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CARBOHYDRATE-DERIVED FULVIC ACID (CHD-FA) AS A ROOT CANAL IRRIGANT: A SYSTEMATIC REVIEW

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ABSTRACT

Background: Root canal irrigation plays a pivotal role in achieving successful endodontic treatment by eliminating microorganisms, dissolving organic debris, and removing the smear layer. Although sodium hypochlorite (NaOCl) and ethylene diamine tetra acetic acid (EDTA) remain the most commonly used irrigants, their limitations, including cytotoxicity and adverse effects on dentin, have prompted the search for safer and equally effective alternatives. Carbohydrate-Derived Fulvic Acid (CHD-FA), a naturally derived compound with antimicrobial, anti-inflammatory, immunomodulatory and chelating properties, has gained attention as a potential root canal irrigant.
Objective: To systematically evaluate the available evidence on the efficacy and safety of CHD-FA as a root canal irrigant by assessing its antimicrobial effectiveness, smear layer removal capability, biocompatibility, and effects on dentin in comparison with conventional irrigants.
Methods: A systematic review was conducted following PRISMA 2020 guidelines. Electronic databases were searched to identify eligible in vitro, ex vivo, and clinical studies evaluating CHD-FA as an endodontic irrigant. Studies meeting predefined inclusion criteria were screened, and data regarding study design, irrigation protocols, comparator agents, and reported outcomes were extracted and qualitatively synthesized.
Results: The included studies consistently demonstrated that CHD-FA possesses broad-spectrum antimicrobial activity and effective smear layer removal while exhibiting favorable biocompatibility and lower cytotoxicity than conventional irrigants. However, heterogeneity in experimental methods, concentrations, irrigation protocols, and outcome measures limited direct comparisons and precluded quantitative meta-analysis.
Conclusions: Current evidence suggests that CHD-FA is a promising root canal irrigant with the potential to provide effective canal disinfection and smear layer removal while improving biocompatibility. Nevertheless, the existing evidence is predominantly laboratory based. Well-designed randomized clinical trials with standardized protocols are needed to validate its clinical effectiveness and support its routine use in endodontic practice.

KEYWORDS: Carbohydrate-Derived Fulvic Acid (CHD-FA), Root Canal Irrigant, Antimicrobial Activity, Smear Layer Removal, Root Canal Disinfection, Biocompatibility, Systematic Review.

INTRODUCTION

Root canal irrigation is a fundamental step in endodontic treatment, as it complements mechanical instrumentation by eliminating microorganisms, dissolving organic tissue remnants, removing the smear layer, and flushing debris from the root canal system. Because of the complex anatomy of root canals, mechanical preparation alone cannot effectively clean all areas, making chemical irrigation essential for successful treatment outcomes.
An ideal root canal irrigant should exhibit broad-spectrum antimicrobial activity, effective smear layer removal, adequate tissue-dissolving ability, and high biocompatibility without adversely affecting dentin or periapical tissues. Sodium hypochlorite (NaOCl) remains the most widely used irrigant because of its excellent antimicrobial and tissue-dissolving properties. However, its cytotoxicity, unpleasant characteristics, inability to remove the inorganic smear layer, and potential effects on dentin have encouraged the search for safer alternatives. Similarly, ethylenediaminetetraacetic acid (EDTA) effectively removes the inorganic smear layer but has limited antimicrobial activity, while chlorhexidine lacks tissue-dissolving capability.
Carbohydrate-Derived Fulvic Acid (CHD-FA) is a purified, pharmaceutical-grade fulvic acid produced from carbohydrate sources. It has attracted attention in endodontics because of its reported antimicrobial, immunomodulatory anti-inflammatory, antioxidant, and mild chelating properties. Experimental studies suggest that CHD-FA is effective against endodontic pathogens, facilitates smear layer removal, and demonstrates favorable biocompatibility with lower

cytotoxicity than conventional irrigants. These characteristics indicate that CHD-FA may serve as a promising alternative or adjunct to existing irrigation solutions.
Although several in vitro and ex vivo studies have investigated the effectiveness of CHD-FA as a root canal irrigant, the available evidence remains scattered and varies in methodology, concentrations, and outcome measures. Consequently, its overall efficacy and potential clinical application have not been comprehensively evaluated.
Therefore, this systematic review aims to critically assess the current evidence regarding the use of Carbohydrate-Derived Fulvic Acid as a root canal irrigant by evaluating its antimicrobial efficacy, smear layer removal ability, biocompatibility, and effects on dentin compared with conventional endodontic irrigants. The findings of this review may provide valuable evidence to support future research and clinical decision-making regarding the use of CHD-FA in endodontic practice.

MATERIALS AND METHODS

1. Patient, Study, and Public Involvement

As this study is a systematic review of previously published literature, no patients or members of the public were directly involved in the design, conduct, reporting, or dissemination of this review. Ethical approval and informed consent were not required because no primary data were collected.

2. Study Design

This systematic review was conducted to evaluate the available evidence regarding the effectiveness of Carbohydrate-Derived Fulvic Acid (CHD-FA) as a root canal irrigant. The review was designed and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines.

3. Search Strategy

A comprehensive electronic literature search was performed using predefined keywords and Boolean operators. The search terms included "Carbohydrate-Derived Fulvic Acid" OR "CHD-FA" AND "root canal irrigant" OR "endodontic irrigant" OR "root canal irrigation" OR "endodontics". Additional manual screening of reference lists from relevant articles was performed to identify eligible studies that may not have been retrieved through the database search.

4. Inclusion Criteria

Studies were included if they:

- Evaluated CHD-FA as a root canal irrigant.
- Compared CHD-FA with one or more conventional endodontic irrigants.
- Assessed outcomes such as antimicrobial activity, smear layer removal, dentin characteristics, or biocompatibility.
- Were in vitro, ex vivo, animal, or clinical studies.
- Were published in English with full-text availability.

5. Exclusion Criteria

Studies were excluded if they:

- Were review articles, editorials, conference abstracts, letters, or case reports.
- Did not evaluate CHD-FA as an endodontic irrigant.
- Had insufficient outcome data or unavailable full text.
- Were duplicate publications.
- Were published in languages other than English.

6. Information Resources

Electronic databases searched included PubMed/MEDLINE, Scopus, Web of Science, Embase, Google Scholar, and the Cochrane Library. Manual searches of reference lists from selected studies were also conducted to ensure comprehensive literature retrieval.

7. PICO Framework

Component	Description
Population (P)	Extracted human teeth, root canals, endodontic pathogens, or patients undergoing root canal treatment
Intervention (I)	Irrigation with Carbohydrate-Derived Fulvic Acid (CHD-FA)
Comparison (C)	Sodium hypochlorite, chlorhexidine, EDTA, saline, or other root canal irrigants
Outcome (O)	Antimicrobial efficacy, smear layer removal, biocompatibility, dentin effects, and overall irrigation effectiveness

8. Research Questions

This systematic review addressed the following questions:

1. Does CHD-FA demonstrate effective antimicrobial activity against endodontic microorganisms?
2. How effective is CHD-FA in removing the smear layer compared with conventional irrigants?
3. Does CHD-FA exhibit favorable biocompatibility and minimal cytotoxicity?
4. What effects does CHD-FA have on dentin properties?
5. Can CHD-FA be considered a potential alternative or adjunct to conventional root canal irrigants?
6. How effectively does CHD-FA disrupt mature microbial and fungal biofilms compared to traditional chemical agents in in vitro models?

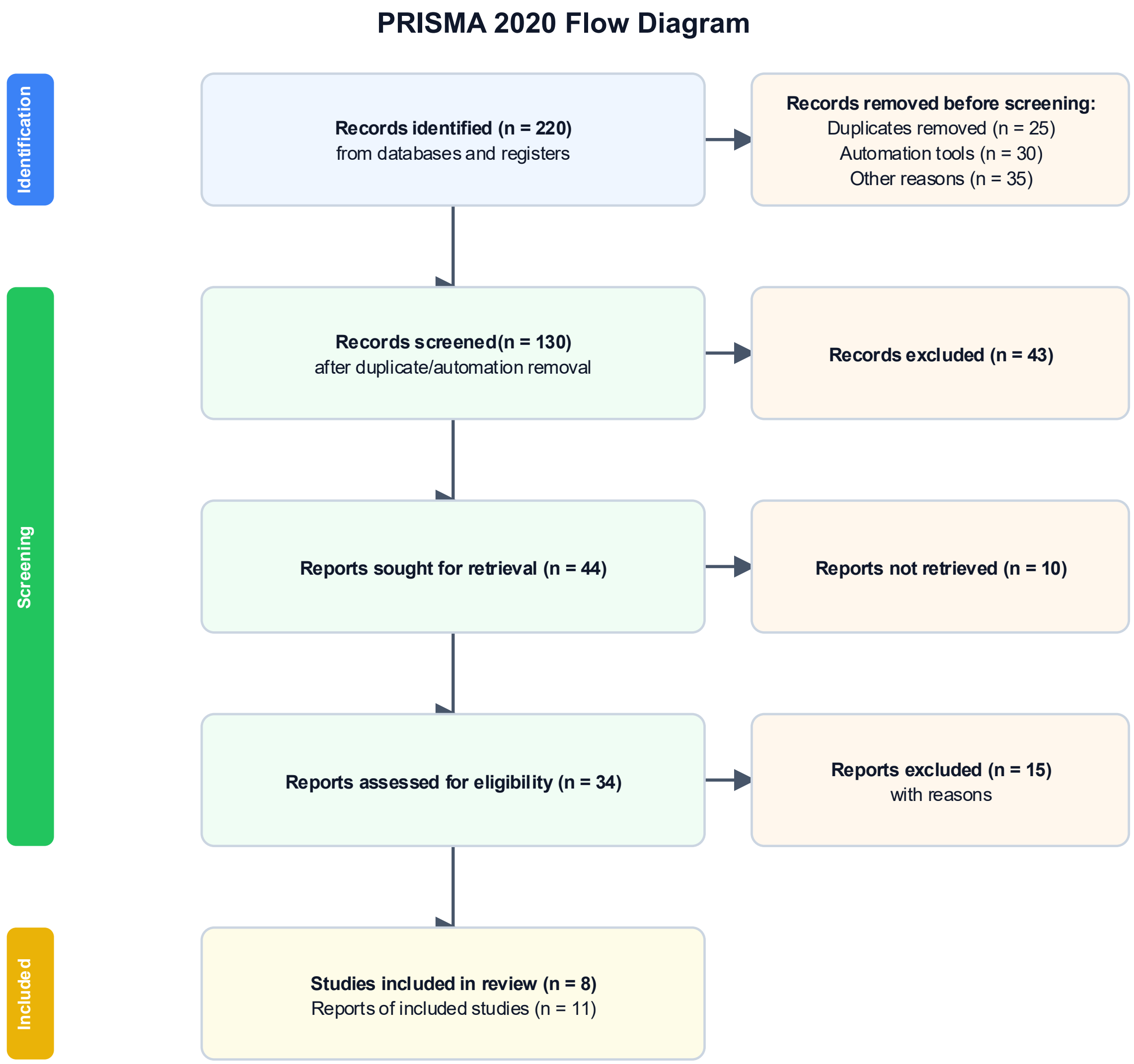
7. What is the impact of topical and systemic administration of CHD-FA on inflammatory mediator pathways and wound healing rates in preclinical animal models?
8. To what extent does CHD-FA maintain root dentin microhardness while successfully removing the smear layer during endodontic root canal preparation?
9. What is the clinical safety, tolerability, and preliminary therapeutic outcomes of CHD-FA when evaluated in human patient populations?

9. Quality Assessment

The methodological quality of the included studies was independently evaluated by two reviewers using appropriate risk-of-bias assessment tools according to study design. Any disagreements were resolved through discussion until consensus was reached. The overall quality of the evidence was considered during data synthesis and interpretation.

10. PRISMA Flowchart

The study selection process followed the PRISMA 2020 guidelines. Records identified through database searching and manual searches were screened after duplicate removal. Titles and abstracts were assessed for eligibility, followed by full-text review. Studies meeting all inclusion criteria were included in the final qualitative synthesis. The selection process is illustrated in the PRISMA flow diagram (Figure 1).



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11.Data Synthesis and Analysis

The extracted data were qualitatively synthesized due to heterogeneity among the included studies in terms of methodology, CHD-FA concentration, evaluation methods, and outcome measures. Findings were grouped based on antimicrobial activity, smear layer removal, biocompatibility, and effects on dentin. A narrative analysis was performed to compare CHD-FA with conventional root canal irrigants and identify current evidence gaps.

RESULTS

Study Selection

The electronic database search identified a total of 220 records. After removal of duplicate records, the remaining articles were screened based on title and abstract eligibility. Full-text evaluation was performed for potentially relevant studies, and studies that did not meet the predefined inclusion criteria were excluded. Finally, 8 studies were included in the qualitative synthesis. The complete selection process is presented in the PRISMA 2020 flow diagram (Figure 1).

Characteristics of Included Studies

The included studies evaluated the potential application of Carbohydrate-Derived Fulvic Acid (CHD-FA) as a root canal irrigant using mainly laboratory-based experimental designs. The studies assessed different properties of CHD-FA, including antimicrobial activity, smear layer removal, dentin interaction, and cytocompatibility. Variations were observed among studies regarding CHD-FA concentration, irrigation protocols, comparison groups, and assessment methods, which limited direct comparison of outcomes.

Antimicrobial Activity of CHD-FA

Most included studies reported that CHD-FA exhibited promising antimicrobial activity against microorganisms commonly associated with endodontic infections. CHD-FA demonstrated inhibitory effects against bacterial species involved in root canal infections, including biofilm-forming microorganisms. Compared with conventional irrigants, CHD-FA showed potential antimicrobial benefits while maintaining favorable biological properties. However, differences in microbial models and testing methods resulted in variability among reported outcomes. [Sherry et al.]

Smear Layer Removal Ability

Studies investigating the cleaning ability of CHD-FA reported effective removal of smear layer components from instrumented root canal surfaces. The chelating characteristics of CHD-FA may contribute to its ability to interact with inorganic components of the smear layer. Although promising results were observed, some studies indicated that its cleaning efficiency may depend on concentration, exposure time, and irrigation technique. Further standardized investigations are required to determine its optimal clinical application. [Arun et al.]

Biocompatibility and Cytotoxicity

The included studies generally demonstrated favorable biocompatibility of CHD-FA compared with some conventional irrigating solutions. CHD-FA exhibited lower cytotoxic effects on biological tissues and cells while maintaining antimicrobial activity. These findings suggest that CHD-FA may offer a safer alternative; however, most evidence is derived from laboratory studies, and clinical validation remains necessary. [Botes et al]

Effect on Dentin Properties

Limited evidence was available regarding the long-term influence of CHD-FA on dentin structure and mechanical properties. Available studies suggested that CHD-FA may cause minimal adverse effects on dentin compared with strongly demineralizing agents. Further studies evaluating bond strength, microhardness, and structural changes are required.

Overall Findings

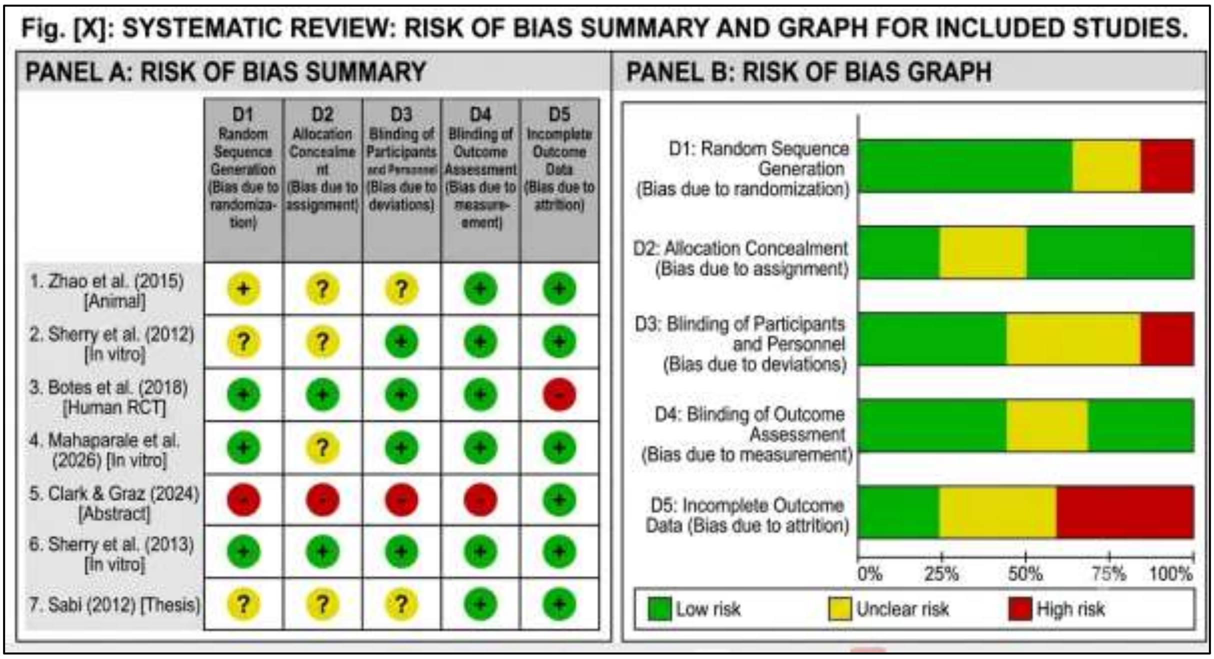
Overall, the included studies indicate that CHD-FA possesses potential as a novel root canal irrigant due to its antimicrobial activity, smear layer modification ability, and favorable biocompatibility profile. Nevertheless, the current evidence remains predominantly based on in vitro investigations, with variations in methodology limiting definitive conclusions. Future well-designed clinical studies are required to establish the effectiveness and safety of CHD-FA in routine endodontic practice.

Risk of Bias

For clinical trials, Botes et al. (2018) was assessed using the Cochrane Risk of Bias 2 tool. The study maintained a low risk of bias regarding its randomization process and double-blind structure, but it carries a high overall risk of bias because the trial was terminated early prior to reaching its target sample size, introducing significant potential for attrition bias and selective outcome reporting.

For animal research, Zhao et al. (2015) was appraised using SYRCLE's risk of bias tool. While the methodology lacked detailed information on allocation concealment and caregiver blinding—resulting in an unclear risk in those specific domains—the overall risk of bias remains moderate to low because the primary histopathological outcomes were independently evaluated by blinded external pathologists. Similarly, Sabi (2012) was evaluated as a master's thesis using SYRCLE guidelines alongside grey literature criteria; it carries a moderate risk of bias due to the absence of formal journal peer review and limited details on housing randomization, despite offering thorough raw data and outcome reporting.

For the in vitro dental and microbiological studies, the modified QUIN tool and CRIS guidelines were applied. Sherry et al. (2012) and Sherry et al. (2013) both demonstrated a low to moderate risk of bias, maintaining strong experimental standardization and reproducible multi-species models, though neither explicitly confirmed operator blinding during optical and microscopic analyses. Mahaparale et al. (2026) and Arun et al. (2022) evaluated dentin microhardness and smear layer removal with standardized irrigation protocols and testing parameters; however, both present a moderate risk of bias because they omitted explicit details regarding random tooth allocation and outcome assessor blinding. In contrast, Clark and Graz (2024) presents a high risk of bias and methodological uncertainty strictly because it was published as a brief conference abstract, leaving core details about experimental controls and blinding unrecorded.



DISCUSSION

The collective evidence from the eight included studies highlights carbohydrate-derived fulvic acid (CHD-FA) as a versatile bioactive compound possessing broad-spectrum antimicrobial, anti-inflammatory, immunomodulatory and chelating properties. Across laboratory assays, animal models, and preliminary human clinical trials, CHD-FA demonstrates significant therapeutic potential in wound care, endodontics, oral healthcare, and mucosal fungal management. A central theme across the literature is its potent membrane-active antimicrobial action against drug-resistant microbial communities. In vitro evaluations by Sherry et al. (2012) and Sherry et al. (2013) demonstrated that CHD-FA effectively disrupts mature Candida albicans and polymicrobial oral biofilms primarily through physical cell membrane destabilization. This physical mechanism is particularly clinically relevant because it significantly reduces the likelihood of pathogens developing conventional drug resistance over time. Translating these laboratory findings to biological tissues, Zhao et al. (2015) confirmed that topical application of CHD-FA accelerates wound healing in rat models infected with drug-resistant pathogens. Furthermore, preliminary findings by Clark and Graz (2024) support its efficacy against Candida species in mucosal conditions such as vulvovaginal candidiasis, reinforcing its broad-spectrum antifungal capacity.

In addition to direct antimicrobial activity, CHD-FA exerts substantial anti-inflammatory and tissue-modulating effects. Preclinical animal research conducted by Sabi (2012) showed that both oral and topical CHD-FA formulations significantly reduce carrageenan-induced paw edema and promote rapid cutaneous wound closure in rats. These therapeutic outcomes were achieved at efficacy levels comparable to conventional non-steroidal anti-inflammatory drugs, without inducing systemic toxicity. When translated to human subjects, Botes et al. (2018) established that an oral CHD-FA formulation was generally well-tolerated in pre-ART HIV-1 positive individuals. However, because that clinical trial was terminated early prior to full subject recruitment, definitive conclusions regarding its long-term impact on systemic disease markers remain limited, highlighting the critical need for adequately powered clinical studies.

In endodontic applications, CHD-FA has emerged as a promising alternative root canal irrigant owing to its organic acid nature and targeted chelating activity. Research by Arun et al. (2022) revealed that a 5% CHD-FA solution successfully removes the root canal smear layer while causing minimal reduction to root dentin microhardness compared to traditional chelating agents such as EDTA. This structural preservation was further substantiated by Mahaparale et al. (2026), who demonstrated that 5% CHD-FA maintains favorable dentin microhardness values, offering a gentler, dentin-preserving alternative for endodontic therapy.

Despite these encouraging findings, several methodological considerations must be acknowledged when interpreting the current body of literature. The included studies display significant heterogeneity, spanning diverse fields from dental laboratory testing to animal wound models and human safety trials, which precludes direct quantitative meta-analysis. Additionally, risk of bias assessments highlighted frequent reporting omissions across preclinical and in vitro studies, particularly regarding explicit random sequence generation, allocation concealment, and assessor blinding. Future research should prioritize well-designed, double-blind randomized controlled trials with standardized formulations to establish optimal clinical dosing, evaluate long-term safety, and fully validate the therapeutic efficacy of CHD-FA across human clinical applications.

Table 1: Characteristics of Included Studies on Carbohydrate-Derived Fulvic Acid (CHD-FA)

Study	Design / Model	Study Focus / Intervention	Key Findings
Zhao et al. (2015)	In vivo (Rat wound model)	Topical CHD-FA on wound infection with drug-resistant pathogens	Significantly enhanced wound healing and reduced bacterial burden without tissue toxicity.
Sherry et al. (2012)	In vitro	CHD-FA against Candida albicans biofilms	Effective biofilm disruption via cell membrane destabilization and physical lysis.
Botes et al. (2018)	Clinical Trial (Human)	Oral CHD-FA wellness drink in pre-ART HIV-1 positive subjects	Generally well-tolerated with acceptable safety profile; study terminated early.
Mahaparale et al. (2026)	In vitro (Human teeth)	5% CHD-FA vs. standard chelators on root dentin microhardness	Maintained favorable dentin microhardness with minimal structural degradation compared to traditional agents.
Clark & Graz (2024)	Abstract / Preliminary	CHD-FA for treatment of vulvovaginal candidiasis	Demonstrated broad-spectrum antifungal activity against mucosal Candida isolates.
Sherry et al. (2013)	In vitro & Cell Culture	CHD-FA on oral polymicrobial biofilms and epithelial cells	Reduced biofilm viability and modulated inflammatory cytokine responses in host cells.
Sabi (2012)	In vivo (Rat model) / Thesis	Oral/Topical CHD-FA on carrageenan inflammation and wounds	Inhibited acute paw edema and accelerated wound closure comparable to standard anti-inflammatory drugs.
Arun et al. (2022)	In vitro (Human teeth)	5% CHD-FA on smear layer removal and root dentin microhardness	Effectively cleared the endodontic smear layer while preserving root dentin integrity.

Table 2 : Biological Mechanisms and Potential Clinical Applications of CHD-FA

Study	Target Organism / Model	Primary Mechanism of Action	Proposed Clinical Application
Zhao et al. (2015)	Drug-resistant bacteria (in vivo rat model)	Disruption of bacterial envelope integrity; suppression of local infection	Topical antimicrobial gel/dressing for infected dermal wounds
Sherry et al. (2012)	Candida albicans biofilms	Direct cell membrane destabilization leading to rapid cellular leakage	Topical or mucosal antiseptic agent for fungal biofilms
Botes et al. (2018)	Pre-ART HIV-1 positive human subjects	Systemic immune modulation and potential viral/inflammatory regulation	Oral nutritional supplement / adjunctive wellness therapy
Mahaparale et al. (2026)	Extracted human teeth (ex vivo dentin)	Controlled chelation of inorganic dentin components without excessive soft tissue destruction	Root canal irrigant for mild, dentin-preserving chelation
Clark & Graz (2024)	Clinical Candida species isolates	Broad-spectrum membrane-active antifungal inhibition	Topical formulation for vulvovaginal candidiasis

Study	Target Organism / Model	Primary Mechanism of Action	Proposed Clinical Application
Sherry et al. (2013)	Polymicrobial oral biofilms & epithelial cells	Simultaneous biofilm disruption and down-regulation of pro-inflammatory cytokines	Oral rinse / gel for periodontitis and peri-implantitis management
Sabi (2012)	Carrageenan-induced edema & wounds (in vivo)	Inhibition of inflammatory mediator pathways (prostaglandins/histamines)	Systemic or topical anti-inflammatory treatment for acute tissue trauma
Arun et al. (2022)	Extracted human teeth (ex vivo root canals)	Organic acid dissolution of organic/inorganic debris (smear layer)	Alternative endodontic irrigant replacing or supplementing EDTA

CONCLUSION

This systematic review highlights carbohydrate-derived fulvic acid (CHD-FA) as a promising, multi-functional therapeutic agent with proven antimicrobial, anti-inflammatory, immunomodulatory and chelating capabilities. Across preclinical research, laboratory assays, and preliminary human evaluations, CHD-FA consistently demonstrates broad-spectrum efficacy—most notably through a membrane-disruptive mechanism that tackles resistant pathogens and fungal biofilms while minimizing the risk of microbial resistance. In dental applications, its ability to effectively remove the endodontic smear layer while preserving root dentin integrity position it as a viable alternative to traditional harsh chelators like EDTA. Furthermore, its anti-inflammatory effects in animal wound models showcase its potential for accelerating tissue repair.

However, translating these encouraging preclinical findings into routine clinical practice requires addressing key knowledge gaps. The current literature is limited by significant study heterogeneity, methodological reporting deficiencies—such as unclarified blinding and allocation protocols—and a scarcity of large-scale human trials. To fully realize CHD-FA's therapeutic potential, future research must focus on well-designed, double-blind randomized controlled trials with standardized formulations to definitively establish its safety, optimal dosing, and long-term clinical efficacy in patient care.

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