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Teaser This review explores the benefits of incorporating various types of nanoparticle into dental biomaterials and their applications in different fields of dentistry.

The use of nanoparticles as biomaterials in dentistry

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Maintenance of oral health is a major challenge in dentistry. Different materials have been used to treat various dental diseases, although treatment success is limited by features of the biomaterials used. To overcome these limitations, materials incorporated with nanoparticles (NPs) can be used in dental applications including endodontics, periodontics, tissue engineering, oral surgery, and imaging. The unique properties of NPs, including their surface:volume ratio, antibacterial action, physical, mechanical, and biological characteristics, and unique particle size have rendered them effective vehicles for dental applications. In this review, we provide insights into the various applications of NPs in dentistry, including their benefits, limitations, properties, actions and future potential.

The need for nanoparticles in dentistry

Oral health is a gateway to the biosystem. Polymicrobial communities in the oral cavity occur as biofilms, which comprise bacteria and yeast, and can lead to dental infections [1]. Prevention of these infections is achieved by the mechanical removal of biofilms from the hard surfaces of the oral cavity, often supplemented by adjunctive antimicrobial agents [2]. However, these biofilms

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maintain their structural integrity and can build resistance to antimicrobial agents [3]. The exposure time of antimicrobial agents to toothpaste and mouthwash is often <30 s [4], and the prolonged use of antibiotic therapy often leads to antibiotic resistance. Thus, oral infections resulting from biofilms remain a major concern. Bacteria populate teeth surfaces and can cause the destruction of enamel, dentin, and pulp. Various restorative materials, such as amalgam, composites, and glass ionomer (GI) cement, have been used to seal dental cavities. For broken teeth, crowns and bridges of ceramic or stainless steel are used to prevent further breakdown. However, all these materials have disadvantages to their use. For example, secondary caries can occur under these restorations, they can fracture because of high occlusal stress, and they can even lead to hypersensitive teeth. Thus, NPs have been introduced in dentistry as an alternative to such materials.

The term 'nanotechnology' was first introduced by Richard Feynman [5] and describes materials that have mechanical and chemical properties superior to those used on a bulk scale, and have a structural range at the atomic level of 1–100 nm [6]. For example, nanocarriers 10 nm in diameter are 100 times larger than a hydrogen atom, but 100 times smaller than a bacterium. Incorporation of nanomaterials can improve the optical, chemical, electrical, and mechanical properties of compounds [7]. Therefore, nanotechnology has become a potent aid for various medical and dental applications, including dental remineralization, soft and hard tissue regeneration, local anesthesia, orthodontic drug delivery systems, permanent hypersensitivity cures, and the treatment of periodontal disease and dental caries [8].

Mechanism of action of nanoparticles

Nanotherapeutics offer the possibility to control biofilms by utilizing the biocidal properties of NPs [1]. NPs include spherical, cubical, or needle-shaped particles with a nanometric size range [9]. Metallic NPs, including oxides and organic NPs incorporated with polymers or coated onto surfaces of different biomaterials can have numerous dental applications [10]. NPs currently in use include nanopores, carbon nanotubes, nanocapsules, nanorings, nanospheres, and dendrimers [11]. The smaller diameter of NPs improves not only their mechanical properties, but also their antimicrobial action because of their high surface:volume ratio [1]. Upon application, NPs damage cellular membranes, impairing the action of microorganisms. This targeted antimicrobial property of NPs, with minimal adverse effects on the host, renders NPs suitable as antimicrobial agents or carriers. Various mechanisms have been proposed to explain how NPs control the growth of bacteria within the oral cavity, including metal ion release [12], oxidative stress [13], and nonoxidative mechanisms [14], although a contact-mediated biocidal action remains the most commonly proposed mechanism. This involves positively charged NPs being electrostatically attracted to the negatively charged bacterial cell membrane (Fig. 1). This attraction alters the cell wall permeability, resulting in membrane rupture and leakage of intracellular organelles. The advantage of NPs over conventional antimicrobial strategies is that NPs are not affected by antibiotic resistance mechanisms because they form a direct contact with the bacterial cell wall, rather than penetrating it.

Application of nanoparticles in dentistry

Nanomedicines used as dental materials have unique physicochemical and biological properties that can be used to overcome the complications associated with more traditional dental treatments [15]. Damaged dental tissues can lead to dental caries, periodontal disease, tooth sensitivity, bad breath, and oral precancerous and cancerous conditions. These can be cured by therapeutic intervention and use of biocompatible synthetic materials. Different types of NP and nanocomposites have been shown to mimic the properties of host tissues [16], although there is a general lack of understanding of such properties among the dental community. Therefore, this review focuses on the properties of different metal and polymer-based NPs used in restorative and adhesive dentistry, periodontology, endodontics, tissue engineering, acrylic resins, implant dentistry, and oral cancer (Table 1).

Silver nanoparticles

The antibacterial properties of silver are widely accepted in biomedicine, thus silver NPs (AgNPs) are combined with different materials to result in additional antimicrobial effects that help decrease biofilm formation and maintain better oral health [17]. Given their small size, AgNPs penetrate cell membranes readily, resulting in damage to, and inactivity of, the bacteria. The bactericidal efficacy of AgNPs is significantly enhanced in those that are <10 nm in diameter [18]. AgNPs target the bacterial peptidoglycan cell wall, leading to structural changes, increased membrane permeability, and ultimately cell death. AgNPs can also interact with bacterial proteins, preventing the replication of DNA, thus restricting cell growth [19]. To avoid the build-up of biofilms over composites and in restorations margins, AgNPs are incorporated into composite resins [20] and adhesive systems [21]. Cheng *et al.* investigated the incorporation of AgNPs at different concentrations (mass fractions of 0.028%, 0.042%, 0.088%, and 0.175%) in a composite resin and their effect on mechanical properties and biofilm formation. Composites with 0–0.042% AgNPs showed mechanical properties similar to commercial composites with no antibacterial activity. More microorganisms were killed by composites with a higher AgNP content, reflecting the therapeutic level required to kill the associated microorganisms. The production of lactic acid metabolites by 0.042% AgNPs was one third of, whereas the count of colony-forming units for total organisms was a quarter of, that of commercial composites.

In addition to their antimicrobial properties, biocompatibility is another vital property of biomaterials [22]. Zhang *et al.* studied the biocompatibility of AgNPs as restorative materials. AgNPs were incorporated at 0.05% by mass into a primer and an adhesive, which were then tested for human gingival fibroblast viability. The incorporation of AgNPs did not induce any cytotoxicity and substantially enhance the antibacterial potency of the primer and the adhesive. Therefore, AgNPs can be used clinically as antimicrobial agents in dentistry without being harmful to the host [23].

Additionally, the incorporation of AgNPs into polymers used as tissue conditioners and as denture bases has shown satisfactory outcomes as treatments for denture stomatitis [24]. Monteiro *et al.* analyzed the distribution and discharge of AgNPs from denture-based resins and observed that AgNPs were not detected in deio-

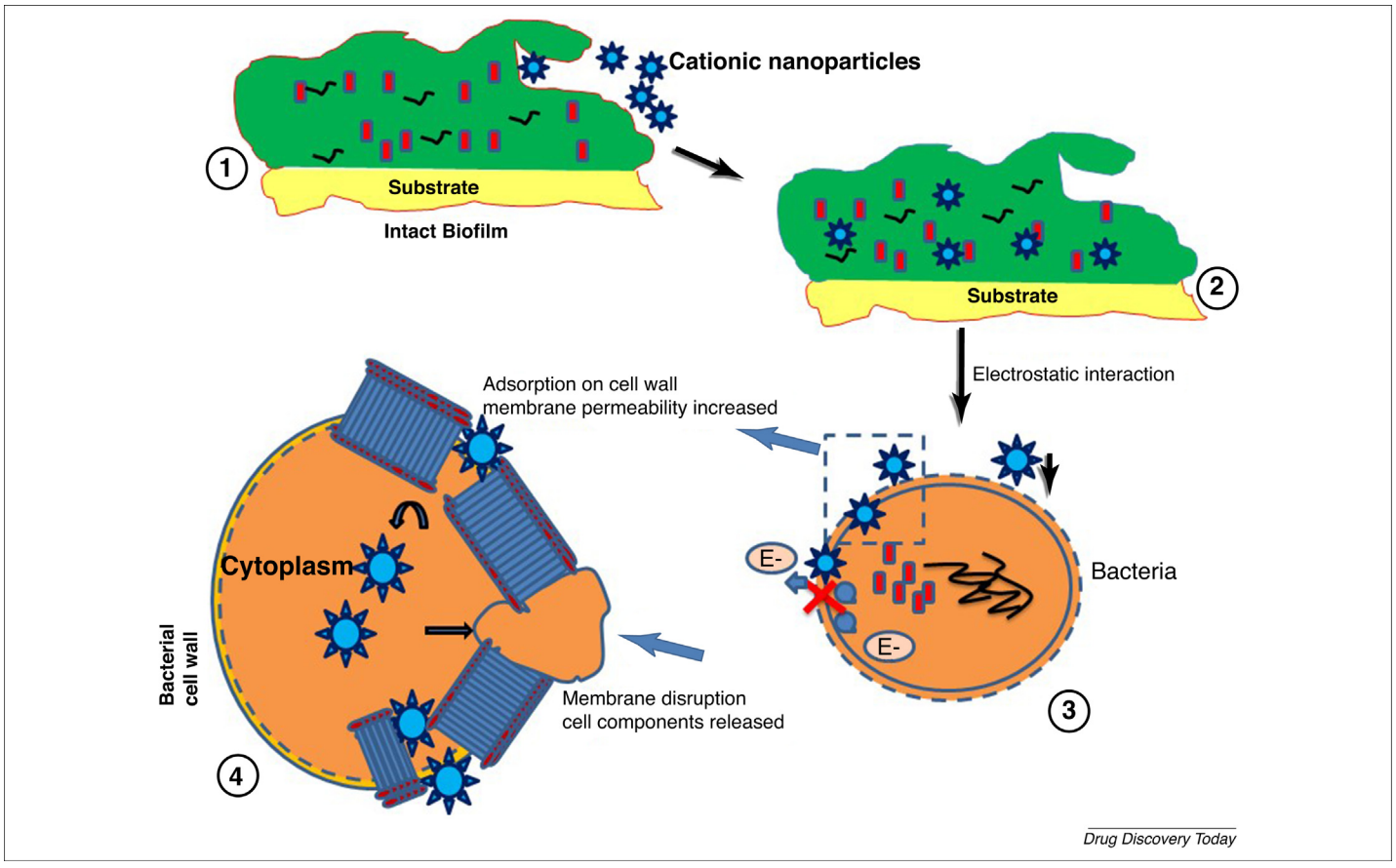

FIGURE 1

The antimicrobial mechanism of positively charged nanoparticles (NPs) by contact-mediated action. (a) Intact biofilm on the hard tissue surface of oral cavity contains numerous bacteria of various species and their exopolysaccharides (EPS). (2) Cationic NPs, when supplemented with local treatment, are attracted towards the negatively charged bacterial cell wall by electrostatic interactions. (c) Formation of reactive oxygen species with resulting damage to the membrane. This causes increase in cell wall permeability and ingress of NPs. (d) Once inside the cell, NPs cause the release of cytoplasmic constituents, resulting in bacterial cell lysis.

nized water. After 4 months of storage, AgNPs were primarily found on the surface of the nanocomposite samples, implying that the AgNPs on the surface would be available for interactions with potential microbes. Thus, the addition of AgNP to dentures could prevent infections associated with mucosal tissues [25].

Thus, AgNP show potential *in vitro* for application in various fields of dentistry based on their remineralization and antibacterial capabilities. However, more work is required to determine the optimized concentration of AgNPs, as well as preclinical evaluations and clinical studies. Nevertheless, we believe that the potential antimicrobial activity of AgNPs could be utilized effectively for local drug delivery (Fig. 2) as periodontal therapy or nanocoating for surgical devices, instruments, and wound healing bandages, among others.

Gold nanoparticles

Gold NPs (AuNPs) have been used as vehicles for the delivery of antimicrobials. Various coating agents have been used with AuNPs to enhance their potency and applications in medicine and dentistry. Importantly, AuNPs exhibit both antibacterial and antifungal actions [26]. Dadkan *et al*. showed that the optimal concentration of NPs in terms of mechanical properties was five times for tensile strength and ten times for flexural strength. However, at higher concentrations, the agglomeration of NPs had a negative effect on strength [27].

Regiel-Futyra *et al*. developed innovative chitosan-based AuNP composite films as a novel material with no cytotoxicity that showed high antibacterial activity against antibiotic-resistant strains of *Pseudomonas aeruginosa* and *Staphylococcus aureus*. They authors concluded that chitosan-Au nanocomposites could be used for many biomedical applications, including wound dressings, adhesive bandages, and coatings [28]. Given their stimulatory effect on osteoblast differentiation, AuNPs can also be used as osteogenic agents. Heo *et al*. observed the potential *in vitro* and *in vivo* effects of AuNP on osteoblast differentiation by coating them on a titanium (Ti) implant surface for the promotion of bone regeneration. The AuNP layer was uniformly immobilized on the Ti surface. The *in vitro* tests showed increased mRNA expression of osteogenic differentiation-specific genes and *in vivo* results were positive for osseous-implant interface formation. Thus, the researchers concluded that Ti–Au can be useful for dental implants for the preservation of nascent bone formation [29].

Furthermore, Braz *et al*. demonstrated the use of AuNPs as contrast agents for imaging. Spherical AuNPs were formed inside dentinal tubules by a *in situ* photothermal reduction procedure. Scanning electron microscopy (SEM) images revealed AuNPs in the

TABLE 1

Studies of different nanoparticles highlighting their applications, methods of preparation, particle sizes and outcomes[a]

Type of nanoparticle	Objective of study	Method of nanoparticle preparation	Particle size (nm)	Outcome of study	Refs
Silver	Explored influence of AgNPs on dental plaque and properties of nanocomposite materials	Combining Ag ethylhexanoate and ethyl methacrylate.	2.7	Decreased biofilm formation and improved mechanical properties of nanocomposites	[22]
	Comparative analysis of antibacterial action of AgNP, CHX, and sodium hypochlorite (NaOCl)	Catalytic chemical vapor deposition with addition of distilled water	35	At lower concentrations, AgNP solution had bactericidal effect similar to 5.25% NaOCl; thus, can be used as intracanal irrigates	[99]
Gold	Investigated influence of AuNP on properties of dental adhesive	Commercially obtained from Nano Natural Gift (BioGNP)	N/A	Increasing concentration of AuNP improved mechanical properties of dentin adhesive	[27]
	CS-AuNP films investigated for biological activity	Solvent evaporation method	10–-20	Did not show any cytotoxicity but high antibacterial activity	[28]
	Investigated coating of AuNPs on implant surface for enhanced bone formation	Reduction of chloroauric acid with trisodium citrate	30–50	Enhanced bone formation and maintenance	[29]
	Investigated AuNPs for dental imaging	Photothermal reduction procedure	40–120	Can be used as contrast enhancers for imaging techniques	[30]
Iron oxide	Evaluated iron oxide NP wettability of biomaterial surface influencing bacterial adhesion and biofilm growth	4 ml ferrous chloride and 1 ml ferric chloride added to sodium hydroxide	10	Combinational strategies, such as polymer brush coating to biomaterial surface and iron oxide NPs, significantly decreased biomaterial-associated infections	[33]
	Investigation of SPIONs in inhibition of plaque biofilm	Iron chloride (Fisher Scientific Inc, Waltham, MA) combined with sodium hydroxide	8	SPIONs alone or in combination prevented biofilm formation	[32]
	Preparation of nanocomposites and effects of size on cytotoxicity and inflammatory responses	Thermal decomposition method	20, 40, 100, and 200	Size-dependent effects on cellular toxicity and inflammatory response	[36]
Copper oxide	Investigated varied concentrations of CuO-NP on antimicrobial properties, resin-dentin bond strength and other mechanical properties in a two-step etch-and-rinse adhesive system	Commercially available (99.9% pure, Sky Spring Nanomaterials, Inc., Houston, TX, USA) 0.0075%, 0.015%, 0.06%, 0.1%, 0.5%, and 1.0%	40–60	Addition of CuO-NPs in concentrations up to 1% in a two-step etch-and-rinse adhesive system was feasible, and could provide antimicrobial properties and preserve bonding to dentin after 1 year, without reducing mechanical properties of adhesive formulations	[100]
	Assessed CuO-NP action on inhibition of biofilm formation on diverse surfaces	Solvo-thermal method	40	Decreased bacterial load and inhibited growth of biofilm organisms	[86]
	Investigated bactericidal and bacteriostatic effects of ZnO, CuO, TiO_2, and AgNP solutions	Commercially purchased (Fanavaran Araz Tajhiz Co., Iran)	40–60	Mouthwash containing nanoTiO_2 was most potent antibacterial	[101]
	Analyzed antibacterial action of CuO-NPs	Tesima™ plasma process	20–95	Efficient against bacteria associated with hospital-acquired infections	[102]

TABLE 1 (*Continued*)

Type of nanoparticle	Objective of study	Method of nanoparticle preparation	Particle size (nm)	Outcome of study	Refs
Hydroxyapatite	Evaluation of bond strength of GI and dentin because of addition of nano-hydroxyapatite and fluorapatite	N/A	100–200	Improved bond strength	[48]
	Use of HAP NP toothpaste for post-bleaching sensitivity	HAP NP paste (Renamel After Bleach, Sangi Co, Ltd, Tokyo, Japan)	–	HAP NP paste showed high efficiency for reduction of sensitivity after tooth whitening	[44]
Titanium dioxide	Analyzed effect of TiO_2 NP on conventional GI cement	Commercially available (batch number: MKBC-4174, Sigma-Aldrich)	21	Incorporation of TiO_2 NP improved antibacterial and physical properties of GI restorative material.	[53]
	Assessed impact of addition of small fraction of TiO_2 NP with dental resins	Provided by Evonik Industries (Essen, Germany)	15–30	Enhanced mechanical properties of resin by addition of TiO_2 NPs	[103]
Calcium fluoride	Prepared nano-sized calcium fluoride as a labile F reservoir and agent to reduce dentin permeability	Spray-drying system	10–15	Anticaries and desensitizing agent	[58]
	Addition of CaF_2 NPs to nanocomposite to improve strength and fluoride release	Spray-drying system	53	CaF_2 composites with CaF_2 NP had high strength and sustained release of fluoride ions	[59]
Calcium phosphate	Development of rechargeable CaP composite with NACP to prevent caries formation	Spray-drying system	116	Novel rechargeable CaP composites showed release of Ca and P ions	[63]
	Formulation of novel rechargeable CaP dental adhesive with NACP mass fractions	Spray-drying system	116	CaP recharge method improved mechanical and antibacterial properties	[104]
Silica	Evaluation of incorporation of SiNP in fillers on mechanical properties of composite restorative material	Sol-gel methods with silanization modification	Spherical particles 30 nm; anisotropic morphology 100–150 nm	Best mechanical properties achieved at low nanofiller concentrations where dispersion of NPs was more homogeneous	[105]
	Evaluation of effects of SiO_2 NPs on properties of silicone elastomer used for maxillofacial prostheses	Hydrophobic SiO_2 coated with silane-coupling agent obtained from Mknano (Mississauga, Canada)	15	Addition of SiO_2 NPs enhanced mechanical properties of elastomer	[106]
	Investigated effect of addition of silica NPs for interim restorations	Commercially purchased (Aerosil® 200, Degussa AG, Germany)	12	Increased fracture toughness of restorations	[107]
	Assessed effectiveness of this strategy as mechanism for remineralization of fully demineralized dentin following immersion in artificial saliva	–	–	Novel strategy for remineralization of fully demineralized dentin-infiltrated with NPs (dd-NPs) using HA and SiO2NPs	[67]

TABLE 1 (*Continued*)

Type of nanoparticle	Objective of study	Method of nanoparticle preparation	Particle size (nm)	Outcome of study	Refs
Chitosan	Analyzed cellular response to scaffolds incorporating chitosan nanofibers	Commercially purchased from Sigma-Aldrich (Milwaukee, WI, USA)	278 ± 98	Improved cell response observed in terms of attachment and proliferation because of addition of chitosan nanofibers	[108]
	Evaluated drug delivery carrier for release of bioactive molecules using chitosan NPs	Chitosan commercially available from Sigma (St Louis, MI, USA)	200	Enhanced adhesion properties, low cytotoxicity, and continuous release of chlorhexidine observed	[71]
Zirconia	Studied effect of zirconia NPs on mechanical properties of adhesive systems	Laser vaporization	20–50	NPs in adhesive layer or in primer increased tensile strength and promoted mineralization	[82]
	Effect of ZrNPs on resin denture bases	Commercially available (99.9% purity, 1314-23-4; Sigma-Aldrich)	90	Addition of ZrNPs enhanced flexural strength but lowered impact strength with increased concentrations of ZrNPs	[81]
	Gauged consequences of incorporation of ZrO^2–TiO^2 nano fillers, which can have antibacterial effects on mechanical properties of orthodontic adhesive	ZrO_2 (HWNANO, China); TiO_2 (Nanoshell, USA)	ZrO_2 70–80 nm; $TiO_2 < 50$ nm	The addition of ZrO_2–TiO_2 NPs to resin-based adhesives increased compressive, tensile, and shear bond strengths of adhesive *in vitro*	[84]
Zinc oxide	Experiment to test antimicrobial action of NZnO	Chemical synthesis	35	Prevented bacterial colonizers responsible for oral biofilm formation	[86]
PLGA	Investigation of PLGA NPs with methylene blue against *Enterococcus faecalis*	NA	NA	Exhibited antibacterial action against organism responsible for root canal infections	[93]
	Assessed PLGA NPs with minocycline for periodontal infections	Ion pairing method	85–424	Incorporation of minocycline with PLGA NPs showed antibacterial effects specifically against *Aggregatibacter actinomycetemcomitans*	[94]

[a] Abbreviation: NA, not available.

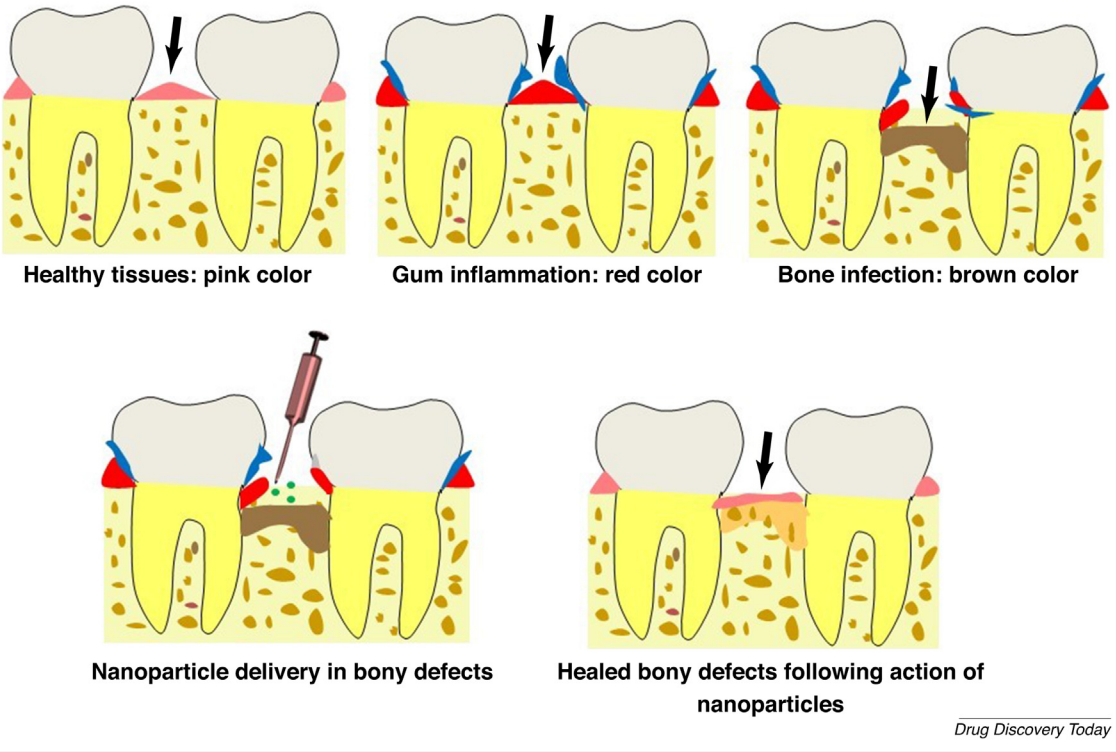

FIGURE 2

Local nanoparticle (NP) drug delivery for periodontal disease, depicting the various stages from healthy to diseased periodontium. Bony defects formed during periodontitis can be treated with the local application of NPs.

size range of 40–120 nm. 2D and 3D images revealed that, when used as contrast enhancers in optical coherence tomography (OCT), AuNPs can provide a non-invasive way to visualize dentinal structures [30]. Thus, AuNPs find implications in the design of nanocarriers for the delivery of antimicrobial agents as well as coatings on dental surfaces. Their osteogenic potential needs to be further investigated to enhance and accelerate the osseointegration of dental implants. This could have long-term benefits because these particles also have intrinsic antimicrobial properties. In addition to their use as potential delivery systems at nanoscale dimensions, these AuNP could also be utilized for the complex engineering of multifunctional nanocarriers with antimicrobial therapeutic actions and as imaging technologies.

Iron oxide nanoparticles

Metal iron oxide NPs with high surface areas and rare crystalline contours have a surface chemistry that is used extensively for contrast enhancement in magnetic resonance imaging (MRI), the delivery of drugs, tissue repair, hyperthermia treatment, and as antibacterial agents [31]. Fe_2O_3_ superparamagnetic iron oxide NPs (SPIONs) promote osteoblast functions and could provide an efficient treatment option for combating biofilms formed over the surfaces of dental implants [32]. It is difficult to eradicate such biofilms because of the exopolymeric matrix of the microorganisms in the biofilm, which is impenetrable by most antibiotics and host immune cells. It is possible to overcome this issue using SPIONs, because they readily penetrate mature biofilms. Thukkaram *et al*. analyzed the effect of diverse concentrations of iron oxide NPs on biofilm formation on different biomaterial surfaces and found that polymer brush-coated surfaces reduced bacterial adhesion compared with bare surfaces. A significant reduction in biofilm growth of *S. aureus*, *Escherichia coli* and *P. aeruginosa* was observed in the presence of iron oxide NPs compared with control. The highest reduction was observed in the presence of iron oxide NPs at 0.15 mg/ml compared with lower concentrations and control. Thus, a novel combination of polymer brush coating of the biomaterial surface and iron oxide NPs could significantly reduce biomaterial-related infections [33]. Taylor and Webster reported that iron oxide NPs in a concentration range of 0.01–2 mg/ml killed up to 25% of *Staphylococcus epidermidis* in a 48-h-old biofilm. Bacteria culture densities decreased at a SPION dose of 100 μg/ml or higher were incorporated into cultures, indicating that SPIONs can prevent biofilm formation [32]. Similar results were reported with iron oxide NPs on *S. aureus* biofilms [34]. By contrast, Haney *et al*. reported that 0.2 mg/ml SPIONs increased the biomass in a *P. aureus* biofilm [35].

In addition to antimicrobial properties, these NPs also have magnetic properties. Compared with other magnetic NPs, iron-oxide NPs are relatively safe and stable, although they can be modified by the addition of silica to enhance their stability and functionality. Different sizes (20, 40, 100, and 200 nm) with varied concentrations (10, 100, and 1000 μg/ml) of nanocomposite were tested for cytotoxicity using an MTT assay [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide]. The

results indicated that the NP size had little influence on fibroblast viability, whereas an NP concentration of 1000 μg/ml regardless of nanocomposite size decreased macrophage viability. In addition, NPs within the size range of 20–40 nm stimulated IL-6 production. Thus, the size-independent but concentration-dependent effects of iron oxide NPs on cellular toxicity and inflammatory response could be applied for the design of new drug carriers [36]. However, the optimized size and final concentration of the iron oxide in the composite mixture needs to be determined and future studies should investigate the biocompatibility associated with the increased concentration of the SPION. Cytotoxicity studies should also be conducted for the commercialization of these nanocomposites as treatment for biofilm formation.

Copper nanoparticles

Copper oxide (CuO) is very stable in terms of its physicochemical properties and, similar to silver, also displays antimicrobial properties. However, the use of such metal ions were restricted because of potential adverse effects caused by residual materials [37]. However, the emergence of nanotechnology has opened new avenues for the use of metal NPs, including CuO. Additionally, in term of its physicochemical properties, CuO is stable, demonstrating inhibitory action against various pathogenic microorganisms. The release of CuO from these NPs could have added advantages when it comes to eradication of pathogenic microorganisms. The antimicrobial action of the CuO NPs results from the generation of reactive oxygen species (ROS), which in turn damage the bacteria by attaching to the cell wall and enhancing the oxidative stress of the cells [38].

Anu *et al*. studied CuO NP-coated dental implants using a standard slurry dipping technique and wet chemical synthesis. Given that biocompatibility and mechanical properties change based on the surface characteristics of titanium, the authors also investigated the influence of different surface coatings of dental implants. Thus, different titanium dental implants were prepared by coating with CuO and these NPs were compared with uncoated titanium dental implants. The antibacterial activity of the titanium implants was expressed as the diameter of the zone of inhibition. Results showed that the CUO NP implant surface exhibited significant inhibitory zones of 31.6–38.6 mm for all test organisms compared with uncoated ones. These results suggested that the qualitative antibacterial activity of CuO NPs holds promise for use in the suppression of dental infections, although their effects on the mechanical and biological properties of implants need to be more thoroughly investigated [39].

Dental plaque forms preferentially on the immobile sites of the oral cavity and comprise a variety of biofilms. This highly organized structure with complex microbial species thrives on specific niches on hard tissues and mucosal surfaces. Khan *et al*. synthesized CuO NPs within the size range of 40 nm and assessed their ability *in vitro* to inhibit oral microbe and biofilm development on diverse matrices [40]. CuO NPs at a concentration of 50 mg/ml significantly prevented the growth of total oral bacteria and their polysaccharide Ren *et al*. observed minimum bactericidal concentrations (MBC) of CuO NPs against methicillin-resistant *S. aureus* and *E. coli* using an experimental concentration of 100–5000 mg/ml. The CuO NPs completely abolished the bacterial population with the addition of sub-MBC concentrations of AgNP. This indicates the potential synergism and possibility of development of composite NPs with enhanced antimicrobial properties [41].

Hydroxyapatite nanoparticles

Hydroxyapatite (HAP) is bioactive (osteoconductive) and, thus, has the ability to support osseous growth when placed near viable bone or cells with osseo differentiation potential. HAP NPs have been investigated for various applications in dentistry. Dental caries formation can be prevented by the use of fluorides. The demineralization process of teeth can be prevented primarily by precipitates of calcium fluoride. However, the fluoride levels required for remineralization are higher than those required for caries prevention [42]. Tschoppe *et al*. investigated the *in vitro* effects of HAP NP toothpastes on remineralization. Samples were obtained from bovine incisors. A quarter of all specimens were covered with acid-resistant varnish, which served as controls. Enamel and dentin lesions were prepared and constant monitoring of pH values of demineralizing solution was performed. After demineralization, the samples were kept in remineralizing solution for 14 and 35 days. Brushing actions were executed with the respective toothpaste and storage solution slurry twice daily. Microradiography was used to evaluate 100-mm sections. Increased remineralization of dentin and enamel was observed with toothpastes containing HAP NPs compared with amine fluoride toothpastes. Thus, the authors speculated that nanohydroxyapatite can promote remineralization [43].

Post-bleaching-related tooth sensitivity results from the presence of dentin and enamel defects. HAP NP toothpastes have the ability to repair these defects. Browing *et al*. investigated the of effect HAP NP paste and placebo on bleaching-related tooth sensitivity. For HAP NP and placebo (zero-HA), 29% and 51% of individuals reported dentinal sensitivity, respectively. The sensitivity was more prolonged for placebo paste compared with HAP NPs. Thus, it was concluded that the use of a toothpaste containing HAP NP can decrease tooth sensitivity in individuals undergoing bleaching without any desensitizing agent [44]. Okada *et al*. reported that HAP NPs can be synthesized via various methods, categorized as either solid-state or wet-state methods. Modifications of HAP NPs can be done with ion substitution methods using cations (such as Mg^{2+}, Sr^{2+}, Zn^{2+}, Fe^{3+}, and Ag^{+}) and/or anions (such as CO_3^{2-}, SiO_4^{3-}, and F^{-}) to alter their biocompatibility, sinterability, and mechanical properties. The other method is by modification with organic molecules, which can be adsorbed on HAP surfaces, and thus, these surfaces can be modified by additives [45]. The bioactivity of nanostructured HAP ceramics is expected to be better than that of conventional HAP ceramics (comprising coarser crystals) because of their nanoscale topography [46]. HAP NPs can be utilized as gene carriers for effective gene transfection, because of their ability to absorb DNA molecules [47]. Given their biological activities, HAP and fluorapatite (FA) can be used as biocompatible restorative materials. Moshaverina *et al*. comprehensively analyzed the effects of adding nano-FA and HAP to GI cement (Fuji II GC). This improved the mechanical properties of GC and its bond strength with dentin. Thus, HAP NP could be a useful addition to different restorative materials [48].

To understand the molecular mechanisms of nano-HAP function, Kasai *et al*. investigated the effect of HAP NP on periodontal

ligament (PDL) cells of human origin. Proliferation of these cells was stimulated with enamel matrix derivative (EMD) and HAP NP paste and was analyzed by addition of bromodeoxyuridine (BrdU). The potential for proliferation for HAP NPs was observed, although it was twice as low compared with EMD. The authors observed that HAP NPs can stimulate cell proliferation to a considerable extent and can contribute to periodontal tissue regeneration [49]. Yamada *et al*. evaluated microrough titanium surfaces coated with nanopolymorphic crystalline HAP to form a non-microroughened surface. The addition of HAP NPs resulted in an enhanced surface area, elevated bone to implant contact, and decreased soft tissue entrapment [50].

Titanium dioxide

Titanium dioxide (TiO_2) NPs are nanosized particles with special photocatalytic properties upon exposure to visible or UV light irradiation [51] and have various applications in medicine and dentistry. The bactericidal activity of TiO_2 is directly related to the formation of hydroxyl radicals by a photocatalytic reaction in the presence of water, which in turn damages polyunsaturated phospholipids in the peptidoglycan cell membrane, finally invading the cell and damaging the DNA [52]. To establish the effectiveness of TiO_2 in dentistry, Elsaka *et al*. investigated the physical and antibacterial properties of TiO_2 NPs incorporated into conventional GI restorative at different concentrations. TiO_2 NPs improved the properties of GI without compromising the bond strength and release of fluoride from GI. Thus, it was concluded that GI incorporated with TiO_2 NPs could be used for the restoration of Class I and II caries with higher stress-bearing areas [53]. Similarly, Sun *et al*. observed the effect of incorporating TiO_2 NPs in dental resins with controlled agglomeration. The improved degree of vinyl conversion led to improvement in resin performance. The shear bond strength and mechanical properties were also improved by incorporating TiO_2 NPs in the composite [54].

Additionally, Thomas *et al*. evaluated the antibacterial potential of TiO_2 NPs against organisms causing dental plaques. TiO_2 NPs showed good antimicrobial activity following the mechanism of action as described above, whereas free TiO_2 had no effect against plaque-causing organisms. TiO_2 NPs showed a greater zone of inhibition against different bacterial and fungal strains, indicating the efficiency of these particles. Finally, minimum inhibitory concentration of the TiO_2 NPs was found to be 15 mg/ml for effective control of invading microorganisms causing dental plaque [55].

Therefore, nanocrystalline semiconductor metal oxides have proved to be important in the field of dental treatments, although the molecular characterization of these NPs is necessary.

Calcium fluoride nanoparticles

Infractured restorations and secondary caries are the most frequent problems in restorative practice. The replacement of restorations is also often required because of caries at the restoration margins [56]. Fluoride helps to control the formation of caries, although its concentration should be optimized. Saliva in the oral cavity acts as a vehicle for fluoride and deposits in on caries by forming calcium fluoride (CaF_2). However, the percentage of CaF_2 formation in the oral cavity is because of the availability of minuscule concentrations of calcium in the cavity and the presence of limited contacts of sodium fluoride during mouthwash rinses [57]. Therefore, CaF_2 NPs can act as labile fluoride reservoirs by using calcium-containing dentifrices or mouth rinses. Furthermore, alteration in levels of CaF_2 NP fillers and reinforcing their quantities can help decrease dentin permeability. Sun and Chow developed nano-sized CaF_2 as a labile fluoride reservoir and compared its *in vitro* efficacy with that of a fluoride rinse. The nano-CaF_2 exhibited increased reactivity and solubility compared with its macro counterpart; because of the higher solubility of nano-CaF_2 compared with macro-CaF_2, an increased amount of fluoride absorption in the apatite product occurred. In addition, nano-CaF_2 could be used to treat exposed permeable dentin tubules in dentin hypersensitivity. Thus, the authors concluded that nano-CaF_2 can act as anticaries agents by increasing the labile fluoride levels in fluids of the oral cavity, enhancing tooth remineralization [58].

Xu *et al*. reported the sustained release of fluoride from CaF_2 nanocomposites compared with resin-modified and conventional GIs. Such a novel composite material offers a unique blend of the strength of a hybrid with the fluoride-releasing action of a resin-modified GI cement. Therefore, these modified materials could be a solution for the associated problems of restorative dentistry, fractured restorations, and secondary caries [59]. Moreover, CaF_2 NPs could be incorporated in conventional composite mixtures or mouth rinses, although, to fully understand the mechanism of prevention, further innovation and collaboration with other scientific disciplines is required.

Calcium phosphate nanoparticles

Advanced research in dental treatment and dentistry is focusing on conserving the original structure of the tooth; thus, dentists favor less invasive procedures and remineralization therapy [60]. However, the diffusion of Ca and PO_4 ions to the inner layer of the affected enamel is limited. As per the minimally invasive treatment concept, it is recommended to treat, rather than remove, infected dentin tissues [61]. Thus, calcium phosphate ($CaPO_4$) NPs (CPNPs) have been introduced. The incorporation of nanometric particle-sized (116 nm) CPNPs in nanocomposites has the potential to release increased amounts of Ca and PO_4 ions. These ions also enhanced the mechanical properties of CPNPs compared with conventional composites. Thus, the nanocomposite with CPNPs can neutralize lactic acid solutions and can accomplish remineralization of the dentin to levels approximately four times that achieved by a fluoride-releasing composite [62].

Recently, Zhang and team investigated the $CaPO_4$ rerelease and recharge efficacy of a novel rechargeable CPNP-incorporated composite. Rerelease with recharge was observed as a result of acidic monomers within the composite. There was sustained rerelease of Ca and PO_4 ions for 42 days without any need for further recharge. Thus, novel rechargeable CPNP-incorporated composites could be used for caries prevention, and in applications in adhesive and esthetic dental materials [63].

Silica and silicon dioxide nanoparticles

Silica and silicon dioxide NPs (SiNsP) have been explored widely for numerous biomedical applications, where their large interface area with bioactive functions make them a potential filler material for restorative dental application. SiNPs can also improve the

overall mechanical properties of fillers, with high resistance to aging and cracking [64].

Hosseinalipour *et al*. studied composites with varied fractions of SiNPs. Interestingly, composites with SiNP fillers (filler mass fractions of 20–50% with particle size of 20–50 nm) showed superior mechanical properties compared with conventional composites (mass fractions of 60% with particle sizes 10–40 μm). These results confirmed that the filler fractions influence the mechanical properties of a restorative material [65]. Additionally, Rezvani and team indicated that SiNPs could enhance the flexural strength and modulus of dental fiber-reinforced composite resins [66].

In combination with HAP NPs, Besinis *et al*. assessed a novel guided tissue regeneration strategy with SiNPs to remineralize dentin. The demineralized dentin specimens infiltrated with $nSiO_2$ (dd-$nSiO_2$) showed the highest remineralization potential when exposed to artificial saliva, restoring up to 20% of the phosphate levels of sound dentin. Microcomputed tomography (CT) data demonstrated a 16% recovery of the mineral volume in dentin infiltrated with SiNPs and a significant decrease in the mineral separation to levels comparable with that of sound dentin. Demineralized dentin infiltrated with SiNPs appeared to encourage the heterogeneous mineralization of the dentin collagen matrix following exposure to an artificial saliva solution [67].

Chitosan nanoparticles

Various authors have reported studies of metallic NPs in dentistry, although their safety remains a concern [68,69]. An ideal NP should be nontoxic, biodegradable, and bioinert in different tissues. Therefore, many research groups have focused on organic NPs, such as chitosan (CS), to avoid the adverse effects of metallic NPs [70]. Consequently, novel drug delivery carriers have been developed for the release of bioactive molecules through the introduction of chitosan NPs (CSNPs).

Chronopoulou *et al*. showed that CSNPs proficiently entrapped chlorhexidine (CHX) at neutral pH and a sustained release profile was observed (for at least 48 h). There was improved release of drug and cytocompatibility because of the functionalization with the peptidomimetic derivative glutathione (GSH). Preliminary research showed that CS-GSH-CHX NPs could hold onto human tooth surfaces because of chemical surface affinity. Thus, formulations of CSNPs can be effectively applied for therapeutic interventions for *in vivo* daily oral care [71]. Early enamel carious lesions can also be remineralized by the use of CSNPs [72]. CSNPs have also shown success in endodontic treatment because of their antibacterial proprieties resulting from their polycationic charge and high reactivity in nanoform particles compared with their bulk form [73–75]. Compared with calcium hydroxide, CSNPs showed a marked reduction in *Enterococcus faecalis* [75]. High antimicrobial effects on biofilms of *Streptococcus mutans* were also observed with low-molecular-weight CS [76]. Given that *S. mutans* is one of the most common organisms associated with caries, controlling its growth could prove to be an effective way of preventing dental caries [77].

Subsequently, Bastami *et al*. fabricated a gelatin-coated 3D β-tricalcium phosphate scaffold with a bone morphogenetic protein 2 (BMP2)-loaded CSNP delivery system for use in bone tissue engineering. This delivery system was found to be osteoinductive because of the sustained release of recombinant BMP (rhBMP2) from the NPs. The framework was biologically compatible and could be used for the delivery of other cells and growth factors in tissue engineering [78].

In addition, CSNPs have also been explored for imaging cancer cells and in controlled drug delivery systems [79]. Thus, polymeric NPs have potential in diversified fields in dentistry, although further studies are required to translate these formulations to the clinic.

Zirconia nanoparticles

Zirconia oxide (ZrO_2) is a metal oxide with numerous applications because of its enhanced surface area, improved mechanical properties, and biocompatible material [80]. It can be used to improve the overall strength of restorative materials [81]. Lohbauer *et al*. investigated the effect of adding ZrO_2 NPs (ZrNPs) to dental adhesive systems. ZrNPs were formulated by a laser vaporization method and led to higher tensile bond strength with dentin [82]. Gad *et al*. assessed the effects of ZrNPs on the strength of repaired denture base resins. NPs were used in increased concentrations of wt% of acrylic powder. Incorporation of a denture resin with ZrNP led to improved flexural strength. These results were in agreement with an earlier study that concluded that the addition of ZrNPs to acrylic resins enhanced the flexural strength of the material [83]. The reasons for these properties are related to the increased distribution and silanization of the NPs. In addition, during this process, cracks in the dentine might have been exposed to compressive stress because of the expansion of ZrO2 crystals, which might have arrested crack propagation. Transformation toughening also prevented the breakage of resins because of the absorbance of energy during phase transformation. At higher concentrations, cracks might increase because of agglomeration affecting the overall impact strength. Thus, the use of ZrNPs for the repair of resins improves resistance to fracture of the denture base [81]. Felemban *et al*. examined the effect of incorporating different concentrations of ZrO_2-TiO_2 NPs on orthodontic adhesive properties. There was an increase in compressive strength, tensile strength, and shear bond strength *in vitro*. Compared with single additives, nanofillers provided a better composite with antibacterial effects on different properties of orthodontic adhesive systems. ZrO_2 was added because of its biocompatibility and aesthetic white color [84]. However, *in vivo* experiments and randomized trials are needed to validate these findings.

Zinc oxide nanoparticles

Teymoornezhad *et al*. evaluated flowable composites resins containing different percentages of nano zinc oxide (NZnO) particles, which have antimicrobial properties. incorporation of NZnO particles did not alter the bond strength and showed antimicrobial effects with decreased microleakage rates [85]. Tabrez Khan *et al*. observed that NZnO inhibited biofilm formation by oral cavity bacteria on different surfaces, highlighting the bactericidal action of oral biofilm colonizers [86].

Polymeric nanoparticles in dentistry

Biodegradable polymeric NPs have shown great therapeutic potential in controlled drug delivery methods. These polymeric NPs can deliver the desired drug to the required site effectively without cytotoxicity on adjacent tissues. Various experiments have been

conducted to investigate drugs loaded with polymeric NPs for controlled release of the drug. Aliphatic polyesters, such as poly (lactic acid) (PLA), poly(glycolic acid) (PGA), poly(3-hydroxybutyrate) (PHB), and poly(ε-caprolactone) (PCL) [87], are used in the fabrication of devices with controlled release efficiency. Mundargi *et al*. analyzed *in vitro* and *in vivo* a novel biodegradable microsphere with combinations of PCL and poly-lactic-co-glycolic acid (PLGA) for the controlled release of doxycycline (DXY). *In vitro* release showed an initial burst effect followed by controlled release of the drug for 11 days. Fourier transform infrared spectroscopy (FT-IR) showed no interaction between polymers and the drug. Clinical parameters, such as probing pocket depth, plaque and gingival index, and relative attachment level, showed larger improvements with the microsphere delivery group and scaling root planning compared with the scaling and root planning group [88].

Dabbagh *et al*. analyzed the effect of polyethylene glycol (PEG)-coated maghemite NPs (PEG-MNPs) in the treatment of dentin hypersensitivity. These MNPs blocked the dental tubules via an external magnetic field because of their superparamagnetic properties. The specimens that were treated with these MNPs for 2 h showed the highest occlusion of tubules. Thus, PEG-MNPs can be used to treat dental hypersensitivity because they tightly seal the tubules with relatively fast diffusion [89]. Priyadarshini *et al*. analyzed the *in vitro* and *ex vivo* effects of novel PCL nanocapsules (nano-PCL) loaded with CHX in various ratios compared with unloaded nanocapsules. A ratio of 125:50 of nano-PCL-CHX showed the best release of CHX and antibacterial effects *ex vivo* and *in vitro*. SEM as well as transmission electron microscopy (TEM) showed deeper diffusion and retention of CHX within dentin tubules *ex vivo* and *in vitro*. Thus, this study revealed PCL-CHX as a novel nanosized drug delivery system for demineralized surfaces of dentin and resin dentin interfaces [90]. A similar study with CHX-loaded PLGA-NPs showed desired physiochemical characteristics with release of CHX for up to 4 weeks, with efficient delivery inside dentin tubules. NPs were in close association with resin tags post bonding, indicating resin infiltration [91].

Poly-lactic-co-glycolic acid nanoparticles

PLGA is approved by the US Food and Drug Administration for biomedical applications because of its biocompatibility and biodegradability, given that its biodegradation results in water and CO_2 [92]. Thus, PLGA is used in a range of medical and pharmaceutical applications, including nanotechnology. Therefore, PLGA NP have various applications in dentistry, including endodontics [93] and periodontics [94].

Along with their biocompatibility and biodegradability properties, the antimicrobial properties of PLGA are evident in dental applications. The main causative organism of endodontic failure is *E. faecalis* [95]. To investigate the antimicrobial property of PLGA NPs, Pagonis *et al*. detected that, in the presence of light and methylene blue, PLGA completely eliminated *E. faecalis* biofilm species from infected root canals in human teeth [93]. Studies also support that encapsulation of antimicrobial agents into the nanocore of PLGA NPs could effectively control the growth of these microorganisms [96]. Others reported that novel minocycline PEGylated PLGA NPs can be used to improve antibacterial efficiency, where the antibacterial potential was found to be comparatively superior compared with other tested NPs [94].

Gentile *et al*. prepared a porous CS-gelatin 3D scaffold incorporated with PLGA NPs with parathyroid hormone (PTH) for tissue regeneration. These were seeded with osteoblast cells and the release profile of PTH and biological activity were investigated. There was improved expression of alkaline phosphatase levels by osteoblast cells, verifying the activity of PTH released from NPs within the scaffolds for bone regeneration [97]. Available literature on polymers used in NPs in dentistry suggests PLGA to be the most widely used polymer in different sectors of dentistry, from periodontology and endodontics to bone healing, although future studies are required to explore its preclinical use in the clinic.

Concluding remarks and future perspectives

The nanoscale size of NPs has a profound effect when it comes to repairing or regenerating lost tissues at the molecular level. Recent developments in NPs and nanotubes in operative dentistry, endodontics, and periodontal management will have a crucial role in dentistry. Their low toxicity, antimicrobial properties, and enhanced protein–surface interactions can be used for dental applications.

For example, in restorative and adhesive systems, the incorporation of NPs into various composite resins and adhesive systems improves the mechanical properties of the restorative material (improving the tensile and compressive strength). This reduces the chance of secondary caries because of the elimination of microleakage and enhanced bond strength between dentin and the adhesive material. Certain NPs also exhibit the potential for remineralization of early carious lesions. In endodontics, NP-based irrigates can be a novel method for canal space irrigation, providing the added benefit of accessing the lateral canals for the removal

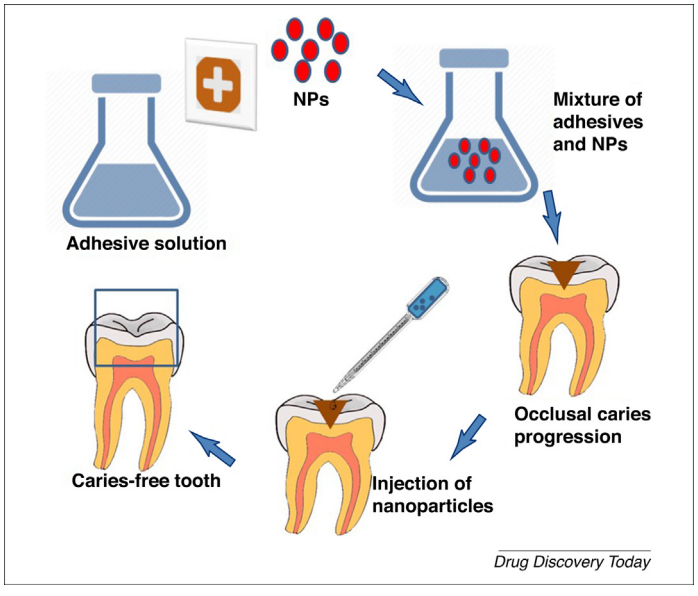

FIGURE 3

Potential use of nanoparticles (NPs) in the treatment for dental caries and their proposed mode of delivery. Caries progression can be arrested by local injections of NPs into the affected areas. NPs can be added with adhesive systems to prevent further microleakage and recurrence of caries.

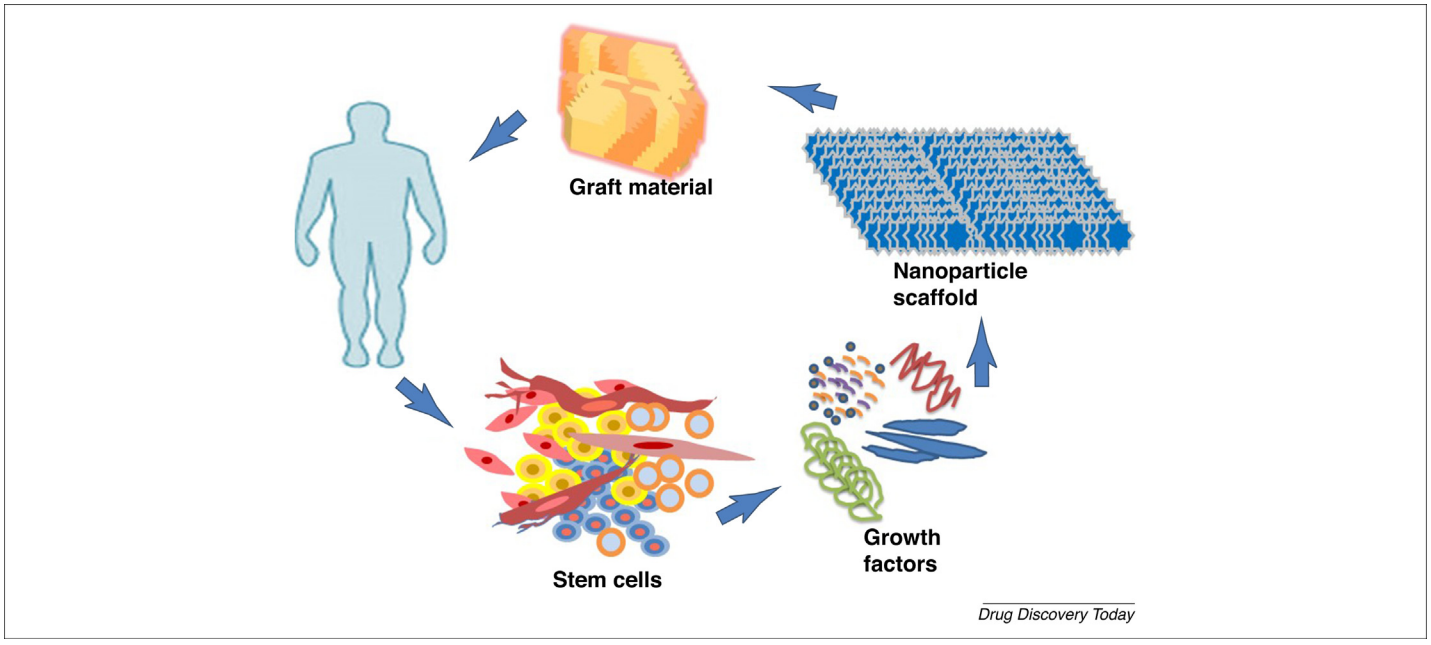

FIGURE 4

Nanoparticle (NP) application in tissue engineering. The key factors of dental tissue engineering are growth factors, stem cells, and scaffolds. NPs can be used as biomaterial scaffolds for tooth biomedical engineering.

of pulp debris. The addition of NPs has also been shown to be effective against root canal-infective organisms and also reduces microleakage in canal spaces, preventing recurrence of infection. For replacement dentures, NPs added to polymers used for tissue conditioners decrease the chance of denture stomatitis. They also improve resistance to fracture of the denture base. With implant dentistry, NP coatings on titanium surfaces prevents peri-implant infection because of their antibacterial action. They can also act as osteogenic agents because of their biocompatibility. For periodontal indications, NPs can stimulate periodontal ligament cells and can have an important role in the regeneration of lost periodontium. When added controlled drug delivery systems, organic NPs cause the apoptosis of tumor cells, preventing further spread of these cells. However, given that many of these applications with biomaterials are based on *in vitro* experiments, there is a growing need for further *in vivo* and *in situ* experiments to confirm these benefits and resolve biocompatibility concerns.

Given that the regeneration capacity of dental tissues is limited, NPs can facilitate the healing of affected tissues. Novel Injectable mixtures (single or composites) of different NPs can be used at the site of dental defects (Fig. 3) because of their increased and improved surface volume, biocompatibility, bioactivity, and enhanced mechanical properties. For periodontal diseases, another option is to orchestrate cellular components from gingiva in tissue regeneration with external factors [98]. Recent developments in nanomaterials and nanotechnology could provide promising insights into the commercial applications of nanomaterials in terms of the 'true' regeneration of periodontal apparatus as a whole, including dentine, cementum, periodontal ligaments, and bone. Scaffolds impregnated with NPs along with tissue engineering triads can mimic an extracellular matrix that can initiate the formation of host tissues (Fig. 4). Thus, given their low toxicity, antimicrobial properties, and enhanced protein–surface interactions, these NPs can be used for various dental applications. Their potential role in the formation of improved biomaterials in different forms (e.g., injectable compounds or fibers) is a significant innovation in dentistry. The combination of continual refinements in conventional treatment modalities and advances in the clinical applications of nanotechnology is promising way to improve dental care.

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