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## Review Article

# Efficiency of casein phosphopeptide amorphous calcium phosphate versus topical fluorides on remineralizing early enamel carious lesions – A systematic review and meta analysis



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### ARTICLE INFO

#### Keywords:

Caesin phosphopeptide amorphous calcium phosphate  
 Caesin phosphopeptide amorphous calcium phosphate fluoride  
 Topical fluorides  
 Dental caries remineralization  
 Early enamel caries  
 ICDAS II  
 Diagnodent score

### ABSTRACT

**Objective:** To assess the remineralizing efficiency of caesin phosphopeptide amorphous calcium phosphate (CPP-ACP) versus topical fluorides on early enamel lesions in vivo.

**Data sources:** PubMed, Web of Science, Scopus, EBSCO were searched based on the PICOS criteria up to December 2022 with English language restriction. All relevant studies were subjected to two separate reviews before being included at the title, abstract, and full text levels.

**Study selection:** 41 studies were reviewed and 11 selected for inclusion in the final sample for the review. All were randomized clinical trials with the follow-up period of the studies ranging from 3 to 12 months. Out of the 11 studies, only two are with low risk of bias on assessment with Cochrane risk of bias assessment tool, while the other nine articles were with the moderate and high risk of bias.

**Conclusions:** Conflicting evidence exists on the clinical efficacy of CPP-ACP compared to the various fluoride forms tested, and no adverse effect associated with CPP-ACP use was discovered in comparison to fluorides that had certain detrimental health impacts. Although, the review results in favor of both fluorides and CPP-ACP with similar clinical efficiency, when ill effects are considered the CPP-ACP can be a choice of remineralizing early enamel lesions. However, before concrete suggestions can be given, high-quality, well-designed clinical research in this area are still necessary.

**Clinical significance:** A considerable remineralizing impact has been shown in both in vitro and in vivo experiments, making CPP-ACP/CPP-ACPF a more promising remineralizing agent than fluorides. Therefore, this can be applied clinically to early enamel carious lesion.

## 1. Introduction

Dental caries is among the most prevalent chronic diseases in humans. Numerous preventive and therapeutic strategies to combat dental caries can be found in the literature. Particularly in developing nations, certain impacts of dental caries, such as toothache and tooth loss, compel patients to consider treatment (Kidd et al., 2000). This condition is reversible at its incipient phase through remineralization with the help of biofilm and salivary calcium and phosphates (Selwitz et al., 2007; Featherstone, 2000). This is further facilitated by various fluoridated and non-fluoridated remineralizing agents.

Fluoride therapy has been the backbone of the non-invasive treatment plan for early carious lesions in dentistry and its beneficial effects

towards dentition making them more resistant to acid attacks, its negative health effects, such as dental and skeletal fluorosis, have led to minimizing fluoride therapies (Fejerskov, 2004).

Thus, non-fluoridated remineralizing agents were developed as an alternative for remineralization and were compared in preventive fraction (PF) with the gold standard fluoride therapies. One of the promising agents in daily practice as non-fluoridated compounds with calcium bases is that a milk-derived nanocomplex called casein phosphopeptide-amorphous calcium phosphate (CPP-ACP) can stabilize larger amounts of calcium and phosphate in an amorphous state to promote remineralization (Cochrane and Reynolds, 2012; Prestes et al., 2013). Later, diffusion of calcium and phosphate into the demineralized lesions can be facilitated by fluoride at low concentrations when combined with CPP-

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<https://doi.org/10.1016/j.sdentj.2024.01.014>

Received 14 October 2023; Received in revised form 29 January 2024; Accepted 31 January 2024

Available online 6 February 2024

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ACP to remineralize the crystalline structures. Recent research has also demonstrated its capacity to remineralize early caries lesions (Prestes et al., 2013; Higgins et al., 2008; Moher et al., 2009; Green, 2011) as well as its anti-cariogenic properties in laboratory, animal, and in situ human studies (DerSimonian and Laird, 1986; Caldwell et al., 2005; Higgins and Thompson, 2002; Fredrick et al., 2013). However, there is a debate concerning the effectiveness of fluorides and CPP-ACP in preventing caries. The findings from two systematic reviews (Memarpour et al., 2015; Llana et al., 2015) indicated that CPP-ACP alone was not “the best clinical practice” but that CPP-ACP combined with fluorides could produce superior results. Thus, this study aims to conduct a comprehensive systematic review of randomized clinical trial studies to compare the efficiencies of fluorides and CPP-ACP/ CPP-ACP F in remineralizing early enamel lesions.

## 2. Materials and methods

### 2.1. Review question

Is there any difference in efficiency between topically applied CPP-ACP and CPP-ACPF and fluorides in remineralizing early enamel carious lesions?

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement and the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al., 2008), respectively, were followed for the review (Moher et al., 2009). Table 1 lists the inclusion criteria for population, intervention/exposure, comparison, outcome, and study design technique. The protocol was registered prospectively into PROSPERO, the Prospective Register of Systematic Reviews, under the accession number CRD42021237900.

### 2.2. Types of study groups

Studies that included intervention of CPP-ACP or CPP-ACPF versus fluorides as control were included. Any type of fluoride-containing product, such as fluoride-containing toothpaste, mouthwash, varnish, or gel, may be included in the fluorides. The term “CPP-ACP” refers to any form of CPP-ACP-containing products, including MI Paste (minimal intervention paste), Recaldent, or Tooth Mousse/Tooth Mousse Plus.

### 2.3. Outcome measures

Included efficacy outcomes were instrumentally measured either through Quantitative light-induced fluorescence (QLF), DIAGNOdent scores, lesion area in mm, or index scores to assess the degree of early caries regions compared to the surrounding healthy tooth structure.

### 2.4. Search strategy for article identification

An extensive electronic search for in vivo randomized clinical trials via four databases, namely Medline (via PubMed), Web of Science, Scopus, and EBSCO, was performed until March 4, 2023, with English language restriction using the keywords Recaldent, GC Tooth mousse, Fluoride. The collected articles were screened for inclusion at the level of title and abstract and at the full-text level by two authors, SS and RM. Disagreements between the two authors were settled by a third reviewer

**Table 1**  
Inclusion criteria.

Key element	Criteria
Population	Early enamel carious lesion
Intervention	Casein phospho peptide amorphous calcium phosphate
Comparator	Topical Fluorides
Outcome	Regression of demineralization
Study design	Randomized controlled trial

MA. Fig. 1 shows a flowchart of the studies that were chosen.

### 2.5. Data extraction and risk of bias

The data extracted were summarized in Table 2. For all included studies, the Cochrane Collaboration technique was used to determine the risk of bias (Green, 2011). Two review authors independently evaluated the risk of bias, while a third reviewer settled any disputes between them.

### 2.6. Statistical analysis

Comprehensive Meta-Analysis Software version 3.3.070 with standardized mean difference (MD) of 95 % confidence intervals (CI) was used for meta-analysis. For studies comparing the similar results, pairwise meta-analysis (PMA) was used. Because of the anticipated heterogeneity across the included studies, the random effect model was chosen (DerSimonian and Laird, 1986) When conducting multiple-armed RCTs, groups were pooled to provide a single pairwise comparison if practicable; otherwise, the shared group was divided into two groups with reduced samples to produce two sufficiently independent comparisons (Caldwell et al., 2005). I<sup>2</sup> analyses were used to quantify statistical heterogeneity, and a substantial level of heterogeneity was defined as an I<sup>2</sup> value greater than 50 %<sup>13</sup>. p < 0.05 was used to define statistical significance for all analyses.

## 3. Results

Of the 450 articles screened for relevancy, 41 articles were retrieved, reviewed, and critically appraised. Of these, 7 studies met the inclusion criteria, used in the present systematic review (Table 2).

### 3.1. Study outcomes

In five of the seven included studies, the primary outcome measure was the laser fluorescence score (LF) using DIAGNOdent while in remaining two studies, one used enamel fluorescence changes via quantitative laser/light-induced fluorescence (QLF), while the other considered the change in white spot lesion area in mm for the evaluation. Also, one study additionally used a visual change assessment, while another used a change in the ICDAS (International Caries Detection and Assessment System) score.

### 3.2. Study characteristics

All the seven articles reviewed in this paper, were randomized controlled trials with the follow-up varied from 1 month to 12 months, depending on the different outcome measures used to detect caries lesions. In all the included studies, the topical fluoride and CPP-ACP complexes were compared for efficiency, and in all studies, CPP-ACP and CPP-ACPF were used as toothpaste. Topical fluoride was used as either fluoridated mouth rinse (Fredrick et al., 2013; Bobu et al., 2019), toothpaste (Al-Batayneh et al., 2020), fluoride varnish (Memarpour et al., 2015; Llana et al., 2015; Güçlü et al., 2016), or APF fluoride gel forms (Mendes et al., 2018).

### 3.3. CPP ACP versus fluoride toothpaste studies

Out of 7 studies, one compared fluoridated toothpaste with CPP-ACP, which infers that there is not much difference in efficiency between fluoridated toothpaste and CPP-ACPF when used individually or in combined form in terms of decrease in white spot lesion area and enamel fluorescence change (Al-Batayneh et al., 2020).

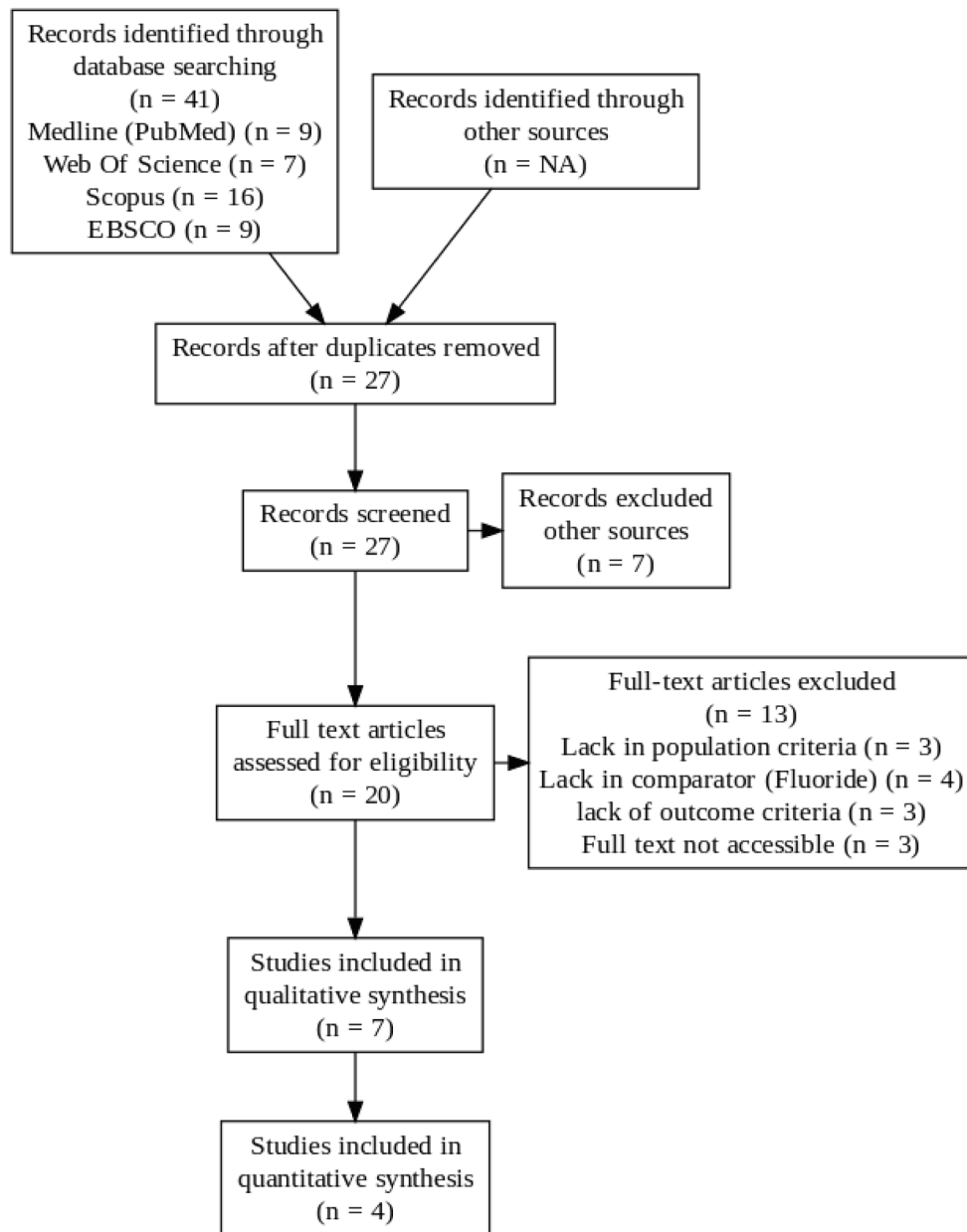


Fig. 1. PRISMA Flow diagram.

### 3.4. CPP ACP versus fluoride varnish studies

In one study (Memarpour et al., 2015), at 12 months of follow-up, the CPP ACP group significantly decreased the mean white spot lesion area by 0.63 mm compared to the F varnish group, which reduced the mean lesion area by 0.51 mm, while the control group without intervention increased the mean lesion area by 1.15 mm in primary dentition. In a study by Llana et al. (2015) which employed fluoride varnish as the comparator, self-applied CPP-ACPF (1.58) showed a higher difference between baseline and 12 weeks than self-applied CPP-ACP and professionally applied fluoride varnish (1.14) in the evaluation of the LF score by DIAGNOdent. Another study by Güçlü et al. (2016) comparing the CPP-ACP, CPP-ACPF paste, and fluoride varnish showed that the CPP-based paste groups had a better prognosis for remineralization of early enamel carious lesions than fluoride varnishes when evaluated using the LF score.

### 3.5. CPP ACP versus fluoride mouth rinse studies

In these studies, the CPP-ACP and CPP ACPF pastes are compared with the 0.5 % NaF fluoride mouth rinse for the difference in LF score between baseline and 1-month follow-up. For CPP ACP, the difference was 2.8, while for CPP ACPF, it was 3.8<sup>14</sup>. For 3 months of follow-up, the difference between mean LF score change at baseline and 12 weeks of follow-up for CPP ACP and CPP ACPF compared with 0.05 % NaF was 1.08 and 3.31, respectively (Bobu et al., 2019).

### 3.6. CPP ACP versus fluoride APF gel as comparator

One study (Mendes et al., 2018) in which 1.23 % APF gel is used as a comparator for CPP-ACP and CPP-ACPF paste, the group that used CPP-ACPF alone showed a statistically significant change with improvement in remineralization of teeth enamel (denoted by decreasing LF score from baseline, 8 days, 30 days, and 90 months) with the highest difference in median LF score value of 14, while for CPP-ACP, 1.23 % APF,

**Table 2**  
Description of studies and its outcome.

S. no	Author	Sample size	Intervention	Control	Assessment measure	Duration (months)	Outcome (Difference from baseline)	Inference
1	Fredrick, C.; et al, 2013	N = 45	Group 1- 10 % CPP-ACPF Group 2- 10 % CPP ACP	Group 3- 0.5 % NaF mouth rinse	DIAGNOdent	1	G1 = 11.33 G2 = 11.00 G3 = 8.13	CPP ACP decreased the mean LF scores by 2.87 and CPP ACPF decreased 3.2 scores from the baseline mean LF scores in permanent dentition.
2	Memarpour, M.; et al, 2015	N = 140	CPP-ACP	Group 1- Control group Group 2- Oral hygiene alone Group 3—5 % NaF varnish	Change in WSL area in mm	12	G1 = +1.15 G2 = -0.10 G3 = -0.51 G4 = -0.63	The CPPACP group significantly decreased the mean white spot lesion area by 0.63 mm compared to the F varnish group, which reduced the mean lesion area by 0.51 mm, while the control group without intervention increased the mean lesion area by 1.15 mm in primary dentition.
3	Llena, C; et al, 2015	N = 786 wsl	Group A-Self applied CPP-ACPF Group B-Selfapplied CPP ACPF	Group C- Professionally applied 5 % NaF varnish.	DIAGNOdent	3	G A = 8.06 G B = 7.35 G C = 8.09 G D = 4.85	F varnish reduced the mean LF scores by 0.03 times more efficiently than CPP-ACP and 0.74 times more efficiently than CPP ACPF in permanent dentition. Thus, the efficiency of reversing the LF scores was seen as F varnish > CPPACP > CPPACPF > Toothpaste.
4	Güçlü, Z.A.; et al, 2016	N = 101 wsl	Group CPP-ACP	Group Fluoride varnish (5 % NaF). Group CPPACP + Fluoride Varnish. Group Control (No intervention)	DIAGNOdent	3	FV = 10.68 CPP-ACP = 13.56 CPP-ACP-FV = 12.57 Control = 10.48	CPP ACP had significantly decreased the mean LF score values by 2.88 more than the F varnish group in permanent dentition.
5	Mendes, A.C. B.; et al, 2018	N = 80	Group 3- CPP-ACP Group 4- CPP-ACPF	Group 1- Placebo control Group 2—1.23 % APF	DIAGNOdent (median)	3	G1 = 4 G2 = 5 G3 = 3 G4 = 14	APF reduced the median LF scores two time more than the CPP ACP group; however, CPP ACPF reduced the median LF scores nine times more than the APF gel from baseline.
6	Bobu, L.; et al, 2019	N = 80	Group1 – 10 % CPP-ACP Group2- 10 % CPP-ACPF,	Group3- 0.05 % NaF mouth rinse Group4 –control	DIAGNOdent	3	G1 = 7.52 G2 = 9.75 G3 = 6.44 G4 = 1.93	The efficiency of decreasing the mean LF scores was seen in the order CPPACPF > CPP ACP > APF in permanent dentition.
					Percentage of Teeth with shift from higher to lower ICDAS score.		G1 = 5.1 % G2 = 6.2 % G3 = 4.8 % G4 = 4.5 %	CPP ACP had mean 1.08 values more efficient than F varnish, while CPP ACPF had mean 3.31 values more efficient than F varnish in permanent dentition. The CPP ACP group had a 0.3 % better effect than the F mouth rinse, while the CPP ACPF group had a 1.4 % better effect than the F mouth rinse.
7	Al-Batayneh, O.B.; et al, 2020	N = 114	Group1- 10 % CPP ACP	Group2- 500 ppm F toothpaste Group3- F toothpaste and CPP ACP	Quantitative light-induced fluorescence score	6	G1 = 3.71 G2 = 4.57 G3 = 2.74	The F toothpaste group had a mean enamel fluorescence change 0.86 times greater than the CPP ACP group in primary dentition.

\*wsl – White spot lesion.

and placebo control were 4, 5, and 3, respectively. Also, it was shown that in the 1.23 % APF gel group, however, there is an improvement in remineralization of the carious lesion from baseline to 8 days, and after 30 days, there is a notable demineralization of more than 50 % at 90 days.

### 3.7. Risk of bias

The risk of bias was assessed in seven domains at three levels of applied scale, low, high, and unclear. All the studies were found to have a low risk of selection bias in terms of randomization. While other types of bias, including selection bias in terms of allocation concealment, performance bias, and detection bias in blinding, attrition bias were found to range from low risk to high risk, Calibration bias was found to

be low among most of the included studies. The biases were plotted and summarized graphically using Revman 5.0 in Fig. 2.

### 3.8. Quantitative synthesis

The efficiency of CPP-ACP was compared to fluorides in four studies, with two using mouth rinse and two using varnish. A pairwise meta-analysis was conducted with four studies, with no further comparisons possible due to the different outcome measures. As the heterogeneity is within the limit, a fixed effects model was used for quantitative evidence synthesis for comparison between CPP-ACP and fluoride as mouth rinse, while for comparing fluoride in the form of varnish, as there is heterogeneity beyond the acceptable limits (92.29 %), a random effect model was utilized for meta-analysis. When used as a mouth rinse, CPP-ACP

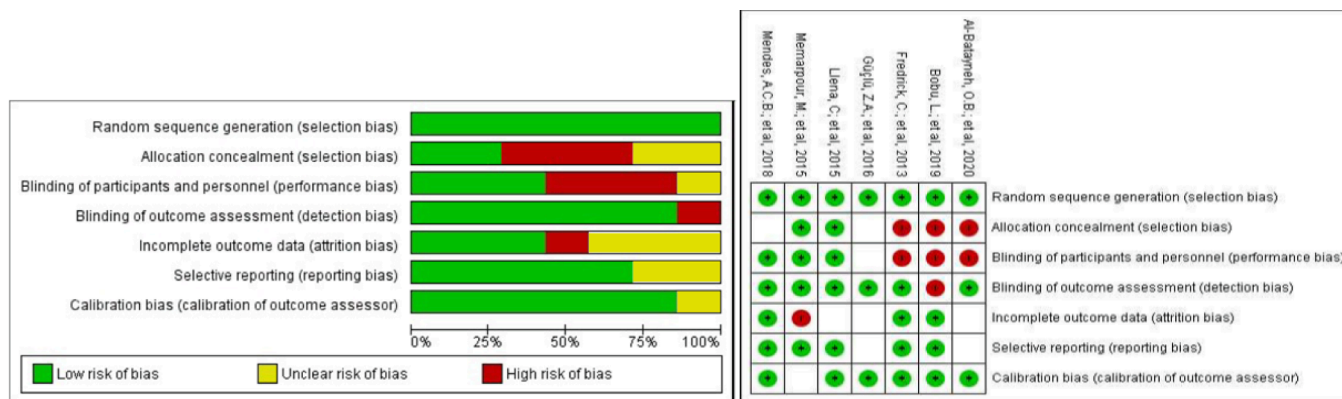


Fig. 2. Risk of Bias graph and summary.

significantly outperformed fluorides in terms of effectiveness in quantitative results [SDM = 0.822; 95 % CI (0.333 to 1.310); p = 0.001; I<sup>2</sup> = 0.00 %]. (Fig. 3). However, when used as a varnish, there was no statistically significant difference between the two treatments [SDM = 0.632; 95 % CI (-0.647 to 1.911); p = 0.333; I<sup>2</sup> = 86 %] (Fig. 4).

#### 4. Discussion

There has been a remineralizing promise of teeth enamel from literature evidence for both fluorides and casein phosphopeptide amorphous calcium phosphate. The topical fluorides work by modifying the morphology of enamel crystal structure to make it more resistant to cariogenic acid, but it was associated with fluoride toxicity in 68 % of tooth paste users, 17 % of mouth rinse users and 15 % by other fluoride supplements as while amorphous calcium phosphate can be delivered using casein phosphopeptide, which can further facilitate the ACP's bonding with dental enamel. Since casein phosphopeptide can be incorporated into the pellicle (Schübach et al., 1996), it can also reduce the number of Streptococcus mutans. According to reports, CPP-ACP has the potential to effectively stimulate enamel remineralization at concentrations of 3 % w/w and 2800 ppm F, respectively (Cai et al., 2003; Reynolds et al., 2008). This review was conducted to highlight the strength of the evidence on remineralizing efficiency towards early enamel carious lesions between CPP ACP based products and topical fluorides.

Apart from clinical examination and radiography are standard techniques fluorescence-based tools like QLF and DIAGNOdent have been developed for early detection of enamel caries. QLF measures enamel fluorescence changes and provides F scores, while DIAGNOdent measures laser fluorescence intensity and provides laser fluorescence scores. DIAGNOdent is a sensitive tool that can detect lesions at the dentine level but sometimes produces false positive results (Bader and Shugars, 2004; Pretty and Ellwood, 2013). A range of caries lesions, such

as secondary caries, smooth surface caries, and demineralization next to orthodontic brackets, can be found with QLF. Results from QLF should be compared to those from DIAGNOdent and other methods of detection. In our review, out of 7 studies included, two studies considered only LF scores by DIAGNOdent, three studies considered LF scores and visual assessment change, one study (Poza-Pascual, 2021) considered enamel fluorescence change by QLF, and one study considered change in the white spot lesion area in mm. However, the assessment of the dmft index by one study was not included in the review as it can only reflect the progression from decay to filling or missing but not the remineralization of carious lesions.

Mouth rinse is effective but has a risk of ingestion, while CPP-ACP-based cream is safe for regular use with no adverse effects. Additionally, CPP-ACP-based products have better remineralization efficiency compared to fluoride mouth rinses. This was supported by the results of previous trials, which found better-remineralizing potential in white spot lesions with CPP-ACP when compared with a fluoride mouth rinse in debonded teeth after post-orthodontic treatment (Andersson et al., 2007). It is interesting to note that one of the previous studies showed that dental erosion, which is again due to acid attack but not from cariogenic bacteria, was reduced more effectively with the use of fluoride-based mouth rinse than the CPP ACP (Bejoy et al., 2020).

Varnishes are a simpler anti-caries technique than gels, requiring less handling time and a lower risk of ingestion by young children. They also adhere to the tooth surface for longer periods and require less patient cooperation, making them effective in preventing caries in people with specific care needs (Poza-Pascual, 2021). This review found that CPP-ACP-based creams have greater remineralizing potential than 5 % sodium fluoride varnish, based on evidence of in vitro studies testing the remineralization capacity of artificial enamel caries-like lesions in permanent teeth (Ramadevi et al., 2020; Shen et al., 2020). However, CPP-ACPF varnish did not possess better remineralization potential than Duraphat varnish (Mohd Said et al., 2017; Üstün and Aktören, 2019). In

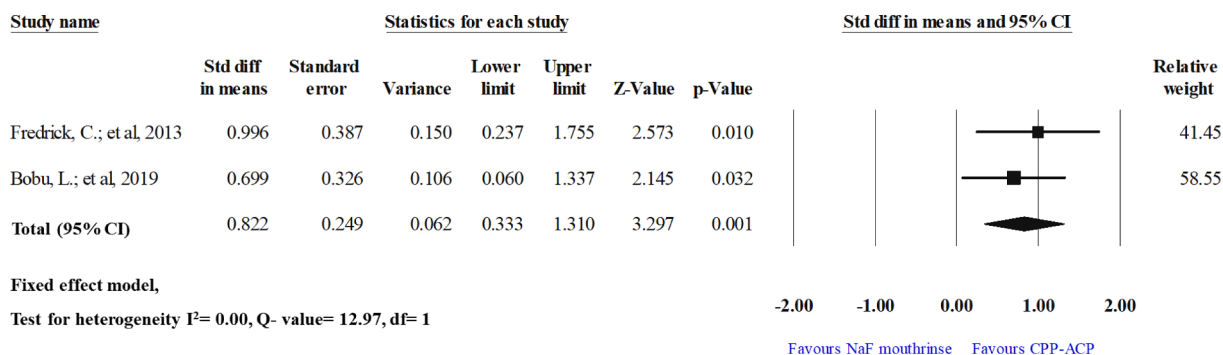


Fig. 3. Forest plot for the standardized mean difference between CPP-ACP and fluoride mouth rinse.

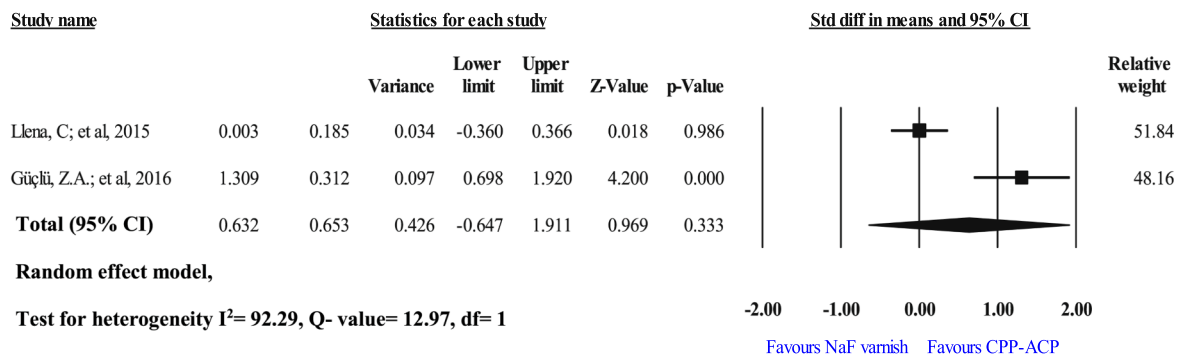


Fig. 4. Forest plot for the standardized mean difference between CPP-ACP and fluoride varnish.

Random effect model,

Test for heterogeneity  $I^2= 92.29$ ,  $Q$ -value= 12.97,  $df= 1$

a clinical investigation conducted by Obradovi et al., CPP ACPF varnish demonstrated superior remineralization versus standard varnish for early smooth surface caries lesions of primary teeth (Obradović et al., 2016). CPP-ACP varnish appears to be equally effective as other fluoride varnishes in remineralizing artificially generated white spot lesions, although the quality of the evidence is low, according to a meta-analysis study (Nadar et al., 2022). Thus, CPP-ACP varnishes can be used with clinical significance, but a clinical trial with a larger sample size without any risk of bias can yield a better conclusive trial result.

Like CPP ACP, CPP ACPF has also been found to have better potential in caries prevention than when CPP ACP is used as a monotherapy agent, according to the results of this review. This was also in line with the report of a previous study highlighting the synergistic activity of CPP ACP and fluoride to combat dental caries (Attiguppe et al., 2019; Srinivasan et al., 2010).

One study (Mendes et al., 2018) included in this review, which compares the CPP ACP cream with the APF gel, shows that CPP ACPF has an increased tendency to cause remineralization of teeth enamel over a while, even at a three-month follow-up. Though APF gel caused a reduction in demineralization, which was reflected in a decreasing LF score over a period, there was a significant demineralization after one month. This might be because the plaque buildup inhibition by CPP ACP is superior to that of APF gel (Kaswindiarti et al., 2020).

Another study (Al-Batayneh et al., 2020) comparing the CPP ACP with fluoridated toothpaste showed no significant difference in remineralization potential between them. It has been reported that 500 ppm fluoridated toothpaste produced a better remineralization effect. This is in contraindication of the pooled effect estimate of this current review.

The review’s limitation was the pooling of only two studies to determine the remineralization potential of CPP ACPF with fluoride mouth rinse and fluoride varnish. One meta-analysis used a fixed effect model, and the other used a random effect model to minimize heterogeneity. However, there may still be uncertainties in the results.

Future recommendations are to conduct a good-quality interventional trial with varying forms of fluorides and CPP ACP-based creams in various type of dentition, caries risk, with difference in concentrations of intervention agents, delivery vehicles, and longer follow-up with aim to produce an odds ratio to discover the probability of caries development with different anti-cariogenic effects.

## 5. Conclusion

Within the limitations of this current review, it can be concluded that casein phosphopeptide amorphous calcium phosphate-based fluoride products are effective preventive measures for young patients when compared with plain CPP ACP and other topical fluorides. However, there is a need for longer follow-ups to justify these supplemental agents.

**Protocol registration:** The study protocol can be accessed through the International Prospective Register of Systematic Reviews, the PROSPERO database with the following register number:

CRD42021237900.

**Patient and public involvement:** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication:** Not applicable.

**Data availability statement:** Data are available on reasonable request.

## CRedit authorship contribution statement

**P. Rahmath Meeral:** Conceptualization, Methodology, Software, Data curation, Writing – original draft. **Srisakthi Doraikannan:** Visualization, Investigation, Supervision, Writing – review & editing. **Meignana Arumugham Indiran:** Validation.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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