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SYSTEMATIC REVIEW

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Remineralizing effect of casein phosphopeptide-amorphous calcium phosphate (CPP-ACP) on enamel affected by molar-incisor hypomineralization (MIH): a systematic review and meta-analysis

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Abstract

Background: Molar-Incisor Hypomineralization (MIH) is a developmental disorder of the dental enamel with significant oral health implications, including caries, dentin hypersensitivity, aesthetic impairment, and pulpitis, driving a high clinical need for intervention. Current non-invasive approaches include Fluoride, Casein Phosphopeptide-Amorphous Calcium Phosphate (CPP-ACP), and Calcium Glycerophosphate (CaGP). This meta-analysis aims to evaluate the effectiveness of CPP-ACP on MIH-affected teeth. **Methods**: A systematic review and meta-analysis were conducted. The search was carried out in four databases (PubMed, Cochrane, Embase, Google Scholar) and manual searches were utilized to identify studies published up to December 2025, with no restrictions on the publication date. Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, a systematic review and meta-analysis were conducted using a Population, Intervention, Comparison, and Outcome (PICO)-based search strategy. Relevant studies were selected based on titles and abstracts, and the full texts were retrieved. The meta-analysis was conducted using Stata version 16.0. **Results**: A total of 18 studies were eligible for the systematic review, and 8 studies were included in the meta-analysis. The systematic review indicated that CPP-ACP may be effective in promoting remineralization, reducing hypersensitivity, improving microhardness, and altering salivary characteristics. Meta-analysis revealed that Casein Phosphopeptide-Amorphous Calcium Phosphate Fluoride (CPP-ACPF) significantly enhanced remineralization after one month of use, whereas the efficacy of CPP-ACP was not statistically significant. The prognosis for microstructural recovery in MIH enamel is dependent on the initial defect. While white spots can nearly recover to their original structure, yellow-brown lesions may require more aggressive and long-term intervention strategies. **Conclusions**: Adding fluoride to CPP-ACP (CPP-ACPF) may accelerate the remineralizing effect, since this integration promotes the development of acid-resistant fluorapatite, which reduces hypersensitivity and shows potential for mitigating the risk of enamel breakdown. **The PROSPERO Registration**: CRD420251103933.

Keywords

MIH; CPP-ACP; Remineralization; Dentin hypersensitivity; Microhardness; Salivary buffer

1. Introduction

Molar-Incisor Hypomineralization (MIH) is a developmental, qualitative enamel defect that affects one to four first permanent molars, frequently associated with affected incisors [1]. The clinical presentation of hypomineralization defects ranges widely, from small well-demarcated areas of discoloration to involvement of the entire crown with a normal thickness of enamel [2]. From a histological perspective, hypomineralised enamel is characterized by reduced hardness and elasticity, increased porosity, an elevated protein content, and an altered carbon/carbonate ratio [3]. These developmental, qualitative

enamel defects can lead to discoloration, increased sensitivity, and post-eruptive enamel breakdown [2], which can potentially affect patients' oral health-related quality of life. Globally, the prevalence of MIH has been estimated at 13–16% [4], and this condition can affect one in six children [5]. Therefore, MIH is receiving increased attention from dental professionals owing to its high prevalence and significant impact on young patients.

Treatment and management strategies for affected teeth include minimally invasive approaches such as remineralization, restorative treatment such as microabrasion, resin infiltration, composite restorations, and extraction [3]. To promote the remineralization of MIH teeth, it is recommended to use products containing Casein Phosphopeptide-Amorphous Calcium Phosphate (CPP-ACP) consistently in the early stages following eruption, when the surface enamel of these new teeth has not yet fully matured [6]. CPP-ACP, which is derived from the milk protein casein, acts as a reservoir for calcium and phosphate ions [7]. It is known to deposit these ions onto the enamel surface and, crucially, facilitates their migration into the subsurface lesions, thereby inhibiting the demineralization cycle and promoting the remineralization of subsurface enamel [7]. Additionally, CPP-ACP contributes to regulating the formation of biofilm on the tooth surface [8]. Despite the significant potential of CPP-ACP in treating MIH, evidence supporting its efficacy remains controversial.

In spite of extensive research into the efficacy of CPP-ACP, controversy persists regarding its effectiveness in preventing dental caries and erosion [8]. Differences in experimental protocols and the substantial variability reported in some studies likely account for the conflicting scientific evidence concerning the remineralizing properties of CPP-ACP, which complicates the interpretation of results [8]. Cavalcante *et al.* [9] (2024) recently conducted a systematic review of CPP-ACP and other non-invasive products for MIH-affected teeth, focusing on remineralization and reduced hypersensitivity, but only included clinical studies. To advance our understanding of MIH aetiology and to guide effective treatment strategies, it is essential to comprehend the ultrastructural, mechanical, and chemical alterations in hypomineralized enamel [3]. Some properties of CPP-ACP, such as improving microhardness, altering calcium and phosphate concentrations, may require laboratory-based evaluations [10]. When assessing the remineralization effects of CPP-ACP, a key difference exists between *in vivo* and laboratory-based studies. Non-invasive clinical tools, like Laser Fluorescence (LF) and Quantitative Light-induced Fluorescence (QLF), are typically utilized in *in vivo* studies [11–13]. However, the results from these clinical studies are susceptible to variability from factors like moisture, plaque, and surface texture [14, 15]. In contrast, laboratory-based studies provide more accurate data by utilizing quantitative methods to precisely measure the mineral content within the enamel.

Given the observed heterogeneities and limitations in prior research, there is a clear necessity for a comprehensive investigation to synthesize and analytically detail the full spectrum of effects of CPP-ACP on MIH-affected enamel. This systematic review and meta-analysis uses a clear search strategy and thorough quality assessment of both clinical and laboratory studies to provide specific conclusions on the effectiveness of CPP-ACP on MIH-affected teeth.

2. Materials and methods

2.1 Protocol

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [16] and was registered in the International Prospective Register of Systematic Reviews (PROSPERO) database under the number CRD420251103933. The PRISMA checklist provides more details and is available as **Supplementary Tables 1,2**.

2.2 Search strategy

A detailed search was conducted across four databases, including PubMed, Embase, Cochrane and Google Scholar, from January–February, 2026. To ensure a comprehensive search and minimize publication bias, Google Scholar was used to identify grey literature. We screened the first 300 results sorted by relevance to maintain a balance between sensitivity and reproducibility. The search keywords were developed based on the Population (P), Intervention (I), and Outcome (O) criteria in PICO, and criteria Comparator (C) was evaluated through the literature screening process.

The search strategy ultilized specific keywords such as "molar incisor hypomineralisation", "demarcated opacities", "mottled enamel", "enamel defect", "CPP-ACP", "GC tooth mousse", "MI paste", "MI varnish", "CPP-ACPF", "remineralization", "desensitize", "saliva characteristics", "enamel microhardness" and "esthetic" using "OR" and "AND" Boolean operators. Details of keywords used in search strategy are available as **Supplementary Table 3**.

After searching, all identified study citations were cross-referenced in the Zotero reference management software. Two reviewers (TKHN, HDD) independently screened articles based on title, abstract, and full-text to identify publications that meet the inclusion criteria. The reasons for excluding any full-text studies were recorded and subsequently reported in the results section of this systematic review. Any disagreements arising between the reviewers at each stage of the study selection process were resolved via consensus discussion, or by consultation with a third investigator.

2.3 Eligibility criteria

The inclusion criteria for studies were as follows: (1) Randomized controlled trials (RCTs), non-randomized studies and *in vitro* studies, (2) Population: Teeth diagnosed with MIH, (3) Intervention: CPP-ACP (Products containing CPP-ACP), (4) Comparator(s)/control: Non-CPP-ACP treatment/intervention group (no treatment, fluoride varnish, fluoride toothpaste, CaGP, placebo, *etc.*), (5) Evaluation of at least one remineralization efficacy of CPP-ACP on hypomineralized molar-incisor teeth (MIH), (6) Articles written in English, (7) Publication timeframe: from database inception to December 2025. The exclusion criteria were as follows: (1) Systematic reviews, unpublished studies, case reports, and case series, (2) Insufficient data on the efficacy of

CPP-ACP, (3) Unavailability of full text.

2.4 Data extraction

Two reviewers (TKHN, HDD) independently extracted data from eligible articles. Information obtained from articles included publication details (first author, publication year, and country), details of the studied population (number of patients, age range, drop-outs, types of teeth and number of teeth), study design, intervention(s), the comparison group, and evaluation of outcomes (remineralization, hypersensitivity, enamel microhardness, preventing dental caries and buffering capacity). Disagreements were resolved by consensus. Missing data could be requested from study authors if applicable.

2.5 Risk of bias assessment

Modified Jadad Scale was used to evaluate the risk of bias of RCTs through three items: randomization, double blinding, and withdrawals and dropouts [17]. Each item was given a score of 1 point for each "yes" or 0 points for each "no". For items 1 and 2, additional point would be given if the method for generating the sequence of randomization and/or the method of double blinding was described and appropriate; 1 point would be deducted if the randomization or blinding was described but the method was inappropriate. The total score for each article ranged from 0 to 5. For non-randomized studies, Methodological Index for Non-randomized Studies (MINORS) score was used, with the global ideal score being 16 for non-comparative studies and 24 for comparative studies [18]. The Quality Assessment Tool For *In Vitro* Studies (QUIN Tool) was used to examine the quality of *in vitro* studies by 12 domains, rated as either adequately specified, inadequately specified, not specified, or not applicable [19]. The study would have low risk of bias if the final score was higher than 70%, moderate risk if the score was 50 to 70%, and high risk if the score was lower than 50%.

Two investigators (MHL, TKHN) performed the quality assessment and the certainty of evidence independently, and any disagreement during the process of assessing study quality was resolved by discussion with the third investigator (TMHT).

2.6 Certainty of evidence assessment

The certainty of evidence for outcomes was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach [20]. The assessment considered five domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias. RCTs were initially rated as high-certainty evidence and downgraded as appropriate based on predefined criteria. Given the heterogeneity in study design, GRADE assessment was applied only to clinical outcomes (*e.g.*, enamel remineralization and hypersensitivity). *In vitro* studies were not formally graded due to their indirect nature and were interpreted as mechanistic evidence.

Two investigators (MHL, TKHN) performed the certainty assessment and the certainty of evidence independently, and any disagreement was resolved by discussion with the third investigator (TMHT).

2.7 Data analysis

Given the complexity of MIH and the multifactorial mechanisms underlying enamel remineralization, this review included both clinical and laboratory-based studies. Clinical studies (RCTs and observational designs) were used to evaluate patient-relevant outcomes, while *in vitro* studies were included to provide mechanistic insights into structural and compositional changes of enamel. These two types of evidence were synthesized separately to avoid inappropriate direct comparison.

Subgroup analyses were conducted based on lesion characteristics (white *vs.* yellow opacities), intervention time points (15 days, 1 month, and 3 months), and intervention types (CPP-ACP, CPP-ACPF) to explore potential sources of heterogeneity. These analyses were not pre-specified in the original protocol, but were performed *post hoc* to provide additional clinically relevant insights.

2.8 Statistical analysis

Meta-analyses and forest plots were performed using Stata version 16.0 (StataCorp, College Station, TX, USA). Only studies evaluating comparable interventions and reporting the same outcome measures were pooled quantitatively. Effect sizes were pooled using a random-effects model based on the DerSimonian-Laird method. For continuous outcomes, pooled effect sizes were calculated using either mean differences (MD) or standardized mean differences (SMD) with corresponding 95% confidence intervals (CI), depending on the measurement scales across studies. Cochrane's Q (χ^2) test was employed to assess statistical heterogeneity, which was then quantified using the I^2 statistic. Heterogeneity was interpreted as follows [21]:

0–25%: low heterogeneity.

26–50%: moderate heterogeneity.

51–75%: substantial heterogeneity.

75%: considerable heterogeneity.

A p-value < 0.10 for the χ^2 test was considered indicative of statistically significant heterogeneity. Given the expected clinical and methodological variability among studies (*e.g.*, differences in lesion type, intervention protocols, and follow-up duration), a random-effects model (DerSimonian and Laird method) was applied as the primary analytical approach. Subgroup analyses were conducted according to intervention type and lesion characteristics to explore potential sources of heterogeneity.

Publication bias was evaluated by visual inspection of funnel plots and quantitatively assessed using Egger's regression test when at least ten studies were available for a given outcome. A p-value < 0.05 in Egger's test was considered suggestive of small-study effects. All statistical tests were two-tailed, and a p-value < 0.05 was considered statistically significant, except where otherwise specified.

3. Results

3.1 Study selection

The study selection process is shown in the PRISMA flow diagram in Fig. 1. The initial search across four electronic databases yielded a total of 535 records (PubMed: 136, Cochrane: 40, Embase: 82, and Google Scholar: 277). An additional 3 records were identified through hand-searching from relevant systematic reviews, resulting in a total of 538 records for initial consideration. 422 records proceeded to title and abstract screening after the removal of 116 duplicate and inaccessible records. During this phase, articles were discarded mainly based on title (n = 131) and having ineligible populations (n = 133). Following the removal of 394 records, 28 articles underwent a full-text assessment. Consequently, 18 studies [10, 22–38] were selected to be included in systematic review, and 8 studies [10, 23, 25–27, 30, 31, 35] were included in meta-analysis.

3.2 Study characteristics

The characteristics of each study are reported in **Supplementary Table 4** (Ref. [10, 22–38]). The study designs were diverse, consisting of ten RCTs, five *in vitro* studies, a pilot study, a prospective cohort study, and a combined *in situ*/*in vitro* trial. All included studies evaluated the efficacy of CPP-ACP or its fluoride-enriched version (CPP-ACPF), often comparing these agents against fluoride varnishes (5% sodium fluoride (NaF)), high-fluoride toothpastes (1450 ppm), or adjunctive therapies, such as Ozone, Photo-bio-modulation therapy (PBMT), and Silver Diamine Fluoride (SDF). The follow-up periods were diverse, ranged from 30 minutes to 3 years. Three studies evaluated the remineralization potential of CPP-ACP using Scanning Electron Microscope (SEM), Environmental Scanning Electron Microscope (ESEM), and Energy-Dispersive X-ray Spectroscopy (EDX), while six studies measured the effect by LF. Two studies assessed the remineralization ability using Raman spectrum to measure the depolarization ratio. Four studies evaluated CPP-ACP's ability to reduce hypersensitivity by measuring the Visual Analog Scale (VAS) and Schiff Cold Air Sensitivity Scale (SCASS) scores before and after intervention. Other effects of CPP-ACP were also evaluated, including the esthetic effect and increasing microhardness.

3.3 Risk of bias assessment among studies

Based on the QUIN tool assessment results in Table 1, four *in vitro* studies had low risk of bias, and two remaining studies were assessed to have medium risk of bias. Most studies clearly defined their objectives and followed the aims throughout, and adequately presented the outcomes based on the pre-stated aims. Methodology explanations in most studies were clear, only one study did not mention details regarding the concentration and type of CPP-ACP used in their intervention.

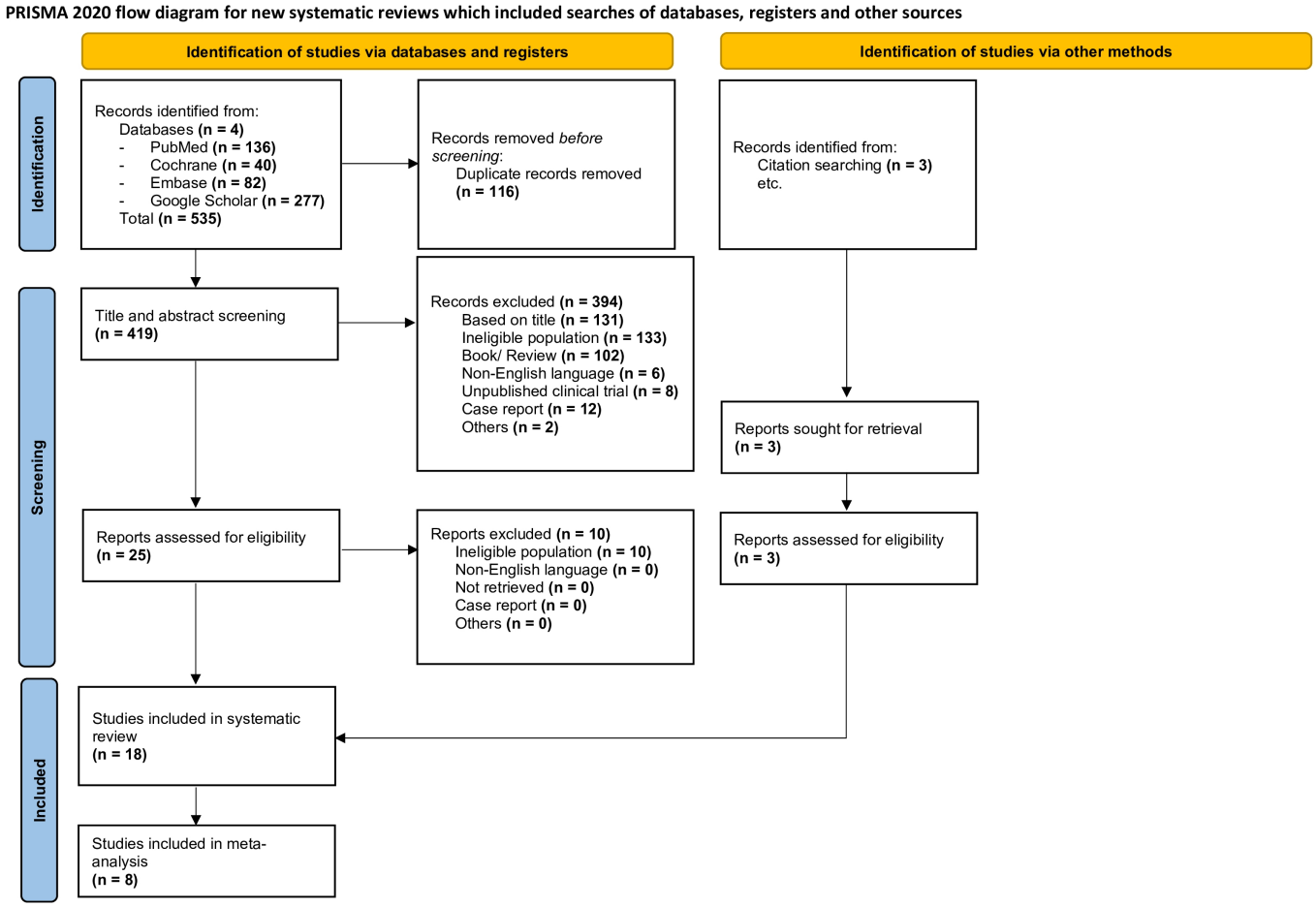

FIGURE 1. The PRISMA flow chart for the literature search. PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

TABLE 1. Quality assessment of the included studies according to the QUIN tool.

Author (Year)	Baroni (2010)	Crombie (2013)	Franco (2021)	Kumar (2021)	Cardoso-Martins (2022)	Cardoso-Martins (2022)
Clearly stated aims/objectives	2	1	2	2	2	2
Detailed explanation of sample size	N/A	N/A	N/A	N/A	2	N/A
Detailed explanation of sampling technique	1	1	0	1	1	1
Details of comparison group	1	2	1	1	2	2
Detailed explanation of methodology	0	2	1	2	2	2
Operator details	N/A	N/A	N/A	N/A	N/A	N/A
Randomization	N/A	0	N/A	2	0	N/A
Method of measurement of outcome	0	2	2	1	2	0
Outcome assessor details	N/A	N/A	N/A	N/A	N/A	N/A
Blinding	N/A	N/A	N/A	0	N/A	N/A
Statistical analysis	2	1	2	2	2	2
Presentation of results	2	2	2	2	2	2
Risk of bias (%)	57.14 (medium risk)	68.75 (medium risk)	71.43 (low risk)	72.22 (low risk)	83.33 (low risk)	78.57 (low risk)

N/A: not applicable.

The majority of the examined studies included sufficient details regarding comparison groups, thus elevating the quality of their comparative analysis. Operator and outcome assessor details were not relevant in all studies, indicating that these aspects were not adequately considered.

Two non-randomized studies were evaluated by MINORS based on 12 distinct criteria (Table 2). A study by Bakkal *et al.* [35] (2017) had a clearly stated aim, inclusion of consecutive patients, appropriate endpoints, unbiased assessment, and adequate statistical analyses, but did not report prospective data collection, loss to follow-up, or a calculation of study size. A study by Biondi *et al.* [25] (2017) received a lower score due to inadequate description of patient inclusion and failure to report on unbiased assessments, follow-up periods, prospective data collection, or the use of contemporary groups.

Among the ten RCTs [22, 24, 26–28, 33, 34, 36–38], half of them scored more than 3, and the study by Bardellini *et al.* [38] (2024) achieved the highest score of 5, fulfilling all the criteria and using appropriate methods of randomization and blinding (Table 3). While most studies were described as randomized, only half of them [22, 26–28, 34, 38] utilized an appropriate method of randomization. Four studies [26, 34, 37, 38] were regarded as double-blind, but only one of them [38] provided an appropriate method of blinding. One study [34] was deducted one point for using inadequate method of blinding.

3.4 Certainty of evidence assessment

Table 4 presents a summary of the certainty of evidence for key outcomes. CPP-ACP showed potential in enamel remineralization, and hypersensitivity reduction; however, the certainty of evidence ranged from very low to low due to methodological limitations, heterogeneity, and imprecision. Evidence from *in vitro* studies was rated as very low certainty due to indirectness. Publication bias could not be formally assessed due to the limited number of included studies.

3.5 Meta-analysis of the included studies

Due to the limited number of studies per outcome (<10), publication bias could not be reliably assessed.

3.5.1 Meta-analysis of clinical studies

The meta-analysis demonstrated that CPP-ACPF significantly improved remineralization outcomes at both 1 month (SMD = 0.42; 95% CI: 0.03–0.81) and 3 months (SMD = 0.43; 95% CI: 0.09–0.78) (Fig. 2). No statistically significant difference was observed between the two time points ($p = 0.968$), suggesting that the remineralization effect appears early and remains stable over time. Heterogeneity was substantial at 1 month but low at 3 months, indicating greater consistency in longer-term outcomes.

The pooled analysis showed a small but statistically significant remineralization effect overall (SMD = 0.33; 95% CI: 0.04–0.62) with no observed heterogeneity ($I^2 = 0\%$) (Fig. 3). However, subgroup analyses at 15 days (SMD = 0.30; 95% CI: −0.10 to 0.71) and 1 month (SMD = 0.36; 95% CI: −0.05 to 0.76) did not reach statistical significance individually. No significant difference was detected between time points ($p = 0.850$).

3.5.2 Meta-analysis of *in vitro* studies

The pooled analysis demonstrated a large and statistically significant improvement in %C following CPP-ACP application (SMD = −1.30; 95% CI: −2.08; −0.52) (Fig. 4). Comparable large effects were observed in the comparator group (SMD = −1.43; 95% CI: −2.24; −0.62). No statistically significant difference was detected between subgroups ($p = 0.818$), indicating that CPP-ACP performs similarly to other

TABLE 2. MINORS scores for non-randomized studies.

Author (Year)	Bakkal (2017)	Biondi (2017)
A clearly stated aim	2	2
Inclusion of consecutive patients	2	1
Prospective collection of data	0	0
Endpoints appropriate to the aim of the study	2	2
Unbiased assessment of the study endpoint	2	0
Follow-up period appropriate to the aim of the study	2	0
Loss to follow up less than 5%	0	0
Prospective calculation of the study size	0	0
An adequate control group	2	2
Contemporary groups	2	0
Baseline equivalence of groups	2	2
Adequate statistical analyses	2	2
Total score	18	11

TABLE 3. Modified Jadad scores for randomized studies.

Author (Year)	Was the study described as randomized?	Was the method of randomization appropriate?	Was the study described as double-blind?	Was the method of blinding appropriate?	Was there a description of withdrawals and dropouts?	Deduct 1 point if the method of randomization is inappropriate	Deduct 1 point if the method of blinding is inappropriate	Final score
Özgül (2013)	1	0	0	0	1	0	0	2
Pasini (2018)	1	0	0	0	0	0	0	1
Bhandari (2019)	1	0	0	0	0	0	0	1
Olgen (2021)	1	1	0	0	1	0	0	3
Prathima (2021)	1	0	1	0	1	0	0	3
Singh (2021)	1	1	0	0	0	0	0	2
Sezer & Kargul (2022)	1	1	0	0	0	0	0	2
Sezer (2022)	1	1	1	0	1	0	0	4
Bardellini (2024)	1	1	1	1	1	0	0	5
Al-Nerabieah (2024)	1	1	1	0	1	0	−1	3

remineralizing agents in decreasing %C.

The pooled analysis demonstrated a large and statistically significant change in %Ca following CPP-ACP application (SMD = 1.05; 95% CI: 0.36–1.75) (Fig. 5). A comparable large effect was observed for other agents (SMD = 0.96; 95% CI: 0.20–1.72). No statistically significant difference was found between subgroups (p = 0.858), indicating that CPP-ACP performs similarly to other remineralizing agents in modifying %Ca. Overall heterogeneity was low (I^2 = 6.8%), supporting the robustness of the findings.

Subgroup analysis showed the largest polarization change in white spot lesions (SMD = 2.00; 95% CI: 0.88–3.12), followed by yellow lesions (SMD = 0.84; 95% CI: −0.09–1.77) and sound enamel (SMD = 0.57; 95% CI: −0.33–1.48) (Fig. 6). Although a gradient trend was observed, the difference between groups was not statistically significant (p = 0.135). Overall, polarization changes were significant (SMD = 1.03; 95% CI: 0.47–1.59) with no observed heterogeneity.

TABLE 4. Certainty of evidence using GRADE approach.

Outcomes	No. of participants (studies)	Effect estimate	Certainty
Enamel remineralization (LF)	818 (4 RCTs, 2 non-randomized studies)	LF value reduction observed across studies	⊕⊕◯◯ LOW[a,c]
Enamel remineralization (SEM, FESEM)	98 (5 *in vitro* studies)	Morphological improvement observed across studies	⊕◯◯◯ VERY LOW[a,d]
Hypersensitivity (VAS, SCASS)	254 (4 RCTs)	Reduction observed across studies	⊕⊕◯◯ LOW[a,b]
Mineral content (EDX, EDS)	66 (3 *in vitro* studies)	Changes in mineral content observed across studies	⊕◯◯◯ VERY LOW[a,c,d]
Enamel microhardness (Vickers Microhardness Test)	15 (1 *in vitro* study)	Structural improvement observed across studies	⊕◯◯◯ VERY LOW[c,d]

EDS: Energy-Dispersive Spectroscopy; EDX: Energy-Dispersive X-ray Spectroscopy; LF: Laser fluorescence; RCT: Randomized Controlled Trial; SCASS: Schiff Cold Air Sensitivity Scale; SEM: Scanning Electron Microscope; VAS: Visual Analog Scale; FESEM: Field Emission Scanning Electron Microscopy.

[a] *Downgraded one level for risk of bias due to limitations in randomization and blinding in several included studies.*

[b] *Downgraded one level for inconsistency due to heterogeneity in intervention protocols and outcome measurements.*

[c] *Downgraded one level for imprecision due to small sample sizes and wide confidence intervals.*

[d] *Downgraded two levels for indirectness for in vitro studies, as laboratory outcomes may not reflect clinical effectiveness.*

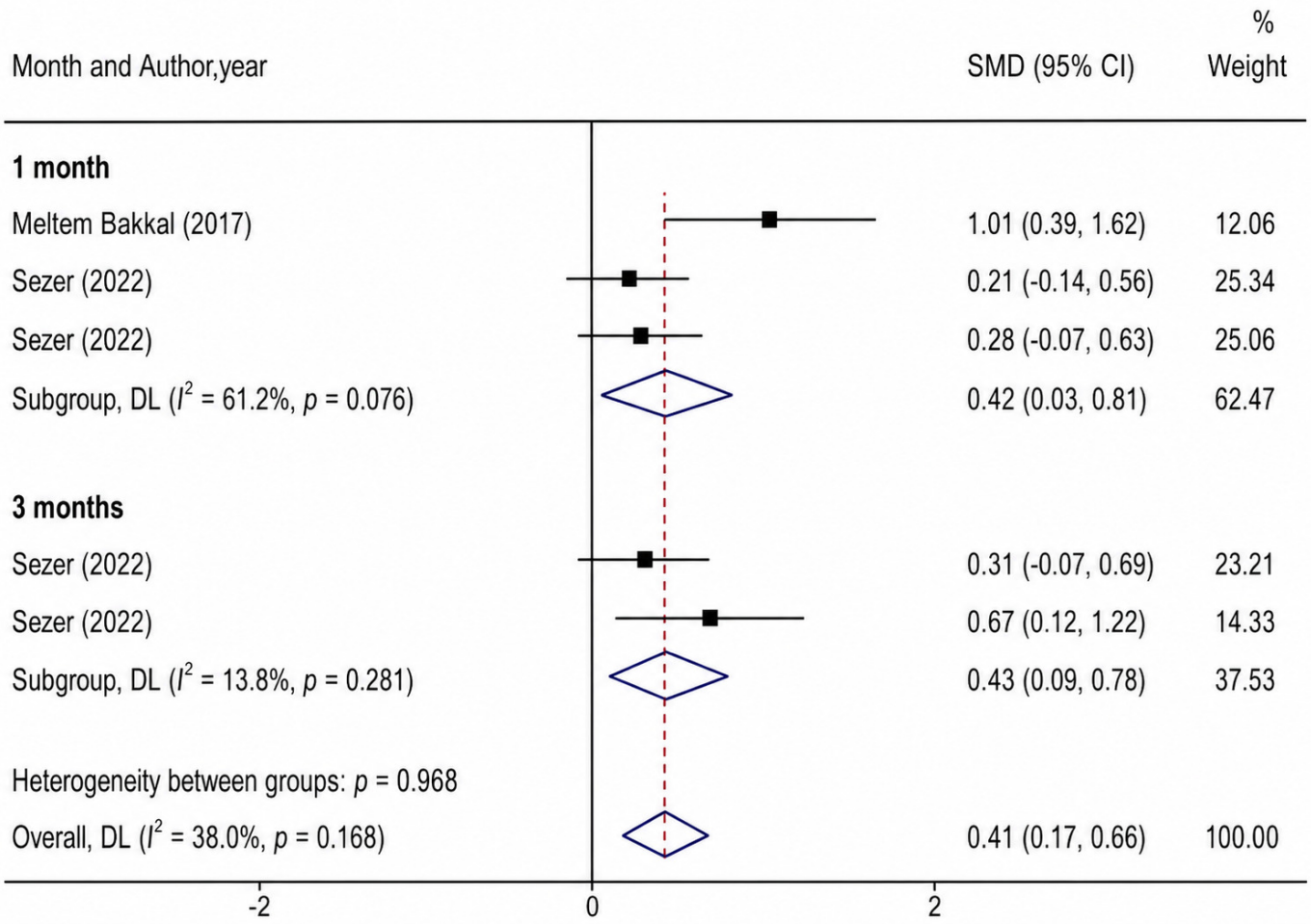

FIGURE 2. Forest plot comparing the remineralization efficacy of CPP-ACPF at 1-month and 3-month intervals. CI: Confidence Interval; DL: DerSimonian and Laird method; SMD: Standard Mean Difference.

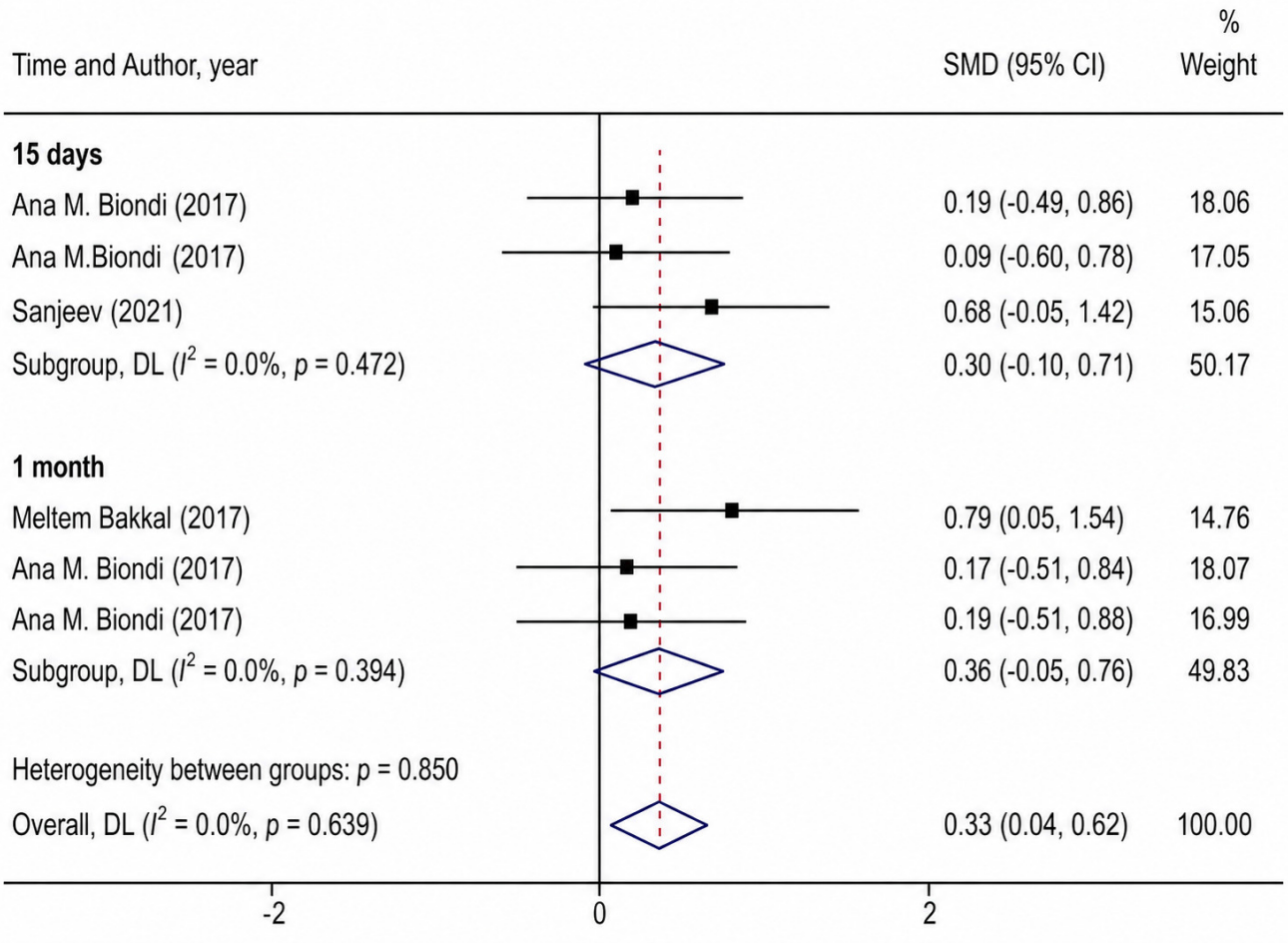

FIGURE 3. Forest plot comparing the remineralization efficacy after using CPP-ACPF for 15 days and 1 month. CI: Confidence Interval; DL: DerSimonian and Laird method; SMD: Standard Mean Difference.

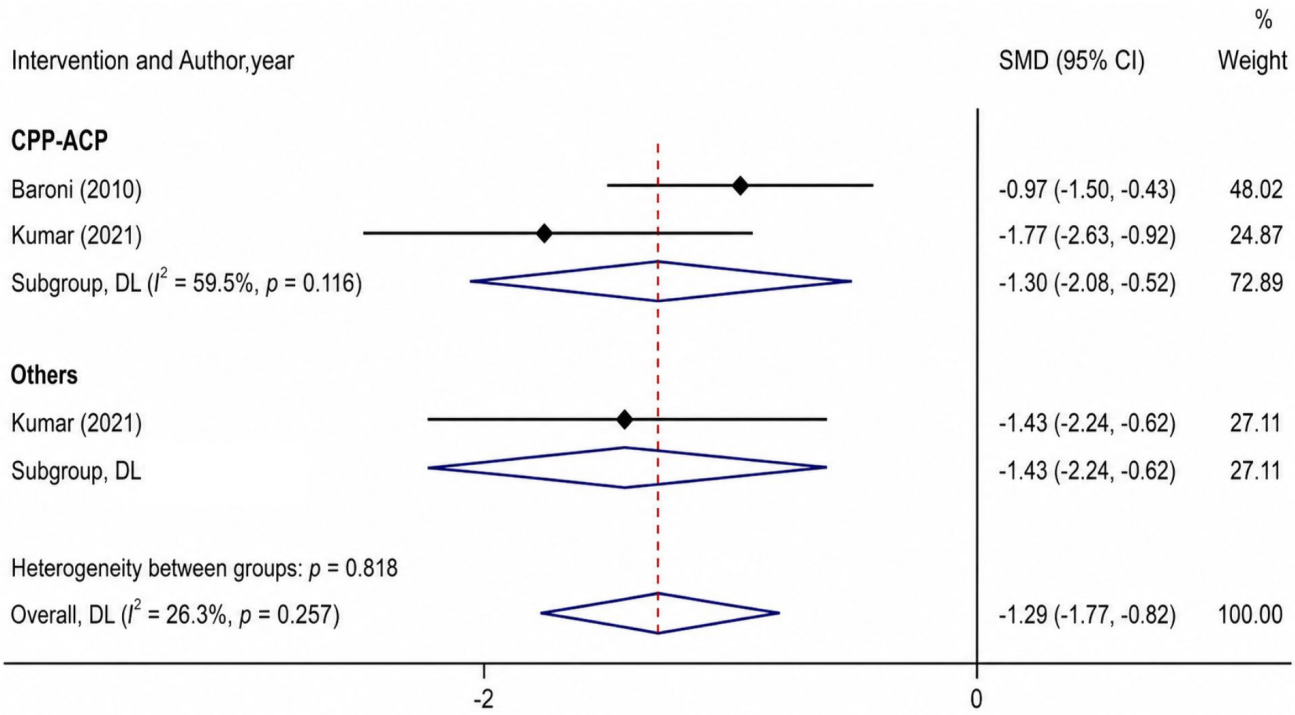

FIGURE 4. Forest plot illustrating the difference in enamel element compositions (%C) after using CPP-ACP and other remineralizing agents. CI: Confidence Interval; DL: DerSimonian and Laird method; SMD: Standard Mean Difference.

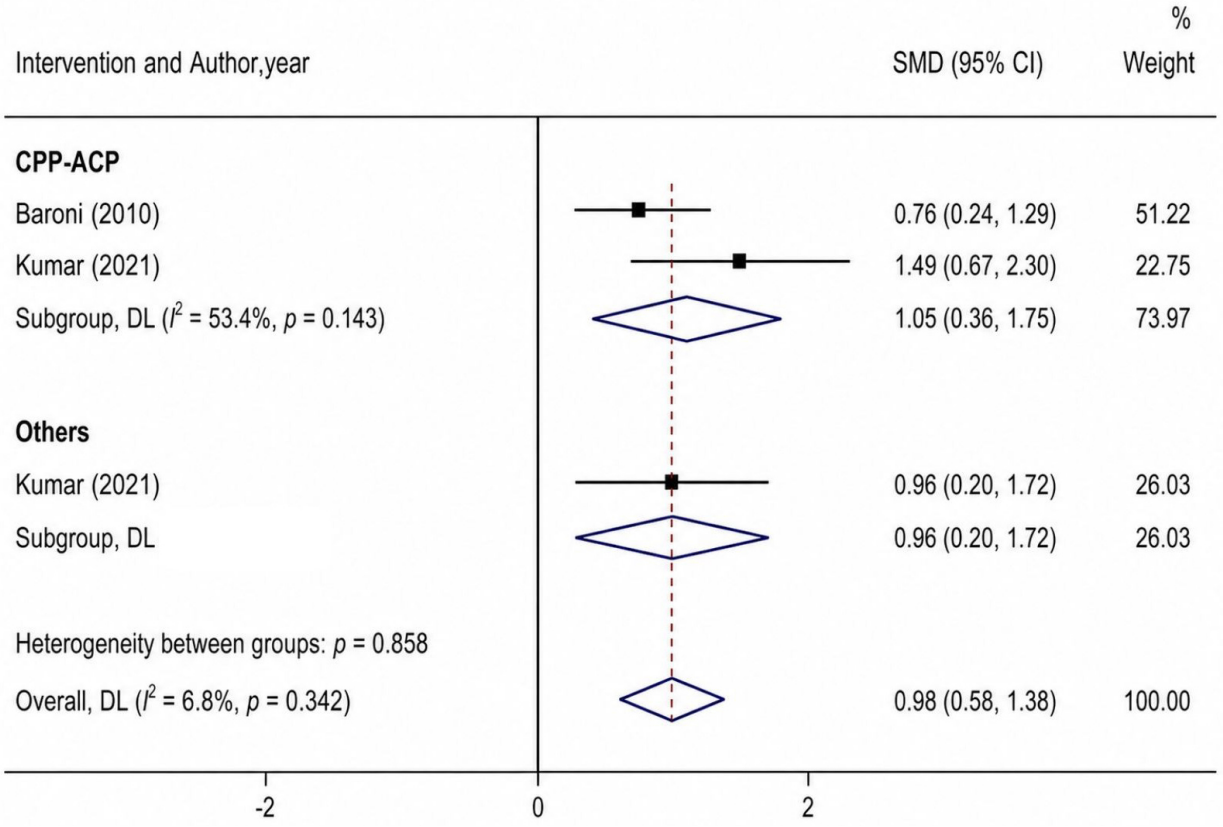

FIGURE 5. Forest plot illustrating the difference in enamel element compositions (%Ca) after using CPP-ACP and other remineralizing agents. CI: Confidence Interval; DL: DerSimonian and Laird method; SMD: Standard Mean Difference.

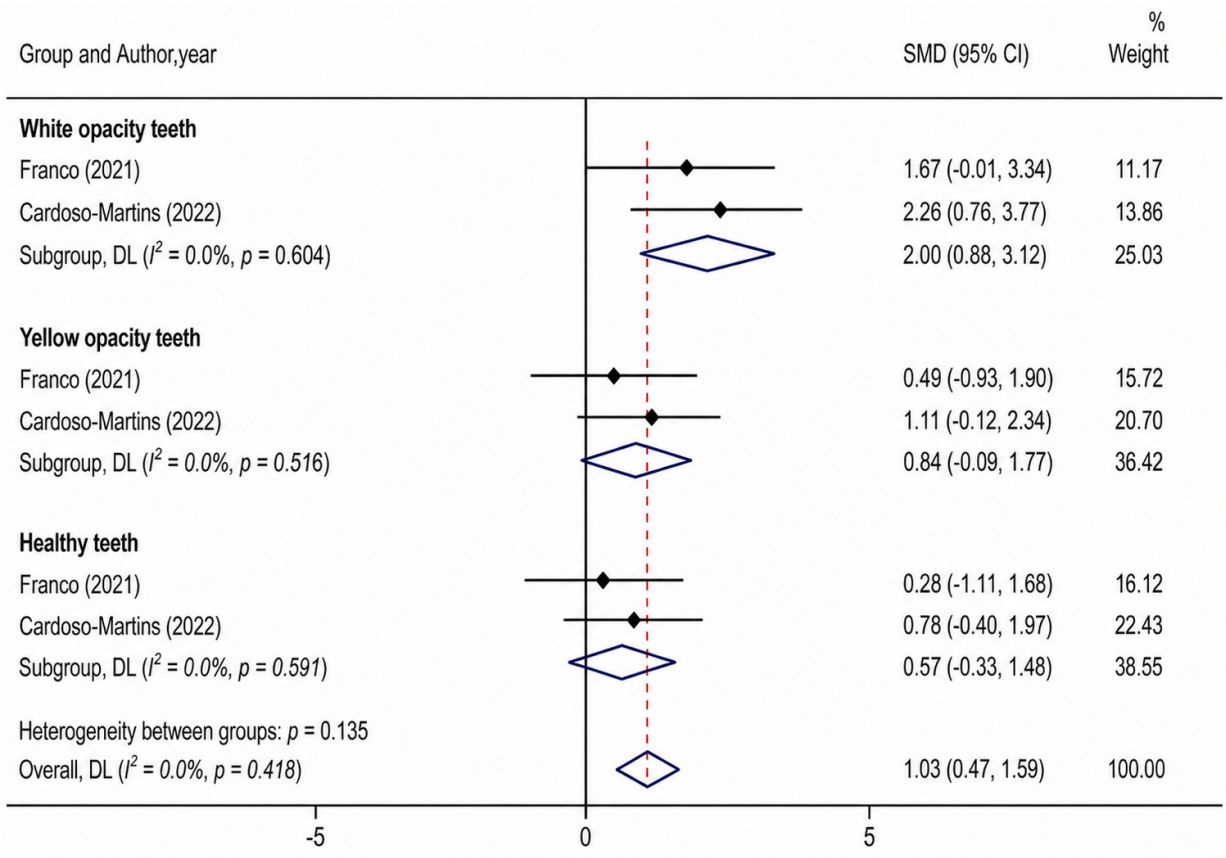

FIGURE 6. Forest plot illustrating the depolarization ratio change in white lesions, yellow lesions, and sound teeth, respectively. CI: Confidence Interval; DL: DerSimonian and Laird method; SMD: Standard Mean Difference.

4. Discussion

It is important to distinguish between clinical and mechanistic evidence in this review. Clinical conclusions regarding the effectiveness of CPP-ACP are primarily based on randomized and observational human studies. In contrast, findings from *in vitro* studies provide mechanistic insights into mineral composition and structural changes, but do not directly translate into clinical outcomes. Therefore, laboratory findings should be interpreted as supportive evidence, rather than definitive proof of clinical efficacy. In terms of effectiveness of CPP-ACP, most studies agreed that CPP-ACP could remineralize the MIH-affected enamel based on experimental and clinical evidence. Baroni *et al.* [31], Crombie *et al.* [32], and Kumar *et al.* [23] reported significant changes in mineral content, with increased compositions of calcium and phosphate, and decreased ratios of carbon and carbonate. Kumar *et al.* [23] reported an increase in Ca/P and Ca/C ratios after intervention, but the difference was not statistically significant. Franco *et al.* [30] suggested that the depolarization ratio decreased significantly after using CPP-ACP in white and yellow lesions, implicating that the enamel was remineralized. CPP-ACP can alter the microhardness of the enamel, as Cardoso-Martins *et al.* [29] suggested that the microhardness increased after intervention, and the increase was greater in white opacities compared with yellow opacities. RCTs [22, 26–28, 34] reported that LF values decrease following the application of remineralizing agents such as CPP-ACP, CPP-ACPF, and CaGP. CPP-ACP also has the capacity of reducing dental hypersensitivity, as suggested by Bardellini *et al.* [38] and Pasini *et al.* [33]. Ozgul *et al.* [24] concluded that the VAS value reduced significantly at all follow-up time points, and after 8 weeks, there was no significant difference between Tooth-mousse, MI paste plus, and fluoride in terms of hypersensitivity reduction. Interestingly, Prathima *et al.* [37] revealed that usage of CPP-ACP improved the salivary characteristics in MIH-affected children by elevating the salivary pH, salivary flow rate, and buffering action.

This systematic review suggests that CPP-ACP is a multifunctional agent in the treatment of MIH. In addition to its primary roles in remineralization and sensitivity reduction (consistent with Cavalcante *et al.* [9]), CPP-ACP modifies inorganic content, improves the enamel morphology, and increases microhardness. Furthermore, it improves tooth color and salivary characteristics. The meta-analysis of *in vitro* studies provides a more specific and detailed view of these effects, which remain consistent with clinical outcomes. It is important to note that the mechanistic interpretations presented in this review are primarily based on indirect evidence from laboratory studies. Therefore, these findings should be interpreted cautiously, as they do not establish definitive causal mechanisms, but rather provide biologically plausible explanations.

Meta-analysis results show that incorporation of fluoride within the CPP-ACPF complex can achieve significant effect within the first month of treatment (Fig. 2). Specifically, Mansy *et al.* [39] suggested that consistent at-home application of CPP-ACPF for one month leads to a significant reduction in LF values and a color improvement of white spot lesions. In contrast, CPP-ACP alone showed less consistent and often non-significant effects during the early follow-up period (Fig. 3). Olgen *et al.* [28] suggested that while both formulations provide long-term remineralization, CPP-ACPF exhibits an advantage in terms of speed of onset. Chemically, the synergy with fluoride allows Ca^{2+} and PO_4^{3-} ions to precipitate, forming stable fluorapatite crystals directly within demineralized zones. This structure possesses significantly higher acid resistance and mechanical strength compared with MIH-affected enamel, showing potential in mitigating the risk of enamel breakdown [34]. Furthermore, the CPP-ACP component serves as a delivery system, facilitating the deep penetration of F^- ions into the lesion, ensuring comprehensive remineralization from the dentin-enamel junction to the surface. For MIH cases accompanied by dentin hypersensitivity, the early occlusion of dentinal tubules through CPP-ACPF remineralization not only rapidly alleviates pain [24], but also significantly improves patient compliance. This facilitates better oral hygiene maintenance at home, enabling clinicians to conduct exams and perform conservative interventions more effectively.

The meta-analysis results in this study show a promising trend in elemental concentration shifts: the use of CPP-ACP significantly increases the percentage of calcium (SMD = 1.05) while simultaneously leading to a sharp decrease in carbon concentration (SMD = −1.30) (Figs. 4,5). This may reflect the microstructural alterations within MIH enamel under remineralization therapy. Pathologically, MIH-affected enamel is characterized by disruptions in the degradation of amelogenin proteins, resulting in excessive retention of organic components and a porous enamel structure [40]. The observed decrease in %C alongside the increase in %Ca suggests a possible replacement process: inorganic ions from the CPP-ACP complex penetrate deeply into the enamel subsurface, gradually displacing and substituting the space previously occupied by water or proteins. This finding is entirely consistent with the conclusions of Crombie *et al.* [32], which indicated that remineralizing agents may not only adhere to the surface, but also infiltrate the lesion, reducing porosity and enhancing the genuine mineral density of the affected enamel. Beyond calcium supplementation, experimental studies by Baroni *et al.* [31] and Kumar *et al.* [23] also reported a concurrent increase in %P. The synergistic rise of calcium and phosphate facilitates the transformation of enamel from a porous structure into a denser and more stable structure. This suggests a remineralization mechanism oriented toward restoring the natural biological architecture of the hydroxyapatite structure, rather than simply depositing minerals passively on the surface layer. The consequence of this improved material density is further evidenced by Vickers microhardness tests in studies by Cardoso-Martins *et al.* [29] and Pavethynath *et al.* [41], which reported a significant increase in enamel physical strength and a clear reduction in lesion size following treatment. It is recommended that CPP-ACP should be applied immediately following the eruption of new teeth. This early intervention is crucial due to the multifaceted benefits of CPP-ACP, which include a significant increase in the microhardness of the enamel surface. In addition, CPP-ACP is highly effective in reducing dental hypersensitivity, alleviates discomfort, particularly during brushing and consumption of hot or cold substances.

The combined effect of improved enamel microhardness and reduced sensitivity makes it easier for patients, especially children and those with high caries risk, to maintain consistent and effective oral hygiene practices.

Analyzing the polarization ratio via Raman spectroscopy provides insight into the efficacy of CPP-ACP, extending beyond mineral quantification to evaluate structural reorganization at the crystalline level. Our meta-analysis recorded a distinct differentiation in response capacity across various lesion zones, with creamy-white lesions showing the most robust changes (SMD = 2.00; 95% CI: 0.88–3.12) (Fig. 6). This substantial effect size, coupled with an absolute heterogeneity index of zero (I^2 = 0%), shows the high consistency and reliability of this finding: CPP-ACP appears to be effective in re-establishing the alignment of hydroxyapatite crystals within white spot areas. Similar improvements in color appearance were also reported by Bhandari *et al.* [36]. Pathologically, creamy-white MIH lesions possess lower porosity and retain a better mineral content compared with yellow-brown lesions [42]. When calcium and phosphate ions from the CPP-ACP complex infiltrate, they may serve as a biochemical template that aids in the re-mineralization of the enamel framework. This reduces light scattering and restores the characteristic optical properties of healthy enamel. In contrast, while yellow-brown lesions showed an improvement trend (SMD = 0.84), but the statistical evidence was insufficient. This discrepancy can be explained by the studies of Franco *et al.* [30] and Cardoso-Martins *et al.* [10], which suggests that yellow-brown areas contain higher residual protein content and have more severely disrupted crystalline structures. The extreme porosity in these zones means that while remineralization can compensate for ion quantity (increased %Ca), it may remain insufficient to fully restore crystalline orientation in the short term. Finally, healthy enamel recorded the lowest variation (SMD = 0.57) with no statistical significance—a result perfectly consistent with biological reality, as healthy enamel is already mineral-saturated and optimally organized. Although direct comparison between the three subgroups did not show a statistically significant difference (p = 0.135), the declining trend of efficacy (creamy-white > yellow-brown > normal enamel) serves as a crucial clinical indicator. This suggests that the prognosis for microstructural recovery in MIH enamel is intimately tied to the nature of the initial defect. Clinicians should clearly identify the lesion type to set appropriate treatment expectations: while white spots may recover to a state near the original structure, yellow-brown lesions will require more aggressive and long-term intervention strategies to achieve spectroscopic and microstructural stability.

Importantly, the overall certainty of evidence was limited. According to the GRADE assessment, most outcomes were supported by very low to low certainty evidence, mainly due to methodological heterogeneity, small sample sizes, and variability in outcome assessment methods. Additionally, the inclusion of *in vitro* studies introduces indirectness, limiting the translation of findings into clinical practice. Therefore, while CPP-ACP shows promising effects, these results should be interpreted with caution, and high-quality, well-designed clinical trials are still required.

A notable strength of this study is the systematic and meta-analytical approach, which yields a more reliable evaluation of CPP-ACP in the pediatric population. By conducting a systematic meta-analysis, we were able to provide a more statistically powerful and reliable estimation of the remineralizing potential of CPP-ACPF compared with individual primary studies. This allows clinicians to make more informed, evidence-based decisions when managing the complex challenges of MIH. Furthermore, this study integrates both clinical and laboratory data for an in-depth analysis of the mechanisms of action of CPP-ACP on MIH-affected teeth. By combining *in vivo* evidence from patients with *in vitro* investigations, the research provides a comprehensive perspective that bridges the gap between mechanistic understanding and clinical outcomes. Additionally, the methodological transparency was supported by the application of design-specific quality assessment tools, including QUIN for *in vitro* studies, the modified Jadad scale for RCTs, and the MINORS scale for non-randomized trials, alongside the GRADE approach. This ensures that the clinical recommendations derived from this study are grounded in a rigorous assessment of both internal validity and the overall certainty of the evidence.

This study, however, has several limitations. Firstly, while there is substantial and diverse evidence supporting the efficacy of CPP-ACP in promoting dental enamel remineralization, there is insufficient data concerning its additional effects, such as color improvement, increasing enamel hardness, and alterations in salivary properties. This shortfall in research limits a holistic understanding of CPP-ACP's overall therapeutic profile and necessitates further investigation beyond its well-established remineralization capabilities to fully characterize its clinical utility. Secondly, the heterogeneity of some meta-analyses, particularly those evaluating one-month CPP-ACPF application, was relatively high, reflecting substantial variations in study protocols. Variations in results are due to methodological differences, such as CPP-ACPF concentration/formulation, application frequency/duration, patient characteristics (age, lesion severity), control group interventions, and outcome assessment methods. The heterogeneity indicates that results from the meta-analysis should be interpreted with caution, as it masks important differences in the treatment effect across diverse clinical scenarios and study designs. Although efforts were made to analyze clinical and laboratory data separately, caution is required when interpreting the overall conclusions. Subgroup analyses were conducted based on lesion characteristics (white *vs.* yellow opacities) to explore potential sources of heterogeneity. These analyses were not prespecified in the original protocol, but were performed *post hoc* to provide additional clinically relevant insights. Finally, the number of long-term clinical studies exceeding one year is still limited, making it challenging to assess the durability and long-term stability of the remineralized enamel layer. Without sustained follow-up, it is difficult to confidently conclude how well the newly-formed or repaired enamel structure resists the continuous challenges posed by acidic environment, abrasive forces from brushing, and general chemical degradation over time. Future research should be designed to conduct longitudinal studies with assessments conducted at multiple, strategically selected time-points. This approach will allow for a comprehensive and dynamic evaluation of CPP-ACP's

sustained effect, therapeutic longevity, and its impact on the remineralization process over an extended period. A significant priority must be placed on robust, long-term clinical trials, which are essential for guiding clinical practice recommendations, and ensuring that clinicians can confidently integrate CPP-ACP into their protocols.

5. Conclusions

This meta-analysis indicates that CPP-ACPF has the potential of remineralizing MIH-affected enamel, particularly within the first month of application. Adding fluoride to CPP-ACP (CPP-ACPF) may accelerate the remineralizing effect, facilitating the formation of acid-resistant fluorapatite that alleviates hypersensitivity and has potential of mitigating the risk of enamel breakdown. In contrast, the pooled results for CPP-ACP were not statistically significant, suggesting that its clinical relevance for structural remineralization remains unconfirmed. Raman spectroscopy indicates that clinical prognosis may depend on the initial defect: creamy-white spots offer the best prognosis for structural recovery, while yellow-brown lesions require more intensive intervention due to severe structural disruption and high protein content. It is essential to note that according to the GRADE assessment, the overall certainty of this evidence is low to very low, primarily due to study heterogeneity and inherent risks of bias. Consequently, these results should be viewed as promising clinical trends, rather than definitive therapeutic guarantees. The limited clinical and laboratory-based evidence stresses the need for further high-quality research to fully assess the comprehensive range of applications for CPP-ACP. Future studies should employ standardized protocols, and utilize appropriate control groups to accurately delineate the specific mechanisms of action, optimal application parameters, and long-term clinical outcomes associated with CPP-ACP use.

ABBREVIATIONS

CaGP, Calcium Glycerophosphate; CPP-ACPF, Casein Phosphopeptide-Amorphous Calcium Phosphate Fluoride; CPP-ACP, Casein Phosphopeptide-Amorphous Calcium Phosphate; CI, confidence intervals; DL, DerSimonian and Laird method; EDS, Energy-Dispersive Spectroscopy; EDX, Energy-Dispersive X-ray Spectroscope; ESEM, Environmental Scanning Electron Microscope; FESEM, Field Emission Scanning Electron Microscopy; GRADE, Grading of Recommendations Assessment, Development and Evaluation; LF, Laser fluorescence; MD, mean differences; MIH, Molar-Incisor Hypomineralisation; MINORS, Methodological Index for Non-randomized Studies; N/A, not applicable; NaF, sodium fluoride; PBMT, Photo-bio-modulation therapy; PICO, Population, Intervention, Comparison, and Outcome; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PROSPERO, International Prospective Register of Systematic Reviews; QUIN, Quality Assessment Tool For *In Vitro* Studies; QLF, Quantitative Light-induced Fluorescence; RCT, Randomized Controlled Trial; SCASS, Schiff Cold Air Sensitivity Scale; SDF, Silver Diamine Fluoride; SEM, Scanning Electron Microscope; SMD, standardized mean differences; VAS, Visual Analog Scale.

AVAILABILITY OF DATA AND MATERIALS

Raw data supporting the findings of this study are available from the corresponding author on request.

AUTHOR CONTRIBUTIONS

TMHT, MHL, TKHN—Conceptualization; Project administration. TKHN, HDD—Data curation. TKHN, DHN—Formal analysis. TKHN, NHLP, HDD—Investigation; Visualization. TMHT, MHL—Methodology; Supervision. TMHT, MHL, DHN—Resources. DHN, CSD—Software. MHL, TKHN—Validation. NHLP, HDD, CSD—Writing–original draft. TMHT, MHL, TKHN, DHN—Writing–Review & Editing. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

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The authors declare no conflict of interest.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found, in the online version, at https://....

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