

Nanoparticle-Assisted Endodontic Irrigation: A Systematic Review of Preclinical Studies

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Background: Conventional root canal irrigants such as sodium hypochlorite (NaOCl) and ethylenediaminetetraacetic acid (EDTA) are widely used because of their antimicrobial and chelating properties; however, their effectiveness may be limited by biofilm resistance and complex root canal anatomy, and they may adversely affect dentin microstructure and regenerative potential.

Objective: This systematic review evaluated preclinical evidence on nanoparticle-based endodontic irrigation with respect to antimicrobial and antibiofilm activity, dentin-related outcomes, and biocompatibility or regeneration-related effects.

Methods: PubMed/MEDLINE and ScienceDirect were systematically searched for English-language studies published from January 2015 to December 2025 using the following Boolean strategy: (“Nanoparticles” OR “Nano-based”) AND (“Root canal irrigant” OR “Antibiofilm”) AND (“Dentin surface” OR “Biocompatibility”). Eligible studies were original preclinical investigations evaluating nanoparticle-assisted irrigation or disinfection in extracted human-tooth models. After screening 695 records against predefined eligibility criteria, 12 studies were included.

Results: Compared with conventional irrigants, nanoparticle-based systems showed promising antibacterial and antibiofilm effects, particularly against *Enterococcus faecalis*. Activation approaches, including photodynamic, sonic, and ultrasonic methods, were frequently associated with enhanced antimicrobial performance. Some studies also reported improved smear-layer removal, preservation of dentin ultrastructure, and favorable mechanical outcomes. In addition, several biology-related studies suggested acceptable cytocompatibility, growth-factor release, and improved healing-related responses under experimental conditions.

Conclusion: Nanoparticle-assisted irrigation shows promising preclinical potential as an adjunct to conventional root canal disinfection. However, heterogeneity in study design and the absence of clinical evidence limit definitive conclusions and preclude routine clinical recommendations at present.

Keywords: biocompatibility, biofilms, dental disinfectants, dentin, nanoparticles, root canal irrigation

Introduction

The root canal system's complicated and challenging structure¹ complicates the chemomechanical debridement and elimination of microbes. Biofilms are structured colonies of bacteria that adhere firmly to surfaces and are very hard to remove. Their presence is a major reason why root canal treatments fail. The main goal of endodontic therapy is to eliminate this biofilm.^{2,3} Although a range of intracanal medicaments and irrigating solutions are employed routinely, many microorganisms exhibit persistence or resistance to conventional irrigants, thereby limiting the efficacy of the current protocols.⁴ Ethylene diamine tetraacetic acid (EDTA) has chelation ability, removing the smear layer, while sodium hypochlorite (NaOCl) is a common irrigant that kills germs, but both have the drawback that they are unable to preserve dentin structure, and may weaken it.⁵ As a result, researchers are investigating new approaches, such as the use of nanotechnology to overcome these issues in conventional irrigants.⁶

Nanotechnology is a new and promising field of research in endodontics that could help solve these problems.⁶ One way to create new interactions with biological systems is to make engineered materials at the nanoscale, which is defined here as 1–100 nm.⁷



The main reason researchers study nanoparticles (NPs) is that they have a complex and tunable structure, which often includes a functionalized core-shell-surface design. Antimicrobials can be carefully designed to target specific areas, control how quickly they are released, and be moved around in the right way.⁸ These structural features may enable deeper penetration into intricate biofilms and dentinal tubules, more controlled and sustained antimicrobial release, and more localized treatment with potentially fewer adverse effects than conventional irrigants. However, some NPs may have the opposite effect, making the dentin more stable or even promoting it remineralize.⁹ Researchers are investigating numerous different NPs to utilize these properties. Some examples are metallic NPs (such as silver) that kill bacteria, polymeric carriers (such as chitosan) that might carry drugs, and ceramic particles (such as nanodiamonds) that can eliminate smear layers.^{6,10}

The oligodynamic effect is what makes many NPs efficient in eliminating bacteria. NPs may reduce infections by breaking down cell membranes, making reactive oxygen species (ROS) that eradicate bacteria, breaking down microbial deoxyribonucleic acid (DNA), and blocking important metabolic pathways. Unlike traditional antibiotics, which often target a single species, nanoparticles may affect multiple microbial targets simultaneously. NPs' ability to affect many species at once makes them a good choice for existing irrigation procedures in root canal treatment, which is especially beneficial in the elimination of bacteria that do not respond to antibiotics. Also, in inhibiting biofilms that last a long time in the mouth.^{9,11}

In vitro evidence backs up this possibility. For example, a 0.1% nanosilver gel worked better against *Enterococcus faecalis* (*E. faecalis*) biofilm than chlorhexidine gluconate (CHX) and camphorated phenol.¹² Chitosan nanoparticles (CNPs) and CHX exhibit a synergistic antibacterial effect,¹³ whereas the suppression of *E. faecalis* biofilm was markedly improved when silver NPs were combined with calcium hydroxide ($\text{Ca}(\text{OH})_2$).¹⁴

The NPs might be helpful for physical debridement as well as killing bacteria. Silver nanoparticles (AgNPs) added to irrigants not only have strong antibacterial properties, but they also facilitate breaking down the biofilm matrix and make it easier to remove debris.^{15,16} In the same way, irrigation fluids made with newer materials such as nanodiamonds work as bioactive abrasives. Their main job is to make the surface cleaner for obturation by promoting the removal of the stubborn smear layer from the walls of the canal. This process may not work with standard chelators such as EDTA.^{10,11}

One potentially important advantage of nanoparticle-based strategies is their possible interaction with dentin itself. Unlike NaOCl, which may weaken dentin structure, some final-rinse formulations containing nanoparticles such as silver, titanium dioxide, or zinc oxide have been associated with increased fracture resistance of root-filled teeth.¹⁷ One proposed explanation is that nanoparticles may penetrate dentinal tubules and interact with the dentin matrix, which could contribute to structural reinforcement and improved sealing with filling materials.

Collectively, owing to their high surface area and unique physicochemical properties, NPs represent a promising alternative capable of serving a dual therapeutic goal: enhancing biofilm eradication while simultaneously supporting dentin remineralization and structural stability.¹⁸

Over the past decade, interest in nanoparticle-assisted strategies in endodontics has increased substantially, and several reviews have discussed nanomaterials in broad endodontic applications. However, a focused synthesis of recent evidence on nanoparticle-based irrigation strategies in extracted human-tooth models remains limited, particularly across the major outcome domains relevant to endodontic irrigation. These domains include antimicrobial and antibiofilm performance, dentin-related effects such as smear-layer removal and mechanical behavior, and biocompatibility or regeneration-related findings. In addition, important translational issues, including formulation variability, lack of protocol standardization, and absence of clinical evidence, remain relevant when interpreting the current literature. Unlike broader reviews of nanomaterials in endodontics, the present review was designed to provide a focused, systematic synthesis of preclinical evidence specifically related to nanoparticle-assisted irrigation strategies in extracted human-tooth models across antimicrobial, dentin-related, and biologic outcome domains.

Accordingly, this systematic review was undertaken to evaluate preclinical studies on nanoparticle-assisted endodontic irrigation and disinfection strategies performed in extracted human-tooth models. The objective was to synthesize evidence regarding antimicrobial and antibiofilm activity, effects on dentin microstructure and mechanical properties, and biocompatibility or regeneration-related outcomes.

Methods

Search Strategy

Two electronic databases, PubMed/MEDLINE and ScienceDirect, were systematically searched for eligible studies. Screenshots of the original database searches corresponding to the initial record counts are provided in [Supplementary Figures S1](#) and [S2](#). The search strategy included the terms “Nanoparticles” OR “Nano-based” AND (“Root canal irrigant” OR “Antibiofilm”) AND (“Dentin surface” OR “Biocompatibility”). The search was restricted to English-language studies published between 1 January 2015 and 31 December 2025. Both databases were last searched on 23 January 2026. The full search strategies and database-specific filters used for each source are provided in [Supplementary Table S1](#).

Eligibility Criteria

The included studies were original research articles evaluating nanoparticle (NP)-based endodontic irrigants or disinfection strategies used as root canal irrigants or final rinse solutions. Eligible studies were required to use extracted human teeth with natural root canal anatomy (ex vivo/in vitro tooth models) and report outcomes related to antimicrobial/antibiofilm efficacy, dentin hard-tissue properties (eg., smear-layer removal, surface morphology, microhardness, remineralization, mechanical performance), and/or cytotoxicity/biocompatibility.

Exclusion Criteria

Scoping reviews, systematic reviews, meta-analyses, and case reports were excluded, as were conference abstracts, editorials, letters, books, guidelines, indexes, and other non-peer-reviewed publications. Studies focusing solely on NP applications in sealers, obturation materials, restorative procedures, or other non-irrigation uses were excluded. Studies not using extracted human teeth were excluded, including those based on bovine/porcine teeth, dentin blocks, synthetic or standardized artificial canal models (eg., resin blocks), hydroxyapatite discs, membrane/plate models, or purely planktonic assays without an extracted-tooth root canal system. Duplicate records and studies lacking sufficient methodological detail were excluded. Retracted articles were excluded. These model-based exclusions were applied to maintain methodological comparability with extracted human teeth and natural root canal anatomy for outcomes related to irrigation, dentin substrate, and canal-wall assessment.

Study Selection

All retrieved records were imported into EndNote (Clarivate, USA) for reference management and removal of duplicate entries; a representative screenshot of duplicate management is provided in [Supplementary Figure S3](#). The study selections were conducted in two sequential stages. Initially, titles and abstracts were screened against the predefined eligibility criteria. Subsequently, full texts of potentially relevant studies were retrieved and assessed for final inclusion. Two reviewers (H.M.H. and A.H.A.) independently screened titles/abstracts and full-text records, and any disagreements were resolved through discussion.

Data Extraction

Data from all included studies were extracted independently by the two reviewers using a standardized and pre-piloted data extraction form in Microsoft Excel (Microsoft, USA). Extracted data included study identification (author and year), NP characteristics, study design, comparator or control protocols, and reported outcomes related to antimicrobial/antibiofilm efficacy, dentin properties, and biological or biocompatibility effects. Outcome data sought from each study included antimicrobial and antibiofilm results (eg., bacterial reduction, colony-forming unit (CFU) counts, biofilm disruption, anti-adhesion effects), dentin-related or mechanical outcomes (eg., smear-layer removal, surface morphology, microhardness, fracture resistance, push-out bond strength, and dentin ultrastructural changes), and biologic or biocompatibility outcomes (eg., cytotoxicity, cell viability, genotoxicity, growth-factor release, and healing-related responses). All reported results that were relevant to these predefined outcome domains were extracted. Other extracted data included

the study model, nanoparticle type, activation or delivery method, comparator groups, and study design. Any missing or unclear information was not estimated and was recorded only as reported in the original studies.

The initial database search yielded 695 records, including 213 from PubMed/MEDLINE and 482 from ScienceDirect. After duplicate removal, 677 records remained for screening. Following application of the predefined eligibility criteria, 12 studies were included in the final review, as shown in [Figure 1](#), which summarizes the study selection and exclusion process used in this review. A detailed breakdown of the full-text articles excluded after eligibility assessment and their primary reasons for exclusion is provided in [Supplementary Table S2](#).^{19–50} For synthesis, included studies were grouped into three predefined outcome domains: antimicrobial/antibiofilm performance, dentin-related/mechanical outcomes, and biologic/biocompatibility outcomes. Studies were assigned to one or more synthesis domains according to the outcomes they reported, and some studies contributed to more than one domain. The review authors did not contact the authors of the included studies to obtain or confirm additional information.

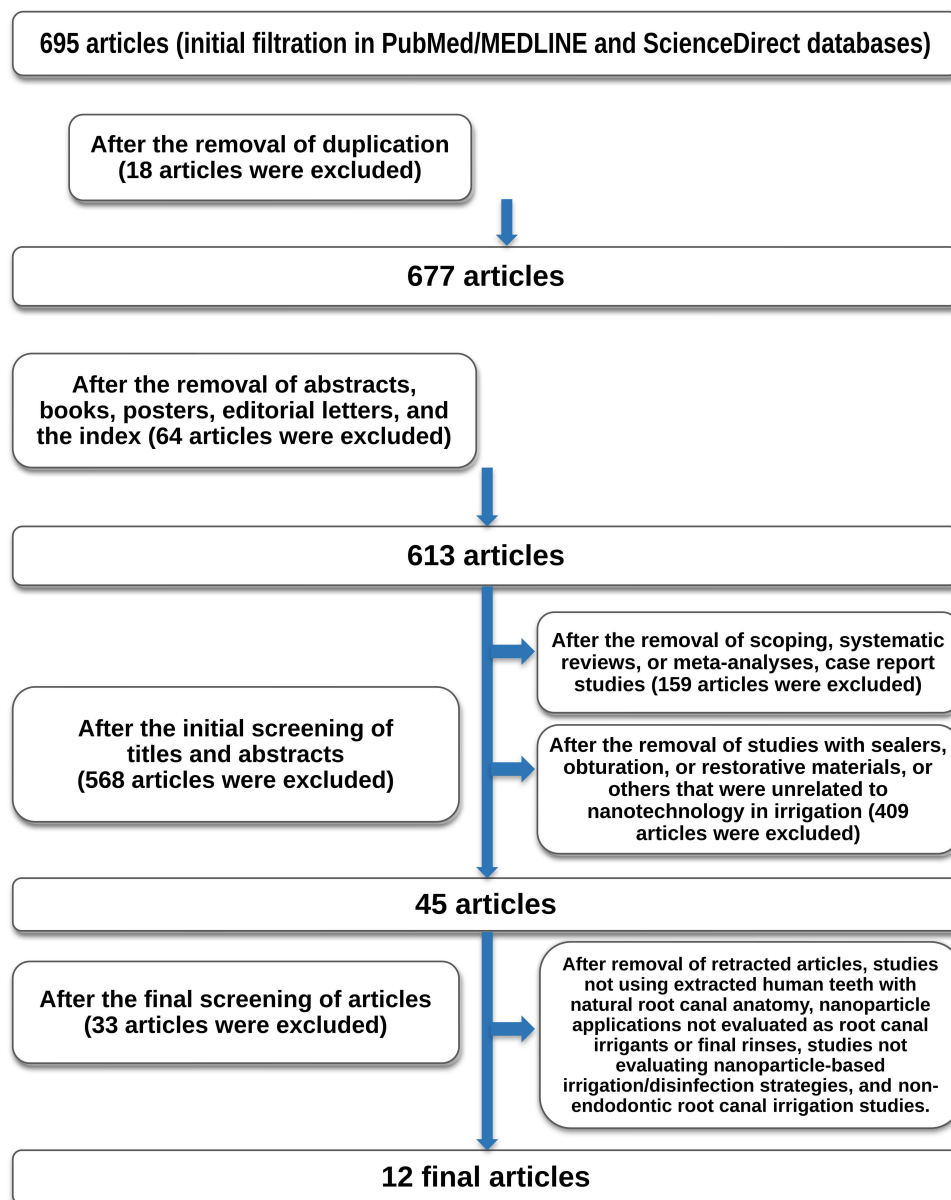


Figure 1 PRISMA flow diagram of study selection.

Methodological Quality Appraisal

The quality of the included studies was assessed independently by two reviewers using a structured approach suitable for preclinical in vitro and ex vivo dental studies. The assessment considered sample selection, use of control groups, reporting of randomization or allocation, blinding where applicable, adequacy of nanoparticle characterization, completeness of outcome reporting, and appropriateness of statistical analysis. Any disagreements were resolved through discussion. Because of substantial methodological heterogeneity across nanoparticle platforms, activation protocols, study models, and outcome measures, no pooled quantitative analysis was performed. Findings were therefore summarized narratively as reported in the original studies. No data conversion or imputation was performed. Study selection was presented in a flow diagram, included study characteristics and findings were summarized in an integrated summary table, and reasons for exclusion of full-text studies were summarized in a [supplementary table](#). This systematic review was not registered. No review protocol was prepared.

Results

A total of twelve original studies met the eligibility criteria and were included in this systematic review. Evidence was synthesized across three outcome domains: (i) antimicrobial and antibiofilm performance, (ii) dentin cleaning and hard-tissue/mechanical effects, and (iii) biocompatibility and regeneration-related biological outcomes. In most studies, extracted human teeth served as models for intracanal infection or biofilm, predominantly using *Enterococcus faecalis* as the test microorganism. The included studies evaluated nanoparticle-based strategies both as standalone irrigants/final rinses and as activation-assisted protocols, including diode-laser/photodynamic and sonic/ultrasonic approaches.

Overall, the included studies showed heterogeneous methodological quality. Common limitations included incomplete reporting of randomization and blinding, variability in nanoparticle characterization, and substantial diversity in activation protocols and outcome measures. The study-level assessment of methodological quality domains in the included studies is summarized in [Supplementary Table S3](#).^{51–62}

The included studies are summarized in a single integrated table ([Table 1](#)), which presents the study groups, model, and key findings across antimicrobial/antibiofilm, dentin-related/mechanical, and biologic/biocompatibility outcome domains. Across the included studies, nanoparticle-assisted protocols produced measurable antimicrobial and antibiofilm effects in extracted-tooth canal infection models, while dentin-related/mechanical and biologic outcomes were more variably reported.

Across the antimicrobial/antibiofilm studies ([Table 1](#)), all NP approaches produced measurable reductions in *E. faecalis* in extracted-tooth canal infection models, but the magnitude and consistency differed by platform and by whether an adjunct activation step was used. Light-mediated protocols were assessed using diode-laser-based strategies and PDT. Afkhami et al in 2017,⁵² reported that all tested groups reduced CFU, with the combined silver nanoparticles (AgNPs)–indocyanine green (ICG)–diode-laser protocol showing the highest mean reduction ($\approx 99\%$), although it was not statistically superior to NaOCl or other activated groups. Alkudhairy and AlRefeai in 2024,⁵⁸ similarly reported that adding Chitosan nanoparticles-Rose Bengal photosensitizer (CNPs-RBP) to a NaOCl and diode-laser PDT protocol resulted in the lowest bacterial survival among their treatment arms.

A second group of studies evaluated catalytic or ROS-amplifying platforms in which antibiofilm effects were assessed with a trigger (eg., ultrasound/sonodynamic protocols or pH-responsive ROS generation). Guo et al⁵⁵ reported near-complete killing and marked biofilm disruption when mesoporous silica nanoparticles carrying protoporphyrin IX (PpIX) and Fe ions (M@P-Fe) were combined with low-dose hydrogen peroxide (H_2O_2) and ultrasound (sonodynamic therapy), with antibacterial performance comparable to NaOCl in their tooth model. Yu et al⁵⁷ reported that lanthanum-doped carbon quantum dots incorporated into a polyvinyl alcohol composite (La@PCDs-PVA) achieved antibacterial activity comparable to 5% NaOCl and demonstrated stronger biofilm removal/disruption on canal walls. Zhao et al in 2022,⁵⁶ showed concentration-dependent antibiofilm activity for ultrasmall Prussian blue nanoparticles loaded into mesoporous calcium-silicate nanoparticles (UPBNPs-MCSNs), with performance at higher concentrations comparable to 1% NaOCl/ $Ca(OH)_2$ and an additional anti-adhesion effect in pretreatment-challenge experiments. Overall, [Table 1](#) indicates consistent antibiofilm activity across NP systems, with activation/delivery steps frequently associated with greater reductions under the reported experimental conditions.

Table 1 Summary of Included Studies, Experimental and Comparator Groups, Models, and Key Findings Across Antimicrobial/Antibiofilm, Dentin-Related/Mechanical, and Biologic/Biocompatibility Outcomes

Study	Experimental & Comparator Groups	Model	Antimicrobial/Antibiofilm Findings	Dentin-Related /Mechanical Findings	Biologic/Biocompatibility Findings
1) Monzavi et al (2015) ⁵¹	Experimental groups: G1: MgONPs solution (ex vivo: 5 mg/L; no activation) Comparator groups: G2: NaOCl 2.5% G3: NaOCl 5.25% G4: CHX 0.12% G5: CHX 2% G6: SS (negative control)	Ex vivo: decoronated infected human teeth with <i>E. faecalis</i> ; CFU/mL monitored from 6 to 168 h after irrigation; LDH cytotoxicity assay.	Initial antibacterial effects of MgONPs were comparable to NaOCl/CHX, with superior sustained suppression and no noticeable regrowth during later intervals (72–168 h).	NR	LDH testing indicated no detectable cytotoxicity at the evaluated concentrations.
2) Afkhami et al (2017) ⁵²	Experimental groups: G1: AgNPs irrigation G2: AgNPs + DL, 810 nm G3: AgNPs + ICG + DL (ICG; modified PDT) Comparator groups: G4: NaOCl 2.5% irrigation G5: DL alone, 810 nm G6: ICG + DL (ICG; conventional PDT)	Extracted single-rooted human teeth infected with <i>E. faecalis</i> biofilm (4 weeks); CFU quantified after irrigation/activation.	All procedures reduced CFU. AgNPs + ICG + DL showed the largest mean reduction (about 99%), but without statistical superiority over NaOCl or other active groups.	NR	NR
3) Chávez-Andrade et al (2017) ⁵³	Experimental groups: G1: AgNPs-PVA (50 µM, 4–11 nm) as final rinse G2: FAR (farnesol 1%) as final rinse Comparator groups: G3: NaOCl (1% in cell assays, 2.5% in ex vivo protocol) G4: SS (physiological solution control) G5: H ₂ O ₂ (positive control for genotoxicity)	Ex vivo: 60 extracted human single-root teeth infected with <i>E. faecalis</i> (21 days); CFU at baseline, post-irrigation, and 7-day recall. In vitro: L929 fibroblasts for MTT and Comet assay (DNA damage).	NaOCl-containing protocols achieved complete elimination immediately after irrigation. AgNPs-PVA or FAR without NaOCl showed bacterial regrowth at 7 days, suggesting an adjunct rather than replacement role.	NR	AgNPs-PVA and FAR showed lower cytotoxicity and minimal genotoxicity compared with NaOCl.
4) Shrestha et al (2018) ⁵⁴	Experimental group: G1: NaOCl + CSRBnps + light (photoactivation 540 nm). Comparator groups: G2: non-contaminated control. G3: LPS only. G4: NaOCl alone. G5: NaOCl + Ca(OH) ₂ .	In vivo: human root segments with standardized canal lumen contaminated with <i>P. aeruginosa</i> LPS, then implanted intraosseously in guinea-pig mandibles; histology, IHC, and TRAP activity.	NR	NR	Photoactivated CSRBnps produced a favorable healing pattern with neotissue formation and without inflammation or resorption, compared with more mixed responses in NaOCl-based regimens.
5) Guo et al (2021) ⁵⁵	Experimental groups: G1: M@P-Fe + H ₂ O ₂ 0.01% + US activation (SDT) G2: M@P-Fe + H ₂ O ₂ (no ultrasound) G3: M@P-Fe + US (no H ₂ O ₂) G4: M@P-Fe alone Comparator groups: G5: H ₂ O ₂ alone (0.01%) G6: NaOCl (5% in vitro/3% root-canal model) G7: PBS (negative control)	Ex vivo/in situ: extracted human single-root premolars with a 4-week intracanal <i>E. faecalis</i> biofilm; CLSM and SEM. Biocompatibility: MC3T3-E1 cells by CCK-8.	Ultrasound-activated M@P-Fe + low-dose H ₂ O ₂ produced near-complete killing and marked biofilm disruption, with antibacterial performance comparable to NaOCl.	NR	Cell-viability testing showed significantly lower cytotoxicity than NaOCl.

6) Zhao et al (2022) ⁵⁶	Experimental groups: G1: UPBNPs-MCSNs (no activation) Comparator groups: G2: NaOCl 1% G3: Ca(OH) ₂ G4: UPBNPs alone G5: MCSNs alone G6: Untreated/vehicle controls Mechanism blockers (supportive tests): EDTA (chelator) and Vc (antioxidant)	Ex vivo (human roots): intracanal <i>E. faecalis</i> biofilm assessed by SEM/CLSM; anti-adhesion pretreatment-challenge model. Biocompatibility: SCAPs by CCK-8 viability assay.	UPBNPs-MCSNs showed concentration-dependent killing; at 10 mg/mL, efficacy was comparable to 1% NaOCl and Ca(OH) ₂ , with added anti-adhesion activity.	NR	Lower cytotoxicity than calcium hydroxide and favorable SCAP viability.
7) Yu et al (2024) ⁵⁷	Experimental groups: G1: La@PCDs-PVA composite (pH-responsive ROS generation, higher at pH 4) Comparator groups: G2: NaOCl 5% (positive irrigant control) G3: LaNPs G4: PBS/H ₂ O (phosphate-buffered saline/water controls)	Ex vivo root-canal model: extracted premolars with a 4-week intracanal <i>E. faecalis</i> biofilm; Dentin surface morphology evaluated by CFU/CLSM/SEM. Biocompatibility: L929 fibroblasts by CCK-8.	La@PCDs achieved antibacterial killing comparable to 5% NaOCl and showed stronger biofilm removal/disruption on canal walls.	Caused less dentin erosion/ultrastructural damage than 5% NaOCl on SEM.	Maintained high fibroblast viability close to controls, whereas NaOCl was highly cytotoxic.
8) Alkhudairy & AlRefeai (2024) ⁵⁸	Experimental groups: G1: NaOCl + CNPs-RBP + DL (NP-PDT protocol) G2: NaOCl + RBP + DL (PDT without nanoparticles) Comparator groups: G3: NaOCl + EDTA (conventional protocol) G4: NaOCl + DL (laser activation only) G5: NaOCl + CNPs (nanoparticles without PDT activation)	Extracted mandibular premolars infected with <i>E. faecalis</i> ; antibacterial outcome by CFU; Smear-layer scores by SEM; push-out bond strength.	The NP-PDT protocol produced the lowest bacterial survival compared with PDT without nanoparticles and conventional/activation controls.	NaOCl + CNPs-RBP + DL produced the cleanest smear-layer scores and the highest push-out bond strength.	NR
9) Ebrahim et al (2024) ⁵⁹	Experimental groups (final rinse after EDTA): G1: AgNPs 0.1% G2: TiO ₂ NPs 0.1% Comparator groups: G3: CHX 2% G4: EDTA + NaOCl 2.5% G5: SS (control)	Extracted maxillary incisors; canals prepared and obturated; fracture resistance tested under compressive loading after final-rinse protocols.	NR	AgNPs and TiO ₂ NPs significantly increased fracture resistance versus controls; EDTA + NaOCl showed the lowest fracture resistance; TiO ₂ NPs showed the highest values.	NR
10) Khangwal et al (2024) ⁶⁰	Experimental groups: G1: 0.2% CNPs (natural chelating agent used as final rinse) Comparator groups: G2: MTAD G3: Pro-EDTA G4: NaOCl-Extra G5: CHX-Ultra G6: SS (control)	Extracted single-root mandibular premolars instrumented to F3; apical-third smear-layer by SEM; dentin microhardness change by Vickers.	NR	CNPs achieved moderate smear-layer removal, inferior to MTAD and Pro-EDTA, but caused less microhardness reduction than stronger chelators.	NR

(Continued)

Table 1 (Continued).

Study	Experimental & Comparator Groups	Model	Antimicrobial/Antibiofilm Findings	Dentin-Related /Mechanical Findings	Biologic/Biocompatibility Findings
11) Alhamdan (2025) ⁶¹	Experimental groups (all followed by EDTA): G1: MgONPs + EDTA G2: KTPL + EDTA (KTPL, 532 nm) G3: AE-PDT + EDTA Comparator groups: G4: NaOCl 2.5% + EDTA	Extracted single-root premolars restored with glass fiber posts; smear-layer by SEM scoring; push-out bond strength.	NR	MgONPs + EDTA achieved the best smear-layer removal and the highest push-out bond strength; AE-PDT + EDTA showed the least favorable cleaning/bonding results.	NR
12) Usta et al (2025) ⁶²	Experimental groups: G1: 17% EDTA + 0.2% CNPs Comparator groups: G2: EDTA alone (17%) G3: CNPs alone (0.2%) Activation subgroups applied within each irrigant group (G1-G3): A1: SNI A2: Irriflex A3: PUI A4: EDDY A5: SWEEPS (Er: YAG laser modality)	Laboratory RET model using extracted single-root human teeth simulating open apices; TGF-β1 release measured by ELISA on days 1 and 7.	NR	NR	Activation increased TGF-β1 release, with SWEEPS highest; EDTA + CNPs released more TGF-β1 than EDTA alone or CNPs alone, and day-7 levels exceeded day-1 levels.

Abbreviations: MgONPs, magnesium oxide nanoparticles; NaOCl, sodium hypochlorite; CHX, chlorhexidine gluconate; SS, saline solution; E. faecalis, Enterococcus faecalis; CFU, colony-forming unit; LDH, lactate dehydrogenase; NR, not reported; AgNPs, silver nanoparticles; DL, diode laser; ICG, indocyanine green; PDT, photodynamic therapy; AgNPs-PVA, silver nanoparticles incorporated into polyvinyl alcohol; FAR, farnesol; H₂O₂, hydrogen peroxide; L929, mouse fibroblast cell line; MTT, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; CSRBnps, chitosan-Rose Bengal nanoparticles; LPS, lipopolysaccharide; P. aeruginosa, Pseudomonas aeruginosa; IHC, immunohistochemistry; TRAP, tartrate-resistant acid phosphatase; M@P-Fe, mesoporous silica nanoparticles carrying protoporphyrin IX and Fe ions; US, ultrasound; SDT, sonodynamic therapy; PBS, phosphate-buffered saline; CLSM, confocal laser scanning microscopy; SEM, scanning electron microscopy; MC3T3-E1, mouse pre-osteoblastic MC3T3-E1 cell line; CCK-8, Cell Counting Kit-8; UPBNPs-MCSNs, ultrasmall Prussian blue nanoparticles loaded into mesoporous calcium-silicate nanoparticles; Ca(OH)₂, calcium hydroxide; UPBNPs, ultrasmall Prussian blue nanoparticles; MCSNs, mesoporous calcium-silicate nanoparticles; EDTA, ethylenediaminetetraacetic acid; Vc, vitamin C; SCAPs, stem cells from apical papilla; La@PCDs-PVA composite, lanthanum-doped carbon quantum dots incorporated into a polyvinyl alcohol composite; ROS, reactive oxygen species; LaNPs, lanthanum nanoparticles; PBS/H₂O, phosphate-buffered saline/water controls; CNPs-RBP, chitosan nanoparticles-Rose Bengal photosensitizer; NP-PDT, nanoparticle-mediated photodynamic therapy; CNPs, chitosan nanoparticles; RBP, Rose Bengal photosensitizer; TiO₂NPs, titanium dioxide nanoparticles; MTAD, mixture of tetracycline isomer, acid, and detergent; Pro-EDTA, ethylenediaminetetraacetic acid-based chelating agent with a surfactant; NaOCl-Extra, sodium hypochlorite with surfactant; CHX-Ultra, chlorhexidine with surfactant; KTPL, potassium titanyl phosphate laser; AE-PDT, aloe-emodin photodynamic therapy; RET, regenerative endodontic treatment; TGF-β1, transforming growth factor beta-1; ELISA, enzyme-linked immunosorbent assay; SNI, syringe-needle irrigation; PUI, passive ultrasonic irrigation; EDDY, sonic irrigant activation device; SWEEPS, Shock Wave-Enhanced Emission Photoacoustic Streaming; Er:YAG, erbium-doped yttrium aluminum garnet.

Within [Table 1](#), dentin-related and mechanical outcomes included smear-layer removal, dentin microhardness changes, fracture resistance, push-out bond strength, and dentin surface preservation. The mechanical factors, such as fracture resistance and/or push-out bond strength, and cleaning efficacy, were investigated in multiple studies, so there was a clinical focus on preserving dentin and canal walls clean.

Two push-out tests analyzed the removal of smear layers and bonding to root dentin. Alhamdan⁶¹ reported that aloe-emodin-photodynamic therapy (AE-PDT) and EDTA had the worst cleaning and bonding findings, while magnesium oxide nanoparticles (MgONPs) and EDTA had the best smear-layer scores and the strongest push-out bond strength, especially in the cervix area. In a related study, Alkudhairy and AlRefeai in 2024,⁵⁸ found that NaOCl, CNPs-RBP, and diode laser (DL) produced the strongest push-out bond strength and the cleanest smear-layer scores when compared to NaOCl, EDTA, and other activation approaches in the same experimental setup.

Other studies emphasized the balance between cleaning and dentin preservation. Khangwal et al⁶⁰ reported that 0.2% CNPs achieved moderate smear-layer removal while producing less reduction in microhardness compared with stronger chelators such as a mixture of tetracycline isomer, acid, and detergent (MTAD) and Pro-EDTA. Mechanical reinforcement was evaluated by Ebrahim et al,⁵⁹ who reported that AgNPs or TiO₂NPs used as final rinses significantly increased fracture resistance compared with control protocols, whereas the EDTA followed by NaOCl sequence showed the lowest fracture resistance. Finally, Yu et al⁵⁷ reported dentin surface morphology outcomes on scanning electron microscopy (SEM), where La@PCDs caused less erosive/ultrastructural change than 5% NaOCl. Overall, [Table 1](#) shows that dentin-related outcomes ranged from enhanced smear-layer removal and higher push-out bond strength to more conservative dentin effects, including lower microhardness reduction, reduced erosive surface changes, and improved fracture resistance in some models.

Within [Table 1](#), biologic and biocompatibility evidence clustered into three main outcome types: in vivo healing responses after endotoxin contamination and disinfection, growth-factor release relevant to regenerative endodontics, and cytotoxicity/viability outcomes in mammalian cells.

Shrestha et al⁵⁴ reported an in vivo model using human root segments contaminated with *Pseudomonas aeruginosa* lipopolysaccharide (*P. aeruginosa* LPS), where photoactivated chitosan–rose bengal nanoparticles (CRBnps) produced a favorable healing pattern (neotissue formation without inflammation or resorption) comparable to non-contaminated controls, while NaOCl-based regimens (\pm Ca(OH)₂) showed mixed inflammatory/resorptive responses. Usta et al⁶² used a laboratory regenerative endodontic treatment (RET) model and reported that both irrigant composition and activation method influenced transforming growth factor beta-1 (TGF- β 1) release: Shock Wave–Enhanced Emission Photoacoustic Streaming (SWEEPS) yielded the highest levels, followed by the EDDY system, a sonic irrigant activation device, and passive ultrasonic irrigation, and EDTA with CNPs consistently produced higher TGF- β 1 than EDTA alone or CNPs alone, with higher release at day 7 than day 1.

Cell-based biocompatibility endpoints were reported for multiple NP strategies, also represented in [Table 1](#). Chávez-Andrade et al reported that silver nanoparticles incorporated into polyvinyl alcohol (AgNPs-PVA) and farnesol (FAR) 1% showed lower cytotoxicity than NaOCl and minimal genotoxicity in the Comet assay after short exposure. Guo et al⁵⁵ reported higher viability (lower cytotoxicity) for their M@P-Fe-based sonodynamic strategy compared with NaOCl in the mouse pre-osteoblastic MC3T3-E1 cell line (MC3T3-E1) cells. Monzavi et al in 2015⁵¹ reported no detectable cytotoxicity for MgONPs at tested concentrations using a lactate dehydrogenase (LDH) assay. Yu et al⁵⁷ reported that La@PCDs maintained high L929 fibroblast viability close to controls, whereas NaOCl was highly cytotoxic under their test conditions. Zhao et al⁵⁶ reported favorable stem cells from the apical papilla (SCAP) viability for ultrasmall Prussian blue nanoparticles loaded into mesoporous calcium-silicate nanoparticles; no activation (UPBNPs–MCSNs) relative to Ca(OH)₂. Collectively, [Table 1](#) indicates that several NP platforms showing antimicrobial activity were also associated with more favorable cytocompatibility outcomes than NaOCl in corresponding cell assays, alongside regeneration-related findings such as dentin growth-factor release under activated irrigation conditions.

[Figure 2](#) provides a conceptual overview of the representative nanoparticle platforms, activation approaches, mechanisms, and principal outcome domains discussed in this review. It links key mechanisms (membrane disruption, ROS/ion release, and biofilm/extracellular polymeric substances (EPS) destabilization) to outcomes across three

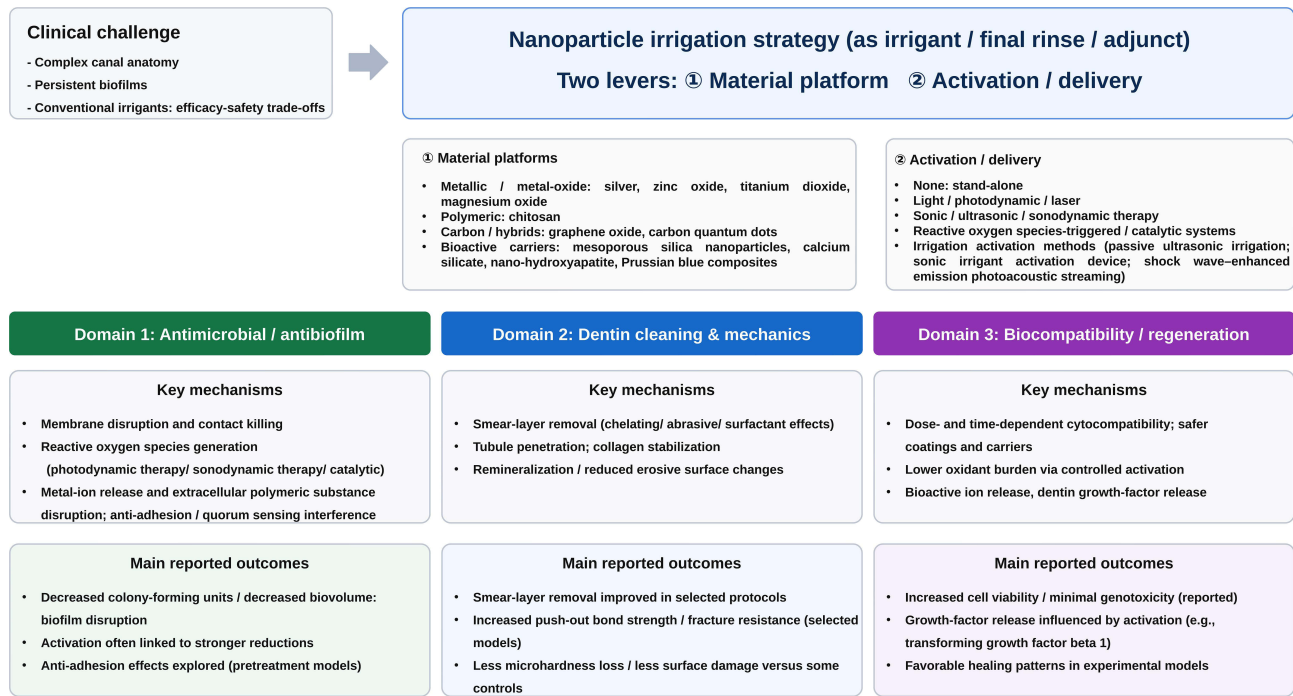


Figure 2 Conceptual summary of nanoparticle-assisted endodontic irrigation.

domains: antimicrobial/antibiofilm efficacy, dentin cleaning/preservation, mechanical performance, and biocompatibility/regeneration-relevant effects. Overall, it illustrates NP irrigation as a multifunctional strategy where material design and activation jointly shape clinically relevant outcomes.

Overview of Nanoparticles in Endodontic Irrigation

To understand why nanoparticles are increasingly being investigated as adjuncts in endodontic irrigation, it is essential first to examine their fundamental physicochemical properties and how these differ from conventional irrigation agents.

General Properties of Nanoparticles

Nanomaterials are defined as materials possessing at least one dimension within the 1–100 nm range.^{9,63} Their ultrasmall size, high surface area-to-mass ratio, and enhanced chemical reactivity enable interactions with biological systems at the subcellular level.^{64,65} The antimicrobial activity of NPs is typically explained by three principal mechanisms: oxidative stress induction, metal ion release, and non-oxidative interactions.⁹ Positively charged NPs can accumulate on negatively charged bacterial cell surfaces, destabilising the cell wall, increasing membrane permeability, and promoting leakage of intracellular contents.^{63,66}

The ROS generation is a central pathway; ROS (including superoxide and hydroxyl radicals) can induce oxidative damage to lipids, proteins, and nucleic acids.^{9,11} This multi-targeted mode of action-affecting membranes, proteins, nucleic acids, and metabolism-may reduce the likelihood of resistance development relative to single-target antimicrobials.⁶⁷

Why Nanoparticles are Promising for Endodontic Irrigation

In endodontics, the ongoing difficulty of eliminating intracanal biofilms using only traditional chemo-mechanical methods is what led to the study of NPs.^{3,65} Endodontic biofilms consist of approximately 10–15% bacterial cells embedded within an EPS matrix, which constitutes about 85–90% of the total composition. This matrix makes things more stable and helps fight off germs at the same time.⁶⁴ *E. faecalis* is one of the most important organisms that has been linked to chronic illness.³

There is a chance that common irrigants such as NaOCl, CHX, and EDTA will break down quickly or only release active chemicals for a short time, which will limit the antibacterial effects that are kept.¹¹ The NPs might be able to get around these problems by going deeper into dentinal tubules and biofilms. Additionally, they might have antibacterial effects that last longer because they are released in a controlled way.¹¹ Their large surface area makes it easier for them to interact with microbial targets, but their very small size makes it easier to reach the complex canal structure.⁶⁷

Evidence supporting specific systems includes reports that AgNPs show efficacy comparable to 5.25% NaOCl against *E. faecalis*.⁶⁸ ZnO NPs have been reported to increase antibacterial activity and reduce bacterial adhesion to dentin walls by up to 95%.⁶⁸ TiO₂ NPs in irrigation solutions have been associated with increased fracture resistance of treated roots.⁶⁸ MgONP solutions (5–10 mg/L) demonstrate antibacterial efficacy comparable to 5.25% NaOCl and 2% CHX against common endodontic pathogens.⁶⁸ In addition, chitosan nanoparticles (CNPs) exhibit chelating capacity and can dissolve inorganic smear layer components.^{69,70} As final irrigants, 0.2% CNPs have shown smear layer removal comparable to 17% EDTA, while producing higher dentin microhardness and lower surface roughness.⁷⁰ CNPs may also penetrate dentinal tubules and maintain antimicrobial effects for up to three months.⁷¹ Graphene oxide (GO) nanosheets have been reported to disrupt established biofilms by penetrating the EPS matrix.^{66,71}

Nanoparticles in Endodontic Irrigation: Overview of Main Classes

Figure 3 illustrates the representative nanoparticle classes discussed in relation to endodontic irrigation.

Metallic and Metal Oxide Nanoparticles (Ag, ZnO, TiO₂, MgO)

- Silver nanoparticles (AgNPs): The AgNPs, which are 1 to 100 nm in size, may get into the small spaces of root canals and dentinal tubules, which makes disinfection better.^{65,67} They kill bacteria by making ROS, breaking down DNA, and stopping adenosine triphosphate (ATP) synthesis.⁷¹ AgNPs work as well as 5.25% NaOCl against *E. faecalis* when used as irrigants.⁶⁸ Long-term exposure may cause bacteria to adapt or become resistant, and AgNPs may change the color of dentin and be cytotoxic in a way that depends on their concentration.^{68,71}
- Zinc oxide nanoparticles (ZnONPs): ZnONPs stop *E. faecalis* from forming biofilms and make it much harder for bacteria to stick to surfaces.⁶⁶ As irrigants, they might cut down on how much bacteria stick to dentin walls by as much as 95%.⁶⁸
- Titanium dioxide nanoparticles (TiO₂NPs) are generally biocompatible and possess photocatalytic antimicrobial properties. Studies have shown that they make endodontically treated roots more resistant to breaking in irrigation solutions.⁶⁸



Figure 3 Representative nanoparticle classes in endodontic irrigation.

- Magnesium oxide nanoparticles (MgONPs): Aqueous MgONP solutions (5–10 mg/L) demonstrate antibacterial efficacy comparable to 5.25% NaOCl and 2% CHX against *Candida albicans* (*C. albicans*), *Staphylococcus aureus* (*S. aureus*), and *E. faecalis*.⁶⁸

Polymeric Nanoparticles (Chitosan)

Chitosan is a natural polysaccharide that kills bacteria by interacting with their membranes through electrostatic forces. This makes the membranes more permeable, which kills the cells.^{11,71} The CNPs have chelating properties that facilitate breaking down the inorganic smear layer components.^{69,70} As a final irrigant, 0.2% CNPs removed smear layers better than NaOCl and as well as 17% EDTA. CNPs had a higher microhardness (49.88 ± 2.34 Vickers hardness number (VHN)) than EDTA (45.04 ± 4.02 VHN) and a lower surface roughness (0.84 ± 0.23 μm) than EDTA (2.41 ± 0.09 μm). This means that they could be used instead of EDTA for final irrigation.⁷⁰

Carbon-Based Nanomaterials (Graphene Oxide)

The GO nanosheets exhibit antibacterial properties through physical membrane disruption, commonly known as the “nano-knife” effect, and the generation of ROS.^{71,72} GO might disrupt established biofilms by penetrating the EPS matrix and hindering quorum sensing (QS).^{66,71} Some researchers think that silver nanoparticle-graphene oxide composites (AgNPs-GO composites) could be good alternatives to NaOCl for irrigation.⁶⁸

Mechanisms of Antimicrobial Action of Nanoparticles

A significant feature of nanoparticle-assisted irrigation strategies is their ability to operate through multiple antimicrobial pathways rather than depending on a single chemical mechanism.

Physicochemical Basis of Activity

The physicochemical properties of NPs have a big effect on how well they kill bacteria or other microorganisms. Because they have a larger surface area, smaller particles are often more active because they can more easily come into contact with microbial targets. The 5 nm AgNPs, for instance, have been shown to have stronger effects.⁷¹ A positive surface charge increases the electrostatic attraction to bacterial cell envelopes that have a negative charge. This helps the bacteria stick to the surface, which can then damage and break down the cell membrane. The shape of the particles, the chemistry of their surfaces, and their composition all have a big effect on how well NPs kill bacteria and how they work in the body.^{6,71}

Contact-Mediated Killing and Membrane Disruption

Direct contact is one of the main ways that NPs kill microbes. Positively charged NPs stick to the walls of bacterial cells, which can change the shape of the cell, make the membrane more permeable, and sometimes even break the membrane, letting the cell’s contents leak out.⁷¹ This mechanism is particularly relevant for cationic polymeric systems such as chitosan, where membrane interaction constitutes a primary route of bactericidal action.

Reactive Oxygen Species Generation and Oxidative Stress

The H_2O_2 and hydroxyl radicals (OH) are two examples of the ROS (ROS) that many NPs produce; these radicals cause oxidative stress and harm to the lipids, proteins, and nucleic acids of bacteria.⁷¹ The PDT accelerates the generation of ROS following irradiation, and other activation-dependent techniques are predicated on this mechanism, which is especially crucial for metallic and metal oxide NPs.⁶

Metal Ion Release

The antibacterial effect of metallic and metal oxide NPs may be amplified by the release of ions, such as silver (Ag^+) and zinc (Zn^{2+}), which disrupt metabolic processes, bind to proteins, and impede enzyme activity.⁷¹ This is why ion release is a good addition to contact-mediated and oxidative processes; it often makes these systems work on more than one target at a time.

Biofilm Penetration and Extracellular Polymeric Substance Disruption

Because they are so small, NPs can get into dentinal tubules and the extracellular polymeric substance (EPS) matrix. This could let them get to microbial niches that regular irrigants cannot reach.^{71,73} Additional evidence indicates that AgNPs may inhibit biofilm development by reducing EPS production, thereby compromising biofilm integrity.⁷³

Inhibition of Quorum Sensing (QS)

The QS controls biofilm growth, pathogenicity, and coordinated behavior in a community. Some NPs, such as AgNPs and chitosan-based systems, can mess with this.^{71,73} So, antibiofilm effectiveness may come from both disrupting QS and killing bacteria directly.

Interaction of Nanoparticles with Dentin

Nanoparticle (NP)-based systems differ from traditional irrigants because they aim to preserve dentin structure, which is becoming a key goal in modern endodontics, not just eliminating bacteria.

Smear Layer Removal and Surface Morphology

It is very important to eliminate the smear layer so that disinfectants can work well and irrigants can get into dentinal tubules. The CNPs are chelating agents that are effective at getting rid of the smear layer while causing less erosion of the dentin than EDTA.^{70,74} This means that CNPs have been linked to less roughness on the surface after treatment than EDTA, which suggests that they protect the dentin microstructure better.⁷⁰

Impact on the Exposed Collagen Matrix

Traditional irrigants can harm the organic parts of dentin. For example, NaOCl breaks down collagen, and EDTA can cause collagen to change shape in some situations. On the other hand, CNPs may stick to dentin collagen, which would make the collagen matrix stronger and less likely to break down, which could make it more resistant to fractures.⁷¹ In studies that compared the two, biosynthesized AgNPs were found to keep the structure of collagen better than NaOCl.⁷⁵

Mechanical Properties and Microhardness

Irrigants may change the way dentin works mechanically, especially its microhardness. EDTA and NaOCl are often linked to lower microhardness because they cause demineralization and/or degradation of the organic matrix. The CNPs, on the other hand, are linked to higher microhardness values than EDTA, which means that less mineral is lost and demineralization is less violent.^{70,74}

Dentin Discoloration

One clinically important drawback of AgNPs is that they can cause dentin to change color or turn black when silver sulfide precipitates are made.^{67,71} On the other hand, other nanoparticle systems, such as chitosan (CS), titanium dioxide (TiO₂), and zinc oxide (ZnO), have not been linked to clinically significant discoloration very often.^{63,71}

Chemical, Remineralisation, and Regenerative Effects

Some NP systems may offer extra benefits for endodontic results in addition to disinfection. Chitosan has been shown to help remineralization by making crystals form on dentin collagen.⁷⁰ Nano-hydroxyapatite (nHAp) may get into dentinal tubules and block them, making it easier to seal them and add minerals back to them.¹¹ In addition, bioactive glass (BG) and mesoporous calcium silicate nanoparticles (MCSNs) can release ions that create an antibacterial environment and promote apatite formation, aligning with regenerative and reparative objectives.⁷¹

How Nanoparticles Work with Tissues Around the Teeth

For clinical translation, antimicrobial performance must be considered alongside biologic compatibility and host-tissue responses.

Cytotoxicity to Fibroblasts and Oral Cells

Biocompatibility is critical for clinical translation, particularly for irrigants that may contact periapical tissues. The cytotoxicity of nanoparticle systems is formulation-dependent and may be influenced by particle size, surface charge, coating, dissolution behavior, concentration, exposure duration, and the target cell type.^{6,66,67,76,77} Accordingly, safety cannot be generalized across nanoparticle classes or even across preparations within the same class, and biologic interpretation should consider the physicochemical characteristics of each formulation.^{6,66,67}

- Silver nanoparticles (AgNPs): Toxicity is frequently linked to the release of Ag⁺ ions and the generation of ROS, typically escalating with increased concentrations. Numerous studies demonstrate that optimizing formulations—by modifying particle size and surface characteristics—can enhance cytocompatibility at reduced doses, indicating that safety cannot be universally applied to all AgNP preparations.^{66,67}
- Zinc oxide nanoparticles (ZnO NPs): Zinc oxide nanoparticles (ZnO NPs) are frequently regarded as less toxic to fibroblasts compared to AgNPs; however, outcomes may differ based on particle size, shape, and the specific cell types examined.⁷⁶
- Iron oxide nanoparticles (IONPs): Numerous studies indicate that iron oxide nanoparticles (IONPs) exhibit low cytotoxicity and favorable biocompatibility, thereby endorsing their prospective applications—particularly in contexts that leverage magnetic activation or directed distribution.⁷⁷
- Polymeric nanoparticles: They are often seen as safer options because they are generally more biocompatible and may reduce the harmful effects that can happen with metal-based materials, especially when they interact with ions. Still, you should not assume that something is biologically compatible just because of the base polymer composition. Realistic biological evaluation is crucial, as formulation-specific factors—such as crosslinking components, residual solvent traces, surface functionalization, and particle charge characteristics—can significantly influence cellular behavior and host tissue responses.⁶

Effects on Dental Pulp Stem Cells and Regenerative Potential

In regenerative endodontics, it is very important for disinfection methods to keep dental pulp stem cells (DPSCs) alive and help tissue heal.

- Nano-hydroxyapatite (nHAp): Because it is similar to natural apatite found in teeth and bone, nHAp is thought to be very biocompatible. It has also been linked to the production of reparative dentin.^{11,78}
- Chitosan nanoparticles (CNPs): Chitosan-based systems are well known for being biocompatible and have been proposed as parts of disinfection methods that are compatible with regeneration. However, the results may vary depending on the molecular properties and formulation parameters.^{63,64}
- Bioactive glass nanoparticles (BGNPs): BGNPs systems may help the development of dentin bridges with little inflammation and have been shown not to slow down DPSCs growth, which is in line with their high levels of bioactivity and ability to regenerate.¹¹

Inflammatory Response and Host-Tissue Compatibility

In addition to direct cytotoxicity, nanoparticle formulations may influence inflammatory signaling and host-tissue responses that are relevant to periapical healing.

- Silver nanoparticles: Some models show that AgNPs may have anti-inflammatory effects by stopping the production of pro-inflammatory cytokines. However, these effects depend on the formulation and dosage.⁶⁷
- CNPs: The antibacterial effects of chitosan may be lessened by clinically important “tissue inhibitors,” such as pulp-derived components and serum albumin. This shows how important it is to test settings that are very similar to those in body.⁶⁶ Functionalized systems, exemplified by rose bengal–chitosan nanoparticles, are proposed to

amalgamate antibacterial and anti-inflammatory attributes, encompassing lipopolysaccharide (LPS) inactivation and diminished inflammatory markers upon photoactivation.⁶⁶

Discussion

Interpretation of the Findings

Overall, the included preclinical studies suggest that nanoparticle-assisted irrigation strategies may enhance antimicrobial and antibiofilm activity and, in some settings, support more favorable dentin-related or biologic outcomes than conventional approaches. However, the evidence remains heterogeneous across nanoparticle platforms, activation methods, study models, and reported endpoints, which limits direct comparison and precludes quantitative synthesis. Accordingly, the findings should be interpreted as promising but preliminary preclinical evidence rather than definitive support for routine clinical use.

Limitations and Safety Considerations

Although nanoparticle-based irrigation offers several potential advantages, its safety, possible toxicity, and clinical reliability must be carefully evaluated before clinical use. This review was also limited by restriction to English-language studies, use of two electronic databases, and substantial methodological heterogeneity across the included preclinical studies, which precluded meta-analysis and formal certainty assessment.

Nanotoxicology and Risk Assessment

Small size, high surface area, and greater reactivity are all things that make antimicrobial drugs work better. However, these same things can also make them more toxic, so each NP formulation needs to be carefully evaluated for risk.⁶⁶ The endodontic failure rate, which is always between 18% and 26%, shows that we need better ways to disinfect. However, candidate nanomaterials need to be tested in conditions that really show how biofilms behave and how the root canal environment limits them.^{64,65} In addition, tissue-derived inhibitors such as serum albumin may alter nanoparticle behavior and antimicrobial performance, further emphasizing the need for *ex vivo* and *in vivo* models that better reflect clinical exposure conditions and biological complexity.⁶⁶

Local and Systemic Adverse Effects

- Silver nanoparticles: Dentin discoloration and dose-dependent cytotoxicity to mammalian cells are the main problems. These are often linked to free Ag⁺ release and oxidative stress caused by ROS.^{66,67}
- Systemic exposure considerations: NP biodistribution is size-dependent; very small particles may undergo rapid clearance, whereas larger particles may be sequestered by the reticuloendothelial system. Accordingly, design must balance canal penetration and antimicrobial efficacy against the need to minimise systemic exposure risk, particularly in the context of potential apical extrusion.⁶⁴

Approaches to Toxicity Assessment

Although many studies report promising *in vitro* findings, robust translation requires clinically relevant models and *in vivo* confirmation, particularly where irrigants may contact periapical tissues.⁶⁶ The current evidence base is limited by inconsistencies in experimental design, variable reporting of NP synthesis/characterisation, and a relative lack of clinical data, contributing to reduced certainty of conclusions.⁶ Comprehensive physicochemical characterization, particularly particle size distribution, surface charge, morphology, coating, and dissolution kinetics, is essential for interpreting both efficacy and biocompatibility outcomes and for enabling meaningful comparison across studies.^{3,64}

Design Strategies to Reduce Nanotoxicity

Multiple “safer-by-design” strategies have been proposed to optimise the balance between antimicrobial efficacy and host compatibility.

- Formulation engineering: For example, positively charged ~9 nm AgNPs have shown strong antibacterial activity while remaining cytocompatible to fibroblasts, illustrating how tuning particle size and surface charge can improve the benefit–risk profile.⁶⁶
- Encapsulation and controlled release: Mesoporous or inorganic carriers (eg., silica coatings) can encapsulate AgNPs to support sustained ion release while reducing acute cytotoxicity compared with free AgNPs.^{66,67}
- Polymeric nanoparticle platforms: Polymeric systems may offer a relative safety advantage by enabling controlled, sustained delivery and reducing reliance on high-concentration bolus exposure, although they still require rigorous evaluation due to formulation-dependent effects.⁶
- Activation-dependent systems: The PDT is one method that uses light to stimulate NPs to make more ROS. This allows for spatial and temporal control of antimicrobial effects and may reduce host-tissue exposure when done correctly.^{11,79}

Clinical Implications and Future Directions

Although several included studies reported favorable antimicrobial, dentin-related, or biologic findings under controlled experimental conditions, the current evidence base remains limited to preclinical *in vitro*, *ex vivo*, and laboratory/*in vivo* models.^{51–62} Broader literature also highlights formulation variability, incomplete protocol standardization, and the absence of clinical trials as major barriers to clinical translation.^{3,6,8,66} Accordingly, nanoparticle-assisted irrigation is not yet established in routine clinical practice. At present, these approaches are more reasonably viewed as adjunctive strategies, such as final-rinse or activation-assisted protocols, rather than direct replacements for conventional irrigants.^{51,53,54,57–62} This broader concept is also supported by non-nanoparticle activation-assisted irrigation studies, such as the SMART approach, which have reported enhanced microbial reduction and root canal cleaning with synergistic irrigant–activation protocols.⁸⁰ Further standardized preclinical investigations and well-designed animal and clinical studies are required to define optimal formulation, dosage, delivery, safety, and true clinical benefit.^{3,6,8,66}

Conclusions

Across the included preclinical studies, nanoparticle-assisted irrigation strategies showed promising antimicrobial and antibiofilm effects, particularly in *Enterococcus faecalis* root canal models. Findings related to smear-layer removal, dentin preservation, and mechanical outcomes were more variable across studies. In addition, biologic and regeneration-related observations, including growth-factor release, cytocompatibility, and healing-related responses, remain preliminary and are based on limited experimental evidence.

Because the current evidence is derived mainly from heterogeneous *in vitro*, *ex vivo*, and laboratory/*in vivo* models, nanoparticle-assisted systems should be regarded as promising adjunctive strategies rather than established clinical alternatives to conventional irrigants. At present, the evidence is strongest for antimicrobial and antibiofilm potential in controlled models, more mixed for dentin-related outcomes, and still preliminary for regenerative relevance, long-term substantivity, safety, and clinical superiority over established irrigants. Further standardized preclinical investigations and well-designed *in vivo* and clinical studies are required before routine clinical implementation can be recommended.

Data Sharing Statement

The data supporting the findings of this review are available from the corresponding author upon reasonable request. No analytic code was generated for this systematic review.

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