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Review Article

Antimicrobial Properties of Metal Nanoparticles and Their Oxide Materials and Their Applications in Oral Biology

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Some scholars have shown that metal nanoparticles have excellent antibacterial properties and can be used as a new type of antibacterial agent. In recent years, with the in-depth research on nanomaterials, its applications in the medical field have gradually increased. The oral cavity has a unique anatomical structure, and for oral infections, the current clinically commonly used treatment measures are oral or topical antibiotics. However, due to bacterial resistance and the special structure of dental plaque, the effect of antibiotics is not ideal. Metal and metal oxide nanoparticles have become the research hotspot of new antibacterial materials due to their small particles, large specific surface area, physical, mechanical, and chemical properties, and antibacterial properties. This article describes the antibacterial effect, antibacterial mechanism, biological toxicity, and application progress of metal nanomaterials in the oral cavity.

1. Introduction

The discovery of antibiotics is considered one of the most important medical achievements of mankind [1]. In recent years, the prolonged abuse of antibiotics has led to the production of super-resistant bacteria in the body, which has greatly increased the mortality rate of infected persons and constitutes a serious threat to public health [2]. Conventional antibiotics have a single target, and bacteria are easily resistant to them [3]. In the 1990s, the WHO first considered that the problem of bacterial resistance to antibiotics was already a global problem. The continuous escalation of multi-drug-resistant pathogens makes it urgent to develop new methods to cope with this global treatment challenge [4], and finding a safe and effective antibacterial agent has become a research hotspot. In order to solve the increasingly serious problems in the postantibiotic era, new strategies for the treatment of microbial infections are urgently needed. As a new type of antibacterial agent, nano-antibacterial material has unique physical and chemical properties, such as ultrasmall size, large surface area to mass ratio, and enhanced chemical reaction activity, and has broad application prospects in antibacterial therapy [5]. Antibacterial nanomaterials can be divided into nanomaterials with antibacterial properties in nature, nanomaterials as carriers of antibacterial agents, and nanomaterials with two functional properties at the same time [6].

Among various types of nanomaterials, precious metal nanomaterials have attracted much attention due to their excellent optical, electronic, and catalytic properties [7]. The antibacterial effect of metal and metal oxide nanoparticles has multitarget characteristics. While changing the permeability of cell membranes, it can also interfere with the functions of sulfur-containing proteins and phosphorus-containing compounds (such as DNA), making it difficult for bacteria to develop resistance to them [8]. Silver, gold, copper, iron, titanium dioxide, zinc oxide, etc., are the main metal nano-antibacterial agents, and metal oxide nanoparticles such as Ag_2O, FeO, CuO, ZnO, MgO, TiO_2-CaO, etc., are considered to have potential antibacterial activity [9]. Nanomaterials can significantly improve the physical and chemical properties of their volume counterparts, such as optical properties, mechanical strength, enzyme-like activity, and antioxidant activity. The enzyme-like activity of nanomaterials has become a research hotspot in recent years due to its strong catalytic activity and potential applications in antibacterial applications, such as biosensing, food safety, and environmental protection [10]. Silver nanoparticles (AgNPs) and gold nanoparticles (AuNPs) have significant antibacterial activity due to their high surface-to-volume ratio and crystal surface structure and have been developed to combat infections of various strains including antibiotic-resistant pathogens [11]. Gold nanoparticles with unique physical and chemical properties have received extensive attention in the fields of biology, chemistry, and biomedicine and are considered to be ideal candidates for colorimetric detection, catalysis, imaging, and photothermal converters [12]. Nanomagnesium oxide (MgO-NP) aqueous solution has good in vitro and in vitro antibacterial activity and low toxicity [13]. ZnO, CuO, and AgNP have many potential applications in the fields of medical treatment, biosensors, catalysts, ceramics, fungicides, and health products [14]. In view of their surface modification quality, multivalence, and photothermal properties, they are expected to move from the laboratory to the clinic [15]. According to reports, some metal nanoparticles have cytotoxic effects on mammalian cells [16].

This article summarizes the antibacterial effect, antibacterial mechanism, biological toxicity, and application progress of metal nanomaterials in recent years, as well as the existing shortcomings and prospects for future research, in order to provide reference for follow-up research.

2. Antibacterial Effect of Nanomaterials

As a new kind of antibacterial agent, nanometal materials can bring good news for the treatment of microbial infection by its effect on drug-resistant and multi-drug-resistant bacteria. The applications in various studies are given in supplementary Table S1.

2.1. Gold Nanomaterials. Gold is one of the most ideal elements. Gold nanoparticles (AuNPs) show great performance and are easily degraded by oxidation and enzymes [17]. Because AuNPs have low toxicity, strong absorption spectrum, and the ability to combine with various organic biomolecules, they play a major carrier role [18]. Metal nanoparticles are known to have nonspecific bacterial toxicity. They do not bind to specific receptors in bacterial cells, which broadens the scope of antibacterial activity [19]. In addition to the above summary, its antibacterial physical and chemical properties are easy to be surface functionalized [20].

Huang et al. tested the antibacterial activity of AuNPs and found that AuNPs have significant antibacterial activity against gram-negative bacteria and gram-positive bacteria, indicating that AuNPs have potential applications in the fields of medicine and biology [21]. Recently, López-Lorente et al. found that spherical AuNPs have no antibacterial activity between 0 and $500\,mg{\cdot}L^{-1}$, while flower-shaped AuNPs and star-shaped AuNPs of the same size have antibacterial properties at high concentrations ($250{\sim}500\,mg{\cdot}L^{-1}$) [22]. Lately, researchers have used plant-synthesized gold nanoparticles to prevent and control infectious diseases and skin wounds. Studies have shown that the antifungal and antibacterial effects of synthetic gold nanoparticles (AuNPs) in the water extract of onion are higher than those of standard antibiotics [23]. Scholars such as Gouyau et al. have prepared 12 nm gold by chemical method. The nanoparticles have weak antibacterial activity against E. coli and Staphylococcus aureus tested [24]. In addition, some studies have used a simple green route to synthesize an aqueous extract containing gold nanoparticles (AuNPs). Microbiological studies have shown that the compound has significant antibacterial activity against pathogenic bacteria such as Enterobacter cloacae and Staphylococcus haemolyticus [25]. The sufficient pharmacokinetic properties and high biosafety of gold nanoparticles paved the way for their potential biomedical applications [26].

In recent years, the application research of AuNPs has made rapid progress. Studies have shown that the presence of nanogold in the nanocomposite will not affect its physical and chemical properties, but due to its characteristics, its antibacterial activity can be enhanced. If starch is introduced, it may affect the biocompatibility and antibacterial activity of the material [27]. Antimicrobial peptides (AMPs) have broad-spectrum anti-infective activity and immunomodulatory properties [28]. Studies have shown that the coupling of AMPs and gold nanoparticles can help improve the serum stability of peptides and has a significant effect on anti-drug-resistant pathogens [4]. Wang et al. showed that AuNPs have no antibacterial activity, but they are produced when they are modified by some molecules without antibacterial activity (thiol or amine, two groups with different binding affinity and gold as anchor group). AuNPs show effective antibacterial activity and can be used for personalized treatment, especially for the treatment of complex infections caused by MDR bacteria [29]. The protein-reduced gold nanoparticles are mixed with gentamicin sulfate and packed into konjac/gelatin sponge, which can heal wounds and kill drug-resistant bacteria [30]. Appropriate use of AuNPs as a carrier to carry antibiotics for adjuvant therapy, to a certain extent, alleviates bacterial sepsis in mice induced by ligation and puncture. Its role is to produce anti-inflammatory response through antibiotic effect and inducing macrophage function [31]. Indian researchers have discovered that AuNPs synthesized from green leaf extract of Jianlan leaves and conjugated with antibiotics exhibit broad-spectrum antibacterial activity against oral pathogenic bacteria and fungi. Broad-spectrum coating of antibiotics on NPs can improve their antibacterial effect. The selected oral pathogens suggest that synthetic AuNPs can be used as a possible tool for new therapeutic drugs to destroy pathogens in the oral cavity [32]. Gold nanoparticles (AuNPs) for the resveratrol nanocarrier system were synthesized using the green synthesis route. It was observed that the AuNPs exhibited greater antimicrobial activity against gram-positive and gram-negative bacteria compared with resveratrol alone. Scholars such as Alsamhary et al. proved that AuNPs synthesized from flavonoid clover are a potential antibacterial nanodrug, which can be used to treat respiratory tract infections that cause conditional pathogens [33]. Using the water extract of alfalfa to synthesize nanoparticles can effectively combat the biofilm of Pseudomonas aeruginosa and can be used as an effective nano-antibiotic to combat biofilm-related infections caused by Pseudomonas aeruginosa [34]. Gold nanoparticles (AuNPs) and copper metal-organic framework nanosheets (Cu-MOFNs) were fabricated. The experimental results show that the material can enhance the antibacterial effect and promote wound healing [35].

2.2. Silver Nanomaterials. Silver nanoparticles (AgNPs) can be used as antibacterial agents just like colloidal silver. Studies have shown that highly active AgNPs have good antibacterial effects and are an excellent antibacterial material [36]. Among metal nanoparticles, AgNPs have attracted much attention due to their broad-spectrum antibacterial activity [37]. The size of the nanomaterial determines the cellular response that will occur, including cytotoxicity, biological barrier penetration, and immune response. Studies have shown that metal nanoparticles such as silver are easily endocytosed by cells due to their small size, which can cause changes in cell morphology and vitality [38].

The antibacterial activity of silver nanoparticles is affected by their shape and size. In the research, scholars have observed that the smallest nanoparticles (5 nm in size) most effectively control the growth of Fusobacterium nucleatum and Streptococcus mutans. In addition, silver nanomaterials have sharp multiple edges, which cause greater mechanical damage to bacteria than smooth nanomaterials (such as nanospheres), so they have higher biocidal activity [39]. Studies have shown that the size and surface coating of AgNPs play an important role in antibacterial activity, and it has been observed that nanoparticles with smaller diameters have higher toxicity. The new synthesis technology of silver nanoparticles has explored biosynthetic methods, including the use of plant extracts, bacteria, fungi, and yeast as solvents, reducing agents or stabilizers [40]. The researchers synthesized AgNPs from freeze-dried water alcohol extracts of cumin seeds and flowers. Tests showed that the compounds were stable and had variable shape, size, and electronegative (capping) properties, which helped their antimicrobial activity [41]. Satish Kumar and other scholars synthesized carbohydrate-coated bimetallic nanoparticles (Au-AgNPs, diameter 30-40 nm). Studies have shown that the particles have excellent antibacterial properties and can be effectively used to cure skin infected by MRSA and other pathogens. Furthermore, the particles do not develop drug resistance or undesirable toxicity. Therefore, Au-AgNPs are safe in vitro and in vivo [42]. However, studies have shown that when exposed nanosilver comes into contact with bacteria, they aggregate and lose active surface area, thereby reducing antibacterial activity. Scholars have prepared nanocomposites composed of AgNPs and graphene. Compared with AgNPs, the synthesized composites have better colloidal stability, light stability, and antibacterial activity against Escherichia coli and Bacillus subtilis [43]. Lu et al. designed and prepared nanosilver-modified mesoporous silica nanoparticles (Ag-MSNs), which combine tissue adhesion and antibacterial activity and have good biocompatibility and high-efficiency antibacterial properties. The nanoadhesive has good antibacterial activity against gram-negative bacteria Escherichia coli and gram-positive bacteria Staphylococcus aureus. And the wound closure is safe and beautiful without causing any infection or side effects [44]. Researchers Kamradgi et al. report that biosynthetic silver nanoparticles (AgNPs) have good antibacterial activity against both gram-positive and gram-negative bacteria, especially against drug-resistant Enterococcus faecalis and Pseudomonas aeruginosa. When evaluating the antitumor activity of this material against human hepatocellular carcinoma (HepG2) cell line, AgNPs showed good inhibitory effect [45]. The electrospinning nanocomposite of silver nanoparticles was synthesized by green synthesis method. The antibacterial activity of this material against Staphylococcus aureus and Pseudomonas aeruginosa reached 90%. It can be used for wastewater disinfection and other antibacterial activities [46]. Bi et al. synthesized silver peroxide nanoparticles (Ag_2O_2-NPs) capable of controlling the release of reactive oxygen species (ROS) to combat bacterial infectious diseases. In vitro and in vivo studies showed that the nanoparticles enhanced antibacterial and biofilm resistance, accelerated skin wound closure in multi-drug-resistant Staphylococcus aureus infection, and had excellent cell-blood compatibility [47]. N. Ahmad et al. reported that green synthesis of silver nanoparticles (AgNPs) using water extract of Euphorbia serpens Kunth showed good antibacterial activity against all tested bacteria. Moderate antifungal activity was observed against C. albicans and A. alternata [48]. The HAp/GO/Ag nanocomposite coating was developed. In vitro experiments demonstrated that the material improved antibacterial activity without cytotoxicity and also prevented electrolyte from entering the substrate to improve the biological corrosion performance [49]. Some scholars have prepared silver monodisperse nanoparticles in soda-calcium glass, which can effectively avoid the agglomeration of nanoparticles and enhance their biocidal activity. The results of antibacterial experiments show that the material can reduce the initial concentration of bacteria by five orders of magnitude. In addition, Ca^{2+} can be leached and inhibit the growth of yeast when antibacterial treatment is performed at relatively low pH values. This material is expected to be a powerful antibacterial agent as well as an inorganic antifungal agent [50].

2.3. Copper Nanoparticles and Copper Oxide Nanoparticles. Copper nanoparticles (CuNPs) have good heat resistance and chemical stability and are an excellent antibacterial agent. Experiments have shown that only when copper precipitates and grows to a certain size can the growth of bacteria be inhibited. A large amount of copper precipitation makes the material have excellent antibacterial properties, but it cannot improve the strength of the material. The copper ions that play a role of precipitation strengthening are very small and uniformly distributed [51]. Studies have shown that the antibacterial, antifungal, and antiviral effects of copper nanoparticles are related to its direct contact with microorganisms and its killing effect [52]. On the other hand, thiol interactions inactivate proteins to reduce bacterial viability. Studies have shown that CuNPs will oxidize on the surface at low redox potentials, thereby reducing the antibacterial properties, while the activity of copper oxide is lower than that of metallic copper, thus becoming copper nanoparticles with high antibacterial properties [53].

Compared with silver and gold nanoparticles, the cost of using copper nanoparticles is lower. CuNPs prepared by different synthesis processes have different antibacterial properties. Rémy et al. improved the classical synthesis method, which beneficially affected the antibacterial properties of CuNPs [54]. Some scholars have prepared nanocopper particles encapsulated with Heterosporium aurantii and combined these nanoparticles on the fabric. It was found that at the highest concentration, the nano-copper-coated fabric has a negative effect on gram-positive and gram-negative bacteria. Effectiveness is 101% and 74%, respectively [55]. The polyol reduction method was used to modify copper acetate hydrate, and the results showed that the method has antibacterial activity against bacteria and fungi, and its antibacterial activity is also different due to different dyeing. Not only that, copper nanoparticles have a wide range of applications in reducing hospital infections, burn treatment, preventing bacterial and fungal colonization and repair, blood vessel transplantation, and dental materials [56]. Antibacterial studies have shown that the antibacterial effect of CuNPs is mainly to produce reactive oxygen species (ROS) to bacteria and cause DNA damage. Because copper has significant antibacterial properties, it has been widely used in fields such as drug delivery, compound food antibacterial packaging, and water filtration treatment [39]. Studies have shown that 1-10 nm is the best size range for nanocopper antibacterial. CuNPs have the characteristics of interaction with pathogens, large specific surface area, high chemical and biological activity, etc., and have broad application prospects in the medical and dental fields [57]. Esteban-Tejeda et al. showed that low-melting sodium-calcium glass powder containing copper nanoparticles had a logarithmic increase in bactericidal activity (for copper content of 0.054 wt%) under the synergistic effect of calcium, demonstrating high antibacterial and antifungal activity [58]. In addition to having sufficient antibacterial activity, the copper-containing nanoparticle nanocomposite developed by Vidakis et al. improved its mechanical properties by about 33.7% [59].

Copper oxide nanoparticles (CuO-NPs) are a class of multiperformance materials, which have broad application prospects in the fields of photoconductivity, gas sensors, electronic devices, etc., and can also be used to prepare various food active packaging films and antibacterial bio-nanocomposite films, etc. [14]. In recent years, people have adopted green methods to synthesize CuO-NPs with antibacterial activity. Studies have shown that the cytotoxicity of green synthesized copper oxide nanoparticles is lower than that of chemical synthesis, making CuO-NPs more widely used in biomedicine. For example, CuO-NPs synthesized from leaf extracts have potential antibacterial activity against multidrug-resistant bacteria such as Bacillus subtilis, Staphylococcus aureus, Escherichia coli, and Pseudomonas aeruginosa [6]. Not only that, the size of the particle also has an impact on the antibacterial performance. CuO-NPs with a size range of 50-100 nm show significant antibacterial activity against Klebsiella pneumoniae, Shigella dysentery, and Vibrio cholerae. The size range is 20-95 nm. CuO-NPs have antibacterial activity against Escherichia coli and methicillin-resistant Staphylococcus aureus (MRSA). Its antibacterial effect is mainly because Cu^{2+} released by NPs causes mutations and DNA damage and triggers the production of reactive oxygen species [39].

2.4. Iron Nanoparticles and Iron Oxide Nanoparticles. Iron oxide nanoparticles (FeO-NPs) have unique properties, including nanometer size, high permeability, low cost, surface modification, good chemical stability, easy synthesis, colloidal stability, and dispersion in aqueous media. Sex has caused widespread concern in the fields of catalysis, food coatings, cosmetics, antibacterial agents, etc. [60]. Nanoparticles, including nanoiron, can target the delivery of antibacterial drugs to the infected site, thereby increasing the effective drug concentration at the infected site, thereby producing antibacterial effects, reducing the dosage of drugs and overcoming bacterial resistance [61]. The chitosan-coated iron oxide nanocomposite has antioxidant activity and has potential antibacterial activity against both gram-positive and gram-negative pathogens. It is a promising bio-nanomaterial [62]. FeO-NPs are toxic to bacterial strains by binding to sulfhydryl compounds in the respiratory group of bacterial cells, thereby exerting antibacterial effects [63].

Biofilms and related infections remain an important medical problem, often life-threatening. The results of the study by Elbourne et al. showed that GLM-Fe particles are a potential material that can utilize physical mechanisms to prevent bacteria. This result will help to develop a new generation of liquid metal-based antibacterial technology and effectively treat biofilms through magnetically activated cell lysis [64]. FeO-NPs are one of the most important transition metal oxides in the progress of nanotechnology and biological applications. Saqib et al. used the coprecipitation method to synthesize FeO-NPs and determined the bactericidal effect of NPs on gram-positive bacteria and gram-negative bacteria. The results showed that the nanoparticles have good antibacterial effects [65]. Bhuiyan developed a green method to synthesize FeO-NPs, and the synthesized nanoparticles have certain antibacterial activity against Klebsiella, Escherichia coli, Pseudomonas, and Staphylococcus aureus [66]. FeO-NPs prepared from medicinal plant Phyllanthus extract showed strong antibacterial effect on Escherichia coli [67]. Passive targeting by adjusting the structure and physicochemical properties of nanoparticles is an effective way of drug delivery, such as FeO-NP-induced magnetothermal therapy, which is a nano-antibacterial system that can deliver effective drugs to the target location [68]. Iron oxide nanoparticles (FeO-NPs) synthesized from guava leaf extract and iron oxide nanorods (FeO-NRs) synthesized with Moringa (MO)-coated FeCl3 are promising antibacterial agents. At a lower concentration, it can inhibit the growth of six human pathogens with higher activity, and the antibacterial activity increases with the increase of the concentration. Moreover, compared with traditional antibacterial drugs, bacterial strains show a strong and effective sensitivity to NPs at lower concentrations [60, 63]. Vallabani et al. described a new method of using adenosine triphosphate disodium salt (ATP) as a synergist to accelerate the coating of Fe_3O_4 nanoparticles with citrate. In the presence of neutral pH and H_2O_2, the particles showed enhanced broad-spectrum antimicrobial activity against gram-positive and gram-negative strains [69]. Sodium alginate-coated nanocomposites have the potential to overcome the barrier of bacterial biofilm. FeO-NPs coated with sodium alginate and magnetite-cotobramycin conjugate coated with sodium alginate can inhibit Pseudomonas aeruginosa growth and biofilm formation [70]. Metal nanoparticles (MNP) showed low cytotoxicity and strong bactericidal activity. Among them, Fe_2O_3 nanoparticle-coated sutures showed strong antibacterial activity against Pseudomonas aeruginosa and Staphylococcus aureus in vitro, and all sutures showed minimal cytotoxicity [71].

2.5. Zinc Nanoparticles and Zinc Oxide Nanoparticles. Zinc is a known important trace element in human bones and plays an important role in a variety of biological functions including DNA synthesis and nucleic acid metabolism. Zinc oxide is rich in content, low in toxicity, environmentally friendly, and low in cost and has excellent photocatalytic performance. It is currently one of the most widely used semiconductor photocatalysts [43].

Zinc oxide nanomaterials (ZnO-NMs) have excellent antibacterial properties and biocompatibility, have significant bactericidal potential against various gram-positive and gram-negative bacteria, and are not toxic to human cells [14], becoming research hotspots of new antibacterial agents [72]. Zinc oxide nanoparticles (ZnO-NPs) are the most common zinc-containing nanomaterials. Studies have reported that ZnO-NPs have antibacterial activity against various pathogens such as Campylobacter jejuni, Salmonella typhimurium, Klebsiella pneumoniae, and Neisseria gonorrhoeae [73]. Compared with other antibacterial materials, ZnO has excellent biocompatibility, safety, and long-term effectiveness, coupled with the gradual maturity of plasma electrolytic oxidation technology and the successful integration of zinc into the material, making it suitable for various biomedical applications [74]. For example, because nanozinc (NZn) and nanozinc oxide (NZnO) have a broad antibacterial spectrum, adding them to the composite resin can synergistically reduce the number of microorganisms [75].

In addition to biocompatibility and biodegradability, ZnO-NMs also have unique semiconductor and piezoelectric properties [40]. Experiments have shown that nanocellulose/zinc oxide composite materials have excellent mechanical properties, anti-ultraviolet properties, and antibacterial properties [76] and have been used in manufacturing with excellent mechanical properties, anti-ultraviolet, photocatalytic properties, thermal stability, hydrophobicity, and production of multifunctional antibacterial film and antibacterial paper [14]. In order to overcome the significant cytotoxicity caused by the release of Zn^{2+}, some scholars prepared a uniform ZnP coating on the surface of metallic zinc, which has the advantages of simple synthesis, stable chemical properties, and good biocompatibility. Experiments show that ZnP can not only improve cell viability, adhesion, and proliferation but also significantly reduce the adhesion of platelets and bacteria [74]. A metal-organic skeleton nanoparticle (Pd(H) @ZIF-8) with pH response of zinc ion (Zn^{2+}) and hydrogen has been reported. In vitro and in vivo experiments have shown that the material can target and adhere to inflammatory sites through electrostatic interactions, avoid intestinal flora imbalance, and effectively kill Helicobacter pylori while alleviating inflammation and repairing damaged gastric mucosa [77]. Green ZnO nanoparticles (Zno-NPs) were synthesized by using Tribulus terrestris extract as reducing agent. The surface morphology of ZnO-NPs showed that it had good antibacterial activity, stability, and biocompatibility [78]. ZnO nanoparticles (ZnO-NPs) synthesized from cyanobacteria cell extracts have good antibacterial ability and can effectively inhibit biofilm formation. When cytotoxicity tests were performed, the results showed low cytotoxicity to normal lung (MRC-5) cells. The material is expected to be widely used in the therapeutic and pharmaceutical industries [79].

2.6. Titanium Nanoparticles and Titanium Dioxide Nanoparticles. Because of its inherent basic characteristics, titanium dioxide (TiO_2) has been developed as an excellent photocatalytic material for many different industrial applications [80]. When titanium is used as a nanomaterial, it has antibacterial activity and has broad application prospects in reducing bacterial growth and reducing infection. It has been reported that the antibacterial activity of titanium is closely related to its photocatalytic performance [40]. The photoactivation of TiO_2-NPs significantly improves its antibacterial activity against sensitive Bifidobacterium, Escherichia coli, Escherichia coli, Staphylococcus aureus, Salmonella typhimurium, and Staphylococcus aureus [39].

Some scholars pointed out that titanium nanomaterials have lower toxicity than other nanometal oxides. Nanozinc oxide is the most toxic at sub-mg/l concentration, followed by nanocopper oxide and nanotitanium dioxide. According to reports, the toxic effect of TiO_2-NPs is not caused by the dissolution of metal ions but by the entrapment of cells [40]. The surface modification method proposed by Rajendran et al. in the experiment can optimize the ratio of Ca^{2+} and Ag^+ ions on the surface of titanium metal to obtain the smallest Ag^+ concentration. This concentration not only has antibacterial activity, but also has cytocompatibility to MG-63 osteoblast-like cells, which is expected to be applied to orthopaedic implants with enhanced bioactivity, antibacterial activity, and cytocompatibility [81]. The hybrid multifunctional humic acid synthesized by scholars through solvothermal method combined with titanium dioxide nanomaterials endows amoxicillin and tetracycline antibiotics with high isolation efficiency and enhances the significant OS-mediated sterilization performance against many pathogenic gram-negative bacteria [82].

2.7. Cerium Nanoparticles and Cerium Oxide Nanoparticles. Cerium oxide nanoparticles (CeO_2-NPs) are one of the important materials of metal nanoparticles. Due to its special physical and chemical properties, including strong redox ability, nontoxicity, good long-term stability, and low cost, it has been widely used as a nanomaterial. [83]. In the biomedical field, CeO_2-NPs have attracted much attention due to their antioxidant properties. Their applications range from fighting inflammation and cancer to radiation to protect cells. In all the studies reported and reviewed in the literature, the mechanism of action was related to the antioxidant properties of NPs [84]. The redox dual nature of CeO_2-NPs is closely related to the reversible combination of oxygen atoms and the existence of oxygen vacancies, and the valence states of Ce^{4+} and Ce^{3+} are continuously cyclically switched. This property protects cells from oxidative stress, inflammation, and potential radiation damage [85]. Many studies have shown that CeO_2-NPs exhibit good antibacterial activity against gram-positive and gram-negative bacteria due to the generation of reactive oxygen species (ROS) [86]. Some scholars have found that CeO_2-NPs can alleviate H_2O_2-induced oxidative stress and the production and apoptosis of reactive oxygen species in BMMSCs. The results indicate that CeO_2-NPs can be used as a potential antibacterial drug, especially against gram-negative bacteria [87]. Studies have shown that CeO_2-NPs may target gram-negative bacteria and fungi through direct contact and imbalance of the outer membrane. At low pH, the nanoparticles become positively charged, making it easier to adhere negatively charged bacteria through electrostatic interactions. During this process, valence conversion occurs on the surface of cerium oxide nanoparticles, and Ce^{4+} is converted into Ce^{3+}, which can obtain the maximum antibacterial activity [88]. The redox sensitivity of ceria nanoparticles can also be used to irreversibly scavenge phosphate ions from microbial growth media. By competing with bacteria for phosphate, the available nutrients for bacterial cell growth and division are limited. Deficiency of phosphate leads to oxidative stress in bacterial cells, further enhancing antibacterial activity [89].

Some scholars have studied the antibacterial properties of CeO_2-NPs synthesized by hydrothermal method, and the characterization technology has verified that the particles are nanoparticles with an average diameter of about 3-5 nm. In vitro antibacterial experiments show that the material has effective antibacterial activity against Enterococcus faecalis, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter spp. Therefore, the particles can be used as potential bionanomaterials for in vivo therapeutic applications [90]. Some scholars have prepared cerium oxide nanoparticles (CeO_2-NPs) by wet chemical method (WCS-SimAdd), which have good antibacterial activity against Escherichia coli, Bacillus typhimurium, Bacillus monocytogenes, Staphylococcus aureus, and Bacillus cereus [86]. Fifere et al. prepared CeO_2-NPs with sizes between 13 and 17 nm by precipitation method. The antibacterial test showed that CeO_2-NPs showed good antibacterial activity against Escherichia coli and Staphylococcus aureus [91]. Some studies have reported that the use of purple bamboo extract mediated synthesis of CeO_2-NPs, evaluation of antibacterial activity against Staphylococcus aureus and Klebsiella pneumoniae, and in vitro test of green synthesis of CeO_2-NPs on cervical cancer cells (HeLa) toxicity. The results showed that the material had good antibacterial effect and reduced HeLa cell viability in a dose-dependent manner [92]. When it was added to chitosan hydrogel membranes as wound dressings, significant improvement in wound healing was observed. Surface modification of CeO_2-NPs by specific ligands, such as triethyl phosphite (TEP) and tris (2,4,6-trimethoxyphenyl) phosphine (TTMPP), can tune its redox properties and reverse oxidation state [93]. Ma et al. prepared molybdenum disulfide-cerium dioxide nanocomposites by 808 nm laser treatment, combining the inherent antibacterial activity and abundant oxygen vacancy of CeO_2-NPs. The results showed that the new composite showed excellent PTT antibacterial activity against both gram-positive and gram-negative bacteria and could remove excessive reactive oxygen species around the wound surface, promote wound healing, and reduce the risk of wound infection [94]. In addition, Cheng et al. reported that hydrogel dressings loaded with CeO_2-NPs showed good ROS scavenging ability. The biocompatibility of the material was further proved by HaCaT cell culture in vitro. Its spray ability, adhesion, antibacterial activity, ROS scavenging, and skin remodeling ability can meet the current requirements of wound dressing materials [95].

In recent years, nanoparticle functionalized scaffolds have been extensively studied. Some studies have shown that CeO_2-NPs functionalized scaffolds show enhanced antibacterial activity against both gram-negative and gram-positive strains. Cell experiment results show that this material supports the growth of human mesenchymal stem cells, confirming the cytocompatibility. The composite material can be used for ROS scavenging and regeneration of bone tissue with antibacterial ability [96]. More and more studies have shown that CeO_2-NPs have antioxidant, antitumor, antibacterial, and angiogenic activities, which make them widely used in the medical field [97].

3. Antibacterial Mechanism

Nanomaterials overcome bacterial resistance due to their unique antibacterial mechanism and are introduced into the biomedical field [98]. Compared with traditional antibiotics, nanomaterials are less likely to produce bacterial resistance and have unique properties, including (A) special form with small size and large specific surface area [99]; (B) easy to suspend in liquid; (C) able to enter cells and organelles; and (D) the optical and magnetic changes are large [100], and it has the potential to become medical antibacterial drugs. In recent years, nanomaterials of metals and metal oxides have been fully used in antibacterial aspects and have achieved excellent responses. Many antibacterial mechanisms of nanoparticles have been proposed. The summary is shown in Figure 1.

(a) Destroy the biofilm to play a role [19, 101]. Various factors leading to the reappearance of drug-resistant microorganisms have been identified, the most important of which is the formation of biofilms, which has led to a significant increase in mortality and morbidity, as well as a prolonged treatment cycle. Traditional antibacterial agents do not have the ability to remove the biofilm of human wounds [102], and many studies have determined the potential of nanomaterials in dealing with bacterial resistance to antibiotics

(b) Produce reactive oxygen species ROS, which can damage DNA, RNA, and protein, thereby destroying microorganisms [19, 39, 103]

(c) By binding to DNA to inhibit DNA replication [104]. Metal nanoparticles with a smaller particle size have a higher binding rate than nanoparticles with a larger particle size and have higher antibacterial activity

(d) Release metal ions to destroy bacterial DNA and protein [19, 74, 103]. For metal nanoparticles, the positively charged metal ions are in contact with the negative charges on the microbial cell membrane. Metal ions can also penetrate the cell membrane and enter the microorganisms. They react with the sulfhydryl group (-SH) on the microbial protein to inhibit the synthesis of protein and nucleic acid [105]. The size and surface charge of nanoparticles affect their antibacterial properties. Due to their larger surface-to-volume ratio and smaller particle size, they have excellent antibacterial effects without affecting the mechanical properties of the material [75]. In addition to the aforementioned antibacterial mechanism that relies on the direct contact of nanoparticles, the bacteria can also be killed by releasing the loaded antibacterial agent [103]

4. Biological Toxicity

With the increasing use of nanoparticles in different fields, people have more and more concerns about their toxicity, biocompatibility, and safety. Although great progress has been made in the research of metal nanostructures in the past ten years, there is still a lack of comprehensive reviews on the cytotoxicity of metal nanostructures. The potential toxicity and biocompatibility of these nanoparticles depend on many factors, such as size, shape, surface area, surface energy, functional groups, levels of degradation products and release of by-products, concentration, oxidative stress function, crystallinity, and particle size life.

Shi et al. have shown that AuNPs are toxic when used in biological systems within a certain concentration range. As early as the 1990s, there were reports that gold colloidal monolayers were selectively toxic to certain cells such as red blood cells. However, toxicity depends on the size, composition, and surface properties of the gold colloid [103]. Nanoparticles often induce the production of ROS after entering cells, which can lead to oxidation-related toxicity such as DNA damage, cell death, and cell cycle arrest [72].

Silver nanoparticles induce DNA damage and oxidative stress in different ways. In addition, it affects cell proliferation, disrupts the cell cycle, and ultimately leads to cell apoptosis [106]. Of course, these toxic effects will also be affected by the selected cell type at the cellular level.

For some metals, such as copper, the toxicity of nanometal oxides can be attributed to the soluble metal ions in the material, and the solubility of nanometals is an important factor affecting its toxicity. Compared with CuO-NPs, which are more soluble than CuO, CuO-NPs are more toxic [40]. According to reports, AgNPs is a double-edged sword, which can both eliminate microorganisms and induce cytotoxicity in mammalian cells. In vitro cell culture experiments show that AgNPs are toxic to human bronchial epithelial cells, red blood cells, hepatocytes, and other cell lines. Based on in vivo animal experiments, AgNPs can cross the mouse brain blood barrier through the circulatory system [107].

The experimental results of Ahmad et al. showed that the antibacterial coating and metal oxide nanoparticles which modified PMMA denture base resin are cytotoxic to oral biofilm microorganisms such as Candida [108]. However, evidence from short-term in vitro studies shows that nanodental materials are noncytotoxic. However, these results cannot be generalized because the dental materials retain their function in the oral cavity for a long time, so the NPs in these materials are likely to leak into the saliva and produce systemic effects [109].

5. Oral Application

Recently, more and more studies showed advantages of the usage of metal nanoparticles in potential treatment of various oral diseases. The representative applications and their advantages were summarized in Figure 2.

5.1. The Treatment of Caries. Oral biofilms of carious teeth appear acidic due to the presence of Streptococcus mutans and other bacteria. FeO-NPs exhibited good antibiofilm effect at pH 4 to 5 [73]. Traditional caries filling materials lack good antibacterial properties, which can easily cause secondary caries and lead to treatment failure. Nanomaterials can interfere with the metabolism of bacteria, inhibit the formation of biofilms, reduce demineralization, and promote remineralization, which is expected to become an effective strategy for caries prevention and treatment. Studies have shown that compared with sodium fluoride toothpaste, the fluorine-containing nanosilver formula has better antibacterial effects and inhibits enamel demineralization, indicating that it has the potential to prevent dental caries [110]. Silver nanoparticles and calcium phosphate nanoparticles, as a new generation of drugs, have protein rejection, antibiofilm, and anticaries functions and can be used in dental polymer composites, adhesives, cements, and coatings. They can be combined with fluoride release and reinforcing fillers for optimal performance. They are not only effective against cariogenic biofilms but also against periodontal pathogens. Experiments have shown that the biological activity and therapeutic effects of such materials are long-lasting [111]. The addition of silver nanoparticles to the adhesive has been successful in antibacterial. The modified tissue regulator combined with silver nanoparticles showed antibacterial properties against Staphylococcus aureus, Streptococcus mutans, and Candida albicans after culture [112]. AgNPs are also added to the anticaries ingredients of toothpaste, such as calcium glycerophosphate [109]. Irene et al. found that polyethylene glycol-coated silver nanoparticles (PEG-NAg) can remineralize dentin caries and inhibit collagen degradation without causing significant tooth staining [105]. Chemically synthesized CuO nanoparticles and CuO-chitosan nanoparticles have great potential in drug delivery and nanotherapy. Compared with CuO nanoparticles, CuO-chitosan nanoparticles have significantly enhanced antibacterial, antioxidant, cytotoxic, and antidiabetic activities in vitro and can effectively treat secondary dental caries. CuO-chitosan nanoparticle-reinforced dental adhesive discs significantly reduce the adhesion of Lactobacillus

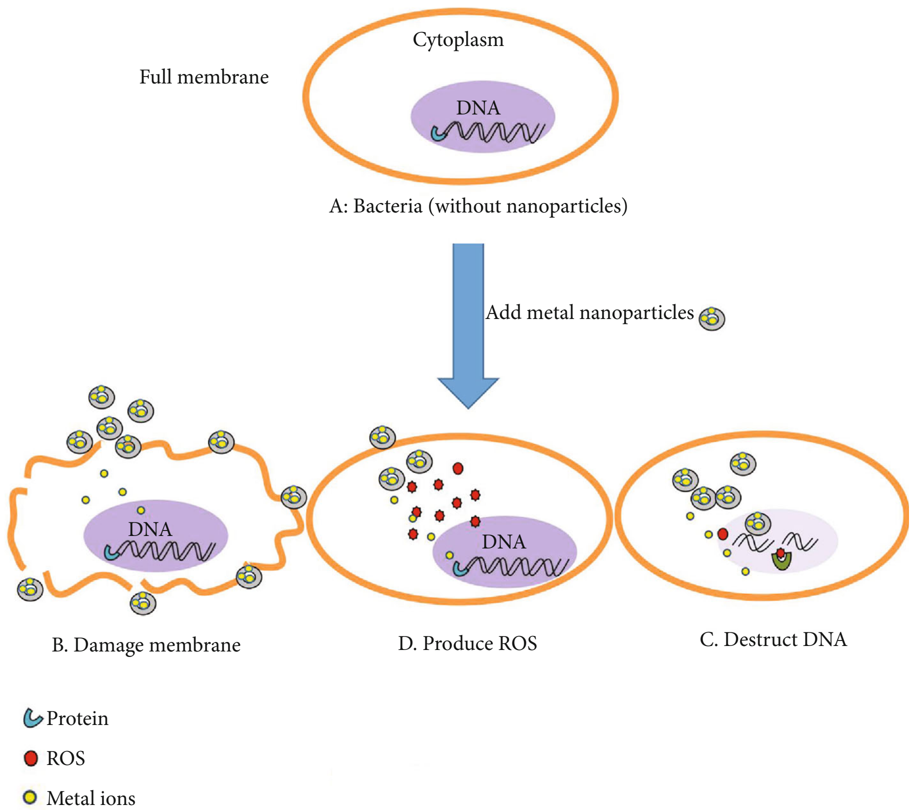

Figure 1: The antimicrobial mechanism of metal nanoparticles. (a) Native bacteria without metal nanoparticles. (b) Metal nanoparticles damage the cell membrane. (c) Metal nanoparticles destruct DNA. (d) Metal nanoparticles produce ROS.

acidophilus and Streptococcus mutans. In addition, it also enhances its mechanical properties, water absorption, and solubility, as well as a slight change in the slow-release curve and shear bond strength [113]. Chen et al. found that adding ZnO-NPs and copper nanoparticles (CuNPs) to the universal adhesive system can provide antibacterial and anti-MMP activities, improve the interface stability of dental caries, and expand dentin [105]. It has been reported that adding copper NPs to the adhesive can improve its shear bond strength and provide antibacterial properties without increasing its inherent cytotoxicity [114].

Zinc oxide nanoparticles (ZnO-NPs) are one of the most suitable nanoparticles for controlling oral pathogens and maintaining good oral hygiene [39]. Scholars analyzed the effects of iron oxide, copper oxide, and zinc oxide nanoparticles on oral infection strains. The zone of inhibition (ZOI), minimum inhibitory concentration (MIC), and minimum bactericidal concentration (MBC) were used to study the influence of different concentrations of TMO-NPs on it. The study found that oxidation zinc nanoparticles have the smallest particle size (37.8 nm) and the highest antibacterial activity, which can be used for the drug treatment of oral infectious diseases [115]. Studies have found that ZnO-NPs are effective against both gram-positive bacteria and gram-negative bacteria. Compared with CuO and AgNPs, ZnO-NPs are relatively less toxic to humans [39]. The ZnO-NPs prepared by Vinotha et al. showed good antibacterial and biofilm inhibitory activities against pathogenic bacteria including Streptococcus mutans and Clostridium spp., and it is expected to be an effective method to control the growth of Streptococcus mutans and the development of caries [116]. MgO nanoparticle- (NMgO-) modified glass ionomer cements have effective antibacterial and antibiofilm activities against two cariogenic microorganisms—Streptococcus mutans and Streptococcus sobrinus. TiO_2 nanoparticles ($NTiO_2$) are added to the glass in different proportions. Among the ionomers, it showed antibacterial activity in a direct contact test against Streptococcus mutans [105].

5.2. The Treatment of Endodontic and Periapical Disease. Pulpitis and apical periodontitis are common infectious diseases in stomatology. The key to treatment is to thoroughly remove the infectious substances in the root canal through root canal therapy. However, the anatomical complexity of the root canal system makes thorough antibacterial treatment very difficult [117]. Experiments have proved that the nanosilver solution can enhance the penetration and fixation of the dentin surface in the process of endodontic treatment and improve the effect of root canal irrigation [118]. Iron oxide nanoparticles (FeO-NPs) with peroxidase activity have been used in experiments as a catalyst for hydrogen peroxide activation in root canal therapy. Compared with traditional dental antibacterial irrigants used for root canal disinfection, irrigating solutions containing nanoparticle-H_2O_2 components can significantly kill more bacteria in the infected root canals [6]. Studies have shown that the combination of antibiotic-carrying nanoparticles and ZnO-NPs

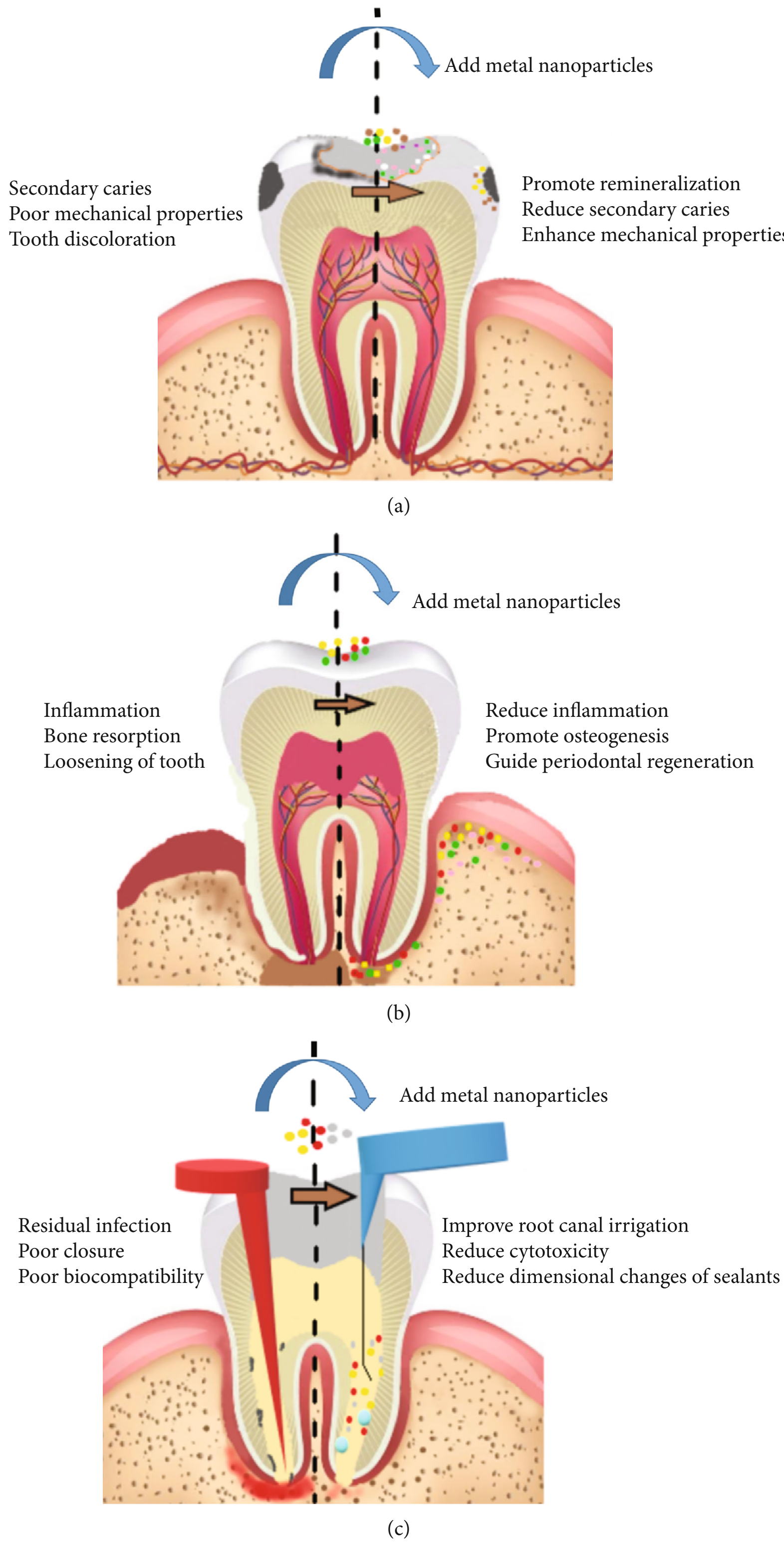

Figure 2: Continued.

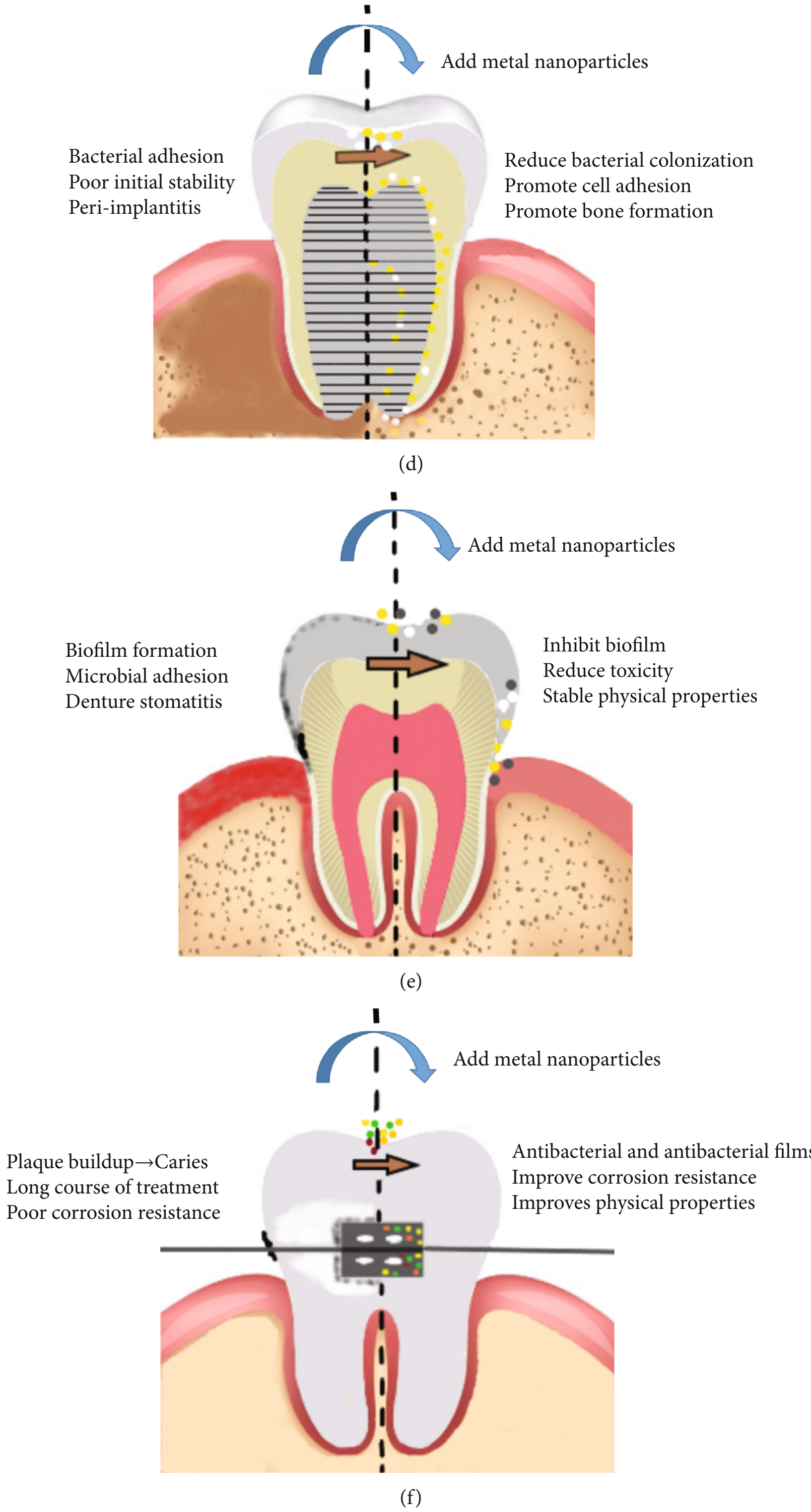

Figure 2: The potential applications of metal nanoparticles in the treatment of various oral diseases. The problems of current treatments were in the left side, and the advantages of the applications in the treatment of caries (a), periodontal diseases (b), endodontic and periapical diseases (c), peri-implantitis (d), denture (e), and orthodontic (f) were listed in the right side.

can improve the disinfection effect of Enterococcus faecalis biofilms in root canals [119]. In order to meet the multifunctional needs of root canal therapy sealants, Lei et al. added ZnO nanoparticles to improve the root canal filling materials. The results showed that the sealants could meet the requirements of root canal sealing materials, and the addition of ZnO nanoparticles sealants showed longer antibacterial activity and lower cytotoxicity, suitable for irregular root canal [120]. Versiani et al. found that the addition of zinc oxide nanoparticles (Zno-NP) to Grossman sealant reduced the solidification time and size change characteristics of the sealant [121]. Compared with traditional materials, nanoparticles have good binding ability and surface chemistry, so they have higher efficiency. The practical application of nanotechnology in endodontics has brought broad prospects for research in this field [122].

5.3. The Treatment of Periodontal Disease. Periodontitis is one of the most common chronic inflammatory diseases. Its devastating effects on alveolar bone and soft tissue can lead to loose teeth and loss [123]. Qian et al. developed a novel silver nanoparticle modified composite scaffold (PP-PDA-AG-COL), which enhanced alveolar bone regeneration in an in vitro mouse periodontal disease model. The experimental results show that the new scaffold has biocompatibility, osteogenic and antibacterial properties, and bone regeneration potential and is effective in the treatment of periodontitis [124]. When the concentration of the analyte is very low, AuNPs especially enhance the electronic signal and are used on the toothbrush together with AgNPs. Due to their antibacterial effect, they enhance the effect of mechanical control of dental plaque, which helps to better reduce periodontal disease [109]. A new type of composite electrode prepared by scholars using the remarkable redox ability of copper oxide nanoparticles can detect hydrogen peroxide in fluid and gingival crevicular fluid samples, laying a solid foundation for the diagnosis of periodontitis. The design of this sensor can also monitor the physiological and dynamic clinicopathological processes of inflammatory diseases [125]. Gan et al. prepared Ni(II) coordination complex by solvothermal method and grinding method, with an average size of 89 nm. This compound has a good therapeutic effect on periodontal disease by inhibiting the formation of Porphyromonas gingivalis biofilm [126]. Nano-CaF 2 particles with an average diameter of 53 nm were produced by spray dryer. The novel nano-CAF 2 composite is biocompatible and supports periodontal ligament stem cells (hPDLSCs), which are expected to fill the root cavity and release Ca and F ions to enhance osteogenesis and osteogenic induction of hPDLSCs and promote periodontal regeneration [127]. Mou et al. added serum albumin microspheres containing minocycline and zinc oxide nanoparticles (ZnO-NPs) into the hydrogel, and the test results showed that the material had significant therapeutic effect and self-healing ability of gingival tissue. In addition, the high cell survival rate of ZnO-NPs below 0.8 mg/L proved its excellent biocompatibility [128]. In vitro and animal model experiments show that the binding membranes prepared from magnesium oxide nanoparticles and biodegradable polymers have considerable antibacterial and osteogenic properties, effectively guide periodontal tissue regeneration, and are very valuable for periodontal regeneration [129]. Scholars have verified the antibacterial effect of platinum nanoparticles (PtNPs) on tooth-related bacteria through in vitro antibacterial experiments, and the results show that the particles have the potential to decompose proteins and periodontal disease-related inflammatory factors LPS. Therefore, platinum nanoparticles are promising for use in the treatment of periodontal and other oral diseases [130].

5.4. The Treatment and Prevention of Peri-Implantitis. Implants of various shapes made from artificial materials are inserted into the bone to repair missing teeth or provide support for dental prostheses. However, the composition of implants at the interface between hard and soft tissues is complex and susceptible to instability and infection [131]. The nanostructure, blood compatibility, excellent biocompatibility, and high fatigue strength of nanomaterials will make the application of nanotechnology the key to the success of orthopedic bioimplants in the future. The surface modification of bioimplants by nanocomposites may enhance the host's response and reduce bacterial adhesion while further inhibiting the formation of biofilms and protecting the implant materials from microbial utilization [132]. Hybrid coatings based on cerium and bioglass have been proposed to make implant surfaces superhydrophilic, promote cell adhesion, and exhibit antibacterial properties. The coating can be customized for soft tissue healing by modifying the composition and structure of the bioglass/cerium oxide nanomixture to prevent biological mineralization [133]. Silver and silver oxide (Ag_2O) nanoparticles have been used in bone tissue engineering to prepare porous titanium implants and deep infiltrate the TiO_2 nanocoating doped with ZnO to enhance the growth of bone marrow stem cells and promote bone formation [6]. Oral antibiotics are commonly used to prevent infection after implant surgery; however, only a small percentage of antibiotics can reach the implant. Porous implants with interconnect 3D structure (I3D) have been designed and fabricated and coated with silver nanoparticles (AgNPs) by electrodeposition for antimicrobial assays and monitoring of bacterial growth inhibition zones (ZOIs). After experiments, it was concluded that I3D implants can retain chemical attractants to recruit stem cells to enhance bone integration. Implants with I3D structure are not only conducive to bone integration but also help prevent infection [134]. Schoon et al. demonstrated that titanium (Ti) surface binding with antibacterial silver nanoparticles (AgNPs) and lactoferrin (Lf) improved preosteoblast adhesion, proliferation, and differentiation while reducing bacterial colonization. The material also improves bone integration, reduces the risk of bacterial infection, and increases the success rate of implants [135]. Studies have shown that the presence of lactoferrin (Lf) and AgNPs reduced bacterial colonization rate by 97.7%. This simple approach could have potential applications in medical devices that could improve patients' quality of life [136].

5.5. The Treatment of Orthodontic. Orthodontic patients often neglect oral health care after wearing orthodontics, resulting in changes in oral microecology [137]. Studies have shown that adding nanoparticles of Ag, Au, ZrO_2, and TiO to orthodontic adhesives can enhance the mechanical properties of materials, such as compression, tensile, and shear bonding strength. Moreover, when applied to the orthodontic bracket, it will produce antibacterial and antibacterial film effect, which can effectively reduce the rate of dental caries in orthodontic patients [109]. In order to improve the corrosion resistance of orthodontic appliances exposed to saliva and food for a long time, scholars conducted in vitro and in vivo studies that silver nanoparticles and other additives applied to orthodontic braces can improve their antibacterial performance. Furthermore, improved coating technology and arch wire composition can eliminate friction and bacterial adhesion problems, reduce complications, and shorten the course of orthodontic treatment [138]. Clove and cardamom green synthetic zirconia nanoparticles have potent antibacterial, anti-inflammatory properties and minimal cytotoxicity, and can be further considered as nanocoatings on orthodontic archwires such as NiTi and stainless steel [139]. Studies have shown that incorporating 1% of TiO_2 nanoparticles into orthodontic adhesives can enhance antibacterial effects for 30 days without compromising physical properties [38]. In vitro experiments by Assery et al. showed that the addition of ZrO_2-TiO_2 nanoparticles improved the compressive strength, tensile strength, and shear bond strength of orthodontic adhesives [140]. Long-term wearing of orthodontic appliances promotes the accumulation of microbial plaque and increases the lesions of oral leukoplakia. Incorporating CuO nanoparticles into orthodontic adhesives, studies have shown that nanoparticles can increase the antimicrobial effect of the adhesive without a decrease in shear bond strength [141].

5.6. The Treatment of Dentures. Metals and their oxide nanoparticles are often used as modified materials in oral treatment due to their strong and broad-spectrum antibacterial properties [142]. Vimbela et al. believe that ZnO-NP-modified acrylic glass is a promising denture material. By combining ZnO-NPs with acrylic glass or polymethyl methacrylate (PMMA), it is found that the formation of biofilm is inhibited, which can be used to treat diseases such as denture stomatitis [40]. Titanium dioxide (TiO_2) is the most commonly used antibacterial agent in medical equipment. TiO_2 nanoparticles exhibit antibacterial activity against gram-negative bacteria, gram-positive bacteria, and fungi. TiO_2 nanomaterials have good antimicrobial adhesion on various dental materials and restorations (including polymethyl methacrylate, ceramic glass, stainless steel, and dental implants) [108]. Raj et al. added titania nanoparticles to heat-cured polymethyl methacrylate (PMMA) resin without a significant reduction in flexural strength compared to conventional resins. Moreover, the modified material is less toxic, has biocompatibility, and can be used as a substitute for traditional denture matrix resin [143]. Nickel and nickel nanoparticles also show bactericidal activity and can reduce the biofilm formed by bacteria on the oral prosthesis [39]. Scholars have studied the antifungal activity and mechanical properties of acrylic denture-based materials, and the results show that the nanoparticles of methyl-polymerized new ligands (containing Ag^+ and Sn^{2+} complexes) have stable thermal and physical properties. The material can be used as the base material for antifungal denture restoration [144].

5.7. The Treatment of Oral Cancer. Oral squamous cell carcinoma is one of the most common malignant tumors in the oral and maxillofacial region [145]. A novel gold nanoparticle (AuNP) composite for the treatment of oral squamous cell carcinoma has been developed by using the high drug loading capacity and excellent photothermal properties and photothermal therapy of nanoparticles. The experimental results showed that the material could effectively inhibit the metastasis and growth of squamous cell carcinoma [146]. Various types of nanomaterials are used to regenerate tissue defects, provide good support for oral health, and promote the recovery of tissue physical functions by imitating natural tissue structure [38]. To achieve targeted drug delivery, Wang et al. modified metal-organic framework nanoparticles by using pulp mesenchymal stem cell membrane. In vitro and in vivo experiments showed that the novel nanoparticles were specific for oral squamous cell carcinoma and had the ability to carry antibiotics, inducing tumor cell death and blocking its growth in vitro [147]. Studies have shown that bimetallic nanoparticles exhibit enhanced anticancer activity. Ahmed et al. synthesized PEG-coated Au-Ag alloy nanoparticles, which showed effective radiosensitization in vitro and showed better CT contrast enhancement compared with clinical contrast agents. The nanoparticles can be used as radiosensitizer and CT contrast agent to treat oral cancer [148]. Satapathy et al. synthesized quinacline and gold mixed nanoparticles (QAuNP), and the results of in vitro and animal experiments showed that the material had antiangiogenesis and antimetastasis effects. Moreover, it can inhibit cell proliferation and induce cell apoptosis and tumor regression. The nanoparticles will be an effective drug for the treatment of metastatic oral cancer [149].

6. Deficiencies and Prospects

With the vigorous development of nanomaterials and technology, dental and oral health care will be further promoted in the near future. The application of nanomaterials reduces the complexity of oral treatment. Nanotechnology is a promising field in the field of dentistry with many applications [150]. However, factors such as pH in saliva, plaque biofilm, and buffer systems may affect the role of these nanomaterials in the oral cavity. Before new nanodental materials enter the market, huge challenges related to biological toxicity and cost-effectiveness need to be overcome and solved, and the effect should be validated in clinical trials.

So far, many types of dental materials have been produced through nanotechnology, which can be used in clinical applications, especially resin composite materials, which can be used to restore missing tooth structure [6]. Nanoparticles with their unique physical and chemical properties, such as ultrafine size, large specific surface area, and enhanced chemical reaction activity, lead the research prospects of preventing and treating tooth infections [151]. The small size of the nanoparticles allows them to penetrate the biofilm matrix and come into close contact with bacterial cells, thereby inhibiting the biofilm. Metal nanomaterials have good antibacterial effects, and antibacterial research is expected to be further developed, in anticipation of moving from the laboratory to the clinic.

7. Conclusion

Metal nanoparticles show good antibacterial properties due to their large specific surface area and volume ratio and have long-term stability and good biocompatibility, making them the most promising antibacterial material. With the enhancement of microbial resistance to antibiotics and the development of drug-resistant strains, metal nanoparticles have aroused increasing interest among researchers [112]. Metal nanoparticles can be used as effective growth inhibitors for a variety of microorganisms, so they are suitable for various medical devices. Compared with microparticles, nanoparticles have the advantages of more controllable, longer-lasting drug release, more specific targeting, and higher surface-to-volume ratio. They can reduce drug load and administration time and are convenient for patients to use [152].

Data Availability

The data supporting this review are from previously reported studies and datasets, which have been cited.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Shujun Zhang and Linghuang Lin contributed equally to this work.

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Supplementary Materials

Table s1: the effect and mechanism of nanometal on drug-resistant and multi-drug-resistant bacteria. *(Supplementary Materials)*

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