REVIEW ARTICLE

CHITOSAN IN PEDIATRIC DENTISTRY : A SYSTEMATIC REVIEW OF CLINICAL EFFICACY, MECHANISMS AND FUTURE PERSPECTIVES

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ABSTRACT

The paradigm shift in pediatric dentistry toward bioactive and immunomodulatory materials has driven the exploration of chitosan, a natural polysaccharide derived from chitin known for its biocompatibility, broad-spectrum antimicrobial activity, and remineralization potential. This systematic review evaluates chitosan's clinical efficacy in caries prevention, vital pulp therapy, and restorative modification compared to gold standards. Electronic databases were searched (2000–2024) for studies involving primary or young permanent teeth.

Results indicate strong clinical outcomes: chitosan achieved a 78% reduction in salivary S. mutans and 56.9% enamel microhardness recovery, significantly surpassing fluoride varnish (29.2%). Furthermore, pulpotomy success reached 96.6%, comparable to formocresol and superior to ferric sulfate, while sealants demonstrated 92.2% retention with reduced caries incidence (7.8% vs. 15.6%). Conclusively, chitosan offers a clinically viable, biologically superior alternative to traditional materials, providing enhanced antimicrobial protection and regenerative outcomes without the toxicity risks associated with aldehydes.

KEY WORDS

Bioactive Materials, Chitosan, Early Childhood Caries, Pulpotomy, Remineralization.

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1. INTRODUCTION

1.1.The Paradigm Shift in Pediatric Biomaterials

The landscape of pediatric dentistry is undergoing a fundamental transformation, moving away from the era of "passive" materials-whose sole function was to occupy space and seal cavities-toward "active" biomaterials that interact dynamically with the host tissues. Historically, the management of Early Childhood Caries (ECC) and pulp pathologies in primary teeth relied on materials like silver amalgam, formocresol, and chemically cured glass ionomers. While functional, these materials presented significant limitations: potential toxicity (as seen with formocresol and amalgam mercury), lack of biological integration, and failure to actively suppress the aggressive microbial biofilms characteristic of ECC.[1]

This "biological apathy" of traditional materials is no longer acceptable in an era prioritizing minimally invasive and regenerative dentistry. The modern pediatric dentist demands materials that can not only restore form but also modulate the immune response, promote tissue regeneration, and actively inhibit cariogenic bacteria without inducing resistance. This need has catalyzed the exploration of natural biopolymers, with chitosan emerging as a frontrunner due to its unique physicochemical properties.

1.2.Chitosan: The Unique Cationic Biopolymer

Chitosan is a linear polysaccharide composed of randomly distributed β-(1→ 4)-linked D-glucosamine (deacetylated unit) and N-acetyl-D-glucosamine (acetylated unit). It is derived from chitin, the structural component of crustacean shells (crabs, shrimp) and fungal cell walls, through a process of deacetylation. What sets chitosan apart from all other natural polysaccharides (like cellulose, starch, or alginate) is its polycationic nature. Under physiological conditions (pH < 6.5), the primary amino groups ($-NH_2$) on the glucosamine units become protonated ($-NH_3^+$). This positive charge density allows chitosan to interact electrostatically with:

1. Bacterial Cell Walls: The negatively charged surface of cariogenic bacteria (e.g., Streptococcus mutans) attracts the cationic chitosan, leading to membrane disruption.[5]

2. Dental Hard Tissues: Both enamel and dentin have net negative surface charges, facilitating the adsorption of chitosan films that can serve as reservoirs for remineralizing ions.[4]

3. Growth Factors and Signaling Molecules: Chitosan can bind and stabilize anionic proteins, making it an ideal scaffold for regenerative endodontics.[33]

1.3. Rationale for this Review

Despite a burgeoning volume of in vitro research, the clinical adoption of chitosan in pediatric dentistry remains fragmented. Practitioners often view it as an experimental material rather than a viable clinical option. Existing reviews have largely been narrative or focused on general dentistry, failing to address the specific physiological challenges of the primary dentition-such as the high organic content of primary enamel, the rapid turnover of primary pulp tissue, and the behavioral constraints of pediatric patients. This systematic review aims to bridge that gap by synthesizing high-level evidence from randomized controlled trials (RCTs) and clinical studies, providing a quantitative "state-of-the-science" assessment of chitosan's efficacy in caries prevention, pulp therapy, and restorative dentistry.

2. MATERIALS AND METHODS

2.1 Protocol and Registration

This systematic review was conducted in strict adherence to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. The review protocol was designed a priori to ensure transparency and reproducibility.

2.2 Search Strategy and Information Sources

A comprehensive, multi-database search was executed to identify all relevant literature published between January 1, 2000, and December 31, 2024. The search encompassed the following electronic databases:

- PubMed / MEDLINE
- Scopus
- Web of Science
- Google Scholar (First 300 results)
- Cochrane Central Register of Controlled Trials (CENTRAL)

The search strategy utilized a combination of MeSH terms and free-text keywords connected by Boolean operators. The core search string was: ("Chitosan"[MeSH] OR "Chitosan derivatives" OR "Chitosan nanoparticles") AND ("Pediatric Dentistry" OR "Primary Teeth" OR "Deciduous Teeth" OR "Mixed Dentition" OR "Child") AND ("Dental Caries"[MeSH] OR "Remineralization" OR "Pulpotomy" OR "Pulp Capping" OR "Fissure Sealants" OR "Antibacterial")

2.3 Eligibility Criteria

Studies were selected based on the following PICOS criteria:

- Population (P): Children (0–18 years) or human primary/young permanent teeth (extracted) used in ex vivo clinical simulations.
- Intervention (I): Administration of any chitosan-based dental formulation (hydrogel, varnish, mouthrinse, restorative material, pulp medicament).
- Comparison (C): Comparison against a "Gold Standard" control (e.g., Formocresol/MTA for pulp therapy, Fluoride Varnish/CPP-ACP for remineralization, Chlorhexidine for antimicrobial efficacy).
- Outcome (O): Quantifiable clinical or laboratory metrics, including:
- Microbiological counts (CFU/mL).
- Surface Microhardness (VHN/KHN).
- Clinical success (absence of pain/swelling).
- Radiographic success (absence of pathology).
- Material retention rates.
- Study Design (S): Randomized Controlled Trials (RCTs), Controlled Clinical Trials (CCTs), and high-quality in vitro studies with direct clinical relevance.

Exclusion Criteria:

- Case reports and case series ($n < 10$).
- Animal studies (unless evaluating toxicity/biocompatibility exclusively).
- Narrative reviews and editorials.
- Studies using chitosan of unknown origin or characterization (lack of deacetylation degree data).

2.4 Study Selection and Data Extraction

Two independent reviewers screened titles and abstracts for relevance. Full-text articles of potentially eligible studies were retrieved and assessed against the inclusion criteria. Discrepancies were resolved by a third expert reviewer. Data extraction was performed using a standardized form, capturing:

- Author/Year/Country.

- Sample size and age group.
- Chitosan characteristics (Molecular Weight [MW], Degree of Deacetylation [DD], Concentration).
- Control material and protocol.
- Follow-up duration.
- Primary and secondary outcomes.
- Statistical significance (P-values).

2.5 Quality Assessment

The risk of bias in RCTs was assessed using the Cochrane Risk of Bias Tool (RoB 2.0), evaluating domains such as randomization process, deviation from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. For in vitro studies, a modified CONSORT checklist for pre-clinical dental studies was applied to ensure methodological rigor.

3. RESULTS

3.1 Search Results and Study Characteristics

The initial search yielded 482 citations. After removing duplicates and screening titles/abstracts, 64 full-text articles were assessed for eligibility. A total of 22 studies met the inclusion criteria and were included in the qualitative synthesis. These studies were categorized into four clinical domains:

1. Preventive Antimicrobial Efficacy (n=6)
2. Enamel Remineralization (n=7)
3. Pulp Therapy and Regeneration (n=5)
4. Restorative Material Modification (n=4)

3.2 Preventive Efficacy: Antimicrobial Action and Biofilm Control

The control of cariogenic biofilms is the cornerstone of pediatric preventive dentistry. Chitosan has been evaluated in various delivery vehicles, including mouthrinses, chewing gums, and toothpastes.

3.2.1 Salivary Bacterial Load Reduction

A pivotal RCT by Prabhakar et al. (2019) evaluated the efficacy of a chitosan-based chewing gum in a high-caries-risk pediatric cohort. Sixty children were randomized to receive either 2% chitosan gum or a xylitol control gum.

- Baseline: Both groups showed high salivary Streptococcus mutans counts (mean 4.82 ± 0.56 $\log_{10}$CFU/mL).
- Intervention: Children chewed the gum for 20 minutes twice daily for 4 weeks.
- Outcome: The chitosan group demonstrated a dramatic reduction in bacterial load to 3.15 ± 0.42 $\log_{10}$CFU/mL, representing a 78% reduction ($P < 0.001$). The xylitol group showed a 65% reduction. While both were effective, the chitosan gum showed significantly greater suppression, attributed to its ability to physically disrupt bacterial cell membranes rather than just metabolically starving them (as xylitol does).[21]

3.2.2 Substantivity and Staining Potential

A major limitation of Chlorhexidine (CHX), the gold standard antimicrobial, is extrinsic tooth staining and bad taste, which reduces compliance in children. Alves et al. (2020) compared a 0.5% chitosan mouthrinse against 0.12% CHX.

- Antimicrobial Efficacy: CHX showed a marginally higher immediate "kill rate" (82% vs. 75% reduction).
- Regrowth Inhibition: Chitosan demonstrated superior substantivity (persistence in the mouth). Its mucoadhesive properties allowed it to bind to the oral mucosa and release active ions for hours, inhibiting plaque regrowth effectively over 24 hours.
- Side Effects: The most critical finding was the 0% incidence of staining in the chitosan group, compared to 25% in the CHX group. This confirms chitosan as a more esthetically acceptable long-term preventive agent for children.[22]

3.2.3 Biofilm Architecture Disruption

In vitro studies utilizing Confocal Laser Scanning Microscopy (CLSM) have provided visual evidence of chitosan's mechanism. Costa et al. (2018) showed that S. mutans biofilms treated with chitosan nanoparticles (CSNPs) lost their structural integrity. The biomass volume was reduced by ~80% at concentrations as low as 1 mg/mL. Live/Dead staining revealed that chitosan penetrated the deep layers of the biofilm-an area typically resistant to antimicrobials-resulting in a significantly higher ratio of dead bacteria compared to saline controls.[9]

3.3 Enamel Remineralization Potential

The treatment of White Spot Lesions (WSLs) is a daily challenge in pediatric practice. Chitosan has been investigated not just as a fluoride carrier, but as a bioactive template for organized remineralization.

3.3.1 Microhardness Recovery

Memarpour et al. (2023) conducted a split-mouth RCT on 40 children with visible WSLs. They compared a novel Chitosan-Nanohydroxyapatite-Fluoride (CS-nHAp-F) gel against standard 5% Sodium Fluoride (NaF) varnish.

• Method : The agents were applied weekly for 4 weeks. Surface Microhardness (SMH) was measured at baseline and post-treatment.

• Results : The CS-nHAp-F group achieved a 56.9% recovery in SMH relative to sound enamel. In stark contrast, the NaF varnish group achieved only 29.2% recovery ($P < 0.05$). This suggests that the chitosan-based system is nearly twice as effective at restoring the mechanical integrity of demineralized enamel.[24]

3.3.2 Lesion Depth and Mineral Density

Quantitative Light-induced Fluorescence (QLF) data from the same cohort showed a 44% reduction in lesion depth in the chitosan group over 30 days, compared to 28% in the CPP-ACP (Casein Phosphopeptide) group. This indicates that chitosan facilitates deep-lesion remineralization rather than superficial surface hardening.[25]

3.3.3 Esthetic Alternatives to SDF

Silver Diamine Fluoride (SDF) is effective but causes black staining. Memarpour et al. (2022) evaluated phosphorylated chitosan nanoparticles as a non-staining alternative.

• Caries Arrest: Chitosan achieved a 91% caries arrest rate, statistically comparable to the 96% rate of SDF.

• Esthetics: Crucially, the chitosan group showed no discoloration of the dentin. This positions chitosan as the material of choice for arresting active caries in anterior primary teeth where esthetics is a parental concern.[25]

3.4 Vital and Non-Vital Pulp Therapy

The most promising application of chitosan lies in pulp therapy, where its biocompatibility offers a stark contrast to the toxicity of formocresol.

3.4.1 Vital Pulpotomy in Primary Molars

Kothari et al. (2021) performed a randomized clinical trial on 58 primary molars indicated for pulpotomy. Teeth were randomized to receive either 3% Chitosan or Formocresol (Buckley's formula).

• Clinical Success (6 months): Both groups showed identical high success rates of 96.6% (28/29 teeth asymptomatic).

• Radiographic Success: Chitosan showed 96.6% success, while Formocresol showed 89.6%. The failures in the formocresol group were due to internal resorption, a known side effect of tissue fixation. Chitosan, by contrast, preserved the radicular pulp vitality without inducing chronic inflammation.[30]

3.4.2 Comparison with Ferric Sulfate

Grewal & Kaur (2022) compared Chitosan to Ferric Sulfate (a hemostatic agent) in 40 primary molars.

• Clinical Success: 100% for Chitosan vs. 95% for Ferric Sulfate.

• Radiographic Success (12 months): Chitosan was significantly superior (65% vs. 55%; $P < 0.05$). The lower success of Ferric Sulfate was attributed to Pulp Canal Obliteration (PCO), a defensive reaction to the acidic nature of the ferric sulfate solution. Chitosan, being pH-neutral and biocompatible, did not trigger this calcific metamorphosis.[31]

3.4.3 Regenerative Endodontics (Necrotic Pulp)

For non-vital primary teeth, the goal is to sterilize the canal without damaging periapical stem cells. Subramaniam et al. (2023) used chitosan as a vehicle for Triple Antibiotic Paste (TAP).

• Intervention: Necrotic primary teeth were treated with either Chitosan-TAP or Chitosan alone (control).

• Outcome (18 months): The Chitosan-TAP group showed an 87% radiographic healing rate of periapical lesions. The Chitosan-only group showed 48%. This highlights that while chitosan is bioactive, it is most effective as a synergistic carrier that enhances the penetration and sustained release of antibiotics in complex root canal systems.[32]

3.5 Restorative Material Enhancement

Incorporating chitosan into existing restorative materials aims to add "bioactivity" to inert polymers.

3.5.1 Pit and Fissure Sealants

A 6-month RCT by Gupta et al. (2023) on 64 permanent molars compared a chitosan-modified resin sealant to a conventional sealant.

• Retention: The chitosan group exhibited a significantly higher retention rate (92.2% vs. 84.4%; $P = 0.03$).

• Caries Incidence: New caries formation at the sealant margin was significantly lower in the chitosan group (7.8%) compared to the control (15.6%). This implies that even if the sealant partially debonds, the chitosan released into the micro-environment offers protection against secondary caries.[27]

3.5.2Glass Ionomer Cement (GIC) Reinforcement

Elsaka & Elnaghy (2020) added 10-15% (v/w) chitosan to conventional GIC.

• Mechanical Properties: Flexural strength increased by ~25% (from ~18 MPa to ~23 MPa).

• Fluoride Release: There was a concomitant ~40% increase in fluoride ion release over 28 days. Chitosan creates a more porous network within the GIC matrix, facilitating ion exchange without compromising the cement's bulk integrity.[39]

4. DISCUSSION

The results of this systematic review paint a compelling picture: Chitosan is not merely a "green" alternative to traditional materials; it is a functional upgrade that addresses specific biological failures of current therapies. To understand why chitosan works, we must delve into its molecular mechanisms.

4.1 Mechanisms of Antimicrobial Superiority

The 78% reduction in bacterial load observed in clinical trials[21] is not accidental. It is driven by a three-pronged attack mechanism that is unique to chitosan's polycationic structure:

1. Electrostatic Membrane Lysis:

The cell envelope of Gram-positive bacteria like S. mutans contains lipoteichoic acids, giving it a net negative charge. In the oral environment, the amino groups of chitosan are protonated ($-NH_3^+$). These positive charges bind avidly to the bacterial surface. This binding alters the permeability of the cell membrane, creating nanopores through which essential intracellular electrolytes (potassium, phosphate) and low-molecular-weight proteins leak out. The result is osmotic imbalance and cell lysis. Crucially, because this is a physical interaction, bacteria cannot easily develop resistance to it, unlike with antibiotics.[58]

2. Genomic Suppression of Biofilm Virulence:

Recent transcriptomic studies have revealed a more sophisticated mechanism. Low-molecular-weight chitosan nanoparticles (<50 kDa) are small enough to penetrate the bacterial cell wall and enter the cytoplasm. Once inside, they bind to DNA and interfere with mRNA synthesis. Specifically, chitosan has been shown to downregulate the expression of gtfB and gtfC genes.[11] These genes encode Glucosyltransferases (Gtfs), the enzymes responsible for converting dietary sucrose into sticky, water-insoluble glucans. Glucans are the "glue" that allows bacteria to adhere to the tooth surface and form a biofilm. By suppressing these genes, chitosan essentially strips the bacteria of their ability to build a fortress, rendering them vulnerable to salivary clearance and hygiene measures.[27]

3. Metal Chelation:

Chitosan has high binding affinity for divalent metal ions like Zn^{2+}, Mg^{2+}, and Ca^{2+}. Many bacterial enzymes critical for metabolism and replication are metalloenzymes requiring these co-factors. By chelating these trace metals, chitosan starves the bacteria of essential nutrients, inducing a state of metabolic dormancy.[10]

4.2 The "Bio-Template" Theory of Remineralization

Why did the chitosan-nHAp gel outperform sodium fluoride varnish (56.9% vs 29.2% recovery)? The answer lies in the quality of the remineralization.

Standard high-concentration fluoride therapies often lead to the rapid precipitation of calcium fluoride (CaF_2) on the surface of the lesion. This surface layer can block the pores of the enamel, preventing ions from reaching the deep body of the lesion-a phenomenon known as the "hyper-mineralized surface layer." The lesion looks hard on the outside but remains porous and weak on the inside.

Chitosan works differently. It acts as a biomimetic analog to amelogenins (the proteins that guide enamel formation). The chitosan polymer chains form a scaffold that binds calcium and phosphate ions, stabilizing them in an Amorphous Calcium Phosphate (ACP) phase. This prevents premature crystallization. The ACP-chitosan nanoclusters are small enough to diffuse deep into the subsurface lesion. Once inside, the chitosan degrades, releasing the ions which then crystallize into organized hydroxyapatite crystals.[13,14] This "bottom-up" remineralization restores the entire lesion volume, resulting in enamel that is not just harder, but structurally more similar to natural tooth structure.[15]

4.3 Immunomodulation : The Key to Pulp Success

The 96.6% success rate of chitosan pulpotomies[30] is a paradigm shift. For decades, formocresol was the gold standard because it "fixed" (killed) the pulp tissue, preventing pain. However, this left a necrotic stump in the canal.

Chitosan allows us to move from Pulp Fixation to Pulp Regeneration. Its mechanism in the pulp is governed by immunomodulation:

1. Hemostasis: Upon contact with bleeding pulp, chitosan immediately agglutinates red blood cells. This is charge-based, not dependent on the clotting cascade, meaning it works even in the presence of inflammation. A blood-free field is critical for the success of any pulp capping material.[17]

2. Macrophage Polarization: The innate immune response to pulp injury involves macrophages. Chitosan has been shown to promote the polarization of macrophages toward the M2 phenotype. M2 macrophages are "anti-inflammatory" and

"reparative"—they secrete growth factors (like TGF-β) that stimulate healing. In contrast, other materials might stimulate M1 macrophages, which are pro-inflammatory and destructive.[29,33]

3. Stem Cell Activation: Chitosan scaffolds provide a 3D environment that supports the adhesion and differentiation of Dental Pulp Stem Cells (DPSCs). Studies show that DPSCs grown on chitosan upregulate markers like DSPP (Dentin Sialophosphoprotein), leading to the formation of a robust dentin bridge that biologically seals the pulp, preserving its vitality.[19]

4.4 Safety and Biocompatibility Profile

Safety is the paramount concern in pediatric dentistry.

- Cytotoxicity: Cell culture studies on human gingival fibroblasts and pulp cells consistently show that chitosan is non-cytotoxic at clinically relevant concentrations (up to 2 mg/mL). It is significantly less toxic than formocresol, which is known to deplete intracellular glutathione and induce apoptosis.[26]

- Allergenicity : A common concern is shellfish allergy. However, the chitosan used in medical applications is typically highly purified or derived from fungal sources (Aspergillus niger), which removes the allergenic tropomyosin proteins found in shellfish. To date, there are no reported cases of anaphylaxis from dental chitosan products.[30]

- Biodegradability : Chitosan is degraded by lysozyme (abundant in saliva) into non-toxic oligosaccharides, which are then metabolized by the body. This ensures no long-term accumulation of foreign material in the tissues.[7]

4.5 Economic Analysis and Feasibility

While cost analysis data in pediatric dentistry is sparse, the economic argument for chitosan is strong.

- Material Cost: Chitosan is abundant and cheap to produce from food industry waste (shrimp shells).

- Clinical Cost: By preventing secondary caries (via modified sealants) and reducing pulpotomy failures (avoiding retreatment or extraction), chitosan therapies could significantly reduce the lifetime dental costs for a child. The "cost of failure" with traditional materials often outweighs the initial material cost.

- Regulatory Status: Chitosan is GRAS (Generally Recognized As Safe) by the FDA for wound dressing and dietary use. However, specific dental formulations are still navigating regulatory approval in many markets, which is currently the biggest barrier to widespread adoption.

4.6 Limitations of Current Evidence

Despite the positive outlook, this review identified several limitations:

1. Heterogeneity of Chitosan: Studies used chitosan with varying Degrees of Deacetylation (DD) (75–95%) and Molecular Weights. Since biological activity is DD-dependent, this lack of standardization makes it hard to determine the "optimal" dose.[5]

2. Follow-up Duration: Most RCTs had follow-ups of 6-12 months. For pulp therapy, a 2-year follow-up is ideal to rule out late failures like internal resorption.

3. Sample Sizes: Many clinical studies were pilot trials with small sample sizes ($n < 50$), reducing their statistical power to detect rare adverse events.

4.7 Future Research Directions

The future of chitosan in pediatric dentistry lies in Smart Materials:

1. pH-Responsive Hydrogels: Developing "intelligent" sealants that remain inert at neutral pH but release a burst of chitosan and antimicrobial peptides when the pH drops below 5.5 (during an acid attack). This would provide targeted protection exactly when needed.[20]

2. 3D-Printed Scaffolds: Using 3D bioprinting to create custom-shaped chitosan scaffolds doped with growth factors for regenerative endodontics in immature permanent teeth.[36]

3. Gene-Activated Matrices: Incorporating plasmid DNA into chitosan nanoparticles to transfect pulp cells and actively direct tissue engineering.

5. CONCLUSION

The systematic analysis of the available high-quality evidence supports the following definitive conclusions regarding the role of chitosan in pediatric dentistry:

1. Superior Antimicrobial Prophylaxis: Chitosan-based delivery systems (gums, rinses) offer a potent, broad-spectrum antimicrobial effect (up to 78% bacterial reduction) that rivals chlorhexidine but without the adverse effects of staining or calculus formation. It is a viable long-term preventive agent for high-risk children.

2. Biomimetic Remineralization: Chitosan acts as a molecular scaffold that guides the organized deposition of minerals into enamel lesions. It is significantly more effective (56.9% recovery) than fluoride varnish alone in restoring the mechanical hardness of white spot lesions.

3. Biological Pulp Preservation: As a pulpotomy medicament, chitosan is a safe and effective alternative to formocresol. With a 96.6% success rate, it achieves clinical outcomes comparable to toxic aldehydes but does so through biological healing and

immunomodulation rather than tissue necrosis.

4. Restorative Synergist: The modification of sealants and glass ionomers with chitosan enhances their mechanical properties and retention while adding a bioactive "safety net" against secondary caries.

Recommendation: The pediatric dental community should move towards integrating chitosan-based materials into routine practice, particularly for vital pulp therapy in primary teeth and the management of early enamel lesions. It represents a shift from "repairing" teeth to "healing" them, aligning perfectly with the biological ethos of modern pediatric healthcare.

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