# Intracanal Medicaments: Current Evidence and Future Directions


## Keywords

Intracanal medicaments; Calcium hydroxide; Chlorhexidine; Root canal disinfection; Endodontic biofilms; Enterococcus faecalis; Nanotechnology; Antimicrobial peptides; Herbal intracanal medicaments; Sustained-release drug delivery; Activation techniques; Regenerative endodontics



## Abstract

Successful endodontic therapy depends on the effective elimination of microorganisms from the root canal system. Despite advances in rotary instrumentation, irrigation solutions, and activation techniques, complete disinfection remains difficult due to the complex root canal anatomy, presence of dentinal tubules, and persistence of biofilm-forming microorganisms such as *Enterococcus faecalis*. Intracanal medicaments, therefore, remain an essential adjunct to chemomechanical preparation by providing sustained antimicrobial activity between appointments, neutralizing bacterial endotoxins, and promoting periapical healing.

This literature review critically analyzes current evidence related to intracanal medicaments, including conventional agents, emerging bioactive materials, novel drug delivery systems, and future therapeutic directions. Calcium hydroxide continues to be the most widely used intracanal medicament and the clinical gold standard because of its high alkalinity, antimicrobial properties, and extensive clinical validation. However, its limitations, particularly reduced efficacy against resistant microorganisms, limited dentinal tubule penetration, and incomplete biofilm disruption, have driven the search for alternative or adjunctive strategies. Chlorhexidine and antibiotic-based medicaments offer broader antimicrobial spectra but are associated with concerns related to cytotoxicity, discoloration, and the potential for antimicrobial resistance.Recent research highlights the promise of emerging intracanal medicaments incorporating nanotechnology, antimicrobial peptides, and herbal or natural agents, which demonstrate enhanced antimicrobial efficacy, improved biofilm disruption, and favorable biocompatibility in experimental studies. In addition, sustained-release and smart delivery systems aim to maintain therapeutic drug concentrations over extended periods while minimizing adverse effects. Activation techniques, including sonic and ultrasonic systems, further enhance medicament penetration and effectiveness.Future directions emphasize precision-based, biologically driven endodontic therapies that integrate antimicrobial control with regenerative and host-modulatory potential. Continued translational research and high-quality clinical trials are required to support the clinical adoption of these advanced intracanal medicaments.


## Rationale for Intracanal Medicaments

The success of endodontic treatment relies on thoroughly eliminating microorganisms from the root canal system and preventing reinfection. Although modern techniques, including rotary

instrumentation and irrigating solutions such as sodium hypochlorite and EDTA, have significantly improved canal cleaning, achieving complete disinfection remains challenging.[1]

**a) Complexity of Root Canal Anatomy**

Complete debridement of the root canal system remains difficult due to its highly complex internal architecture. Anatomical structures such as apical ramifications, lateral and accessory canals, dentinal tubules, and isthmuses cannot be fully instrumented and often receive insufficient penetration from conventional irrigants.[2] As a result, microorganisms may persist in these inaccessible areas.

**b) Need for Sustained Antimicrobial Action**

Given the limitations of mechanical instrumentation and the transient action of irrigating solutions, intracanal medicaments serve as an effective means of delivering continuous antimicrobial activity between treatment visits. Their prolonged presence within the canal allows sustained exposure of residual microorganisms, which is particularly important in combating biofilm-forming bacteria that exhibit increased resistance to routine disinfection protocols.[3]

**c) Role Against Persistent Endodontic Pathogens**

Enterococcus faecalis biofilms play a critical role in the development of persistent and secondary endodontic infections. These microorganisms are capable of surviving under unfavorable conditions, penetrating deep into dentinal tubules, and tolerating elevated pH levels. Intracanal medicaments are essential in disrupting biofilms and inhibiting bacterial regrowth during inter-appointment periods.[4]

**d) Neutralization of Endotoxins and Periapical Healing**

A significant advantage of intracanal medicaments is their ability to inactivate bacterial endotoxins, particularly lipopolysaccharides produced by gram-negative bacteria. These endotoxins contribute to periapical inflammation and alveolar bone resorption. By reducing inflammatory mediator activity, intracanal medicaments promote periapical healing and help minimize postoperative pain and flare-ups.[5]

**e) Clinical Indications in Multi-Visit Endodontics**

In multi-visit endodontic procedures, intracanal medicaments are indispensable when immediate obturation is not feasible, such as in cases of persistent exudation, acute infection, or retreatment. These medicaments help maintain canal sterility, reduce bacterial load, and improve the predictability of treatment outcomes. While single-visit endodontics may be appropriate in selected cases, complex infections often require inter-appointment medicament placement.[6]

**f) Overall Significance in Contemporary Endodontics**

Overall, intracanal medicaments serve as essential biological adjuncts that complement mechanical and chemical canal preparation. Their ability to maintain prolonged antimicrobial activity, penetrate dentinal tubules, neutralize endotoxins, and reduce postoperative discomfort underscores their enduring importance in contemporary endodontic practice (Figure 1).[7]

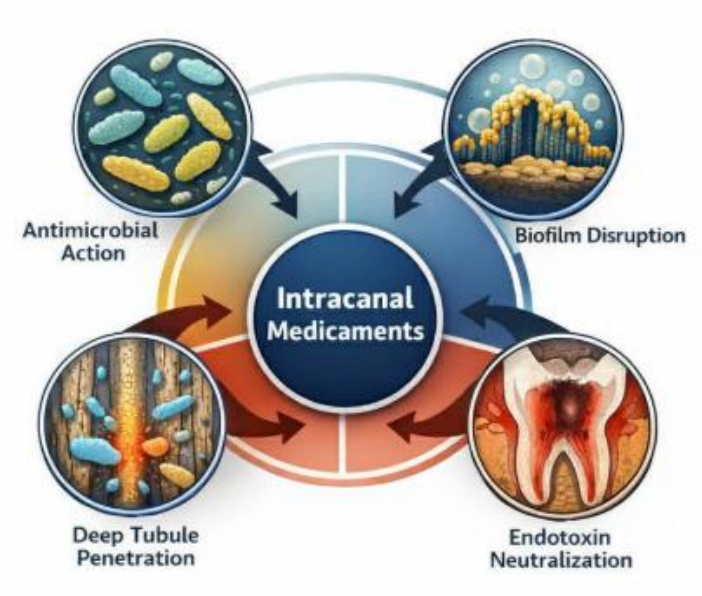


*Figure 1: Synergistic role of intracanal medicaments in enhancing root canal disinfection.*

## Conventional Intracanal Medicaments

Chemo-mechanical preparation requires adjuncts like intracanal medicaments to reduce residual microbial load within the root canal system. Due to anatomical complexities such as lateral canals, isthmuses, and dentinal tubules, complete microbial elimination by instrumentation and irrigation alone is often unachievable. These remaining microorganisms get suppressed by conventional intracanal medicaments and also help prevent recolonization between appointments and promote periapical healing.[8] Calcium hydroxide, chlorhexidine, and antibiotic-based medicaments are some of the most extensively studied and clinically applied intracanal agents.[9]

### a) Calcium Hydroxide

Calcium hydroxide is the most widely used intracanal medicament used in endodontics and is often considered the benchmark against which other medicaments are compared to.[9] Its high pH which is exceeding 12, is the primary reason for its antimicrobial action resulting in bacterial membrane damage, protein denaturation, and enzymatic inactivation.[9,10]

In addition to its antibacterial effects, calcium hydroxide is also valuable in cases involving periapical lesions and immature teeth as it neutralizes bacterial endotoxins and also promotes hard tissue formation. However, studies have demonstrated that calcium hydroxide has reduced effectiveness against resistant microorganisms such as Enterococcus faecalis and Candida albicans. The buffering capacity of dentin and tissue fluids further diminishes its long-term antimicrobial efficacy.[9,10,11]

**b) Chlorhexidine**

Chlorhexidine is a broad-spectrum antimicrobial agent that is commonly used as an intracanal medicament. It is usually used in concentrations ranging from 0.2% to 2% and acts by disrupting the integrity of bacterial cell membranes, leading to leakage of intracellular contents and finally bacterial cell death.[12]

A major advantage of chlorhexidine is its substantivity, which allows prolonged antimicrobial activity due to adsorption onto the dentin surfaces[5]. Its effectiveness against Enterococcus faecalis has been well documented, particularly in cases of persistent endodontic infection. However, chlorhexidine lacks tissue-dissolving properties and does not neutralize endotoxins. Furthermore, its interaction with sodium hypochlorite can result in the formation of a potentially toxic precipitate, necessitating careful clinical protocols.[11,12]

**c) Antibiotic-Based Medicaments**

Antibiotic-based intracanal medicaments were developed to address polymicrobial infections resistant to conventional disinfectants.[13] The triple antibiotic paste which is the most commonly used formulation, consists of metronidazole, ciprofloxacin, and minocycline, provides broad antimicrobial coverage against both aerobic and anaerobic bacteria.[13]

These medicaments have shown particular clinical relevance in regenerative endodontic procedures and the management of immature teeth with necrotic pulps.[13] Despite their antimicrobial efficacy, concerns exist regarding bacterial resistance, tooth discoloration caused by minocycline, potential allergic reactions, and cytotoxic effects on stem cells of the apical papilla.[14] As a result, antibiotic-based medicaments are recommended primarily for selective clinical indications rather than routine endodontic use.[14]

## Emerging and Novel Intracanal Medicaments

Persistent intraradicular infection and biofilm-mediated resistance remain major challenges in endodontic therapy, particularly against microorganisms such as *Enterococcus faecalis*. Conventional intracanal medicaments often exhibit limited dentinal tubule penetration and reduced efficacy against mature biofilms, necessitating the development of advanced therapeutic alternatives.[15]

**a) Nanotechnology-Based Medicaments**

Nanotechnology-based intracanal medicaments have attracted increasing interest due to their nanoscale dimensions, enhanced surface area, and improved physicochemical reactivity, which collectively enable superior penetration into dentinal tubules and disruption of microbial biofilms .[16] Nanoparticles such as silver, chitosan, zinc oxide, and bioactive glass have demonstrated significant antimicrobial activity against endodontic pathogens.[17]

Silver nanoparticles exert antimicrobial effects through multiple mechanisms, including bacterial membrane disruption, reactive oxygen species generation, and interference with DNA replication.[18] Studies have shown that silver nanoparticles, either alone or combined with calcium hydroxide, exhibit enhanced antibiofilm efficacy compared with conventional calcium hydroxide formulations.[19] Chitosan nanoparticles additionally offer favorable properties such as biodegradability, bioadhesion, and intrinsic antimicrobial activity, making them promising intracanal agents.[17]

Nano-calcium hydroxide has been developed to overcome the limited effectiveness of conventional calcium hydroxide against resistant microorganisms. The reduced particle size facilitates deeper dentinal penetration and sustained calcium ion release, resulting in improved antimicrobial efficacy.[20] Despite encouraging in vitro and ex vivo findings, concerns related to cytotoxicity, long-term biocompatibility, and clinical translation remain, highlighting the need for further in vivo studies.[16]

**b) Antimicrobial Peptides**

Antimicrobial peptides (AMPs) are short cationic molecules that form part of the innate immune defense and exhibit broad-spectrum antimicrobial activity. Their primary mechanism involves electrostatic interaction with negatively charged microbial membranes, leading to membrane destabilization and rapid cell death.[21]

In endodontics, AMPs such as defensins, histatins, and synthetic peptide analogs have demonstrated potent antimicrobial and antibiofilm activity against *E. faecalis*, even within complex root canal biofilms.[22] Unlike conventional antibiotics, AMPs have a low propensity for resistance development due to their non-specific and rapid mechanism of action.[21] However, their clinical application is currently limited by high production costs, susceptibility to enzymatic degradation, and reduced stability in the dentin-rich environment .[22]

**c)Herbal and Natural Medicaments**

Herbal and natural intracanal medicaments have gained renewed attention due to their favorable biocompatibility, antimicrobial properties, and patient acceptance. Agents such as propolis, neem (*Azadirachta indica*), turmeric (*Curcuma longa*), aloe vera, and *Morinda citrifolia* have demonstrated antimicrobial efficacy against endodontic pathogens, along with anti-inflammatory and antioxidant effects.[23]

Propolis has shown significant antibacterial activity against *E. faecalis* with lower cytotoxicity compared to calcium hydroxide, while neem extracts inhibit bacterial adhesion and biofilm formation.[23] Curcumin, the active constituent of turmeric, provides additional anti-inflammatory

benefits, and aloe vera has demonstrated antimicrobial activity with minimal adverse effects on dentin microhardness.[24] Despite promising laboratory evidence, lack of standardization and limited high-quality clinical trials restrict the routine clinical use of herbal medicaments.[23]

## Advanced Delivery Systems and Activation Techniques

### Sustained-Release Systems

The evolution of endodontic therapy has highlighted the need for medicaments capable of maintaining prolonged antimicrobial activity within the root canal system, especially between appointments. Conventional intracanal medicaments, although initially effective, often exhibit rapid dissociation and insufficient penetration into deeper dentin, leading to inconsistent therapeutic outcomes.[25] Sustained-release delivery systems address these shortcomings by providing controlled and extended drug release profiles, maintaining therapeutic concentrations for longer durations, and improving penetration into complex anatomical regions while minimising cytotoxicity.[26]

### Polymer-Based Systems

Biodegradable polymer carriers such as polylactic-co-glycolic acid have become central to sustained-release applications in endodontics due to their biocompatibility and predictable degradation behaviour.[27] PLGA microspheres release drugs through an initial diffusion phase followed by polymer matrix erosion, producing a biphasic release pattern characterised by an early burst and extended maintenance phase.[27] In vitro studies demonstrate that PLGA microspheres loaded with modified triple antibiotic pastes can sustain antimicrobial release for up to 21 days, with initial high concentrations including 31 µg/mL ciprofloxacin, 160 µg/mL metronidazole, and 18 µg/mL penicillin G, followed by a gradual decline.[27]

In addition to microspheres, polymer-based gels incorporating antimicrobial agents such as cetylpyridinium chloride have shown favorable handling characteristics, controlled viscosity, and the ability to solidify in situ upon exposure to intracanal moisture.[28] These hydrophilic gels, composed of polymethacrylate and ammoniomethacrylate matrices, form a fluid-tight seal that inhibits periapical fluid influx while ensuring sustained drug delivery for up to 14 days.[28] Their release profiles follow an initial burst on day one, transitioning to steady, moderate release rates thereafter.[28]

### Ceramic and Hybrid Microparticle Systems

Ceramic-based systems involving β-tricalcium phosphate and hydroxyapatite microparticles represent another promising avenue for intracanal drug delivery.[27] These bioactive materials, typically 150–240 nm in size, feature smooth spherical morphologies to reduce inflammatory reactions.[27] When coated with PLGA and loaded with antimicrobial agents, these hybrid microparticles synergize the osteoconductive properties of ceramics with the controlled-release functions of polymers.[27] Their Ca/P ratio of 1.8 supports bioactivity and potential periapical tissue regeneration.[27] Material characterisation using energy dispersive X-ray spectroscopy and FTIR confirms structural stability following drug loading.[27] Encapsulation efficiency depends on polymer concentration, drug saturation levels, and coating conditions, all of which can be optimized for enhanced drug loading without compromising particle stability.[27]

Mechanisms of Sustained Release

In polymeric systems, drug release is governed by surface diffusion and gradual polymer degradation.[27] The initial burst derives from dissolution of drug molecules near the particle surface.[28] Subsequent sustained release depends on diffusion through the polymer matrix and hydrolytic cleavage of PLGA's ester bonds, which drive mass based degradation.[27] Hydrogel systems differ by relying on polymer swelling properties and solvent interactions; the inclusion of N-methyl-2-pyrrolidone enhances drug solubility and enables uniform gel formation with clinically favourable viscosity.[28]

**Clinical Advantages and Applications**

Sustained-release formulations offer significant benefits over conventional pastes by achieving deeper dentinal penetration up to 400 μm while maintaining effective antimicrobial concentrations for longer durations.[28] Comparative studies show markedly lower colony-forming units at both superficial (200 μm) and deep (400 μm) dentin levels at 1, 7, and 14 days when using sustained-release gels containing cetylpyridinium chloride, outperforming calcium hydroxide and chlorhexidine gel ($P < 0.001$).[28]

Their physical properties, ideal viscosity, syringe-based delivery, and moisture-induced solidification allow effective placement and formation of a coronal seal that limits reinfection.[28] Additionally, polymer-based systems are easier to remove than calcium hydroxide, which can leave residues that interfere with sealer adaptation.[25,29]

Sustained-release systems also show strong antimicrobial activity against resistant pathogens such as Enterococcus faecalis and Aggregatibacter actinomycetemcomitans.[27,28] Inhibition zones of 25.3 mm and 42.3 mm, respectively, have been observed within 24 hours, with antimicrobial effects persisting up to 48 hours.[27] Minimum inhibitory concentration analyses further demonstrate broad-spectrum efficacy, with activity maintained at dilutions up to 1:256 .[27]

Biocompatibility and Safety Cytotoxicity assessment using MTT assays on human gingival fibroblasts shows cell viability exceeding 70% at 24 and 72 hours, meeting ISO 10993-5 biocompatibility standards.[27] The polymethacrylate and ammoniomethacrylate matrices in sustained-release gels have also been validated as safe in studies involving human mesenchymal stem cells .[28] Their near-physiological pH over 7 days minimizes potential tissue irritation.[27]

**Recent Innovations**

To avoid discoloration associated with minocycline, recent research has replaced it with penicillin G in modified triple antibiotic formulations .[27] The combination of penicillin G, metronidazole, and ciprofloxacin maintains broad antimicrobial activity and reduces aesthetic concerns .[27] Incorporating these new antibiotic blends into PLGA-coated ceramic microparticles enhances their potential for regenerative endodontics and targeted drug delivery .[27]

## Activation Methods

Activation techniques are essential for enhancing irrigant penetration, improving fluid dynamics, and maximizing the effectiveness of intracanal medicaments. These methods are particularly important in complex root canal anatomies where conventional irrigation alone may be insufficient.[29]

**Ultrasonic Activation**

Passive ultrasonic irrigation (PUI) uses oscillating tips or files at frequencies of 25–40 kHz to generate acoustic microstreaming and cavitation.[29] Systems such as the COXO Ultra Smart (38 kHz) produce rapid vortex-like fluid motion, enabling improved debris removal and deeper antimicrobial penetration.[29] Ultrasonic activation has demonstrated superior removal of calcium hydroxide-iodoform paste compared with sonic activation, although complete removal is rarely achieved.[29] Typical clinical use involves placing the ultrasonic tip 2 mm short of working length to prevent extrusion while optimizing acoustic effects.[29] Protocols commonly combine 17% EDTA with ultrasonic activation in 30-second cycles for a total of 2 minutes.[29]

**Sonic Activation**

Sonic devices such as the EndoActivator (EQ-S) operate at lower frequencies (150–200 Hz) and use flexible polymer tips to agitate irrigants.[29] While safer and less aggressive than ultrasonics, sonic activation generates weaker acoustic streaming and little to no cavitation.[29] Studies show sonic activation to be less effective for removing calcium hydroxide-iodoform paste, although differences between activation methods are not statistically significant ($P = 0.209$).[29] Standard protocols use amplitudes of 2–4 mm and frequencies of 217 Hz.[29]

**XP-Endo Finisher**

The XP-endo Finisher utilizes the shape-memory properties of NiTi alloys, transitioning from a straight configuration (M-phase) to an expanded shape (A-phase) at body temperature.[29] With a core size of 25 and zero taper, the file can expand to a 6-mm diameter, accessing up to 100 times the area of similarly sized files.[29] Operating at 800 rpm and 1 Ncm torque, the file is activated for 60 seconds with gentle 5–6 mm in-and-out motions.[29] While it shows better medicament removal than sonic activation, its performance is comparable to ultrasonic activation.[29] Control over file-wall contact is limited, and longer operating times may be needed for complete medicament removal.[29]

**Comparative Effectiveness**

No activation method achieves complete elimination of intracanal medicaments.[29] Although trends favor ultrasonic activation followed by XP-endo Finisher and sonic activation, these differences are not statistically significant ($P = 0.206$).[29] Importantly, treatment success is multifactorial and influenced by canal preparation, irrigant chemistry, needle depth, volume, medicament type, and flow velocity.[29]. Clinical evidence indicates that minor remnants of calcium hydroxide do not necessarily compromise periapical healing.[25]

Integration of Sustained-Release Systems with Activation Techniques

Combining sustained-release systems with activation methods offers a comprehensive strategy for root canal disinfection. Sustained-release systems maintain antimicrobial efficacy between visits, while activation enhances initial distribution and facilitates removal prior to obturation .[28,29] The viscosity and in situ solidification properties of sustained-release gels ensure consistent placement, while their improved removability complements activation techniques .[28]. Optimizing the synergy between these modalities may contribute to improved clinical outcomes, particularly in complex or resistant infections.[25,28]

**a)Sustained-Release Systems, b)Activation Methods**

## Future Directions

### 5.1 Refining indications and patient-specific strategies

Over the next decade, intracanal medicament use is expected to move from routine placement in most multi-visit cases to more selective, indication-driven protocols. Recent reviews and expert statements emphasize tailoring medicament choice, concentration, and duration to factors such as lesion size, microbial complexity, systemic conditions, and whether the goal is conventional healing or regeneration.[3,30,31,35]

This shift will require integration of clinical findings with radiographic and, where feasible, microbiological or biomarker data to individualize medicament type, concentration, and duration. In complex or high-risk cases, prolonged use of potent, multi-target medicaments or combinations may be justified, whereas simpler cases with effective chemomechanical preparation might be managed successfully with minimal or no interappointment dressing, thereby shortening treatment time and reducing material-related adverse effects.[3,17]

### 5.2 Nanotechnology-driven multifunctional systems

Nanotechnology is expected to play a central role in the next generation of intracanal medicaments. Recent work has shown that chitosan, calcium-silicate, and bioactive glass nanoparticles can enhance penetration into dentinal tubules, provide sustained antimicrobial activity, and release bioactive ions that favor remineralization and tissue repair.[36,37,38]

A 2025 study on calcium-hydroxide-loaded nanoparticles demonstrated improved antibacterial efficacy, favorable pH profiles, and controlled drug release compared with conventional formulations, supporting their potential as advanced intracanal dressings.[38]

Beyond simple antimicrobial loading, future nanoparticle platforms are envisioned as multifunctional systems capable of delivering antimicrobial agents, anti-inflammatory molecules, and pro-regenerative cues simultaneously. To reach clinical practice, these systems will require standardized characterization, robust biocompatibility and discoloration assessments, and well-designed in vivo and clinical studies that define optimal particle types, concentrations, and exposure times within the root canal environment.[3,36,37,38]

### 5.3 Smart sustained-release carriers: hydrogels, fibers, and hybrid systems

Advanced delivery vehicles that provide controlled, localized release over clinically relevant intervals represent another major future direction. Injectable antimicrobial hydrogels and fibrous or microparticle systems have demonstrated the ability to sustain antibiotic or antiseptic release over several days while maintaining activity against endodontic pathogens.[39,40,41]

Emerging “smart” hydrogels and hybrid hydrogel–fiber constructs are designed to respond to environmental cues such as pH, enzymes, or inflammatory mediators, modulating drug release according to the local disease state.[41] Future intracanal medicaments are likely to exploit these

materials to achieve more predictable dosing in anatomically complex regions while optimizing handling, radiopacity, and compatibility with contemporary obturation techniques.[39,40,41]

### 5.4 Novel antimicrobial classes and host-modulating agents

There is growing interest in incorporating new classes of antimicrobials, particularly antimicrobial peptides (AMPs), as part of intracanal therapy. Recent reviews highlight that AMPs can show rapid, broad-spectrum antibiofilm activity with a lower propensity for resistance and can be immobilized within hydrogels or nanoparticle carriers to improve stability and controlled release inside the canal.[3,31,36,39]

At the same time, host-modulating medicaments aimed at attenuating destructive inflammation and promoting resolution could become especially important in regenerative endodontic procedures.[33,34,35] Botanical and herbal intracanal agents with demonstrated antimicrobial and antioxidant effects continue to attract attention, but future work must focus on standardizing their composition, defining safe and effective concentrations, and integrating them into advanced carriers rather than relying on crude extracts alone.[31,32,33]

### 5.5 Integration with regenerative endodontics

As regenerative endodontic procedures (REPs) gain wider acceptance, intracanal medicaments must be re-engineered to balance disinfection with preservation of stem cell viability and promotion of tissue regeneration. Recent consensus documents stress that high-concentration antibiotic pastes can be detrimental to stem cells of the apical papilla and may interfere with dentin matrix–derived growth factor release, prompting interest in low-dose antibiotic combinations, calcium hydroxide, and nano-engineered alternatives with reduced cytotoxicity.[34,35]

Newer studies evaluating chitosan- and bioactive glass–based nanomaterials, nano-hydroxyapatite, and bioactive hydrogels suggest that certain formulations can simultaneously reduce bacterial loads and support cell attachment, mineral deposition, and angiogenic signaling.[36,37,38] Future regenerative protocols are likely to employ staged or layered approaches in which early medicament phases prioritize disinfection, while later phases use bioactive carriers that deliver pro-regenerative molecules and provide a scaffold for pulp–dentin complex regeneration.[34,36,37,38]

### 5.6 Optimizing activation technologies in conservative preparations

Modern activation technologies such as sonic and ultrasonic agitation, multisonic devices, laser-assisted activation, and negative pressure systems are expected to be more tightly integrated with how intracanal medicaments are formulated and used.[3,30,35]

Recent reviews and consensus papers emphasize that medicament diffusion into isthmuses, fins, and lateral canals can be enhanced when activation parameters are optimized, especially

in minimally invasive preparations.[3,34,35] Looking forward, medicament development and activation research will likely proceed in parallel, with rheology, surface tension, and particle size engineered to work synergistically with specific activation protocols in conservative canal geometries.[3,30,35,36]

5.7 Methodological and translational advances

Progress in intracanal medicaments will depend not only on new materials but also on more rigorous and clinically relevant research designs. Recent articles have called for standardized multispecies biofilm models on dentin, clinically realistic exposure times, and endpoints that extend beyond colony counts to include biofilm architecture, resistance development, and host-tissue responses.[3,34,36]

Translationally, there is an increasing push toward high-quality clinical trials and registries, including ongoing studies comparing different intracanal medicaments in regenerative protocols.[42]Regulatory frameworks will need to adapt to complex combination products that merge drugs, biologics, and devices, necessitating collaboration among endodontists, material scientists, and regulators.[34,36,42]

## Conclusion

Intracanal medicaments continue to play a pivotal role in achieving effective microbial control during multi-visit endodontic therapy. Calcium hydroxide remains the most widely used and well-established medicament due to its high alkalinity, antimicrobial activity, tissue-dissolving ability, and long history of clinical success.[43] However, accumulating evidence has highlighted its limitations, particularly against resistant microorganisms such as Enterococcus faecalis, its reduced effectiveness within dentinal tubules, and its inability to completely disrupt mature biofilms.[44]

Recent advances in endodontic research have shifted focus toward emerging intracanal medicaments that integrate nanotechnology, biologically active molecules, and advanced delivery systems. Nanoparticle-based medicaments have demonstrated superior penetration into dentinal tubules, enhanced biofilm disruption, and sustained antimicrobial release compared with conventional formulations.[45] Nano-modified calcium hydroxide, silver nanoparticles, chitosan nanoparticles, and bioactive glass systems show particular promise as adjuncts or alternatives to traditional medicaments.[16]

Antimicrobial peptides represent a biologically inspired strategy that offers broad-spectrum antimicrobial activity with a low risk of resistance development. Their ability to target biofilm-associated pathogens and modulate host immune responses positions them as potential next-generation intracanal medicaments, although challenges related to stability, cost, and clinical translation remain.[22] Similarly, herbal and natural medicaments have gained attention due to their favorable biocompatibility, anti-inflammatory properties, and patient acceptance. Despite encouraging in vitro findings, their routine clinical application is limited by lack of standardization and insufficient high-quality clinical evidence.[46]

Future developments in intracanal medicaments are increasingly oriented toward multifunctional systems that combine antimicrobial efficacy with regenerative and host-modulatory potential. Smart delivery platforms, controlled-release systems, and bioactive materials capable of supporting periapical healing and tissue regeneration represent a paradigm shift toward biologically driven and precision-based endodontic care.[17,47] Nevertheless, robust in vivo studies and randomized clinical trials are essential to validate the safety, efficacy, and long-term outcomes of these emerging strategies.

In conclusion, while calcium hydroxide remains the current gold standard, emerging intracanal medicaments offer promising avenues to overcome the limitations of conventional therapies. The integration of nanotechnology, bioactive agents, and regenerative concepts has the potential to significantly enhance root canal disinfection and treatment predictability, shaping the future of contemporary endodontic practice.[48,49]

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