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SYSTEMATIC REVIEW

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Comparative evaluation of biomaterial-based and fluoride toothpastes for enamel remineralization: a PRISMA-compliant systematic review

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Abstract

Background: Fluoride remains the benchmark for caries prevention due to its well-established capacity to enhance enamel remineralization. However, growing concerns regarding fluoride overexposure have stimulated interest in biomaterial-based alternatives. Ingredients such as calcium phosphate derivatives, nano-hydroxyapatite (nHAP), casein phosphopeptide–amorphous calcium phosphate (CPP-ACP), calcium silicate, and bioactive glass (BG) have been proposed to support enamel repair through biomimetic or ion-releasing mechanisms. **Methods**: This Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)-compliant systematic review searched PubMed, ScienceDirect, EBSCO, and LILACS for studies published between January 2020 and March 2025 comparing biomaterial-based toothpastes with conventional fluoride formulations using human permanent teeth. Eligible *in vitro*, *in situ*, and *in vivo* studies were screened independently in duplicate. The risk of bias was assessed using Faggion's checklist for *in vitro* studies and the Cochrane Risk of Bias (RoB) 2 tool for *in vivo* and *in situ* studies. **Results**: Of 294 records identified, 11 studies met the inclusion criteria. Biomaterials evaluated included calcium silicate, calcium phosphate derivatives, nano-hydroxyapatite, CPP-ACP, and bioactive glass. Several biomaterial formulations demonstrated remineralization outcomes comparable to fluoride under controlled experimental conditions. Some fluoride–biomaterial combinations have been suggested to exhibit potential synergistic effects. However, interpretation is limited by substantial methodological heterogeneity, short intervention periods, and a limited number of well-designed *in vivo* trials. **Conclusions**: Biomaterial-based toothpastes show promise as adjuncts or potential alternatives to fluoride for enamel remineralization. Nonetheless, the current evidence base is dominated by *in vitro* and short-term *in situ* studies. High-quality, long-term *in vivo* trials are required to establish clinical effectiveness and inform evidence-based preventive strategies. **The PROSPERO registration**: The protocol for this systematic review was registered with the International Prospective Register of Systematic Reviews (PROSPERO) under registration number CRD420251027747.

Keywords

Dental caries; Fluoride toothpaste; Remineralisation; Biomaterials; Nano-hydroxyapatite; Casein phosphopeptide; Bioactive glass; Calcium phosphate; Systematic review

1. Introduction

Oral diseases affect nearly 3.5 billion people worldwide, with untreated dental caries representing the most common condition and affecting over a quarter of the global population [1]. Dental caries is a multifactorial disease influenced by socioeconomic, behavioral, biological, and dietary factors, with high sugar intake being the most significant modifiable risk [2, 3]. These determinants interact with local factors, such as frequent exposure to fermentable carbohydrates, acidogenic biofilm, inadequate oral hygiene, reduced salivary flow, and limited fluoride availability, to drive sustained demineralization. When pathological processes outweigh natural protective mechanisms like salivary buffering and remineralization, early enamel lesions develop [4]. Such lesions remain reversible with appropriate preventive measures, including regular tooth-

brushing [5].

Dentin hypersensitivity, which affects nearly 30% of the population, is another condition linked to demineralization or exposed dentinal tubules [6]. Its management often relies on agents that promote mineral deposition or occlude tubules [7].

Toothbrushing remains central to plaque control—the primary etiological factor for both caries and periodontal disease [8, 9]. Fluoride-containing toothpastes are considered the gold standard for caries prevention because of their ability to inhibit demineralization, promote remineralization, and exert antibacterial effects [10, 11]. Nevertheless, concerns regarding excessive fluoride exposure—including dental and skeletal fluorosis—highlight the need for effective fluoride-sparing or fluoride-free alternatives [12–14].

Several biomaterial-based agents have emerged as potential substitutes [15]. Calcium phosphate derivatives increase calcium and phosphate availability for remineralization [15, 16], nano-hydroxyapatite (nHAP) mimics the natural enamel apatite structure [16, 17], bioactive glass (BG) releases mineral ions that form a hydroxycarbonate apatite layer [17], and casein phosphopeptide (CPP) stabilizes calcium ions more efficiently than salivary proteins [18]. These biomaterials offer biologically compatible mechanisms that may support enamel repair.

Despite growing interest in these alternatives, there is limited consolidated evidence comparing their remineralization performance with that of conventional fluoride toothpastes across *in vitro*, *in situ*, and *in vivo* models. Therefore, this systematic review aimed to evaluate and compare the remineralizing potential of biomaterial-based toothpastes versus fluoride formulations to inform evidence-based strategies for preventive oral care.

2. Materials and methods

2.1 Overview

This systematic review was designed per the guidelines of PRISMA 2020 (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [19]. The completed PRISMA 2020 checklist is provided as **Supplementary material 1**. The protocol for this systematic review was registered with the International Prospective Register of Systematic Reviews (PROSPERO) under the registration number CRD420251027747. The research question was developed using the Population, Intervention, Comparator, Outcomes, and Study Design (PICOS) framework, where the population included demineralized human permanent teeth studied under *in vitro*, *in vivo*, or *in situ* conditions. The intervention of interest was biomaterial-based toothpaste formulations, compared against conventional fluoride-based toothpastes. The primary outcome evaluated was the remineralization capacity of the intervention. Studies of any design that addressed these criteria were considered eligible for inclusion.

2.2 Eligibility criteria

Studies were included in this review if they investigated the remineralization potential of toothpaste formulations using permanent human teeth under *in vitro*, *in vivo*, or *in situ* conditions. Only studies published in English between January 2020 and March 2025 with full-text availability were considered. Exclusion criteria were defined to maintain focus on the core objective. Studies were excluded if they did not conform to the predefined PICOS framework, lacked clarity in the intervention or evaluation methods description, or primarily focused on properties, such as toxicity or adhesion, unrelated to remineralization. To minimize potential commercial bias, studies authored by individuals with direct affiliations to toothpaste manufacturers or studies reporting undisclosed industry funding were excluded. This approach reduces the influence of conflicts of interest, but may also limit the inclusion of some relevant datasets. The eligibility criteria are summarized in Table 1.

2.3 Data sources and search strategy

In April 2025, a comprehensive electronic search was conducted across four databases: PubMed, ScienceDirect, EBSCO, and LILACS. The search strategy employed a combination of controlled vocabulary (where applicable) and free-text terms, including “remineralization”, “toothpastes”, “fluorides”, and “biomaterial-based toothpaste”, linked using Boolean operators AND & OR. The full search syntax for each database is detailed in **Supplementary Table 1**.

The search was restricted to studies published in English, with full text available, and within the January 2020 to March 2025 publication window. All retrieved citations were exported to the reference management software Zotero for organization and duplicate removal. Following deduplication, a three-stage screening process was undertaken: initial title screening and abstract and full-text evaluations. Articles meeting the inclusion criteria were retained for qualitative synthesis and, where applicable, quantitative analysis.

2.4 Selection of studies

The selection process was conducted in three sequential stages: title screening, abstract review, and full-text evaluation. All records retrieved through database searches were initially imported into Zotero, and duplicate entries were identified and removed. Two reviewers (WCH and PKH) independently screened the titles of the remaining articles to assess their potential relevance. Articles that appeared eligible or unclear based on the title alone were then screened for the abstract. The same two reviewers then independently assessed the abstracts to determine whether they aligned with the predefined eligibility criteria. Any discrepancies or uncertainties during this stage were resolved through discussion or consultation with a third reviewer (SS). Full-text versions of potentially eligible studies were retrieved and thoroughly evaluated against the inclusion and exclusion criteria. Studies meeting all criteria were selected for final inclusion in the review and entered into the data extraction and risk-of-bias assessment phases.

2.5 Data extraction

Data from the included studies were extracted independently by two reviewers using a standardized and pre-piloted data extraction form. Extracted information included the first author’s

TABLE 1. Eligibility criteria for study inclusion.

Criterion Type	Description
Population	Permanent human teeth (*in vitro*, *in vivo*, or *in situ*)
Intervention	Biomaterial-based toothpaste formulations
Comparator	Conventional fluoride toothpaste
Outcome	Remineralization capacity
Language	English
Publication Date	January 2020 to March 2025
Exclusions	Studies focusing on toxicity, adhesion, or non-remineralizing properties; unclear methodology; brand-affiliated authorship; undisclosed funding

name, year of publication, country of origin, study design (*in vitro*, *in vivo*, or *in situ*), type and number of samples used, description of the test and control toothpaste formulations, intervention protocols, outcome assessment methods, and key findings related to remineralization capacity. Particular attention was given to the type of the biomaterial incorporated in the test formulations, the presence and concentration of fluoride, and the specific remineralization metrics used (such as surface microhardness, lesion depth, or mineral content analysis). Any discrepancies between the reviewers during the extraction process were resolved through discussion, and when necessary, by involving a third reviewer.

2.6 Risk-of-bias assessments

Two assessors (WCH and PKH) independently assessed the methodological quality of the included studies, using tools appropriate to each study type. For *in vitro* studies, the Faggion's checklist was employed. This tool evaluates six key domains across the study sections—abstract, methods, results, discussion, and other relevant information—to determine potential bias.

For *in vivo* and *in situ* studies, the Cochrane Risk of Bias Tool (RoB 2) was applied. This tool assesses bias across seven domains, including the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of reported results. Each domain was judged as presenting "low risk of bias", "some concerns", or "high risk of bias". Any assessor disagreements were resolved through discussion and, if needed, consensus with the other authors.

3. Results

3.1 Study selection

The database search identified 294 records related to toothpastes containing remineralizing agents. After screening titles and abstracts, 45 studies underwent full-text assessment. Eleven studies met the predefined eligibility criteria and were included in the final review. The study selection process is summarized in the PRISMA flow diagram (Fig. 1).

3.2 Characteristics of included studies

The included studies evaluated various biomaterials—including calcium phosphate derivatives, calcium silicate, hydroxyapatite (HAP), casein phosphopeptide–amorphous calcium phosphate (CPP-ACP), and bioactive glass—compared against conventional fluoride-containing toothpastes. Study designs comprised *in vitro*, *in situ*, and *in vivo* approaches using human permanent teeth, enamel slabs, or dentine specimens. Key characteristics, intervention protocols, and outcome measures are presented in Table 2 (Ref. [20–30]).

The methodological quality of *in vitro* studies was assessed using Faggion's checklist [31], which evaluates reporting transparency, procedural detail, and analytical rigor (**Supplementary Table 2**, Ref. [22–30]). Most studies met several quality criteria, although information on randomization, allocation concealment, and blinding—typically rare in laboratory designs—was commonly missing.

Two studies were randomized controlled trials [20, 21] and were evaluated using the Cochrane RoB 2 tool [32]. Both trials demonstrated low risk of bias across key domains, including randomization process, blinding where applicable, completeness of outcome data, and selective reporting (Table 3, Ref. [20, 21]).

3.3 Qualitative synthesis of findings

3.3.1 Calcium phosphate derivatives

Calcium phosphate forms the primary inorganic structure of enamel [33]. During demineralization, replenishment of calcium and phosphate ions is essential for enamel repair [34, 35]. Ionescu *et al*. [23] reported that calcium phosphate nanoparticles induced epitaxial mineral growth on demineralized enamel surfaces, forming a crystallographic pattern resembling native hydroxyapatite—an effect less evident in sodium fluoride controls. These findings indicate that nano-scaled calcium phosphate formulations may achieve remineralization outcomes comparable to fluoride under controlled laboratory conditions. However, limited *in vivo* validation restricts conclusions regarding clinical performance.

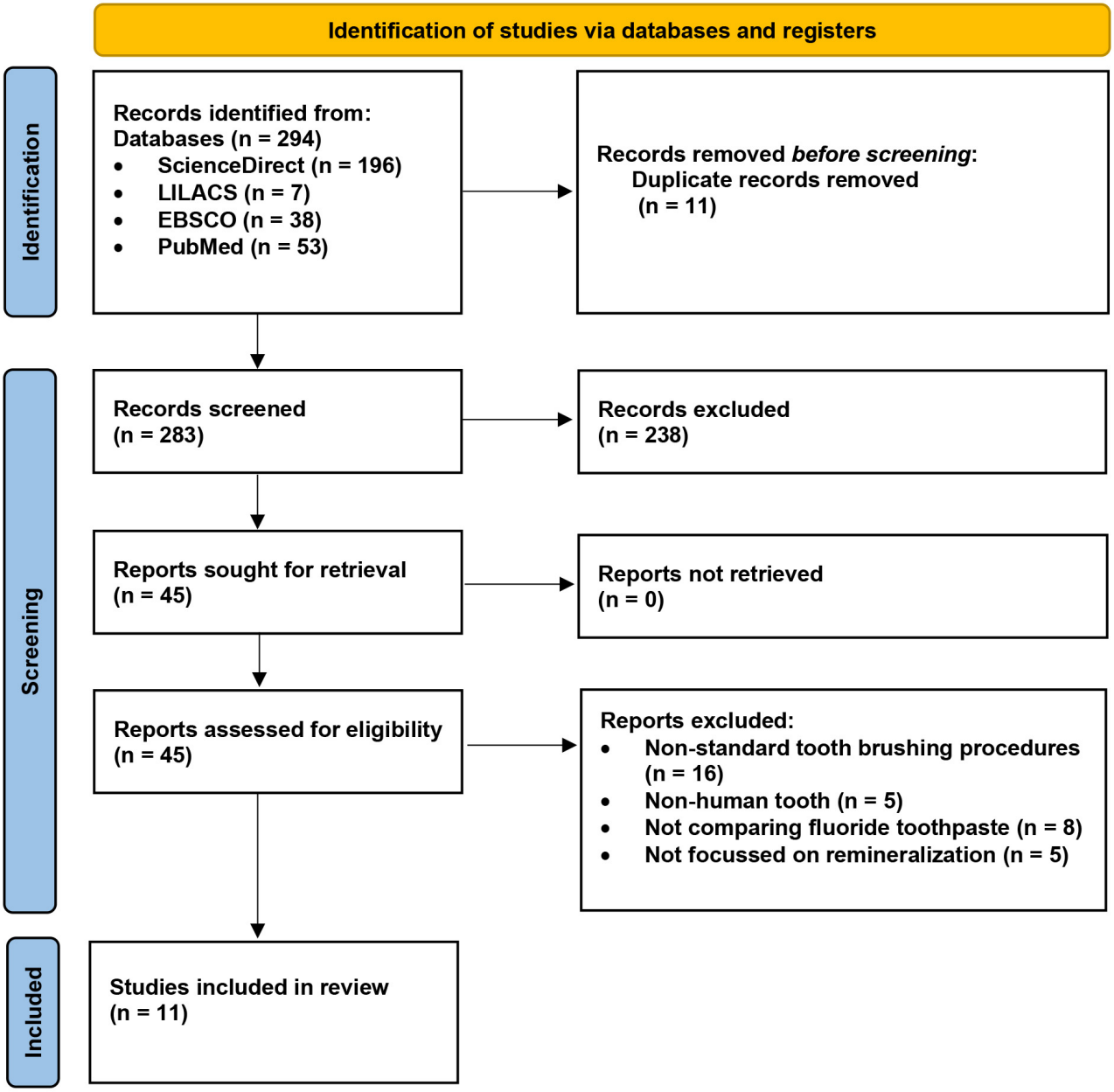

FIGURE 1. PRISMA flow diagram.

3.3.2 Calcium silicate derivatives

Calcium silicate (CaSi) promotes hydroxyapatite formation on both eroded and sound enamel surfaces [24, 36]. Li *et al*. [24] observed that CaSi–sodium phosphate (CSSP) toothpaste occluded dentinal tubules more effectively than 1450 ppm fluoride, supported by focused ion beam-TEM (Transmission Electron Microscopy) and SAED (Selected Area Electron Diffraction) evidence of intratubular HAP formation. Buzalaf *et al*. [25] reported greater protection against enamel erosion with CaSi toothpaste than with fluoride after short-term exposure. Although these *in vitro* findings suggest that CaSi can perform as well as, or better than, fluoride in specific experimental setups, the absence of long-term or *in vivo* data limits generalizability.

3.3.3 Hydroxyapatite (HAP)

Hydroxyapatite is widely recognized for its biocompatibility and structural similarity to natural enamel [37]. Amaechi *et al*. [26] demonstrated that a 20% micro-HAP toothpaste improved remineralization of MIH (Molar Incisor Hypomineralization) lesions more than 1450 ppm fluoride *in situ*. Ionescu *et al*. [23] also found that HAP-based formulations produced a uniform remineralized layer resembling native tissue, with performance comparable to fluoride. In a clinical study, Cagetti *et al*. [20] reported a reduction in caries incidence among children after prolonged use of HAP toothpaste. However, Guntermann *et al*. [27] presented divergent findings, noting that fluoride outperformed HAP in initial and repeated remineralization cycles *in vitro*. Collectively, evidence indicates that HAP can produce remineralization outcomes similar to fluoride, but the relative effectiveness varies across lesion types, concentrations, and experimental conditions.

TABLE 2. Summary of included studies comparing the remineralization effects of different biomaterial-based toothpastes.

Study	Design	Sample	Material	Outcome Measure	Follow-up	Best Material	Main Outcome
Cagetti *et al.* [20] (2022)	*In vivo*	306 children (HAF = 152; NaF = 154)	HAF (1450 ppm), NaF (1450 ppm)	ICDAS	12 and 24 mon	HAF	After two years, HAF showed significantly lower caries risk than NaF.
Ashour *et al.* [21] (2021)	*In vivo*	51 participants (n = 17/group)	CPP-ACP, CPP-ACFP, fluoridated toothpaste	VistaCam, pH meter, ion electrode	T1 to T6 (6 mon)	CPP-ACFP	CPP-ACFP showed highest remineralization, pH improvement, and fluoride release.
Farooq *et al.* [22] (2021)	*In vitro*	72 premolars (n = 24/group)	Distilled water, NaF (1450 ppm), BG-F (530 ppm)	VHN, Ra, Micro-CT	1 cycle	BG-F	BG-F group had highest Vickers hardness and lowest surface roughness.
Ionescu *et al.* [23] (2022)	*In vitro*	18 extracted wisdom teeth (n = 36 slices)	F-HAP + MgSrCHA-Chi, ZnCHA, NaF (1450 ppm)	SEM, EDX	1 wk	F-HAP + MgSrCHA-Chi, ZnCHA	All except NaF showed enamel remineralization and dentin occlusion.
Li *et al.* [24] (2020)	*In vitro*	Coronal dentine (n = 3)	CSSP (1450 ppm), NaF (1450 ppm)	SEM, EDX, TEM, SAED	2–14 cycles	CSSP	CSSP fully occluded dentinal tubules and formed hydroxyapatite layer.
Buzalaf *et al.* [25] (2021)	*In vitro*	48 human third molars	Non-fluoride, NaF (1450 ppm), CaSi (1450 ppm MFP)	Contact profilometry	3 and 7 d	CaSi	CaSi toothpaste showed significantly better enamel protection than NaF and non-fluoride.
Amaechi *et al.* [26] (2022)	*In situ*	15 patients, 60 MIH enamel blocks	20% HAP, NaF (1450 ppm)	Micro-CT	14 d	HAP	HAP group had higher remineralization than NaF for MIH lesions.
Guntermann *et al.* [27] (2022)	*In vitro*	19 wisdom teeth	Untreated, acid only, fluoride-free HAP, amine fluoride (1400 ppm), fluoride- and HAP-free	SEM	1 cycle	Amine fluoride	Fluoride toothpaste showed best remineralization and protection after demineralization.

TABLE 2. Continued.

Study	Design	Sample	Material	Outcome Measure	Follow-up	Best Material	Main Outcome
de Oliveira *et al*. [28] (2022)	*In situ*	10 adults; 160 enamel slabs (n = 20/group)	Silica (no F), CPP-ACP, CPP-ACP + NaF (900 ppm), NaF (1100 ppm)	KHN, %SH	10 d	CPP-ACP + NaF, NaF	Both treatments showed significant hardness recovery.
Chen *et al*. [29] (2023)	*In vitro*	23 extracted teeth (n = 15 root segments)	BG-F (540 ppm), 1450 ppm F, 5000 ppm F, deionized water	ICP-OES, KHN, XRD, 19F-MAS-NMR, F-ISE	13 d	BG-F	BG-F showed higher Ca and P ion release; 1450 F and 5000 F had more fluorapatite formation.
Chen *et al*. [30] (2024)	*In vitro*	3 extracted teeth (n = 3)	BG (540 ppm), NaF (1450, 5000 ppm), deionized water	XMT, SEM, 19F-MAS-NMR	13 d	BG (540 ppm)	BG showed mineral gain and fluoride apatite formation; NaF caused subsurface loss.

d: day; mon: month; wk: week; NaF: Sodium fluoride; CaSi: Calcium silicate; HAF: Fluoride-substituted hydroxyapatite; BG: Bioactive glass; CSSP: Calcium silicate and sodium phosphate; HAF + MgSrCHA-Chi: Fluoride-hydroxyapatite, Magnesium-Strontium-Carbonate Hydroxyapatite conjugated with Chitosan; ZnCHA: Zinc carbonate hydroxyapatite; CPP-ACFP: Casein Phosphopeptide–Amorphous Calcium Fluoride Phosphate; HAP: Hydroxyapatite; ICDAS: International Caries Detection and Assessment System; KHN: Knoop hardness test; F-ISE: Fluoride-Ion Selective Electrode; ICP-OES: Inductively Coupled Plasma-Optical Emission Spectroscopy; XRD: X-ray Diffraction; 19F-MAS-NMR: 19F Magic Angle Spinning-Nuclear Magnetic Resonance Spectroscopy; SEM: Scanning Electron Microscopy; EDX: Energy Dispersive X-ray Spectroscopy; TEM: Transmission Electron Microscopy; SAED: Selected Area Electron Diffraction; Ra: Surface Roughness; micro-CT: Micro-Computed Tomography; VistaCam: Light-Induced Fluorescence Intraoral Camera; XMT: X-ray Microtomography; %SH: Microhardness Recovery; ACP: amorphous calcium phosphate; MFP: Monofluorophosphate; VHN: Vickers Hardness Number; MIH: Molar Incisor Hypomineralization.

TABLE 3. RoB 2 risk of bias evaluation for *in vivo* and *in situ* included studies.

Study	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Cagetti Maria Grazia *et al*. [20] (2022)	Low	Low	Some concern	Some concern	Low	Low	Low
Ashour Doaa Gamal, *et al*. [21] (2021)	Low	Low	Low	Low	Low	Low	Low

3.3.4 Casein phosphopeptide–amorphous calcium phosphate (CPP-ACP)

CPP-ACP stabilizes calcium and phosphate ions at the tooth surface, supporting remineralization [38]. Ionescu *et al*. [23] reported that CPP-ACP induced remineralization, but was less effective than nanohydroxyapatite. *In situ* findings by de Oliveira *et al*. [28] showed that both CPP-ACP and CPP-ACP combined with fluoride (CPP-ACFP) increased enamel microhardness, with CPP-ACFP performing similarly to 1100 ppm NaF toothpaste. Ashour *et al*. [21] showed that CPP-ACP alone had a limited effect, whereas its combination with fluoride improved white-spot lesion progression and salivary pH. These results suggest that CPP-ACP is an effective adjunct, but its performance is more variable than HAP or CaSi, and it appears to benefit substantially from co-administration with fluoride.

3.3.5 Bioactive glass

Bioactive glass (BG) releases calcium and phosphate ions that form a hydroxycarbonate apatite layer upon contact with saliva [39]. Farooq *et al*. [22] found that fluoride-containing BG toothpaste improved enamel hardness and reduced surface roughness more than fluoride alone. Chen *et al*. [29] reported enhanced ion release and surface rehardening with BG-fluoride formulations, although 5000 ppm fluoride paste demonstrated higher fluorapatite crystallinity. A later study by Chen *et al*. [30] showed that BG-fluoride toothpaste offered better protection against demineralization than fluoride-only formulations despite residual subsurface mineral loss across all groups. Overall, BG-fluoride toothpastes demonstrate remineralization performance comparable to fluoride alone, with possible advantages in ion release dynamics and surface conditioning.

4. Discussion

The findings of this systematic review align with an emerging body of research evaluating biomaterial-based alternatives to fluoride for enamel remineralization. Across included studies, several agents—such as calcium phosphate derivatives, calcium silicate, hydroxyapatite (HAP), CPP-ACP, and bioactive glass, demonstrated remineralization outcomes comparable to fluoride under specific laboratory or short-term clinical conditions [21, 23, 25, 26]. However, the consistency of these effects varied across materials, study designs, lesion types, and methodological approaches, warranting cautious interpretation.

Calcium phosphate derivatives, particularly in nanoparticle form, have shown promising remineralization behavior. Ionescu *et al*. [23] demonstrated epitaxial mineral growth resembling native hydroxyapatite, and Hamba *et al*. [40] reported deeper mineral penetration than fluoride in a pH-cycling model. While these findings suggest potential advantages under controlled conditions, evidence remains primarily *in vitro*, and the extent to which these outcomes reflect clinical situations is uncertain.

Calcium silicate derivatives also showed favorable performance, with studies reporting dentinal tubule occlusion and enamel surface protection [24, 25]. Li *et al*. [24] observed intratubular hydroxyapatite formation, whereas Tavangar *et al*. [41] demonstrated mineralizing potential in caries-affected dentin. These results indicate that CaSi may be a useful adjunct in managing early enamel and dentine lesions, although long-term clinical validation remains limited.

Hydroxyapatite (HAP) continues to attract interest because of its biomimetic properties. Studies by Amaechi *et al*. [26] and Ionescu *et al*. [23] reported HAP-associated remineralization comparable to fluoride, and clinical data suggest possible benefits in reducing caries incidence [20]. Conversely, other investigations reported greater remineralization with fluoride [27, 42], highlighting the variability in outcomes. Taken together, HAP appears capable of achieving fluoride-like performance in certain contexts, but the evidence does not support a consistent advantage over conventional fluoride formulations.

CPP-ACP demonstrated mixed results. Although it facilitated remineralization, it was generally less effective than HAP or CaSi and performed inconsistently compared to fluoride [21, 23]. Studies evaluating CPP-ACP–fluoride combinations reported enhanced outcomes compared with either agent alone, suggesting that synergistic effects may depend on the co-presence of fluoride [28, 38]. CPP-ACP, therefore, appears to function best as an adjunctive material, rather than a standalone alternative.

Bioactive glass (BG) formulations showed improved surface rehardening and ion release when combined with fluoride [22, 29, 39]. BG-fluoride toothpastes demonstrated comparable or enhanced remineralization outcomes relative to fluoride alone in several studies. However, in highly acidic or high-challenge conditions, high-concentration fluoride pastes produced greater fluorapatite crystallinity [30]. BG may represent a potentially valuable complementary agent, but comparative long-term evidence remains sparse.

Beyond material-specific findings, several methodological considerations limit the overall strength of the available evidence. The predominance of *in vitro* experiments constrains ecological validity, as these models do not replicate salivary flow, oral microbiota, dynamic pH changes, or dietary influences. Short study durations, single-modality assessment methods, and limited reporting of randomization and blinding further restrict interpretation. Some studies were affected by external disruptions, such as the COVID-19 pandemic, which affected participant adherence. Additionally, heterogeneity in lesion creation methods, remineralization protocols, and outcome metrics complicates direct comparisons across studies.

This review also has limitations inherent to its scope. The scarcity of well-designed *in vivo* trials restricts clinical conclusions, and extraction-based analysis is often not feasible in clinical settings. Differences in fluoride chemistry, ion availability, and kinetic behavior across formulations add complexity to comparative assessment. Most included studies evaluated only one alternative agent at a time, limiting head-to-head comparisons among biomaterials. Furthermore, studies with industry involvement were excluded to minimize commercial bias; although this enhances neutrality, it may also omit potentially informative datasets.

Despite these constraints, the collective evidence indicates that several biomaterial-based toothpastes can achieve rem-

ineralization outcomes comparable to fluoride in controlled settings, and some may offer complementary benefits when used in combination with fluoride. These materials, particularly when incorporated into accessible over-the-counter formulations, have the potential to support non-invasive management of early carious lesions, especially in populations at risk for fluorosis or with limited fluoride exposure.

This review also excluded studies with company sponsorship or authorship affiliations to specific toothpaste brands to minimize the risk of commercial bias. While this approach enhances the methodological neutrality of the evidence synthesis, it may introduce selection bias by excluding some potentially relevant data. The findings should, therefore, be interpreted with an awareness of this trade-off between reducing conflict-of-interest influence and maintaining comprehensive inclusion of available studies.

Future research should prioritize standardized, adequately powered *in vivo* trials with longer follow-up periods, consistent lesion models, and multimodal assessment techniques. Comparative studies examining particle size, material composition, and interactions among formulations—particularly fluoride–biomaterial combinations—will be essential for determining optimal clinical applications. Evaluating affordability, accessibility, and patient-centred outcomes will further support integration of these agents into preventive dental care.

5. Conclusions

In summary, this systematic review indicates that several biomaterial-based toothpastes—including calcium phosphate derivatives, calcium silicate, hydroxyapatite, CPP-ACP, and bioactive glass—show potential as alternatives or adjuncts to fluoride for supporting enamel remineralization. Across included studies, these materials produced remineralization outcomes that were generally comparable to fluoride under specific experimental conditions, and some fluoride–biomaterial combinations suggested possible additive or complementary benefits. However, the evidence base is dominated by *in vitro* and short-term *in situ* studies, and substantial methodological heterogeneity limits the ability to draw strong clinical conclusions. Well-designed, longer-duration *in vivo* studies with standardized protocols are needed to clarify the clinical relevance of these materials and to determine their appropriate role within evidence-based caries prevention strategies.

AVAILABILITY OF DATA AND MATERIALS

This study is a systematic review and does not involve generating or analysing primary data. All data supporting the findings of this review are derived from previously published studies, which are cited within the manuscript. Further details can be obtained from the corresponding author upon reasonable request.

AUTHOR CONTRIBUTIONS

SS, WCH, PKH, VSV—conceptualisation. ART, RMW, PJW—data curation. WCH, ART, PJW—formal analysis. RMW, WCH, PKH, DM—investigation. SS, ART, PKH, VSV—methodology. SS, DM, VSV—project administration; validation; writing–review & editing. SS, WCH, RMW—supervision; visualisation. WCH, PKH, DM, VSV—roles/writing–original draft. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethical approval and informed consent were not required for this study, which is a systematic review of previously published literature and does not involve new experiments with human participants or animals.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found, in the online version, at https://oss.jocpd.com/files/article/2072885708412862464/attachment/Supplementary%20material.zip.

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