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Effectiveness of propolis nanoparticles as endodontic therapeutic agents: a systematic review

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ABSTRACT

Introduction: Persistent microbial biofilms and complex root canal anatomy continue to challenge effective endodontic disinfection. This systematic review aimed to evaluate the antimicrobial, antibiofilm, anti-inflammatory, and regenerative effects of propolis nanoparticles (PNPs) in endodontic applications.
Methods: A comprehensive search of Web of Science, PubMed, Scopus, EMBASE, and the Cochrane Library was conducted from database inception to April 2026 according to PRISMA guidelines. *In vitro*, animal, and clinical studies evaluating PNP-based delivery systems in endodontics were included. Risk of bias and methodological quality were assessed using Quality Assessment Tool for In Vitro Studies (QUIN), SYRCLE, and RoB 2 tools.
Results: Fifteen studies met the inclusion criteria, most of which were *in vitro* investigations. PNP-based systems demonstrated antimicrobial and antibiofilm activity, particularly against *Enterococcus faecalis*. Several studies also reported reduced inflammation, improved dentinal tubule penetration, sustained bioactive release, and favorable biocompatibility compared with conventional materials and pure propolis formulations.
Conclusion: PNPs show promising potential as adjunctive endodontic therapeutic agents due to their antimicrobial and biocompatible properties. However, current evidence is limited by the predominance of heterogeneous preclinical studies; well-designed clinical studies are required to confirm their efficacy and safety.

Implication for health policy/practice/research/medical education:
Propolis nanoparticles showed potential as effective, biocompatible alternatives or complementary treatments in endodontics. These results could provide a background for use as root canal irrigants, intracanal medicaments, and sealers, and support reduced toxicity in clinical practice. The emerging role of nanotechnology highlights the need for standardized regulatory frameworks to ensure safety and quality. Future research should prioritize well-designed clinical trials and standardized methods to confirm efficacy, investigate effective dosage, and their long-term efficacy and outcomes. Furthermore, the integration of nanotechnology-based approaches into medical and dental education could facilitate evidence-based adoption of these innovations in endodontic treatments.

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Introduction

The main goal of endodontic treatment is the prevention and management of pulpal and periapical pathologies, and the preservation of the tooth from pain, discomfort, apoptosis, and deep caries by eradicating microbial infection within the root canal system (1). This biological treatment method is based on root infection control, mechanical debridement, and chemical disinfection, which is finally completed by three-dimensional filling of the disinfected canal space (2). The efficacy of endodontic therapy is primarily determined by the successful biofilms within the intricate anatomy of the root canal system, including accessory canals, isthmuses, and dentinal tubules, during chemomechanical preparation (3). Endodontic infections present a persistent clinical challenge attributable to the intricate morphology of the root canal system. Such infections are strongly linked to periapical inflammation, postoperative pain, and the risk

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of therapeutic failure, and long-term success becomes compromised (4). There are several treatment strategies available, each with its own limitations. Mechanical debridement is a fundamental aspect of endodontic therapy, yet it often fails to achieve complete cleaning of the intricate root canal architecture (5). Moreover, sodium hypochlorite (NaOCl) is widely regarded as the gold standard irrigant and in chemical preparation, owing to its strong antimicrobial efficacy and tissue-dissolving capability. However, its cytotoxicity and potential to adversely affect the physical and structural properties of dentin represent significant limitations (6). To improve canal sterilization, intracanal medicaments are frequently employed between treatment appointments, particularly in cases involving asymptomatic apical periodontitis, chronic infection, and pulp necrosis. Calcium hydroxide ($Ca(OH)_2$) has been the most commonly utilized intracanal medicament, attributed to its elevated pH and antimicrobial action (7). Nonetheless, resistant bacterial species, such as *Enterococcus faecalis* and *Candida albicans*, may persist despite conventional disinfection approaches, leading to ongoing apical periodontitis and potential treatment failure (5). After thorough disinfection, obturation of the root canal system is performed with gutta-percha, along with root canal sealers, to establish a hermetic seal and prevent microbial reinvasion (8,9). However, it is toxic before setting, and precautions are necessary to prevent the extrusion of sealers beyond the root apex into the periapical tissues. Moreover, the quality of obturation, along with coronal restoration, is critical for ensuring long-term therapeutic success (8). Despite progress in techniques and materials, endodontic therapy remains challenging by microbial resistance and anatomical complexity. Recently, phytochemicals and natural substances have received attention due to their antioxidant, anti-inflammatory, and antimicrobial properties (10-13). One such substance with these properties is propolis, which has been reported in several studies for its regenerative effects on tissue, osteoinductive properties, and non-cytotoxicity (14,15).

Recently, propolis, a natural resinous substance produced by honeybees, has attracted substantial interest in endodontic research owing to its wide-ranging biological properties, due to its including flavonoids and phenolic acids (16). Propolis is a resinous material produced by honeybees from plant secretions and is distinguished by its complex and chemically varied composition. Its bioactive components include flavonoids, as well as phenolic and aromatic acids, ketones, aldehydes, amino acids, and vitamins (17,18). However, these compounds in propolis are chemically unstable, and their absorption in the gastrointestinal tract is affected by their solubility and stability; only a small amount of the phytochemicals ultimately becomes available to the target tissue (19). Nanoparticles (NPs), which enhance surface area, solubility, and bioavailability, may consequently improve penetration into tissues (20,21). In this regard, several studies have revealed that propolis-NPs (PNPs) improve propolis chemical and physical characteristics and have remarkable biological potential for addressing various disease-related challenges and for dental health (22-24).

However, a thorough synthesis of current evidence is necessary to elucidate the mechanisms and therapeutic potential of PNPs in endodontic practice. This systematic review aimed to evaluate the antimicrobial, antibiofilm, anti-inflammatory, and regenerative effects of PNPs in endodontic applications.

Methods

Search strategy

In this systematic review, a comprehensive literature search was performed across high-coverage databases, including Web of Science, PubMed, Scopus, EMBASE, and the Cochrane Library, encompassing all records from database inception to April 22, 2026. The search strategy was developed in collaboration with an experienced information specialist and incorporated both keywords extracted from the MeSH browser and relevant free-text keywords related to our aim of maximizing sensitivity and specificity. These keywords were including: ((“Propolis” OR “Bee Bread” OR “Bee Glue”) AND (“Root canal sealer” OR “Root canal obturation” OR “Root canal filling” OR “Endodontic sealer” OR “Root canal filling” OR “Dental cements” OR “Root canal irrigants” OR “Endodontic irrigants” OR “Root canal irrigation” OR “Intracanal medicament” OR “Endodontic medicaments” OR “Medicaments”)) (Supplementary file 1).

Reference lists of included articles and pertinent review articles were also screened to identify additional relevant articles. After that, all retrieved records were imported into EndNote (version 21.0.2; Thomson Reuters) for systematic review.

Eligibility criteria

Inclusion and exclusion criteria, data extraction procedures, and quality assessment protocols were predefined and documented in a review protocol. The research question was defined in accordance with the PICO (Population, Intervention, Comparison, Outcome) framework and the critical analytical components of the present systematic review (Table 1).

Due to the emerging and limited evidence on the application of PNPs systems in endodontics, this review incorporated *in vitro*, animal, and clinical studies to present a comprehensive summary of the existing preclinical and clinical data. The inclusion of diverse study designs facilitated a broader assessment of the antimicrobial, biological, and physicochemical characteristics of PNPs across multiple experimental models and clinical settings. All types of clinical trials, as well as *in vitro* and animal studies, were eligible for inclusion if they used PNPs solutions during canal irrigation, sealing ability testing,

Table 1. PICO framework applied in the present systematic review

Component	PICO structure and description
Population (P)	Teeth, including extracted patients, animal or cell specimens, type of pathogen, and endodontic infections such as primary or secondary apical periodontitis, and framework.
Intervention (I)	PNPs are employed as endodontic irrigants, intracanal medicaments, and root canal sealers
Comparison (C)	Untreated controls or conventional treatment like NaOCl, CHX, calcium hydroxide, epoxy resin, or bioceramic sealers.
Outcomes (O)	Clinical symptoms, molecular and cellular outcomes related to antimicrobial efficacy or biofilm inhibition/disruption, anti-inflammatory effects, analgesic effects, biocompatibility, and periapical healing. Moreover, the preparation methods for NPs and their biological benefits were studied.

PNPs: Propolis nanoparticles; NaOCl: Sodium hypochlorite; CHX: Chlorhexidine.

intracanal medicament applications, and antimicrobial studies in the procedures mentioned. The exclusion criteria encompassed all types of review designs, grey literature, letters to the editor, case reports, unpublished protocols, conference articles, publications available only as abstracts, studies lacking full-text availability, and non-English-language records. Moreover, non-PNPs are not relevant to endodontics, and periodontal-only studies were excluded.

Study selection process

After removing duplicate and irrelevant references, the full texts of all articles were retrieved and stored in EndNote for further review. Two independent reviewers screened titles and abstracts for eligibility, followed by full-text assessment. Discrepancies were referred to another investigator and resolved by consensus or consultation with a third reviewer.

Data extraction

Data were systematically extracted using a standardized form, capturing key variables such as article title, publication year, experimental model (patients, animal subjects, cell lines, and type of pathogen), dosage and duration of PNPs administration, investigated molecular pathways, observed mechanistic outcomes, nanoparticle preparation methods, and reported biological benefits, including release profiles and bioavailability.

Quality assessment

The methodological bias of the included studies was evaluated utilizing risk-of-bias instruments tailored to the respective study designs. For preclinical animal studies, the SYRCLE Risk of Bias (RoB) tool was employed to systematically assess potential sources of bias, including sequence generation, baseline comparability, allocation concealment, randomization methods, blinding of caregivers and investigators, randomization of outcome assessment, blinding of outcome assessors, management of incomplete outcome data, selective outcome reporting, and other relevant domains. Each domain was categorized as “low risk,” “high risk,” or “unclear risk” when reporting was insufficient (25).

In evaluating *in vitro* studies, the Quality Assessment Tool for In Vitro Studies (QUIN) was used. This instrument assigns a score of 2 for parameters that are adequately documented, 1 for those that are inadequately described, and 0 for those with no information reported (26,27).

For randomized controlled trials (RCTs), we use the Cochrane Risk of Bias 2 (RoB 2) tool, which systematically assesses potential bias related to the randomization process, deviations from intended interventions, completeness of outcome data, outcome measurement, and the selection of reported results (28).

Additionally, visual representations of the risk-of-bias evaluations were generated utilizing the Robvis package. These visualizations, including traffic light plots, offered a comprehensive overview of bias across all assessed domains for each animal study (29).

Reporting guidelines

The systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, thereby upholding methodological transparency, comprehensiveness, and reproducibility.

Results

Search results

Figure 1 presents the PRISMA flowchart depicting the search strategy. The initial electronic search identified 2,189 titles and abstracts. Of these, 87 articles were excluded due to duplication. Additional titles and abstracts were removed based on predefined exclusion criteria. One record was excluded because it was a conference abstract without full-text availability (30).

Finally, after reviewing the full text of the articles and considering the inclusion and exclusion criteria, 15 articles were included in this study (8,31-44).

Description of the included studies

Among the 15 included articles, only one study was designed *in vivo*, and two were randomized controlled clinical trials; the rest were *in vitro*. PNPs revealed multiple antimicrobials and antibiofilm activities. They

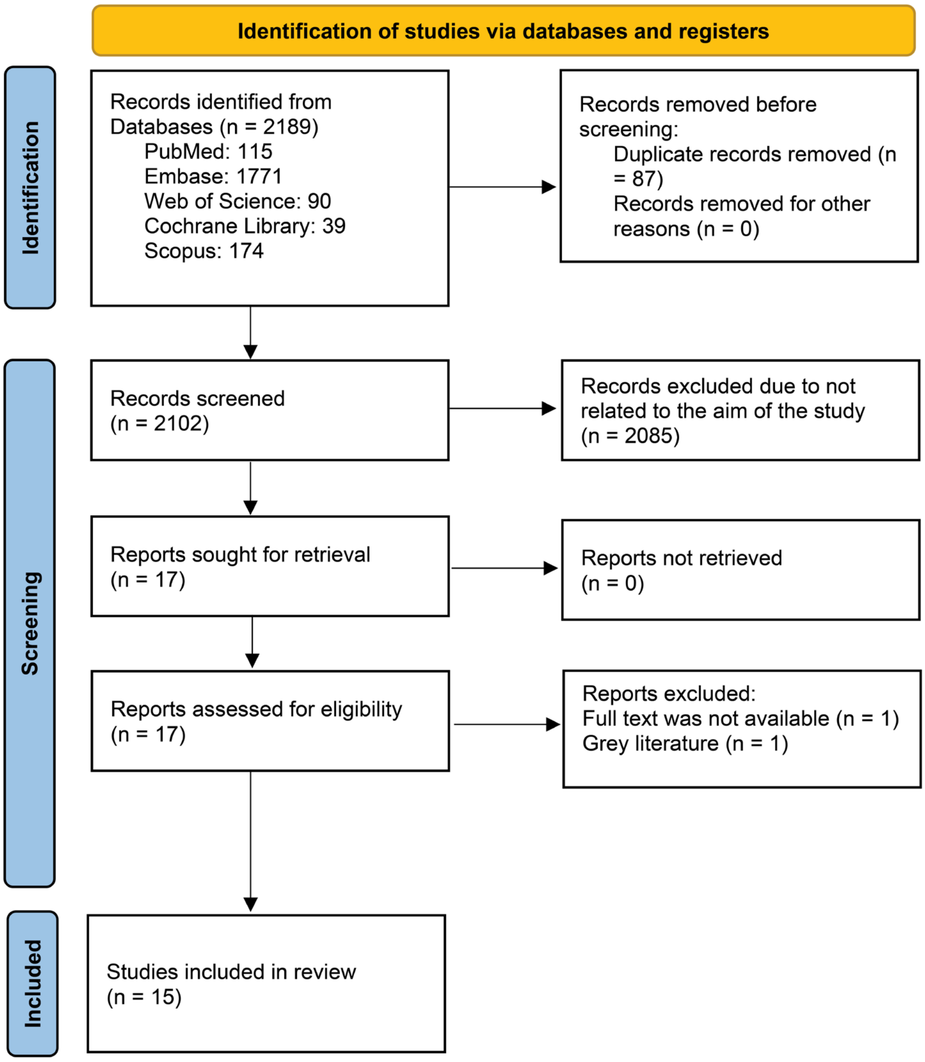


Figure 1. Flowchart illustrating the selection process for studies included in the systematic review.

also facilitate enhanced penetration, increased stability, and sustained release. This results in enhanced efficacy at reduced dosages and greater compatibility with endodontic tissues and materials (Table 2).

Risk of bias results

Risk of bias in the included RCTs was assessed using the Cochrane Collaboration RoB 2 tool across five domains. The studies by ElAbbasy and Elaguizy et al (8,44) were both rated "some concerns." ElAbbasy (44) raised concerns about the randomization process, deviations from intended interventions, and selective reporting. On the other hand, Elaguizy et al (8) revealed a low risk across most domains, with concerns only regarding the selection of reported results (Figure 2A).

Additionally, the quality evaluation of each *in vitro* study included in the evaluation, conducted using the QUIN tool, is summarized in Figure 3.

The risk of bias in the included *in vitro* studies was evaluated using the QUIN tool. Study quality ranged from moderate to low (ranging from 12 to 24) risk of bias. Most publications provided adequate information concerning their objectives, experimental designs, control groups, outcome measurement methods, statistical approaches, and data presentation. Only a small proportion of studies were categorized as low risk of bias, reflecting high methodological standards, including thorough randomization, standardized operator procedures, and comprehensive reporting across all QUIN domains. In summary, although the laboratory studies generally demonstrated sound methodological frameworks, the frequent omission or incomplete reporting of strategies to minimize bias indicates persistent methodological uncertainty in the current evidence base.

Discussion

This systematic review examined the effectiveness of PNPs in managing endodontic infections and pain, with specific emphasis on their application as root canal irrigants, intracanal medicaments, and sealers. The results of this

Table 2. Information, characteristics, and main outcomes of the included studies

First author (year) (Reference)	Type of study	Purpose of using PNPs	Examined populations/animals/ cells/pathogens	Treatment and preparation of nanoformulation details	Principal therapeutic mechanisms and NPs' advantages
Del Carpio-Perochena (2017) (31)	*In vitro* and *in situ*	Intracanal medicament	*In vitro*: Human dentin discs and dentin blocks infected with *E. faecalis* *In situ:* multispecies intraoral biofilms	CNPs incorporated into calcium hydroxide [$Ca(OH)_2$ paste (5 mg CNPs); comparison with $Ca(OH)_2$ alone and $Ca(OH)_2$ + EPE (50 g propolis) and root canals treated and incubated for 7 and 14 days.	Increased antibacterial activity through nanoparticle-mediated penetration into dentinal tubules and biofilm disruption, and sustained bactericidal effect over time Enhanced killing of *E. faecalis* biofilms without altering $Ca(OH)_2$ alkalinity, and increasing the reduction of viable bacterial cells compared with conventional formulations
Ong (2017) (32)	*In vitro*	Intracanal medicament	*E. faecalis* biofilms (planktonic, developing, and pre-formed biofilm models)	CNPs prepared by ionic gelation using ethanol extract of Malaysian propolis. optimal formulation (F1): 0.2% chitosan, 1 mg/mL propolis, 0.4% positive zeta potential. Tested at concentrations 100-400 µg/mL and sustained release (~53.8% over 48 h)	Increased antibacterial and antibiofilm activity via improved penetration into biofilms, electrostatic interaction with bacterial cell membranes, and significant disruption of biofilm Reduced the architecture of bacterial survival in both planktonic and biofilm states, and virulence and biofilm-associated genes. Improved sustained and controlled release of bioactive compounds, bioavailability, and stability.
Abdel Raheem (2019) (33)	*In vitro*	Root canal sealer	WI-38 fibroblasts; *E. faecalis*, *S. mutans*, *C. albicans*	0.5% propolis ethanolic extract loaded into PLGA NPs via nanoprecipitation and incorporated into Carbopol/HPMC gel and tested at 0, 20, 40, 60, 80, and 100 µg/mL for 48 h (cytotoxicity) and up to 24 h (antimicrobial)	Broad-spectrum antimicrobial (anti-biofilm). Improved prolonged release, cytocompatibility, biocompatibility, stability, and therapeutic effect, with low in vitro cytotoxicity.
Abdel Raheem (2020) (34)	*In vitro* and *in vivo*	Root canal sealer	*In vitro*: Extracted human single-rooted teeth *In vivo:* Wistar albino rats	Propolis ethanolic extract (0.5%) loaded into PLGA NPs via nanoprecipitation (PDLGA 0.6%, PVA 2%) and lyophilized with trehalose (5%) and incorporated into Carbopol/HPMC gel as nanosealer and evaluated after 24 h (sealing) and *in vivo* at 2 and 4 weeks	Improved sealing ability with reduced microleakage, sustained release, handling properties, biocompatibility, and tissue healing. Reduced inflammation, cytotoxicity, and apoptotic changes
Moukarab (2020) (35)	*In vitro*	Root canal irrigant	Extracted human mandibular premolars infected with *E. faecalis*	PNPs prepared by ball milling and dissolved in ethanol (20 mg/mL) were used as an irrigation solution (5 mL administered over 5 min: 3 min of syringe irrigation + 2 min of manual agitation).	Increased antibacterial activity against *E. faecalis*, and more efficient comparable to NaOCl Reduced toxicity
Parolia (2020) (36)	*In vitro*	Intracanal medicament	Extracted human teeth (dentin block model) and *E. faecalis* (ATCC 29212) and clinical isolates from failed endodontic cases	Propolis ethanolic extract (1 mg/mL) incorporated into chitosan NPs (CPN) via ionotropic gelation (0.2% chitosan + 0.15% TPP) and applied as intracanal medicament at 100 and 250 µg/mL and incubation for 1, 3, and 7 days	Increased antibacterial activity with reduced colony-forming units (CFUs), enhanced penetration into dentinal tubules, and biofilm disruption.
Arab (2021) (37)	*In vitro*	Root canal sealer	*Streptococcus mutans*, *Streptococcus sanguinis*, *Lactobacillus acidophilus*, *C. albicans*	Propolis extracted in ethanol, precipitated with water, sonicated to form colloidal PNPs, centrifuged, freeze-dried, and incorporated into acrylic resin discs at 0.5%, 1%, and 2%, and antimicrobial evaluation after 24 h, 72 h, and 48 h (biofilm test)	Reduced microbial CFU counts Inhibited biofilm formation, sustained antimicrobial effect via eluted components

Table 2. Continued

First author (year) (Reference)	Type of study	Purpose of using PNPs	Examined populations/animals/cells/pathogens	Treatment and preparation of nanoformulation details	Principal therapeutic mechanisms and NPs' advantages
Parolia (2021) (38)	*In vitro*	Root canal irrigant	Extracted human anterior teeth, dentine block model infected with *E. faecalis* (ATCC 29212)	PNPs were prepared via ultrasonication of 0.01 g propolis with Tween 80 in distilled water, yielding NPs. Ethanolic extracts characterized (rich in flavonoids: pinocembrin, kaempferol, quercetin). 5 mL irrigant, exposure times 1, 5, and 10 minutes.	Increased antibacterial and antibiofilm activity against *E. faecalis*, Reduced CFUs and disruption of biofilm matrix
Abd El Nasser (2022) (39)	*In vitro*	Intracanal medicament	Extracted single-rooted human mandibular premolars (dentin half model)	PNPs were prepared via ethanolic extraction, precipitation, and ultrasonication (20-30 min) to obtain nanoparticles. Medicament incorporated into HPMC gel and applied as a 1 mL intracanal dressing. Specimens were incubated for 14 days.	Reduced dentin microhardness and structural damage compared to antibiotic pastes
Madani (2022) (40)	*In vitro*	Root canal irrigant	*E. faecalis* (PTCC 1778)	PNPs were formulated using oil phase, followed by incorporation of 30 mg propolis into 2 g oil phase, stirring (100 rpm, 2 h), sonication (1 h), and addition of deionized water (5:1 ratio) to form nanoemulsion. MIC range tested after 24 h incubation.	Increased antimicrobial and antibiofilm activity, lower minimum inhibitory concentration (MIC), stronger bactericidal effect, and reduced bacterial adhesion
Shamma (2022) (41)	*In vitro*	Intracanal medicament	Extracted human primary second molars infected with *E. faecalis*	Chitosan 2% was prepared by dissolving in 2% acetic acid. Ethanolic extract of propolis was obtained by dissolving crude propolis in 80% ethanol, followed by evaporation and filtration. Then, 1.5 g EEP was incorporated into 2% chitosan solution, and 1% sodium alginate was added to form a gel dressing. Each root canal was incubated for 24 h, 72 h, and 7 days	Sustained antimicrobial activity against *E. faecalis* and antibacterial efficacy over time.
Karimitabar (2023) (42)	*In vitro*	Root canal irrigant	*E. faecalis* (ATCC 29212) and fibroblastic cell line (cell line L 929)	A hydroalcoholic extract of propolis was prepared (50 mg propolis). AgNPs@propolis were synthesized via dropwise addition of propolis extract to an $AgNO_3$ solution until a yellow-to-yellow-brown transition. Exposure duration was 24 h for antibacterial testing.	Increased antimicrobial activity through synergistic interaction between silver nanoparticles and propolis, with reduced cellular toxicity at lower concentrations
Wahyuni (2023) (43)	*In vitro*	Root canal sealer	Human-extracted single-rooted mandibular premolars inoculated with *E. faecalis* (ATCC 29212)	Pre-formulated commercial PNPs 5% incorporated into epoxy resin (Adseal, Metabiomed) and bioceramic sealer. Sealers were tested in obturated canals and incubated for 8 days.	Improved antimicrobial efficacy against *E. faecalis* and dentinal tubular penetration.
ElAbbasy (2024) (44)	RCT	Root canal irrigant	Patients with single-rooted, non-vital permanent maxillary anterior teeth	PNPs (Nanotech, Dreamland, Egypt) were prepared using a PGA solution	Synergistic antimicrobial action with reduced endotoxin level
Elaguizy (2024) (8)	RCT	Root canal irrigant	Human patients with necrotic mandibular premolars with apical periodontitis	PNPs (20 mg/mL) prepared via liquid anti-solvent precipitation using PEG as stabilizer and postoperative follow-up up to 48 h and microbiological sampling pre- and post-instrumentation	Increased antimicrobial activity with reduced bacterial load and postoperative pain, comparable to NaOCl

PNPs: Propolis-nanoparticles; CNPs: Chitosan-based propolis nanoparticles; EPE: Ethanolic propolis extract; PLGA: poly(lactic-co-glycolic acid); PVA, Polyvinyl alcohol; CPN: Chitosan-propolis nanoparticles; PGE: Polyethylene glycol, MIC: Minimal inhibitory concentration; AgNPs: Silver nanoparticles; NaOCl: Sodium hypochlorite; PEG: Polyethylene glycol; PGA: Polyglycolic acid; RCT, Randomized controlled clinical trial.

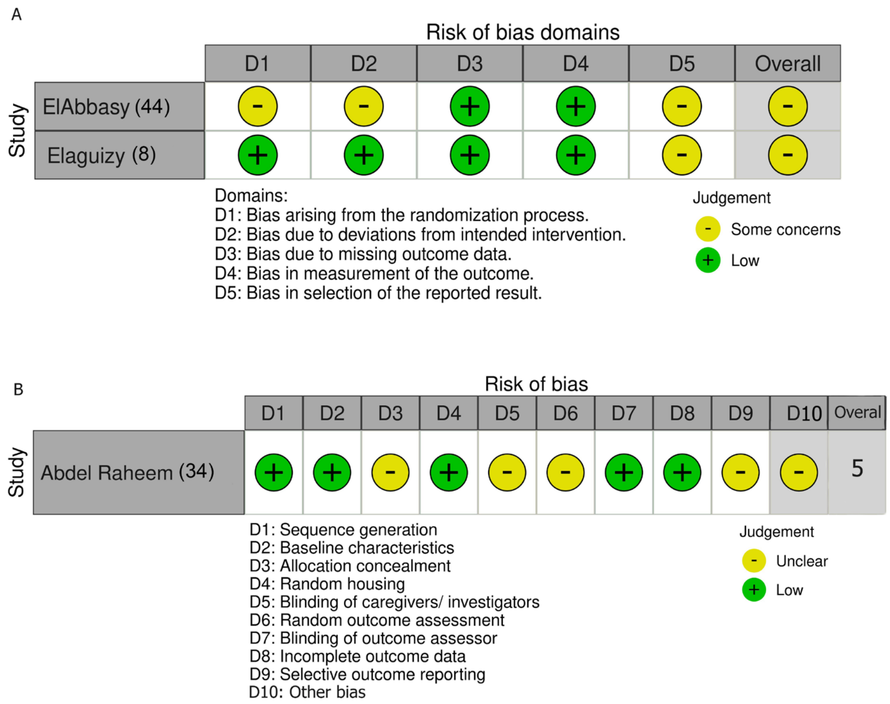


Figure 2. Risk-of-bias assessment of randomized controlled trials (RCTs) and *in vivo* studies. (A) Risk-of-bias assessment of the included RCTs. (B) Risk-of-bias assessment of the included *in vivo* studies.

study showed satisfactory effects of PNPs in controlling endo infections, including *E. faecalis* and *C. albicans*. These findings align with previous studies demonstrating that nanoparticle-based interventions enhance antimicrobial efficacy and reduce bacterial minimum inhibitory concentrations. Comparative analyses frequently indicate that metallic nanoparticles possess greater antimicrobial potency. Thus, while polymeric nanoparticles are effective, they may offer superior biocompatibility but comparatively reduced antimicrobial strength within the broader spectrum of nanoparticles (22). This suggests that polymeric NPs represent a promising option that achieves a balance between antimicrobial efficacy and biocompatibility, rather than serving as the most potent antimicrobial agent.

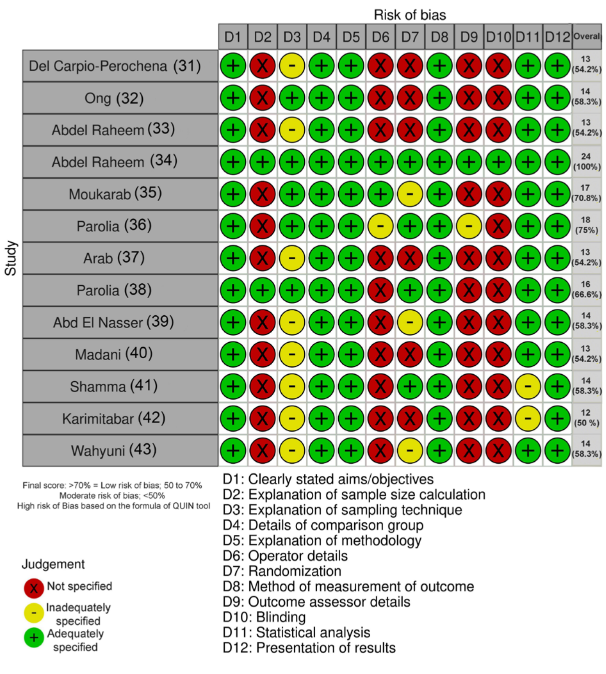


Figure 3. Evaluation of methodological quality for the included *in vitro* studies using the QUIN tool.

Another review conducted by Kustiawan et al indicates that PNPs have considerable potential for wound-healing applications, largely due to their multifaceted bioactivity. In particular, its synergistic antibacterial, antioxidant, and anti-inflammatory properties, along with other relevant biological effects, collectively contribute to enhanced tissue repair processes and overall therapeutic efficacy (23). However, a review of clinical studies using pure propolis found insufficient evidence to support its use as a superior alternative to other materials for endodontic treatment of permanent teeth (45). Due to limited clinical data and variability in reported outcomes, propolis cannot be recommended as a definitive treatment modality. Nevertheless, further high-quality randomized controlled trials are needed to provide more conclusive evidence of its clinical efficacy. In contrast, this review indicates that PNPs may overcome certain limitations of conventional propolis, particularly regarding antimicrobial efficacy and material performance. This finding suggests that NP engineering could help translate promising *in vitro* bioactivity into clinically meaningful outcomes.

A recent systematic review evaluated nanoparticle-coated gutta-percha, including PNPs, silver-curcumin, chitosan, silver, and zinc oxide, for their efficacy against oral pathogens. The findings indicated that higher NP concentrations and longer coating durations enhanced antimicrobial activity compared with conventional gutta-percha. Nonetheless, the strength of the evidence was limited by a high risk of bias, particularly in areas of randomization, blinding, and sample size reporting, as well as considerable methodological heterogeneity, which prevented definitive conclusions regarding the optimal coating strategy (46). PNPs also improve tissue penetration, enhance stability, and enable controlled release of bioactive compounds. Such characteristics contribute to synergic therapeutic efficacy at lower dosages and improved biocompatibility with endodontic tissues and materials. Saad et al in their study reported that PNPs can enhance therapeutic efficacy while preserving propolis's inherent properties. Propolis is recognized for its diverse biological activities, such as anti-inflammatory, antioxidant, anticancer, and antifungal effects. However, the clinical application of conventional propolis is limited by poor bioavailability, resulting in low systemic absorption and insufficient targeted delivery (10).

This synthesis advances current understanding by demonstrating that nanoengineering can address key limitations of conventional propolis, notably poor bioavailability and restricted targeted delivery, thereby enhancing its translational potential in endodontic therapy.

In the following, we review and discuss the most important findings of the present study.

Direct antimicrobial activity and antibiofilm activity

PNPs are generally defined as particles with diameters ranging from 1 to 100 nanometers, produced through specialized engineering methods to improve their functional efficacy while preserving their inherent properties (22,47). Alternatively, some classifications extend the nanoparticle size range to 10-1000 nanometers, thereby including propolis particles under 1000 nanometers within this category (22). Including studies demonstrate that PNPs possess significant antibacterial activity. Ong et al. in their study reported that at the microbial level, PNPs primarily exert their effects by disrupting cellular integrity. The high surface charge and reduced particle size of PNPs enable electrostatic interactions with microbial cell membranes, leading to increased membrane permeability, leakage of intracellular contents, changes in virulence genes, and disruption of *E. faecalis* biofilm matrix formation (32). In addition to this membrane-targeting mechanism, studies show that propolis can interfere with intracellular processes, including protein synthesis and enzymatic activity, and inhibition of bacterial division, thereby compromising essential metabolic functions (33,48).

According to studies included in the review, a significant advantage of PNPs is their ability to inhibit biofilm formation and destabilize established biofilms (31,32,36-38,40). Biofilms (as complex microbial communities) represent a highly resistant mode of microbial growth, and altered gene expression (49). Due to their nanoscale dimensions and high surface area, PNPs can efficiently penetrate these structures, disrupt extracellular polymeric substances, and attenuate quorum-sensing mechanisms. As a result, microbial adhesion, colonization, and persistence are considerably diminished (31,32,36-38,40).

In addition to their direct antimicrobial activity, PNPs promoted the formation of well-organized, highly vascularized fibrous connective tissue, characterized by dense collagen bundles and numerous elongated fibroblasts. PNPs also demonstrated notable immunomodulatory and tissue-regenerative properties, including reduced inflammatory responses, enhanced fibroblast proliferation, and support for tissue repair. Histological assessment revealed only a mild inflammatory response, with limited infiltration of inflammatory cells localized near the propolis nanosealer tubes (34). These attributes are particularly advantageous in clinical settings where effective infection management and tissue regeneration are critical for optimal therapeutic outcomes.

Advantages of PNPs as a delivery system and their biological effects

As previous studies report, propolis, as a traditional medicine, demonstrates effective therapeutic potential attributed to its complex composition, which includes polyphenols, flavonoids, and various bioactive compounds, including phenolic acids and flavones (50,51). Nevertheless, clinical applications are frequently limited by inadequate aqueous solubility, chemical instability, and restricted bioavailability (51). The propolis matrix, rich in phenolics and flavonoids, together with NPs and ions, facilitates the formation of a stable hybrid nanostructure. This nanoflower configuration markedly improves peroxidase-like catalytic activity and enhances radical scavenging capacity relative to unmodified propolis (52,53). The application of propolis with NPs-based delivery systems offers notable improvements in pharmacological efficacy by enhancing dispersion, precision, and versatility, safeguarding labile constituents from degradation, and enabling controlled release profiles (54). Furthermore, nanoscale encapsulation of propolis increases the available surface area for interactions with biological membranes, thereby facilitating more efficient absorption of active constituents within the gastrointestinal tract and across cellular barriers (32,40,55).

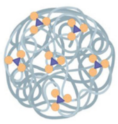
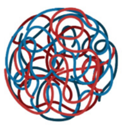
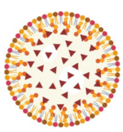
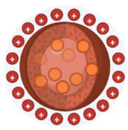
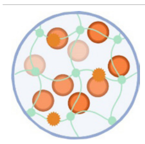
The enhanced penetration capacity of PNPs is especially relevant in structured biological environments such as dentinal tubules, where conventional antimicrobial agents often demonstrate limited penetration and diffusion. Various included studies revealed that NPs-mediated delivery systems enable deeper infiltration into microanatomical niches, ensuring that antimicrobial activity is achieved at locations otherwise inaccessible to traditional agents. This characteristic is critical for addressing persistent infections and minimizing the risk of reinfection (31,36,43).

Another key mechanism of action involves the controlled and sustained release of bioactive constituents. Propolis comprises a diverse set of bioactive compounds, which contribute to its antimicrobial and anti-inflammatory properties. Nanoencapsulation protects these compounds from premature degradation and enables their gradual release, thereby maintaining therapeutic concentrations over extended periods and enhancing bioavailability (32-34).

Moreover, incorporating PNPs into hybrid or composite systems can lead to synergistic interactions that enhance their therapeutic efficacy in both experimental and clinical studies (40,44). For example, the combination of PNPs with polymeric carriers or metallic nanoparticles can enhance stability capacity and antimicrobial potency through complementary mechanisms, including oxidative stress induction and improved drug delivery kinetics. Studies by Karimitabar et al and Islam et al showed that the phenolic components of propolis increase microbial membrane permeability, thereby enabling deeper penetration of silver nanoparticles (AgNPs) and silver ions (Ag^+) into bacterial cells. Concurrently, AgNP-induced membrane disruption facilitates the intracellular delivery of propolis-derived phytochemicals. This combined mechanism intensifies oxidative stress and disrupts essential metabolic processes, leading to increased bacterial cell death at lower concentrations than when either agent is used alone. Such synergistic effects are especially effective against multidrug-resistant bacteria and biofilm-forming pathogens, as they disrupt multiple cellular pathways simultaneously (42,56).

Included studies in this systematic review show that PNPs are incorporated into various nanocarriers to enhance their properties and effectiveness in endodontics. Chitosan-based and other polymeric systems are favored for their stability, biocompatibility, and ability to control drug release. Lipid-based nanoemulsions improve solubility and sustain delivery of hydrophobic agents. Metallic hybrids, such as AgNPs-PNPs, enhance antimicrobial activity, particularly against resistant biofilms. Nanocomposite systems integrate PNPs into dental materials, providing controlled release and targeted antimicrobial action within the root canal (Table 3).

Table 3. Classification of PNPs delivery systems and representative formulations in endodontic applications

Category	Key characteristics	Representative examples (from included studies)
 Chitosan-based polymeric nanoparticles	Chitosan NPs can modulate protein-loading efficiency and affect key preparation parameters. They exhibit high stability and efficient protein encapsulation, may be formulated as lyophilized powders, and are readily stored and transported (57).	Chitosan-PNPs and chitosan-alginate gel
 Synthetic polymeric nanoparticles (PLGA and derivatives)	These NPs are formulated as either nanocapsules, in which the drug is encapsulated within the polymer matrix, or nanospheres, in which the drug is homogeneously distributed throughout the polymer. Commonly used biocompatible polymers include alginate, gelatin, and PLGA (58, 59).	Propolis-loaded PLGA NPs in Carbopol/HPMC gels
 Lipid-based nanoemulsions	Oil-water systems stabilized by surfactants or cosurfactants. Oils and lipids, aided by surfactants, improve the solubility and absorption of hydrophobic drugs. Microemulsions and nanoemulsions provide stable, controlled drug delivery (60).	PEG-based nanoemulsions with glyceryl monooleate and castor oil derivatives
 Metallic nanoparticle hybrids	Metallic NPs hybrids are composite systems in which metal nanoparticles, including gold, copper, silver, FeCl3, and other materials, are used, and these particles have many applications in drug targeting and in reducing multidrug resistance (61).	Silver nanoparticles functionalized with propolis (AgNPs@propolis)
 Nanocomposite delivery systems	Nanocomposite delivery systems possess a high surface area, adjustable particle size, and multifunctional interfaces, facilitating controlled drug encapsulation and targeted release (62).	Propolis NPs in acrylic resins, nanoparticle-enriched root canal sealers; Carbopol/HPMC gels

PNPs: Propolis-nanoparticles; PLGA: poly(lactic-co-glycolic acid); PEG: Polyethylene glycol; AgNPs: Silver nanoparticles.

Limitations

The present systematic review included mainly *in vitro* studies and only two clinical studies, which limits the clinical applicability of the results and leads to heterogeneity in study design. A principal limitation of this study is the lack of long-term clinical evidence, which limits the ability to draw conclusions about sustained efficacy, safety, and real-world therapeutic outcomes. Also, various propolis varieties can have different compositions, which may affect the development of guidelines for their uses and the generalizability of the results (51). Furthermore, there is significant heterogeneity across studies in nanoparticle synthesis methods, formulations, concentrations, and application protocols, which prevents methodological standardization and limits comparability between studies, thereby constraining the development of evidence-based clinical guidelines. The lack of standardized nanoparticle preparation protocols represents an additional barrier to reproducibility and clinical translation. Although several studies investigated *E. faecalis*, the overall evidence base remains limited in scope, with insufficient diversity of tested pathogens and experimental conditions, further restricting external validity. Therefore, further clinical studies are recommended, considering different propolis doses and a wider range of pathogens and clinical symptoms. Another limitation of this study is that the systematic review protocol was not prospectively registered in PROSPERO.

Conclusion

Our results highlight the promising effect of PNPs in the management of endodontic infections based on studies and inflammation involving antimicrobial, antibiofilm, anti-inflammatory, and regenerative processes. The multifunctionality of PNPs, combined with the enhanced properties conferred by nanoscale delivery systems, establishes these nanoparticles as a robust platform for developing advanced therapeutic strategies in endodontics. Although the included studies were mostly *in vitro*, they demonstrated that PNPs exhibited antimicrobial and antibiofilm activity against key endodontic pathogens, particularly *E. faecalis*, in both planktonic and biofilm forms and reduced endotoxins. Due to their higher bioavailability, lower doses of these substances are required, thereby reducing potential cytotoxicity at higher doses. In comparative studies with pure propolis, PNPs also showed more favorable effects in root canal treatments. PNP's efficacy was demonstrated across various delivery methods, including root canal irrigants, intracanal medicaments, and sealers, indicating their versatility in endodontic treatment and lack of cytotoxicity. However, further well-designed randomized clinical trials and standardized methodologies are necessary to validate their clinical efficacy.

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Writing–review & editing: All authors.

Conflict of interests

The authors declared no conflict of interest, financial or otherwise.

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Supplementary files

Supplementary file 1. Database-specific bibliographic search strategies for keywords identifying propolis studies in endodontic procedures.

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