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Review
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Effectiveness of non-fluoride agents in combination with fluorides for dental caries prevention: A systematic review and meta-analysis

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Highlights

- Combining fluoride with agents like chlorhexidine, CPP-ACP, povidone iodine, or herbal products may improve remineralization and antimicrobial effects in prevention.
- Meta-analysis showed fluoride combined with non-fluoride agents, especially CPP-ACP, reduced caries activity and lesion area more effectively short term than fluoride alone.
- Non-fluoride remineralizing agents may support fluoride-based caries management, but long-term multicenter randomized trials are needed to confirm lasting benefits.

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Abstract

Although fluoride has been known as anti-caries agents for many years, its usage is associated with some side-effects. Owing to antimicrobial and remineralization-enhancing properties, non-fluoride agents such as chlorhexidine, povidone iodine, casein phosphopeptide-amorphous calcium phosphate (CPP-ACP), and various herbal products have gained attention as remineralization strategies for the prevention and management of dental caries. The present study aimed to evaluate the effectiveness of combined therapy using topical fluoride (TF) with these non-fluoride agents over TF monotherapy for the prevention of dental caries. Following PRISMA guidelines, a literature search was conducted across PubMed, ScienceDirect, SpringerLink, Wiley Online Library and Google Scholar for studies published between 2005 and 2025. Articles that evaluated the use of non-fluoride agents (chlorhexidine, CPP-ACP, povidone iodine, herbal products) in combination with fluoride-containing products were included. Totally, 21 articles were included in the review and 17 articles were included in the meta-analysis. Most of the reviewed studies used CPP-ACP as non-fluoride remineralizing agents, while only few used povidone iodine and chlorhexidine. Findings revealed that fluoride, when used in combination with non-fluoride agents, was significantly more effective than fluoride monotherapy in reducing caries activity in less than two months and at three months in both primary and permanent teeth. Additionally, this combination therapy resulted in a significant reduction in lesion area after three months of treatment. However, no statistically significant difference was observed between fluoride combination therapy and fluoride monotherapy with respect to caries increment in either the short-term or long-term follow-up. Fluoride, when combined with non-fluoride agents, particularly CPP-ACP, showed better remineralization potential compared with fluoride alone, particularly in the short-term basis. These findings support the adjunctive use of such combinations in caries management; however, further long-term, multicenter RCTs are warranted to confirm their clinical durability and sustained effectiveness.

Keywords: Chlorhexidine, CPP-ACP; Dental Caries; Fluoride; Povidone Iodine

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INTRODUCTION

Human teeth are primarily composed of hydroxyapatite.[1] In its biological form, hydroxyapatite contains carbonate (CO_3^{2-}) and hydrogen phosphate (HPO_4^{2-}) ions, which increase its solubility[2–4] and make it more susceptible to demineralization, especially when exposed to sugary and acidic foods.[5] Dental caries develop when sugars are metabolized by acidogenic bacteria into organic acids, leading to demineralization of enamel.[6] Although remineralization can occur naturally via saliva, caries progress when demineralization exceeds remineralization over time.[7] Early-stage caries appear as non-cavitated white spot lesions (WSLs), which can worsen into cavitated lesions, if left untreated.[8] Dental decay is a global public health concern and the most common chronic disease affecting people of all ages.[9–11] Hence, early diagnosis and proper treatment are essential for effective management of this global oral health problem.[8]

Fluoride has been reported as an anti-caries agent over two centuries, particularly in developed countries.[12,13] It can replace hydroxide ions of tooth enamel to form fluorapatite, which is more resistant to acid dissolution.[14] Today, fluoride is a common ingredient in toothpastes, mouthwashes, and dental varnishes, administered both topically and systemically.[15] Fluoride's primary action is topical, enhancing remineralization and reducing enamel demineralization.[16] While topical use is safe, excessive ingestion, especially in children under six who often lack adequate swallowing control, can lead to fluorosis or gastrointestinal issues.[17–19] Moreover, emerging fluoride resistance in cariogenic bacteria[20,21] has prompted researchers in exploring combination therapies for improved prevention.

In this context, non-fluoride agents, such as chlorhexidine, povidone iodine (PI), casein phosphopeptide-amorphous calcium phosphate (CPP-ACP), and various herbal products, have gained attention for their antimicrobial and remineralization-enhancing properties. Studies have shown that a varnish containing chlorhexidine and fluoride arrested root caries among older adults.[22] Similarly, a varnish combining PI and sodium fluoride (NaF) proved more effective than NaF alone in preventing dental caries in children.[23] One derivative of milk protein, termed as CPP-ACP, is recognized for its ability to enhance remineralization and is increasingly used in non-invasive treatments for early enamel lesions.[24] Herbal formulations are also being incorporated into oral care due to their natural antimicrobial potential.[25] The rationale for combining topical fluorides with these non-fluoride agents lies in their potential synergistic effects, i.e., enhancing caries prevention while possibly reducing the risks associated with fluoride overuse.

While several systematic reviews and meta-analyses have examined the efficacy of combination therapies, many have focused exclusively on pediatric populations and have yielded mixed and inconclusive results. For example, two systematic reviews[26,27] concluded that combined therapies were effective, but the findings were limited to children. In contrast, one study[28] reported that fluoride alone outperformed a combination of fluoride and CPP-ACP in managing white spot lesions (WSLs), while another study[29] found no significant difference between monotherapy and combination therapy for early smooth-surface caries. Moreover, previous meta-analyses have typically assessed only one type of non-fluoride agent, lacking a broader comparative approach. Therefore, a comprehensive systematic review and meta-analysis are warranted to evaluate the overall effectiveness of various combination therapies across diverse populations and clinical outcomes.

The present study aimed to systematically review and identify studies that compared the effectiveness of combined therapy using topical fluoride with non-fluoride agents (such as povidone-iodine, chlorhexidine, CPP-ACP, or herbal products) versus topical fluoride monotherapy in the prevention of dental caries. The extracted data were subsequently subjected to meta-analysis to assess whether combination therapy demonstrates superior clinical outcomes in terms of dental caries incidence, salivary bacterial counts, lesion area, and remineralization potential across various follow-up durations. By consolidating the available data, this review will provide a comprehensive evaluation of the comparative effectiveness of fluoride monotherapy and combination regimens in the prevention and management of caries.

METHODS

The guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[30] were adhered to in this systematic review and meta-analysis. The PRISMA checklist for the present work is available in Supplementary Table 1.

PICO Framework

The Population, Intervention, Comparison/Control, and Outcome (PICO) framework was used to formulate the following research question:

"Does the combination of non-fluoride agents with fluoride enhance the effectiveness of dental caries prevention compared with fluoride monotherapy alone?"

For this study, the population comprised patients (both children and adults) diagnosed with dental caries or identified as being at higher risk of caries. The intervention of interest was the combined therapy involving fluoride agents used in conjunction with non-fluoride agents (chlorhexidine, CPP-ACP, povidone iodine, herbal products). The comparator was fluoride monotherapy. The outcomes assessed included increment of dental caries, remineralization potential measured using fluorescence-based method values (QLF and LF), lesion area, and bacterial count.

Selection Criteria

The inclusion criteria for the study were as follows: (1) Studies involving patients (both adult and children) diagnosed with dental caries or identified as being at higher risk of caries; (2) Studies that evaluated the use of non-fluoride agents (chlorhexidine, CPP-ACP, povidone iodine, herbal products) in combination with fluoride-containing products or herbal products compared with fluoride; (3) Studies focusing on the prevention or management of dental caries, including remineralization and/or demineralization processes along with the caries continuum and antibacterial effects; (4) Studies that included randomized controlled trials (RCTs), observational studies, and clinical trials conducted on human teeth and; (5) Studies published in peer-reviewed journals between 2005 and 2025.

The exclusion criteria included: (1) Systematic reviews, case reports, conference abstracts, posters, and book chapters; (2) Studies that focused on nanoparticles, herbal extracts, or other natural products (e.g., probiotics), or studies that used non-fluoride agents without combination with fluoride; (3) Studies that investigated non-fluoride products other than chlorhexidine, CPP-ACP, povidone iodine, or herbal products; (4) Studies that included oral health education interventions as a strategy for managing dental caries; and (5) Studies that addressed oral conditions (such as dental erosion, gingivitis, or dental plaque) without a direct association with caries prevention.

Search Strategy

Five electronic databases, namely, PubMed, ScienceDirect, Wiley Online Library, Springer, and Google Scholar, were used to screen articles. Besides electronic databases, an extensive manual search was done within the references lists of selected studies and review articles to find eligible records. The following keywords identified from prior research were used to search the databases for relevant articles: "fluorides", "fluoride treatment", "chlorhexidine", "chlorhexidine varnish", "povidone-iodine", "casein phosphopeptide amorphous calcium phosphate", "CPP-ACP", "caseins", "herbal mouthwash", "herbal mouthrinse", "dental caries", "tooth decay", "dental plaque", "Lactobacillus", and "Streptococcus". Logical combinations of appropriate keywords and Medical Subject Headings (MeSH) terms were applied using Boolean operators for conducting the search. Supplementary Table S1 provides comprehensive details on electronic databases, search terms, filters, and number of results retrieved.

Study Selection and Data Screening Process

The study selection involved a systematic search across multiple databases, including PubMed, Wiley Online Library, ScienceDirect, SpringerLink, and Google Scholar, using pre-specified search terms. Initially, titles and abstracts of the retrieved articles were screened to exclude irrelevant studies that did not address the research question. Duplicate entries and redundant publications were also removed during this stage. Full-text versions of the shortlisted articles were then obtained and evaluated against a set of predefined inclusion and exclusion criteria. To facilitate structured organization and subsequent analysis, all references from the selected studies were systematically documented in an Excel spreadsheet.

Two researchers independently searched and screened the articles, and any discrepancies that arose were resolved through consultation with a third researcher.

Data Extraction

Relevant data were extracted from each included study independently by two researchers, covering various aspects such as study details (first author's name, year of publication, and the country), patients' characteristics (total number of participants, age of sample population, type of teeth affected), compounds used in experimental and control groups, follow-up period and outcomes measurements (DIAGNOdent scores, QLF indices, mean values of lesion area and indices of caries, such as ICDAS, EDI, DMFT/S). Disagreements, if any, were settled by a third researcher. Following this extraction process, the data were subjected to a quantitative analysis.

Outcome Measurement

For the comparative evaluation of caries-preventive effectiveness between fluoride monotherapy and combination therapy, outcome measures were categorized into primary and secondary. The primary outcomes focused on remineralization potential, which was evaluated using changes in mean DIAGNOdent scores and quantitative light-induced fluorescence (QLF) radiance values. These outcomes were assessed at short-term follow-up periods of less than two months and at three months post-intervention. Secondary outcomes examined caries progression in terms of reduction in lesion area and caries increment after treatment. Lesion area reduction was recorded at three months while the mean increment in dental caries was recorded at longer follow-up intervals of 6, 12, and 24 months. Studies investigating the use of herbal mouthrinses in combination with fluoride were not identified in the available literature and were therefore not included in the analysis.

Risk of Bias Assessment

The risk of bias in the included randomized studies was assessed using the revised Cochrane Risk-of-Bias tool (RoB 2).[31] This tool evaluates five key domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective outcome reporting. Studies were classified as having a *low risk of bias* when more than half of the assessed domains were judged to be at low risk, whereas a *high risk of bias* was assigned when at least two domains were rated as high risk. The assessment was independently conducted by two reviewers, and any disagreements were resolved through consultation with a third investigator.

Statistical Analysis

The meta-analysis was performed using RevMan software (v5.4, The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark). Standardized mean differences (SMDs) were calculated for individual and pooled statistics. The corresponding 95% confidence intervals (CIs) were estimated using the restricted maximum-likelihood estimator. Meta-analysis was conducted utilizing the fixed-effect and random-effect models as and where required. Heterogeneity was quantified using I^2 statistic, which was classified as (i) I^2 = 0%–25% referring to no heterogeneity (ii) I^2 = 25%–50% as moderate heterogeneity, (iii) I^2 = 50%–75% as high heterogeneity, and (iv) I^2 = 75%–100% extreme heterogeneity. Statistical significance was determined by a probability value of < 0.05. Forest plots were applied to display the measured effect sizes with their 95% CIs for all studies included. Publication bias was assessed through funnel plots.

RESULTS

Literature Screening

Following PRISMA guidelines, the study selection, evaluation and synthesis process was meticulously documented. Figure 1 illustrates the flowchart of the review process. A total of 495 articles were retrieved, with contributions from PubMed (206 articles), ScienceDirect (211), SpringerLink (29 articles), Wiley Online Library (46), and Google Scholar (3). After removing three duplicate records, 439 articles were excluded after the screening of title and abstract due to irrelevance. Fifty-three studies underwent manual screening and 32 full-text articles that did not satisfy all eligibility criteria were removed. Finally, 21 studies were included in the qualitative analysis and 17 articles were considered for meta-analysis. However, studies investigating the usage of herbal mouthrinses in combination with fluoride were not identified in the available literature using the specified search terms. Therefore, only studies evaluating CPP-ACP, chlorhexidine, or povidone iodine in combination with fluoride were included in the analysis.

Risk of Bias Assessment

The risk of bias of the included studies was assessed using the Cochrane Risk of Bias 2 tool and the results are summarized in Table 1. With respect to the randomization process, several studies were judged to be at low risk of bias; however, a number of trials showed some concerns or a high risk due to inadequate reporting or lack of allocation concealment. Bias arising from deviations from the intended interventions was generally assessed as low across most studies. In contrast, bias arising from missing outcome data was frequently rated as high risk, as many trials reported incomplete follow-up or did not clearly explain whether missing data were related to the true outcome. The domain assessing outcome measurement was largely judged to be at low risk, reflecting the use

of standardized and validated assessment methods, although a few studies raised some concerns. Bias in the selection of the reported results was predominantly assessed as low risk. Overall, only a limited number of studies were classified as having a low risk of bias, while the majority were rated as high risk, primarily driven by concerns related to missing outcome data and, in some cases, deficiencies in the randomization process.

The risk of bias of the included studies was assessed using the Cochrane Risk of Bias 2 (ROB 2) tool and is presented in Table 1. With respect to the randomization process, several studies were judged as low risk; however, a number of trials showed some concerns or high risk due to inadequate reporting or lack of allocation concealment.

Bias due to deviations from intended interventions was generally low across most studies. In contrast, bias arising from missing outcome data was frequently rated as high risk, as many trials reported incomplete follow-up or did not clearly explain whether missingness was related to the true outcome. The domain assessing measurement of the outcome was largely judged as low risk, reflecting the use of standardized and validated assessment methods, although a few studies showed some concerns. Bias in the selection of the reported result was predominantly low risk. Overall, only a limited number of studies were judged as low risk of bias, while the majority were rated as high risk, primarily driven by concerns related to missing outcome data and, in some cases, the randomization process.

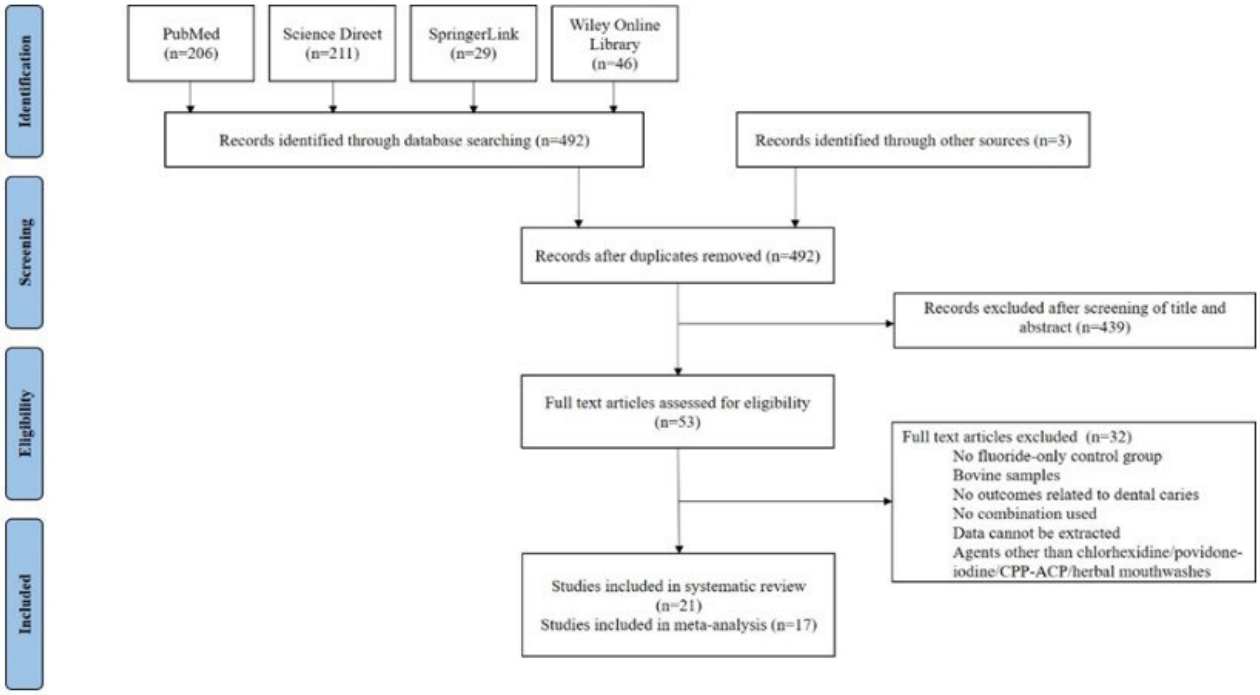

Figure 1. PRISMA 2020 flow diagram illustrating the study selection process in the systematic review and meta-analysis

Table 1. Risk of bias assessment

Study ID	Randomization process	Deviation from the intended intervention	Missing outcome data	Measure of the outcome	Selection of the reported result	Overall bias
Bobu (2019)	!	+	+	+	+	!
Yazicioğlu (2017)	!	+	+	+	+	!
Singh (2016)	+	+	-	+	+	-
Mendes (2018)	+	+	-	+	+	-
Lena (2015)	+	+	+	+	+	+
Esparza-Villalpand (2021)	+	+	-	+	+	-
Mekky (2021)	+	+	+	+	+	+
Güçlü (2016)	+	+	!	+	+	!
Al Batayneh (2019)	+	+	-	+	+	-
Beerens (2018)	+	+	-	+	+	-
Park (2022)	-	+	+	+	+	-
Bröchner (2011)	+	+	-	+	+	-
Beerens (2010)	+	+	-	+	+	-
Zhan (2006)	-	+	!	+	+	-
Pukallus (2013)	+	+	-	+	+	-
Sundell (2013)	-	+	-	+	+	-
Sitthisettapong (2012)	+	+	-	+	+	-
Milogram (2021)	+	+	-	+	+	-
	+	Low risk	!	Some concerns	-	High risk

Study Characteristics

The main characteristics of the studies included in this review are presented in Table 2. A total of 21 studies published between 2005 and 2022 were included in this review. The population age ranged from 2 to 79 years. Studies were performed across diverse geographical regions including Romania,[32] Turkey,[33,34] India,[35,36] Brazil,[37] Spain,[38] Mexico,[39] Egypt,[40] Jordan,[41,42] The Netherlands,[43,44] Denmark,[45] Germany,[22] USA,[46] Australia,[47] Sweden,[48] Thailand,[49] Micronesia,[23] and Saudi Arabia.[50] Most studies (n = 11) were conducted on primary dentition particularly in younger populations, although several (n = 7) focused on permanent teeth.

All patients had caries lesions that were treated with either fluoride monotherapy (control group) or combination therapy (combined with non-fluoride agents) (experimental group). In most studies (n = 14), CPP-ACP either alone or in

combination with fluoride (CPP-ACFP) were used as remineralizing agents, in concentrations ranging from 0.2% to 10%. Apart from CPP-ACP, four studies used 10% povidone iodine,[23,35,46,50] whereas three studies used chlorhexidine[22,47,48] as non-fluoride agents to manage caries lesions. Studies using herbal mouthrinses in combination with fluoride were not identified in the available literature and were therefore not included in the analysis. All participants in the experimental group were administered with these non-fluoride agents alongside fluoridated dentifrices (similar to the control group). Participants in the control group underwent conventional fluoride-based regimens, including sodium fluoride (NaF) mouthrinse, varnish, dentifrice, or acidulated phosphate fluoride (APF) gel, while a few of them were given placebo or fluoride-free control pastes. Outcomes were predominantly assessed in terms of caries activity, lesion progression or regression, bacterial counts, and lesion area, with follow-up durations varying considerably from 10 days[39] to as long as 24 months.[23,47,48]

Synthesis of Results

Primary Outcome: Remineralization Potential

A total of 185 patients in the experimental group and 216 patients in the control group from four included studies were compared for reductions in caries activity based on DIAGNOdent (laser fluorescence) scores. The pooled analysis across all studies showed a significant overall benefit of fluoride and non-fluoride combined therapy compared with fluoride monotherapy at follow-up periods of less than two months (SMD = −0.60; 95% CI: −0.93 to −0.28; p = 0.0003), with moderate heterogeneity (I^2 = 55%, p = 0.05) (Figure 2). Subgroup analysis demonstrated that in primary teeth, the combination of fluoride and non-fluoride interventions resulted in a significant reduction in caries activity compared with fluoride controls (SMD = −0.84; 95% CI: −1.44 to −0.25; p = 0.005; I^2 = 71%, p = 0.06). In permanent teeth, the effect of combination intervention was also significant but of smaller magnitude (SMD = −0.44; 95% CI: −0.80 to −0.09; p = 0.01, I^2 = 31%, p = 0.22).

Figure 3 depicts that all studies were distributed symmetrically around the pooled SMD, indicating no publication bias. Subgroup analysis demonstrated no significant difference in caries activity between "non-F+F" and "F" groups when CPP-ACP was used as a non-fluoride agent (SMD = 0.24; 95% CI: −0.30 to 0.78; p > 0.05). Heterogeneity was not significant among the pooled studies (I^2 = 59%; p = 0.12). Similarly, the pooled analysis showed no significant effect between the two groups when CPP-ACFP was used (SMD = −0.46; 95% CI: −1.04 to 0.11; p = 0.12; I^2 = 43%, p > 0.05) (Figure 4). Overall, the pooled analysis across all studies showed no significant benefits in experimental group in less than two months of treatment (SMD = −0.12; 95% CI: −0.60 to 0.36; p > 0.05; I^2 = 69%, p = 0.01).

Figure 5 depicts that all studies were distributed symmetrically around the pooled SMD, indicating no publication bias. After three months of treatment, a significant reduction in DIAGNOdent scores was observed when fluoride was used in combination with CPP-ACP or CPP-ACFP (SMD = −0.28; 95% CI: −0.52 to −0.04; p < 0.05), with no heterogeneity (I^2 = 2%, p = 0.39) (Figure 6). Subgroup analysis revealed that patients who used CPP-ACFP as non-fluoride agent along with fluoride had significantly lowered DIAGNOdent scores compared to fluoride controls (SMD = −0.41; 95% CI: −0.75 to −0.08; p = 0.02), with no heterogeneity (I^2 = 0%, p = 0.38). However, no significant difference was found between the two groups when CPP-ACP was used in "non-F+F" group (SMD = −0.14; 95% CI: −0495 to 0.21; p > 0.05; I^2 = 0%, p = 0.33).

Table 2. Characteristics of included studies

First Author (Year)	Country	Sample Size	Age of Participants	Affected Teeth	Experimental Group	Control Group	Outcomes Measurement	Follow-up period
Bobu (2019)	Romania	86	21 to 26 yrs	permanent teeth	(10% CPP-ACP + 0.2% NaF) + fluoride dentifrice (1450 ppm F)	(0.05% NaF mouthrinse) + fluoride dentifrice (1450 ppm F)	caries activity	1, 2 and 3 months
Yazicioğlu (2017)	Turkey	109	18 to 30 yrs	permanent teeth (smooth surfaces)	(10% CPP-ACP + 900 ppm F) + fluoride dentifrice (1450 ppm F)	fluoride dentifrice (1450 ppm F)	caries activity	1 month
		176		permanent teeth (occlusal surfaces)	(10% CPP-ACP+ 900 ppm F) + fluoride dentifrice (1450 ppm F)	fluoride dentifrice (1450 ppm F)	caries activity	
Singh (2016)	India	28	16 to 25 yrs	permanent teeth	(10% CPP-ACP + 900 ppm F) + fluoride dentifrice (1000 ppm F)	fluoride dentifrice (1000 ppm F)	caries activity	1, 3 and 6 months
		27		permanent teeth	(10% CPP-ACP + 900 ppm F) + fluoride dentifrice (1000 ppm F)	fluoride varnish (5% NaF) + fluoride dentifrice (1000 ppm F)	caries activity	
Mendes (2018)	Brazil	18	5 to 13 yrs	permanent teeth	10% CPP-ACP + 900 ppm NaF	fluoride dentifrice (1450 ppm F)	caries activity	1 and 3 months
		18		permanent teeth	10% CPP-ACP + 900 ppm NaF	1.23% APF gel	caries activity	

Table 2. Characteristics of included studies (continued)

First Author (Year)	Country	Sample Size	Age of Participants	Affected Teeth	Experimental Group	Control Group	Outcomes Measurement	Follow-up period
Lena (2015)	Spain	111	6 to 14 yrs	permanent teeth	(10% CPP-ACP + 900 ppm NaF) + fluoride dentifrice (1100 ppm F)	5% NaF + fluoride dentifrice (1100 ppm F)	caries activity	1, 2 and 3 months
		119		permanent teeth	(10% CPP-ACP) + fluoride dentifrice (1100 ppm F)	5% NaF + fluoride dentifrice (1100 ppm F)	caries activity	
Esparza-Villalpand (2021)	Mexico	84	3 to 7 yrs	primary teeth	(10% CPP-ACP + 900 ppm NaF) + fluoride dentifrice (1450 ppm F)	fluoride dentifrice (1450 ppm F)	caries activity	10, 21 days
Mekky (2021)	Egypt	44	3 to 5 yrs	primary teeth	2% CPP-ACP + 5% NaF	5% NaF	caries activity	1.5, 4.5, 7.5 months
Güçlü (2016)	Turkey	11	8 to 15 yrs	permanent teeth	10% CPP-ACP + fluoride dentifrice (1450 ppm F) + 5% NaF	fluoride dentifrice (1450 ppm F) + 5% NaF	caries activity	3 months
Al-Batayneh (2019)	Jordan	79	4 to 5 yrs	primary teeth	10% CPP–ACP + fluoride dentifrice (500 ppm F)	fluoride dentifrice (500 ppm F)	changes in caries lesions, lesion area	3 and 6 months
Al-Batayneh (2017)	Jordan	54	extracted teeth	primary teeth	10% CPP–ACP + fluoride dentifrice (500 ppm F)	fluoride dentifrice (500 ppm F)	changes in caries lesions	10 weeks

Table 2. Characteristics of included studies (continued)

First Author (Year)	Country	Sample Size	Age of Participants	Affected Teeth	Experimental Group	Control Group	Outcomes Measurement	Follow-up period
Beerens (2018)	The Netherlands	51	12 to 19 yrs	not specified	(0.2% CPP-ACP + 900 ppm NaF) once a day + fluoride dentifrice	Ultradent (fluoride-free control paste once a day + calcium) + fluoride dentifrice	changes in caries lesions, bacterial count, lesion area	6 weeks, 3, 6 and 12 months
Park (2022)	Germany	38	60 to 79 yrs	permanent teeth	0.3% CHX + Ammonium fluoride (1400 ppm F)	NaF (22,600 ppm F)	changes in caries lesions	2 weeks, 6 and 12 months
Bröchner (2011)	Denmark	50	Not mentioned	not specified	10% CPP–ACP + fluoride dentifrice (1,100 ppm F)	fluoride dentifrice (1,100 ppm F)	changes in caries lesions, lesion area	1 month
Beerens (2010)	The Netherlands	54	12 to 19 yrs	not specified	0.2% CPP-ACP + 900 ppm NaF + fluoride dentifrice	(fluoride-free control paste + calcium) + fluoridated dentifrice	changes in caries lesions, lesion area	6 weeks, 3 months
Zhan (2006)	USA	22	2 to 6 yrs	primary teeth	10% Povidone iodine + 1.23% APF gel	1.23% APF gel	dental caries increment, bacterial count	12 months
Pukallus (2013)	Australia	199	2 to 4 yrs	primary teeth	0.12% CHX gel + fluoride dentifrice (304% fluoride)	fluoride dentifrice (304% fluoride)	dental caries increment	24 months

Table 2. Characteristics of included studies (continued)

First Author (Year)	Country	Sample Size	Age of Participants	Affected Teeth	Experimental Group	Control Group	Outcomes Measurement	Follow-up period
Sundell (2013)	Sweden	78	2 to 5 yrs	primary teeth	1% CHX gel + fluoride varnish + fluoride dentifrice (250 ppm F)	fluoride varnish + fluoride dentifrice (250 ppm F)	dental caries increment	24 months
		83			1% CHX gel + fluoride varnish + fluoride dentifrice (250 ppm F)	0.2% sodium fluoride gel + fluoride varnish + fluoride dentifrice (250 ppm F)	dental caries increment	
Sitthisettapong (2012)	Thailand	296	2½ and 3½ yrs	primary teeth	10% CPP-ACP + fluoride dentifrice	Placebo + fluoride dentifrice	dental caries increment	6 and 12 months
Parsa (2021)	India	200	4 to 7 yrs	primary teeth	10% Povidone iodine + fluoride varnish (2% NaF)	fluoride varnish (2% NaF)	dental caries increment	6 and 12 months
Milogram (2021)	Micronesia	273	49 to 84 months	primary teeth	10% Povidone iodine + 5.0% NaF	5.0% NaF	dental caries increment	12 months
		262			10% Povidone iodine + 5.0% NaF	5.0% NaF	dental caries increment	24 months
El-Houseiny (2005)	Saudi Arabia	54	4-6 years	primary teeth	10% Povidone iodine + 1.23% APF gel	1.23% APF gel	dental caries increment	6 and 12 months

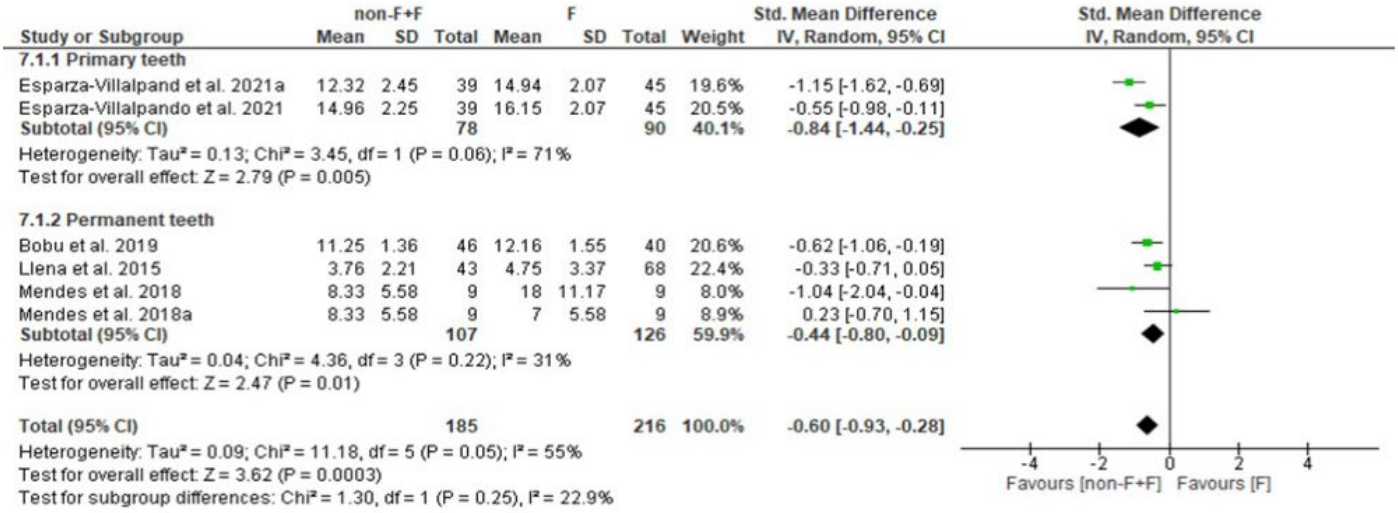

Figure 2. Forest plot comparing the effect of fluoride monotherapy versus fluoride combined with non-fluoride agents on caries activity (DIAGNOdent scores) in primary and permanent teeth at short-term follow-up (< 2 months)

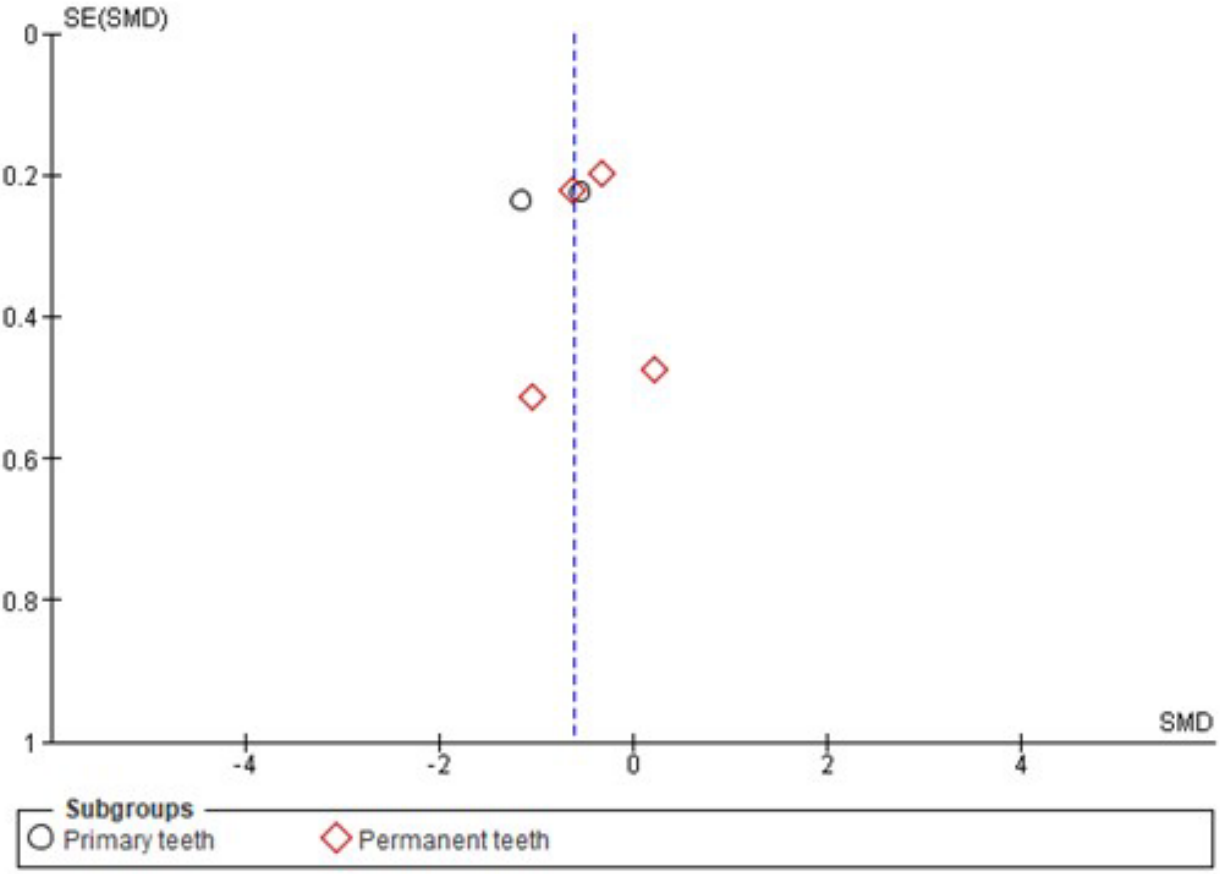

Figure 3. Funnel plot assessing publication bias for studies reporting DIAGNOdent-based caries activity outcomes at < 2 months

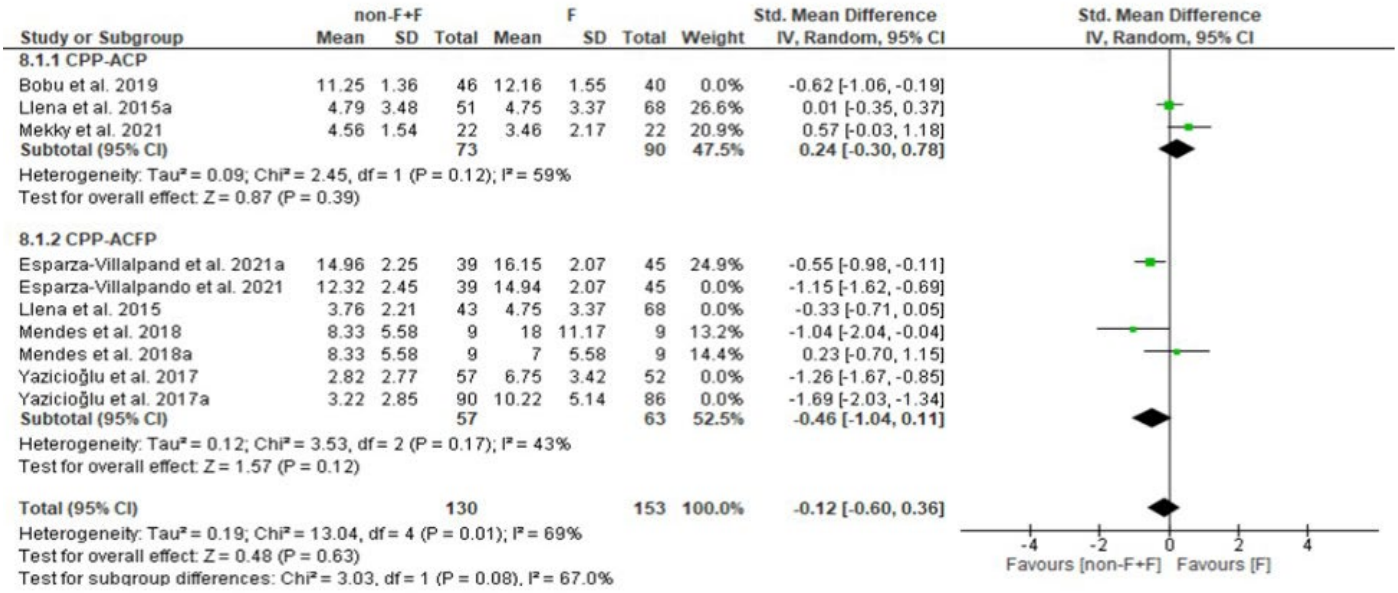

Figure 4. Forest plot presenting subgroup analysis by type of non-fluoride adjunct (CPP-ACP and CPP-ACFP) for caries activity measured using DIAGNOdent at < 2 months

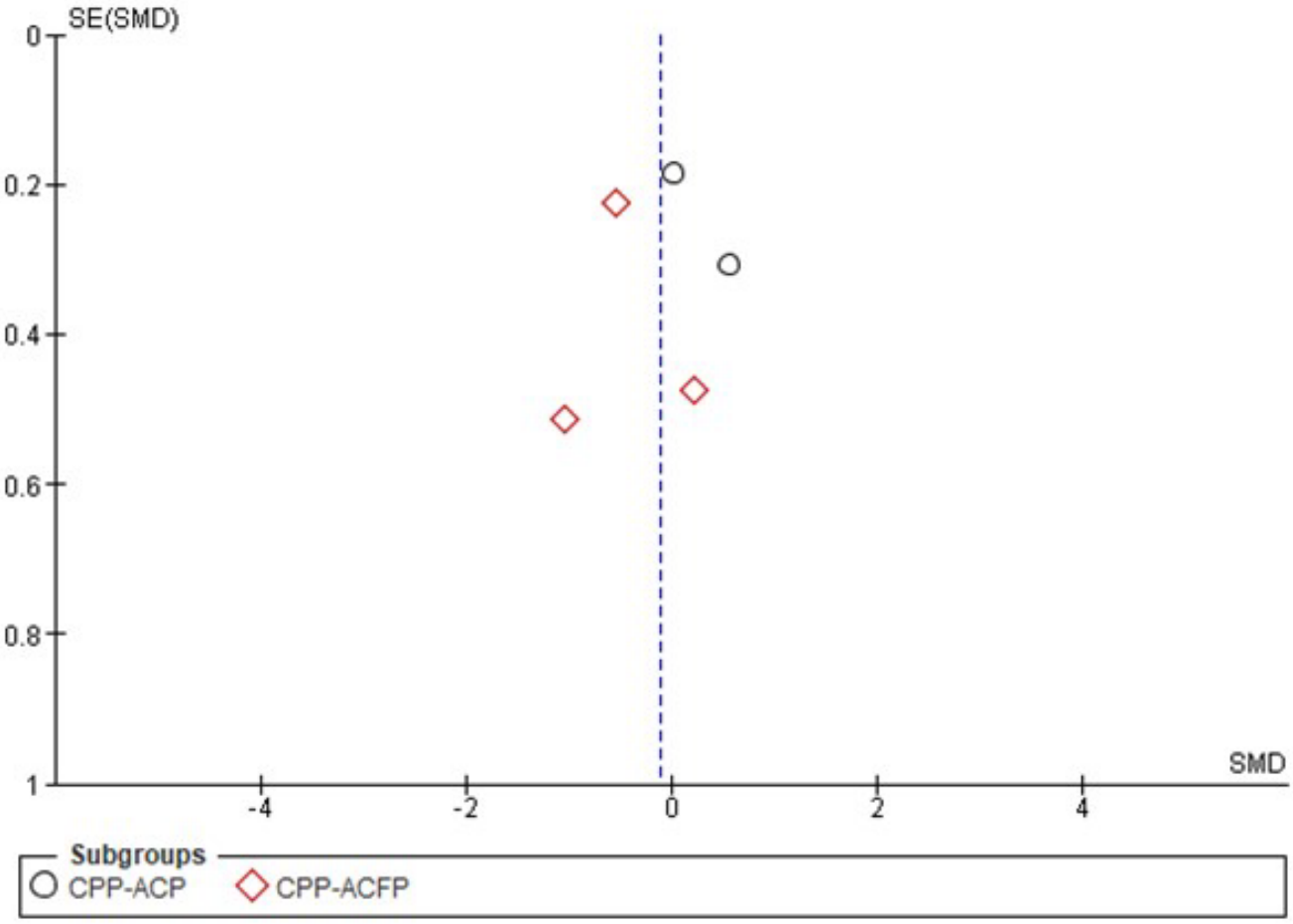

Figure 5. Funnel plot evaluating publication bias for subgroup analyses of DIAGNOdent outcomes at < 2 months

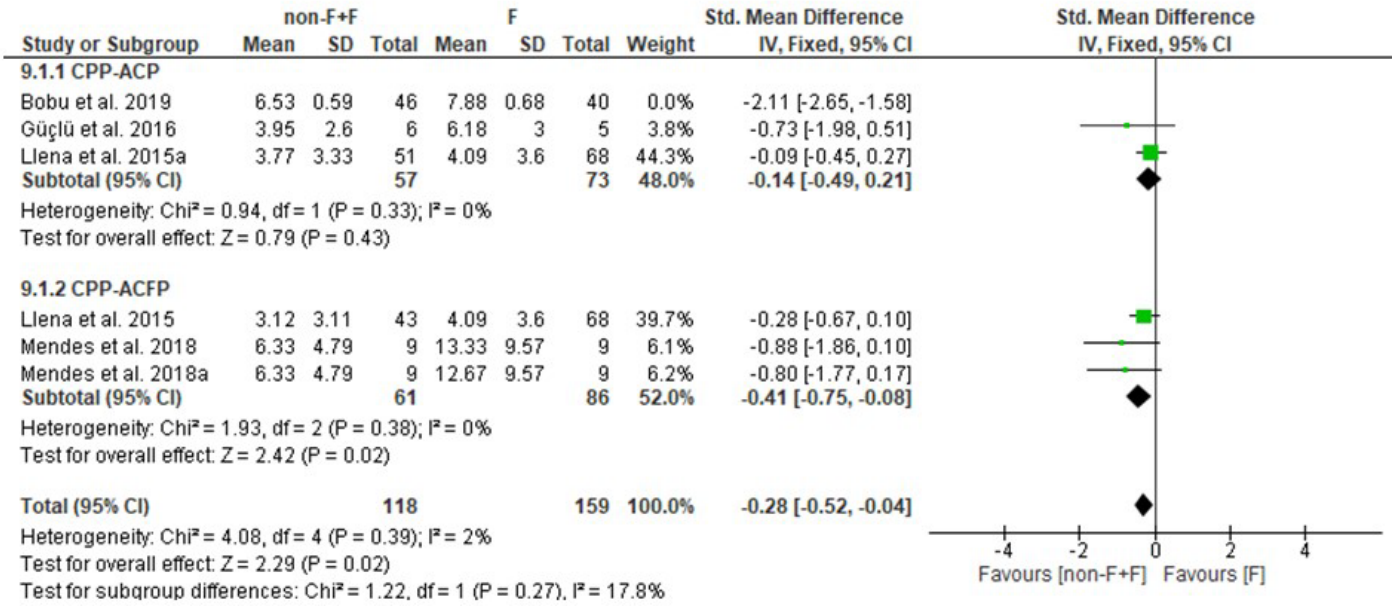

Figure 6. Forest plot presenting subgroup analysis by type of non-fluoride adjunct (CPP-ACP and CPP-ACFP) for caries activity measured using DIAGNOdent at 3-month follow-up

A symmetrical distribution of studies around the pooled effect estimates in the funnel plot indicated no apparent publication bias (Figure 7).

A total of three studies reported changes in caries lesions in 184 teeth based on QLF readings after three months of treatment. The pooled analysis across all studies showed no significant lesion changes when fluoride was used alone or in combination with non-fluoride agents (SMD = 0.22; 95% CI: −0.08 to 0.51; p > 0.05). Heterogeneity was not significant among the pooled studies (I^2 = 36%; p = 0.21) (Figure 8).

Figure 9 depicts that all studies were distributed symmetrically around the pooled SMD, indicating no publication bias.

Secondary Outcome: Reduction in Lesion Area

A total of 89 patients in the experimental group and 95 patients in the control group were compared for mean reduction in lesion area in the three studies included. The pooled analysis showed a significant difference in the outcomes between the two groups favoring combined therapy (SMD = −0.31; 95% CI: −0.60 to −0.02; p < 0.05). There was no heterogeneity among the pooled studies (I^2 = 0%, p = 0.98) (Figure 10).

Figure 11 depicts that all studies were distributed symmetrically around the pooled SMD, indicating no publication bias.

Secondary Outcome: Dental Caries Increment

Overall, the pooled analysis across all studies showed no significant difference in caries increment among patients undergoing fluoride monotherapy and combined therapy after 6 months (SMD = −0.06; 95% CI: −0.23 to 0.11, p > 0.05; I^2 = 10%, p = 0.33), 12 months (SMD = 0.10; 95% CI: −0.23 to 0.04, p > 0.05; I^2 = 23%, p = 0.27), and 24 months (SMD = 0.07; 95% CI: −0.09 to 0.23, p > 0.05; I^2 = 0%, p = 0.74) of treatment (Figure 12).

Figure 13 depicts that all studies were distributed symmetrically around the pooled SMD, indicating no publication bias.

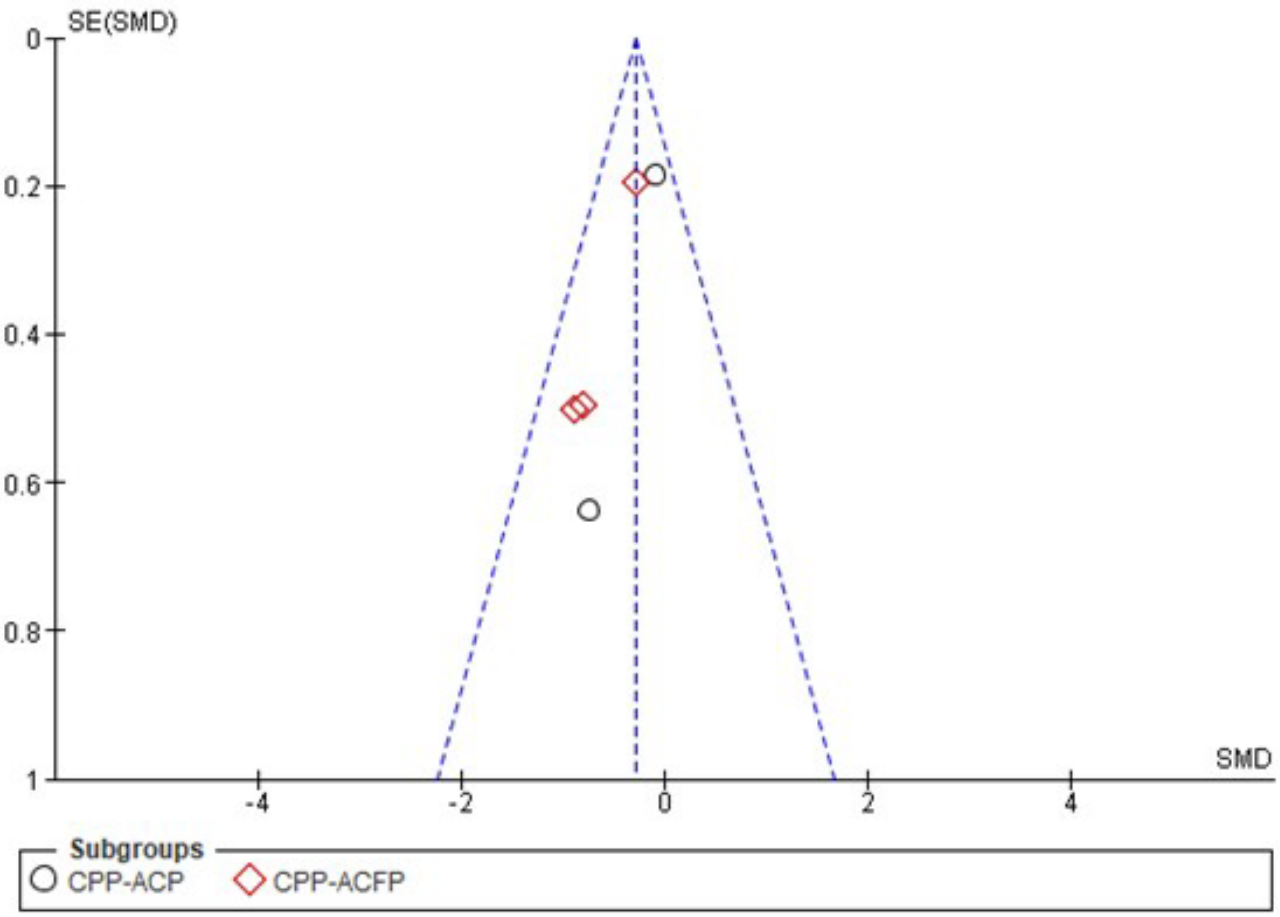

Figure 7. Funnel plot assessing publication bias for subgroup analyses of DIAGNOdent outcomes at 3-month follow-up

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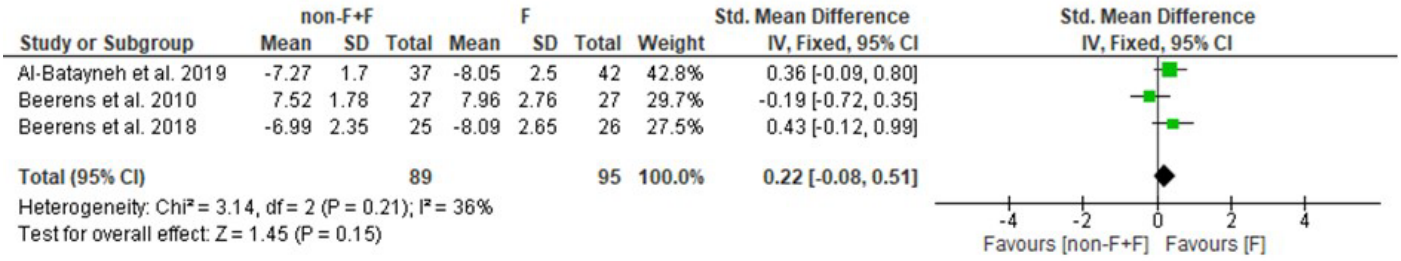

Figure 8. Forest plot comparing changes in lesion characteristics based on quantitative light-induced fluorescence (QLF) values at 3 months post-treatment between fluoride monotherapy and combination therapy

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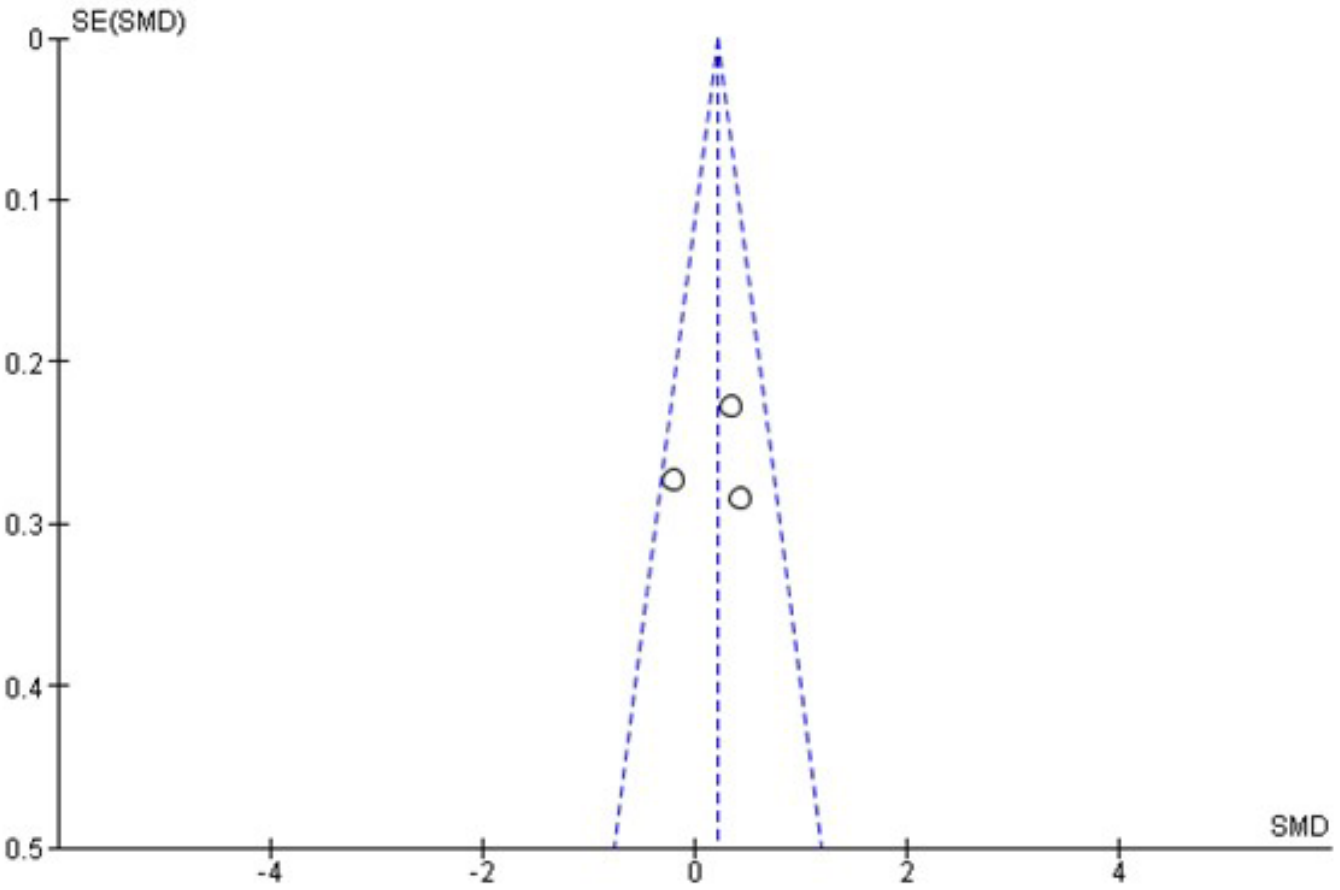

Figure 9. Funnel plot evaluating potential publication bias for QLF-based lesion change outcomes at 3 months

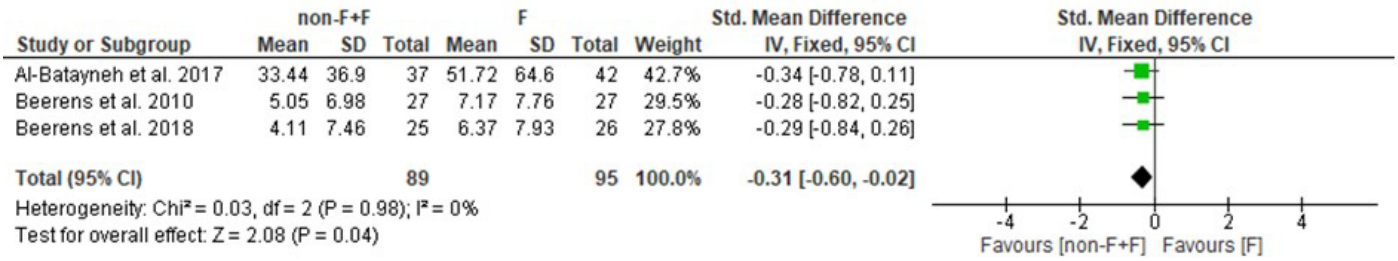

Figure 10. Forest plot demonstrating the effect of combination therapy versus fluoride monotherapy on lesion area reduction at 3 months

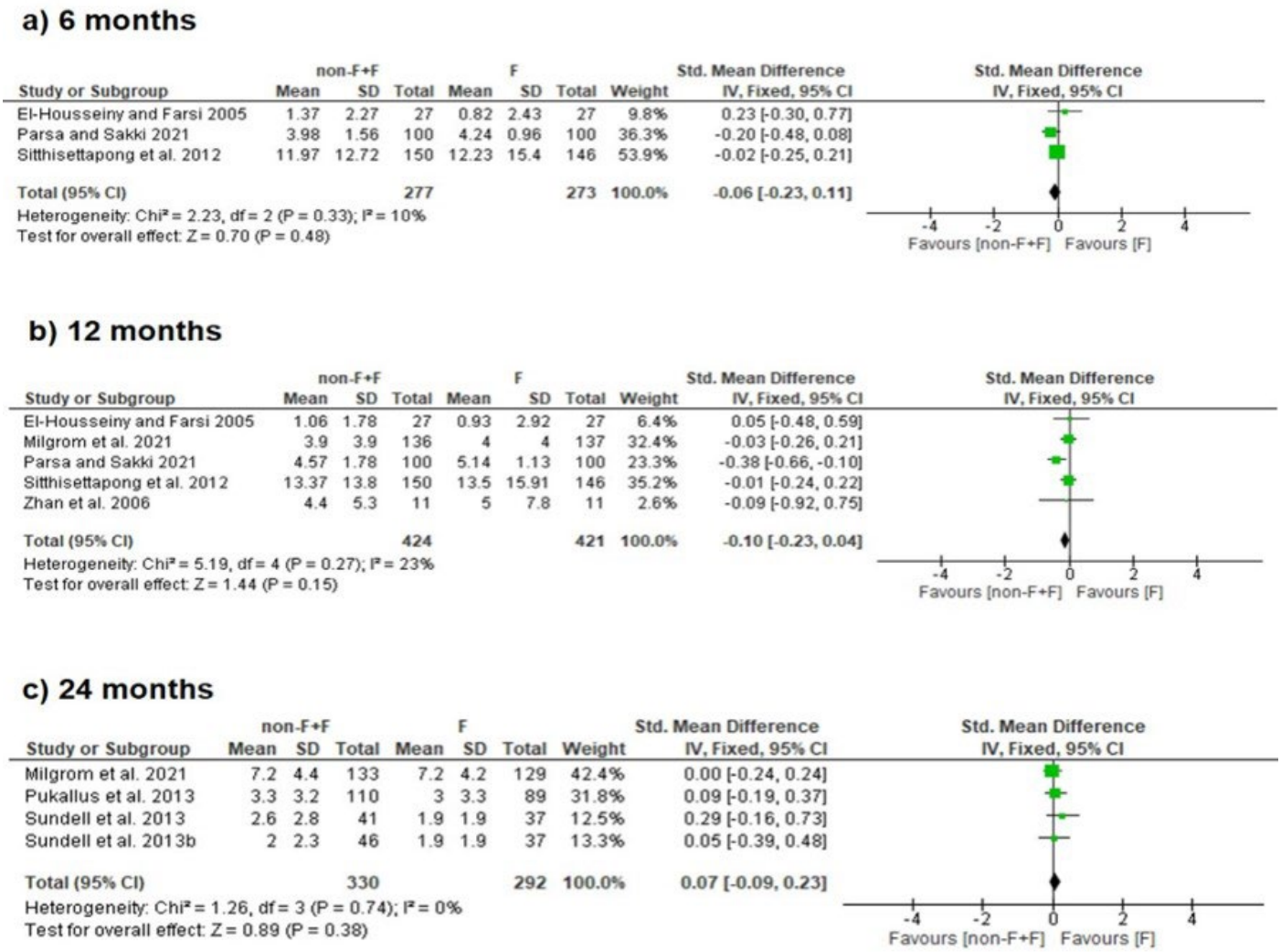

Figure 11. Funnel plot assessing publication bias for lesion area reduction outcomes at 3 months

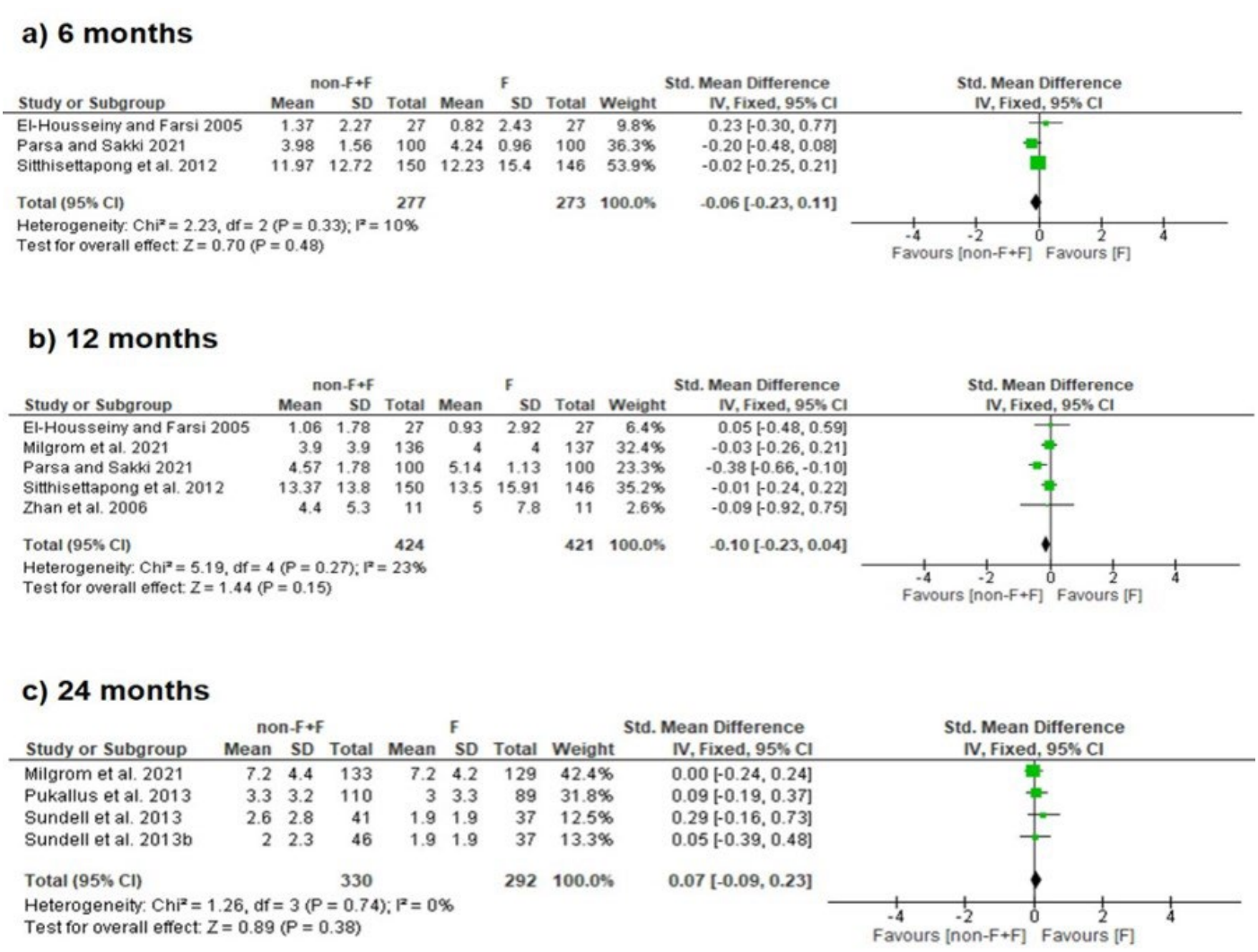

Figure 12. Forest plot comparing dental caries increment between fluoride monotherapy and combination therapy across different long-term follow-up periods (6, 12, and 24 months)

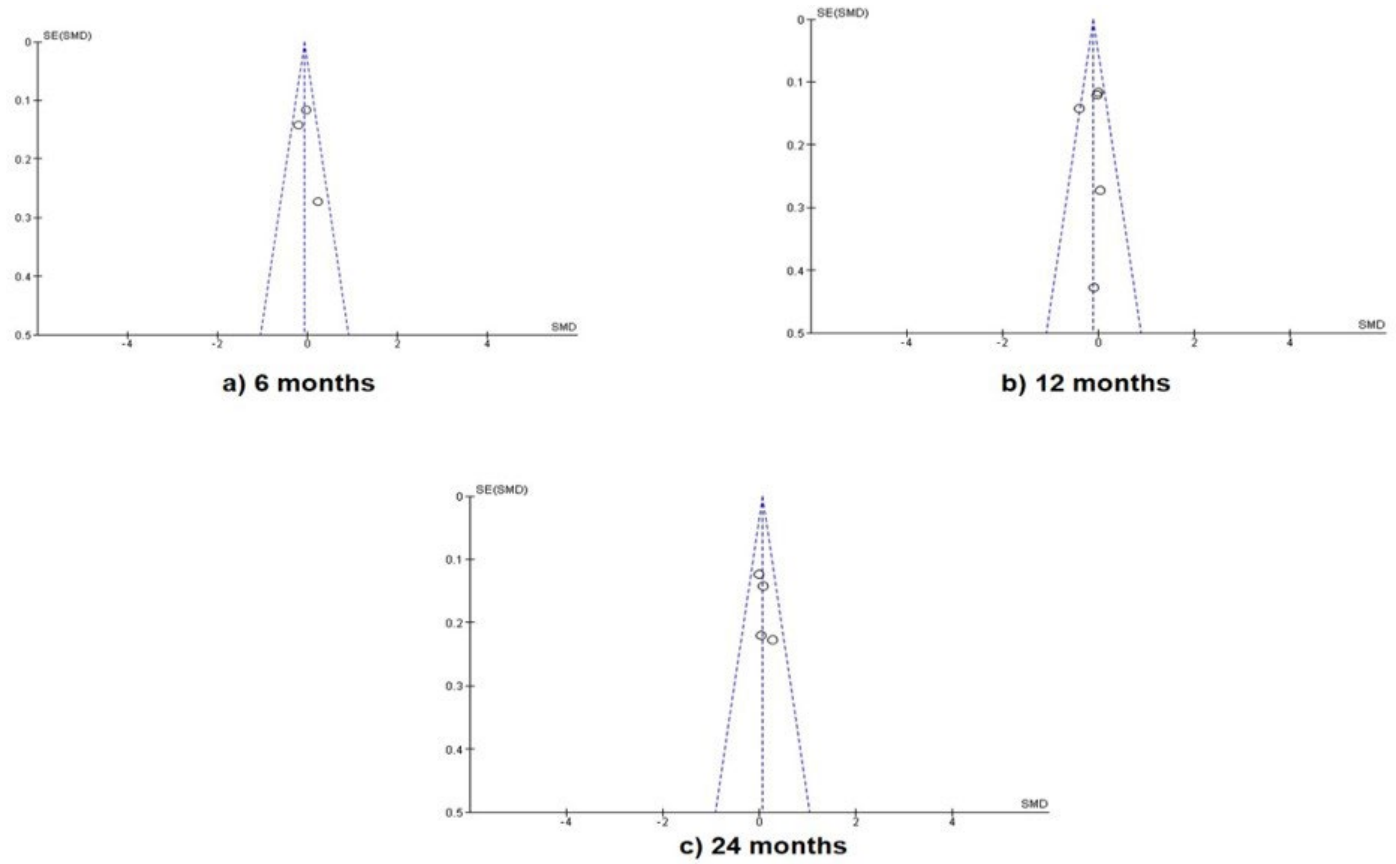

Figure 13. Funnel plots assessing publication bias for long-term caries increment outcomes at different post-treatment timepoints

DISCUSSION

The present systematic review and meta-analysis synthesized available evidence from RCTs to evaluate the effectiveness of fluoride combined with non-fluoride adjunctive agents compared with fluoride monotherapy in the management of dental caries. Outcomes were primarily evaluated through fluorescence-based detection methods, including laser fluorescence (DIAGNOdent) and QLF, both of which are widely accepted as sensitive tools for monitoring changes in the mineralization of enamel. Laser fluorescence techniques, such as DIAGNOdent, have been extensively used to measure the remineralization potential of dental products by detecting changes in fluorescence that correspond to mineral loss or gain. Previous research has shown that decreases in DIAGNOdent values after treatment indicate successful remineralization and lesion arrest, confirming the utility of this method in short-term clinical trials.[51,52] Similarly, QLF provides a non-destructive and reproducible approach for the quantification of lesion area and fluorescence loss,[53] enabling detection of early, subclinical mineral changes in enamel surfaces. Both techniques offer valuable insights into early remineralization dynamics that are difficult to capture with purely clinical measures. However, these methods provide indirect surrogate outcomes and do not directly measure long-term caries prevention or cavitation.

The pooled analysis revealed that combination therapy, particularly with CPP-ACP, was associated with significantly greater short-term improvements in remineralization potential and reductions in lesion area compared to fluoride alone at follow-up periods of less than two months

and three months of treatment. These findings suggest that adjunctive agents may enhance the early biochemical and physicochemical effects of fluoride in controlling caries activity and supporting remineralization in the short-term basis. Fluoride remains the cornerstone of caries prevention and management, with a history of over two centuries of use.[12,13] Its primary mechanism of action involves enhancing the deposition of calcium and phosphate ions during remineralization, resulting in the formation of fluoridated hydroxyapatite crystals that are more resistant to subsequent acid dissolution.[14,16] While bioavailable calcium and phosphate are typically supplied by saliva, their availability may be compromised by individual lifestyle, diet, or salivary function.[54] This limitation provides the rationale for combining fluoride with calcium- and phosphate-containing formulations, to further suppress demineralization and enhance remineralization.[55]

CPP-ACP has emerged as an important biomimetic agent in this context. CPP-ACP stabilizes calcium and phosphate ions in an amorphous, bioavailable state and maintains high concentrations of these ions in close proximity to enamel lesions.[56,57] This mechanism not only facilitates mineral deposition but also buffers fluctuations in the oral environment, reducing the risk of repeated demineralization. When used along with fluoride, the complex is capable of delivering calcium, phosphate, and fluoride ions simultaneously at the lesion site. Studies have shown that this synergistic action may promote the formation of enamel-like mineral phases and enhance lesion repair.[58,59] This is in consistent with the subgroup findings of the present review where CPP-ACP when used along with fluoride, demonstrated significant reductions in caries activity, highlighting the importance of fluoride incorporation along with the complex. Overall, these mechanisms align with the observed short-term remineralization benefits rather than durable caries prevention.

An important observation of this meta-analysis is the differential effect between primary and permanent dentition. The subgroup analysis revealed that combination therapy conferred greater short-term benefits in primary teeth, with effect sizes nearly twice as large as those seen in permanent teeth. This may be attributable to the structural differences between primary and permanent enamel, including thinner enamel, lower mineral content and higher porosity of primary teeth.[60,61] In permanent teeth, although combination therapy demonstrated significant benefits, the effect was smaller, suggesting that enamel maturity and exposure history may reduce the magnitude of benefit.

Despite favorable short-term outcomes, no significant differences were noticed between fluoride monotherapy and combination therapy for long-term caries increment at 6-24 months. This finding suggests that while adjunctive agents may accelerate early remineralization or reduce fluorescence-detected lesion activity, these short-term improvements do not translate into sustained reductions in new caries formation. One possible methodological explanation lies in the nature of the outcome measures. Short-term benefits were primarily detected using fluorescence-based techniques (e.g., DIAGNOdent, QLF), which are sensitive to early mineral changes but represent surrogate markers rather than definitive clinical endpoints, such as cavitation or caries incidence. These methods may capture transient mineral gains that are not maintained over time in real-world conditions. On the other hand, previous research indicated that the combination of povidone iodine and topical fluoride was more effective in preventing new lesions, particularly in permanent teeth among children aged 1-12 years, but the quality of evidence was rated very low.[27] Evidence also suggests that chlorhexidine and povidone iodine can help in caries prevention.

Chlorhexidine, though primarily recognized for its antimicrobial activity, can contribute to remineralization by inhibiting collagen degradation in dentin and facilitating mineral deposition along with collagen fibrils.[62] Similarly, povidone-iodine acts as an antimicrobial agent that reduces cariogenic *Streptococcus mutans* populations and limits acid production, thereby indirectly helping caries prevention.[27,63,64] Although agents such as chlorhexidine and povidone-iodine possess antimicrobial properties and may indirectly support caries control, the present study showed a lack of long-term effectiveness of these agents in caries prevention. This time-dependent discrepancy may reflect the influence of broader behavioral, dietary, and environmental factors on caries progression that cannot be fully mitigated by topical agents alone. From a clinical perspective, caries is a multifactorial disease influenced by behavioral, dietary, and environmental determinants that extend beyond the localized effects of topical agents. Unhealthy dietary habits, such as frequent consumption of sugary food, fast foods, or salty snacks, can directly increase the incidence of caries and indirectly promote cariogenic biofilm formation.[65,66] Longitudinal evidence indicates that improved diet quality reduces caries experience, while frequent snacking, consumption of sour milk products and salty snacks, and eating behaviors like food fussiness increase caries risk in children and adolescents.[67] Addictive behaviors including tobacco and alcohol use further alter oral biofilm ecology, indirectly accelerating caries progression.[65] Environmental influences, including neighborhood disadvantage and exposure to passive smoking, are also associated with higher increments of caries, underscoring the broader social determinants of oral health.[68] Therefore, the lack of sustained long-term benefits of adjunctive agents in the present analysis suggests that modifying the oral microenvironment alone may be insufficient to counteract persistent behavioral and environmental risk factors. Taken together, the study highlights the need to interpret short-term remineralization benefits cautiously and emphasizes the importance of long-term clinical endpoints in future trials.

This study has several limitations that should be acknowledged. First, most included studies evaluated CPP-ACP or CPP-ACFP in combination with fluoride, while evidence for other non-fluoride agents such as chlorhexidine and povidone-iodine was limited, and no studies evaluating the use of herbal products in combination with fluoride were identified. As a result, the findings of this meta-analysis largely reflect the effectiveness of CPP-ACP–based combination therapies, which restricts the generalizability of the results to other adjunctive agents. Second, a considerable level of heterogeneity was observed among the included studies. In addition to variations in the study design, participant age groups, and intervention protocols, there was considerable variability in fluoride concentrations and delivery methods, ranging from low-dose dentifrices to high-concentration professional applications. This variability has important clinical implications, particularly in pediatric populations where fluoride dosage must be carefully balanced against the risk of dental fluorosis and unintended ingestion. Differences in fluoride potency may have influenced treatment effects, making it difficult to attribute observed benefits solely to adjunctive agents. Consequently, the generalizability of the findings to standardized and age-appropriate clinical protocols may be limited. Third, the search strategy did not extend to certain major databases, such as Scopus and Web of Science. As a result, it is possible that some relevant studies were not captured, potentially influencing the comprehensiveness of the review. Finally, many of the included studies relied on fluorescence-based methods, such as laser or quantitative light-induced fluorescence, which provide indirect estimates of

remineralization potential rather than direct clinical confirmation of lesion prevention.

Clinical Implications for Pediatric Dentistry

The findings of this review have particular relevance for pediatric dental practice. Subgroup analysis indicated that combination therapy demonstrated greater short-term remineralization benefits in primary teeth compared to permanent teeth. This may be attributed to the structural characteristics of primary enamel, which is thinner, more porous, and less mineralized, making it more responsive to remineralization interventions but also more susceptible to rapid caries progression. Therefore, early non-invasive management strategies are especially critical in pediatric population.

The enhanced short-term effects observed with CPP-ACP combination suggest potential value in managing non-cavitated lesions and white spot lesions in children. However, the absence of a consistent long-term reduction in caries increment highlights that adjunctive topical therapies should not replace comprehensive preventive strategies. In pediatric patients, caries progression is strongly influenced by dietary habits, feeding practices, oral hygiene behavior, and caregiver supervision. Additionally, variability in fluoride concentration across included studies has important safety implications in children. Since excessive fluoride ingestion during enamel development increases the risk of dental fluorosis, careful consideration of fluoride dosage, frequency of application, and supervision during home use remains essential. The benefits of combination therapy must therefore be balanced with age-appropriate fluoride recommendations.

CONCLUSIONS

The present systematic review and meta-analysis evaluated the effectiveness of non-fluoride adjunctive agents used in combination with fluoride compared with fluoride monotherapy for the prevention and management of dental caries. A total of 21 studies from different countries, involving children, adolescents, and adults across primary and permanent dentitions, were included. The review primarily evaluated short-term remineralization outcomes using fluorescence-based methods and long-term caries increment as a clinical endpoint. The pooled results indicated that the combination therapy, particularly fluoride used with CPP-ACP, demonstrated enhanced short-term remineralization and greater reduction in early lesion activity compared with fluoride alone. These benefits were primarily observed in fluorescence-based outcomes within short follow-up periods, supporting the potential role of combination therapy in the management of early caries lesions. However, current evidence did not demonstrate a consistent long-term advantage of combination therapy over fluoride monotherapy in reducing caries increment at extended follow-up periods (6-24 months). Therefore, while adjunctive agents may offer additional benefits in early lesion management, especially in high-risk groups such as children and young adults, their sustained effectiveness in long-term caries prevention is not currently supported by robust clinical evidence. Given that most included studies relied on surrogate fluorescence-based outcomes and that CPP-ACP–based formulations constituted the majority of interventions evaluated, the generalizability of these findings to other adjunctive agents and long-term clinical outcomes remains limited. Future studies should focus on standardized protocols, larger sample sizes, and longer follow-up durations to confirm the long-term clinical effectiveness of non-fluoride-based adjuncts. Direct clinical endpoints, such as cavitation or lesion arrest, should be prioritized over fluorescence-based measures to better guide clinical practice and public health policy.

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