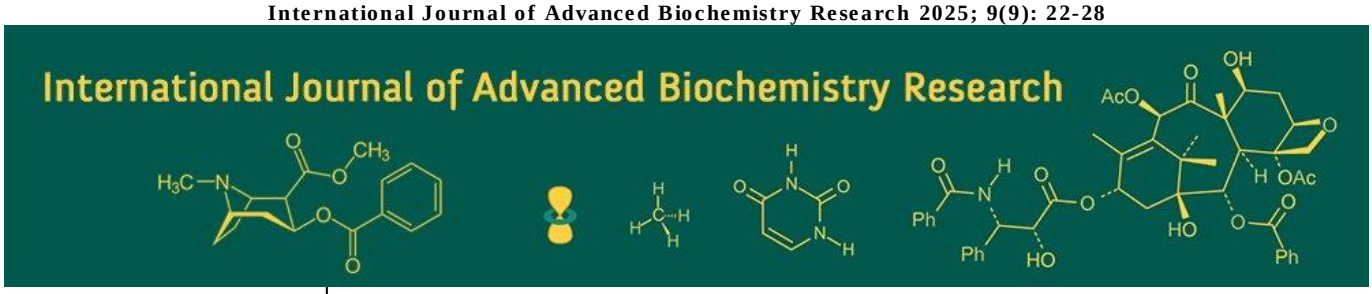

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Inorganic metallic nanoparticles in dentistry from synthesis and characterization to clinical applications: A comprehensive review

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Abstract
Inorganic metallic nanoparticles (NPs)-including silver (Ag), zinc oxide (ZnO), titanium dioxide (TiO_2), gold (Au), copper oxide (CuO), and iron oxide (Fe_3O_4)-represent a transformative advancement in dental materials science. At the nanoscale (1-100 nm), these materials exhibit distinctive physicochemical properties such as high surface-to-volume ratio, surface plasmon resonance (SPR), photocatalytic activity, and controlled ion release, all of which enable a wide spectrum of applications beyond the limitations of conventional passive restorations.

The clinical potential of these nanoparticles derives from their tunable parameters, including size, shape, crystallinity, and surface functionalization. Various synthesis strategies-chemical reduction, physical ablation, sol-gel, hydrothermal, and environmentally friendly green biosynthesis-provide precise control over these properties. When incorporated into dental materials, nanoparticles enhance antimicrobial activity, reduce bacterial adhesion, promote remineralization, and enable photothermal or photoactivated disinfection. As summarized in Tables 1, 2, Ag and ZnO are especially effective in restorative and endodontic applications, TiO_2 demonstrates photocatalytic disinfection, and Au serves as a platform for advanced diagnostic and sensing technologies.

Despite these benefits, significant barriers hinder clinical translation. As outlined in Table 3, challenges include cytotoxicity at high concentrations, nanoparticle aggregation in complex oral environments, formation of a biologically active protein corona, and the absence of standardized synthesis and regulatory frameworks. Addressing these concerns is crucial to ensuring reproducibility, long-term biocompatibility, and patient safety.

Looking forward, the development of smart nanocomposites with pH-responsive ion release, multifunctional hybrid systems such as Ag-ZnO, AI-driven nanoparticle design, and integration into 3D printing technologies are highlighted as future directions (Table 4). By uniting advances in inorganic chemistry, nanotechnology, and clinical dentistry, inorganic metallic nanoparticles hold strong potential to reshape modern oral healthcare into a preventive, precise, durable, and biologically integrated practice.

Keywords: Inorganic metallic nanoparticles, dental nanomaterials, antimicrobial nanoparticles, nanoparticle synthesis, green synthesis, zinc oxide nanoparticles, silver nanoparticles

Introduction

Oral diseases such as dental caries, periodontitis, endodontic infections, and peri-implantitis are among the most prevalent chronic conditions globally, affecting over [3].5 billion people according to the Global Burden of Disease Study [1]. Despite significant advancements in preventive strategies, restorative materials, and infection control protocols, microbial biofilms, recurrent infections, and the limitations of conventional passive materials continue to compromise long-term clinical outcomes. The persistence of pathogenic microorganisms-including *Streptococcus mutans*, *Lactobacillus* spp., *Enterococcus faecalis*, and *Porphyromonas gingivalis* within complex extracellular polymeric matrices (biofilms) necessitates innovative, bioactive solutions that transcend traditional antimicrobial agents and inert restorative approaches.

In this context, inorganic metallic nanoparticles (NPs) have emerged as a transformative class of materials in dentistry, offering a unique convergence of antimicrobial, photocatalytic, mechanical, regenerative, and diagnostic functionalities.

These nanoscale entities-typically 1-100 nm in size-exhibit size- and shape-dependent physicochemical properties due to quantum confinement effects, high surface-to-volume ratios, and enhanced reactivity. The most extensively studied inorganic metallic nanoparticles include silver (Ag), gold (Au), zinc oxide (ZnO), titanium dioxide (TiO_2), copper oxide (CuO), and iron oxide (Fe_3O_4), as well as doped or hybrid variants [2, 3].

Their integration into dental adhesives, composites, cements, irrigants, and tissue engineering scaffolds is driven by their ability to generate reactive oxygen species (ROS), release biologically active metal ions (e.g., Ag^+, Zn^{2+}), disrupt microbial membranes, and modulate host cellular responses. Moreover, their optical properties, such as surface plasmon resonance (SPR), enable applications in diagnostics and photothermal therapy.

The rational design of these nanoparticles is rooted in inorganic chemistry, where principles of redox reactions, nucleation kinetics, and crystal growth govern their formation. Techniques such as chemical reduction, sol-gel processing, hydrothermal synthesis, and green biosynthesis allow for precise control over size, morphology, crystalline phase, surface charge, and functionalization-all of which directly influence biological efficacy and biocompatibility. [5]

Recent evidence highlights the clinical potential of these nanomaterials. Ag nanoparticles inhibit biofilm formation on composite resins and orthodontic brackets, while ZnO nanoparticles enhance remineralization of demineralized dentin by promoting hydroxyapatite nucleation [6]. TiO_2 nanoparticles, when activated by light, enable photocatalytic degradation of endotoxins and organic debris in root canals, offering a non-antibiotic disinfection strategy [7]. Furthermore, hybrid systems such as Ag-ZnO or Au-TiO_2 are being engineered to synergistically combine multiple mechanisms of action, thereby overcoming the limitations of single-agent approaches [8].

However, clinical translation faces significant challenges. Issues related to long-term biocompatibility, dose-dependent cytotoxicity, nanoparticle aggregation in physiological environments, and regulatory hurdles must be thoroughly addressed [9]. The formation of a protein corona upon exposure to saliva or serum further complicates the biological identity and behavior of nanoparticles in the oral cavity [10]. Additionally, the lack of standardized synthesis and characterization protocols limits reproducibility and hinders regulatory approval.

This comprehensive review aims to bridge the gap between fundamental inorganic chemistry and clinical dentistry by providing an in-depth, evidence-based analysis of inorganic metallic nanoparticles in oral healthcare. We systematically examine:

- Advanced synthesis methodologies and their implications for reproducibility and scalability.
- Key physicochemical properties governing biological interactions.
- State-of-the-art characterization techniques essential for quality control.
- Current and emerging clinical applications across dental disciplines.
- Toxicological considerations and risk assessment frameworks.

Future directions, including stimuli-responsive systems, multifunctional hybrids, nanoparticle delivery platforms, and AI-driven nanomaterial design.

To enhance clarity and scientific rigor, this review integrates four comprehensive tables that summarize nanoparticle types and functions (Table 1), clinical applications (Table 2), toxicological profiles (Table 3), and future translational challenges (Table 4). These tables are referenced throughout the text to support critical analysis and guide clinical decision-making.

Synthesis methods of inorganic metallic nanoparticles

The synthesis of inorganic metallic nanoparticles is a cornerstone of modern nanotechnology, enabling precise control over size, morphology, crystallinity, and surface chemistry-parameters that critically influence their biological and functional performance in dental applications. Over the past two decades, a wide array of synthetic strategies has been developed, broadly categorized into chemical, physical, biological (green), and wet-chemical (sol-gel, hydrothermal) methods. Each approach offers distinct advantages and limitations in terms of scalability, cost, environmental impact, and compatibility with biomedical use.

Chemical Reduction Methods

Chemical reduction is the most widely employed technique for producing metallic nanoparticles such as silver (Ag), gold (Au), and copper (Cu). This method involves the reduction of metal salts (e.g., $AgNO_3$, $HAuCl_4$) in liquid solution using reducing agents such as sodium borohydride ($NaBH_4$), trisodium citrate, ascorbic acid, or hydrazine. The process is typically conducted in the presence of stabilizing agents (capping agents) like polyvinylpyrrolidone (PVP), sodium dodecyl sulfate (SDS), or citrate ions, which prevent nanoparticle aggregation through electrostatic or steric stabilization [11].

The Turkevich method enables the synthesis of spherical gold nanoparticles (10-20 nm) by reducing $HAuCl_4$ with Trisodium citrate, where citrate acts as both a reducing and capping agent. Similarly, Ag nanoparticles can be synthesized via borohydride reduction, yielding highly monodisperse particles with strong surface plasmon resonance (SPR) in the visible range (~420 nm). The size and shape of NPs can be further tuned by adjusting parameters such as pH, temperature, reaction time, and molar ratios of reagents [12].

While chemical methods offer excellent control over nanoparticle characteristics, they often involve toxic reagents and solvents, raising concerns about residual contaminants and environmental sustainability-particularly when intended for clinical dental applications [13].

Physical Methods

Physical approaches, including laser ablation, arc discharge, sputtering, and thermal evaporation, provide a clean, surfactant-free route to nanoparticle production. In laser ablation in liquid (LAL), a pulsed laser is focused on a bulk metal target immersed in a liquid medium (e.g., water or ethanol), resulting in the ejection of atoms or clusters that nucleate into nanoparticles. This method produces ligand-free NPs with high purity, making them suitable for studies requiring minimal surface interference [14].

LAL-synthesized Ag and Au nanoparticles have demonstrated potent antibacterial activity and have been incorporated into dental cements and coatings. However, physical methods are generally energy-intensive, less scalable, and offer limited control over particle size distribution compared to chemical routes [15].

Green (Biological) Synthesis

In response to the environmental and biocompatibility challenges of conventional synthesis, green synthesis has emerged as a sustainable and eco-friendly alternative. This approach utilizes biological entities-such as plant extracts (e.g., *Azadirachta indica*, *Camellia sinensis*), fungi, bacteria, or algae-to reduce metal ions and stabilize the resulting nanoparticles [16].

Plant-based synthesis leverages natural phytochemicals (e.g., flavonoids, terpenoids, polyphenols) that act as both reducing and capping agents. For instance, ZnO nanoparticles synthesized using Aloe vera extract have shown enhanced antimicrobial effects against *S. mutans* and improved biocompatibility with human gingival fibroblasts [17]. Similarly, Ag nanoparticles derived from green tea extract exhibit strong activity against endodontic pathogens while demonstrating lower cytotoxicity than chemically synthesized counterparts [18].

Green synthesis aligns with the principles of green chemistry and offers significant advantages for dental applications, including reduced toxicity, cost-effectiveness, and the potential for dual functionality (e.g., antioxidant and antimicrobial properties from phytochemical capping layers). However, challenges remain in standardizing extract composition, controlling reaction kinetics, and ensuring batch-to-batch reproducibility [19].

Sol-Gel and hydrothermal methods for metal oxide nanoparticles

For inorganic metal oxides such as ZnO, TiO_2, and CuO, sol-gel and hydrothermal/solvothermal techniques are particularly effective.

The sol-gel process involves the hydrolysis and condensation of metal alkoxides or salts to form a colloidal suspension (sol) that evolves into a gel network, which can then be calcined to yield crystalline nanoparticles. This method allows for high purity and homogeneity and is widely used to produce TiO_2 nanoparticles for photocatalytic dental applications [20].

The hydrothermal method involves crystallizing materials in aqueous solutions at elevated temperatures and pressures (typically 100-250°C in autoclaves). This technique enables precise control over crystal phase (e.g., anatase vs rutile TiO_2) and morphology (nanorods, nanospheres), which are crucial for optimizing photocatalytic efficiency under visible or UV light [21].

Comparative Overview and Selection Criteria

The choice of synthesis method must balance efficacy, safety, scalability, and regulatory compliance, particularly for clinical translation. A comparative overview of these methods is presented in Table 1, which summarizes the common inorganic metallic nanoparticles, their composition, key properties, and primary dental functions. For example, Ag NPs are ideal for antimicrobial applications due to their broad-spectrum activity, while ZnO NPs are preferred for remineralization due to their biocompatibility and ion release.

Physicochemical properties and characterization of inorganic metallic nanoparticles

The functional performance of inorganic metallic nanoparticles in dental applications is fundamentally governed by their physicochemical properties, including size, shape, surface charge, crystalline structure, optical behavior, and chemical stability. These characteristics not only determine the nanoparticles' interaction with biological systems but also influence their integration into dental materials and their response to environmental stimuli such as light, pH, and mechanical stress. A deep understanding of these properties-supported by advanced characterization techniques is essential for rational design and clinical translation.

Size and Morphology

Nanoparticle size typically ranges from 1 to 100 nm, a scale at which quantum effects and high surface-to-volume ratios become significant. In dentistry, particle size directly affects penetration depth into dentinal tubules, biofilm disruption efficiency, and cellular uptake. For instance, Ag nanoparticles smaller than 20 nm exhibit superior antimicrobial activity due to their ability to penetrate bacterial cell walls and induce intracellular damage [22].

Morphology-whether spherical, rod-shaped, cubic, or plate-like-also plays a critical role. Anisotropic shapes such as Nano rods or Nano prisms offer enhanced surface plasmon resonance (SPR) and increased contact area with microbial membranes. ZnO Nano rods, for example, have demonstrated stronger bactericidal effects than spherical counterparts due to mechanical piercing of bacterial surfaces [23].

Surface charge and zeta potential

The surface charge of nanoparticles, measured as zeta potential (ζ), influences colloidal stability and interaction with biological substrates. A high absolute zeta potential (typically > |±30| mV) indicates good electrostatic stabilization, preventing aggregation in aqueous environments such as saliva or irrigation solutions [24].

Positively charged nanoparticles (e.g., amine-functionalized Ag NPs) tend to adhere more effectively to the negatively charged surfaces of bacterial membranes (due to lipoteichoic acids in Gram-positive and lipopolysaccharides in Gram-negative bacteria), enhancing their antimicrobial efficacy. However, excessive positive charge may also increase cytotoxicity toward human cells, necessitating a balance between activity and biocompatibility [25].

Crystalline structure and phase composition

The crystallinity and crystal phase of metal oxide nanoparticles significantly affect their reactivity. For example:

TiO_2 exists in three main phases: Anatase, rutile, and brookite. Anatase exhibits the highest photocatalytic activity under UV light due to its wider bandgap (~3.2 eV) and slower electron-hole recombination rate [26].

ZnO typically adopts a wurtzite structure, which contributes to its piezoelectric and photocatalytic properties, useful in self-cleaning dental surfaces or mechanically responsive coatings

High crystallinity generally correlates with improved stability and functional performance, although defects or dopants (e.g., nitrogen-doped TiO_2) can be introduced to enhance visible-light activation [28].

Optical properties and Surface Plasmon Resonance (SPR)

Noble metal nanoparticles, particularly Au and Ag, exhibit strong surface plasmon resonance (SPR)-a collective oscillation of conduction electrons when excited by light. This phenomenon results in intense absorption in the visible region (e.g., ~420 nm for Ag, ~520 nm for Au) and enables applications in:

- **Photothermal therapy:** Localized heat generation to kill bacteria in periodontal pockets [29].
- **Surface-enhanced Raman spectroscopy (SERS):** Ultrasensitive detection of oral pathogens at low concentrations [30].
- **Colorimetric sensors:** Visual detection of pH changes or bacterial metabolites in saliva [31].

SPR is highly sensitive to size, shape, and dielectric environment, allowing tunability across the visible and near-infrared spectrum for targeted dental diagnostics and therapies.

Bandgap energy and photocatalytic activity

For metal oxides like TiO_2, ZnO, and CuO, the bandgap energy determines their ability to generate electron-hole pairs under light irradiation, leading to the production of reactive oxygen species (ROS) such as hydroxyl radicals (•OH) and superoxide anions ($O_2^{\bullet -}$). These ROS degrade organic biofilms, neutralize endotoxins (e.g., LPS), and disinfect root canals [32].

TiO_2 (bandgap ~3.0-3.2 eV) requires UV light for activation, limiting its clinical use.

Doping strategies (e.g., with nitrogen, carbon, or silver) reduce the band gap, enabling visible-light photocatalysis-a major advancement for intraoral applications where UV exposure is impractical [33].

Surface Functionalization and Stability

To improve dispersion, targeting, and biocompatibility, nanoparticles are often surface-modified with polymers (e.g., PEG, chitosan), silanes, or biomolecules (e.g., antibodies, peptides). Chitosan-coated Ag nanoparticles, for example, show enhanced mucoadhesion and sustained release in the oral cavity, prolonging antimicrobial action [34].

However, nanoparticles may aggregate in physiological environments due to high ionic strength or protein adsorption (forming a protein corona), which alters their size, charge, and biological identity. Therefore, stability studies in artificial saliva or serum are crucial for predicting *in vivo* behavior [35].

Key Characterization Techniques

A variety of advanced analytical techniques are employed to characterize the physicochemical properties of nano-particles. Table 2 provides a detailed overview of the clinical applications of inorganic metallic nanoparticles, categorized by dental specialty, common NPs used, application forms, mechanisms of action, and evidence levels from current research.

Applications in Dentistry

Antimicrobial Restorative Materials

Secondary caries remains the leading cause of restoration failure. Incorporating Ag, ZnO, or CuO nanoparticles into dental composites reduces bacterial adhesion by up to 80% without compromising mechanical properties at optimal loadings (0.05-0.1 wt%) [6] ZnO-doped glass ionomer cements (GICs) show sustained Zn^{2+} release and reduced biofilm formation in clinical trials [36]. These findings are summarized in Table 2, which highlights the evidence levels and mechanisms of action across different dental specialties.

Endodontic Disinfection

Ag NPs in chitosan nanoparticles penetrate dentinal tubules and exhibit prolonged antimicrobial activity against E. faecalis [37]. TiO_2 and ZnO NPs used in photo activated disinfection (PaD) significantly reduce microbial load when combined with laser irradiation [38]. These applications leverage the photocatalytic properties of metal oxides, as detailed in Table 1.

Periodontal and peri-implant therapy

Local delivery systems with Ag or ZnO NPs reduce probing depth and bleeding on probing [29]. Implant coatings with Ag or TiO_2 prevent biofilm formation and improve osseointegration [40]. The biocompatibility and antimicrobial efficacy of these nanoparticles are further evaluated in Table 3, which presents a comprehensive toxicological profile.

Remineralization and Regeneration

ZnO NPs upregulate dentin sialoprotein (DSP) and DMP-1. Bioactive glass nanoparticles (BGNs) and Sr-doped hydroxyapatite promote remineralization [41]. Cu-doped NPs enhance angiogenesis in pulp capping [42]. These regenerative applications are supported by the ion-releasing and bioactive properties outlined in Table 1.

Diagnostic and Sensing Applications

SERS using Au/Ag NPs enables detection of IL-1β and bacterial metabolites in saliva. Colorimetric sensors detect pH shifts associated with caries [43]. These diagnostic tools are enabled by the optical properties of noble metal nanoparticles, as described in Table 2.

Safety, toxicity, and regulatory considerations

Despite their promise, concerns regarding cytotoxicity, genotoxicity, and long-term biocompatibility persist. Ag NPs may induce oxidative stress in human cells at high concentrations [44]. The toxicological profiles of common dental nanoparticles, including cytotoxicity levels, target cells, ROS generation, safe concentrations, and clinical notes, are systematically presented in Table 3.

Regulatory frameworks such as ISO/TS 22516:2020 and FDA guidelines emphasize the need for standardized testing [45]. Table 4 outlines future research directions and translational challenges, including smart nanocomposites, hybrid systems, AI-driven design, 3D printing integration, regulatory approval, and environmental impact-providing a roadmap for the clinical translation of Nano dental technologies.

Conclusion

Inorganic metallic nanoparticles represent a paradigm shift in dental materials, offering multifunctional solutions to

persistent clinical challenges. Their integration into restorative, endodontic, periodontal, and regenerative applications is supported by a growing body of evidence, as summarized in Tables 1-4. These tables provide a structured, evidence-based framework for evaluating nanoparticle selection, balancing efficacy with biocompatibility, and guiding future research. Future efforts must focus on standardization, long-term safety assessment, and regulatory harmonization to ensure the safe and effective translation of these innovative nanomaterials into routine clinical practice.

Table 1: Summary of common inorganic metallic nanoparticles in dentistry: Properties and primary functions

Nanoparticle	Composition	Key Properties	Primary Dental Functions
Silver (Ag NPs)	Metallic Ag	Broad-spectrum antimicrobial, SPR, high conductivity	Biofilm inhibition, restorative coatings, endodontic disinfection
Zinc Oxide (Zn O NPs)	Zn O	Antimicrobial, pH buffering, ROS generation, biocompatible	Remineralization, antibacterial composites, pulp capping
Titanium Dioxide (Ti O_2 NPs)	Ti O_2	Photocatalytic, UV/visible-light activated, ROS generation	Self-cleaning surfaces, photoactivated disinfection (PaD), implant coatings
Copper Oxide (Cu O NPs)	Cu O	ROS generation, cost-effective, antimicrobial	Antibacterial adhesives, hybrid composites
Gold (Au NPs)	Metallic Au	SPR, biocompatible, photothermal, SERS-active	Diagnostics, photothermal therapy, sensing
Iron Oxide (Fe_3O_4 NPs)	Fe_3O_4	Magnetic, MRI contrast, ROS generation	Targeted drug delivery, imaging, hyperthermia
Strontium-doped Hydroxyapatite (Sr-HA)	$Ca_{10}(PO_4)_6(OH)_2$: Sr	Ion release, remineralization, low solubility	Caries prevention, enamel repair
Bioactive Glass Nanoparticles (BGNs)	Si O_2-Ca O-P_2O_5	Ca^{2+}/PO_4^{3-} release, hydroxyapatite nucleation	Dentin remineralization, pulp regeneration

Table 2: Clinical applications of inorganic metallic nanoparticles in dentistry

Specialty	Common NPs	Application Forms	Mechanism	Evidence Level
Restorative Dentistry	Ag, Zn O, Cu O	Resin composites, adhesives	Ion release, ROS, membrane disruption	*In vitro* / Clinical trials
Endodontics	Ag, Ti O_2, Zn O, nano-Ca $(OH)_2$	Irritants, intracanal medicaments	Biofilm penetration, photocatalysis, pH elevation	*In vitro* / Animal studies
Periodontics & Peri-Implantitis	Ag, Zn O, Ti O_2	Gels, fibers, implant coatings	Local antimicrobial delivery, osseointegration enhancement	Clinical trials / RCTs
Regenerative Dentistry	Zn O, BGNs, Sr-HA, Cu-doped NPs	Scaffolds, pulp capping agents	Odontoblast stimulation, angiogenesis, remineralization	*In vitro* / Preclinical
Diagnostics	Au, Ag	SERS substrates, colorimetric sensors	Pathogen detection, pH sensing, biomarker identification	*In vitro* / Proof-of-concept
Orthodontics	Ag, TiO_2	Bracket coatings, adhesives	Biofilm prevention on appliances	*In vitro* studies

Table 3: Toxicological profile and biocompatibility of common dental nanoparticles

Nanoparticle	Cytotoxicity Level	Target Cells	ROS Generation	Safe Concentration	Notes
Ag NPs	High (dose-dependent)	Gingival fibroblasts, pulp cells	Yes (ROS-mediated)	< 0.1 wt% in composites	Risk of argyria at high doses
Zn O NPs	Moderate	Osteoblasts, fibroblasts	Low-moderate	< 5 wt% in cements	Safer than Ag; promotes biomineralization
TiO_2 NPs	Low (anatase > rutile)	Epithelial cells	Controversial (UV-dependent)	Up to 10 wt%	Generally recognized as safe (GRAS)
Cu O NPs	High	Fibroblasts, macrophages	Yes	< 1 wt%	Strong ROS generation; better in hybrids
Au NPs	Very low	Various cell lines	No	Up to 0.5 mM	Excellent biocompatibility
Fe_3O_4 NPs	Low	Stem cells, fibroblasts	No	Up to 100 µg/mL	Used in MRI and targeted delivery

Table 4: Future directions and translational challenges in nanodentistry

Research Direction	Current Status	Expected Benefits	Key Challenges
Smart Nanocomposites	pH-responsive Zn O/BGNs in development	On-demand ion release, self-healing	Stability, controlled kinetics
Hybrid Nano systems	Ag-Zn O, Au-Ti O_2, Cu-Zn O tested *in vitro*	Multifunctional (antimicrobial + regenerative)	Complex synthesis, characterization
AI-Driven Design	Early computational models	Predictive modeling of NP properties/toxicity	Data scarcity, validation
3D Printing Integration	Pilot studies with NP-doped resins	Customized bioactive restorations	Viscosity, printability, homogeneity
Regulatory Approval	No FDA-approved NP dental material	ISO/ADA nanomaterial standards	Standardization, long-term safety
Environmental Impact	Limited studies on NP release	Green synthesis, lifecycle analysis	Ecotoxicity, disposal protocols

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