Osteonectin (ON), Osteocalcin (OCN), RUNX Family Transcription Factor 2 (RUNX2), and Collagen type I alpha 1 (COL1). Additionally, ALP and calcium content assays confirmed the osteoconductive effect of a polycaprolactone (PCL) scaffold treated with A. vera on ADSCs (Teymori et al., 2023). Importantly, existing literature supports the potential of mesenchymal stem cells (MSCs) to differentiate into bone and cartilage (Khorasani et al., 2021). Notably, these results gain additional significance when considering recent advances in stem cell biology that highlight ADSCs' remarkable plasticity and differentiation potential in bone tissue engineering applications.

In another in vitro study, Soltani et al. examined the impact of A. vera on bone regeneration using MG-63 osteoblast-like cells, treated with scaffolds made from A. vera-incorporated starch-64S bioactive glass and quail eggshells. Their findings highlighted the osteogenic differentiation and extracellular matrix mineralization in MG-63 cells, as evidenced by increased ALP activity, calcium deposition, and expression of osteogenic markers, including Osteopontin (OPN) and OCN (Soltani and Alizadeh, 2022). This aligns with the emerging understanding of how natural polysaccharides can modulate the bone microenvironment by influencing mineral deposition and collagen matrix formation. The study by Tahmasebi et al. further reinforced

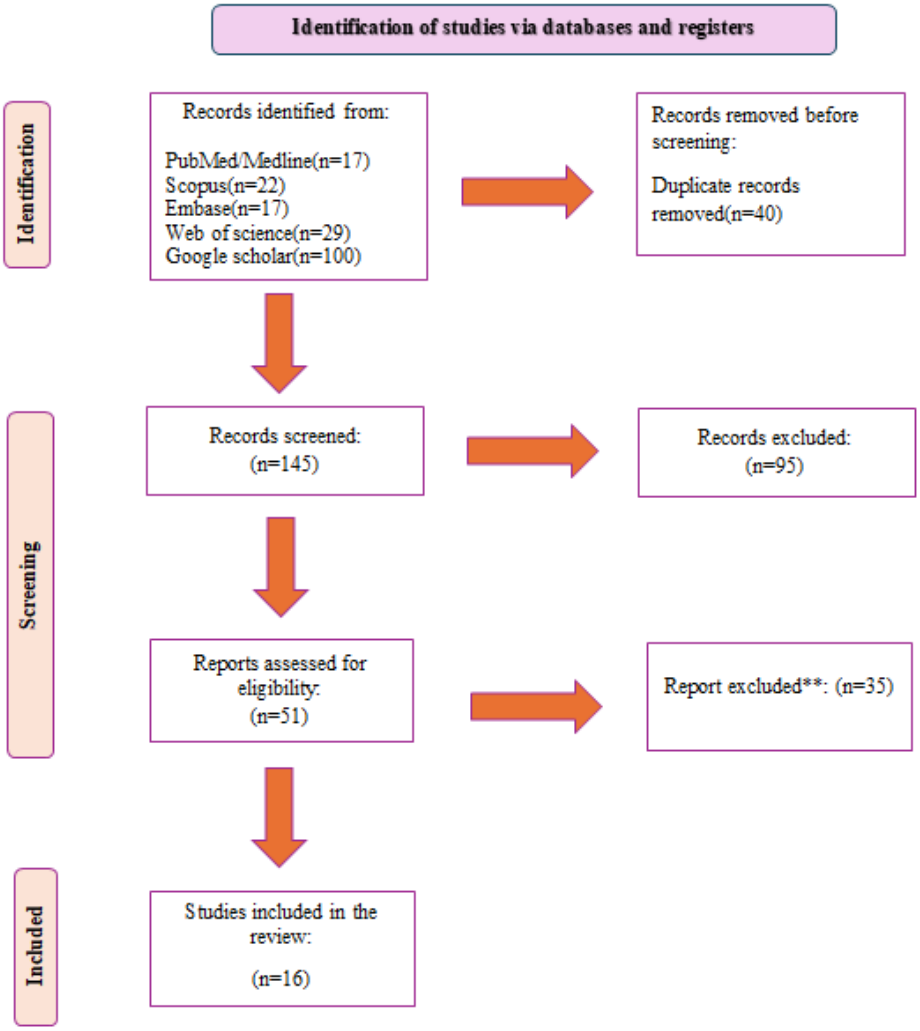

Figure 1. The flowchart of the search strategy.

Table 2. Molecular mechanisms of acemannan in osteoinduction.

Mechanism	**Description**
Cell Proliferation	Stimulates the proliferation of bone marrow stromal cells (BMSCs) and dental pulp cells, increasing the pool of cells available for bone formation.
Growth Factor Upregulation	Increases the expression of BMP-2 and VEGF, which are essential for osteoblast differentiation and angiogenesis.
Osteoblast Differentiation	Enhances alkaline phosphatase (ALP) activity, a key marker of early osteoblast differentiation, promoting the maturation of bone-forming cells.
Extracellular Matrix Synthesis	It upregulates the production of bone sialoprotein (BSP), osteopontin (OPN), and type I collagen, which are critical for forming the structural framework of bone.
Mineralization	Promotes calcium deposition and mineralization, essential for the hardening of bone tissue.
Immunomodulation	Activates macrophages, stimulates T cells and dendritic cells, induces nitric oxide (NO) production, and enhances hematopoiesis, creating a favorable environment for bone healing.
Scaffolding Properties	It acts as a natural scaffold, facilitating cell attachment, migration, and growth factor retention and supporting bone regeneration.
Bone regeneration	Triggers osteoblast proliferation and differentiation under the influence of multiple signaling pathways, including BMP, TGF-β, and Wnt

these observations using human-induced pluripotent stem cells (iPSCs) on nanofibrous poly(3-hydroxybutyrate-co-3-hydroxyvalerate) (PHBV) scaffolds, demonstrating excellent biocompatibility and osteoinductive potential (Tahmasebi et al., 2020).

The in vivo studies provided particularly compelling evidence for clinical translation. Rasoulian et al. showed the biocompatibility, antioxidant properties, and osteodifferentiation potential of A. vera in vitro. Their docking and in silico analysis results revealed the strong affinity of A. vera for the type I bone morphogenic protein receptor (BMPR1A), a key cell surface receptor involved in bone regeneration. Furthermore, in vivo investigation demonstrated that the injection of A. vera in rats with critical-size calvarial defects induced overexpression of RUNX2, ALP, OCN, and bone morphogenic protein-2 (BMP2), leading to the formation of denser bone with elevated ALP activity (Rasoulian et al., 2019). This dual computational-experimental approach represents a significant methodological advancement in natural product research for bone regeneration. Godoy and colleagues evaluated the effect of acemannan on calvarial defect healing through microcomputed tomography (micro-CT) and histopathology investigations in an animal model. They created calvarial defects in 35 female Sprague-Dawley rats and assessed the bone repair effects of different concentrations of acemannan sponges. They found that acemannan significantly increased bone surface area and volume at lower concentrations, while enhancing tissue mineral density at higher concentrations, indicating a denser bone matrix in treated specimens (Godoy et al., 2018). These findings are particularly relevant for clinical applications where optimal dosing strategies remain a critical challenge. Additionally, Soares et al. investigated the effect of A. vera combined with human dental pulp stem cells (hDPSCs) on bone regeneration in tibial defects in an animal model. They created a tibial defect in Rattus norvegicus rats and then filled it with collagen sponges, both with and without A. Vera and hDPSCs. The results monitored over 30 days demonstrated that the combination of collagen sponge, A. vera, and hDPSCs effectively promoted the repair of non-critical bone defects, helping to mitigate the effects of the inflammatory cascade (Soares et al., 2019).

Additionally, three experimental studies evaluated the bone repair properties of acemannan specifically. In a survey by Boonyagul et al., researchers showed acemannan's proliferative and angiogenic effects on primary rat bone marrow stromal cells (BMSCs). This biological activity is essential for capillary formation and osteoblast differentiation. Notably, treatment with acemannan resulted in increased ALP activity, enhanced expression of vascular endothelial growth factor (VEGF), BMP-2, OPN, bone sialoprotein (BSP), and promoted mineralization. Utilizing a tooth extraction rat model, findings revealed that treatment with acemannan increased bone mineral density (BMD) and accelerated bone healing with pronounced ingrowth of bone trabeculae in treated groups (Boonyagul et al., 2014). Chantarawaratit et al. investigated acemannan sponges for the regeneration of alveolar bone, cementum, and periodontal ligament using both an in vitro model with primary human periodontal ligament cells (PDLCs) and an in vivo rat canine furcation defect model. In another study in the field of orthopedics, silver oxide and silica-doped HA coatings, when further layered with acemannan and chitosan, not only improved osteoblast viability in vitro but also significantly enhanced osseointegration and new bone formation in a rat femoral model. The chitosan layer effectively modulated the release profile of acemannan, allowing for a sustained biological effect. These findings offer valuable insights for future

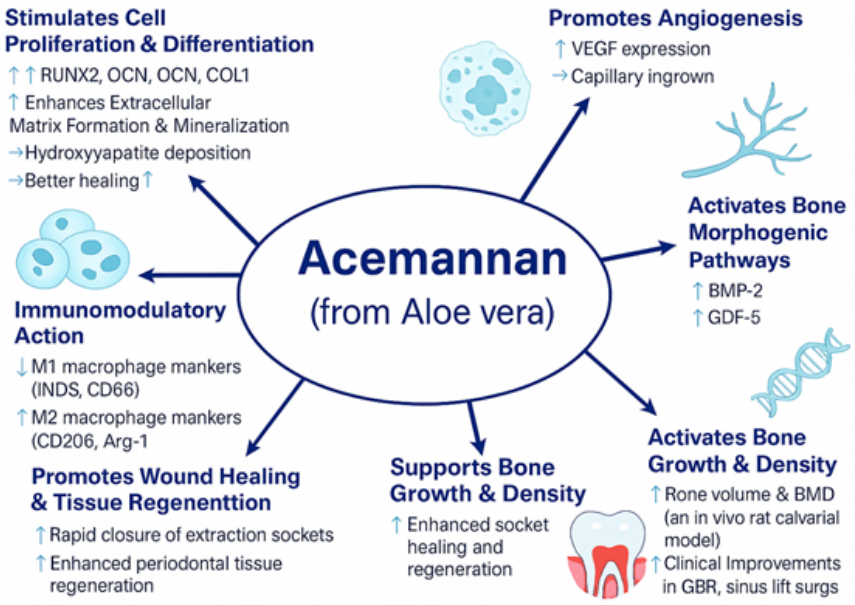

Figure 2. A schematic of the proposed mechanisms of acemannan in promoting bone regeneration.

load-bearing implant designs in regenerative medicine and dentistry (Banerjee and Bose, 2019). Consistent with other experimental studies mentioned, acemannan boosted the proliferation of PDLCs and increased the levels of several important factors, including growth/differentiation factor 5 (GDF-5), RUNX2, VEGF, BMP-2, COL1, ALP activity, and mineral deposition. Additionally, the in vivo model results showed that acemannan significantly accelerated the formation of new alveolar bone, cementum, and periodontal ligament (Chantarawaratit et al., 2014).

Acemannan stimulates osteogenesis by enhancing bone marrow stem cell proliferation and the promotion of their differentiation into osteoblasts. This process is facilitated by the induction of growth factor secretion, including VEGF, TGF-β, PDGF, and BMPs, which collectively contribute to bone regeneration. Furthermore, acemannan modulates the immune response by promoting the polarization of macrophages from the pro-inflammatory M1 phenotype to the pro-healing M2 phenotype, thereby creating a conducive microenvironment for bone repair (Godoy et al., 2018; Tao et al., 2020).

Acemannan is a naturally occurring, biocompatible, and biodegradable polysaccharide that exhibits minimal adverse effects. In contrast to recombinant growth factors, acemannan stimulates osteogenesis and actively regulates the immune response, thereby creating a favorable environment for bone repair. It also facilitates the regeneration of both soft and hard tissues, and its cost-effectiveness and ease of sourcing make it a valuable option. The efficacy of acemannan can be further enhanced by combining it with osteoconductive materials (Godoy et al., 2018; Tabatabaeian and Esfahanian, 2023; Trinh et al., 2020).

Preliminary clinical observations from case reports

Yakira et al. reported four cases involving two men with spinal stenosis, one man with prostate cancer and bone metastasis, and one woman with osteoporosis. Each patient received varying doses of A. vera juice (AVJ) with or without analgesics over a monitoring period of $2-3$ years. In this case series, the authors reported that AVJ alleviated pain, increased BMD in the osteoporosis case, and contributed to managing bone metastasis. However, as a case series with no control group, these findings are observational only and cannot be used to establish a causal relationship or confirm efficacy (Yagi, 2023). While case reports have inherent limitations, these observations suggest potential systemic applications that warrant further investigation through controlled clinical trials. Comparatively, bisphosphonates-the gold standard for osteoporosis-show more robust BMD improvements in RCTs (e.g., $5-8\%$ increase over 3 years) (Tabatabaeian and Esfahanian, 2023). However, AVJ's anti-inflammatory properties (via TNF-α suppression) and cost-effectiveness may position it as an adjunct therapy, particularly in resource-limited settings (Taalab et al., 2023).

Trinh et al. presented a case of a 57-year-old woman with an atrophic left posterior maxilla who underwent a lateral sinus lift procedure using an acemannan sponge placed between the sinus floor and the lifted membrane. The findings of cone beam computed tomography (CBCT) images and histological analysis showed that new bone had formed, and the height of the alveolar bone increased after six months. These results suggested that acemannan sponges may be effective biomaterials for promoting bone growth in sinus lift surgeries (Trinh et al., 2020). However, acemannan's rapid resorption rate (evident in rat calvarial defects (Godoy et al., 2018)) may limit its use in significant defects unless combined with slower-degrading scaffolds like β-tricalcium phosphate (β-TCP)-a strategy shown to improve bone volume by 40% in canine furcation defects (Taalab et al., 2023) (Table 4).

Chansamart et al., in a 5-year case report, presented the

placement of acemannan sponges in infrabony periodontal defects during minimally invasive periodontal surgery, resulting in significant clinical and radiographic improvements in patients with chronic periodontitis. The percentage of radiographic bone fill achieved-70% in three-walled, 60% in combined defects, and 20% in two-walled defects, demonstrating the material's favorable influence on periodontal regeneration, particularly in more contained defect morphologies. These findings suggest that acemannan supports bone formation and may also modulate wound healing responses within the periodontium (Chansamart et al., 2023).

Evidence from human clinical trials

A pivotal randomized clinical trial (RCT) by Deesricharoenkiat et al. investigated the efficacy of acemannan in GBR during simultaneous dental implant placement. The study compared deproteinized bovine bone (DBB) alone versus DBB combined with particulate acemannan in alveolar ridge preservation. Cone-beam computed tomography (CBCT) analysis revealed that the acemannan-enriched group exhibited significantly reduced buccal bone resorption after three months, suggesting that acemannan may enhance bone stability and minimize postoperative bone loss (Deesricharoenkiat et al., 2022). This finding aligns with previous in vitro studies demonstrating acemannan's ability to stimulate osteoblast proliferation and collagen synthesis, which is crucial for bone matrix formation (Godoy et al., 2018). However, a similar survey of Miron et al. reported that DBB + collagen membranes provided superior ridge preservation over acemannan-based grafts in long-term (6-month) assessments (Miron et al., 2017). This discrepancy may stem from differences in graft resorption rates-acemannan degrades faster than collagen-stabilized xenografts, potentially affecting long-term bone volume stability.

While acemannan enhances osteoblast differentiation, its osteogenic potency appears weaker than recombinant human BMP-2 (rhBMP-2) (Table 4). A meta-analysis by Nguyen et al. concluded that rhBMP-2 induces faster bone formation in sinus augmentation but carries risks of swelling and ectopic bone formation (Nguyen et al., 2020). Similarly, Vu et al. filled lower third molar sockets with acemannan sponges post-extraction, observing that 50 mg of acemannan sponges significantly reduced socket volume during a 12-month follow-up (Vu et al., 2021). These results corroborate earlier findings by Jansisyanont et al. (Jansisyanont et al., 2016). Furthermore, Gonna et al. observed the effect of acemannan in inducing dentin bridge formation and reducing inflammation in primary tooth pulpotomy after 12 weeks (Ghoname et al., 2017).

The efficacy of acemannan is influenced by its formulation, which can take the form of sponges, gels, or nanoparticles, as well as the chosen delivery strategy. Sponge-based formulations have been shown to provide biocompatibility and osteoinductive effects, although they are associated with limited bone volume increase. This suggests that the use of controlled release systems and composite scaffold systems may be necessary to enhance therapeutic outcomes (Trinh et al., 2020).

Molecular mechanisms of acemannan in osteoinduction

The literature discusses different molecular mechanisms of Acemannan in osteoinduction (Chan and Leong, 2008; Chow et al., 2005; Godoy et al., 2018; Jittapiromsak et al., 2010; Songsiripradubboon et al., 2016). Table 2 mentions these mechanisms.

Strengths, limitations, and clinical relevance of acemannan in bone regeneration

This systematic review assesses acemannan's osteoinductive and osteoconductive activities by synthesizing evidence from clinical, in vivo, and in vitro studies. By including a wide range of study designs (experimental studies, clinical trials, and case reports), this review provides a comprehensive overview of the currently available literature.. Methodologically, the review follows PRISMA guidelines using an exhaustive search strategy in several databases and independent screening by researchers to reduce the risk of bias. The results are also supported by a convergence of molecular events observed in preclinical studies (e.g., BMP-2/VEGF induction, immunomodulation) with the healing trends reported in clinical outcomes, which helps close the translational gap. Additionally, the review identifies acemannan's dual function in bone regeneration and anti-inflammatory response as paramount to its therapeutic use in GBR and implantology.

Despite its strengths, this review has several limitations. First, heterogeneity of studies included—varied models (cell lines, animal species, human patients), acemannan preparations (sponges, scaffolds, extracts), and outcome measures-prevents meta-analysis and direct comparison. Second, optimal dosing remains undetermined. The reviewed studies utilized a wide range of concentrations, from $1-8$ mg sponges in rat calvarial defects to 50 mg sponges in human extraction sockets (42, 58), which makes it difficult to establish a standardized dose for different clinical indications. Third, most included literature consists of preclinical studies (Ferraz, 2023; Tao et al., 2020) or small-sample clinical trials (Milinkovic and Cordaro, 2014; Tao et al., 2020), underscoring the need for larger, standardized human trials to establish efficacy. Fourth, no extensive long-term data on bone quality (e.g., biomechanical properties, remodeling kinetics), and potential immunogenic reactions to acemannan in humans are not well studied. Fifth, including two case reports means that some of the discussed clinical applications, particularly for systemic conditions like osteoporosis, are based on low-certainty evidence that should be interpreted cautiously. Finally, publication bias is conceivable because negative results or failed experiments would be less likely to be published.

While acemannan seems safe, and no significant adverse events were reported in the reviewed clinical trials, potential long-term immunogenic reactions in humans have not been well-studied and must be investigated in future research.

Future research should prioritize:

Table 3. The summary of studies on A. vera and acemannan in bone regeneration.

Authors & Year	Country	Study Type	Objective	Participants	Mean Age	Duration of Follow-up	Intervention	Outcome Measures	Key Findings	Adjustments	Conclusion
(Yagi, 2023)	Japan	Case Series	Investigate A. vera Gel (Acemannan) for bone regeneration & pain relief	4 case reports (2 spinal stenosis, one prostate cancer with bone metastasis, one osteoporosis)	42-89 years	2-3 years	A. vera Juice (AVJ) + Kampo drug, Loxonin, or enzalutamide	Pain relief, Bone mineral density (BMD), Quality of life (QOL)	AVJ improved pain relief, increased BMD in osteoporosis, and aided bone metastasis management	No control group, case-specific adjustments	A. vera Gel (Acemannan) plays a role in pain mitigation and bone regeneration
(Teymori et al., 2023)	Iran	Experimental Study	Evaluate the osteoconductive effect of polycaprolactone (PCL) scaffold treated with A. vera on adipose-derived mesenchymal stem cells (ADSCs)	In vitro study with ADSCs	—	21 days	A. vera-modified PCL scaffold	Osteogenic differentiation, ALP activity, calcium content, gene expression (RUNX2, COL1, OC, ON)	A. vera-treated PCL scaffold improved biocompatibility, promoted osteogenic differentiation, increased ALP activity and calcium deposition	Controlled for scaffold properties and ADSC culture conditions	A. vera-modified PCL scaffold has osteoconductive potential and may enhance bone regeneration
(Trinh et al., 2020)	Thailand & Vietnam	Case Report	Evaluate the effect of acemannan-induced bone regeneration in lateral sinus augmentation using CBCT and histopathology	A 57-year-old female patient with an atrophic posterior maxilla	57 years	6 months	Lateral sinus lift using an acemannan sponge, with radiographic and histopathological assessment.	CBCT-based bone height measurement, histological bone formation assessment	Acemannan sponge induced new bone formation, increased alveolar bone height, and demonstrated biocompatibility.	Controlled for baseline bone height and healing period	Acemannan sponge shows potential as a biomaterial for sinus lift procedures and bone regeneration
(Godoy et al., 2018)	Thailand & Belgium	Experimental Study	Investigate the effect of acemannan on calvarial defect healing in skeletally mature rats	35 female Sprague-Dawley rats	6 months	4 weeks	Acemannan sponges at different concentrations (1mg, 2mg, 4mg, 8mg) in calvarial defects	Bone surface, bone volume, tissue mineral density (TMD), and histopathological evaluation	Acemannan enhanced bone regeneration, with 1mg and 2mg improving bone surface and volume, and 4mg and 8mg improving tissue mineral density.	Controlled for bone healing stage and acemannan concentration variations	Acemannan significantly promotes bone healing and could be an effective bioactive agent for bone regeneration
(Soares et al., 2019)	Brazil & Portugal	Experimental Study	Evaluate the effect of A. vera combined with mesenchymal stem cells from dental pulp on bone regeneration in tibial defects	75 Rattus norvegicus rats	—	7, 15, and 30 days	Collagen sponge (HemosponÂ®) with and without A. Vera and human dental pulp stem cells (hDPSCs)	Histological analysis, immunohistochemistry for osteopontin expression, and immunofluorescence	A. vera combined with hDPSCs reduced inflammation and promoted early bone repair, with osteopontin expression correlating with bone formation	Controlled for treatment groups and observation periods	A. vera and hDPSCs enhance bone regeneration by modulating inflammation and supporting bone formation in tibial defects

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Authors & Year	Country	Study Type	Objective	Participants	Mean Age	Duration of Follow-up	Intervention	Outcome Measures	Key Findings	Adjustments	Conclusion
(Vu et al., 2021)	Thailand & Vietnam	Randomized Controlled Trial	Investigate the effect of acemannan on tooth socket healing using CBCT over 12 months	35 patients with partial impaction of lower third molars	18-25 years	12 months	Tooth socket treated with either 20 mg or 50 mg acemannan sponges versus spontaneous blood clotting (control)	Socket volume reduction measured via CBCT at 3, 6, and 12 months postoperatively.	The 50 mg acemannan group showed a significantly greater reduction in socket volume at all time points, indicating enhanced bone healing.	Controlled for baseline socket volume and healing time points	Acemannan sponges accelerate bone healing in tooth sockets and may serve as a biomaterial for post-extraction bone regeneration
(Deesricharoenkiat et al., 2022)	Thailand & Sweden	Randomized Controlled Trial	Investigate the effect of acemannan in guided bone regeneration (GBR) with simultaneous implant placement in the anterior maxilla	20 patients needing single-tooth implants in the anterior maxilla	50.5 years	6 months	Test group: deproteinized bovine bone with particulate acemannan; Control group: deproteinized bovine bone only	CBCT-based measurement of vertical and horizontal buccal bone changes at 0, 2, 4, 6, and 8 mm from the implant platform.	Dimensional reduction of buccal bone was significantly lower in the test group at 3 months but not at 6 months. Acemannan enhanced the early stability of regenerated tissue.	Controlled for initial bone volume, healing time points, and implant positioning	Acemannan is a safe biomaterial that improves GBR outcomes in the early stages, but long-term benefits remain inconclusive.
(Soltani and Alizadeh, 2022)	Iran	Experimental Study	Investigate the osteogenic potential of A. vera-incorporated starch-64S bioactive glass-quail eggshell scaffolds for bone regeneration.	In vitro study using MG-63 osteoblast-like cells	—	14 days	Freeze-dried starch-BG-AV-QE scaffolds with varied compositions	Cell viability, ALP activity, calcium deposition, osteogenic marker expression (osteocalcin & osteopontin)	Scaffolds exhibited high biocompatibility, enhanced osteogenic differentiation, and mineralization potential	Controlled for scaffold composition and biomaterial properties	A. vera-incorporated scaffolds show promise as biodegradable, bioactive materials for bone regeneration applications
(Jansisyanont et al., 2016)	Thailand	Clinical Trial	Evaluate the effect of acemannan on alveolar bone healing after third molar extraction	99 patients undergoing mandibular third molar extraction	—	3 months	Application of acemannan sponge in the extraction socket	Radiographic bone density, clinical healing assessment	Acemannan increased bone density by 15-17%, enhancing alveolar healing	Controlled for baseline bone density and surgical trauma	Acemannan sponge is effective in promoting post-extraction alveolar healing
(Ghoname et al., 2017)	Egypt	Clinical Trial	Compare acemannan with formocresol in primary tooth pulpotomy	40 children with primary molar pulpitis	4-7 years	6 months	Acemannan vs. formocresol as a pulpotomy agent	Clinical success rate, radiographic healing	Acemannan induced better dentin bridge formation and lower inflammation	Controlled for initial pulp condition and follow-up duration	Acemannan is a promising alternative to formocresol in pulpotomy
(Tahmasebi et al., 2020)	Iran	Experimental Study	Investigate A. vera gel-blended PHBV scaffolds for bone tissue engineering.	In vitro study with human-induced pluripotent stem cells (iPSCs)	—	2 weeks	PHBV nanofibrous scaffold coated with A. vera gel	Cell viability, osteogenic differentiation, ALP activity, calcium content, gene expression (RUNX2, COL1, OC, ON)	A. vera gel improved biocompatibility, promoted osteogenic differentiation, increased ALP activity, and calcium deposition	Controlled for scaffold composition and stem cell culture conditions	A. vera gel-blended PHBV scaffold has osteoinductive potential and can be a promising bioimplant for bone regeneration

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Continued of Table 3.

Authors & Year	Country	Study Type	Objective	Participants	Mean Age	Duration of Follow-up	Intervention	Outcome Measures	Key Findings	Adjustments	Conclusion
(Banerjee and Bose, 2019)	United States	Experimental Study (In vitro, in vivo)	Assessing osteoblast cell viability and bone formation through evaluating the effects of acemannan-dipped coating on doped hydroxyapatite (HA)-coated titanium implants	In vitro with cultured osteoblast cells In vivo study with adult rats (distal femur model)	—	5 weeks	Titanium implants coated with silver oxide and silica-doped hydroxyapatite, and dip-coated with acemannan and chitosan versus identical doped hydroxyapatite-coated implants without acemannan or chitosan coatings.	Osteoblast cell viability, osseointegration quality	Chitosan-mediated controlled release of acemannan, enhanced osteoblast viability, strong osseointegration with good integration of the tissue-implant interface, increased new bone formation at 5 weeks	The controlled release system (via chitosan) was key to modulating biological effects	Improved early osseointegration and bone formation compared to controls when using acemannan-coated implants
(Chansamart et al., 2023)	Thailand	Case report	Assessing the efficacy of acemannan sponges combined with periodontal surgery on periodontal regeneration in chronic periodontitis patients	3 patients with chronic periodontitis and $\geq$ 6 mm pockets with 2-or 3-walled vertical infrabony defects	51-57 years	5 years	Minimally invasive periodontal surgery with placement of acemannan sponges in defects	Clinical attachment level (CAL), probing pocket depth (PPD), percentage bone fill via radiographs	Acemannan sponges resulted in clinical improvement and radiographic bone fill, more in contained defects (three-walled) in comparison with less contained defects (two-walled)	No control group, measurement reliability was examined	Acemannan sponges when used particularly in contained defect morphologies, may enhance long-term periodontal regeneration
(Rasoulian et al., 2019)	Iran	Experimental Study (In vitro, in vivo, in silico)	Investigate A. vera constituents binding to BMPR1A for bone regeneration	In vitro with osteoblast-like MG-63 cells; In vivo in rats	—	60 days (in vivo)	A. vera gel (Aloin, Aloe-emodin, etc.)	Cell viability, LDH release, ROS, gene expression (BMP2, ALP, OCN), bone density	Enhanced osteogenesis, increased BMP2, ALP, and OCN expression, and higher bone density	Controlled experimental conditions	A. vera shows osteoconductive and antioxidant effects; potential as a bone substitute
(Boonyagul et al., 2014)	Thailand	Experimental Study (In vitro, in vivo)	Evaluate the effect of acemannan on BMSCs proliferation, differentiation, ECM synthesis, mineralization, and bone formation.	In vitro study with rat BMSCs; In vivo rat tooth extraction model	—	4 weeks (in vivo)	Acemannan polysaccharide from A. vera	DNA synthesis, VEGF, BMP-2, ALP activity, BSP, OPN expression, mineralization, BMD	Acemannan increased BMSC proliferation, osteogenic differentiation, VEGF, BMP-2, ALP, BSP, OPN expression, enhanced mineralization, and BMD.	Controlled experimental conditions	Acemannan promotes bone formation, suggesting potential as a natural biomaterial for bone regeneration
(Chantarawaratit et al., 2014)	Thailand	Experimental Study (In vitro, in vivo)	Evaluate acemannan sponges for alveolar bone, cementum, and periodontal ligament regeneration in furcation defect.	In vitro with human periodontal ligament cells; In vivo canine furcation defect model	—	60 days (in vivo)	Acemannan sponges	DNA synthesis, GDF-5, Runx2, VEGF, BMP-2, type I collagen expression, ALP activity, mineralization, histomorphometry	Acemannan sponges significantly increased cell proliferation, gene expression, ALP activity, mineral deposition, and accelerated alveolar bone, cementum, and periodontal ligament regeneration	Controlled experimental conditions	Acemannan sponges are effective biomolecules for periodontal tissue regeneration.

Table 4. Comparative overview of acemannan and other established agents used in Guided Bone Regeneration (GBR).

Feature	Acemannan	Platelet-Rich Fibrin (PRF)	β-Tricalcium Phosphate (β-TCP)	rhBMP-2
Source/Origin	Natural (Aloe vera)	Autologous (Patient's blood)	Synthetic	Recombinant DNA
Primary Mechanism	Osteoinductive, Immunomodulatory	Bioactive (Growth factors)	Osteoconductive scaffold	Potently Osteoinductive
Advantages	Low cost, high biocompatibility, anti-inflammatory, readily available	Autologous (no disease transmission), provides growth factors	Predictable resorption, no disease risk, provides a scaffold	High osteoinductive potential, rapid bone formation
Disadvantages	Mild osteoinductive potential, variable formulations, rapid resorption	Technique-sensitive preparation, variable growth factor concentration	Not osteoinductive, brittle, variable resorption rates	High cost, significant side effects (inflammation, swelling), risk of ectopic bone
Clinical Use	Socket preservation, adjunct to GBR, periodontal defects	Sinus lifts, ridge augmentation, soft tissue healing	Scaffolding for significant defects, sinus augmentation	Severe bone defects, spinal fusion, non-unions

1. **Standardized protocols:** Optimizing acemannan concentrations, delivery systems (e.g., 3D-printed scaffolds), and treatment durations across studies to facilitate reproducibility.
2. **Mechanistic studies:** Elucidating signaling pathways (e.g., BMP/SMAD, Wnt/β-catenin) through omics technologies (transcriptomics, proteomics) to refine targeted applications.
3. **Clinical trials:** Large-scale RCTs comparing acemannan with established biomaterials (e.g., PRF, rhBMP-2) in GBR, sinus lifts, and critical-size defects, with extended follow-ups ($>$ 2 years).
4. **Safety profiles:** Investigating immunogenicity, cytotoxicity thresholds, and interactions with comorbid conditions (e.g., diabetes, osteoporosis).
5. **Combination therapies:** Investigating synergies with stem cells, growth factors, or antimicrobial agents to maximize regenerative outcomes.
6. **Regulatory approval and manufacturing standardization:** For acemannan to become a clinical product, establishing standardized Good Manufacturing Practices (GMP) for its extraction, purification, and formulation is critical to ensure consistency and safety. Future efforts should also focus on generating the robust safety and efficacy data needed to navigate regulatory approval pathways (e.g., via the U.S. Food and Drug Administration), which is essential for clinical applications.

Preclinical and preliminary clinical evidence validates acemannan's promise as an inexpensive and natural substitute for synthetic growth factors in bone healing. Acemannan's anti-inflammatory and immunomodulatory effects, which are demonstrated in animal models and human trials, may benefit high-risk patients like those with periodontal disease or extraction sockets by minimizing complications of fibrosis or infection. Acemannan sponges/scaffolds would make GBR procedures clinically easier by eliminating the donor-site morbidity of autografts. Its potential to expedite alveolar ridge preservation in dental use can lead to shorter implant placement times. As summarized in Table 3, acemannan has a special clinical niche compared to other agents in Guided Bone Regeneration (GBR). While it lacks the high osteoinductive potency of costly rhBMP-2, it provides a clear advantage with its combination of immunomodulatory effects, high safety profile, and low cost. This makes acemannan a valuable and safe adjunctive material for GBR, particularly in applications like socket preservation where its anti-inflammatory properties are beneficial. However, clinicians should wait for further evidence of its efficacy in humans before general application.

Conclusion

This systematic review confirms that acemannan, from *Aloe vera*, is a promising natural agent for bone regeneration. It effectively promotes osteogenic differentiation and enhances the immune response. It can be a low-cost and safe alternative to traditional growth factors. Further research, including large-scale randomized clinical trials, must standardize its use and confirm long-term efficacy before clinical adoption.

Authors contributions
Authors have contributed equally in preparing and writing the manuscript.

Availability of data and materials
The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Conflict of interests
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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