REVIEW ARTICLE

Role of Alginate-based Scaffolds for Periodontal Regeneration of Intrabony Defects: A Systematic Review

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Abstract

Aim: This systematic review aims to evaluate the effectiveness of scaffolds based on alginate in the regeneration of intrabony defects in periodontal tissue.

Materials and methods: A thorough exploration was conducted in databases such as "PubMed," "Google Scholar," "Cochrane Library," and "Science Direct," adhering to predefined eligibility criteria. Following meticulous screening, studies involving *in vitro* and *in vivo* assessments of alginate's efficacy as a scaffold were chosen for inclusion.

Results: The eight chosen studies investigated the involvement of alginate-based scaffolds in the regeneration of periodontal tissues. Among these, five *in vivo* studies utilized histologic and histometric analyzes, while the remaining *in vitro* studies examined bone regeneration by assessing alkaline phosphatase activity (ALP) through various staining methods. Comparisons were made with other biopolymers, molecules, or stem cells. Across all eight studies, alginate scaffolds consistently demonstrated superior outcomes in terms of bone regeneration.

Conclusion: Combining alginate with other biopolymers can enhance its regenerative efficacy. Therefore, future researchers should concentrate on integrating novel biopolymers for further improvement.

Clinical significance: Scaffolds made from alginate possess the ability to restore tissue lost as a result of periodontitis, demonstrating significant clinical relevance.

Keywords: Alginate, Intrabony defects, Periodontitis, Periodontal regeneration, Polymers, Scaffold.

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Introduction

Periodontitis is a chronic inflammatory state caused by microbial infiltration, triggering an inflammatory reaction that damages the supportive tissues around the teeth, such as the gingiva, bone, and periodontal ligament.[1] While nonsurgical mechanical treatments can typically achieve the resolution of basic periodontal inflammation and eliminate microbial biofilm in subgingival regions, the full restoration of structures supporting the teeth, particularly in cases involving alveolar bone defects, necessitates the regeneration of affected areas. In response to this challenge, diverse biomaterials have been created, playing a constructive role in advancing the field of oral tissue engineering.[2]

In the context of regenerative procedures, it is customary to employ bone grafts (BGs) to promote the regeneration of supporting structures while preventing the migration of epithelium. Autografts have been observed to support new attachment apparatus. Similarly, other grafts (xenograft and allograft) have not demonstrated substantial improvements in achieving attachment. Consequently, there exists a lack of a robust biological rationale for regenerating the periodontium, posing a fundamental challenge shared by all bone fillers.[3]

The challenge of regenerating complex damaged or absent tissues becomes more formidable as the structure's complexity increases. Revitalizing the supportive structures of lost teeth involves a highly intricate biological process that requires the coordination of cellular and molecular interactions.[4] A common obstacle is the swift migration of epithelial tissues into the wound, impeding periodontal regeneration.[5] To tackle this issue, regenerative techniques have been employed, such as the placement of a barrier membrane for selective repopulation of the cells, leading to bone regeneration. Traditional procedures, like periodontal flap surgery, provide sufficient accessibility to eradicate the etiological factors from the root surfaces. Nonetheless, these methods have limited potential when it comes to fully restoring or reconstructing the diverse components of periodontal tissues.[6]

Scaffolds employed in tissue engineering commonly consist of natural and synthetic polymers tailored to exhibit properties similar to the extracellular matrix. One noteworthy natural polymer is alginate, derived from brown seaweeds. Chemically, alginate is a linear polymeric acid. When exposed to specific divalent cations at low concentrations, it can form stable hydrogels through ionic interactions.[7] Alginate is recognized for its high hydrophilicity, biocompatibility, and cost-effectiveness. Due to its robust hydrophilicity, cells will easily imbibe onto alginate-based scaffolds. Following cross-linking, alginate becomes insoluble in aqueous solutions. These biomaterials function as three-dimensional (3D) frameworks, with surfaces conducive to cellular attachment,

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growth, and specialization, creating an environment favorable for tissue regeneration.[8] Moreover, whether obtained from natural sources or synthesized, these biomaterials can interact directly with living tissues without eliciting adverse immune responses. When introduced to the affected site, these innovative biomaterials initiate a series of processes triggering regenerative cellular responses and replacing the absent tissue; hence, there is a need to develop such biomaterials for regeneration purposes. Therefore, this systematic review aimed to assess the effectiveness of alginate-based scaffolds in regenerating intrabony defects and hypothesized that there is a difference in the effectiveness of alginate-based scaffolds on bone regeneration.

Materials and Methods

Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines for systematic review have been followed. The population, intervention, control, and outcomes (PICO) for this study was the population with intrabony defects, and the intervention involved alginate in conjunction with other biomaterials, molecules (titanium dioxide), or stem cells like bone marrow stromal cells (BMSCs) compared with comparing alginate-based scaffolds alone or other scaffolds (collagen, chitosan, and polylactic acid) to evaluate their effectiveness in promoting bone regeneration. The research question was, are alginate alone as a scaffold or other scaffolds effective for bone regeneration of intrabony defects compared to alginate in conjunction with other biomaterials, molecules or stem cells? The search strategy included publications of interest within the scope of this focused, systematic review, which were searched in PubMed, Google Scholar, Cochrane Library, and Science Direct by using the search terms "intrabony defects" and "alginate" or "Sodium alginate" or "calcium alginate" or "alginic acid," and "periodontal regeneration." Relevant studies from the past 15 years were selected. The search duration was from 28th March to 4th August 2023. The eligibility criteria were research encompassing intrabony defects, incorporating randomized controlled trials (RCTs), *in vitro* and *in vivo* studies utilizing scaffolds based on alginate. The investigation explored the use of alginate-based scaffolds in comparison with other biomaterials, growth factors, and stem cells. Exclusion criteria comprised studies involving calvarial defects, those related to periimplantitis, case reports, reviews, abstracts only, and literature published in languages other than English.

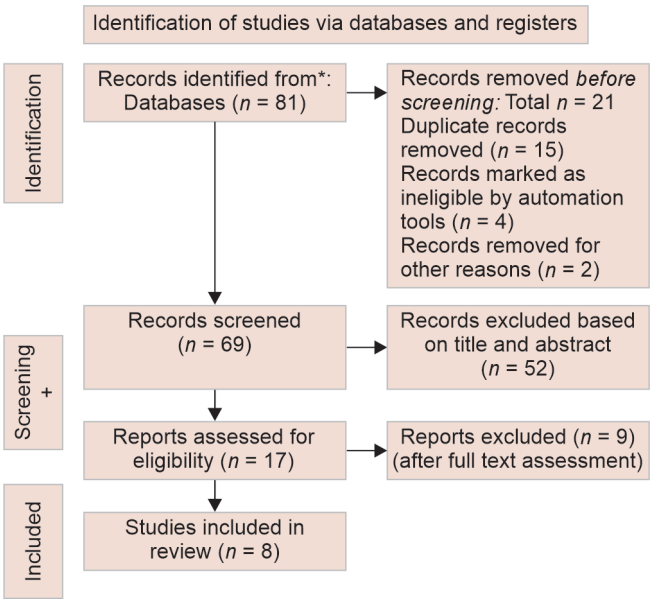
Bone regeneration in terms of mineralized bone volume (BV) and total volume (TV) was evaluated. Two reviewers independently extracted data from the included studies using a tailored data extraction method, which was then entered into an electronic spreadsheet. Information such as the authors' names, year of publication, study design, study groups, bone regeneration measurement, and results were meticulously recorded. Two review authors evaluated the risk of bias (RoB). The RoB *in vitro* studies were assessed using the updated Cochrane RoB instrument (RoB2), while for *in vivo* studies, the QUINN tool (scoring criteria 0, 1, and 2) and SYRCLE tool (scoring criteria—yes, no, and unclear) were utilized.

Results

Search Methodology

Following the predefined eligibility criteria, a total of 81 articles were identified through PubMed, Cochrane Library, Science Direct, and Google Scholar databases. After eliminating duplicate records using automated tools, the initial pool of 69 records underwent screening. Of these, 52 records were excluded based on title and abstract, leaving 17 records for further eligibility assessment. After a thorough evaluation of the full texts, nine reports were excluded, and ultimately, eight records were retained as they met the eligibility criteria (Flowchart 1).

Flowchart 1: Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flowchart



Search Result

An exploration of electronic databases identified a total of 81 publications. After eliminating duplicates, 69 documents remained. The screening of titles and abstracts led to the exclusion of 52 papers, leaving 17 papers for full-text evaluation. The examination of these 17 full-text publications resulted in the selection of eight studies that met the inclusion criteria for further analysis (Table 1).

In the chosen set of eight studies, alginate was employed in conjunction with various biomaterials, molecules, or cells. Among these, four studies were conducted *in vivo*, three were *in vitro*, and one study encompassed both *in vivo* and *in vitro* experiments. The materials combined with alginate included polylactic-co-glycolic acid (PLGA), pure polylactic acid (PLA), and polycaprolactone. Additionally, other molecules such as basic fibroblast growth factor, periodontal ligament stem cells (PDLSCs) and human BMSCs were utilized in conjunction with alginate. This review aimed at measuring bone regeneration and review assessed bone regeneration levels by measuring cellular proliferation and viability through 3-(4, 5-dimethylthiazolyl-2)-2, 5-diphenyltetrazolium bromide (MTT) and Alamar Blue assays, as well as mineralization levels assessed using von Kossa, alizarin Red S (ARS), Masson's trichrome staining, immunofluorescent staining for osteocalcin (OCN), alkaline phosphatase (ALP) activity, and microcomputed tomography (CT) analysis.

In Vivo Studies Involved in the Use of Different Animal Models

A total of 30 Sprague Dawley rats with mandibular defects, 45 adult male Japanese white rabbits with mandibular defects, three adult M. fascicularis with mandibular premolar defects, and 15 mongrel dogs with mandibular premolar defects. Various parameters were analyzed in these studies using different measurement methods.

Table 1: Characteristics table of included studies

Serial number	*Author and year*	*Study design*	*Groups*	*Sample size*	*Site*	*Bone regeneration measurement*	*Bone regeneration measurement method*	*Follow-up period*	*Results*	*Observation*
1	Elango et al. 2020[9] (Shanghai, China)	*In vitro*	Control—collagen scaffolds Positive control—collagen, TiO Experimental—collagen, alginate and TiO, scaffold	N/A	N/A	cALP activity of hPLFcells OCN of hPDLFs	ARS	21 days	At day 21 CALP (mol/minute/mg protein) Control—8; PC—15 Experimental—20 OCN (mmol) At day 21 Control—20; PC—30 Experimental—40 ($p < 0.05$)	The experimental group supported differentiation of hPDLF cells as compared to the control group
2	Chang et al. 2017[10] (Taipei, Taiwan)	*In vivo* (Sprague–Dawley rats)	Each group—$n = 10$ Control—unfilled defects Experimental A—nonoxidized RAM Experimental B—oxidized RAM	30 male rats	4 mm diameter defect was created on the lateral border of mandible	MV/TV and BV/TV (New bone formation)	4 mm micro-CT analysis (Masson trichromatic staining)	4 weeks	MV/TV control—15% Experimental A—55%; experimental B—60% BV/TV; control—16% Experimental A—30%; experimental B—35%; $p < 0.001$ Histologic evaluation Control—little NB deposited Experimental A and B—defect was almost filled with NB; $p < 0.001$	Oxidized RAM was more helpful in regeneration of bone when compared with nonoxidized or unfilled group
3	Chen et al. 2017[11] (Osaka, Japan)	*In vitro* *In vivo*	Control—PLA Experimental—calcium alginate A—12.5 mg/mL B—25 mg/mL	Six rabbits	Mandible of rabbits	Absorbance values (490 nm); BV/TV	MTT assay (hPDLCs); Micro-CT scanning (ARS)	28 days	OD value control—0.6 ExperimentalA—0.8; experimental B—0.9 Number of mineralized nodules; control—40; experimental A—70; experimental B—110 ($p < 0.05$ vs control) BV/TV control—22%; experimental A—35%; experimental B—50% ($p < 0.05$)	Experimental group had superior osteoinductive property in comparison to the PLA
4	Duruel et al. 2017[12] (Ankara, Turkey)	*In vitro*	Control—chitosan Experimental A—chitosan/alg B—chitosan/PLGA C—chitosan/alg/PLGA	N/A	N/A	Optical density	MTT assay (osteoblasts); mineralization assay (Von Kossa staining)	12 days	OD values Control—1.7; Experimental A—2.5; exp B—2.5; experimental C—2.7 Von Kossa staining—staining was more evident in chitosan/PLGA and hybrid structure	Hybrid scaffold (group C) showed proliferation of osteoblasts the most
5	He et al. 2008[13] (Hang Zhou, China)	*In vivo* (adult male Japanese white rabbits)	$n = 45$ rabbits $n = 3$ each group Control—no membrane Experimental A—collagen membrane Experimental B—calcium alginate film	45	5 mm circular defect created in mandible bilaterally	Histologic evaluation; histometric assessment (defect diameter)	H&E staining	8 weeks	Histologic evaluation Control—cartilage and bone trabeculae were immature Experimental A and B—defects were filled with reticular trabeculae, lamellar bone was observed Defect diameter (mm^2) Control—7.49; experimental A—12.23; experimental B—19.39; $p < 0.01$ compared to no membrane	Calcium alginate was more effective than collagen membrane

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Serial number	*Author and year*	*Study design*	*Groups*	*Sample size*	*Site*	*Bone regeneration measurement*	*Bone regeneration measurement method*	*Follow-up period*	*Results*	*Observation*
6	Srinivasan et al. 2011[14] (Kochi, India)	*In vitro*	Control—alginate Experimental A—Alg/nBGC 0.5% Experimental B—Alg/nBGC 1%	N/A	N/A	Biomineralization assay; cell viability (hPDLF) ALP activity of hPDLF cells to OB at 21 days	XRD spectra; Alamar Blue assay	21 days	Biomineralization assay peaks; control—11.7 experimental A—31.8; experimental B—46.7 Alamar blue assay OD control—0.6; experimental A—0.5; experimental B—0.5 ALP (ng/mL) Control—7; experimental B—16	Composite scaffolds were more effective than alginate alone
7	Wang et al. 2019[15] (Nijmegen, Netherlands)	*In vivo* (*Macaca fascicularis*)	Three adult monkeys Control—calcium phosphate cement Experimental group—BMP loaded PGA	3	Mandibular 2nd premolar bilaterally	Histologic evaluation; histometric assessment	H&E staining and Masson's trichromatic staining; bone volume regeneration %		Increase in collagen formation in experimental group as compared to control in 12 weeks Histometric assessment Volume of bone regeneration (%) Control—40 Experimental—60 ($p < 0.01$)	Experimental group promoted bone regeneration when compared to the control group
8	Weng et al. 2006[16] (Shanghai, China)	*In vivo* (Mongrel dogs)	15 dogs $n = 5$ each group Control A—no scaffold Control B—CaAlg alone Experimental—CaAlg/BMSCs	15	Mandibular premolar	ALP activity of BMSCs; radiographic assessment	Von Kossa staining; BR and DH	6 weeks	Von Kossa staining—more mineralized bone nodules formation in control B and experimental group as compared to control A ALP activity-positive staining with darker periphery in experimental and control B; BR (mm) control A—0.98; control B—0.78; experimental—2.43 DH (mm) control A—4.97; control B—4.74; experimental—5.05 ($p < 0.01$)	BMSC loaded scaffold showed potential for bone regeneration

ALP, alkaline phosphatase; BMP, bone morphogenetic protein; BMSCs, bone marrow stem cells; BR, bone regeneration; DH, defect height; Exp, experimental; hPDLF, human periodontal ligament fibroblasts; MV/TV, mineralized volume/total volume; NB, new bone; nBGC, nano bioactive glass composite; OCN, osteocalcin; OD, optical density; PGA, polyglycolic acid; RAM, RGD-modified alginate membrane

Bone Volume in Comparison with Total Volume

In a study conducted by Chang et al.,[9,10] micro-CT analyzes were performed on a sample that included mineralized volume (MV)/TV and BV/TV measurements at 4 weeks. Histological assessment of new bone formation was conducted through Masson trichromatic staining, revealing that MV/TV in the control group was 15%, while in the test group I group, it was 60%. Similarly, BV/TV in the control group was 16%, whereas in the other group, it was 35%. Wang et al.[11–15] also conducted a similar assessment, measuring the volume of bone regeneration as a percentage. A significant difference was observed, with the control group at 40% and the experimental group at 60%. The histological assessment indicated a *p*-value of <0.001.

Staining (Hematoxylin and Eosin, Von Kossa, Alamar Blue, Alizarin Red, and Masson's Trichromatic Staining)

In the study by He et al.,[13] the evaluation of defect diameter was carried out using hematoxylin and eosin (H&E) staining. The defect diameter in mm^2 was assessed, revealing that in the control group, it was 7.49, whereas in experimental groups I and II, it was 12.23 and 19.39, respectively. Weng et al.[16] measured the ALP activity of BMSCs using Von Kossa staining. The results indicated increased formation of mineralized bone nodules in the calcium alginate scaffold. In *in vitro* studies, Duruel et al.[12] and Chen et al.[11] evaluated MTT assay results for cementoblasts and human periodontal ligament cells (hPDLCs), respectively. The absorbance values at days 6 and 12 were obtained, showing 1.7 and 0.6 for the control group and 2.5 and 0.9 for the experimental group, respectively. Elango et al.[9] and Srinivasan et al.[14] conducted cytosolic alkaline phosphatase (cALP) activity assessments of human periodontal ligament fibroblast (hPLF) cells using Alamar Blue stain and ARS, respectively. Optical density (OD) values were obtained, and higher peaks were observed for the experimental group. Cell viability in a study by Srinivasan et al. was assessed through an Alamar Blue assay, and the OD values showed a significant difference between the control and experimental groups ($p < 0.001$).

Biomineralization Assay

Srinivasan et al.[14] conducted a biomineralization assay using X-ray diffraction (XRD) spectra. The peaks for the control group were found to be 11.7, while in experimental groups I and II, they were 31.8 and 46.7, respectively.

Risk of Bias Assessment

The evaluation of study quality utilized the RoB II tool, with the QUINN tool applied for *in vitro* studies and the SYRCLE tool for *in vivo* studies. In the realm of *in vitro* research, Duruel et al. study demonstrated a low RoB, while Srinivasan et al. and Elango et al. studies exhibited a moderate RoB (Tables 2 and 3). In the context of *in vivo* studies, there was minimal selection bias, low-performance bias, elevated detection bias, uncertain selective outcome reporting bias, high attrition bias, and indeterminate other bias (Table 4).

Discussion

Increased understanding of the causes of periodontal disease and the responses of tissues to various surgical techniques has led to significant advancements in periodontal therapy. In the field of periodontal regeneration, ongoing research and presentations focus on innovative therapies and additions to established treatment methods. Various approaches to periodontal regeneration, such as barrier membranes, BGs, and growth factors, have been employed.[17] Substantial histological evidence in humans supports the use of BGs, indicating the regeneration of the periodontal unit with the development of new cementum, alveolar bone, and a functional periodontal ligament. The introduction of nanotechnology has spurred the creation of numerous materials for treating bone deformities, showing promising outcomes.[18]

The present systematic review provided an updated insight into the utilization and effectiveness of alginate-based scaffolds, whether used independently or in combination with other biomaterials, molecules, and cellular components. Alginate, owing to its diverse properties, has been a staple in bone regeneration techniques for an extended period. The analysis of the latest literature emphasizes that this polymer can be effectively paired with other naturally or synthetically derived polymers, resulting in the formation of scaffolds. These scaffolds enable the simultaneous regeneration of various tissues within the periodontal apparatus.

Table 3: Inference for RoB for *in vitro* studies

Study	*Score*	*Percentage*	*RoB*
Elango et al.[9] 2020	17/24	70.8%	Low
Duruel et al.[12] 2017	13/24	54.1%	Medium
Srinivasan et al.[14] 2011	12/24	50%	Medium

Table 2: Risk of bias assessment for *in vitro* studies

Serial number	*Quinn tool criteria*	*Elango et al.[9] 2020*	*Duruel et al.[12] 2017*	*Srinivasan et al.[14] 2011*
1	Clearly stated aims/objectives	2	2	2
2	Detailed explanation of sample size calculation	1	0	1
3	Detailed explanation of sampling technique	1	1	0
4	Details of comparison group	2	2	2
5	Detailed explanation of methodology	2	2	2
6	Operator details	1	0	0
7	Randomization	1	0	0
8	Method of measurement of outcome	2	2	1
9	Outcome assessor details	1	0	0
10	Blinding	0	0	0
11	Statistical analysis	2	2	2
12	Presentation of results	2	2	2

Table 4: RoB assessment for *in vivo* studies

Syrcle's criteria	*Chang et al.*[10] *2017*	*Chen et al.*[11] *2017*	*He et al.*[13] *2008*	*Wang et al.*[15] *2019*	*Weng et al.*[16] *2006*
Random group allocation (selection)	Yes	Yes	Unclear	Yes	No
Groups similar at baseline (selection)	Yes	Yes	No	Yes	Yes
Blinded group allocation (selection)	Yes	Yes	No	Yes	Unclear
Random housing (performance)	Unclear	Yes	Yes	Yes	No
Blinded interventions (performance)	Yes	Yes	No	Yes	Unclear
Random outcome assessment (detection)	Yes	No	Unclear	No	Yes
Blinded outcome assessment (detection)	No	No	Yes	No	Yes
Selective outcome reporting bias	Unclear	Unclear	Unclear	Unclear	Unclear
Attrition bias	Unclear	No	No	Yes	Yes
Other bias	Unclear	No	No	Unclear	Unclear

This versatility underscores the rationale for employing alginate-based scaffolds in the realm of periodontal tissue engineering. Alginate, characterized by its anionic and hydrophilic nature, stands out as one of the most abundant biosynthesized biomaterials globally, primarily sourced from brown seaweed.[19]

Creating an appropriate biological microenvironment that supports the growth and differentiation of periodontal cells poses a significant challenge in the treatment of periodontitis. An innovative strategy involving the development of a 3D matrix composed of collagen, sodium alginate, and titanium oxide has been introduced. This combination of materials is designed to enhance osteogenesis. Furthermore, hPLF cells differentiated within the 3D matrix exhibit heightened secretion levels of noncollagenous proteins. Scaffolds made from alginate composites, which include nanobioactive glass-ceramic particles (nBGC), were developed to enhance the regeneration of periodontal tissues. The introduction of nBGC into these scaffolds notably increased the ALP activity in human periodontal ligament fibroblast (hPDLF) cells cultured on them, as evidenced in the study conducted by Srinivasan et al. in 2011. Furthermore, other research, such as the work by Liao et al., has also illustrated the beneficial effects of mesoporous bioactive glass modified with alginate on the repair of bone tissue.[20]

Alkaline phosphatase (ALP) serves as a pivotal early indicator for osteogenic differentiation and osteoblast biochemistry. Culturing hPDLF cells on composite scaffolds of alginate/nBGC showed that ALP activity peaked around the 7th day and gradually declined thereafter. This reduction aligns with previous research, such as the study by Donzelli et al.[21]

The success of periodontal regeneration relies on the coordinated interaction between competence factors and progression factors. However, the limited substantivity of these growth factors restricts their therapeutic action. To overcome this limitation, scientists have developed chitosan-based carriers/scaffolds loaded with microparticles to enable the controlled and sequential release of insulin-like growth factor 1 (IGF-1) and bone morphogenetic protein 6 (BMP-6).[22] Alginate and PLGA facilitated the early and sustained release of IGF-1 and BMP-6, respectively. In cell culture experiments, it became evident that the chitosan/alginate/PLGA hybrid scaffolds induced a more effective proliferation and osteoblastic differentiation of cementoblasts compared to chitosan scaffolds lacking IGF-1 and BMP-6. This controlled delivery system holds promise for enhancing the effectiveness of growth factors in the context of periodontal regeneration, as discussed by Vo et al.[23]

The periodontium, an intricate structure encompassing various tissues, such as cementum, bone, periodontal ligament, and gingival tissue, presents a challenge for simultaneous regeneration. Utilizing alginate-based bilayered and trilayered scaffolds emerges as a feasible strategy for achieving this goal. In this multilayered approach, a substrate is immersed in an alginate solution with cationic properties, leading to the deposition of a thin film on the surface and the creation of distinct layers.[24] Each layer serves a specific function aligned with the therapeutic actions of its constituent components. For example, marrow-derived mesenchymal stem cells hold promise for contributing to periodontal regeneration, given their ability to differentiate into cementum, bone, and periodontal ligament.

This systematic review has a few limitations that need acknowledgment. Firstly, it should be noted that the study involves outcomes from regenerative procedures performed in defects with diverse shapes and characteristics, attributed to the use of different species *in vivo* analyzes and the incorporation of scaffolds with various biomolecules. Furthermore, the lack of uniformity in the study groups may potentially contribute to the diversity observed in the results.

Conclusion

This systematic review has highlighted the considerable potential of alginate for regenerating periodontal tissues. Nevertheless, the integration of growth factors and stem cells into scaffolds based on alginate holds the promise of enhancing its biological characteristics, resulting in more efficient regeneration. Furthermore, our analysis emphasizes that when combined with other polymers, it has the capacity to facilitate the simultaneous regeneration of various periodontal supporting tissues.

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