International Journal of Dentistry and Oral Science (IJDOS)
ISSN: 2377-8075

Recent Advances Of Metal Nanoparticles Applications In Soft And Hard Tissue Regeneration: Dental Overview

Research Article

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Abstract

Nanoparticles are solid colloidal particles showing unique physical and chemical features. Metallic nanoparticles (MNPs) are broadly used in biomedical therapeutic applications and tissue engineering. They have gained attention due to their massive potential in nanotechnology. In this review, we aimed to highlight the recent updates of MNPs applications in hard and soft tissue regeneration from histological point of view. Researches revealed enhanced osteogenic differentiation potential of MNPs, successful remineralizing effect on dental hard tissues, together with effective periodontal ligament regeneration and accelerated wound healing process.

Keywords: Metal Nanoparticles; Bone Regeneration; Dental Tissue Regeneration; Supporting Tissue Regeneration; Wound Healing.

Abbreviations: METALLIC NANOPARTICLES (MNPS); NANOPARTICLES (NPS); GOLD NANOPARTICLES (AUNPS); SILVER NANOPARTICLES (AGNPS); IRON OXIDE NANOPARTICLES (IONPS); ALUMINUM NANOPARTICLES (ALNPS); COPPER NANOPARTICLES (CUNPS); ZIRCONIUM NANOPARTICLES (ZRNPS); TITANIUM DIOXIDE NANOPARTICLES (TIO2NPS); ZINC OXIDE NANOPARTICLES (ZNONPS); CERIUM OXIDE NANOPARTICLES (CEO2NPS); EXTRACELLULAR MATRIX (ECM); TISSUE ENGINEERING (TE); HUMAN MESENCHYMAL STEM CELLS (HMSCS); HUMAN BONE MARROW MESENCHYMAL STEM CELLS (HBM-MSCS); REACTIVE OXYGEN SPECIES (ROS); POLYETHYLENEIMINE (PEI); ALKALINE PHOSPHATASE (ALP); OSTEOCALCIN (OCN); OSTEOPONTIN (OPN); RUNT-RELATED TRANSCRIPTION FACTOR 2 (RUNX2); TETRAMETHYLPIPERIDINE-N-OXYL (TEMPO); PERIODONTAL LIGAMENT STEM CELL (PDLSC); HYPOXIA-INDUCIBLE FACTOR 1A (HIF1A); INTERLEUKIN 8 (IL8); SILVER HYDROXYAPATITE (AG-HA); SILK FIBROIN (SF); MITOGEN-ACTIVATED PROTEIN KINASE (MAPK); HUMAN SERUM ALBUMIN (HSA); FIBROBLAST GROWTH FACTOR 2 (FGF2); VASCULAR ENDOTHELIAL GROWTH FACTOR (VEGF); CHITOSAN (CS); BONE MORPHOGENIC PROTEIN (BMP); NANO SILVER FLUORIDE (NSF); POLYETHYLENE GLYCOL (PEG); DENTAL PULP STEM CELLS (DPSCS); PERIODONTAL LIGAMENT FIBERS (PDL); POLYCAPROLACTONE (PCL).

Introduction

Human tissues consist of highly organized and specialized cells associated with extracellular matrix (ECM). This offers support for cellular adhesion and proliferation, as well as regulation of intercellular communication [1]. Regenerative medicine based on tissue engineering (TE) depends onsetting up systems that restore, replace or regenerate destroyed tissues [2].

Nanoparticles (NPs) have exciting properties as they interact with living systems, and possess variable characteristics which provide biocompatibility and circumstantial bioactivity [3, 4]. Small size of NPs, similar to ECM components, and their large surface to volume ratiomake them compatible to be used in TE [5]. Different types of NPs are available such as ceramic, metallic, carbon-based and composite-based [6]. Metallic nanoparticles (MNPs) are biocompatible materials nevertheless, they necessitate long term cytotoxicity testing [7]. They have variable applications in

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Received: February 17, 2022
Accepted: March 06, 2022
Published: March 09, 2022

Citation: Mona El Deeb, Amany A. Rabea, Yasmin M. Elghazawy, Esraa G. Hassan, Aya M. Reyad. Recent Advances Of Metal Nanoparticles Applications In Soft And Hard Tissue Regeneration: Dental Overview. *Int J Dentistry Oral Sci.* 2022;9(3):5254-5263. doi: http://dx.doi.org/10.19070/2377-8075-220001054

biomedicine, due to their unique physicochemical features, such as high energy atoms [8], high ratio of surface area-to-volume and high surface energy [9]. MNPs can be prepared with different chemical, physical or biological methods [10].

With the rapid progress of nanotechnology, nanomaterials such as NPs, nanofibers, nanotubes, and others have been widely used in dental and cranio-maxillofacial TE. We summarized here the recent updates of nanometals'applications in dental hard and soft tissues.

Bone Regeneration

Gold nanoparticles (AuNPs)

It is proved that there is a link between AuNPs and osteogenic differentiation of stem cells due to their shape, size, and surface properties. A study reported that AuNPs of size 70 nm could increase the osteogenic differentiation of human mesenchymal stem cells (hMSCs) [11] by affecting Wnt/β-catenin and p38 signaling pathways [12]. However, small sized AuNPs (4nm) suppress osteogenic differentiation, but enhance adipogenic differentiation of human bone marrow mesenchymal stem cells (hBM-MSCs). This could be related to reactive oxygen species (ROS) production by the small sized AuNPs [13].

In hBM-MSCs and MC3T3-E1 cells, miR-29b-delivered polyethyleneimine (PEI)-capped AuNPs efficiently promoted osteogenic differentiation by enhancing the expression of alkaline phosphatase (ALP), osteocalcin (OCN), osteopontin (OPN), and Runt-related transcription factor 2 (Runx2)[14]. Also, 2,2,6,6-Tetramethylpiperidine-N-oxyl (TEMPO) conjugated AuNPs allowed osteogenic differentiation of human MSCs, though suppressing the adipogenic differentiation [15].

AuNPscan act as vehicles to deliver miRNA to permit the growth and differentiation of BM-MSCs [16], and enhance Runx2 gene expression, thusfacilitating their osteoblastic differentiation [17]. Moreover, AuNPs allows osteogenic differentiation of periodontal ligament stem cell (PDLSC) and osteoid tissue formationthrough enhancing bone-related protein expression and mineralization [18].(Table 1)

Silver nanoparticles (AgNPs)

Silver based scaffolds are highly efficient due to their good adhesion and spreading potential on cells. They also exhibit antibacterial activity, enhanced osteogenic ability and proliferative effect on osteoblasts [19].

AgNPs could combine with DNA of human MSCs, and trigger the expression of hypoxia-inducible factor 1α (HIF1α) and interleukin 8 (IL 8) gens that activate cell proliferation [20]. An *in vivo* study of mouse model showed that AgNPs enhanced osteogenic differentiation of MSCs, but had very little effect on adipocyte or chondrocyte differentiation [21]. Ongoing, Hasan et al (2018) [5] reported that AgNPs modified scaffolds possess appropriate porosity for bone TE applications by promoting vascularization and osteogenesis. Scaffolds embedded with silver hydroxyapatite (Ag-HA) nanoparticles showed continued release of metallic ions, and efficient adhesion and osteogenic potency on mammalian cells [22, 23].

Additionally, nanotubular titanium oxide coated with Ag nanowires appeared to be suitable for osteoblast-like cells adhesion and proliferation, together with apatite crystal formation [24]. Similar data were demonstrated for titanium implants coated with AgNPs [25, 26]. Again, HA coating by nanosilver promoted osseointegration of implants [27, 28]. Moreover, electrospun composites with AgNPs increased the formation of bone-like apatite [29, 30], while calcium silicate scaffold and silk fibroin (SF) incorporated AgNPs showed bactericidal propertiesand osteogenic effect [31, 32].(Table 1)

Iron nanoparticles

Iron oxide nanoparticles (IONPs) promote osteogenic differentiation of stem cells. Polyglucose sorbitol carboxymethyl-ether (PSC) coated IONPs are structurally stable in hMSCs and allowtheir osteogenic differentiation in vitro through activation ofclassical mitogen-activated protein kinase (MAPK) signal pathway [33].

However, stimulation of IONPs-loaded bovine serum albumin showed high uptake rate into hBM-MSCs withincreased osteogenic differentiation [34]. Moreover, coating of IONPs with human serum albumin (HSA) permitted its binding to fibroblast growth factor 2 (FGF2) and differentiation of hBM-MSCs into bone cells[35].(Table 1)

Aluminum nanoparticles (AlNPs)

Chen et al. (2017) [36] investigated the osteogenic potential of macrophage cell culture on nanotopographic aluminum. BM-MSCs interacted with the nanoporous and showed that the spread of cells was influenced by pore size. This resulted indecreased pro-inflammatory cytokine gene expression and ROS together with increased mineralization, OPN and collagen type I expressions.(Table 1)

Copper nanoparticles (CuNPs)

Copper has the ability to stimulate collagen fiber deposition and angiogenesis [37]. It induces the differentiation of mesenchymal cells to the osteogenic lineage [38] and treatsosteoporosis [39, 40] by enhancing angiogenic activity and gene expression of vascular endothelial growth factor (VEGF) and angiogenic growth factor 2 [41]. So,CuNPs have been considered as new additives in bone TE [42].(Table 1)

Zirconium nanoparticles (ZrNPs)

Zirconium (Zr) is considered as an osteoinductive and biocompatible material of low cytotoxicity [43, 44]. Bhowmick et al. (2017) [45] synthesized a composite scaffold containing zirconium oxide nanoparticles, which showed ideal properties for bone TE due to its resemblance to cancellous bone. Further, Doostmohammadi et al. (2019) [46] fabricated zirconium modified nanoparticles that stimulated the proliferation of BM-MScs in a boney defect, showing complete regeneration after 6 weeks. Additionally, Maghsoudlou et al. (2020) [47] designed a biodegradable nanocomposite containing chitosan (CS), HA, and ZrNPs that improved the porosity of the scaffold. (Table 1)

Table 1. Effect of metal nanoparticles on bone regeneration.

Metal nanoparticle	Additional materials	Effect	Reference
AuNPs loaded on (70 nm)	Bovine serum albumin	Increased osteogenic differentiation of hMSCs	[3]
AuNPs (4nm)	----------	- Suppressed osteogenic differentiation of hBM-MSCs - Enhance adipogenic differentiation of hBM-MSCs	[13]
AuNPs loaded on	Polyethyleneimine with miR-29b	- Upregulated osteogenic differentiation-related genes - promoted osteogenic differentiation of hBM-MSCs	[14]
AuNPs	2,2,6,6-Tetramethylpiperidine- N-oxyl	- Allowed osteogenic differentiation of hMSCs - Suppressed adipogenic differentiation of hMSCs	[15]
AuNPs loaded on	Polyethylenimine and liposomes	- Efficiently delivered miRNA - Enhanced BM-MSCs differentiation into osteoblast-like cells	[16]
Polyethylene gylated hollow AuNPs	Fibrin and poly-caprolactone -based scaffolds	- Enhanced Runx2 gene expression - Enhanced osteoblastic differentiation of MSCs	[17]
AuNPs	----------	- Upregulated bone-related protein expression and mineralization - Allowed osteogenic differentiation of PDLSC	[18]
AgNPs	hMSCs	- Triggered expression of HIF1α and IL8 gens - Activated cell proliferation	[20]
AgNPs	MSCs	- Enhanced osteogenic differentiation of MSCs - Little effect on adipocyte or chondrocyte differentiation	[21]
AgNPs loaded on	Cellulose nanowhiskers on chitosan/sodium carboxymethyl cellulose scaffolds	- Enhanced angiogenesis and vascularization Improved biomineralization for bone growth - Antimicrobial effect	[5]
AgNPs loaded on	HA on gelatin, alginate, and poly vinyl alcohol scaffolds	- Increased osteogenic potential - Bactericidal effect	[22]
AgNPs loaded on	HA on Electrospun Polycaprolactone scaffolds	- Enhanced differentiation of MSCs into osteoblasts - Antimicrobial effect	[23]
AgNPs/ TiO2NPs	----------	- Increased adhesion and differentiation of osteoblasts - Antimicrobial effect	[24]
AgNPs	Graphene oxide on titanium/niobium oxide implants	- Improved differentiation of pre-osteoblastic cells - Antimicrobial effect	[25]
AgNPs	poly(lactic-co-glycolic) acid on titanium implants	- Increased osteogenic potential - Bactericidal effect	[26]
AgNPs	Zirconium oxide &HA on zirconium/titanium implant	Enhanced osseointegration	[28]
AgNPs	poly-L-lactic acid/graphene oxide on Magnesium implant	- Enhanced development and proliferation of osteoblast-like cells - Bactericidal effect	[29]
AgNPs	HANPs on polylactic acid/cellulose acetate or poly caprolactone polymers	- Promoted formation of bone-like apatite - Bactericidal effect	[30]
AgNPs loaded on	Calcium-silicate scaffold	- Provided apatite-forming ability - Bactericidal effect	[31]
AgNPs	Silk fibroin & gentamycin	- Enhanced osteoinductive potential - Antibacterial effect	[32]
IONPs loaded on	Polyglucose sorbitol carboxymethyl-ether	Promoted osteogenic differentiation of hMSCs	[33]
IONPs loaded on	Bovine serum albumin	Increased osteogenic differentiation of hBM-MSCs	[34]
IONPs	Human serum albumin	- Enhanced the biological efficacy of FGF2 - Enhanced the proliferation of hBM-MSCs - Promoted differentiation of hBM-MSCs to osteogenic cells	[35]
AlNPs	----------	- Decreased pro-inflammatory cytokine gene expression - Enhanced the expression of osteogenic factor genes	[36]
CuNPs	Reduced graphene oxide hybrid particles in polycaprolactone matrix	- Enhanced gene expression of angiogenic markers - Exhibited osteogenic and bactericidal properties	[41]
ZrO2NPs	Chitosan, poly ethylene glycol, nHA	- Cytocompatibility with osteoblastic MG-63 cells - Antimicrobial effect - Ideal to be used for bone TE	[42]
ZrNPs	Calcium silicate nanoparticles	- Stimulated proliferation of BM-MSCs - Completely regenerated boney defect after 6 weeks	[46]
ZrNPs	Chitosan, HA, wollastonite	- Improved porosity of the scaffold - Beneficial in bone TE applications because of its similarity to natural bone structure	[47]
CeO2NPs	HA	- Promoted proliferation and osteogenic differentiation of BMSCs - Activated BMP signaling - Reduced inflammatory reactions	[48]
CeO2NPs	----------	- Improved proliferation of MSCs - Increased expression of angiogenic factors and VEGF	[49]
CeO2NPs loaded on	Titanium	- Improved osteogenic differentiation of BMSCs - Enhanced new bone formation and mineralization	[50]
ZnONPs	----------	- Increased adhesion and activity of osteoblast cells - Upgraded osteoblast density, ALP and calcium deposition	[51]
ZnONPs	Multiwall carbon nanotubes on polyurethane -based bioactive scaffolds	- Elevated ALP activity and secretion of collagen type I - Increased osteogenic differentiation of pre-osteoblasts - Antimicrobial effect	[52]

Nanoceria

The incorporation of cerium oxide nanoparticles (CeO_2NPs) into a HA covering allowed motivation of bone morphogenic protein (BMP) signaling [48]. Also, bone scaffold containingCeO_2NPs helped the proliferation of MSCs by increasing intracellular calcium level and expression level of angiogenic factors and VEGF [49]. Li et al. (2018) [50] deposited CeO_2NPs on titanium surface to detect the biological response of new bone formation. The prepared NPs were in mixed Ce^{3+}/Ce^{4+} valence state, and the increase in the surface Ce^{3+}/Ce^{4+} ratio enhanced new bone formation and mineralization. The valence promoted bone regeneration with no need for exogenous osteogenic inducer.(Table 1)

Zinc nanoparticles

Human osteoblasts were cultured onnano-sized zinc oxide (ZnO) ceramic compacts. The adhesion and activity of osteoblast cells were significantly raised with upgraded osteoblast density, ALP and calcium mineral deposition. Consequently, this allows ZnONPs to be promising in application for orthopedic implants [51]. Furthermore, the incorporation of ZnONPs, with multiwall carbon nanotubes, allowed better osteogenic differentiation of pre-osteoblasts. This was certified by elevated ALP activity and the secretion of collagen type I [52].(Table 1)

Dental and Supporting Tissue Regeneration

In recent years, dental tissue regeneration has gradually drawn great attention [53].(Table 2)

Enamel regeneration

Nano silver fluoride (NSF) and AgNPs couldbind to HA crystals in carious lesions and inhibited the reduction of pH and attachment of Streptococcus mutans to the enamel surface leading to remineralization of primary teeth [54, 55]. Reduced graphene oxide- nanosilver could prevent mineral loss after biofilm challenge [56]. They also lessen the mineral loss of children's first molars when incorporated with dental sealants [57].

Another investigation reported that zeolite-zinc oxide nanoparticles showed high remineralization efficacy on enamel surface against polymicrobial biofilms induced enamel lesions [58].

Dentin regeneration

Nanosilver and/or nanozinc incorporated with calcium-silicate nanoparticles showed well adherence to the root canal walls and infiltration into the dentinal tubules, suggesting their use as a root canal disinfectant [59]. Meanwhile, an endodontic sealer embedded with AgNPs displayed effective remineralizing and strengthening influence on dentin [60].

AgNPs was able to produce silver chloride in dentin elevating its mineral density [61]. In addition, bioactive multifunctional composite containing AgNPs induced effective remineralization by minerals precipitated on root dentin surfaces [62]. Moreover, demineralized dentine blocks were subjected to a topical application of sodium fluoride with polyethylene glycol (PEG)-AgNPs. The mixture could remineralize dentine caries and prevent collagen degradation [63].

On the other hand,Sereda et al. (2016) [64] revealed that titanium oxide nanoparticles (TiO_2NPs)with chondroitin sulphate inhibited the attachment of acidogenic microbes which cause caries and enhanced dentin remineralization. Onwubu et al. (2019) [65] in another report documented thatTiO2NPs allow proper dentine occlusion resulting incoverage of wide area of dentine.

It is considerable to mention that ZnO powder is added as a preservative to toothpastes. The suspension hinders dentin demineralization and shows antimicrobial property by releasing zinc ions and ROS [66]. Furthermore, toothpastes having ZnONPs can obturate dentinal tubules exposed to citric acid [67].

Nanomaterials offer substitutionalapproaches for dentin regeneration by inducing odontogenic differentiation of human dental pulp stem cells (DPSCs) [53]. DPSCs incorporated within IONPs containing scaffolds could be differentiated into odontoblast-like cells expressing dentin sialophosphoprotein and dentin matrix protein 1 [68].

Pulp tissue regeneration

Pulp regeneration depends on revascularization at the root apex [69]. Nano sized iron oxide -labeled SF/HA composite scaffold was found to be good enhancerfor regeneration of DPSCs [68]. Nano scaffolds and nano drug deliver approacheslead the homing of stem cells to realize dental pulp regeneration [70, 71].

Periodontium regeneration

Recent studies revealed promising results in the regeneration of the periodontal apparatus [72]. Light microscopic examination of old age rats' periodontium receiving an oral dose of AgNPs demonstrated increased thickness of bone trabeculae with decrease in size of bone marrow cavities. Reestablishment of oblique, interradicular and apical groups of periodontal ligament fibers (PDL) were also observed. Nearly smooth surface of cementum with amelioration of cementum degeneration and hypercementosis was noticed [73].

Treatment with AuNPs in periodontitis inducedthe formation of new periodontal attachment, bone and cementum in periodontal defects, and reduced tissue destruction. Also, AuNPs could modify the differentiation of hPDLCs, and control the early inflammatory response by regulation of macrophage phenotypes andelevation of anti-inflammatory cytokine levels and BMP-2 [74]. However, in a recent study, L/D-cysteineanchored AuNPs could raise the expression of ALP, collagen type 1, OCN and Runx- 2 with promising effect on periodontal tissue regeneration [75].

Regarding ZnNPs, polycaprolactone (PCL) scaffolds loaded with ZnONPs were utilized in periodontal regeneration and exhibited antibacterial effect [76] and increased the osteoconductive ability [77]. As well, local administration of chitosan-based risedronate/zinc-hydroxyapatite nanoparticlesin dental pockets showedmarked improvement in the mesial and distal periodontal bone support, bone mineral density, and repressed alveolar bone resorption [78].

Besides, combination of ZnONPs withMyristica fragrans could-

have antibacterial and antibiofilm efficacy, which has major role in periodontitis [79]. Additionally, a serum albumin containing ZnONPs showed high physicochemical properties and superior antibacterial action for gingival tissue repair [80].

The protective effect of nano-selenium was studied on induced aflatoxin B1 toxicity on PDL of rats. Jaw specimens presented reestablishment and condensation of collagen fibers with normal appearance of fibroblasts. Furthermore, gingiva regained its slender, long and irregular epithelial ridges with intact basement membrane. The lamina propria showed declinein collagen fiber degeneration with reduction of the inflammatory cells. Surface epithelium and lamina propria presented weak to moderate positive immunostaining for caspase 3 [81].

Oral Mucosa and Salivary Glands

It was reported that AgNPs are safe for human keratinocytes and exhibited high antimicrobial efficiencyfor concentrations up to 6 µg/mL [82, 83].

Nevertheless, AuNPs improved 5-florouracil induced oral mucositis in hamsters and improved the parameters of inflammation and oxidative stress. Re-epithelialization and hyperkeratinization with areas of hyperplasia were noticed. The lamina propria presented irregular collagen fibers with fibroblasts and mild to moderate inflammatory cell infiltrate [84]. On contrary, examination of the tongue of rats exposed to toxic over dose of AuNPs solution revealed atrophic changes. Degenerationincluded the surface epithelium and lamina propria of the dorsal and ventral surfaces as well as the lingual salivary glands. The taste buds were degenerated with destruction of their cells [85].(Table 2)

Wound Healing

MNPs are increasingly being used in skin and mucosal wounds, as they speed up wound healing process andinhibit bacterial infections. Moreover, they are easily to be used with lessened frequency of dressing changes [86].(Table 3)

Silver nanoparticles (AgNPs)

AgNPshave significant role in wound dressings [87, 88]. They induce wound closure by enhancing the proliferation and migration of keratinocyte as well as differentiation of myofibroblasts with better collagen fibril alignment in repaired skin [89]. AgNPs poly gamma-glutamic acid hydrogel copolymer promoted collagen deposition and epithelization during healing of mouse wound in vivo [90]. Furthermore, application of Aloe vera and AgNPs on induced oral ulcers in mice showed regained epithelial thickness and upgraded alpha smooth muscle actin [91].

Composite hydrogels loaded with AgNPs accelerated the healing process of normal and diabetic ulcers by enhancing epithelial formation, collagen deposition and modulation of the host immune response [92-96]. It is supposed that the slow and continued release of metallic ions is required for wound healing applications [97].

Additionally, Bergonzi et al, (2020) [98] manufactured 3D-printed scaffolds of alginate and cellulose combined with AgNPs. The nanocomposites showed significant antibacterial effect. Same results were obtained with the application of sodium alginate containing silica coated AgNPs [99] Bacterial cellulose/polydopamine scaffolds embedded AgNPsalso showed enhanced removal of necrotic tissue, induced collagen synthesis and epithelization, andincreased expression of growth factor genes involved in wound healing [100]. Similarly, nanofibrous electrospun mats of hyaluronic acid and polygalacturonic acid loaded with nanosilver revealed antibacterial activity and wound epithelization [101].

It is worthy to mention that chronic wounds and burns are highly susceptible to infection. Therefore, existence of antimicrobial agents such as AgNPs in the scaffold design for wound healing is mandatory [6, 102].

Gold nanoparticles (AuNPs)

AuNPs have good biocompatibility and multifunctionality that aid the wound healing process [103]. It was demonstrated that AuNPs can damage the bacterial cell wall and bind to its DNA. Also, they may support the healing process by acting as antioxidants [104].

Burn-induced wounds in mice treated with AuNP-containing thermoresponsive gels revealed undamaged normal histology of epidermis and dermis with some hyalinosis of the underlying skeletal muscle and scanty inflammatory cells [105]. Marza and Magyari (2019) [106] and Fathi et al., (2019) [6] study results showed that bioactive glass combined with AuNPs, and AuNPs containing wet electrospun SF were able to stimulate angiogenesis and granulation tissue formation. Furthermore, AuNPs incorporated collagen scaffolds exhibited higher wound healing ability compared to pristine collagen scaffolds [107].

Zinc nanoparticles

ZnONPs are powerful antibacterial agents as they attack the bacterial cell membrane causing perforations [108]. Wound dressings containing these particles showincreased keratinocyte migration and rapid epithelialization [104]. Increased fibroblastic proliferation resulted when ZnONPs werecombined with polymethylmethacrylate fibers [109]. Another research demonstrated that Ag/ZnONPs loaded with CS accelerated wound healing process in mice. The dressings showed rapid blood clot formation, thick collagen fiber deposition and high antibacterial property [110]. Identical results were documented with the use of electrospun polyvinilidine - trifluoroethelene zinc oxide nanocomposites [111] or nanoconjugates containing ZnONPs and sodium alginate-gum acacia hydrogels [112]. Added to this, Gao et al. (2017) [113] and-Balaure et al. (2018) [114] described dressings having ZnONPs which promote wound closure, hinder bacterial growth and show superior biocompatibility.

Titanium dioxide nanoparticles (TiO_2NPs)

TiO_2NPs were verified toincrease ROS production, which make them beneficial in wound management [115]. Sivaranjani et al. (2016) [116] synthesized TiO_2NPs from Moringa oleifera leaves under certain conditions. They displayed enhanced wound healing and antimicrobial activities against gram-negative and gram-positive bacteria. Furthermore, TiO_2NPs containing sca olds revealed good adhesion, and prolife ration of cells during in vitro tests

Table 2. Effect of metal nanoparticles on dental tissues, supporting tissues & mucosa.

Metal nanoparticle	Additional materials	Dental Tissue	Effect	Reference
AgNPs	Fluoride	Enamel	High remineralization efficacy of primary teeth by binding to HA in carious lesions	[54]
AgNPs	Fluoride	Enamel	- Inhibited reduction of pH - Inhibited attachment of Streptococcus mutans to enamel surface of primary teeth	[55]
AgNPs	Reduced graphene oxide	Enamel	Inhibited mineral loss in artificial enamel caries	[56]
AgNPs	----------	Enamel	- Lessened mineral loss of children's first molars - Increased remineralization ability	[57]
ZnONPs	zeolites	Enamel	- Increased remineralization - Reduced polymicrobial biofilms on orthodontic brackets	[58]
AgNPs/ZnNPs	calcium-silicate nanoparticles	Dentin	- Well adherence to the root canal walls - Infiltration into the dentinal tubules	[59]
AgNPs	Dimethylaminohexadecyl methacrylate, amorphous calcium phosphate nanoparticles	Dentin	- Effective remineralizing effect on dentin - Strong bactericidal activity	[60]
AgNPs	---------	Dentin	- Inhibited the growth of a cariogenic biofilm - Increased mineral density	[61]
AgNPs	Aamorphous calcium phosphate nanoparticles, 2-methacryloyloxyethyl phosphorylcholine, dimethylaminohexadecyl methacrylate	Dentin	Effective remineralization on root dentin	[62]
AgNPs	Sodium fluoride, polyethylene glycol	Dentin	- Remineralization of dentine caries - Prevention of collagen degradation	[63]
TiO2NPs	Chondroitin sulphate	Dentin	- Inhibited attachment of acidogenic microbes - Enhanced dentin remineralization	[64]
TiO2NPs	Eggshell	Dentin	- Proper occlusion of dentinal tubules - High acid resistant stability	[65]
ZnONPs	Fluoride-containing bioactive glass	Dentin	- Proper occlusion of dentinal tubules	[67]
AgNPs	----------	- Alveolar bone - Cementum - PDL	- Increased thickness of bone trabeculae - Decreased size of bone marrow cavities - Reestablishment of PDL fibers - Decreased cementum degeneration	[73]
AuNPs	hPDLCs	- Alveolar bone - Cementum - PDL	- Differentiation of hPDLCs - Formation of new PDL, bone and cementum in periodontal defects - Regulated macrophage phenotypes - Elevated anti-inflammatory cytokine levels and BMP-2	[74]
AuNPs	L/D-cysteine	- Alveolar bone - PDL	- Raised the expression of ALP, collagen type 1, OCN and Runx- 2 - Enhanced periodontal tissue regeneration	[75]
ZnONPs loaded on	Polycaprolactone (PCL) and gelatin scaffolds	PDL	Antibacterial effect	[76]
ZnONPs loaded on	PCL scaffolds	- Alveolar bone - PDL	- Increased the osteoconductive ability - Increased antibacterial activity - Promoted periodontal tissue regeneration	[77]
ZnNPs	chitosan-based risedronate hydroxyapatite	Alveolar bone	- Improved mesial and distal periodontal bone support - Improved bone mineral density - Repressed alveolar bone resorption	[78]
ZnONPs	Myristica fragrans	PDL	antibacterial and antibiofilm efficacy	[78]
ZnONPs	minocycline	Gingiva	- Ability of gingival tissue self-repairing - Antibacterial effect	[80]
nano-selenium	----------	- Gingiva - PDL (induced toxicity of PDL)	- Gingiva regained normal histological appearance - Reestablishment of PDL fibers	[81]
AgNPs	polyethylene glycol	mucosa	Nontoxic effect on human keratinocytes	[82]
Biosynthesized AgNPs	----------	mucosa	- Nontoxic effects on human melanocytes - Antimicrobial efficiency	[83]
AuNPs	----------	mucosa (induced oral mucositis)	-Hyperkeratinization with areas of hyperplasia - Irregular collagen fibers - Mild to moderate inflammatory cells	[84]
AuNPs (toxic dose)	----------	Tongue	- Degeneration of epithelium & lamina propria - Degeneration of lingual glands - Degeneration of taste buds	[85]

[117]. Bacterial celluloseimpregnated TiO_2NPs induced epithelial and granulation tissue synthesis, fibroblast migration and neovascularization in burns of mice models [118].

Conclusion

MNPs can be manufactured and improved with several chemical functional groups, thus allowing them to be combined with various ligands and drugs. This permits opening wide ranging uses in biotechnology, which is credited to their unique physicochemical properties.

In this overview, we have reviewed the possible beneficial applications of MNPs in hard and soft tissues regeneration and in wound

Table 3. Effect of metal nanoparticles on wound healing.

Metal nanoparticle	Additional materials	Effect	Reference
AgNPs	----------	- Enhanced proliferation and migration of keratinocyte - Differentiation of myofibroblasts - Better collagen fibril alignment in repaired skin	[59]
AgNPs coat on	Poly gamma-glutamic acid hydrogel composite dressing	Promoted collagen deposition and epithelization	[90]
AgNPs	Aloe vera	- Regained epithelial thickness of induced oral ulcer - Increased alpha smooth muscle actin	[91]
AgNPsloaded on	Polyvinyl alcoholpatches	- Enhanced re-epithelialization - Effective antibacterial activity	[92]
AgNPs embedded with	Thiolated chitosan and dextran grafted with maleic acid	Local recruitment and activation of immune cells	[93]
AgNPsloaded on	Chitosan-poly ethylene glycol	- Fast re-epithelialization and collagen deposition - Reduced inflammation - Increased angiogenesis - Antibacterial potential	[94]
Biosynthesized AgNPs	----------	- Fast re-epithelialization of burn wounds - Intense collagen deposition	[95]
AgNPsloaded on	Composite hydrogels of alginate/gelatin	- Improved formation and maturation of granular tissue - Earlier formation of primary collagen scars	[96]
AgNPs	3D-printed scaffolds of alginate and cellulose	Antibacterial effect	[98]
AgNPs coating	Sodium alginate containing silica	Antimicrobial and antibiofilm activities	[99]
AgNPs impregnated	Bacterial cellulose / polydopamine scaffolds	- Induced epithelization and collagen synthesis of burn wounds - Enhanced removal of necrotic tissue - Upregulated growth factor genes involved in wound healing	[100]
AgNPsloaded on	Nanofibrous electrospun mats of hyaluronic acid and polygalacturonic acid	- Enhanced antibacterial activity - Fast wound epithelialization - Reduced tissue inflammation	[101]
AuNPs	Pluronic F127	- Normal histology of epidermis and dermis - Some hyalinosis of the underlying skeletal muscle - Scanty inflammatory cells	[105]
AuNPs	Bioactive glass	- Stimulated angiogenesis - Stimulated fibroblast proliferation	[106]
AuNPs containing	Wet electrospun silk fibroin	- Stimulated angiogenesis - Stimulated granulation tissue formation	[6]
AgNPsloaded on	Collagen scaffolds	- Promoted granulation tissue formation - Promoted neovascularization - Suppressed inflammation	[107]
ZnONPs	Polymethylmethacrylate fibers	Increased fibroblastic proliferation	[109]
ZnONPs	Electrospun polyvinilidine- trifluoroethelene	- Extensive networks of collagen fibers - Increased neovascularization	[111]
ZnONPs	sodium alginate-gum acacia hydrogels	- Increased fibroblast proliferation and migration rate - Antibacterial effect	[112]
ZnONPs	----------	- Promoted wound closure - Antimicrobial effect	[113]
ZnONPs	Collagen and orange essential oil	- Promote wound closure - Prevented bacterial growth	[114]
Ag/ZnONPs	----------	- Thick collagen fiber deposition - Rapid blood clot formation - High antibacterial property	[110]
TiO2NPs (from Moringa oleifera)	----------	- Accelerated wound closure - Antimicrobial activity	[116]
TiO2NPs loaded on	zein–polydopamine polymeric scaffold	Improved adhesion, proliferation and proliferation of cells during in vitro tests	[117]
TiO2NPs loaded on	Bacterial cellulose	- Promoted re-epithelization of burn wounds - Enhanced fibroblast migration and granulation tissue synthesis - Increased neovascularization	[118]

healing. It can be emphasized that metal nanoparticle-based materials have favorable features for enhancing tissue regeneration, hard tissue remineralization and stimulating wound healing. This may point out a reference to investigators who are concerned in metal nanomaterials biomedical uses, and offer high value of significance as upcoming treatment modalities.

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