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Antimicrobial Applications of Metal Nanoparticles in Medicine and Dentistry: Mechanisms, Current Uses, and Future Perspectives: A Comprehensive Review

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***Abstract* - The growing threat of antimicrobial resistance necessitates innovative strategies to combat pathogenic microorganisms. Metal nanoparticles, including silver, gold, copper, titanium dioxide, zinc oxide, and magnesium oxide, have emerged as promising antimicrobial agents due to their broad-spectrum efficacy. These nanoparticles exhibit unique mechanisms of action, including microbial membrane disruption, oxidative stress induction through reactive oxygen species generation, and biofilm inhibition. Consequently, metal nanoparticles are increasingly incorporated into medical and dental applications, including wound dressings, surgical instruments, implant coatings, and restorative dental materials, to enhance sterility and reduce microbial colonization. Despite their advantages, challenges such as cytotoxicity, potential immune response activation, and environmental impact must be addressed to optimize their clinical use. This review provides a comprehensive analysis of metal nanoparticles applications in medicine and dentistry, discussing their mechanisms, current clinical applications, and future prospects.**

Keywords: Metal nanoparticles, Antimicrobial resistance, Medical application, Dental application, Nanotechnology.

I. INTRODUCTION

The emergence of antimicrobial resistance (AMR) has created an urgent global health crisis, necessitating the exploration of innovative and effective strategies to combat pathogenic microorganisms. Conventional antibiotics, while historically transformative, are increasingly rendered ineffective due to the rapid evolution and adaptation of resistant microbial strains [1]. This growing resistance threatens the efficacy of standard treatments, leading to prolonged infections, increased healthcare costs, and higher mortality rates.

In response, researchers have turned to nanotechnology - particularly metal nanoparticles (NPs) - as a groundbreaking approach to address this challenge [2]. According to the World Health Organization (WHO), metal-based nanoparticles have demonstrated significant efficacy against pathogens classified as priority threats [3]. Their nanoscale size allows for enhanced interaction with bacterial cells, while their unique physicochemical properties enable multiple mechanisms of bacterial inhibition, reducing the likelihood of resistance development. Unlike conventional antibiotics that target specific bacterial structures or metabolic pathways, metal nanoparticles act through non-specific interactions, disrupting microbial functions at multiple levels. This multifaceted mode of action impedes the emergence of resistant strains and broadens the spectrum of antibacterial activity, positioning NPs as a promising tool in the fight against multidrug-resistant (MDR) pathogens [4].

Metal nanoparticles exhibit unique physicochemical properties, such as a high surface area-to-volume ratio and the ability to generate reactive oxygen species (ROS), enabling them to disrupt microbial cell membranes, inhibit enzyme activity, interfere with genetic material, and prevent biofilm formation [5,6]. Their broad-spectrum antimicrobial potential has been leveraged in medical and dental applications, including wound dressings, drug delivery systems, implant coatings, and antimicrobial dental materials (Figure 1). Integration of NPs into endodontic therapies, orthodontic adhesives, and restorative dental composites has further reinforced their role in infection prevention and biofilm control. Additionally, advances in nanoparticle surface modifications and functionalization have enhanced their selectivity and biocompatibility, paving the way for more targeted antimicrobial interventions [7,8].

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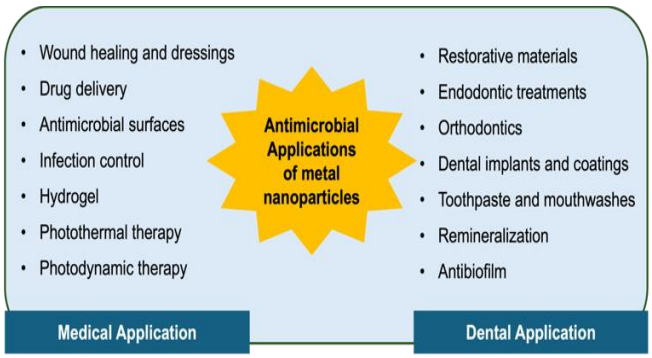

Figure 1: Metal Nanoparticles in Medical and Dental Applications

Despite their demonstrated efficacy, the widespread adoption of metal nanoparticles is tempered by challenges related to cytotoxicity, long-term biocompatibility, and environmental safety [9]. Prolonged exposure to high concentrations of metal nanoparticles can induce oxidative stress and unintended toxicity in human cells, raising concerns regarding their clinical translation. For instance, exposure to metal oxide nanoparticles such as titanium and iron has been reported to cause tissue damage and abnormal cellular stress responses via lipid peroxidation. Furthermore, the environmental impact of nanoparticle accumulation in ecosystems remains an area of active investigation [10]. These hurdles underscore the need for continued research to optimize nanoparticle formulations, enhance their safety profiles, and develop controlled-release systems to minimize adverse effects.

This review aims to provide a comprehensive overview of the antimicrobial mechanisms of metal nanoparticles, their current applications in medicine and dentistry, and ongoing efforts to address their limitations. By examining both their potential and challenges, we seek to highlight the transformative role of metal nanoparticles in advancing antimicrobial strategies and shaping the future of infection control in healthcare.

II. TYPES OF METAL NANOPARTICLES AND THEIR CHARACTERISTICS

Metal NPs represent a diverse class of nanomaterials with distinct physicochemical properties, antimicrobial mechanisms, and biomedical applications. Key characteristics such as size, shape, composition, surface charge, and functionalization significantly influence their efficacy in medical and dental fields [4,11]. Table 1 provides an overview of commonly studied metal nanoparticles and their defining properties.

Table 1: Comparison of Metal Nanoparticles

Metal Nanoparticle	Typical Size & Morphology	Key Antimicrobial Mechanisms	Representative Biomedical Applications
Silver (AgNPs)	1–100 nm various shapes (spherical, rod, etc.)	Membrane disruption; metabolic enzyme inhibition; ROS generation	Wound dressings; implant coatings; dental materials
Gold (AuNPs)	5–100 nm spherical, rod, star, cubic, branched	Inert core with surface functionalization (e.g., with antimicrobial agents); strong photothermal effect; anti-biofilm activity via functionalization	Drug delivery and imaging; photothermal therapy; anti-biofilm treatments
Copper (CuNPs)	1–100 nm require stabilizing coatings (high reactivity)	Release of Cu^{2+} ions causing ROS production; disruption of microbial enzymes and biofilms	Antimicrobial coatings on devices; dental adhesives and sealers
Zinc Oxide (ZnO NPs)	10–100 nm nanospheres, rods, platelets	Photocatalytic ROS generation (especially under UV); membrane interaction; antibiofilm and anti-inflammatory effects	Dental composites and adhesives; wound dressings; anti-biofilm therapies
Titanium Dioxide (TiO_2 NPs)	10–200 nm common crystal forms: anatase, rutile	Photocatalytic ROS generation under UV light; disruption of bacterial membranes, proteins, DNA	Implant coatings (self-cleaning surfaces); orthodontic adhesives
Iron Oxide (Fe_3O_4 or γ-Fe_2O_3 NPs)	4–100 nm often superparamagnetic	ROS generation and lipid peroxidation; enzyme-mimetic (peroxidase-like) activity; physical disruption via magnetic interactions	Targeted drug delivery (magnetic guidance); biofilm disruption; magnetic resonance imaging contrast agents
Magnesium Oxide (MgO NPs)	10–200 nm often spherical or cubic	Alkaline pH and Mg^{2+} ion release disrupt membranes; ROS generation; high stability and biodegradability	Wound healing membranes; bone tissue scaffolds; antibacterial implant coatings
Aluminium Oxide (Al_2O_3 NPs)	5–200 nm often spherical or irregular	Release of Al^{3+} ions; ROS production; interaction with microbial cell walls causing structural damage	Orthopedic and dental implant composites (for hardness and biocompatibility); vaccine adjuvants (alum-based)
Cerium Oxide (CeO_2 NPs)	~5–50 nm redox-active nanospheres	Switchable oxidation state (Ce^{3+}/Ce^{4+}) allows scavenging or generation of ROS; membrane interaction leading	Antibacterial coatings; neuroprotective agents (due to antioxidant properties); food

III. MECHANISMS OF ANTIMICROBIAL ACTION IN METAL NANOPARTICLES

Metal NPs exhibit antimicrobial activity through multiple concurrent pathways, leveraging their unique physicochemical properties (e.g., high surface area, nanoscale dimensions, catalytic reactivity) to interact with microorganisms in ways conventional antibiotics cannot [12,13]. Figure 2 provides a schematic representation of the key antimicrobial mechanisms of metal nanoparticles.

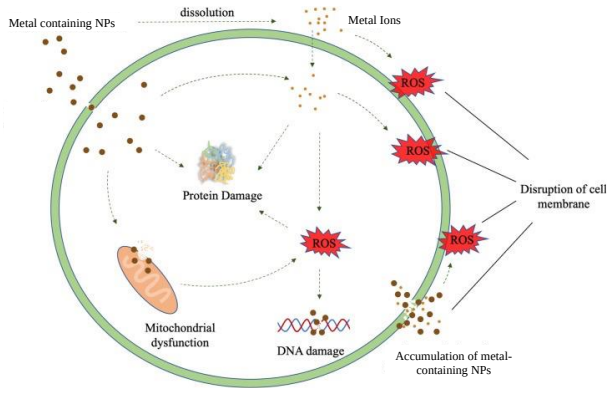

Figure 2: Mechanisms of Antimicrobial Action of Metal Nanoparticles

3.1 Disruption of Microbial Membranes

Electrostatic interactions between negatively charged bacterial membranes and positively charged or neutral NPs

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facilitate close adhesion of nanoparticles to microbial surfaces [14]. This leads to:

Membrane Integrity Disruption: Bacterial membranes contain negatively charged components (lipopolysaccharides in Gram-negative bacteria, teichoic acids in Gram-positives) that are susceptible to NP binding. These interactions compromise membrane integrity, increasing permeability and causing leakage of essential cellular contents [15–17].

Membrane Protein Targeting: NPs can bind to membrane proteins involved in ion transport and respiration, disrupting their function. For example, Silver Nanoparticles (AgNPs) target sulfur-containing membrane proteins and phosphate groups, leading to enzyme inhibition, membrane destabilization, and ultimately cell death [18–20].

3.2 Generation of Reactive Oxygen Species (ROS)

Metal NPs induce oxidative stress in microbial cells by generating ROS, which damage cellular components such as DNA, proteins, and lipids [21]. Key ROS include superoxide anions (O2-), hydroxyl radicals (•OH), and hydrogen peroxide (H_2O_2), which causes:

DNA Strand Breaks: Oxidative damage to nucleotides leads to mutations and impaired replication [22].

Protein Oxidation and Enzyme Inactivation: Oxidation of amino acid residues causes protein misfolding and loss of enzymatic function [23]

Lipid Peroxidation: ROS attack phospholipid membranes, increasing permeability and resulting in cell lysis [23].

Photocatalytic metal oxides like Titanium dioxide (TiO_2) and zinc oxide (ZnO) further amplify ROS production upon UV or visible light exposure, enhancing antimicrobial effects by improving charge separation, increasing the stability of charge carriers, and facilitating more efficient interfacial charge transfer to absorbed substrates [24], [25]. For instance, TiO_2/ZnO bilayer films exhibit >95% inhibition of Escherichia coli, Staphylococcus aureus, and Candida. albicans under illumination. Such ROS generation mechanisms enable metal NPs to kill bacteria through oxidative damage [26].

3.3 Inhibition of Biofilm Formation

Bacterial biofilms – communities of microbes encased in an extracellular polymeric substance (EPS) matrix – protect bacteria from antibiotics and immune responses [27]. Metal nanoparticles prevent biofilm formation by:

Disrupting Quorum Sensing (QS): NPs interfere with bacterial cell–cell communication pathways that regulate biofilm formation and virulence [21,27]. For example, ZnO NPs inhibit Pseudomonas aeruginosa QS pathways, reducing expression of virulence factors and biofilm-related genes [28].

Degrading EPS Matrix Components: NPs (e.g., α-Fe_2O_3) can interact with and break down biofilm matrix polysaccharides, proteins, and DNA, weakening the biofilm structure [29]. Smaller NPs like AgNPs penetrate biofilms more effectively, enhancing antimicrobial impact [30].

3.4 Interaction with Microbial Genetic Material

Metal NPs can directly interact with microbial DNA and RNA, impairing replication, transcription, and translation.

DNA Damage and Mutagenesis: NPs (particularly AgNPs and AuNPs) bind to DNA bases and the phosphate backbone, causing strand breaks, inhibiting polymerases, and destabilizing DNA structure [31,32]. This genetic damage can be lethal or prevent bacterial proliferation.

Ribosomal Inhibition: Some NPs interfere with ribosome function, blocking tRNA binding or inducing misreading, thereby halting protein synthesis [33]. Iron oxide NPs, for example, have been used to bind bacterial RNA for diagnostic capture [34], illustrating their strong affinity for genetic material.

3.5 Protein and Enzyme Inactivation

Nanoparticles can inactivate essential bacterial proteins and enzymes by binding to key functional groups (thiols, amines, phosphates). Mechanisms include:

Respiratory Chain Inhibition: Released metal ions (e.g., Zn^{2+} from ZnO NPs) disrupt respiratory enzyme complexes, impairing electron transport and promoting intracellular ROS accumulation [35].

ATP Synthesis Disruption: AgNPs inhibit proton pumps (H^+-ATPases), depleting ATP and causing energy collapse in the cell [36,37].

Stress Protein Suppression: NPs can inhibit bacterial heat shock proteins and other stress response regulators, reducing bacterial ability to cope with hostile conditions [38,39].

Additionally, metal NPs have been used to neutralize bacterial enzymes that confer antibiotic resistance. For example, nanoparticle-based zinc chelators can inhibit metallo-β-lactamase enzymes like NDM-1, restoring β-lactam antibiotic efficacy [40,41].

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3.6 Immune System Modulation

Metal NPs can modulate the host immune system, enhancing the clearance of pathogens. They activate key immune cells such as macrophages and neutrophils:

Macrophage and Neutrophil Activation: Macrophages readily internalize NPs, triggering enhanced cytokine secretion and antigen presentation. Notably, AgNPs and ZnO NPs stimulate phagocytosis and pro-inflammatory cytokine release, bolstering the innate immune response against bacteria. Neutrophils can also be stimulated to produce extracellular traps that capture microbes [42].

Immune Adjuvant Potential: NPs can act as vaccine adjuvants by improving antigen delivery and presentation, thereby enhancing adaptive immune responses [43]. Iron oxide NPs, for instance, influence macrophage polarization and modulate inflammation [44,45]. However, excessive accumulation of certain NPs (e.g., iron) can drive a pro-inflammatory state that impairs healing [46], underscoring the need for dose control.

IV. APPLICATION OF NANOPARTICLES IN MEDICINE

Metal NPs are increasingly utilized in medical applications due to their unique physicochemical properties, broad-spectrum antimicrobial efficacy, and ability to combat multidrug-resistant pathogens. Below, we outline key medical uses of metal NPs.

4.1 Wound Healing and Antimicrobial Dressings

Metal NPs play a pivotal role in wound healing by preventing infections and promoting tissue regeneration. Among them, AgNPs are the most widely used due to their potent antibacterial properties.AgNPs disrupt bacterial membranes, impair metabolic functions, and even induce a “zombie effect” where silver-killed bacteria release additional silver ions to kill neighboring microbes [47,48].Integrating AgNPs into wound dressings has shown clinical promise for chronic wounds, burns, and surgical sites. For instance, Quan et al. [49] developed a chitosan–silk fibroin asymmetric dressing loaded with AgNPs and exosomes, which accelerated angiogenesis, nerve repair, and healing in Pseudomonas aeruginosa-infected wounds. AgNP-based dressings also demonstrate strong activity against E. coli and S. aureus, promoting full-thickness wound closure in diabetic mice [50]. Commercial products (e.g., Acticoat®, Silvasorb®) validate the clinical relevance of AgNP wound dressings [51,52]. Despite their efficacy, concerns about AgNP cytotoxicity and argyria (skin discoloration from silver) drive exploration of alternatives. Magnesium oxide (MgO) NPs have emerged as a promising alternative, as they promote collagen synthesis, tissue regeneration, and reduced scarring while exhibiting minimal cytotoxicity. Unlike silver, magnesium ions are biocompatible and integrate into normal physiology. MgO NPs show strong antimicrobial activity and can stimulate endothelial cell proliferation and VEGF expression, enhancing angiogenesis and modulating inflammation [53,54]. Electrospun polycaprolactone/gelatin/MgO nanofiber membranes accelerate granulation tissue formation and resolution of inflammation in wounds. Polymer-coated magnesium hydroxide NPs (MHNPs) have also shown promise: PEGylated MHNPs promoted rapid re-epithelialization in animal wound models with no observed toxicity [55].AuNPs offer optical stability and facile surface modification. They are effective against E. coli, P. aeruginosa, S. aureus, and even methicillin-resistant S. aureus (MRSA) [56,57]. However, rapid clearance and potential toxicity at wound sites limit their direct use. Encapsulating AuNPs in hydrogels can improve retention and reduce side effects [58,59]. ZnO NPs have strong wound-healing potential due to their biocompatibility and ability to enhance tissue regeneration. They promote keratinocyte migration, collagen deposition, and activate zinc-dependent MMP enzymes that aid remodeling [60]. Novel ZnO-loaded electrospun nanofiber dressings showed enhanced antibacterial and healing properties in vivo, with faster re-epithelialization and collagen deposition [61]. Biogenic ZnO NPs in CMC/PVP hydrogel films were effective against S. aureus and E. coli, shortening burn wound healing from 20 days (untreated) to ~12 days [62]. ZnO-conjugated cinnamic acid NPs further improved infection control and wound closure without toxicity [63].

4.2 Drug Delivery Systems

Nanoparticle-based drug delivery systems can enhance drug solubility, control release kinetics, evade immune clearance, enable targeted delivery, and allow co-delivery of multiple agents. They can interact directly with pathogens, modulate bacterial resistance mechanisms, or even act as co-therapeutics with drugs [64]. Notably, certain metal NPs can disrupt bacterial efflux pumps, increasing intracellular antibiotic retention and thus improving efficacy [65]. AgNPsnot only have intrinsic antimicrobial activity (disrupting membranes, altering ATP production, interfering with ion transport), but also synergize with antibiotics. AgNPs conjugated with antibiotics like amoxicillin or ampicillin show superior efficacy against resistant E. coli, as the NPs facilitate drug penetration and simultaneously attack bacterial DNA synthesis. AgNPs can also carry and release antibiotics in a controlled manner at infection sites [66]. AuNPs can be functionalized with antibiotics to improve their delivery. For example, AuNPs conjugated with amoxicillin exhibited enhanced drug bioavailability and penetration into bacteria,

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leveraging electrostatic attraction between the positively charged AuNP-drug complex and negatively charged bacterial membranes. AuNPs can also bypass efflux mechanisms, delivering higher intracellular antibiotic concentrations [67]. Fe_3O_4 NPscan generate ROS and physically damage bacterial cell structures. Fe_3O_4 NPs inhibit E. coli growth by inducing ROS production, cytoplasmic condensation, and membrane rupture [68]. When combined with silver, Fe_3O_4–Ag composite NPs accelerate Ag^+ release, boosting bactericidal activity while reducing toxicity to human cells. These magnetic NPs can also be guided to infection sites using external magnetic fields, concentrating drug payloads [69]. ZnO NPsare effective drug carriers due to their biocompatibility and capacity to impede bacterial efflux pumps, thereby increasing antibiotic retention. ZnO–ciprofloxacin conjugates (e.g., CIP-PEG-ZnO NPs) show strong activity against S. aureus, providing sustained antibiotic release and improved stability and tissue penetration. In vivo studies confirm their potential in wound healing, and biocompatibility tests indicate minimal cytotoxicity [70].

4.3 Antibacterial Surfaces and Infection Control

Metal NPs have revolutionized infection control strategies in medical settings by providing durable antimicrobial coatings, enhancing sterility in clinical environments, and preventing biofilm formation on medical devices. Their unique properties enable integration into surfaces for long-term protection against microbes.

Antibacterial Surface Coatings: Coating medical implants, surgical instruments, catheters, and hospital surfaces with metal NPs can significantly reduce bacterial adhesion and biofilm formation, thereby mitigating healthcare-associated infections [71]. For example, silver-ion-functionalized coatings show broad-spectrum antibacterial activity against E. coli and S. aureus [72]. “Smart” thermo responsive coatings embedded with AgNPs can be activated by changes in pH, light, or temperature to release antimicrobials as needed, effectively inhibiting E. coli and Bacillus subtilis [73]. Composite coatings containing both silver and copper NPs have demonstrated long-lasting efficacy even against MRSA and fungal pathogens [74]. Such coatings are being applied to indwelling devices (e.g., urinary catheters, end tracheal tubes) to prevent infection.

Infection Control in Surgical Environments: Incorporating NPs into surgical masks, gowns, gloves, and drapes can reduce microbial contamination during procedures. For instance, adding metal NPs to mask filters and glove materials imparts an extra layer of antimicrobial action, ensuring a more sterile field [75]. Chitosan–Au NP composites have been shown to enhance wound hemostasis and promote repair, useful in managing surgical wounds and preventing post-surgical infections [76]. Additionally, Rezk et al. [77] developed a multifunctional surface by coating magnesium alloy implants with a polydopamine film embedding Ag/Au NPs. This coating improved corrosion resistance and provided antibacterial activity while promoting cell attachment and proliferation. Such NP-based modifications can be extended to surgical tools and implantable hardware to reduce infection risks.

4.4 Antimicrobial Hydrogels

Metal-based nanocomposite hydrogels offera transformative approach for infection control, wound healing, and tissue regeneration by integrating antimicrobial properties, controlled drug release, and enhanced biocompatibility [78]. These hydrogels combine polymer networks with metal NPs or metal ions to achieve sustained antimicrobial effects in a moist, biofriendly matrix.

Silver- and Copper-Infused Hydrogels: Chitosan hydrogels containing tea tree oil and silver ions have shown potent activity against C. albicans, S. aureus, and P. aeruginosa, making them effective antimicrobial wound dressings [79]. Polydopamine-linked Ag “nanozyme” hydrogels produce enhanced antibacterial effects under near-infrared (NIR) light, due to catalytically generated hydroxyl radicals [80]. Likewise, hybrid hydrogels with borax-crosslinked polydopamine and nano-silver achieved long-term antimicrobial efficacy [81]. Chitosan/CuO nanocomposite hydrogels also exhibit significant antibacterial effects against S. aureus and E. coli, indicating the potential of copper for hydrogel-based wound care [82].

ZnO Hydrogels: ZnO-NP/polymer hydrogels provide cost-effective, antimicrobial wound care with added benefits like UV protection. For example, chitin/ZnO nanoparticle hydrogels showed controlled swelling, improved blood clotting, and strong antibacterial activity while accelerating healing [83,84]. ZnO NPs functionalized with biopolymers (e.g., hydroxyethylcellulose) improved tissue regeneration by ~24% compared to micro-ZnO formulations [85]. ZnO-functionalized hydrogel pads demonstrated remarkable wound closure (~99.7%) in rats, far outperforming untreated controls [86]. These examples illustrate how ZnO-incorporated hydrogels can maintain a moist, antimicrobial wound environment and speed healing.

4.5 Photothermal and Photodynamic Therapy

Metal NPs are key players in emerging light-based antimicrobial therapies, including photothermal therapy and photodynamic therapy, especially for drug-resistant infections.

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Photothermal Therapy (PTT): This approach uses photothermal agents (PTAs) that convert light into heat to kill pathogens via hyperthermia. Metal NPs (especially Au, Ag, Cu-based nanostructures) have high photothermal conversion efficiencies. Under NIR light, they can raise local temperatures to disrupt bacterial membranes and proteins. For example, Cu2O NPs act as theranostic agents by catalyzing hydrogen peroxide into hydroxyl radicals, enhancing PTT's bactericidal effect [87]. A quaternized chitin polymer loaded with silver NPs achieved ~65% photothermal conversion efficiency and eliminated 99.9% of S. aureus and E. coli biofilms under NIR irradiation [88]. Black phosphorus nanosheets decorated with AgNPs showed synergistic photothermal and oxidative stress effects, successfully treating MRSA-infected wounds in mice [89]. Gold nanostructures are also potent PTAs: multi-tipped gold nanostars (~92 nm) reached ~28.7% conversion efficiency, effectively eradicating S. aureus under 808 nm laser[90]. Polyhexamethylene biguanide-stabilized AuNP composites synergistically killed S. aureus under NIR. Targeting can be improved by conjugating AuNPs with antibodies, achieving specific photothermal killing of S. aureus with minimal collateral damage [91].

Photodynamic Therapy (PDT): PDT uses photosensitizer molecules that, upon light activation, generate ROS to kill microbes. Metal oxide NPs like ZnO and TiO_2 serve as excellent photocatalysts and photosensitizers. Under UV or visible light, they produce hydroxyl radicals and superoxide ions that exert potent bactericidal effects [92–94]. ZnO/Au hybrid NPs improve ROS generation by facilitating charge separation, thereby increasing PDT efficacy against E. coli and S. aureus [95]. Doping ZnO with silver (Ag-ZnO) further boosts ROS production and antimicrobial performance [96]. TiO_2 NPs irradiated with UV (<385 nm) effectively eradicated MRSA and Acinetobacter spp. [97]. Moreover, composite nanoparticles combining multiple oxides (Fe_2O_3–TiO_2) can generate singlet oxygen and enhance PDT outcomes [98]. These findings underscore the potential of metal-based nanoparticles to serve as photosensitizers or co-catalysts in antimicrobial PDT, offering a way to inactivate drug-resistant bacteria through light-triggered ROS.

Both PTT and PDT offer localized treatment of infections (such as infected wounds or implant-associated biofilms) without systemic antibiotics, and metal NPs are central to advancing these therapies due to their tunable optical properties and catalytic activities.

V. APPLICATION OF NANOPARTICLES IN DENTISTRY

Metal NPs have revolutionized dentistry by offering innovative antimicrobial solutions that enhance dental materials and treatments. Their ability to integrate seamlessly into restorative and therapeutic applications has made them indispensable in modern oral healthcare [99].

5.1 Restorative Dental Materials

Metal NPs are incorporated into restorative materials (resins, cements, composites) to prevent secondary caries and improve antimicrobial efficacy. AgNPs areWidely used in dental composites and cements to inhibit bacterial colonization and extend restoration longevity. Incorporating AgNPs into a bisacrylic resin significantly reduces Streptococcus sanguinis and Actinomyces naeslundii biofilm formation while maintaining fibroblast viability [100]. ZnO NPs Enhance the antimicrobial and remineralization properties of resin-based composites and adhesives without compromising mechanical strength. ZnO-fluoride nanoparticle additives improve resin–dentin bonding and antibacterial activity, strengthening restoration durability [101]. ZnO NPs also outperform AgNPs in inhibiting Streptococcus mutans, the primary cavity-causing bacterium [102]. Adding CuNPs to dental resins imparts antimicrobial activity by reducing bacterial growth and biofilm formation, thereby potentially increasing restoration lifespan [103].

5.2 Endodontic Treatments

Metal NPs have significantly improved the success of endodontic (root canal) therapies by enhancing the antimicrobial efficacy of root canal disinfectants and sealers [104]. Ag and ZnO NPs are used in root canal irrigation solutions to improve disinfection. They can penetrate dentin tubules and have been shown to increase the fracture resistance of treated roots [105]. ZnO NPs-based sealers exhibit strong antibiofilm activity, particularly against Enterococcus faecalis, a common cause of root canal failure [106]. Hadi et al. [107] reported that endodontic sealers containing ZnO NPs show significant antibacterial activity against both Candida albicans and E. faecalis at all tested concentrations. In PDT adjunct to endodontics, TiO_2 NPs generate ROS upon light activation, eliminating bacteria in root canals. This photocatalytic process causes peroxidation of microbial membrane lipids and respiratory inhibition, leading to cell death [108]. Modified glass-ionomer cements with TiO_2 NPs exhibit enhanced antibacterial activity and improved mechanical properties [109].

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5.3 Orthodontic Adhesives and Brackets

Orthodontic treatments often lead to prolonged plaque accumulation around brackets, increasing the risk of white spot lesions and caries. Incorporating metal NPs into orthodontic adhesives and brackets provides an effective antimicrobial strategy to mitigate these risks. When added to orthodontic bonding agents, TiO_2 and ZnO NPs reduce enamel demineralization and bacterial adhesion. Behnaz et al. [110] found that nano-TiO_2 and nano-ZnO in bonding resin significantly decreased white spot lesions and enamel demineralization over 4 weeks. TiO_2 NPs, due to their photocatalytic ROS generation, prevent plaque accumulation and microbial adhesion around brackets. Similarly, adding TiO_2 NPs to orthodontic composite resins effectively inhibited S. mutans and S. sanguinis growth while maintaining adequate shear bond strength [111]. Furthermore, chitosan-TiO_2 modified adhesives markedly reduced S. mutans counts on teeth in an in vivo study [112]. AgNPs-coated brackets and archwires exhibit strong antimicrobial properties, reducing bacterial colonization and thus the occurrence of white spot lesions during orthodontic therapy [113,114]. Jasso-Ruiz et al. demonstrated that AgNP coatings on metal and ceramic brackets effectively inhibit S. mutans adhesion and exhibit significant antimicrobial activity against S. aureus and E. coli [114]. These findings underscore AgNPs' potential to reduce plaque-related dental decay and periodontal issues during orthodontic treatment.

5.4 Dental Implants and Coatings

Nano-engineered coatings on dental implants can improve osseointegration and prevent peri-implant infections by imparting antimicrobial properties and enhanced biocompatibility. NP-integrated implant coatings reduce bacterial adhesion, minimize peri-implantitis, and improve long-term success rates. They can also stimulate osteogenic activity (cell adhesion, differentiation, extracellular matrix deposition), benefiting bone regeneration around implants [115,116]. Key examples include:

TiO_2 NPs: TiO2 NPs are widely used in implant surfaces for their excellent biocompatibility, mechanical stability, and antibacterial effect. TiO_2 nanoporous or nanoparticulate coatings improve implant integration and resistance to microbial colonization [117]. Chifor et al. enhanced TiO_2 coatings by doping with Au, Ag, and embedding lysozyme, achieving strong antibacterial activity (including singlet oxygen generation under visible light) and sustained enzymatic activity [113]. TiO_2 NPs also promote osteoblast proliferation and differentiation, accelerating osseointegration and implant stability [119,120].

AgNPs: Silver-doped implant coatings (e.g., Ag-infused calcium phosphate or hydroxyapatite layers) effectively inhibit bacterial colonization and biofilm formation, reducing the risk of peri-implantitis. In vivo, silver-ion-coated titanium implants prevented infection by Porphyromonasgingivalis, a major contributor to implant failure [121]. Clinical-grade products utilize AgNP coatings on implants to provide long-term antimicrobial protection without compromising osseointegration [122].

ZnO NPs: ZnO NPs coatings offer broad antibacterial activity and good biocompatibility. ZnO coatings on titanium or magnesium alloys inhibit E. coli and S. aureus growth and can improve corrosion resistance of metal implants. Notably, ZnO initially promotes a minor biofilm which then degrades, providing sustained antimicrobial effects. ZnO is often combined with other materials: for example, ZnO in hydroxyapatite (HA) composites improves mechanical strength and stability for bone regeneration [123]. Coatings of nano-HA and ZnO NPs (with conductive polymers) showed good antibacterial properties while supporting mineralization [124]. Electrospun scaffolds with polycaprolactone (PCL), nano-HA, and ZnO (10 wt%) significantly reduced S. aureus and E. coli adhesion while remaining compatible with bone cell [125].

MgO NPs: MgO NPs provide an optimal balance of antimicrobial efficacy and biocompatibility for implant coatings. MgO NPs exhibit broad-spectrum antibacterial activity and also support osteogenic differentiation. They can bind serum proteins (like albumin) that promote stem cell adhesion and growth on implant surfaces [126]. Yu et al. incorporated MgO NPs into 3D-printed Zn scaffolds, enhancing biodegradation and biocompatibility; these scaffolds had >99% antimicrobial efficacy and fully integrated into bone within 12 weeks [127]. MgO-coated titanium surfaces (via micro-arc oxidation) achieved 81–98% reduction in S. aureus biofilms [128].

Al_2O_3 (Alumina) NPs: Alumina NPs contribute exceptional mechanical strength and are inert, minimizing tissue irritation. Nano-alumina implant coatings influence cell behavior and improve bone-implant contact. For example, alumina-coated implants upregulate bone-specific genes and increase bone formation at the interface [129]. Alumina-titanium composites serve as load-bearing implant materials with superior biocompatibility; in vivo, they showed excellent bone healing and remodeling [130]. However, high alumina NP concentrations can be toxic to bone tissue, so optimal dosing is critical [131].

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5.5 Preventive and Therapeutic Applications

Metal NPs are increasingly incorporated into oral healthcare products to prevent disease and promote oral health, leveraging their antimicrobial and remineralization properties.

Toothpaste and Mouthwashes: NPs such as AgNPs and ZnO NPs are added to oral care formulations to enhance antibacterial efficacy against S. mutans (the primary cause of dental caries) and pathogens associated with gingivitis and periodontitis. In vitro studies show that toothpaste containing 1% ZnO NPs exhibits higher antibacterial activity, significantly reducing S. mutans levels compared to non-nano formulations [132]. Similarly, toothpaste with gum arabic-capped silver nanoparticles (GA-AgNPs) maintained strong antimicrobial activity, effectively reducing oral bacteria within one hour [133,134]. Although mild cytotoxicity was observed at longer exposure times, the brief contact during normal use minimizes risk.

Remineralization Therapies: ZnO NPs play a crucial role in remineralization treatments by restoring enamel and dentin integrity and counteracting acid-producing bacteria responsible for dental erosion. Studies show ZnO NPs enhance remineralization of demineralized dentin, especially when combined with fluoride, improving microhardness and enamel integrity [120]. ZnO NPs also inhibit bacterial adhesion and biofilm formation on tooth surfaces, suppressing acidogenic bacteria [134]. These properties make ZnO NPs valuable for strengthening tooth enamel and preventing demineralization.

5.6 Antibiofilm Strategies in Dentistry

Dental biofilms (plaque) are complex microbial communities that drive caries, gingivitis, periodontitis, and peri-implantitis. CuO NPsexhibit potent antimicrobial and antibiofilm properties, making them promise for dental applications. Morales et al. [135] showed that CuO NP-coated biomaterials effectively controlled oral biofilm formation and prevented peri-implant infections. Additionally, a CuO–calcium hydroxide endodontic paste demonstrated significant antimicrobial efficacy against S. aureus, P. aeruginosa, and C. albicans biofilms. This nano-formulation reduced microbial growth, inhibited biofilm matrix production, and decreased virulence factor release, highlighting its potential in disrupting biofilm-associated infections [136].Fe_3O_4 NPs have intrinsic peroxidase-like catalytic activity, enabling them to decompose hydrogen peroxide into ROS. This catalytic action can disrupt biofilm EPS matrices and kill cariogenic bacteria like S. mutans. For instance, ferumoxytol (an FDA-approved iron oxide NP formulation) has been shown to disrupt oral biofilms and prevent dental caries via peroxidase-like activity [137]. Gao et al. [138] reported that Fe_3O_4-based "nanozyme" particles generate free radicals from peroxide, degrading plaque biofilm matrix. Daily application of these particles protected enamel from demineralization and significantly reduced caries in vivo, without harming healthy tissues. ZnO NPseffectively inhibits biofilm formation by Porphyromonasgingivalis and Alcaligenes faecalis, leading to reduced EPS production and disruption of established biofilms [139]. In an orthodontic context, ZnO NP-coated mini-screws combined with antimicrobial photodynamic or sonodynamic therapy significantly reduced biofilm bacteria (P. gingivalis, Prevotella intermedia, Aggregatibacteractinomycetemcomitans) on the screws [140]. This indicates ZnO NPs can be used in synergy with light- or ultrasound-activated therapies for enhanced antibiofilm effects. AuNPscan disrupt biofilm integrity, reducing microbial adhesion and viability. Al-Fahham et al. [141] showed AuNPs have strong antibiofilm activity against S.oralis, a key plaque colonizer, significantly decreasing biofilm biomass. AuNPs also enhance PDT for biofilm eradication. Sherwani et al. [142] demonstrated that AuNP-conjugated photosensitizers improved PDT efficacy against C. albicans biofilms. Biomimetically synthesized AuNPs combined with photosensitizers (methylene blue or toluidine blue) effectively eliminated both planktonic and biofilm-associated C. albicans in vitro.

VI. LIMITATION AND FUTURE PERSPECTIVES

Despite their significant antimicrobial potential, metal NPs face several limitations that hinder widespread clinical use. A major concern is cytotoxicity: high concentrations of NPs can induce oxidative stress, DNA damage, and inflammatory responses in host tissues [143]. Studies have shown that while metal NPs effectively kill bacteria, they may also disrupt mammalian cell homeostasis by generating excessive ROS, leading to apoptosis in human cells [144]. Additionally, prolonged accumulation and persistence of metal NPs in the body raise concerns about systemic toxicity and environmental impact. Certain NPs (notably Ag and TiO_2) tend to accumulate in vital organs, potentially altering gene expression and contributing to organ dysfunction [145-147].

Another challenge is the immune system's response to nanoparticles. The body's defense mechanisms (e.g., macrophage phagocytosis) can recognize and clear foreign NPs, reducing their therapeutic efficacy. Surface modification and stealth coating of NPs (e.g., with polymers like PEG) are often necessary to minimize immune clearance and prolong circulation. The stability and reproducibility of NP formulations also remain critical hurdles for clinical translation – small changes in size, shape, or surface chemistry can markedly influence NP behavior in biological systems and thus their safety and effectiveness [148].

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Future research should focus on optimizing NP design to enhance biocompatibility while minimizing toxicity. Strategies such as careful surface functionalization (to target specific microbes or tissues), development of hybrid nanocomposites (combining multiple materials to balance properties), and controlled-release systems can improve the precision of NP-based therapies and reduce off-target effects. Importantly, large-scale clinical studies are needed to validate the long-term safety and efficacy of metal NPs in medical and dental applications. Regulatory guidelines and standardized evaluation protocols will be crucial for translating laboratory successes into clinical practice. Integration of nanotechnology with smart drug delivery (responsive to infection or environmental cues), bioresponsive coatings, and regenerative biomaterials offers exciting opportunities to expand the use of metal NPs. In tissue engineering, NP-enhanced scaffolds could simultaneously promote tissue regeneration and prevent infection. Large-scale clinical trials and comprehensive toxicity studies are imperative to bridge the gap between laboratory research and real-world applications. By systematically addressing current limitations – cytotoxicity, immune clearance, stability, and environmental concerns – the next generation of metal nanoparticle technologies can be made safer and more effective. Ultimately, overcoming these challenges will allow metal NPs to play a transformative role in revolutionizing antimicrobial strategies, offering more potent and targeted solutions for combating infections in healthcare and dentistry.

VII. CONCLUSION

Metal nanoparticles have emerged as promising antimicrobial agents in medicine and dentistry due to their unique physicochemical properties, broad-spectrum efficacy, and potential to combat multidrug-resistant pathogens. Their integration into wound dressings, dental materials, drug delivery systems, and antimicrobial coatings has significantly enhanced infection control and therapeutic outcomes. These nanoparticles employ diverse mechanisms – including membrane disruption, ROS generation, biofilm inhibition, and immune modulation – providing a multifaceted approach to addressing antimicrobial resistance. Despite these advantages, challenges remain regarding NP cytotoxicity, long-term biocompatibility, immune recognition, and environmental impact. Concerns over nanoparticle accumulation in organs and the potential to induce oxidative stress necessitate rigorous evaluation of safety for clinical applications. Furthermore, stability and reproducibility issues must be resolved to ensure consistent performance in biomedical formulations. Future research should prioritize optimizing NP design through surface modifications, hybrid nanocomposites, and controlled-release systems to enhance therapeutic precision while minimizing toxicity. Advancements in nanotechnology – particularly in smart drug delivery, responsive coatings, and regenerative biomaterials – hold great promise for expanding metal NP applications in infection control and tissue engineering. Moving forward, large-scale clinical trials and standardized toxicity assessments are critical to translate these innovations into practice. By overcoming current limitations, metal nanoparticles can provide a powerful arsenal in the fight against infections, offering safer and more effective solutions in healthcare and dentistry.

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