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REVIEW ARTICLE

Next-generation antibacterial nanopolymers for treating oral chronic inflammatory diseases of bacterial origin

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Abstract

Background: 'Periodontitis' refers to periodontal destruction of connective tissue attachment and bone, in response to microorganisms forming subgingival biofilms on the root surface, while 'apical periodontitis' refers to periapical inflammatory processes occurring in response to microorganisms within the root canal system. The treatment of both diseases is based on the elimination of the bacterial challenge, though its predictability depends on the ability of disrupting these biofilms, what may need adjunctive antibacterial strategies, such as the next-generation antibacterial strategies (NGAS). From all the newly developed NGAS, the use of polymeric nanotechnology may pose a potential effective approach. Although some of these strategies have only been tested in vitro and in preclinical in vivo models, their use holds a great potential, and therefore, it is relevant to understand their mechanism of action and evaluate their scientific evidence of efficacy.

Objectives: To explore NGAS based on polymeric nanotechnology used for the potential treatment of periodontitis and apical periodontitis.

Method: A systemic search of scientific publications of adjunctive antimicrobial strategies using nanopolymers to treat periodontal and periapical diseases was conducted using The National Library of Medicine (MEDLINE by PubMed), The Cochrane Oral Health Group Trials Register, EMBASE and Web of Science.

Results: Different polymeric nanoparticles, nanofibres and nanostructured hydrogels combined with antimicrobial substances have been identified in the periodontal literature, being the most commonly used nanopolymers of polycaprolactone, poly(lactic-*co*-glycolic acid) and chitosan. As antimicrobials, the most frequently used have been antibiotics, though other antimicrobial substances, such as metallic ions, peptides and naturally derived products, have also been added to the nanopolymers.

Conclusion: Polymeric nanomaterials containing antimicrobial compounds may be considered as a potential NGAS. Its relative efficacy, however, is not well understood since most of the existing evidence is derived from in vitro or preclinical in vivo studies.

KEYWORDS

antimicrobials, nanofibres, nanoparticles, nanopolymers, periodontitis

INTRODUCTION

Pulpal and periodontal tissues are connected by anatomical structures (i.e. apical foramen, lateral canals and dentinal tubules) forming communication pathways with potential transmission and translocation of different substances, irritants and even microorganisms (Duque et al., 2019; Gomes et al., 2009). Although chronic inflammatory conditions in these tissues lead to distinct pathological entities (periodontal and periapical infections), they share pathogenic mechanisms since they both are chronic inflammatory processes triggered by a polymicrobial microbiota conductive to connective tissue and bone destruction (Cavalla et al., 2021). These destructive processes are not caused by the bacteria, but rather by an unresolved chronic inflammatory process mediated by host-derived cytokines and other metabolites triggered in response to the bacterial challenge (Alvarez et al., 2019; Cavalla et al., 2021; Duque et al., 2019; Garcia de Aquino et al., 2009; Reife et al., 2006).

In terms of the microbiotas associated with either periapical and periodontal diseases, although there are specific pathogens identified in each of these conditions and there is a high inter-individual variability, there are also similarities, since the predominant microbiota of both diseases is mainly composed of obligate and facultative anaerobic bacteria and they share relative abundances of common microbial communities (Gomes et al., 2015; Kobayashi et al., 1990; Lopes et al., 2021; Pereira et al., 2011; Siqueira & Rôças, 2009, 2022). In fact, more than 68 common taxa have been identified in both root canal and periodontal pocket biofilms (Lopes et al., 2021) and pathobionts such as *Fusobacterium nucleatum*, *Dialister* species, *Porphyromonas endodontalis*, *Porphyromonas gingivalis*, *Prevotella* species, *Tannerella forsythia* and *Treponema* species have also been identified in both (Siqueira & Rôças, 2022).

While the modes of therapy to treat these pathologies differ significantly, they share a common objective, the mechanical disruption of the biofilms, frequently combined with adjunctive antimicrobial strategies aimed to further control the infective challenge (Cavalla et al., 2021). In periodontitis, by subgingival instrumentation, as recommended in the EFP S3-level clinical practice guideline for the treatment of periodontitis (Herrera et al., 2022; Sanz et al., 2020); and in the treatment of apical periodontitis, by root canal instrumentation as recommended in the recently published ESE S3-level clinical practice guideline for the treatment of pulpal and apical disease (Duncan et al., 2023). These therapies, however, are not always predictable and it is estimated that around 35% of deep pockets may not achieve the end point of treatment (probing pocket depth reduction and absence of bleeding on probing) following subgingival instrumentation, regardless of the type of mechanical therapy implemented (Suvan et al., 2020; Tomasi et al., 2023). Similarly, in the treatment of apical periodontitis, the estimated failure rate in primary root canal treatments ranges between 14% and 20% (Meire et al., 2023; Ng et al., 2007; Torabinejad et al., 2007). This may indicate that one out of five teeth with apical periodontitis will not achieve the desired outcome after regular treatment (Meire et al., 2023). These failures may be mainly attributed to persistence of intra-radicular infection, usually lodged in isthmuses, ramifications, deltas or irregularities that are not affected by conventional endodontic protocols (Karamifar et al., 2020). In the study of 106 biopsy tooth specimens with apical periodontitis, the prevalence of intra-radicular biofilms was of 80% in untreated root canals and 74% in treated ones (Ricucci & Siqueira, 2010; Siqueira & Rôças, 2022).

Within this context, the advent of next-generation antibacterial strategies (NGAS) could be of special interest in the treatment of both pathologies. One of such strategies is the use of nanomaterials, shaped as particles or fibres with a diameter of 1–100 nm (according to the ISO/TS 80004-1:2023, biomaterials dimensioned in the nanoscale, ranging between 1 and 100 nm). These nanoparticles and nanofibres have a high reactivity and a high surface-to-volume ratio (Gao et al., 2023), what makes them ideal as delivery methods for different active agents, such as antimicrobial compounds, either by doping with the active drug or constructed as controlled drug release (Gao et al., 2023; Suriyaamporn et al., 2023). On the downside, however, nanomaterials, due to their size and ability to perfuse different body compartments, are highly regulated for assuring their safety (Boverhof et al., 2015).

The potential therapeutic use of these nanomaterials to treat periodontal and peri-implant diseases is, however, unknown since most of the existing evidence derives from in vitro or preclinical in vivo studies. It was, therefore, the main objective of this report to explore this evidence and review both their mechanism of action and their relative efficacy for their potential as adjunctive therapies to treat periodontitis and periradicular periodontitis.

METHODS

This narrative review was conducted following the Scale for the Assessment of Narrative Review Articles (SANRA) (Baethge et al., 2019).

Using the National Library of Medicine (MEDLINE by PubMed), The Cochrane Oral Health Group Trials

Register, EMBASE and Web of Science (WOS), a literature search was performed for papers, including peer-reviewed publications up to September 2023. Only publications in English were eligible. Letters to editor, lectures and personal opinion letter were excluded.

Combinations of several search terms such as 'periodontal', 'periodontitis', 'antibacterial', 'antimicrobial', 'polymer', 'polymeric', 'nanotechnology', 'nanoparticles' and 'nanofibers' were applied. In addition, bibliographies of eligible articles were also manually searched for missing papers after the electronic search.

RESULTS AND DISCUSSION

Polymers

Polymeric materials for antibacterial-loaded nanofibres

Several polymers have been used in the design of nanofibres constructed as antibacterial carriers. Although nanofibres can be resorbable or nonresorbable, most of the reported antibacterial nanofibres used to treat oral diseases are constructed in bioabsorbable biomaterials, mainly polymers (Table 1). Among these, polycaprolactone (PCL) has been the most used, being a synthetic organic polymer with good biocompatibility, permeability and flexibility (Zhao et al., 2022). Furthermore, it does not release acidic by-products during its degradation (Zhao et al., 2022), which is one of the main disadvantages of the polyglycolic polymeric biomaterials (Toledano-Osorio, Manzano-Moreno, Ruiz, Toledano, & Osorio, 2021). PCL is also more stable than other resorbable polymers such as polylactides, due to the lower proportion of ester bond per monomer, and thus, each PCL chain fragment takes longer time to be enzymatically hydrolysed (Malikmammadov et al., 2018). In relation to its use as nanocarrier, PCL's hydrophobic nature is especially effective when loaded with lipophilic drugs (Malikmammadov et al., 2018; Wang et al., 2009), such as tetracycline and doxycycline, which are two of the mostly used antibiotics for local delivery (Table 1). Hydrophobic drugs can also be used, but they tend to move towards the interface, thus remaining in an adsorbed state (Malikmammadov et al., 2018; Wang et al., 2009). The manufacturing process of nanofibres is usually by electrospinning, what creates ultrafine fibres (ranging from 3 nm to 10 μm) when applying an electrostatic field (Bottino et al., 2014, 2017; Budai-Szűcs et al., 2021; Chen et al., 2022; Deepak et al., 2018; Ekambaram et al., 2021; Lee et al., 2014, Lee, Heo, et al. 2016; Monteiro et al., 2017; Reise et al., 2023; Ribeiro et al., 2020; Shahi et al., 2017; Tsai et al., 2018; Zupančič, Sinha-Ray, et al., 2016). These fibres exhibit a high porosity and a high surface area-to-volume ratio, what makes them particularly useful as drug carriers (Toledano et al., 2020). In most of the reported constructs, the antibacterial compound is entered into the initial polymer solution, what increases its efficiency, though in some studies the antibacterial compound was incorporated by adsorption once the electrospinning process was completed (Bottino et al., 2014, 2017; Deepak et al., 2018; Shahi et al., 2017).

Although other bioresorbable biomaterials, such as polylactic acid (PLA), polydioxanone (PDO) or chitosan, can be constructed as nanofibres, either in single formulations or as combination of nanomaterials, the studies reporting their use are very scarce and heterogeneous (Table 1). However, most of the combined materials include the use of a hydrophobic polymer base, such as polycaprolactone, polyurethane or poly(methyl methacrylate) (Table 1). The rational of using these polymers with β-cyclodextrin (Monteiro et al., 2017), chitosan (Zupančič, Sinha-Ray, et al., 2016) or gelatin (Lee et al., 2016) is the increase in nanomaterial's resorption time, since the active component embedded in the polymer will de-resorb slowly, what implies a longer release of the active substance (Srikar et al., 2008; Zupančič, Sinha-Ray, et al., 2016). The combination of different polymeric substances as carriers is mainly explored in order to improve the physico-chemical properties of the nanomaterial, in most of the cases the life span of the material.

Polymeric materials for antibacterial-loaded nanoparticles

Polymeric NPs may be defined as solid colloids or polymeric mixtures synthesized at a nano-scale dimension using natural and/or synthetic polymers, either resorbable or nonresorbable (Shakya et al., 2023). These polymers are usually doped with chemical compounds, hence acting as drug carriers. Depending on where the active component or drug is located, they are termed nanospheres when located at the surface of the NP; or nanocapsules, when located in the core of the NP (Shakya et al., 2023).

The most used polymers as NPs is poly(lactic-*co*-glycolic acid) (PLGA) (Table 1), a biodegradable aliphatic polyester-based polymer, composed by two α-hydroxyacids, lactic acid (LA) and glycolic acid (GA). By varying the proportions of each co-polymer, its degradation rate and biodegradability can be modified (Owen et al., 2010; Sun et al., 2017) and when LA is reduced, its crystallinity will increase (Sun et al., 2017). Since both LA and GA are degraded via tricarboxylic acid cycle, producing carbon dioxide and water, their toxicity is minimal (Sun et al., 2017).

TABLE 1 Nanomaterials used in the literature as carriers for antimicrobial substances.

Carrier			Articles
Pure formulations	Nanofibres	Polycaprolactone nanofibres	Chen et al. (2022), Dias et al. (2019) and Monteiro et al. (2017)
		Carbon nanofibres	Zheng et al. (2023)
		Poly(L-lactide-*co*-D,L-lactide) (PLA)	Reise et al. (2023)
		Strontium-substituted hydroxyapatite nanofibre	Tsai et al. (2018)
		Chitosan	Lee et al. (2014)
		Polydioxanone	Bottino et al. (2014)
	NPs	PLGA nanospheres/NPs	Kalia et al. (2017), Lecio et al. (2020) and Mahmoud et al. (2019)
		Chitosan	Martin et al. (2019), Nagahara et al. (2013) and Suriyaamporn et al. (2023)
		Polycationic poly(2-(dimethylamino)ethyl methacrylate)	Shi et al. (2021)
		Carbon quantum dots	Liang et al. (2020)
		Hydroxyapatite NPs	Deepak et al. (2018)
		Polycaprolactone nanocapsules	Pramod et al. (2016)
	Hydrogels	Chitosan	Aminu et al. (2019), Srinivasan et al. (2013) and Xu, Zhou, et al. (2020)
		Collagen	Lin et al. (2023)
		2-Hydroxyethyl methacrylate	Wong et al. (2023)
		Poloxamer	Qi et al. (2022)
		Gelatin	Budai-Szűcs et al. (2021)
		Sodium alginate	Xu, Zhao, et al. (2020)
		Gelatin methacryloyl	Ribeiro et al. (2020)
Combined formulations	Nanofibres	Poly(D,L-lactide) + poly(e-caprolactone) + gelatin	Bottino et al. (2017) and Shahi et al. (2017)
		Sulfonated poly(ether ether ketone) (SPEEK) + aminated zirconia	Ekambaram et al. (2021)
		Collagen + chondroitin 4-sulphate + fibronectin	Craciunescu et al. (2021)
		Collagen + HA NPs	Shoba et al. (2020)
		Polycaprolactone nanofibres + chitosan	Guarino et al. (2017)
		Chitosan + polyethylene oxide nanofibres	Zupančič, Potrč, et al. (2016)
		Polycaprolactone fibres + β-cyclodextrin	Monteiro et al. (2017)
		Polyurethane nanofibres + gelatin	Lee, Heo, et al. (2016)
		Poly(methyl methacrylate) + chitosan	Zupančič, Sinha-Ray, et al. (2016)
		Poly(methyl methacrylate) + polyethylene glycol	Zupančič, Sinha-Ray, et al. (2016)
		Poly(methyl methacrylate) + polyvinyl alcohol	Zupančič, Sinha-Ray, et al. (2016)
	NPs/ Nanocomposites	PLGA + chitosan	Lee et al. (2016), Lin et al. (2018) and Xue et al. (2019)
		Ethylene glycol dimethacrylate + methacrylic acid	Bueno et al. (2022) and Sánchez et al. (2019)
		Poly(glycerol sebacic)-urethane (PGS-U) + cloisite 30B	Tirgar et al. (2022)

TABLE 1 (Continued)

Carrier		Articles
	κ-Carrageenan oligosaccharides + cellulose nanofibre	Johnson et al. (2021)
	PEG + chitosan	Hu et al. (2021)
	PLGA + methoxy-polyethylene glycol PLGA NPs	Mahmoud et al. (2018)
	Chitosan + liposome	Hu et al. (2019)
	Chitosan NPs + poly(trimethylene carbonate)	Zhang et al. (2017)
	Poly(ethylene glycol) + poly(lactic acid)	Yao et al. (2014)
	Calcium-deficient hydroxyapatite nanocarrier	Madhumathi and Sampath Kumar (2014)
	PLGA NPs + poly(lactic acid) nanofibres	Feng et al. (2010)
Hydrogels	Poloxamer 407 + hydroxypropyl methylcellulose	Suriyaamporn et al. (2023)
	Carboxymethyl chitosan + hyaluronic acid	Tan et al. (2023)
	Chitosan + polyethylene glycol + PGLA	Xu et al. (2023)
	Chitosan + β-glycerophosphate	Ma et al. (2022)
	Hydroxyethyl cellulose gel + solid lipid nanoparticles	Ho et al. (2022)
	Cellulose nanofibres + κ-carrageenan oligosaccharides nanoparticles	Johnson et al. (2021)

These NPs are usually produced by methods of emulsion and solvent evaporation/displacement and they can also be synthesized by combining several polymers, though studies reporting their use are very scarce and heterogeneous (Feng et al., 2010; Ho et al., 2022; Lee et al., 2016; Lin et al., 2018; Nagahara et al., 2013; Pramod et al., 2016; Yao et al., 2014) (Table 1). The antibacterial compound is most frequently added directly into the reacting solutions, though in some studies nanoparticles have been synthesized by the polymerization precipitation technique. In these cases, the antibacterial loading was done by adsorption, once the NPs were synthesized (Bueno et al., 2022; Sánchez et al., 2019; Shi et al., 2021).

NPs made of the natural polysaccharide chitosan have also been developed by ionic gelation (Arancibia et al., 2013; Martin et al., 2019; Suriyaamporn et al., 2023; Xu, Zhou, et al., 2020).

The use of nanoparticles implies numerous advantages including: (i) stability of the doped drug, (ii) optimum bioavailability and (iii) increased distribution and improved pharmacokinetics (Shakya et al., 2023).

Polymeric materials for antibacterial-loaded nanostructured hydrogels

Hydrogels are three-dimensional water-swollen insoluble matrices made of cross-linked hydrophilic polymers (Ayala-Ham et al., 2021). Hydrogels have a rubbery and soft consistency and are able to retain large amounts of water or other biological fluids (Toledano et al., 2020). In hydrogels, the most used material is chitosan, a natural polysaccharide with a similar structure and biological properties to glycosaminoglycan, a major component of extracellular matrix (Li et al., 2022) (Table 1). This biomaterial has good biocompatibility, bioadhesivity and bioactivity, promoting cell adhesion, proliferation and differentiation (Zupančič, Potrč, et al., 2016). Chitosan has also proven to have certain antimicrobial activity per se (Lee et al., 2023; Li et al., 2022).

Hydrogels are produced by in situ polymerization forming electrostatic interactions or covalently linear/cross-linked networks (Toledano et al., 2020).

Antimicrobial substances

Locally delivered antibiotics such as metronidazole, doxycycline and tetracycline are the most used antibacterial compounds formulated in nanomaterials (Table 2).

Metronidazole is a nitro-imidazolone, which due to its low molecular weight has the ability to diffuse across the bacterial cell membrane, and once in the cytoplasm, it is reduced to hydroximetronidazol, its active molecule that causes irreversible DNA damage and bacterial death (Bury-Moné, 2014). This activity depends on enzymes that

TABLE 2 Studied antimicrobial substances doped onto the nanomaterials.

Active component		Articles
Antibiotics	Metronidazole	Bottino et al. (2014), Ho et al. (2022), Liang et al. (2020), Lin et al. (2018), Reise et al. (2023) and Zupančič, Potrč, et al. (2016)
	Doxycycline	Bueno et al. (2022), Feng et al. (2010), Hu et al. (2019), Lecio et al. (2020), Sánchez et al. (2019) and Xu, Zhou, et al. (2020)
	Tetracycline	Bottino et al. (2017), Madhumathi and Sampath Kumar (2014), Monteiro et al. (2017), Shahi et al. (2017) and Tsai et al. (2018)
	Ciprofloxacin	Bottino et al. (2014), Ribeiro et al. (2020) and Zupančič, Sinha-Ray, et al. (2016)
	Minocycline	Martin et al. (2019) and Yao et al. (2014)
	Tinidazole	Liang et al. (2020)
	Oxytetracycline	Dias et al. (2019)
	Amoxicillin trihydrate	Guarino et al. (2017)
	Vancomycin	Zhang et al. (2017)
Antiseptics	Chlorhexidine	Suriyaamporn et al. (2023) and Wong et al. (2023)
Peptides	Peptide Nal-P-113	Hu et al. (2021) and Ma et al. (2022)
	BAR	Kalia et al. (2017) and Mahmoud et al. (2018)
	Polydopamine	Ma et al. (2022)
Salts/metallic ions	Silver NPs/silver	Craciunescu et al. (2021), Lee et al. (2014, 2016), Sánchez et al. (2019), Wong et al. (2023) and Xue et al. (2019)
	Zinc oxide/zinc	Bueno et al. (2022), Dias et al. (2019) and Sánchez et al. (2019)
	Calcium	Bueno et al. (2022) and Sánchez et al. (2019)
Host modulators	Phenacylthiazolium bromide (PTB)	Lin et al. (2018)
Flavonoids	Icariin	Zheng et al. (2023)
Plants/insects/animals derivates	Chitosan	Arancibia et al. (2013) and Budai-Szűcs et al. (2021)
	Turkish gall NPs	Qi et al. (2022)
	Curcumin	Ekambaram et al. (2021)
	Alginate	Budai-Szűcs et al. (2021)
	Eugenol	Pramod et al. (2016)
Photosensitizers	Indocyanine green	Nagahara et al. (2013) and Shi et al. (2021)
Surfactants	Surfactin	Johnson et al. (2021)
Combined therapies	Alcalase + copper sulphide NPs	Gao et al. (2023)
	Cysteine-modified ε-poly(L-lysine) (ε-PL-SH) + polypyrrole NPs	Lin et al. (2023)
	Curcumin + polydopamine nanoparticles + metformin	Tan et al. (2023)
	Antimicrobial peptide Tet-213 + curcumin	Xu et al. (2023)
	Silver NPs + chlorhexidine	Wong et al. (2023)
	Antimicrobial peptide Nal-P-113 + polydopamine	Ma et al. (2022)
	Metronidazole + tetracycline	Tirgar et al. (2022)
	Copper oxide + polydopamine + titanium dioxide	Xu, Zhao, et al. (2020)
	Surfactin + herbmedotcin	Johnson et al. (2020)
	Bromelain + magnesium	Shoba et al. (2020)
	Triclosan + flurbiprofen	Aminu et al. (2019)

TABLE 2 (Continued)

Active component	Articles
Oxytetracycline + zinc oxide	Dias et al. (2019)
Silver + metronidazole	Deepak et al. (2018)
Tetracycline + lovastatin	Lee et al. (2016)
Silver NPs + bioactive glass ceramic NPs	Srinivasan et al. (2013)

reduce the nitro group, which are only present in anaerobic bacteria, being this mechanism the reason for its indication to treat infections caused by obligate anaerobes.

Doxycycline has a wider spectrum of activity, being bacteriostatic against a broad range of Gram-positive and Gram-negative microbes. Doxycycline binds reversibly to the 30S ribosomal subunit, blocking the binding of the tRNA and thus inhibiting the protein synthesis (Raval et al., 2018). Besides this antimicrobial activity, doxycycline has also anti-collagenolytic effect, by inhibiting collagenase activity in vitro (Raval et al., 2018). When doped in nanostructured membranes and nanoparticles, this antibiotic has shown, in vitro, to accelerate osteoblasts proliferation and differentiation (Toledano-Osorio et al., 2023; Toledano-Osorio, Manzano-Moreno, Toledano, Medina-Castillo, et al., 2021; Toledano-Osorio, Manzano-Moreno, Toledano, Osorio, et al., 2021), to increase the differentiation potential of human bone marrow stem cells (Toledano-Osorio et al., 2022) and to enhance human periodontal ligament stem cells into osteoblasts/cementoblasts (Osorio et al., 2023). All these characteristics may be beneficial in the treatment of both periodontitis and apical periodontitis, since they are chronic inflammatory conditions resulting in destruction of connective tissue and bone. However, antibiotics have limited substantivity and are rapidly cleared, what may be overcome with nanotechnology, since their doping or encapsulation in designed polymers will allow for longer resorption rates and special affinity for the target cells, tissues or environments (Shakya et al., 2023). In addition, locally derived antibiotics have been combined with different substances in order to increase their substantivity and antimicrobial efficacy. A clear example could be the combination of metronidazole with silver (Deepak et al., 2018), in which silver's capacity to disrupt the bacterial cell and increase its permeability was used to increase the relative amount of antibiotic that reached the inner of the bacteria. This capacity of silver to disrupt the bacterial cell was also used by Wong et al. (2023), who combined this metallic ion with chlorhexidine.

Endodontic infections are polymicrobial, and therefore, the use of broad-spectrum antibiotics, such as tetracyclines, has been frequently proposed for intracanal topical application. However, the use of antibiotics during root canal treatment has not been supported by the scientific evidence. Another concern is the increasing occurrence of antibiotic bacterial resistant strains within the oral cavity (Segura-Egea et al., 2017). It is, therefore, a clear need for searching for different antimicrobials.

Other antimicrobial substances have also been incorporated onto nanomaterials for locally delivered systems (Table 2). Among them, salts and metallic ions such as silver have been successfully incorporated in NPs. Due to electrostatic attraction and affinity to sulphur proteins, silver NPs may adhere to the bacterial cell wall and alter its permeability (Khorrami et al., 2018; Yin et al., 2020). In addition, if silver ions are able to enter the cytoplasm, they may deactivate respiratory enzymes, leading to the production of reactive oxygen species (ROS) and lead to DNA destruction (Yin et al., 2020). Since Gram-positive microbes have a thicker cell wall, its permeability may be more difficult to disrupt; and hence, silver-doped NPs are more effective with Gram-negative bacteria (Khorrami et al., 2018; Meikle et al., 2020). Similarly, zinc and zinc oxide have also been used as antimicrobials incorporated in NPs. Zinc oxide is considered as a bacteriostatic agent and its antibacterial capacity is attributed to membrane disruption and release of intracellular Zn^{2+} ions, as well as the production of ROS (Dias et al., 2019). This antibacterial capacity has been enhanced in vitro when using chitosan as a carrier; what may be attributed to the synergistic antimicrobial activity of chitosan and ZnO (Javed et al., 2020). In adjunctive endodontic treatments, silver and zinc have been tested when incorporated in nanocomposites (Jose et al., 2022), endodontic fillers (Al-Quraine et al., 2023; Rosa et al., 2022) and irrigants (Ertem et al., 2017) either individually or in combinations.

Peptides as antimicrobial compounds have also been incorporated in nanomaterials for therapeutic use. These peptides are used constructed mimicking the natural antimicrobial peptides (AMPs) present in saliva and gingival crevicular fluid, usually released by polymorphonuclear neutrophils (PMNs) and epithelial cells, as part of the innate immune response (Li et al., 2018). Among them, peptide Nal-P-113 has been incorporated to nanomaterials. This AMP belongs to the family of the cationic

antimicrobial peptides (CAMPs) able to disrupt bacterial cell membranes, leading to their lysis, although its structural stability in biological fluids such as blood, plasma or gingival crevicular fluid is low (Wang et al., 2018). When stabilized in a hydrogel of chitosan + β-glycerophosphate, this peptide (Nal-P-113) demonstrated a sustained release up to 12 days. Other peptides interfere with the development of the biofilm by inhibiting the adhesion of certain bacteria. For example, peptide BAR inhibits the adhesion of the 'keystone pathogen' *P. gingivalis* by preventing the protein-to-protein interaction between the fimbria antigen of *P. gingivalis* and antigen I/II of some streptococcal species (Kalia et al., 2017). The incorporation of this peptide on the surface of PGLA and these NPs have demonstrated an enhanced inhibition of *P. gingivalis* compared to an equimolar quantity of BAR peptide alone (Kalia et al., 2017). Another example of enhancement of the AMPs antibacterial capacity is by combining the AMPs with other active substances, such as Tet-213, a membrane-active peptide, or other naturally derived antimicrobial substances like curcumin, which also shares anti-inflammatory and antioxidant properties (Xu et al., 2023). This combination of AMPs with naturally derived products with anti-inflammatory and antioxidant properties has also been carried out by Ma et al. (2022) by incorporating polydopamine to the chitosan hydrogels with the AMP Nal-P-113 (Table 2).

Another family of active antimicrobial compounds are naturally derived products. As previously reported, chitosan is obtained from shells of shrimp and other sea crustaceans, and it has a structure and biological properties similar to glycosaminoglycan. Its antimicrobial activity has been related to the interaction with the bacterial polysaccharide absorption, what leads to cell membrane alterations and bacterial death (Thangavelu et al., 2021). It also interferes with bacterial co-aggregation, inhibiting the biofilm growth (Thangavelu et al., 2021). In addition to this, chitosan has been suggested to possess anti-inflammatory and pro-healing capacities. Another naturally derived active component is curcumin. Curcumin is *bisα*, β-unsaturated β-diketone produced by plants of the *Curcuma longa* species having multiple potential biological activities, including antimicrobial, anti-inflammatory, antioxidant, anti-diabetic and anti-carcinogenic (Shakya et al., 2023). Its antimicrobial activity includes its ability of inhibiting the activity of arginine-specific proteases and a lysine-specific protease, which are known to be gingipains of *P. gingivalis* (Izui et al., 2016; Singh et al., 2018), as well as inhibiting biofilm formation. However, its low bioavailability, aqueous solubility and high degradability limit its therapeutic use, though its nanostructured vehiculation may improve these pharmacokinetic limitations (Shakya et al., 2023). The introduction of agents with anti-inflammatory and antioxidant capacity such as curcumin or polydopamine is also promising due to the fact that the nonresolving chronic inflammation may be more successfully arrested if, in addition to treating the bacterial origin, the immune reaction is also covered and diminished.

Antibacterial release kinetics

The release kinetics are usually evaluated in in vitro studies by detecting the biomaterial in the supernatant by UV–vis spectrophotometry (Chen et al., 2022; Ekambaram et al., 2021; Feng et al., 2010; Lee et al., 2014, Lee et al., 2016; Ma et al., 2022; Monteiro et al., 2017; Reise et al., 2023; Tan et al., 2023; Tirgar et al., 2022) and high- or ultra-performance liquid chromatography (Bottino et al., 2017; Ho et al., 2022; Ribeiro et al., 2020; Shahi et al., 2017; Yao et al., 2014), after its immersion during hours or days in PBS or distilled water. Inductively coupled plasma atomic emission spectrometry (Lee, Heo, et al., 2016) and fluorescence (Zupančič, Sinha-Ray, et al., 2016) are also techniques used to determine the concentration of the released substances.

The sustained drug release is relevant in the successful treatment of apical periodontitis, since this process is a nonresolved chronic inflammation originated by bacteria. When formulated in nanopolymers, antibacterials are released in two different phases. An initial burst release, where 20%–100% of the loaded compound is liberated within the first 24 h (Deepak et al., 2018; Dias et al., 2019; Ekambaram et al., 2021; Guarino et al., 2017; Ho et al., 2022; Johnson et al., 2020, 2021; Mahmoud et al., 2018; Martin et al., 2019; Pramod et al., 2016; Reise et al., 2023; Shoba et al., 2020; Tan et al., 2023; Xu et al., 2023); and a second phase in which the antibacterial is liberated in lower concentration but in a relative sustained release (Ekambaram et al., 2021; Feng et al., 2010; Martin et al., 2019; Pramod et al., 2016; Qi et al., 2022; Shoba et al., 2020; Tirgar et al., 2022; Zhang et al., 2017). Most of them are measured up to 48 h, with the longest release period being about 6 weeks (Feng et al., 2010). It is noted that the profiles of drug release usually reveal a short duration initial burst release that is followed by a longer period of continuous but declining release (Huang & Brazel, 2001). A different release kinetic has been described for some antimicrobial peptides, with a slower release during the first phase and then a sustained increase up to 160 h (Hu et al., 2021).

When designing antibacterial polymeric carriers some important points should be taken into consideration: (i) small molecular weight drugs (as most antimicrobial

peptides) tend to release more quickly than large molecular weight drugs, (ii) polymer hydrophilicity will favour the antimicrobial release, as a result of swelling and rapid diffusion of the water molecules within the polymer, which will facilitate the drug delivery (Hiraishi et al., 2008), (iii) the rate and mode of degradation of the polymer carrier will undoubtedly modify the drug delivery kinetic and (iv) hydrophilic drugs will be more easily liberated from polymers than lipophilic ones (Hiraishi et al., 2008; Zou et al., 2012).

Although it is difficult to make any definitive conclusions due to the difference in release conditions between studies, the choice of appropriate polymer type will depend on the release kinetics desired for each antibacterial activity. Hydrogels generally release high concentrations of drug for shorter time periods, whereas other polymers have a more sustained release profile. Interestingly, combined hydrogel/particle carriers can show a moderate burst release, followed by sustained release despite the high water content of hydrogels (Zou et al., 2012).

However, antibacterial efficacy testing should be necessary since lipophilic antibacterial drugs have a rapid cellular uptake, while those which are hydrophilic are essentially distributed in the extracellular fluid (Shah et al., 2015), leading to important differences in antimicrobial activity, independently of the antimicrobial concentration.

Antibacterial efficacy testing of antimicrobial-loaded nanomaterials

The reported activity of these antimicrobial-loaded nanomaterials has been mainly tested by in vitro antibacterial testing against the most common pathogens associated with periodontal and periapical diseases (Table 3), such as *P. gingivalis*, *Aggregatibacter actinomycetemcomitans* and *F. nucleatum* in periodontal diseases and *Prevotella* spp., some Streptococci including *Streptococcus mitis*, *Streptococcus gordonii*, and *Streptococcus oralis*; Lactobacilli, Staphylococci, *Enterococcus faecalis*, *Parvimonas micra*, *Pseudoramibacter alactolyticus*, *Propionibacterium* spp., *Actinomyces* spp., *Bifidobacterium* spp. and *Eubacterium* spp. in periapical infections (Narayanan & Vaishnavi, 2010).

Most of the antimicrobial testing has been done by placing the nanomaterials in contact with pure cultures of the target bacteria. However, two recent studies have used multispecies biofilm models, hence, improving its external validity, since biofilms comprise bacterial communities with developed interactions, such as sophisticated bacterial communication systems (quorum sensing, cell-to-cell signalling, gene transfer, etc.) (Marsh & Zaura, 2017), converting the phenotype of these bacteria growing in biofilms very different from the same bacterial growing planktonically. In these reports, a validated subgingival biofilm model, composed by six different bacteria: *S. oralis*, *Actinomyces naeslundii*, *Veillonela parvula*, *F. nucleatum*, *P. gingivalis* and *A. actinomycetemcomitans* was used (Bueno et al., 2022; Sánchez et al., 2019).

To evaluate the antibacterial effect, most of the included reports (Table 3) have used the in vitro agar diffusion method, which in spite of being an old method to study antibacterial capacity of antimicrobials, it is still frequently used. Although some have evaluated the antibacterial impact by quantitative polymer chain reaction (qPCR) or gene expression of biofilm-related genes, what has a higher sensitivity and higher detection threshold. Although scarce, some in vivo studies have used open-ended approaches such as proteomics and genomics to assess for the antimicrobial effect.

There is only one randomized clinical trial included in this review, where collected biofilm samples were analysed by real-time PCR to detect the changes on the levels of detected *P. gingivalis*, *A. actinomycetemcomitans*, *T. forsythia* and *F. nucleatum* (Lecio et al., 2020). Thus, they only obtained information that was the one from those targeted microorganisms. Employing open-ended approaches would have provided further information about the impact of the therapeutic agent on the subgingival microbiome of the patients.

Other biological activities of nanostructured polymers

In addition to their antimicrobial activity, some of the tested biomaterials have also been shown to have other biological properties (Table 4), such as (i) osteogenicity (Bottino et al., 2017; Cheng et al., 2016; Lee et al., 2016), (ii) anti-inflammatory effects (Arancibia et al., 2013; Craciunescu et al., 2021; Johnson et al., 2020, 2021; Lin et al., 2018; Tan et al., 2023; Xu et al., 2023), (iii) antioxidant and immunomodulatory properties (Johnson et al., 2020, 2021; Lin et al., 2023; Ma et al., 2022; Tan et al., 2023; Xu et al., 2023) and (iv) angiogenesis (Craciunescu et al., 2021; Lin et al., 2023; Shoba et al., 2020).

The mentioned adjunctive biological activities, such as osteogenicity, angiogenesis, anti-inflammatory and immunomodulatory, may be clinically relevant in the treatment of apical periodontitis, since its pathogenic mechanisms include a chronic and exacerbated inflammatory process leading to bone destruction (Cavalla et al., 2021; Duque et al., 2019).

TABLE 3 Analysed bacteria and testing methods of the included studies.

Bacteria	References	Testing method	References
Aggregatibacter actinomycetemcomitans	Arancibia et al. (2013), Bottino et al. (2017), Budai-Szűcs et al. (2021), Bueno et al. (2022), Dias et al. (2019), Guarino et al. (2017), Lee et al. (2016), Monteiro et al. (2017), Reise et al. (2023), Shahi et al. (2017) and Xu et al. (2023)	Agar diffusion	Bottino et al. (2014), Budai-Szűcs et al. (2021), Chen et al. (2022), Craciunescu et al. (2021), Dias et al. (2019), Ho et al. (2022), Hu et al. (2021), Johnson et al. (2021), Lee et al. (2016), Liang et al. (2020), Lin et al. (2023), Ma et al. (2022), Mahmoud et al. (2019), Monteiro et al. (2017), Qi et al. (2022), Reise et al. (2023), Ribeiro et al. (2020), Srinivasan et al. (2013), Suriyaamporn et al. (2023), Tan et al. (2023), Tsai et al. (2018), Xu et al. (2023) and Zhang et al. (2017)
Porphyromonas gingivalis[a]	Arancibia et al. (2013), Bueno et al. (2022), Chen et al. (2022), Craciunescu et al. (2021), Dias et al. (2019), Hu et al. (2021), Johnson et al. (2020), Kalia et al. (2017), Lee, Heo, et al. (2016), Liang et al. (2020), Ma et al. (2022), Mahmoud et al. (2018, 2019), Monteiro et al. (2017), Nagahara et al. (2013), Qi et al. (2022), Reise et al. (2023), Sánchez et al. (2019), Shahi et al. (2017), Shi et al. (2021), Suriyaamporn et al. (2023), Wong et al. (2023), Xu, Zhou et al. (2020) and Xu et al. (2023)	Bacterial kinetic	Monteiro et al. (2017)
Prevotella intermedia[a]	Bottino et al. (2017), Chen et al. (2022), Dias et al. (2019), Lee, Heo, et al. (2016) and Shahi et al. (2017)	Biofilm inhibition assay	Liang et al. (2020), Mahmoud et al. (2018), Ribeiro et al. (2020) and Shahi et al. (2017)
Fusobacterium nucleatum[a]	Bottino et al. (2017), Bueno et al. (2022), Craciunescu et al. (2021), Dias et al. (2019), Hu et al. (2021), Johnson et al. (2020, 2021), Ma et al. (2022), Reise et al. (2023), Sánchez et al. (2019), Shahi et al. (2017) and Xu et al. (2023)	Broth microdilution method	Dias et al. (2019)
Streptococcus gordonii	Kalia et al. (2017), Ma et al. (2022) and Mahmoud et al. (2018, 2019)	Inhibition of adherence	Kalia et al. (2017)
Pseudomonas aeruginosa	Johnson et al. (2020, 2021), Lee et al. (2014) and Tsai et al. (2018)	Cell viability assay	Arancibia et al. (2013), Bueno et al. (2022), Johnson et al. (2021), Ma et al. (2022), Nagahara et al. (2013), Sánchez et al. (2019) and Shi et al. (2021)
Lactobacillus lactis	Bottino et al. (2014)	Lactate dehydrogenase	Arancibia et al. (2013) and Johnson et al. (2020, 2021)
Streptococcus sanguis[a]	Bottino et al. (2014)	MTS/MTT assay	Arancibia et al. (2013) and Johnson et al. (2020, 2021)

TABLE 3 (Continued)

Bacteria	References	Testing method	References
Prevotella nigrescens[a]	Lee et al. (2016)	Gene expression of biofilm-related genes	Liang et al. (2020)
Escherichia coli	Aminu et al. (2019), Feng et al. (2010), Guarino et al. (2017), Ho et al. (2022), Lin et al. (2023), Shoba et al. (2020), Srinivasan et al. (2013) and Tan et al. (2023)	Plate counting method	Xu, Zhao, et al. (2020)
Staphylococcus aureus	Feng et al. (2010) and Srinivasan et al. (2013)	In vitro planktonic monoculture	Wong et al. (2023)
Streptococcus gordonii	Hu et al. (2021)	Broth transfer assays	Chen et al. (2022)
Streptococcus mutans	Budai-Szűcs et al. (2021), Johnson et al. (2020) and Xu et al. (2023)	SEM	Bueno et al. (2022), Ma et al. (2022) and Sánchez et al. (2019)
Enterococcus faecalis[a]	Chen et al. (2022) and Xu et al. (2023)	qPCR	Bueno et al. (2022) and Sánchez et al. (2019)
Staphylococcus aureus	Aminu et al. (2019), Guarino et al. (2017), Ho et al. (2022), Lin et al. (2023), Shoba et al. (2020), Suriyaamporn et al. (2023), Tan et al. (2023), Tsai et al. (2018) and Zhang et al. (2017)	CCK8 analysis	Shi et al. (2021)
Candida albicans[a]	Suriyaamporn et al. (2023)	TEM	Shi et al. (2021)
Actinomyces viscosus	Qi et al. (2022)		
Streptococcus oralis	Bueno et al. (2022) and Sánchez et al. (2019)		
Veillonella parvula	Bueno et al. (2022) and Sánchez et al. (2019)		
Actinomyces naeslundii	Bueno et al. (2022) and Sánchez et al. (2019)		

[a]Species detected in endodontic infections according to Narayanan and Vaishnavi (2010).

TABLE 4 Additional biological effects encountered in doped nanopolymers that may be useful in endodontics.

Biological properties	Active compounds	Articles
Osteogenicity	Tetracyclines	Bottino et al. (2017) and Lee et al. (2016)
Anti-inflammatory	Chitosan	Arancibia et al. (2013), Lin et al. (2018), Tan et al. (2023) and Xu et al. (2023)
	Collagen plus chondroitin 4-sulphate with fibronectin	Craciunescu et al. (2021)
	Surfactin-loaded κ-carrageenan oligosaccharides	Johnson et al. (2021)
	Surfactin with herbmedotcin	Johnson et al. (2020)
Antioxidant and immunomodulation	Surfactin-loaded κ-carrageenan oligosaccharides	Johnson et al. (2021)
	Chitosan with antimicrobial peptides and polydopamine	Ma et al. (2022)
	Antimicrobial peptides with curcumin and chitosan	Xu et al. (2023)
	Carboxymethyl chitosan and hyaluronic acid	Tan et al. (2023)
	Collagen hydrogels with cysteine and hyaluronic acid nanoparticles	Lin et al. (2023)
	Surfactin and herbmedotcin loaded hydrogel	Johnson et al. (2020)
Angiogenesis	Bromelain enzyme and Mg-doped hyaluronic acid nanoparticles	Shoba et al. (2020)
	Collagen with chondroitin 4-sulphate and fibronectin	Craciunescu et al. (2021)
	Collagen-based hydrogels with cysteine-modified ε-poly(L-lysine) and in situ polymerized polypyrrole-hyaluronic acid nanoparticles	Lin et al. (2023)

Future development of antibacterials nanopolymers

A variety of nanopolymers with antimicrobials properties have been proposed. Among the polymers, it seems that the combination of hydrogel/particle carriers may be the most efficient for apical periodontitis, since they show a moderate burst release, followed by sustained drug liberation. Moreover, there is an active search for nonantibiotic antimicrobials, either by combining naturally derived antimicrobials with AMPs or through the design of new antimicrobial polymeric substances that combine immunomodulatory, anti-inflammatory or osteogenic properties. However, the best kinetic release or the best combination of antibacterials have not been yet established, as future testing procedures require not only the use of clinical models and open-ended approaches, but the study of the impact of the therapeutic agent on the patient's microbiome.

CONCLUSIONS

The results of this review show the potential of polymeric nanomaterials containing antimicrobial compounds as potential NGAS in the treatment of periodontitis or apical periodontitis. However, their relative efficacy is not, yet, completely understood, since most of the existing evidence is derived from in vitro or preclinical in vivo studies.

AUTHOR CONTRIBUTIONS

Conceptualization: R.O., M.T.-O., M.S. *Data curation*: R.O., M.T.-O., J.B., C.V., M.V.-R. *Investigation*: M.T.-O., R.O., J.B., C.V., M.V.-R., M.S. *Methodology*: M.T.-O., R.O., J.B., C.V., M.V.-R., M.S. *Writing—original draft preparation*: M.T.-O., R.O., J.B., C.V., M.V.-R., M.S. *Writing—review and editing*: M.T.-O., R.O., J.B., C.V., M.V.-R., M.S.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

None.

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