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Review Article

Antibacterial Efficacy of Chlorhexidine in Endodontic Treatments: A Systematic Review of Recent Evidence on Biofilm Inhibition and Clinical Outcomes

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CLINICAL SIGNIFICANCE

Chlorhexidine, particularly at a 2% concentration, significantly reduces bacterial load and inflammatory markers in endodontic treatments. Optimized use improves periapical healing, making it an effective final irrigant while minimizing cytotoxic risks through

ABSTRACT

Objectives: This systematic review aims to evaluate the recent evidence on the antibacterial efficacy, biofilm inhibition, and clinical outcomes of chlorhexidine (CHX) in endodontic treatments. Recognized for its potent antimicrobial properties and minimal toxicity, CHX is widely utilized as an irrigant, yet its clinical benefits and potential cytotoxic effects require further exploration.

Materials and Methods: Following PRISMA guidelines, a comprehensive search was conducted in PubMed, focusing on studies published within the last three years. Nineteen studies meeting the inclusion criteria were analyzed. Data on CHX concentrations, application methods, and clinical outcomes were extracted, and the findings were categorized based on diagnoses, concentrations used, and effects observed.

Results: Among the included studies, 63% investigated CHX as a standalone irrigant, while 37% assessed its combination with other solutions. The most commonly used concentration was 2%, demonstrating significant efficacy in reducing bacterial loads and inflammatory markers, particularly in apical and asymptomatic apical periodontitis. As a final irrigant, CHX effectively reduced E. faecalis and lipopolysaccharide levels, promoting periapical healing. However, 0.12% CHX showed limited efficacy and cytotoxic effects, especially on periodontal ligament fibroblasts. Studies highlighted concerns about cytotoxicity and tissue solubility, emphasizing the importance of concentration optimization.

Conclusion: Chlorhexidine, especially at a 2% concentration, is effective in endodontic treatments, offering antimicrobial and anti-inflammatory benefits. Careful application protocols are essential to minimize cytotoxic risks. Further research is needed to refine its clinical use and establish standardized guidelines.

1. Introduction

Chlorhexidine has been identified as a highly effective endodontic agent, recognized for its broad-spectrum antibacterial properties and minimal toxicity. These attributes, along with its lack of tissue-dissolving capabilities, underscore its significance in endodontic applications. Notably, chlorhexidine exhibits antimicrobial effects comparable to sodium hypochlorite in endodontic procedures.[1] Furthermore, its sustained antimicrobial activity post-application significantly reduces intra-canal microbial flora, making it a valuable asset in endodontic practice.[2,3]

In addition to its use as an irrigant, chlorhexidine has found application in various aspects of endodontic treatment. It is commonly employed in endodontic re-treatment procedures, particularly as a final irrigant to eliminate resistant microorganisms such as Enterococcus faecalis.[1] Furthermore, chlorhexidine is sometimes combined with calcium hydroxide as an intracanal medicament to enhance periapical healing. Its prolonged antimicrobial effect, even after application, helps in reducing the microbial load in persistent infections.[2]

Chlorhexidine plays a crucial role in maintaining the stability of dentin collagen fibrils during endodontic treatments. This is particularly relevant in preventing the degradation of the hybrid layer, which can be caused by enzymatic activity.[2,4-7] By inhibiting matrix metalloproteinases (MMPs), chlorhexidine preserves the integrity of the dentin bonding interface.[7-9] Additionally, it can be applied alongside other bonding agents, ensuring stronger adhesion between composite materials and acid-etched enamel. This application supports both the durability of the adhesive bond and long-term treatment success.[9-11]

The objective of this systematic review is to critically evaluate the recent literature on the use of chlorhexidine in endodontic treatments, focusing on studies published in the last three years. The review will systematically assess chlorhexidine's antibacterial efficacy, particularly in biofilm inhibition, and its clinical success at different concentration levels. This approach aims to synthesize current evidence and provide a comprehensive understanding of chlorhexidine's effectiveness as an irrigating solution, offering valuable insights for endodontic practitioners in clinical decision-making.

2. Materials and Methods

2.1. Guidance

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The PRISMA checklist was followed to ensure comprehensive reporting, including transparent study selection, data extraction, and analysis.

2.2. Search strategy

A systematic electronic search was conducted in PubMed, utilizing the keywords "chlorhexidine" and "endodontics treatment," while excluding terms such as "antibiotics" and "probiotics." The search was restricted to articles published in the last three years to ensure the inclusion of recent studies. No additional filters were applied beyond limiting the search to English-language studies. The screening process involved reviewing titles, abstracts, and full-texts to identify relevant studies for further analysis. The last search was conducted on 21.06.2024.

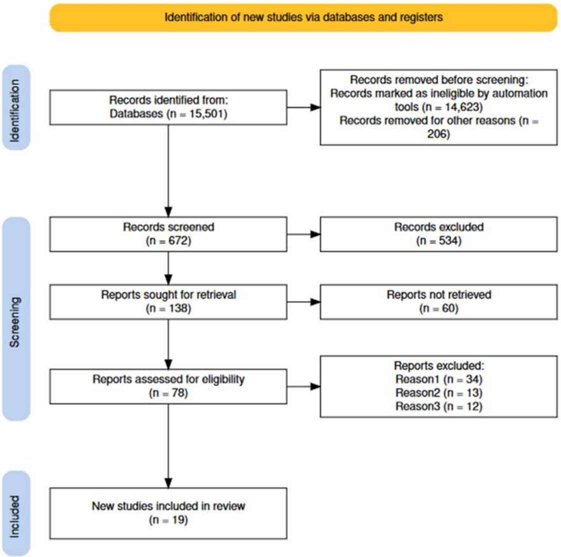

Fig. 1. Flow diagram of the study protocol

2.3. Eligibility Criteria

This review included studies that specifically examined the use of chlorhexidine as an irrigation solution during endodontic procedures. Articles were included if they were published in the last three years, written in English, and contained the keywords "chlorhexidine" and "endodontic treatment." Studies combining chlorhexidine with antibiotics or probiotics were considered eligible if the data focused on chlorhexidine's application within the pulp chamber or root canals. This review included original research and review articles that investigated the application of chlorhexidine in endodontic treatments. Studies such as case reports, and editorials were excluded to ensure the inclusion of primary data and clinical trials focusing on chlorhexidine's use as an irrigant.

2.4. Study Selection Process

Three independent reviewers (IR, MK, and KS) conducted the initial screening and analysis of the articles. The reviewers were familiarized with the study's objectives and applied predefined inclusion and exclusion criteria. Any disagreements during the selection process were discussed and resolved through consensus with the assistance of a fourth expert (SH) to ensure impartiality. The final selection of articles was determined collaboratively. A thorough screening and selection process was conducted to identify relevant studies for inclusion in this review. Initially, 15,501 records were identified from various databases. Of these, 14,623 records were removed by automation tools due to ineligibility, and 206 records were excluded for other reasons. This left 672 records to be screened. After screening, 534 records were excluded, and 138 reports were sought for retrieval. Unfortunately, 60 of these reports could not be retrieved.

Subsequently, 78 reports were assessed for eligibility. At this stage, 34 reports were excluded for Reason 1, 13 for Reason 2, and 12 for Reason 3, which could reflect methodological issues, incomplete data, or failure to meet specific criteria. Ultimately, 19 studies 1-19 met the inclusion criteria and were incorporated into the final review. This selection process demonstrates the rigorous approach used to ensure that only high-quality and relevant studies were included in the analysis (Fig.1).

Table 1. Data on the type of articles included in the study presented depend on the indication of the application of chlorhexidine as a canal irrigant, undiluted as a solution by itself, or as combined with other irrigating solutions.

CHX	**CHX-other irrigators**
Karaoglan F et al.[2]	Tonini R et al.[1]
Kichler V et al.[4]	Jeong JW et al.[3]
Rasaiah SR et al.[5]	Gabrielli ES et al.[7]
da Silva TA et al.[6]	Corrazza BJM et al.[10]
Minavi B et al.[8]	Teixeira FFC et al.[16]
Tandon J et al.[9]	Godoi-Jr EP et al.[17]
Eren SK et al.[11]	Martinho FC et al.[18]
Teixeira FFC et al.[12]	
Yao Y et al.[13]	
Hajihassani N et al.[14]	
Jose J et al.[15]	
Kurt SM et al.[19]	
12 articles – 63%	7 articles – 37%

2.5. Data Extraction

Data were extracted based on predefined criteria, including the method of chlorhexidine application (as a standalone irrigant or in combination with others), the specific endodontic diagnosis where chlorhexidine was indicated for root canal irrigation, and the concentration of chlorhexidine used. The extraction focused on identifying the most effective concentrations and their associated success rates, as reported in the selected studies.

2.6. Risk of Bias Assessment

Due to the wide range of included studies, spanning from clinical trials to in vitro studies, a formal risk of bias assessment using standardized criteria was deemed inappropriate. The variability in study designs and methodologies made it challenging to apply a uniform assessment tool. As a result, a risk of bias evaluation was not performed for this review.

3. Results

PRISMA diagram flow shows the process of selecting articles in a visual way shown in Figure 1. After analyzing the studies selected in this study, based on the selection criteria, data collection and processing are presented in the following tables. Table 1 shows the distribution of articles based on whether chlorhexidine is indicated to be used alone as a solution or in combination with other endodontic solutions during the irrigation process of the canal where it is applied. In the analysis of studies investigating the use of irrigants in endodontic treatment, a total of 19 articles were reviewed. Among these, 12 articles (63%) focused exclusively on the use of CHX as the primary irrigant. These studies, conducted over several years, assessed the effectiveness, and application of CHX in root canal treatments. In contrast, 7 articles (37%) explored the use of CHX in combination with other irrigators or compared

Table 2. The division of articles according to the in vivo, in vitro or review category and specific endodontic diagnoses. This classification method once again specifically shows the effect of chlorhexidine as an endodontic irrigant based on the type of study performed.

Type of study **Endodontic diagnosis**	**In vivo**	**In vitro**	**Total**
Apical Periodontitis	7 articles[7,9,10,12,13*,16,18] – 36%	2 articles[8,13*] – 11%	9 articles – 47%
Asymtomatic apical periodontitis	3 articles[2,6,19] – 16%	1 article[17] – 5%	4 articles – 21%
Symptomatic apical periodontitis	1 articles[10] - 5%	-	1 article – 5%
No specific diagnosis	0 – 0%	5 articles[3,4,11,14,15] - 26%	5 articles – 26%
Total	11 articles – 58%	8 articles – 42%	19* – 100%

* This article has been mentioned twice since the analysis carried out in the study included in this article was carried out in parallel both in vivo in humans and in vitro for laboratory analysis of samples taken from oral cavities. Hence, the number of articles in total endodontic comes out at or 1 greater. The percentages were calculated from the total number of items from table no. 2.

it to alternative solutions.

Table 2 presents the articles based on the type of case report study, cross-sectional or retrospective of the in vivo category articles, divided according to specific endodontic diagnoses. The included studies were categorized based on their focus on different types of endodontic diagnoses and the methodology used. A total of 19 studies were analyzed, with 58% (11 studies) being in vivo, 42% (8 studies) in vitro, and 5% (1 study) as a review. The most commonly investigated condition was apical periodontitis, accounting for 47% of the studies, with 36% being in vivo and 11% in vitro. Asymptomatic apical periodontitis was the second most common diagnosis, with 21% of the studies, 16% of which were in vivo and 5% in vitro. Only 5% of the studies focused on symptomatic apical periodontitis, represented by a single in vivo study. Additionally, 32% of the studies did not specify a particular diagnosis, with 26% of these being in vitro and 5% being a review. This distribution highlights a stronger focus on apical periodontitis and a preference for in vivo studies across the included literature.

Table 3 shows data on the indicated proportion of chlorhexidine as an endodontic irrigant. The studies were categorized based on the concentration of CHX used and the type of endodontic diagnosis. Out of 19 total studies, the majority (84%) used 2% CHX, while only 10% used 0.12% CHX, and 5% did not specify the CHX concentration. Apical periodontitis was the most commonly studied condition, with 42% of the articles focusing on this diagnosis, all using 2% CHX. Similarly, 21% of the studies investigated asymptomatic apical periodontitis, with all of them also using 2% CHX. Symptomatic apical periodontitis was addressed in just 1 study (5%), which used 0.12% CHX. For studies with no specific diagnosis, 31% of the articles fell into this category, with a mix of CHX concentrations: 5% used 0.12%, 21% used 2%, and 5% did not specify. Overall, the data shows a clear preference for 2% CHX in the majority of the included studies, especially for apical and asymptomatic apical periodontitis.

Table 4 shows specifically the effects of chlorhexidine 0.12% classified as negative or positive effects, based on the dune data of the articles included in the analysis. The effects of 0.12% CHX were examined in two distinct endodontic contexts. In studies with no precise diagnosis, 0.12% CHX was found to have a negative effect due to its cytotoxicity against periodontal ligament fibroblasts. On the other hand, in cases of symptomatic apical periodontitis, 0.12% CHX demonstrated a positive effect by effectively reducing contamination during emergency pulpotomy, targeting microorganisms such as S. epidermidis, S. aureus, P. aeruginosa, and fungi. Overall, the findings show an equal balance between positive and negative effects, with one article reporting cytotoxic risks and another highlighting its antimicrobial benefits.

Table 4. This table shows the data or conclusions of the articles included in the study classified as positive or negative effects of endodontic application of chlorhexidine 0.12%.

Effect of 0.12% CHX Endodontic diagnoses	Negative effect	Positive effect
No precise diagnosis	0.12% CHX has cytotoxicity against periodontal ligament fibroblasts.(4)	-
Symptomatic apical periodontitis	-	Reduces contamination during emergency pulpotomy by acting on S. epidermidis, S. aureus, P. aeruginosa and fung.(5)
Results	1 article / 1article - rate 1:1	

Table 5 shows all the articles that analyze the clinical effect of the application of chlorhexidine 2% during root canal treatments, classified as negative effects or positive clinical effects. The effects of 0.12% CHX as an endodontic irrigant were analyzed across various diagnoses, showing both positive and negative outcomes. For apical periodontitis, CHX had negative effects such as failing to reduce periapical inflammation markers and being less effective in reducing bacterial load across multiple species. However, its positive effects included reducing lipopolysaccharide levels, being highly effective against E. faecalis, and decreasing inflammation markers like IL-10, IL-17, and IL-21 after 14 days, making it a recommended final irrigant for endodontic re-treatments. In cases of asymptomatic apical periodontitis, while CHX did not contribute to periapical tissue healing and factors like gender and age influenced the prognosis, it was found to significantly reduce bacterial load, aiding in the healing of endodontic lesions. For symptomatic apical periodontitis, no effects—positive or negative—were reported.

In studies with no precise diagnosis, negative effects included CHX toxicity to human fibroblasts and interactions with heavy metals in irrigants, while positive effects included effectiveness against E. faecalis. Overall, with a ratio of 1:1.3 between negative and positive effects, 0.12% CHX demonstrated some cytotoxic risks but also showed strong antimicrobial properties, particularly in reducing inflammation and bacterial load in endodontic treatments.

Table 3. This table presents the data collected from the processing of the articles included in the study classified according to endodontic clinical diagnoses and the chlorhexidine solution that was taken in the study.

Percentage of CHX Endodontic diagnoses	0.12%	2%	No % specified	Total
Apical Periodontitis	-	Gabrieli et al.2022[7] Minavi et al.2021[8] Tandon et al.2022[9] Corazza BJM et al.2021[10] Teixera FFC et al.2022[12] Yao Y et al.2021[13] Teixeira FFC et al. 2022[16] Martinho FC et al.2023[18] – 8 articles 42%	-	8 – 42%
Asymtomatic apical periodontitis	-	Karaoglan F et al.2022[2] da Silva TA et al.2023[6] Godoi-Jr Ep et al.2023[17] Kurt SM et al.2022[19] – 4 articles 21%	-	4 – 21%
Symptomatic apical periodontitis	Rasaiah et al. 2021[5] – 1 article (5%)	-	-	1 – 5%
No specific diagnosis	Kichler et al. 2021[4]- 1 artikull (5%)	Jeong JW et al. 2021[3] Eren SK et al. 2022[11] Hajihassani N et al. 2022[14] Jose J et al. 2021[15] - 4 articles 21%	Tonini R et al. 2022[1] – 1 article 5%	6 – 31%
Total	2 articles– 10%	16 articles – 84%	1 article – 5%	19 – 100%

Table 5. Data collected from the articles included in the study based on the conclusions with positive effects or negative effects of the application of chlorhexidine as an endodontic irrigant.

Effect of 0.12% CHX Endodontic diagnoses	Negative effect	Positive effect
Apical periodontitis	$CHX\text{-}Ca(OH)_2$ does not reduce PA inflammation markers, whereas N-acetylcysteine does.[10] $CHX\text{-}Ca(OH)_2$ reduces the bacterial load in quantity but not in multiple species of bacteria .[18]	Intracanal $CHX\text{-}Ca(OH)_2$ reduces lipopolysaccharide but not lipoteichoic acid levels that cause clinical symptoms.[7] Effective from E.faecalis is even taken as a control unit for other equally effective solutions.[8] Superior effect to E.faecalis is recommended as a final irrigator for endodontic re-treatments.[9] $CHX\text{-}Ca(OH)_2$ reduces the level of MMP1, MMP-2, MMP-9 after 14 days intra-canal.[12] CHX is taken as a control for the effect against E.faecalis.[13] $CHX\text{-}Ca(OH)_2$ decrease the level of IL-10, IL-17, IL-21 causing pain in percussion.[16]
Asymptomatic apical periodontitis	Irrigation stops but does not affect periapical tissue healing.[2] Gender and age influence as prognostic factors after application.[6]	Significantly reduces the bacterial load in the root canals of teeth with indication for endodontic re-treatment.[17] Final rinse to aid in the healing of asymptomatic mandibular endodontic lesions.[19]
Symptomatic apical periodontitis	-	-
No precise diagnosis	NaOCl-CHX toxicity not only to bacteria but also to human fibroblasts.[3] Irrigant that promotes tissue solubility and crystal precipitation.[11] Endodontic sealants interact with heavy metals in irrigants at various incidences.[15]	Effective against E.faecalis.[14]
Results	7 articles / 9 articles - rate 1:1.3	

4. Discussion

This systematic review comprehensively evaluated the efficacy and usage trends of chlorhexidine in endodontic treatments. The majority of the reviewed studies highlighted the widespread use of chlorhexidine, particularly at a 2% concentration, in the treatment of apical periodontitis. Findings emphasize chlorhexidine's antibacterial properties and its effectiveness in reducing microbial load within root canals. However, negative effects such as cytotoxicity risks associated with chlorhexidine were also identified. This study contributes to a better understanding of chlorhexidine's potential positive and negative impacts on clinical success, elucidating its role in endodontic applications.

The data reviewed in this study indicate that the most commonly used concentration of chlorhexidine is 2%, particularly for endodontic diagnoses such as apical periodontitis.[20] This concentration is notable for its positive effects, such as reducing microbial load within root canals and controlling inflammatory markers.[21] However, caution must be exercised, as the extrusion of 2% chlorhexidine into periapical tissues can lead to toxic effects.[22] Conversely, 0.12% chlorhexidine demonstrated a negative profile in certain studies due to its cytotoxic impact on periodontal fibroblasts.[23] These findings underscore the need for careful clinical application of chlorhexidine, emphasizing the importance of optimizing its concentration based on specific treatment protocols.

The findings of this study support the efficacy of chlorhexidine in endodontic treatments while also highlighting significant limitations that must be considered in clinical applications. The effect of chlorhexidine is shown to vary greatly depending on the concentration used, the duration of application, and the type of tissue it interacts with.[24] Given the cytotoxic risks associated with lower concentrations and the potential toxic effects of higher concentrations, establishing appropriate application protocols is crucial. Moreover, further clinical studies are needed to determine whether chlorhexidine is more effective when used alone or in combination with other irrigants. Such research could play a critical role in enhancing the clinical success of chlorhexidine and maximizing patient safety.

Table 2 highlights that the largest proportion of articles on chlorhexidine as an endodontic irrigant focuses on specific endodontic diagnoses. This reflects the primary goal of initial endodontic treatments: the mechano-chemical removal of canal biofilm, which can lead to apical periodontitis due to bacterial virulence factors. Several studies [8,9,17] analyze the efficacy of chlorhexidine as a final irrigant for achieving clinical success in endodontic re-treatments. However, this data contrasts with the greater number of articles that evaluate chlorhexidine as the primary irrigant for asymptomatic apical periodontitis [2,6,17,19], comprising about 13%, compared to only 3% of articles addressing its use in symptomatic apical periodontitis 5. These studies assessed periapical lesions based on radiographic radiolucency changes. Notably, an in vivo study[6] on asymptomatic apical periodontitis concluded that factors such as gender and age influenced the effectiveness of 2% chlorhexidine.

The fact that a significant portion of studies on the efficacy of chlorhexidine were conducted in vivo highlights its importance in evaluating the compound's effectiveness and safety in clinical settings. With in vivo studies comprising 34% of the articles, compared to 25% for in vitro studies, this discrepancy may point to some limitations in correlating laboratory findings with clinical practice. Data from Table 3 reveal that 2% chlorhexidine is the most frequently used concentration, particularly in specific endodontic pathologies such as apical periodontitis, underscoring its effectiveness in reducing bacterial load. However, the limited number of studies focusing on 0.12% chlorhexidine [4,5], especially in symptomatic apical periodontitis cases, suggests a narrower clinical application and possible concerns about cytotoxicity. These findings emphasize the need for careful selection of chlorhexidine concentrations and the development of tailored protocols for specific endodontic diagnoses in clinical practice.

The positive effects of 0.12% chlorhexidine outlined in Table 4 appear to hold less clinical significance compared to its negative effects. Although data is limited, it is clear that irrigation pressure with chlorhexidine, especially when used as a final rinse before endodontic canal filling, must be carefully controlled to avoid passage into the periodontal ligament. According to Table 5, the effectiveness of 2% chlorhexidine, measured as a ratio of negative to positive effects, stands at 1:1.3—indicating a somewhat inconclusive balance. Notably, one of the key negative effects is its potential to impede periapical tissue healing, emphasizing that its application should be restricted to the canal territory. On the positive side, 2% chlorhexidine shows a reduction in inflammatory markers at the periapical level and a significant decrease in bacterial flora, particularly E. faecalis, which is a major cause of endodontic treatment failure.

5. Conclusion

The clinical value of chlorhexidine as a periodontal irrigant is well-established due to its potent antimicrobial properties. Recent trends in scientific research have highlighted its potential in endodontic applications, where it combats periodontal bacterial flora that can extend to the periapex through the root canal system. Chlorhexidine demonstrates favorable clinical effects on periapical endodontic lesions and is often recommended as a final rinse before canal filling, including in cases of endodontic re-treatments. Among the various concentrations, 2% chlorhexidine is the most commonly indicated for endodontic treatments due to its proven effectiveness in reducing bacterial load and controlling inflammation. However, careful attention must be paid to the irrigation technique and pressure during its application, as excessive force may lead to the solution's passage into the periodontal ligament, potentially causing undesirable effects. Therefore, optimizing the use of chlorhexidine by balancing its concentration and application protocol is crucial to maximizing its clinical benefits while minimizing risks.

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Data Availability Statement
The datasets analyzed during the current study are available from the corresponding author.

Ethics Approval
This study was approved by the Albanian University Institutional Ethics Committee (02.11.2023), Tirana, Albania, according to national regulations.

Conflict of Interest
The authors declare that no conflict of interest is available

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