Review Article

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Application of antibacterial nanoparticles in orthodontic materials

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Abstract: During the orthodontic process, increased microbial colonization and dental plaque formation on the orthodontic appliances and auxiliaries are major complications, causing oral infectious diseases, such as dental caries and periodontal diseases. To reduce plaque accumulation, antimicrobial materials are increasingly being investigated and applied to orthodontic appliances and auxiliaries by various methods. Through the development of nanotechnology, nanoparticles (NPs) have been reported to exhibit excellent antibacterial properties and have been applied in orthodontic materials to decrease dental plaque accumulation. In this review, we present the current development, antibacterial mechanisms, biocompatibility, and application of antibacterial NPs in orthodontic materials.

Keywords: antibacterial, nanomaterial, nanoparticle, orthodontics

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1 Introduction

Orthodontic materials, including fixed and removable orthodontic appliances and orthodontic auxiliaries, are essential components in orthodontic treatments. However, the potential adverse effects associated with these appliances and auxiliaries remain unresolved. Increased microbial biofilm accumulation on orthodontic appliances and auxiliaries and subsequent dental caries and periodontitis are common complications during orthodontic treatment [1,2]. Various attempts have been made to inhibit biofilm accumulation on orthodontic appliances and auxiliaries [3], and the addition of antimicrobial agents to these appliances is one of the most effective strategies [4,5]. Some particles have been reported to exhibit excellent antibacterial properties against both gram-positive bacteria and gram-negative bacteria when transformed into nanometer size [6–10], and these nanosized antibacterial agents are preferred to be added to dental materials due to the greater surface-to-volume ratio of nanoparticles (NPs), which have intimate interactions with microbial membranes and provide a considerably larger surface area for antibacterial activity [11–13]. NPs can be used in dental materials through two mechanisms, including mixing NPs with dental materials or preparing NP coatings on the surface to reduce microbial adhesion and prevent caries [14,15]. In orthodontic treatment, NPs have been proposed for a variety of purposes, such as inhibiting bacteria [15], reducing friction [16], and increasing bond strength [17]. The purpose of this article is to review the antibacterial mechanism, biocompatibility, and application of NPs in orthodontic materials and put forward the prospect of the possible research direction of the combination of antibacterial NPs and orthodontic materials in the future.

2 Antibacterial mechanism of NPs applied in orthodontic materials

When the particles applied for orthodontic material modification are reduced to nanometer size, new physicochemical
and mechanical properties can be obtained, and some NPs can improve the antibacterial ability of orthodontic materials in different ways [18]. NPs can exhibit antibacterial function when in contact with bacterial cells through electrostatic attraction [19], van der Waals forces [20], receptor–ligand interactions [21], and hydrophobic interactions [22]. At present, the antibacterial mechanism of NPs is not clearly understood, and many details of the dynamic process of their interaction with bacterial cells are not clearly known, but with the help of numerous analytical tools and research methods, some common understandings have been accumulated (Figure 1).

2.1 Inhibition of biofilms

Biofilms are complex communities that form when a group of microorganisms self-secrete a polysaccharide matrix that retains nutrients for the constituent cells and protects them from both the immune response and antimicrobial agents [23]. Reducing the adhesion of biofilms is an effective way to prevent oral infections. Some evidence shows that NPs can affect bacterial adhesion and biofilm formation [24,25], and the mechanisms that have been concluded are as follows:

1) Reduction of the formation of biofilms: The mechanism by which NPs inhibit the formation of bacterial biofilms is related to the regulation of bacterial metabolism, which is an important activity of biofilms. NPs were reported to adhere to and diffuse into biofilms, act on the ion channels in bacterial biofilms that are helpful for the long-distance electrical signal conduction of bacteria in a biofilm, disrupt the membrane potential, and lead to enhanced lipid peroxidation and DNA binding, thus regulating the metabolic activity of bacteria and decreasing the ability of bacteria to form biofilms [26–28].

2) Reduction of the adhesion of biofilms: NPs can modify the surface of the material and make it not conducive to the adhesion of the biofilm. Jasso-Ruiz demonstrated that the orthodontic brackets coated with nanosilver present smoother surfaces, which reduced the adhesion of both Streptococcus mutans and Streptococcus sobrinus to the orthodontic brackets, demonstrating the antibacterial properties of silver NPs (Ag NPs) [15]. In the study of Lee, an anti-adherent effect against Candida albicans

Figure 1: Antibacterial mechanism of NPs applied in orthodontic materials.
and Streptococcus oralis was observed with the incorporation of mesoporous silica NPs (MSNs) into poly(methyl methacrylate) (PMMA) [29].

2.2 Extracellular antibacterial effects

Before penetrating bacteria cells, NPs exhibit antibacterial effects through the disruption of the bacterial cell membrane. The main disruption methods are as follows:

1) Depositing on the surface and interaction with the components of the cell membrane: Visualization methods such as electron microscopy and atomic force microscopy have shown that the appearance of the bacterial cell membrane could be changed when NPs deposit on the surface of bacteria. This deposition causes large holes that cannot be repaired on the surface of the bacterial cell [30], which is followed by the NP’s penetration into the bacterial cell [31]. The destruction of cell morphology and integrity was observed after the deposition of ZnO NPs [32], and depressions in the cell membrane of Escherichia coli and a large amount of Ag NPs embedded in the cell membrane of bacteria were found after the deposition of Ag NPs on the bacterial cell membrane [33–36]. In addition, some NPs were reported to exhibit the antibacterial effects through the direct interaction with bacterial cell membrane components, which is followed by cell death due to the increasing membrane permeability and the leakage of cellular contents [37].

2) Reactive oxygen species (ROS)-induced oxidative stress: NPs reduce oxygen molecules to produce different types of ROS, including superoxide radicals (O2−), hydroxyl radicals (·OH), hydrogen peroxide (H2O2), and singlet oxygen (O2), which have strong positive redox potential and exhibit different levels of dynamics and activity [38]. The excess of ROS disrupts the balance between the production and clearance of ROS in bacterial cells and causes oxidative stress, which damages the individual components of bacterial cells [24,39]. Oxidative stress has been proven to be a key factor in changing cell membrane permeability, which can lead to the destruction of the bacterial cell membrane, causing the leakage of cellular contents and resulting in bacterial death [40]. Danilczuk reported Ag-generated free radicals through the electron spin resonance (ESR) study of Ag NPs [41], and Kim confirmed the production of free radicals by ESR analysis of Ag NPs and concluded that the antibacterial mechanism of Ag NPs is related to the formation of free radicals and subsequent free radical-induced membrane damage [42]. As reported, titanium dioxide NPs can produce hydroxyl radicals with a strong bactericidal effect [43].

3) Effects of dissolved metal ions: The positively charged metal ions of NPs are released to bind with the negatively charged functional groups of the bacterial cell membrane, resulting in the confusion and dispersion of the originally ordered and closely spaced cell membranes, destroying their inherent function and leading to bacterial death [44,45]. Sondi and Salopek-Sondi demonstrated that sulfur-containing proteins/key enzymes in the membrane or inside the cells are likely to be the preferred binding sites of Ag NPs, and the accumulation of Ag NPs on the bacterial membrane can cause permeability and lead to cell death [33].

2.3 Intracellular antibacterial effects

NPs penetrate in bacterial cells and interact with important functional molecules, resulting in the inhibition of the growth of bacterial cells in the following ways:

1) ROS-induced oxidative stress: NPs introduce ROS and metal ions into bacteria by diffusion, and ROS can help to improve the gene expression level of oxidized proteins, which is an important mechanism of bacterial apoptosis [46]. ROS can attack proteins and inhibit the activity of certain periplasmic enzymes essential for maintaining the normal morphology and physiological processes of bacterial cells [44,47].

2) Effects of dissolved ions: Metal ions absorbed into bacterial cells directly interact with the functional groups of proteins and nucleic acids, including mercapto (−SH), amino (−NH), and carboxyl (−COOH) groups, damaging enzyme activity, changing the cell structure, affecting normal physiological processes, and ultimately inhibiting microorganisms [38,42,48,49]. Morones et al. [50] and Sondi and Salopek-Sondi [33] studied the bactericidal effect of Ag NPs and found that these NPs were able to penetrate inside the bacteria and cause further damage, possibly by interacting with sulfur- and phosphorus-containing compounds, such as DNA. Feng et al. [51] found that DNA lost its replication ability and that the protein became inactivated and Yamanaka et al. [52] found that the expression of ribosomal subunit proteins and other cellular proteins and enzymes necessary for ATP production was inactivated after Ag+ treatment.
3 NPs applied for antibacterial purposes in orthodontic materials

NPs applied for antibacterial purposes in orthodontics are mainly combined with dental materials or coated over the surfaces of orthodontic materials. According to the sources and modes of action, they can be roughly divided into three types: inorganic NPs, organic NPs, and natural macromolecule compound NPs.

3.1 Inorganic NPs

Inorganic NPs include metals, metal oxides, their doped form, and some novel surface-modified NPs.

3.1.1 Nanoparticulate metals

Metals have been used as antimicrobial agents for centuries, and they can obtain stronger antibacterial activity when the size is reduced to the nanometer scale.

3.1.1.1 Ag

According to recent studies, nanosilver is the most commonly used antibacterial nanometal in orthodontic materials. Whether used alone or in combination with other reagents, Ag NPs have shown excellent antibacterial properties. Ag NPs formed in situ show substantial antibacterial activity through oxidative stress and the release of silver ions [53,54]. Silver ions are very active and can quickly bind to negatively charged proteins, RNA, DNA, and so on, which is the most important part of their antibacterial mechanism [55]. It has been observed that Ag NPs can attach to the bacterial cell membrane and penetrate the bacterial internal respiratory chain, leading to bacterial cell leakage and eventual cell death [56]. As expected, Ag NPs have been studied in a variety of orthodontic appliances and auxiliaries and have shown extraordinary antibacterial effects [15,57–60].

3.1.1.2 Au

Gold NPs (Au NPs) exert favorable biocompatibility and can be easily modified due to their controllable size and chemical stability [61]. 4,6-Diamino-2-pyrimidinethiol-conjugated Au NPs (AuDAPT) were previously reported to effectively kill multidrug-resistant gram-negative bacteria and induce drug resistance to a much smaller extent than conventional antibiotics [62]. AuDAPT-coated aligners have been proven to have antibacterial effects on the suspension of Porphyromonas gingivalis, slow biofilm formation, and favorable biocompatibility [63].

3.1.1.3 Cu

As an NP with an antibacterial effect, copper is significantly more affordable than silver or gold, so it is economically attractive. Antibacterial effects on Staphylococcus aureus, E. coli, and S. mutans were observed in the study of Argueta-Figueroa et al. when Cu NPs were added to orthodontic adhesives [64].

3.1.2 Nanoparticulate metal oxides

Highly ionic nanoparticulate metal oxides are very valuable as antimicrobial agents, since they can be prepared with extremely high surface areas and special crystal morphologies with a large number of edges and corners, as well as other potentially reactive sites [65].

3.1.2.1 CuO

Khan et al. showed that CuO NPs had a strong inhibitory effect on the growth and colonization of microbial plaque [66]. The study of Toodehzaeim et al. showed that orthodontic adhesive containing CuO NPs had antibacterial properties and could inhibit the growth of S. mutans [67].

3.1.2.2 ZnO

Previous studies have proven that nanozinc oxide has a strong bactericidal effect on gram-positive and gram-negative bacteria as well as spores resistant to high temperature and high pressure. The antibacterial mechanism of ZnO includes the reduction of bacterial viability, the generation of hydrogen peroxide, the accumulation of ZnO NPs on the surface of bacteria, the production of ROS on the surface of particles, the release of zinc ions, the dysfunction of bacterial cell membranes, and the internalization of ZnO NPs [68]. ZnO NPs were used to prepare a unique coating on the surface of NiTi archwire,
and the coating had a superior antibacterial effect on both gram-negative bacteria and gram-positive bacteria and had superior frictional performance [69]. In addition, cationic curcin-doped zinc oxide NPs (cCur/ZnO NPs) have been added to orthodontic adhesives to control a variety of cariogenic biofilms and reduce their metabolic activity [70].

3.1.2.3 TiO₂

Among all kinds of nanomaterials, titanium dioxide NPs have excellent properties, such as high chemical stability, good biocompatibility, and nontoxicity. Previous experiments have shown that titanium dioxide can generate superoxide anion radicals and hydroxyl radicals with strong chemical activity and bactericidal activity due to its electronic structure [43,71]. These ROS are strong oxidants that react with biomolecules, such as lipids, proteins, and nucleic acids, resulting in oxidative damage to cell membranes and bacterial death [72–74]. TiO₂ NPs were reported to be added to glass ionomer cement in orthodontic treatment and the results showed that TiO₂ NPs caused rapid intracellular bacterial damage and could significantly improve the antibacterial effect [43]. In addition, fixed retainer composites filled with TiO₂ NPs showed a statistically significant increase in antibacterial activity [75].

Although the nanometals and nanometal oxides listed above exhibit effective antibacterial properties, their biocompatibility and safety are still not confirmed and still need to be determined by further intraoral studies. Silver and copper ions have been reported to be cytotoxic in in vitro studies for several types of cells, and the toxicity mechanism is not yet clear, which may be mostly attributed to the size and concentration of NPs [76,77]. Au NPs exert favorable biocompatibility, while the cost is a vital problem when Au NPs are applied in orthodontic materials for bacterial inhibition. ZnO and TiO₂ NPs show biocompatibility and minimum cytotoxicity [43,70], making them possible types of antibacterial NPs for application in orthodontic materials.

3.1.3 Fluoride NPs

During an acidic challenge, the presence of fluoride initiates the formation of fluorapatite to replace the dissolved hydroxyapatite, which is conducive to remineralization [78]. Fluorides with significant antibacterial activity have been found to affect bacterial metabolism mainly through intracellular antibacterial effects. They can act either directly or by forming metal–fluoride complexes that have significant effects on a variety of enzymes and regulatory phosphatases [79]. Released F-ions can act as glycolytic enzyme inhibitors and transmembrane proton carriers to inhibit oral microorganisms by inducing cytoplasmic acidification and have long-distance antibacterial activity [80,81]. Fluoride NPs can exhibit antibacterial effect and play a role in demineralization and remineralization processes, while many oral bacteria are insensitive to the direct action of fluoride unless they are prepared as metal–fluoride complexes. Asiry et al. evaluated the antibacterial effect of a conventional orthodontic composite resin blended with yttrium fluoride (YF₃) NPs and a remarkable antibacterial effect was proven [82]. In addition, Yi developed a resin-modified glass ionomer containing NPs of calcium fluoride (nCaF₂) with antibacterial and remineralization capabilities to combat enamel white spot lesions [83].

3.1.4 Mesoporous bioactive glass NPs (MBNs)

MBNs are bioactive substances consisting of SiO₂, CaO, Na₂O, and P₂O₅. MBNs have been widely used as biological materials because of their high chemical stability, mechanical stability, and effective bioactive functions [84]. They can remineralize enamel and dentin with high bioactivity, lower cytotoxicity to dental pulp stem cells, and antibacterial activity against intraoral bacteria [85,86]. MBNs exhibit the antibacterial effects mainly through extracellular antibacterial effects. It has been hypothesized that the antibacterial activity of bioactive glass is attributed to the increase in local pH following the exchange of sodium ions with protons in body fluids, and the alteration to a highly alkaline environment stresses bacteria and induces them to modify their form and ultrastructure, thus changing numerous genes and protein phenotype patterns [87]. Another factor that contributes to antibacterial activity is the release of ions, such as silica, calcium, and phosphate, which interfere with bacterial membrane perturbation, resulting in higher osmotic pressure [84]. In addition, resin-modified glass ionomers and adhesives containing MBN can release calcium and phosphate, thus improving the mechanical properties of demineralized hard tissues [85,86,88]. Nam confirmed the antibacterial effect of fluorinated bioactive glass NPs added to orthodontic bonding resin on S. mutans [89], and the remineralization ability of MBNs added to a self-adhesive resin and its antibacterial effect on both gram-negative and gram-positive bacteria was further proven by Choi et al. [90].
3.1.5 MSNs

The direct bactericidal effect of MSNs has not been reported. Lee et al. first utilized MSNs themselves as antimicrobial additives and an anti-adherent effect against C. albicans and S. oralis was observed with the incorporation of MSNs into PMMA [29]. The major mechanism of the anti-adherent effect against microbes is related to the hydrophilic surface energy. Moreover, in this study, MSN was reported to be a carrier of amphotericin B and the performance after loading amphotericin B into MSN-incorporated PMMA suggested a long-term antimicrobial effect [29].

3.1.6 Nanographene oxide (N-GO)

N-GO has antibacterial activity because it has several chemical groups, which makes it able to form different interactions between covalent and noncovalent, and N-GO may show more activity at the edges than at the surface due to ROS [91]. Pourhajibagher and Bahador [92] highlighted that 5 wt% N-GO could be considered an orthodontic adhesive additive to reduce the microbial count and biofilm with no adverse effect on the shear bond strength and adhesive remnant index. The antibacterial property of N-GO has been proven, and its high water solubility, good biocompatibility, low toxicity, good mechanical properties, and high cost-effectiveness allow it to be used for bacterial inhibition in orthodontic materials.

3.2 Organic NPs

3.2.1 Quaternary ammonium compounds

Polymerizable quaternary ammonium salt (QAS) is a broad-spectrum cationic biocide and possesses significant antibacterial activities against a variety of bacteria, fungi, and viruses [93]. Cationic QAS exhibits the antibacterial effects mainly through extracellular antibacterial effects by attracting and penetrating negatively charged bacterial cell membranes [93,94]. Studies have shown that the addition of insoluble antibacterial quaternary ammonium polyion on polyethyleneimine (PEI) NPs to orthodontic adhesives and cements, such as NeoBond and GC Fuji Ortho LC, results in stable antibacterial properties and may prevent S. mutans from growing adjacent to orthodontic appliances [95]. Sharon et al. [96] also confirmed that the addition of quaternary ammonium polyethyleneimine (QPEI) NPs to orthodontic cement appeared to significantly reduce the number of viable S. mutans and Lactobacillus casei, as well as bacterial biomass around orthodontic brackets. In addition, these NPs could be highly effective for months without compromising the chemical, physical, or biological compatibility of the combined base materials [97].

3.3 Natural macromolecule compound NPs

The delivery of traditional antibacterial natural macromolecule compound materials in the form of nanoliposomes and NPs can improve the transport efficiency of drugs and enhance the stability and targeting of drugs, which is the main form of clinical use of nanoantimicrobials at present. Some natural macromolecule compound nanomaterials are reported to exert antimicrobial effects with high levels of biodegradability and biocompatibility without causing toxicity and have been applied in orthodontic materials for antibacterial purposes.

3.3.1 Chitosan NPs

Chitosan is a cationic material, as it contains one primary amine group and chitosan has shown antifungal activity in the free form of the polymer [37] or its derivatives [98,99], especially against C. albicans. Chitosan NPs inhibit bacteria mainly through extracellular antibacterial effects. The antibacterial and antifungal activity of chitosan is mostly associated with its polycationic nature, which interacts with negatively charged phospholipid components on the bacterial and fungal membrane, resulting in increased membrane permeability and the leakage of cellular contents, which subsequently leads to cell death [37,100–102]. Hosseinpour et al. [2] added chitosan NPs to orthodontic primers and found their antibacterial activity against S. mutans, Streptococcus sanguinis, and Lactobacillus acidophilus lasted up to 7 days in a rat model.

3.3.2 Curcumin NPs and curcumin-doped poly lactic-co-glycolic acid (PLGA) NPs

Curcumin is a natural hydrophobic compound derived from the common food spice rhizome of Curcuma longa (turmeric) with therapeutic properties, including antimicrobial, anti-inflammatory, and wound healing properties [103]. Curcumin can inhibit the growth and proliferation of many bacterial strains, such as staphylococci, lactobacilli, and streptococci, and its antibacterial activity is attributed...
to the destruction of the bacterial peptidoglycan cell wall [104]. Curcumin has been proven to have antibacterial activity against *S. mutans*, *S. sanguinis*, and *L. acidophilus* when added to orthodontic adhesives [105]. The application of curcumin has been limited by its poor bioavailability due to its low water solubility, poor permeability, and rapid metabolism. PLGA has been used to carry curcumin for antibacterial purposes because of its sustained drug delivery, biocompatibility, biodegradability, and high stability in biological fluids and during storage [106,107], and curcumin-doped poly lactic-co-glycolic acid NPs (Cur-PLGA-NPs) have been proven to serve as an orthodontic adhesive additive with anti-biofilm activity and can be used to control *S. mutans* biofilm formation [108].

### 4 Biocompatibility and safety of antibacterial NPs applied in orthodontic materials

The biocompatibility and safety of nanomaterials and NPs remain uncertain. The toxicity of antibacterial NPs is affected by many factors, such as NP type, dose, particle size, distribution, action duration, concentration, and interaction with other compounds. Some researchers have pointed out that there are current limitations of NPs applied in the dental sector related to the topics of biocompatibility and safety [109], while others have suggested that there is little evidence for these limitations [110]. Previous studies on NPs applied in orthodontic materials usually investigated the antibacterial characteristics for very short periods, varying from days to a few weeks, and were mostly carried out under *in vitro* conditions, which could not provide sufficient evidence for biocompatibility and safety. The long-term performance of orthodontic materials with NPs needs further investigation to develop fully biocompatible and safe nanomaterials [111–113].

### 5 Materials with antibacterial NPs and the main bacteria inhibited in orthodontic therapy

Microorganisms mainly exist in the form of biofilms on the surface of teeth, oral mucosa, and oral materials. Oral flora imbalance during orthodontic treatment can lead to oral infectious diseases, including dental caries, periodontal disease, candidiasis, endodontic infections, orthodontic infections, and peri-implantitis [65,114]. The antibacterial NPs applied in orthodontic materials are mainly used to prevent and solve these oral infections. Commonly used orthodontic appliances and auxiliaries with NPs for antibacterial usage are described as follows.

#### 5.1 Orthodontic appliances and the components

##### 5.1.1 Orthodontic stainless-steel brackets

Brackets are necessary tools in fixed orthodontic treatment, and the potential accumulation of microbial biofilm may lead to enamel demineralization around the brackets [115]. Stainless-steel brackets are mostly used in fixed orthodontic treatment. As shown in Table 1, various NPs used in orthodontic brackets have been proven to have effective antibacterial activity. Jasso-Ruiz evaluated the anti-adherent and antibacterial properties of different nanosilver-modified orthodontic brackets with radiomarkers and found that nanosilver-modified brackets could inhibit the biological activities of *S. mutans* and *S. sobrinus*, indicating that nanosilver-modified brackets can prevent the accumulation of dental plaque and the occurrence of dental caries during orthodontic treatment [15]. Furthermore, Metin-Gursoy also confirmed the antibacterial effect of nanosilver-coated orthodontic brackets on *S. mutans* through an *in vivo* experiment in rats [56]. Salehi found that N-doped TiO$_2$-coated orthodontic brackets could prevent the growth of *S. mutans* for at least 3 months and could effectively prevent enamel decalcification during orthodontic treatment [116]. Ghasemi found that 60 and 100 μm films of Ag NPs and titanium oxide NPs can be coated on brackets to efficiently reduce bacterial count after 3 h [117]. Zhang *et al.* suggested that nano-Ag/TiO$_2$-coated brackets had antibacterial activity against several kinds of bacteria in the dark, and the antibacterial activity after 20 min could reach 79% (Table 1 and Figure 2a) [118].

##### 5.1.2 Orthodontic metal archwires

As an indispensable role in fixed orthodontic treatment, archwires have mainly been studied to reduce the coefficient of friction to improve treatment efficiency [119]. With the development of nanotechnology in the dental field, some NPs were reported to be combined with
orthodontic archwires and exhibited the ability to reduce friction and inhibit bacteria in the form of coatings. As shown in previous studies, NPs are deposited on the orthodontic archwire as a spacer to decrease the surface sharpness and frictional forces between the archwire and the orthodontic bracket \cite{120,121} and protect the metallic wires against oxidation \cite{122} to achieve the goal of friction reduction. In addition, surface modification of orthodontic archwires with Ag NPs has been reported to prevent the accumulation of dental plaque and the development of S. mutans, S. sobrinus, and S. mutans in vitro study.

Table 1: Previous antibacterial NPs used in orthodontic appliances and the components

<table>
<thead>
<tr>
<th>Ref.</th>
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<th>NPs used</th>
<th>Bacterial tested</th>
<th>Study type</th>
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<td>Ag NPs</td>
<td>S. mutans</td>
<td>In vitro</td>
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<td>Ag NPs</td>
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Figure 2: (a) Orthodontic stainless-steel brackets; (b) orthodontic metal archwires; and (c) orthodontic stainless-steel bands (black arrow points).
dental caries during orthodontic treatment [123]. Orthodontic archwires coated with ZnO NPs also exhibit significant antibacterial activity against S. mutans [124], S. aureus, Streptococcus pyogenes, and E. coli while reducing friction [69]. Since few studies have been conducted on both friction reduction and the antibacterial properties of orthodontic archwires coated with NPs, no correlation between these two characteristics has been reported (Figure 2b).

5.1.3 Orthodontic stainless-steel bands

Orthodontic bands are seated in supra- and subgingival areas, which may compromise the health of the surrounding periodontal tissues and can be associated with the occurrence of periodontopathogenic bacteria [125]. Prabha et al. coated orthodontic bands with Ag NPs and concluded that the coated bands were biocompatible, possessed distinct antimicrobial activity, and could be potential antimicrobial dental bands for future clinical use (Figure 2c) [126].

5.1.4 Removable orthodontic appliances

The use of orthodontic acrylic resins in the fabrication of removable orthodontic appliances and retainers (Figure 3a) is increasing due to the growing demand for orthodontic treatments [11]. The accumulation of microorganisms on acrylic resins increases the incidence of caries and oral diseases and jeopardizes the efficiency of orthodontic treatments [127]. The use of antibacterial materials in acrylic resin of removable orthodontic appliances and retainers is helpful to reduce bacterial aggregation during orthodontic treatments. In a randomized clinical trial, Ghorbanzadeh found that the average levels of test cariogenic bacteria in saliva decreased approximately 2- to 70-fold (30.9–98.4%) in patients wearing orthodontic appliances with in situ-generated Ag NPs compared to those wearing normal baseplates of orthodontic appliances [128]. Farhadian found that Ag NPs with a 500 ppm concentration and 40 nm size incorporated into the acrylic plate of retainers had a strong antimicrobial effect against S. mutans colony-forming units under clinical conditions [59]. An anti-adherent effect against C. albicans and S. oralis was observed with the incorporation of MSNs into PMMA and MSN has been reported to be a carrier of amphotericin B. The performance after loading amphotericin B into the MSN-incorporated PMMA suggested a long-term antimicrobial effect (Figure 3) [29].

Despite the traditional removable orthodontic appliances made of acrylic resins, clear aligners (Figure 3b) are made of a transparent polymer material, which is a new trend in orthodontic treatment in recent years, and more patients tend to choose clear aligners as orthodontic appliances than fixed appliances and traditional removable orthodontic appliances due to their esthetics and comfort. During clear aligner treatment, both the teeth and gingiva are covered for nearly the entire day with aligners. Thus, with proper modification, clear aligners may be used as a long-term drug delivery system for patients with P. gingivalis infection [63]. Zhang coated antibacterial AuDAPTs over clear aligners, and these AuDAPT-coated aligners exhibited antibacterial effects on a suspension of P. gingivalis, affecting the neighboring area of the material, slowing biofilm formation, and showing favorable biocompatibility [63].

5.2 Orthodontic auxiliaries

5.2.1 Orthodontic adhesives and primers

Orthodontic resin, including orthodontic adhesive and primer, is a binder between an orthodontic bracket and
Table 2: Previous antibacterial NPs used in orthodontic auxiliaries

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Orthodontic auxiliaries</th>
<th>NPs used</th>
<th>Bacterial tested</th>
<th>Study type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sanchez-Tito and Tay [58]</td>
<td>Orthodontic adhesives and primers</td>
<td>Ag NPs</td>
<td>S. mutans</td>
<td>In vitro</td>
</tr>
<tr>
<td>Eslamian et al. [130]</td>
<td>Orthodontic adhesives and primers</td>
<td>Ag NPs</td>
<td>L. acidophilus</td>
<td>In vitro</td>
</tr>
<tr>
<td>Bahador et al. [131]</td>
<td>Orthodontic adhesives and primers</td>
<td>Ag NPs</td>
<td>S. mutans</td>
<td>Animal study</td>
</tr>
<tr>
<td>Sanchez-Tito and Tay [58]</td>
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<td>Ag NPs</td>
<td>S. sanguinis</td>
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<td>Ag NPs</td>
<td>L. acidophilus</td>
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</tr>
<tr>
<td>C. acidophilus</td>
<td>Orthodontic adhesives and primers</td>
<td>Ag NPs</td>
<td>S. mutans</td>
<td>In vitro</td>
</tr>
<tr>
<td>Bahador et al. [131]</td>
<td>Orthodontic adhesives and primers</td>
<td>Ag NPs</td>
<td>S. sanguinis</td>
<td>In vitro</td>
</tr>
<tr>
<td>Argueta-Figueroa et al. [64]</td>
<td>Orthodontic adhesives and primers</td>
<td>Copper NPs</td>
<td>S. mutans</td>
<td>In vitro</td>
</tr>
<tr>
<td>C. acidophilus</td>
<td>Orthodontic adhesives and primers</td>
<td>Copper NPs</td>
<td>S. mutans</td>
<td>In vitro</td>
</tr>
<tr>
<td>Nam et al. [89]</td>
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<td>Fluorinated bioactive glass NPs</td>
<td>S. mutans</td>
<td>In vitro</td>
</tr>
<tr>
<td>Choi et al. [90]</td>
<td>Orthodontic adhesives and primers</td>
<td>Mesoporous bioactive glass NPs</td>
<td>Gram-negative and gram-positive bacteria</td>
<td>In vitro</td>
</tr>
<tr>
<td>Toodehzaeim et al. [67]</td>
<td>Orthodontic adhesives and primers</td>
<td>CuO NPs</td>
<td>S. mutans</td>
<td>In vitro</td>
</tr>
<tr>
<td>Eslamian et al. [130]</td>
<td>Orthodontic adhesives and primers</td>
<td>Copper NPs</td>
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<td>Argueta-Figueroa et al. [64]</td>
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<td>Copper NPs</td>
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<td>In vitro</td>
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<td>Asiry et al. [82]</td>
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<td>Yttrium(II) fluoride NPs</td>
<td>S. mutans</td>
<td>In vitro</td>
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<tr>
<td>Pourhajibagher et al. [70]</td>
<td>Orthodontic adhesives and primers</td>
<td>Cationic curcumin-doped zinc oxide NPs</td>
<td>Biofilm</td>
<td>In vitro</td>
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<tr>
<td>Liu et al. [134]</td>
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<td>Amorphous calcium phosphate NPs</td>
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<td>In vitro</td>
</tr>
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<td>Sodagar et al. [105]</td>
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<td>Curcumin NPs</td>
<td>S. mutans</td>
<td>In vitro</td>
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<tr>
<td>Ahmadi et al. [108]</td>
<td>Orthodontic adhesives and primers</td>
<td>Curcumin-doped poly lactic-co-glycolic acid NPs</td>
<td>Biofilm</td>
<td>In vitro</td>
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<tr>
<td>Hosseinpour et al. [2]</td>
<td>Orthodontic adhesives and primers</td>
<td>Chitosan NPs</td>
<td>S. mutans</td>
<td>Animal study</td>
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<tr>
<td>Zaltsman et al. [135]</td>
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<td>QPEI NPs</td>
<td>S. mutans</td>
<td>In vitro</td>
</tr>
<tr>
<td>Pourhajibagher and Bahador et al. [92]</td>
<td>Orthodontic adhesives</td>
<td>Graphene oxide NPs</td>
<td>S. mutans</td>
<td>In vitro</td>
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<tr>
<td>Ren et al. [43]</td>
<td>Orthodontic cement</td>
<td>TiO₂ NPs</td>
<td>S. mutans</td>
<td>In vitro</td>
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<td>Zhang et al. [57]</td>
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<td>Ag NPs</td>
<td>S. mutans</td>
<td>Biofilm and plaque</td>
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<tr>
<td>Wang et al. [136]</td>
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<td>Ag NPs</td>
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<td>Biofilm and plaque</td>
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<td>Moreira et al. [137]</td>
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<td>S. mutans</td>
<td>Biofilm and plaque</td>
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<td>Yi et al. [83]</td>
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<td>In vitro</td>
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<td>Sharon et al. [96]</td>
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<td>Quaternary ammonium polyethyleneimine NPs</td>
<td>S. mutans, L. casei</td>
<td>In vitro</td>
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<td>Varon-Shahar et al. [95]</td>
<td>Orthodontic cement</td>
<td>Polycationic PEI-based NPs</td>
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<tr>
<td>Mirhashemi et al. [139]</td>
<td>Fixed retainer composites</td>
<td>Ag NPs</td>
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<td>In vitro</td>
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<td>Kotta et al. [75]</td>
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<td>Hernandez-Gomora et al. [60]</td>
<td>Orthodontic elastomeric ligatures</td>
<td>Ag NPs</td>
<td>S. mutans</td>
<td>In vitro</td>
</tr>
</tbody>
</table>

(Continued)
tooth enamel that contacts the tooth surface directly. White spot lesions or enamel demineralization caused by acid biofilms usually develop in areas adjacent to orthodontic brackets [129]. To overcome these damages, antibacterial adhesives and primers containing different NPs were studied. As a commonly used antibacterial material, silver has been added to orthodontic adhesives in the form of NPs, which showed obvious antibacterial effects [58,130,131], and a 5% concentration was reported to be the minimum concentration of Ag NPs with optimal antimicrobial efficacy against S. sanguinis, L. acidophilus, and S. mutans [131]. The antibacterial effect of Cu NPs on S. aureus, E. coli, and S. mutans was also found when 0.0100 wt% Cu NPs were added to the orthodontic adhesive [64]. Bioactive glass NPs were added to a self-adhesive resin and a statistically significant antibacterial effect was found at the concentrations of 1, 3, and 5 wt% [90]. In addition, the antibacterial properties of other NPs in orthodontic resin were studied and their antibacterial effects were reported, including CuO NPs at the concentration of 0.01, 0.5, and 1.0 wt% [67]; TiO₂ NPs at the concentration of 1, 5, and 10 wt% [132]; Ag/hydroxyapatite NPs at the concentration of 5 and 10 wt% [133]; yttrium(III) fluoride NPs at the best concentration of 1 wt% [82]; cCur/ZnO NPs at the best concentration of 7.5 wt% [70]; fluorinated bioactive glass NPs [89]; amorphous calcium phosphate NPs at a concentration of 5 wt% [134]; curcumin NPs at the best concentration of 1 wt% [105]; curcumin-doped poly lactic-co-glycolic acid NPs at the best concentration of 7 wt% [108]; chitosan NPs at the best concentration of 5 wt% [2]; polycationic PEI-based NPs at the best concentration of 1.5 wt% [135]; and graphene oxide NPs at a concentration of 5 wt% (Table 2 and Figure 4a) [92].

<table>
<thead>
<tr>
<th>Study type</th>
<th>Bacterial tested</th>
<th>Orthodontic auxiliaries</th>
<th>NPs used</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>In vitro</td>
<td>L. casei, S. aureus, E. coli</td>
<td>Micro-implants</td>
<td>Ag NPs</td>
<td>Venugopal et al. [143]</td>
</tr>
<tr>
<td>In vitro</td>
<td>S. mutans, S. sanguinis, Aggregatibacter actinomycetemcomitans, E. coli</td>
<td>Micro-implants</td>
<td>Ag NPs</td>
<td>Qiang et al. [142]</td>
</tr>
</tbody>
</table>

5.2.2 Orthodontic cement

As a new adhesive material, glass ionomer cement is the product of the interaction between fluoro aluminosilicate glass powder and polyacrylic acid aqueous solution [43]. It is widely used in the bonding of brackets and bands and so on in orthodontic treatment. The performance of orthodontic cement directly affects the curative effect of orthodontic treatment. To improve the antibacterial performance of orthodontic cement, different kinds of NPs were added to the orthodontic cement, and their antibacterial properties were tested. Ren added different proportions of titanium dioxide NPs to traditional glass ion cement and found that the antibacterial effect against S. mutans of glass ion cement significantly improved at a concentration of 10 wt% [43]. In addition, some different
NPs, including Ag NPs at a concentration of 0.1 wt% [57,136,138], nano-CaF2 at a concentration of 20 wt% [83], quaternary ammonium polyethylenimine NPs at a concentration of 1 wt% [96], and polycationic PEI-based NPs at a concentration of 1 wt% [95], were added to orthodontic cement and proved to be effective antibacterial agents (Figure 4a).

### 5.2.3 Fixed retainer composites

Many orthodontists presume that fixed bonded retainers are the only way to obtain the desired alignment after the debonding of orthodontic appliances, especially in the lower anterior segment [138]. The fixed bonded retainer is made of a piece of wire and composite resin bonded to teeth, which means there would be potential bacterial accumulation around the retainer. To overcome microorganism aggregation, researchers have tried to add Ag NPs into the composites of the fixed retainer and more antibacterial effects were observed as the concentration of Ag NPs increased, especially against S. mutans, S. sanguis, and L. acidophilus at the best concentration of 5 wt% [139]. Kotta et al. evaluated the antibacterial activity of retainers bonded with conventional and NP (TiO2)-containing composites and found that composites containing TiO2 at a concentration of 1 wt% showed a statistically significant increase in antibacterial activity (Figure 4b) [75].

### 5.2.4 Orthodontic elastomeric ligatures

Orthodontic elastomeric ligatures are synthetic elastics made of polyurethane material, with advantages, such as quickness of application, patient comfort, and lower cost than self-ligation clips [140]. However, apart from their practical benefits, elastomeric ligatures exhibit a greater number of microorganisms in the plaque around the brackets than steel ligatures [141]. In the study of Hernandez-Gomora et al., Ag NPs were synthesized in situ on orthodontic elastomeric ligatures and this study suggested the potential of the material to combat dental biofilms and in turn decrease the incidence of demineralization in dental enamel (Figure 4a) [60].

### 5.2.5 Micro-implants

With the rapid development and advancement in orthodontic and orthopedic technologies, micro-implants are increasingly used for absolute anchorage. Ti-based implants are susceptible to bacterial infections, leading to poor healing and osteointegration and resulting in implant failure or repeated surgical intervention [142]. To reduce bacterial infections and increase the success rate of implants, NPs were used on the micro-implants. Venugopal found that titanium micro-implants modified with AgNP-coated biopolymers exhibited excellent antibacterial properties [143] and in Qiang’s study, the antibacterial properties of Ag NP/silk sericin-coated Ti surfaces were demonstrated to prevent bacterial cell adhesion as well as early-stage biofilm formation and exhibited a negligible level of cytotoxicity in L929 mouse fibroblast cells (Figure 4b) [142].

### 6 Conclusions and perspectives

Microbial accumulation is a common problem during the orthodontic process. Orthodontic appliances and auxiliaries promote supra- and subgingival biofilm accumulation and hinder oral hygiene, causing adverse effects, such as dental caries and periodontal disease. Studies
have shown that, during orthodontic treatment, there is an elevated level of major oral pathogenic pathogens, such as S. mutans [144] and P. gingivalis [145]. Various attempts have been made to increase the antimicrobial properties of orthodontic appliances and auxiliaries, and research on the application of nano-antibacterial materials in orthodontics is also increasing. However, current nanomaterials have not yet achieved the perfect balance of antimicrobial effect and biocompatibility, which should still be further studied. From the aspect of orthodontic materials, clear aligners are a new trend in orthodontic appliances, while there are few studies on the application of NPs in clear aligners for microbe inhibition at present, and antibacterial NPs combined with clear aligners should be given more attention.

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Data availability statement: All data generated or analysed during this study are included in this published article and its supplementary information files.

References


Application of antibacterial nanoparticles in orthodontic materials


