



## Evaluation of the Antimicrobial Effects of Mesoporous Silica Nanoparticles Carrying Nanosilver for Endodontic Treatment: A Systematic Review and Meta-analysis

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### ABSTRACT

**Background and aim:** The present study aimed to evaluate the antimicrobial effects of mesoporous silica nanoparticles carrying nanosilver in endodontic treatment.

**Material and methods:** The literature was screened via international databases Cochrane, Embase, and MEDLINE (PubMed and Ovid) up to October 2024 with English language restriction. Two reviewers independently performed screening and evaluation of articles. The ToxRTool® checklist information contained eighteen items to evaluate Methodological quality. The mean difference was used as an effect size indicator to analyze each included study. The random-effect model combined the effect size with the Restricted maximum likelihood method. All meta-analyses were performed using Stata software (version 17).

**Results:** A total of 143 articles were retrieved from all the databases; after applying eligibility criteria, eight studies were included. Biofilm was significantly lower in the nMS-nAg groups compared to the control group (MD: -64.94 95% CI: -76.43, -53.44; P<0.001).

**Conclusions:** Based on the present meta-analysis, nMS-nAg-Chx showed strong antibacterial activity to reduce biofilms.

### 1. Introduction

Endodontic and periapical diseases are mainly caused by microbial root canal infections.<sup>[1]</sup> Most conditions requiring immediate dental treatment are caused by acute apical periodontitis.<sup>[2]</sup> Despite the significant advances in modern endodontics and the introduction of new tools and methods, eliminating the microorganisms still present in root canals remains a challenge.<sup>[3]</sup> Therefore, it is crucial to eliminate the microbe and prevent its reintroduction into the root canal system.<sup>[4]</sup> Aerobic bacteria, facultative anaerobes, and strict anaerobes are all involved in the dynamic and complicated process of endodontic infection. The primary microbiota of unsuccessful endodontic treatment consists of facultative gram-positive anaerobic bacteria.<sup>[5]</sup> Infections caused by root canal treatment are often successfully treated. Intracanal medications can promote recovery, inhibit bacterial growth, and prevent reinfection, especially in dead pulp and receding teeth with swelling, chronic pain, and sinus passages.<sup>[6]</sup> Common intracanal medications include chlorhexidine (Chx), calcium hydroxide (Ca(OH)<sub>2</sub>), and antibiotics. Ca(OH)<sub>2</sub> is the most popular option.<sup>[7]</sup> However, several recent studies have shown that it has a negative impact on the fracture resistance of

teeth.<sup>[8, 9]</sup> Long-term treatment with Ca(OH)<sub>2</sub> drastically reduced fracture strength and increased the risk of tooth fractures.<sup>[10]</sup> Antibiotics are less effective against quiescent and dormant bacteria in the nutrient-poor root canal system.<sup>[11]</sup> Cytotoxicity, resistance, and root fracture risk are issues with conventional intracanal drugs.<sup>[12]</sup> Nanoparticles are small and have a high surface area-to-volume ratio. Their positive charge properties can interact with electronegative complex groups on bacterial membranes to alter the permeability of cell membranes and lead to leakage of contents.<sup>[13]</sup> Silver atoms form monolithic silver particles or silver nanoparticles (AgNPs), among the most well-researched metallic nanoparticles.<sup>[14]</sup> The disruption of cellular respiration and DNA synthesis are the main mechanisms of AgNPs.<sup>[15]</sup> According to research, mesoporous silica nanoparticles (MSNs) are currently considered one of the best delivery systems for various drugs.<sup>[16]</sup> It is particularly useful and applicable in drug delivery systems due to its sustainability, biocompatibility, and ease of synthesis and modification. Second, when drugs are released from mesoporous structures, the required dose is reduced, and drug toxicity is prevented, as this increases the local

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concentration of the drugs. Finally, various targeting agents, polymers, stimulus responders, and other substances can functionalize the surface of mesoporous silica nanoparticles, thereby extending the duration of the drug cycle.<sup>[17-19]</sup> Therefore, the present systematic review and meta-analysis aimed to evaluate the antimicrobial effects of mesoporous silica nanoparticles carrying nanosilver for endodontic treatment.

## 2. Material and methods

### Search strategy and Information sources

Relevant keywords were searched in the international databases Cochrane, Embase, and MEDLINE (PubMed and Ovid) to evaluate the antimicrobial effects of mesoporous silica nanoparticles carrying nanosilver for endodontic treatment up to October 2024.

### The search strategy used in MEDLINE (via PubMed)

(((((("Anti-Infective Agents"[Mesh] OR "Anti-Infective Agents"[Pharmacological Action] OR "Biofilms"[Mesh]) AND "Nanoparticles"[Mesh]) OR ( "Nanoparticles/adverse effects"[Mesh] OR "Nanoparticles/microbiology"[Mesh] OR "Nanoparticles/statistics and numerical data"[Mesh] OR "Nanoparticles/toxicity"[Mesh] )) AND "Silicon Dioxide"[Mesh]) AND "Silver"[Mesh]) AND "Chlorhexidine"[Mesh]) AND ( "Root Canal Obturation"[Mesh] OR "Regenerative Endodontics"[Mesh] ).

### The search strategy used in Cochrane

"Root Canal Therapy" OR "Root Canal Irrigants" AND "Nanoparticles" OR "silver nanoparticles" OR "AgNPs" AND " Silica Nanoparticles " OR " nMS " OR " mesoporous silica nanoparticles" AND " chlorhexidine" OR " Chx "AND "antimicrobial effects" OR "Antimicrobial Activity".

### The search strategy used in Embase

(Root Canal treatment) OR (Root Canal Therapy) OR (Root Canal Irrigants): ab, ti, kw.

Nanoparticles: ab, ti, kw.

(silver nanoparticles) OR (AgNPs) OR (Silica Nanoparticles) OR mesoporous silica nanoparticles) OR (nMS) OR (chlorhexidine): ab, ti, kw

chapter' OR 'conference abstract' OR 'conference paper' OR 'conference review' OR 'editorial' OR 'erratum' OR 'letter' OR 'note' OR 'preprint' OR 'short survey'/it (Filter).

In addition to Google Scholar, the Cochrane Central Register of Controlled Trials, Web of Science, EBSCO, ISI, Elsevier, and the Scopus Wiley Online Library were consulted. The current study is based on the 27-point checklist PRISMA 2020.<sup>[20]</sup>

### Selection criteria

English-language publications met the inclusion requirements for this study. The answers to the questions in the current study were based on the PICO strategy (Table 1). Review studies and books; qualitative studies; animal studies; studies without comprehensive and relevant data.

Table 1. PICO strategy.

PICO Strategy	
Population (P)	Endodontic treatment
Intervention (I)	Mesoporous silica nanoparticles carrying nano-silver
Comparison (C)	Control group
Outcome (O)	Antimicrobial effects

### The process of selection and data collection

Two blind researchers collected data from the selected studies and, after completion, blindly and independently reviewed all cases. The research team included information such as the author's name, year of publication, study design, Nanoparticles, Assessment of Antibacterial Activity, and type of bacteria in the original form.

### Heterogeneity and publication bias

The heterogeneity across studies was examined using the Chi-square ( $\chi^2$ ) test and quantified by the  $I^2$  statistic. According to the  $I^2$  value, heterogeneity was classified as low (less than 50%), between 50 and 74% means moderate heterogeneity, and above 75% is considered high heterogeneity.

The chi-square test ( $\chi^2$ ) was used to analyze heterogeneity between studies, and the  $I^2$  statistic was used to quantify it. Based on the  $I^2$  value, heterogeneity was classified as low (less than 50%), moderate (between 50% and 74%), and high (above 75%).

### Methodological quality

ToxRTool® checklist information contained eighteen items.<sup>[21]</sup> first

determined whether the content of the article met the requirements and answered "yes" or "no." A "yes" response received a score of 1, and a "no" response received a 0. Second, the ratings were used to categorize the studies into three levels. Climatic level 1 was assigned values between 15 and 18, indicating reliable and unqualified data; Level 2 was assigned values between 11 and 14, indicating reliable and limited type data; and Level 3, which declared unreliable data, was assigned values below 11 points or that did not meet the red standard qualification.

### Data analysis

The present meta-analysis used mean difference (MD) as an effect size indicator to analyze each included study. The random-effect model combined the effect size with the Restricted maximum-likelihood (RMEL) method. All meta-analyses were performed using Stata software (version 17).  $P < 0.05$  was considered statistically significant.

## 3. Results

### Description of studies

In the initial search with related keywords, 143 articles were obtained from international databases. After two independent and blind researchers reviewed the articles and removed duplicates unrelated to the study topic, the abstracts of 69 articles were carefully reviewed in the next step. Articles that

did not meet the inclusion criteria were excluded, and the full text of 21 articles was examined. Among these articles, only eight were consistent with the purpose of the present study and were included in the study. (Fig. 1).

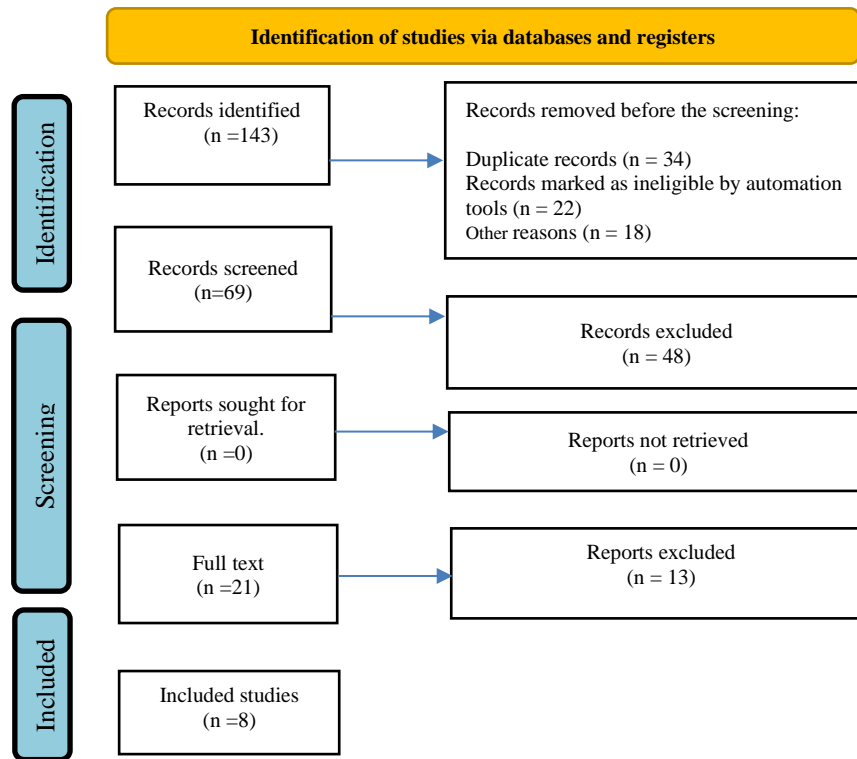


Fig. 1. PRISMA 2020 Checklist.

**Study characteristics**

All included studies used SEM visual assessment to assess antibacterial activity. In four studies, the type of bacteria was *Enterococcus faecalis*, and in one study, *Porphyromonas gingivalis*, *Bacillus cereus*, and *Salmonella*

*enterica*. two studies *Escherichia coli*, *Staphylococcus aureus*. The characteristics of the studies are reported in Table 2.

**Bias Assessments**

The risk of bias in all studies was classified as moderate risk of bias.

Table 2. Summary of characteristics of the included studies.

Study. Years	Study Design	Nanoparticle	Assessment of Antibacterial Activity	Bacteria
Wang et al., 2014 <sup>[22]</sup>	In-vitro	nMS-nAg-Chx	SEM visual assessment	<i>Enterococcus faecalis</i>
Wang et al., 2024 <sup>[11]</sup>	In-vitro	nMS-nAg-Chx	SEM visual assessment	<i>Enterococcus faecalis</i>
Mohammed et al., 2024 <sup>[23]</sup>	In-vitro	nMS-nAg	SEM visual assessment	<i>Enterococcus faecalis</i>
Fang et al., 2024 <sup>[24]</sup>	In-vitro	nMS-nAg-Chx	SEM visual assessment	<i>Porphyromonas gingivalis</i>
Nuti et al., 2024 <sup>[25]</sup>	In-vitro	nMS-nAg	SEM visual assessment	<i>Escherichia coli</i> <i>Bacillus cereus</i> <i>Salmonella enterica</i> <i>Candida glabrata</i>
Abbasi et al., 2023 <sup>[26]</sup>	In-vitro	nMS-nAg-Chx	SEM visual assessment	<i>Candida albicans</i> <i>Candida tropicalis</i> <i>Candida parapsilosis</i>

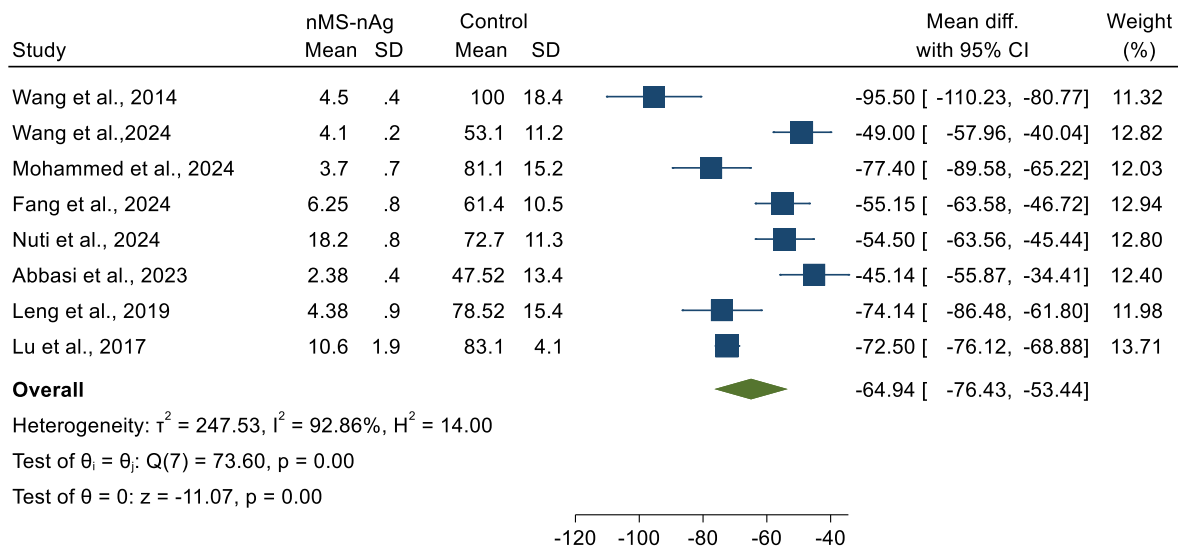
				Candida dubliniensis Candida krusei Escherichia coli Staphylococcus aureus
Leng et al., 2019 <sup>[27]</sup>	In-vitro	nMS-nAg	SEM visual assessment	Enterococcus faecalis
Lu et al., 2017 <sup>[28]</sup>	In-vitro	nMS-nAg-Chx	SEM visual assessment	Staphylococcus aureus Escherichia coli

**Reduced Biofilm**

Biofilm was significantly lower in the nMS-nAg groups compared to the control group (MD: -64.94 95% CI: -76.43,-53.44; P<0.001 (I<sup>2</sup>= 92.86 P<0.001)) (Fig. 2).

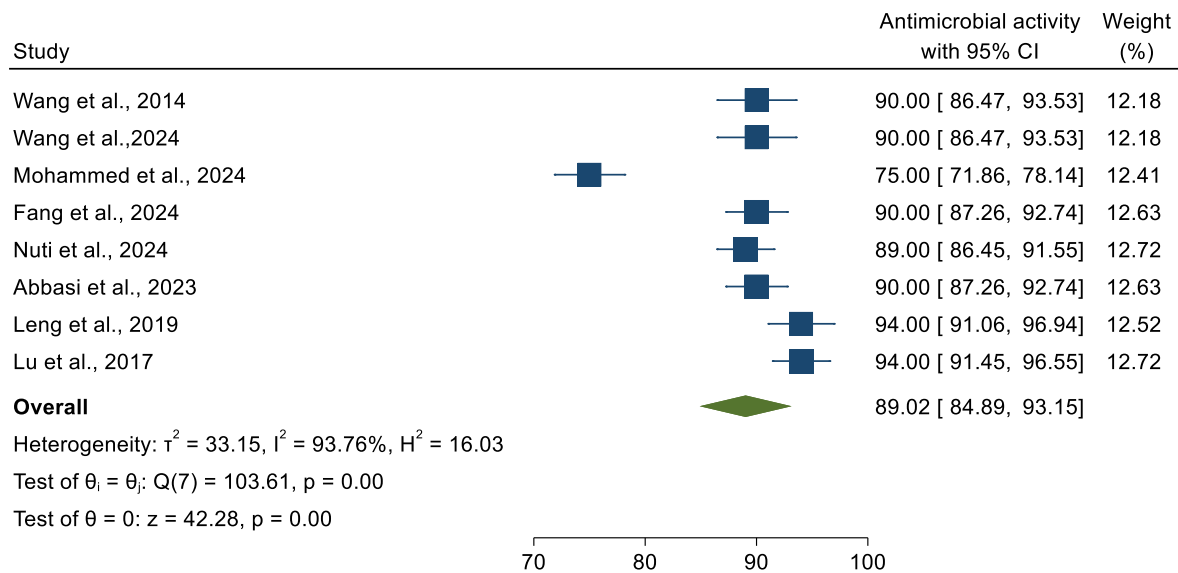
**Antimicrobial Activity of nMS-nAg in Human Root Canals**

The antimicrobial activity of nMS-nAg in human root canals was 89.02% (ES: 89.02) % 95% CI; 84.89%,93.15% (I<sup>2</sup>= 93.76% P<0.001)) (Fig. 3). The number of bacteria after using nMS-nAg was visibly reduced.



Random-effects REML model

Fig. 2. Forest plot showed Mean differences in Biofilm between the nMS-nAg and the control groups.



Random-effects REML model

Fig. 3. Forest plot showed antimicrobial activity of nMS-nAg in Human Root Canals.

#### 4. Discussion

Periodontitis and periodontal treatments often cause gum recession, exposing the roots to the oral environment and increasing the risk of root tooth decay.<sup>[29]</sup> nMS is a promising drug delivery platform characterized by intelligent, targeted delivery, pH-dependent drug release, and high drug loading capacity.<sup>[30]</sup> MS-nAg-Chx has good biosafety and strong antibacterial properties.<sup>[22]</sup> Modified nMS could deliver active ingredients to microorganisms and achieve targeted tissue release.<sup>[26]</sup> Previous studies examined the influence of nMS-nAg-Chx on the viability of different cell types.<sup>[22, 31]</sup> All included studies showed that nMS-nAg had no adverse effects in vivo and had lower cytotoxicity than Chx and nAg. The research found that nMS-nAg-Chx with acid responsibility can specifically target infectious sites to sterilize them without causing an imbalance in oral balance. Active drug release is enabled by the direct placement of nMS-nAg-Chx at subgingival sites to combat microbial attacks in a sustained or controlled manner.<sup>[32]</sup> Therefore, the antibacterial efficacy and biocompatibility of nMS-nAg-Chx were superior to those of Chx or nAg alone, indicating a lower risk of sustained-release drug resistance. The present study showed high antimicrobial activity of nMS-nAg in Human Root Canals, and Biofilm was significantly lower in the nMS-nAg group. It may be easier for nMS-nAg to penetrate complex root canal sites such as the apical divergence than for other drugs because, in the included studies, the diameter of nMS-nAg in SEM is significantly smaller than the diameter of dentinal tubules. According to another study, the biggest advantage of nanomaterials is their small size, which allows them to penetrate the side canals and the third apical branches of the apical canal. There is now an improvement in the depth of penetration into the dentinal tubules. The use of nanomaterials has increased. The main factors that allow it to work at low concentrations are its effective use and release in response to the unique environment in which microorganisms are found. However, further studies are required to determine the effectiveness of nMS-nAg as an intracanal drug in stimulating and promoting the mineralization of periodontal tissues. The advantages of nanoparticles over macroactive agents such as Ca(OH)<sub>2</sub> include antimicrobial activity, mechanical reinforcement, aesthetics, and therapeutic effect. In endodontics, it can be argued that the advent of nanomedicine has revolutionized the field. But first, the legal, ethical, and regulatory concerns must be clarified.

#### 5. Conclusion

According to the present meta-analysis, nMS-nAg exhibits potent antimicrobial activity for endodontic treatment. To eradicate any remaining pathogens associated with periodontitis and stop root caries, nMS-nAg holds promise as an adjuvant treatment for periodontitis.

#### Conflict of Interest

The authors declared that there is no conflict of interest.

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