Systematic Review Article

ANTIMICROBIAL ACTIVITY OF NATURAL INTRACANAL MEDICAMENTS IN ENDODONTIC MANAGEMENT OF PERMANENT TEETH: A SYSTEMATIC REVIEW OF IN VIVO STUDIES

ABSTRACT

Background:
Endodontic therapy has long been recognized as the modality for the elimination of microbial infections from the root canal system. Traditionally, calcium hydroxide has been prevalent in the history of intracanal medicaments because of their inherent antimicrobial activity. However, interest in recent years has been in the area of endodontic therapy incorporating natural intracanal medicaments from plant extracts into their protocols. The biocompatibility of these agents, its reduced cytotoxic potential, and other therapeutic properties such as anti-inflammatory and tissue regenerative have all been promising. But the clinical effectiveness of these natural agents is yet to be clearly established, especially in permanent teeth.
Objective:
This systematic review aims at assessing the effectiveness of natural intracanal medicaments in the endodontic treatment of permanent teeth by pooling evidence from in vivo studies regarding their antimicrobial activity, as compared to traditional synthetic agents .
Methodology:
Electronical databases, such as Google Scholar, Web of Science, PubMed, and Scopus were searched for articles published between 2014 and 2021. Rayyan software was used in the screening and management of all articles and, during the study selection, title and abstract screening were done independently by two reviewers. Meta-analysis assessed the pooled effect size of such agents.
Results
Of nearly 2500 articles, only 6 qualified for inclusion. The natural agents Neem, Curcumin, and Propolis demonstrated high antimicrobial activity compared to conventional agents such as calcium hydroxide and chlorhexidine. Neem had the highest antibacterial activity, and Curcumin demonstrated anti-inflammatory effects superior to all else. While results from these natural medicaments demonstrated a broad efficacy, significant heterogeneity was found among the studies at 96% (I^2 =).
Conclusion:
Natural intracanal medicaments are a promising future of efficacy: as good as or even better than traditional synthetic agents applied in endodontic therapy. Some of

them are Aloe vera, Curcumin, Neem, and Propolis, which have been shown to exhibit not only good antimicrobial efficacy but also some degree of anti-inflammatory and tissue-regenerating properties. However, more standardized clinical trials should be designed and well executed to validate their effectiveness, thus defining clear clinical guidelines for permanent teeth use.

Keywords: Antimicrobial activity, Antibacterial effects, Endodontics, Intracanal medicaments, Natural materials

1. INTRODUCTION

Endodontic therapy is crucial for managing microbial infections within the root canal system, necessitating the use of effective intracanal medicaments to eradicate pathogens and promote periapical healing [1]. Conventional agents, such as calcium hydroxide, are widely used in endodontic treatment due to their potent antimicrobial properties and ability to stimulate the formation of mineralized tissue. **Chlorhexidine (CHX)** is also a key agent, particularly valued for its efficacy in retreatment cases. **Triple antibiotic paste (TAP)**, composed of ciprofloxacin, metronidazole, and minocycline, has gained prominence as an effective intracanal medicament, especially in cases involving regenerative endodontics. [2].

Natural intracanal medicaments, derived from plant extracts, present a compelling option due to their biocompatibility, reduced cytotoxicity, and additional therapeutic benefits. Many of these substances exhibit inherent antimicrobial properties while also offering anti-inflammatory and tissue-regenerative effects, making them attractive candidates for endodontic therapy [3]. The ability of these agents to mitigate inflammation and enhance healing processes aligns with the evolving focus on minimally invasive and biologically compatible treatments in dentistry.

Despite the promising potential of natural intracanal medicaments, uncertainty remains regarding their clinical efficacy, particularly in permanent teeth. While numerous in vitro studies have demonstrated the antimicrobial activity of various natural substances, their clinical relevance is often limited. Therefore, understanding their effectiveness in vivo is essential for optimizing treatment outcomes and advancing evidence-based endodontic practice. Randomized controlled trials and prospective clinical studies are imperative to thoroughly evaluate the true effectiveness of these natural agents in clinical settings, establishing standardized protocols for their application in routine endodontic therapy.

This systematic review and meta-analysis aim to consolidate existing literature on the antibacterial efficacy of natural intracanal medicaments, highlighting their mechanisms of action and potential advantages over conventional agents. By synthesizing the findings of these studies, we aim to provide clinicians with valuable insights into the clinical effectiveness of natural intracanal medicaments and emphasize the importance of conducting well-designed, standardized research to inform evidence-based endodontic practice.

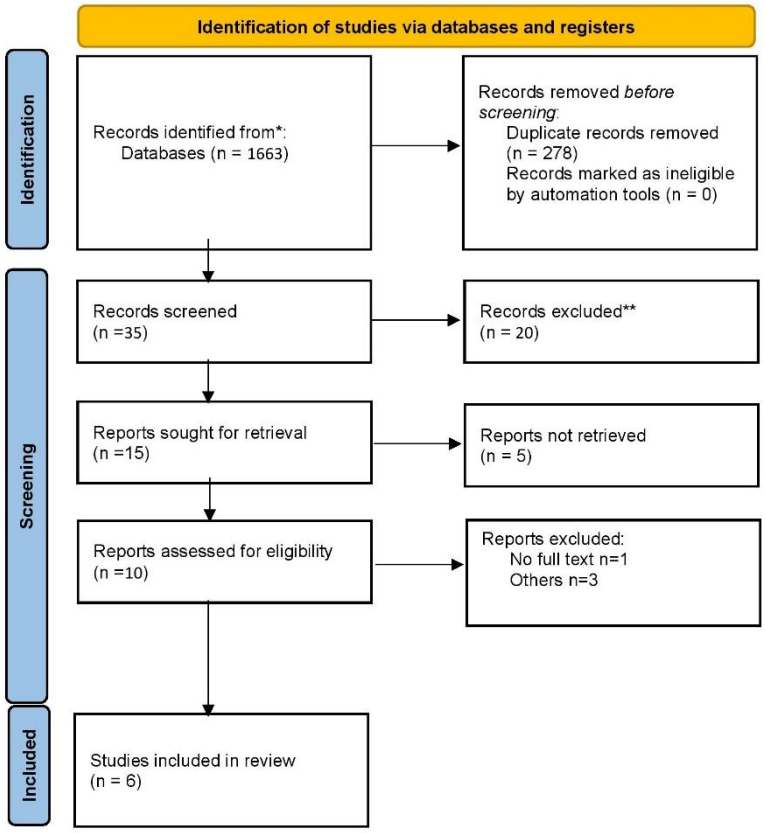
2. MATERIAL AND METHODS

This systematic review followed PICO statement for including the studies, on patients undergoing endodontic treatment in permanent teeth. The intervention under investigation is the utilization of natural materials as intracanal medicaments during endodontic treatment. These natural materials encompass a range of substances including propolis, neem, garlic extract, and others derived from plants. These materials are applied with the aim of disinfecting the root canal system and facilitating healing.The comparison group comprises conventional synthetic medicaments commonly employed in endodontic treatment.The primary outcome of interest is the assessment of the antimicrobial properties of the

intracanal medicaments. This assessment is based on the reduction in microbial colony counts within the root canal system.

2.5 Search Strategy: A comprehensive search strategy was employed, utilizing various electronic databases including PubMed, Scopus, Web of Science, and Google Scholar. The search terms utilized encompassed keywords intracanal medicament OR root canal medicament OR endodontic medicament OR root canal disinfectant AND natural materials OR plant-based materials OR organic materials OR non-synthetic materials AND antimicrobial efficacy OR antimicrobial activity OR antibacterial effectiveness OR microbial eradication OR microbial suppression.The Rayyan software was employed for efficient screening and management of search results.

2.6 Study Selection: The study selection followedPreferred Reporting Items for Systematic Reviews and Meta - analysis(PRISMA) guidelines. Inclusion criteria for study selection encompassed studies published between 2017 to 2021, in vivo studies conducted exclusively in permanent teeth, evaluating the efficacy of natural materials as intracanal medicaments in endodontic treatment, and reporting microbial colony counts as an outcome measure. Exclusion criteria included studies conducted in primary teeth and those not meeting the specified inclusion criteria. (Figure:1)



In total 6 articles are selected based on inclusion and exclusion criteria.

Figure 1: PRISMA flowchart for included studies.

2.7 Data Extraction: Data extraction involved gathering pertinent information from each included study, including author details, publication year, study design, sample size, the

natural material used as an intracanal medicament, and outcomes related to microbial colony counts. (Table 1)

2.8 Quality Assessment: The quality assessment of included studies was conducted using the Risk of Bias 2.0 (ROB 2.0) tool. This comprehensive tool evaluates various domains of study quality, including randomization procedures, allocation concealment, blinding of participants and personnel, completeness of outcome data, selective outcome reporting, and other sources of bias. Any disagreements between reviewers(1st author and 2nd author)were handled through discussion or consultation with a third reviewer (3rdAuthor)to reach a consensus.

3. RESULTS

3.1 Quality assessment results:

The quality assessment using the ROB 2.0 tool found that the majority of studies had a low risk of bias. Overall, while the majority of the included studies demonstrated a high level of methodological rigor, Samta Khetarpal et al. (2014) stood out as having a high risk of bias in certain aspects. (Figure2)

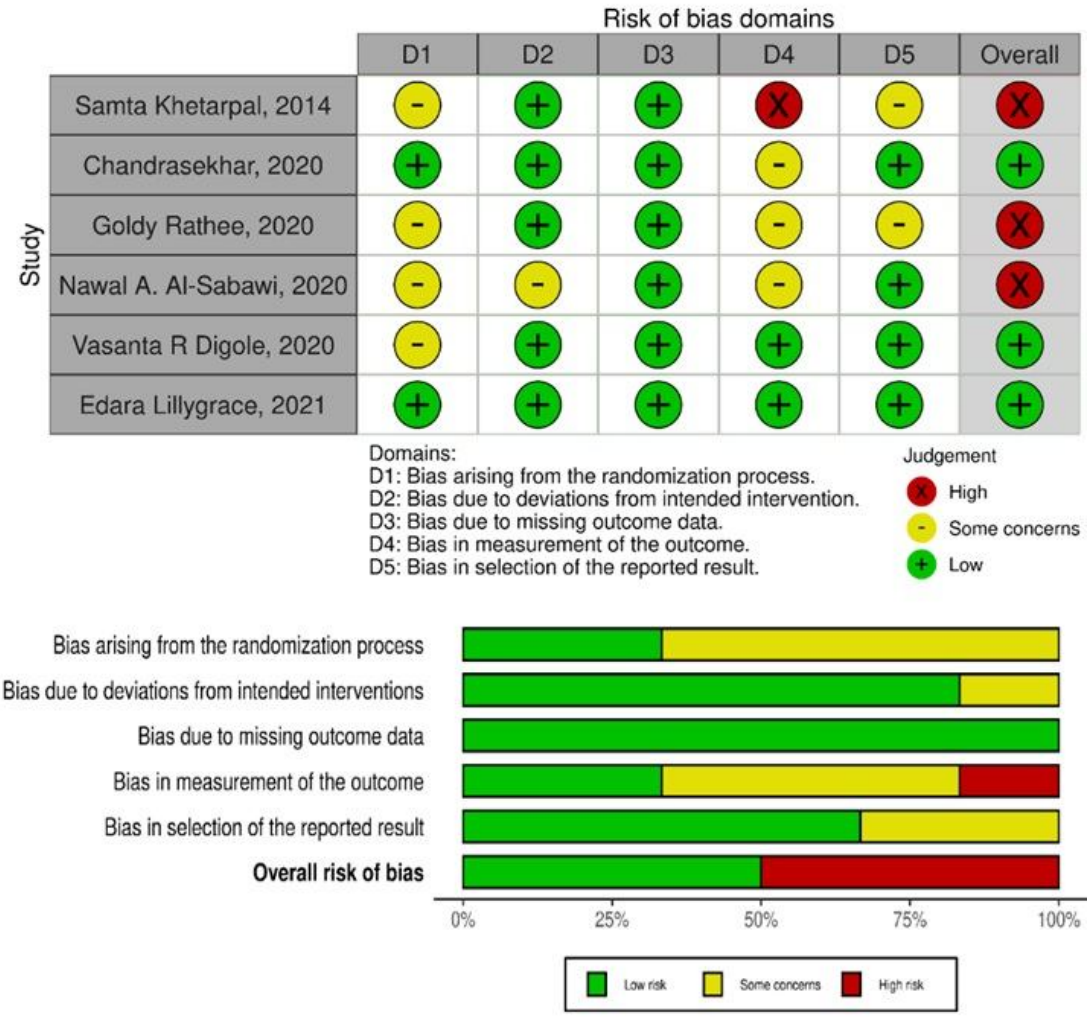


Figure 2: Risk of Bias Assessment graph using ROB 2.0 tool

3.2 Data extraction Result:

A total of six studies were included in the systematic review, comprising research conducted in India and Saudi Arabia between 2014 and 2021. The studies varied in design, with two randomized controlled trials, one non-randomized controlled trial, one experimental study, one prospective randomized controlled study, and one randomized single-blinded clinical trial.

Regarding the antimicrobial efficacy of different intracanal medicaments, including natural materials and conventional synthetic chemicals, notable findings emerged as mentioned in table 1.Overall, the reviewed studies provide valuable insights into the antimicrobial efficacy of various intracanal medicaments, emphasizing the potential of natural materials as alternatives to conventional synthetic chemicals in root canal therapy.

3.3Meta analysis result:

In the meta-analysis, the effect sizes varied across the six individual studies. The pooled effect size, represented by the diamond at the bottom of the forest plot, indicated aInverse variance method to compare the standardized mean difference (SMD), there is no statistical difference between the two cohorts, the summarized standardized mean difference (SMD) is -0.9 with a 95% confidence interval of -11.47 - 9.68. The test for overall effect does not show a significant effect. A significant heterogeneity was detected ($p<0.01$), suggesting inconsistent effects in magnitude and/or direction. The I2 value indicates that 96% of the variability among studies arises from heterogeneity rather than random chance. These findings highlight the significant impact of the experimental condition compared to the control, warranting further investigation and consideration of potential sources of heterogeneity in future research. (Figure 3)

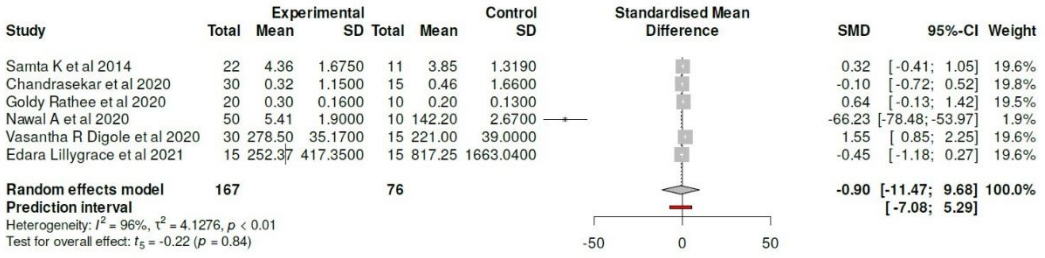


Figure 3: Meta analysis results shown as forest plot mentioning all included studies A to F.

Table 1: Data extracted results from the included studies

Name Year Region	Sample size	Group	Study design	Independent variables	Dependent variables	Outcome measures	Results	Main findings	Limitations	Summary
Samta Khetarpal 2014 India [4]	Total: 33 - Control (Chlorhexidine) : 33 - Neem: 11 - Curcumin: 11 - Aloe vera: 11	Group A – Neem Group B – Curcumin Group C – Aloe vera Control - Chlorhexidine	Non-randomized controlled trial with a parallel design	Type of intracanal medicament used (Neem, Curcumin, Aloe vera, Chlorhexidine)	Antimicrobial and anti-inflammatory properties of the intracanal medicaments (Neem, Curcumin, Aloe vera)	The outcome measured in the study includes antimicrobial activity assessed through microbial colony count scores, anti-inflammatory activity assessed through the Visual Analogue Pain Scale, and the comparison of antimicrobial and anti-inflammatory properties between the test groups (Neem, Curcumin, Aloe vera) and the control group (Chlorhexidine).	The results were statistically non-significant when Neem was compared with Chlorhexidine, and statistically significant when Curcumin and Aloe vera were compared with Chlorhexidine in terms of anti-microbial effect.	Neem showed the highest antibacterial activity, while Curcumin exhibited the highest anti-inflammatory activity compared to Aloe vera and Neem. Curcumin and Aloe vera showed statistically significant results compared to Chlorhexidine in terms of antimicrobial and anti-inflammatory properties.	Many limitations include no hypothesis is stated, inclusion and exclusion criteria is not give properly, whether the guidelines are followed are not is given properly.	The study evaluated the antimicrobial and anti-inflammatory properties of Neem, Curcumin, and Aloe vera as intracanal medicaments in root canal therapy, highlighting their effectiveness compared to Chlorhexidine.
Chandrasekar 2020	Total: 45 - Propolis with	Group I: Propolis with moxifloxacin	Randomized clinical trial,	Type of intracanal	Viable colony-	Reduction in microbial	At the end of the study,	- The study showed a	The limitations	The paper discusses

India [5]	moxifloxacin: 15 - TAP: 15 - Calcium hydroxide: 15	Group II: TAP Group III:Calciumhydroxide	controlled	medicament used (Propolis with moxifloxacin, TAP, Calcium hydroxide),	forming unit counts of E. faecalis and Streptococcus spp. in the root canals after instrumentation and medication sessions	count of Streptococcus spp. and Enterococcus faecalis in the root canals of Type II DM patients with chronic apical periodontitis after treatment with different intracanal medicaments	intragroup differences in E. faecalis and Streptococcus species mean CFU counts in postinstrumentation samples (S1) and postmedication samples (S2) were statistically significant for each of the Groups 1, II, and III. However, intergroup differences and pair wise comparison of E. faecalis and Streptococcus species mean CFU counts from S1 to S2 were statistically nonsignificant ($P > 0.05$) among all the study groups.	significant reduction in microbial count in all study groups from the first to the second session, with no significant difference in the decrease of microbial load between the three groups at the end of 1 week. - The antimicrobial efficacy of TAP, propolis with moxifloxacin, and calcium hydroxide was concluded to be comparable.	of the study include issues related to the sensitivity and specificity of the culture techniques and CFU counts, as well as the experimental design.	the comparable antimicrobial efficacy of TAP, propolis with moxifloxacin, and calcium hydroxide in diabetic patients with chronic apical periodontitis, emphasizing the importance of intracanal medicaments in root canal treatment success.

GoldyRathee 2021 India [6]	Total: 30	Group I: 2% Chlorhexidine gluconate. Group II: Neem juice extract Group III: Tulsi juice extract	Randomized controlled trial	Types of intracanal medicaments used (2% Chlorhexidine gluconate, Neem juice extract, and Tulsi juice extract)	The antibacterial efficacy measured by counting colony-forming units from the samples taken at different stages	Reduction in colony-forming units (CFU) at different stages of root canal treatment: after access opening (S1), after biomechanical preparation and irrigation (S2), and after placing intracanal medicaments (S3)	The results showed a statistically significant reduction among all the groups during intragroup comparison. Among these stages, a significant reduction was seen in group I and group II, group I and group III.	The main findings of the study suggest that herbal products exhibit significant antimicrobial activity in treating primary endodontic infections compared to 2% CHX, supporting their recommendation as effective endodontic irrigants and medicaments. The study underscores the potential of herbal alternatives in root canal therapy.	The limitations of the study are not explicitly stated in the paper. The only indirect reference to limitations is the mention of "within the limitations of this study" before drawing the conclusion. The paper does not provide a specific list of limitations such as sample size, generalizability, bias, or methodological errors.	The paper evaluates the antimicrobial efficacy of herbal products as root canal irrigants and medicaments, showing their significant activity compared to chlorhexidine gluconate, supporting their recommendation for endodontic use.
NawalA Al-Sabawi 2020 Saudi Abrabia [7]	Total - 60	Group I: NS (control –ve) Group II: 2% CHX (control +ve) Group III: FX Group IV: 8% FL Group V: 8% OL Group VI: 8% SP	Experimental study without randomization, blinding, control groups, or placebos, involving both in vitro and in vivo experiments.	- Concentrations of plant extracts (2%, 4%, and 8%) - Types of plant extracts (FX, FL, OL, SP) - Groups for	The dependent variables in Nawal A Al-Sabawi, Ali M Al-Naimi, Eman M Yahya (2020) are: - The antibacterial	Antibacterial effect of plant extracts and chlorhexidine against Enterococcus faecalis for the elimination of E. faecalis	The study found that Ficuscarica latex, Ficuscarica leaves, olive leaves, and Salvadora persica can be used successfully as intracanal	Ficuscarica latex and ethanolic extracts of Ficuscarica leaves, olive leaves, and Salvadora persica roots were effective in eliminating	sample size and distribution, potential bias in patient selection,	The paper evaluates the antibacterial activity of different plant extracts and chlorhexidine against Enterococcus faecalis,

				in vivo study (NS, 2% CHX, FX, 8% FL, 8% OL, 8% SP)	effect of different plant extracts (Ficuscarica latex, Ficuscarica leaves, olive leaves, and Salvadora persica roots) and 2% chlorhexidine against Enterococcus faecalis when used as intracanal medicaments - The mean absorbance values of the different plant extracts and chlorhexidine in vitro - The bacterial counts of the different plant extracts and chlorhexidine in vivo	from the root canal when used as intracanal medicaments	medicaments due to their antibacterial effect against most microbial flora in the root canal, especially E. faecalis. The in vivo study confirmed their antibacterial effect against E. faecalis, which was considered the first clinical study evaluating the effectiveness of these intracanal medicaments against E. faecalis. These plant extracts were biocompatible and some of them had chelating effect. The bacterial counts of these plant extracts	Enterococcus faecalis, potentially serving as alternative intracanal medicaments. - The antibacterial effect of these plant extracts was comparable to 2% chlorhexidine. - These plant extracts could be valuable in endodontic treatments for disinfection of the root canal system.		concluding that certain plant extracts can be effective intracanal medicaments.

							were nearly similar and significantly not different from each other, and significantly different from NS.			
Vasantha R Digole 2020 India [8]	Total: 45 - Curcumin: 15 - Aloe vera: 15 - Calcium hydroxide: 15	Group I – Curcumin Group II – Aloe vera Group III - Calcium hydroxide	prospective randomized controlled study	Type of intracanal medicament used (Curcumin, Aloe vera, Calcium hydroxide)	Post-operative bacterial CFU counts	Percentage decrease in bacterial numbers in postoperative samples compared to preoperative samples for each group	The study analyzed the effects of disinfection procedures on microbial colony counts in endodontic treatments using Curcumin, Aloe vera, and Calcium hydroxide. The data was statistically analyzed using Statistical Package for Social Sciences (SPSS). P-value<0.05 is considered to be statistically significant.	Curcumin showed the highest antibacterial efficacy as an intracanal medicament, followed by calcium hydroxide and aloe vera.	The limitations of the study include a small sample size per group, inaccessibility of paper points to accessory canals, and the suggestion for a longer follow-up study and radiographic assessment of periapical lesions.	The paper evaluates the antimicrobial efficacy of curcumin, aloe vera, and calcium hydroxide as intracanal medicaments, with curcumin showing the highest antibacterial efficacy.

EdaraLillygrace 2021 India [9]	Total: 30 - Triple antibiotic paste: 15 - Propolis: 15	Group I—triple antibiotic pasteGroup II - propolis	Randomized single-blinded clinical trial	Type of intracanal medicament used (Triple antibiotic paste and Propolis extract)	Bacterial count in the root canal samples collected at different stages of treatment	Bacterial colony count in the root canals at three different time intervals: after access opening, after irrigation, and after 3-4 weeks	Both group results are shown with their standard deviations, as well as p-values. The p-values for S1 in both groups were significant. However, none of the mean colony counts for the two groups were statistically significant, meaning there were no significant differences in antibacterial efficacy between the two groups.	propolis was found to be more effective at reducing bacterial colonies in the root canal system. The mean colony count of the samples treated with propolis was significantly lower than that of samples treated with triple antibiotic paste	small sample size, no long term follow-up (Not mentioned in article)	The study evaluates propolis and triple antibiotic paste as intracanal medicaments in young permanent teeth, finding propolis to have comparable antimicrobial efficacy to triple antibiotic paste.

4. DISCUSSION

The results of this systematic review and meta-analysis underscore the potential of natural intracanal medicaments as viable alternatives to conventional synthetic agents in endodontic therapy. Various natural agents, including *Aloe barbadensis* (Aloe vera), *Curcuma longa* (Curcumin), *Azadirachtaindica* (Neem), *Ocimum sanctum* (Tulsi), *Propolis*, *Salvadora persica* (Miswak), and *Ficuscarica* (Fig), were highlighted for their antimicrobial efficacy against endodontic pathogens.

4.1 Aloe Vera (A. vera)

The antibacterial properties of *A. vera* are primarily due to its ability to disrupt the bacterial cell membrane, inhibit cellular respiration, and interfere with membrane synthesis, leading to cell leakage and subsequent bacterial death.Aloe vera (*Aloe barbadensis miller*) exhibits antimicrobial activity through its bioactive compounds like anthraquinones, saponins, and aloin, which disrupt microbial cell membranes and inhibit protein synthesis. It targets both Gram-positive and Gram-negative bacteria, offering anti-inflammatory and healing benefits.[10], [11][The gel contains active ingredients such as anthraquinones, tannins, myristic acid, curcumin, and nimbidin, which exhibit potent antibacterial and anti-adherence properties, thereby reducing bacterial colonization and adhesion to dentin [12]. Aloe vera also stimulates fibroblast growth and collagen synthesis, promotes pulp cell proliferation, differentiation, and extracellular matrix mineralization, making it a potential agent for use as a medicament in regenerative cases. [13-16]. However, the inferior molecule-binding capacity of *A. vera* to *E. faecalis*, and limited membrane permeability, reduce its efficacy against this specific bacterium Additionally, compared to other herbal remedies that have been tried, anthraquinones in *A. vera* might not be as effective against E. faecalis.[17].

4.2 Curcumin (C. longa)

Curcumin has shown moderate effectiveness in disinfecting dentinal tubules due to its ability to disrupt the bacterial extracellular polysaccharide matrix, affecting cell wall integrity [18]. As a polyphenolic compound, curcumin strongly inhibits bacterial proliferation by hindering the dynamics of FtsZ assembly within the Z-ring, a critical component for bacterial cell division [19]. Furthermore, photoactivated curcumin has been found to be as effective as triple antibiotic paste (TAP) and was able to penetrate deeper into the dentinal tubules [20,21]. However, more research is needed to identify the complete mechanism of action of curcumin as an antibacterial agent.

4.3 Neem (Azadirachtaindica)

The antibacterial properties of neem are largely attributed to nimbidin, a bitter principle extracted from neem that exhibits disrupting microbial cell walls, increasing membrane permeability, and inhibiting protein synthesis[22]. Margolone, margolonone, and isomargolonone, tricyclic diterpenoids isolated from the stem bark, have also been shown to possess potent antibacterial activities [23].

4.4 Tulsi (Ocimum sanctum)

The antibacterial activity of Tulsi is due to the presence of linolenic acid, which has been shown to inhibit the growth of a wide range of bacteria [24]. Tulsi also possesses immunomodulatory effects, enhancing levels of interferon, interleukin-4, and T-helper cells, thereby strengthening the host's defense against infections [25]. Moreover, the ability of Tulsi to reduce silver ions to silver nanoparticles adds to its antibacterial efficacy against both Gram-positive and Gram-negative bacteria [26].

4.5 Propolis

Propolis exerts its antibacterial effect by increasing the permeability of the bacterial cell membrane, disrupting membrane potential, and inhibiting ATP production, which decreases bacterial motility [27,28]. Its efficacy is generally higher against Gram-positive bacteria, due to the distinct structural differences in the outer membrane of Gram-negative bacteria and the presence of hydrolytic enzymes that degrade propolis' active components. Artepillin C, a phenolic compound found in Brazilian propolis, has been shown to exhibit strong antibacterial activity against MRSA *S. aureus* [29].

4.6 Salvadora persica (Miswak)

The antibacterial efficacy of *S. persica* is mainly due to the presence of flavonoids in its ethanolic extract, which interact with bacterial cell walls and inhibit bacterial growth [30]. Flavonoids exert multiple actions, such as inhibiting nucleic acid synthesis, energy metabolism, and disrupting cytoplasmic membrane function.

4.7 Ficuscarica (Fig leaves)

The antibacterial activity of fig leaves is attributed to the presence of flavonoids, tannins, and terpenoids [31]. Flavonoids interfere with bacterial energy metabolism and disrupt membrane integrity, causing bacterial cell death [32,33]. Additionally, tannins bind to bacterial cell walls, leading to protein denaturation and disruption of bacterial metabolism [34]. The terpenoids present in fig leaves may further disrupt bacterial membranes, enhancing their bactericidal effects.

Overall, the herbal agents reviewed in this study show varied mechanisms of antibacterial action, including cell membrane disruption, protein denaturation, and inhibition of bacterial metabolism. While some agents, like *C. longa* and *Propolis*, have shown superior penetration and deeper disinfecting abilities, others like *A. vera* and *Tulsi* provide additional benefits like anti-inflammatory effects and immune modulation. The observed variability in the efficacy of these natural medicaments can be attributed to differences in study design, sample sizes, concentrations used, and variations in intervention protocols.

From a clinical perspective, the transition from conventional agents to natural medicaments in endodontics offers several potential benefits, such as improved biocompatibility, reduced cytotoxicity, and additional therapeutic effects, including anti-inflammatory and tissue regenerative properties. However, the current evidence limited by the lack of standardized protocols and the limited number in vivo studies, making it challenging to establish definitive clinical guidelines for the use of these agents in permanent teeth. Future research should focus on addressing these limitations by employing well-designed randomized controlled trials with larger sample sizes and standardized methodologies

5. CONCLUSION

This systematic review demonstrates the potential of natural intracanal medicaments as effective alternatives to conventional synthetic agents in endodontic therapy. The evidence supports the antimicrobial efficacy of various natural substances, including Aloe vera, Curcumin, Neem, and Propolis, which also offer additional benefits like anti-inflammatory and tissue-regenerative properties.

COMPETING INTERESTS

"Authors have declared that no competing interests exist.".

Disclaimer (Artificial intelligence)

Author(s) hereby declare that generative AI technologies such as Large Language Models, etc. have been used during the writing or editing of manuscripts. This explanation will include the name, version, model, and source of the generative AI technology and as well as all input prompts provided to the generative AI technology

Details of the AI usage are given below: Grammer correction and logical flow

1. Quillbot, Grammerly and ChatGPT 3

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