Nanoparticle-Based Therapeutics for Regenerative Dentistry: A Systematic Review

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Abstract

Background: Nanotechnology's addition may enable bioactive systems that can control cell responses and facilitate tissue repair. Several types of nanoparticle-based materials are being examined for their potential to regenerate the dentin-pulp complex and promote healing of peri-implant bone.

Objective: This systematic review has assessed *in vitro* studies on various nanoparticles and their potential contributions to the regenerative processes of dental tissues.

Materials and Methods: This review was conducted according to PRISMA 2020 guidelines. The review evaluated studies published between 2010 and 2020 that used the electronic databases PubMed (MEDLINE), Scopus, and Web of Science. The search was based on MeSH terms and included the following: "nanoparticles," "silver nanoparticles," "endodontic," "root canal treatment," and "regenerative dentistry." For data extraction, the study parameters, nanoparticle type, targeted tissue, control group, and documented regenerative outcomes were extracted.

Results: The findings of the trials included in this review indicated that nanoparticles had a positive overall effect on dental and periodontal regeneration. Notably, the investigated nanoparticles (PEG-PEI, bioactive glass nanoparticles, gold nanoparticles, chitosan nanoparticles, boron-modified bioactive glass nanoparticles) enhanced cell proliferation and mineralization as well as alkaline phosphatase activity, odontogenic differentiation potential in dental pulp stem cells (DPSCs), osteogenic differentiation potential in mesenchymal stem cells, and regenerative signaling pathways. Sure, some nanoparticles also inhibited inflammatory mechanisms, but not in all cell types, especially in dental pulp cells.Citosan/PLA nanofibers cause a significant increase in the expression of various inflammatory mediators compared with the bioclimatic tissue response, and this effect is probably influenced by the dose and the toxin substance, which may influence the outcome.

Conclusion: Finally, nanoparticle-based scaffolds and delivery systems should represent a promising method for regenerative dentistry. It has been said that these materials may promote the repair of dentin, sound dental pulp, periodontal ligament, and even periodontal bone by directly stimulating cellular infiltration and increasing the quantity of an enriched matrix through augmented activity in vital cells associated with mineral deposition and differentiation pathways. All included studies were found to be at moderate risk of bias, as they were mainly in vitro experiments; therefore, additional well-designed clinical and in vivo studies are required to validate the safety, efficacy, and long-term regenerative effects.

Keywords: Nanoparticles, dentistry, dental pulp stem cells, osteogenic differentiation, peri-implant bone regeneration.

1. INTRODUCTION

Nanotechnology refers to the manipulation of materials with controlled shape and size at the nanoscale, typically 1-100 nm. Due to this size range, engineered nanoparticles have attracted considerable interest because they exhibit unique or enhanced properties, including increased reactivity, strength, and distinct electrical and optical characteristics, compared with the same materials at larger scales. These changes in behavior are mainly attributed to the increased relative surface area and greater surface reactivity of nanoparticles [1-3]. In contemporary dentistry, nanomaterials have firmly established themselves in tissue-engineering approaches to address bone and tooth abnormalities resulting from various causes, including trauma and malignancy. In addition to their superior physicochemical properties, the biomimetic attributes of nanomaterials enhance cellular proliferation and facilitate tissue regeneration. The individual units of these chemical compounds are diminutive particles, typically 1-100 nm in size, in an unbound state. This unbound condition enables particles to form aggregates with one or more exterior dimensions, thereby increasing surface area. Nanomaterials have facilitated the transition of advancements in regenerative dentistry from the laboratory to clinical use. They are specifically employed in the development of innovative biomimetic nanostructures for cellular regeneration, targeted therapies, diagnostics, imaging, and the fabrication of dental materials [4-6].

In regenerative dentistry, nanostructured matrices and scaffolds enhance the regulation of cell differentiation. Nanomaterials replicate the natural dental architecture and structure, forming functional tissues more effectively than traditional autologous, allogenic tissues, or alloplastic materials. Novel nanostructures offer an enhanced platform for facilitating and regulating cell proliferation, differentiation, and migration [7-9]. Nanomaterials are extensively utilized in restorative dentistry for the fabrication of nanocomposite resins, bonding agents, endodontic sealants, coating materials, and bioceramics. They are also used in the production of daily dental hygiene products, including mouth rinses [10-13].

The use of nanoparticles in dental materials has positively impacted several aspects of dentistry (periodontics, endodontics, dental/bone regeneration, and preventive and restorative dentistry), including the treatment of chronic periodontitis. In this context, numerous systems based on nanomaterials, such as PLGA (Poly Lactic-co-Glycolic Acid) nanoparticles, poly(dopamine) nanoparticles, and chitosan nanoparticles (among others), have been studied [14-18]. Notably, hydroxyapatite nanoparticles with included tetracyclines have demonstrated a positive contribution to the maintenance and improvement of the health of the periodontal ligament and condition of the periodontal tissues [19-22].

Due to the close resemblance of Nanohydroxyapatite to the inorganic component of bone, it is extensively used in bone regenerative applications in implant-associated surgeries, including periodontal and root-related applications. Also, the modification of the implant surface with nanoparticles (i.e., Hydroxyapatite, calcium/phosphate nanoparticles, gold, chitosan, titanium oxide, and graphene oxide) has been evaluated to improve osseointegration and surface adhesion [23-25].

Further evidence suggests that this enhancement of periodontal and implant outcomes may stem from improved osseointegration, reduced bacterial biofilm formation, or even mineralized tissue regeneration in the presence of certain nanoparticles additionally, as a

surface modification agent with antimicrobial activity to reduce the risk of peri-implant infections and consequently contribute to the stability of dental implants, graphene oxide nanoparticles have been investigated for application in this area [26-29].

Nanoparticles are widely being researched as drug-delivery vehicles, antimicrobial agents, and regenerative mediators that can modulate inflammation and promote healing in periodontology and implant dentistry [30-32]. An important Ca-containing nanoparticle relevant for hard tissue regeneration, due to its high resemblance to the natural mineral composition, is calcium phosphate nanoparticles, which have a mineral phase comparable to that of bone and dentin and can support remineralization and tissue repair processes [33].

Likewise, zirconia nanoparticles are reported to enhance the mechanical strength, biocompatibility, and esthetic performance of dental materials. In contrast, zinc oxide and gold nanoparticles offer additional antimicrobial, anti-inflammatory, and diagnostic benefits [34].

In summary, nanotechnology is an essential avenue within regenerative dentistry, providing multifunctional materials to augment healing, control infection, or assist tissue integration, as well as long-term clinical performance of implants; but further clinical studies are critical to determine safety, dosage, and effectiveness (long-term) [34]. Therefore, this systematic review intends to gather and summarize *in vitro* studies regarding various nanoparticles as potential agents for dental regeneration.

2. MATERIALS AND METHODS

2.1. Declaration and Protocol

This systematic review follows the PRISMA 2020 guidelines [35].

2.2. Inclusion and Exclusion Criteria

The inclusion criteria for eligibility were:

- *In vitro* design.
- Specific evaluation of the role of nanoparticles in the regeneration of dental tissues.
- Evaluation of the regenerative capacity of nanoparticles in dentistry.
- The publication was in English.

The criteria for exclusion were:

- The study dealt only with antibacterial/disinfectant effects and did not consider issues related to regeneration.
- Studies that are systematic reviews.
- Studies in languages other than English.

Using the PIO eligibility framework as follows:

Population (P): teeth and dental cells applicable to regenerative dental procedures.

Intervention: (I), the use of different types of nanoparticles.

Outcomes (O): some of the indicators of regenerative/therapeutic potential.

2.3. Search Strategy

2.3.1. Databases/Sources of Information

A detailed search of the studies included in the review (2010-2020) in the PubMed, Scopus, and Web of Science databases is documented.

2.3.2. Search Terms

To maintain uniformity and ease of retrieval, the search terms were selected based on the MeSH lists. For the literature search, the following electronic databases were used: MEDLINE (PubMed), Scopus, and Web of Science, and the search strategy applied was: ((“silver

nanoparticles") OR (nanoparticles)) AND ((endodontic) OR ("root canal treatment") OR ("regenerative dentistry")).

Table 1. Search method.

Databases	Search Strategy	Number of Identified Studies
MEDLINE (PubMed)	(("silver nanoparticles") OR (nanoparticles)) AND ((endodontic) OR ("root canal treatment") OR ("regenerative dentistry"))	29
Scopus	(("silver nanoparticles") OR (nanoparticles)) AND ((endodontic) OR ("root canal treatment") OR ("regenerative dentistry"))	24
Web of Science	(("silver nanoparticles") OR (nanoparticles)) AND ((endodontic) OR ("root canal treatment") OR ("regenerative dentistry"))	18
Total	—	71

2.3.3. Studies Selection

All studies obtained from the various databases were exported to Excel for reference screening and management, and duplicate entries were removed. Screening was carried out in stages: first, the reviewer read the title and abstract to determine whether the document met the pre-established inclusion and exclusion criteria, and if it did, it warranted further review.

2.3.4. Data Extraction

For each included study, data were extracted using a pre-established set of variables, including: author(s), publication year, presence of a control group, study type, target tissue/cell type, type of nanoparticle, observed outcomes/effects, and method of application. The risk of bias was evaluated using an *in vitro* study quality assessment framework. The following domains were assessed: randomization of samples, blinding of outcome assessment, standardization of samples, calculation of sample size, completeness of outcome data, and selective outcome reporting. Each domain was assessed for low, high, or unclear risk of bias. The overall risk of bias for each study was determined from the aggregate evaluation of the domains.

3. RESULTS

3.1. Study Selection and Flowchart

The PRISMA flow diagram is a schematic overview of the systematic process for study selection used in this review. We identified 71 studies published between 2010 and 2020 (Figure 1) via database searches. Sixty-seven studies remained after removal of four duplicate records and were screened by title and abstract. 52 studies were excluded because they did not meet the inclusion criteria. Then, 15 full-text articles were assessed for eligibility, and eight studies were excluded during the detailed full-text evaluation. Ultimately, seven studies met all inclusion criteria and were included in the qualitative analysis for the review.

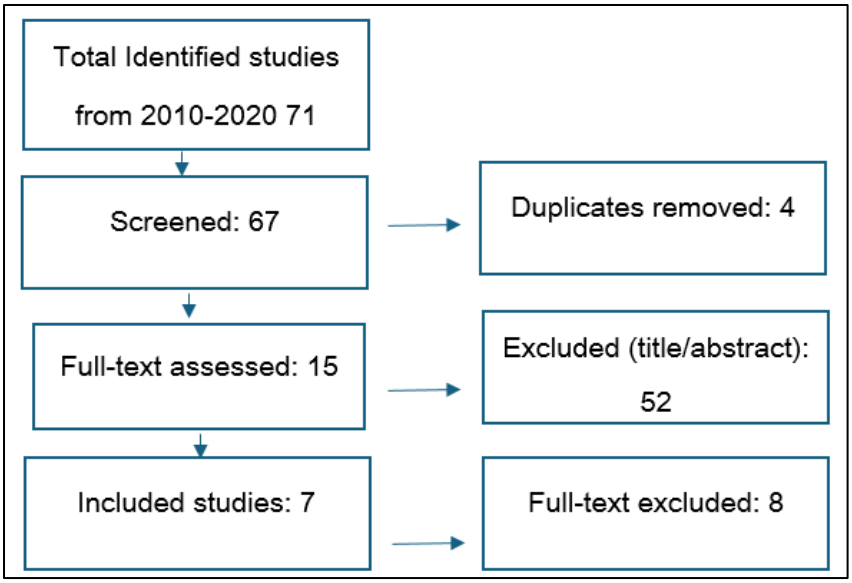

Figure 1. The chart of selected studies according to Prisma 2020 [35].

NP can have some regenerative effect on dental and periodontal tissues with varying mechanisms depending on the type of NP used. The majority of studies were laboratory-based experimental studies that primarily studied dental pulp, dentin, periodontal ligament, and periodontal bone tissues. The nanoparticles utilized ranged from PEG-PEI NPs, bioactive glass NPs, gold NPs, and chitosan NPs to boron-doped bioactive glass NPs. In general, these nanoparticles improved cellular proliferation, decreased inflammation, and promoted remineralization of dentin through odontogenic or osteogenic differentiation in human pulp stromal cells (hPSCs), mineralization of hPSCs, alkaline phosphatase activity of hPSCs, and regrowth of organogenically farmed organs 45. Another study found that induction of inflammatory mediator expression is higher with chitosan/PLA nanofibers, suggesting that nanoparticle effects may also be material-, dose-, and tissue-dependent.

Table 2. Characteristics of included studies

Author	Year	Type of Study	Control Group	Affected Tissue	Type of Nanoparticle	Effect
Liu et al. [36]	2016	In vitro experimental study	LPS-treated cells / lipo2000 control	Dental pulp tissue	miR-146a/bFGF PEG-PEI nanoparticles	Reduced inflammation, enhanced cell proliferation, promoted odontogenic differentiation, mineralization, and tissue regeneration of dental pulp cells.
Lim et al. [37]	2016	In vitro experimental study	DEX-free medium/nanofi	Dental pulp tissue	Bioactive glass nanoparticles (BGNs) loaded	Stimulated odontogenic differentiation,

Author	Year	Type of Study	Control Group	Affected Tissue	Type of Nanoparticle	Effect
			ber matrix without BGN		with dexamethasone	ALP activity, mineralization, odontogenic gene expression, and activated integrin/BMP/mTOR signaling pathways.
Niu et al. [38]	2017	In vitro experimental study	Untreated hPDLSCs / osteogenic induction medium without AuNPs	Periodontal ligament tissue	Gold nanoparticles (AuNPs)	Promoted osteogenic differentiation, increased ALP activity, mineralization, RUNX2, collagen type I, osterix expression, and activated p38 MAPK signaling pathway.
Shen et al. [39]	2018	In vitro experimental study	Pure PLA nanofibers / Tissue culture plate (TCP)	Periodontal bone and periodontal ligament tissue	Chitosan nanoparticles incorporated into PLA nanofibers	Improved hydrophilicity, cell adhesion, proliferation, osteogenic differentiation, ECM mineralization, and expression of osteogenic genes; however, increased inflammatory mediators and TLR4 expression.
Moonesi Rad et al. [40]	2018	In vitro experimental study	Undoped bioactive glass nanoparticles	Dental tissue / dental pulp stem cells	Boron-doped bioactive glass nanoparticles	Enhanced bioactivity, apatite formation, stem cell viability, intracellular calcium levels, and odontogenic differentiation

Author	Year	Type of Study	Control Group	Affected Tissue	Type of Nanoparticle	Effect
						with improved ALP activity.
Moonesi Rad et al. [41]	2019	In vitro experimental study	Bilayered membrane without bioactive glass nanoparticles / 0B-BG membrane	Periodontal bone tissue	7% boron-modified bioactive glass nanoparticles (7B-BG NPs)	Improved surface wettability, biodegradability, calcium–phosphate layer formation, stem cell proliferation, osteogenic differentiation, and guided bone regeneration.
Moonesi Rad et al. [42]	2019	In vitro experimental study	Scaffold without bioactive glass nanoparticles	Dentin tissue	Boron-modified bioactive glass nanoparticles	Enhanced dentin regeneration, mineral deposition, alkaline phosphatase activity, intracellular calcium levels, stem cell proliferation, and odontogenic differentiation.

3.3. Quality Evaluation Results

In Table 2, most included studies had an overall risk of bias rated as moderate based on the methods used to assess bias. In all studies, the risk of bias regarding sample standardization, incomplete outcome data, and selective reporting was low; however, many important methodological criteria related to randomization procedures, blinding methods, and sample size calculation remained unclear or poorly reported. Due to the largely in vitro experimental design of the included studies, these methodological constructs are often not fully addressed. Nonetheless, given the remarkable consistency across the studies evaluated, the reproducibility of the findings indicates that nanoparticles could play a beneficial role in the regenerative treatment of dental and periodontal tissues.

Table 3. Risk of Bias Model Assessment

Study	Randomization	Blinding	Sample Standardization	Sample Size Calc.	Incomplete Data	Selective Reporting	Overall Risk
Liu et al., 2016 [36]	Unclear	Unclear	Low	Unclear	Low	Low	Moderate
Lim et al., 2016 [37]	Unclear	Unclear	Low	Unclear	Low	Low	Moderate
Niu et al., 2017 [38]	Unclear	Unclear	Low	Unclear	Low	Low	Moderate
Shen et al., 2018 [39]	Unclear	Unclear	Low	Unclear	Low	Low	Moderate
Rad et al., 2018 [40]	Unclear	Unclear	Low	Unclear	Low	Low	Moderate
Moonesi Rad et al., 2019 [41]	Unclear	Unclear	Low	Unclear	Low	Low	Moderate
Moonesi Rad et al., 2019 [42]	Unclear	Unclear	Low	Unclear	Low	Low	Moderate

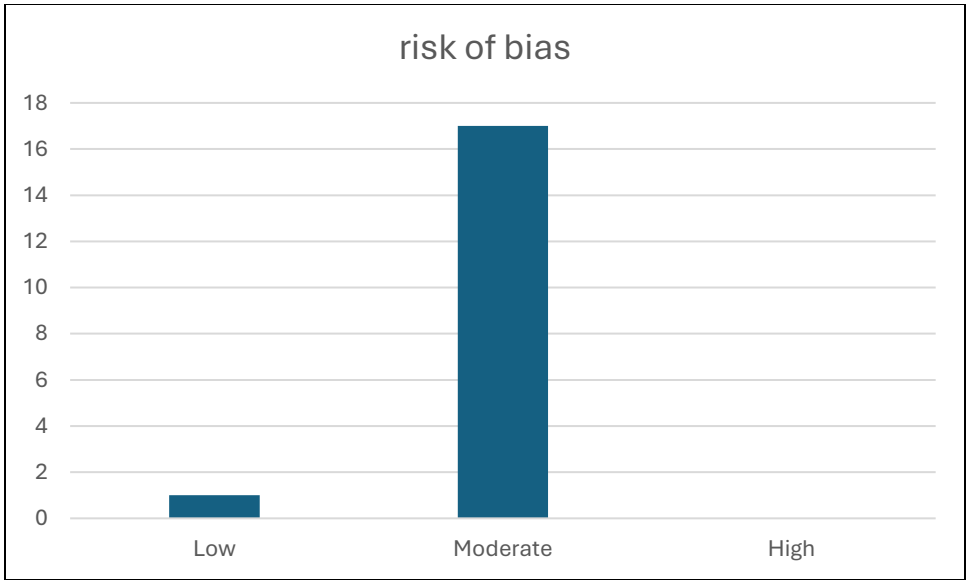

Figure 2. Representation of studies according to the risk of bias.

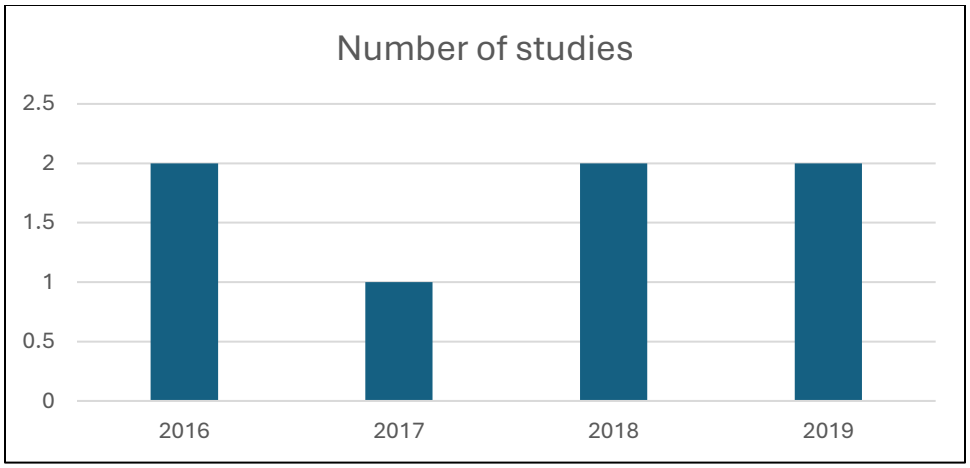

Figure3.Analysis of the literature according to its year of publication

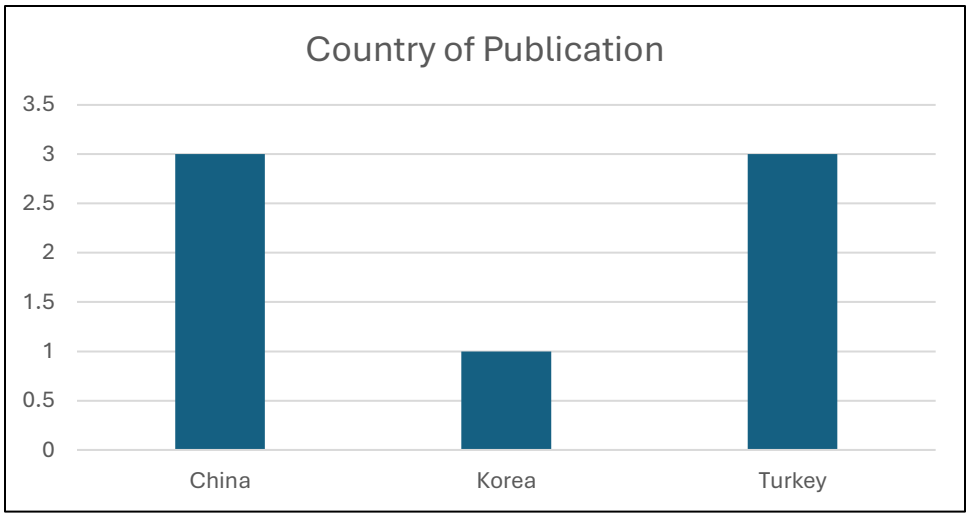

Figure 4. Analysis of the literature according to its country of publication.

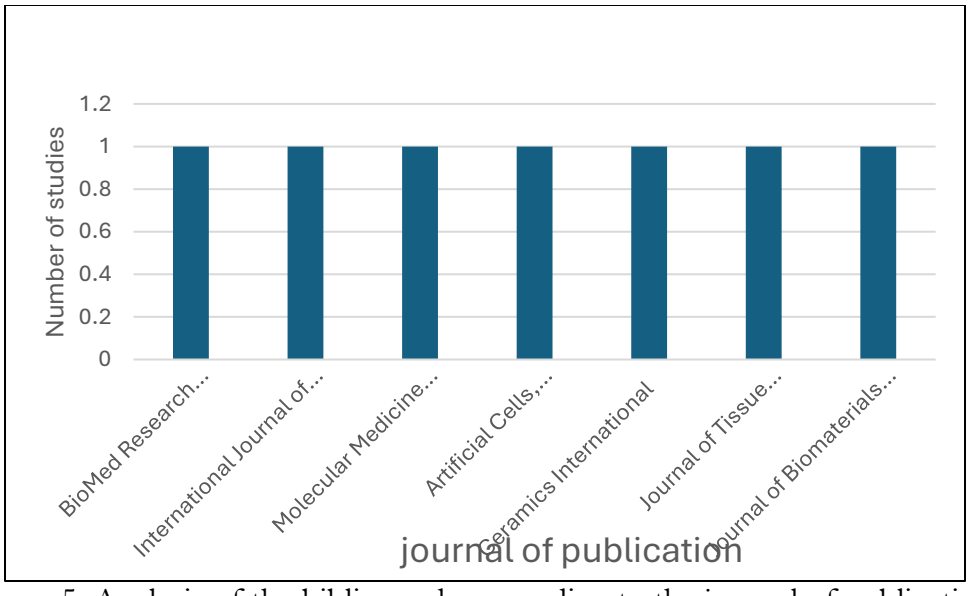

Figure 5. Analysis of the bibliography according to the journal of publication.

Liu et al. [36] studied miR-146a/basic fibroblast growth factor (bFGF)/polyethylene glycol-polyethyleneimine (PEG-PEI) nanoparticles therapy in human dental pulp cells. They suggested that these nanomedicine strategies offer a potential approach to modulate the inflammatory response and promote tissue regeneration using nonviral vectors. Methods An alginate hydrogel method was established to combine PEG-PEI nanoparticles loaded with miR-146a and bFGF. The system was evaluated for release, cytotoxicity, cell proliferation, and odontogenic differentiation under lipopolysaccharide-induced inflammatory conditions. Lipopolysaccharide inhibited the proliferation and differentiation of dental pulp cells. At the same time, miR-146a/bFGF/PEG-PEI hydrogel promoted cell proliferation (363% in 3 days compared to control), mineralized nodule formation, and increased expression of odontogenic markers. The data suggest that using miR-146a and bFGF NPs with these compounds may alter the inflammatory-resolving effects, thereby promoting endogenous reparative processes at the cellular level. This study concluded that miR-146a and bFGF delivered by PEG-cystamine-PEI nanoparticles exhibit anti-inflammatory properties and promote regenerative effects in dentin-pulp tissue engineering.

Lim et al. [37] reported the use of bioactive nanofiber matrices loaded with dexamethasone to induce odontogenic differentiation of human dental pulp cells. In the in vitro methodology, dexamethasone was loaded onto bioactive glass nanoparticles (BGNPs) and incorporated into nanoparticle/polymeric nanofiber matrices via electrospinning. Drug release, cell viability, alkaline phosphatase activity, mineralization, gene expression, and related signaling pathways were assessed. Results showed prolonged dexamethasone release, adequate cell viability, increased alkaline phosphatase activity and mineralization, and upregulation of the odontogenic markers dentin matrix protein and dentin sialophosphoprotein. The study found that the dexamethasone-releasing bioactive glass nanoparticles/dex nanofibers could serve as a potential therapeutic scaffold for dentin-pulp regeneration.

Niu et al. [38] investigated that gold nanoparticles cytobone no sign of promoting the osteogenic differentiation period when using human periodontal ligament stem cells Methods: Methodologically, we characterized the gold nanoparticles using transmission electron microscopy, assessed their cytotoxicity and conducted osteogenic differentiation assays with alkaline phosphatase activity (ALP) counts, mineralization assays detected by alizarin red staining as well quantitative polymerase chain reaction (Q-PCR) and western blotting. The results revealed that the gold nanoparticles exhibited a spherical, monodisperse profile and were non-toxic at the tested concentrations. In contrast, they promoted significant alkaline phosphatase activity, mineralized nodule formation, and markers of osteogenic expression, such as RUNX2, collagen type I, osterix, and alkaline phosphatase, more effectively. This study concluded that, at least in part, gold nanoparticles stimulated osteogenic differentiation by activating the p38 MAPK signaling pathway in periodontal ligament stem cells.

Shen et al. [39] prepared Pure polylactic acid and chitosan/polylactic acid nanofibers. They evaluated their morphology, mechanical properties, hydrophilicity, degradation behavior, cell adhesion, cell proliferation, osteogenic differentiation, and inflammatory gene expression. Chitosan then has a positive effect on both the hydrophilicity and mechanical behavior of PLA nanofibers; it also improves cell adhesion and early proliferation, as well as osteogenic differentiation and extracellular matrix mineralization. The expression of representative inflammatory mediators and Toll-like receptor 4 was also higher in human periodontal ligament cells. Results suggested that chitosan/polylactic acid nanofibers may promote periodontal regeneration, but the inflammatory response should be considered.

Moonesi Rad et al. [40] studied boron-doped bioactive glass nanoparticles with varying properties for research purposes in dental tissue applications. Bioactive glass nanoparticles with three boron concentrations were synthesized to investigate the effect of boron. They were characterized for physicochemical properties, simulated body fluid (SBF) release, ion release tests, cytotoxicity testing, and odontogenic differentiation of human dental pulp stem cells. Results indicated that boron enhanced bioactivity, apatite formation, and ion release; at appropriate concentrations, it promoted cell viability and augmented tooth-related key markers, including alkaline phosphatase activity and intracellular calcium deposition. It was found that boron-doped bioactive glass nanoparticles could be a promising candidate for dental tissue engineering when applied at appropriate, non-toxic concentrations.

Moonesi Rad et al. [41] characterized boron-modified bioactive glass nanoparticles in functionally graded nitrogen-containing bilayered membranes for guided bone regeneration. This study's methods comprised the preparation of cellulose acetate-based bilayered membranes containing bioactive glass nanoparticles at different concentrations, followed by characterization of morphology, wettability, degradation, mineralization, and mechanical properties, as well as an evaluation of human dental pulp stem cell attachment, proliferation, and osteogenic differentiation. The findings showed that the 7% boron-containing bioactive glass membrane enhanced surface wettability, promoted biodegradation, facilitated calcium-phosphate layer formation and analysis, and enhanced cell attachment and proliferation (cellular biology), as well as alkaline phosphatase activity, intracellular calcium deposition, and mineralized matrix formation. This bilayered membrane had a functionally graded structure, suggesting a potential role as an engineered barrier for guided bone regeneration in regenerative dentistry.

Moonesi Rad et al. [42] studied polycaprolactone-bioactive glass nanoparticle-filled poly(e-caprolactone)- and tricalcium phosphate-based scaffolds for dentin regeneration: synthesis and characterization. Methods: The preparation of three-dimensional cellulose acetate/oxidized pullulan/gelatin scaffolds incorporating bioactive glass nanoparticles was performed, followed by degradation and water absorption tests, porosity evaluation, morphology analysis, biomineralization (Simulated Body Fluid) biodistribution studies for boron ion release and cell cultures to assess in vitro biological potential by evaluating cell viability, alkaline phosphatase activity (ALP), intracellular calcium deposition index (CDI) and mineralization. The results demonstrated that the scaffolds possess appropriate porous structures, support human dental pulp stem cell viability, promote calcium phosphate deposition, enhance alkaline phosphatase activity, and stimulate mineralization, with boron-modified groups being significantly better than non-boron-mediated groups. This study concluded that the work presented boron-modified bioactive glass nanoparticle scaffolds as new constructs for dentin regeneration.

Despite the promising regenerative potential of nanoparticles in dental tissues, the assessment of their toxicity remains an important issue that was not sufficiently addressed in all included studies. The findings of the present systematic review indicated that most nanoparticle-based materials demonstrated favorable biological effects on dental and periodontal regeneration. These effects included enhancement of cell proliferation, mineralization, alkaline phosphatase activity, odontogenic differentiation of cells. However, the biological response influenced by several factors, including nanoparticle composition, concentration, exposure time, targeted cell type, and the presence of toxic or inflammatory components.

In relation to inflammatory and cytotoxic responses, the results showed that some nanoparticles were able to reduce inflammatory mechanisms and support tissue repair, while

others induced undesirable inflammatory reactions in specific cell types. This finding suggests that the regenerative effect of nanoparticles is not universal and may vary according to the material structure, dosage, degradation behavior, and interaction with the surrounding cellular environment.

Overall, the evidence obtained from this review suggests that nanoparticle-based scaffolds and delivery systems represent a promising approach in regenerative dentistry. Nevertheless, the included studies were mainly in vitro investigations, and all were judged to have a moderate risk of bias. This limits the strength of the evidence and reduces the ability to generalize the findings to clinical practice. Therefore, further well-designed in vivo and clinical studies are required to confirm the safety, efficacy, dose-dependent effects, and long-term regenerative outcomes of nanoparticle-based materials in dental tissue regeneration.

Regarding the limitations of this systematic review, the available literature specifically addressing the regenerative applications of nanoparticles in dentistry remains limited. In addition, the inclusion criteria restricted the review to in vitro studies published between 2010 and 2020 and retrieved from PubMed (MEDLINE), Scopus, and Web of Science. Although this approach ensured methodological consistency, it may have excluded relevant animal, clinical, or non-English studies.

In conclusion, nanotechnology may offer valuable bioactive platforms for enhancing dental and periodontal tissue regeneration. However, concerns remain regarding inflammatory reactions, cytotoxicity, dose-dependent responses, and the lack of strong in vivo and clinical evidence. Therefore, future research should focus on standardized experimental designs, broader toxicity assessment, and long-term biological evaluation to determine whether nanoparticle-based materials can be safely and effectively integrated into regenerative dental therapy.

CONCLUSION AND RECOMMENDATIONS

Taken together, the reviewed references indicated more or less impressive effects of numerous nanoparticles, e.g., PEG-PEI, bioactive glass nanoparticles, gold nanoparticles, chitosan, and boron-modified bioactive glass nanoparticles, on dental and periodontal tissue regenerative potential. The use of nanoparticles-initiated cell proliferation, mineralization, and differentiation into odontogenic and osteogenic lineages, as well as inducing alkaline phosphatase activity and regenerative signaling pathways, some of which even resulted in decreased inflammation. In summary, these results indicate that future successful options for dentin, dental pulp, periodontal ligament, and periodontal bone regeneration can be achieved via nanoparticle-based scaffolds and delivery systems.

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