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REVIEW

Fluoride-Free Toothpastes for Caries Prevention: A Systematic Review of Clinical Evidence on Active Ingredients

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Objective: To systematically identify and evaluate clinical trials assessing the caries-preventive efficacy of fluoride-free active ingredients in toothpaste formulations.

Data: Randomized clinical trials analyzing the caries preventive effect of fluoride-free active ingredients in toothpastes.

Sources: A PRISMA-related systematic review of MEDLINE and Embase was conducted. Inclusion criteria were human in vivo clinical trials on toothpastes, fluoride-free interventions, and caries-focused outcomes; exclusion criteria were in vitro or animal studies, non-toothpaste products, fluoride-only products, and non-English publications. The review followed the PICO framework: Population - participants of all ages with primary, mixed, or permanent dentition; Intervention - use of a toothpaste with a non-fluoride active ingredient; Comparison - a fluoride-containing toothpaste as control; Outcome - a measurable oral health effect based on in vivo caries estimation.

Study Selection: Fifteen clinical trials met the inclusion criteria. Eleven used fluoride-free, non-therapeutic abrasive toothpastes as placebo controls. Three trials evaluated the caries-preventing efficacy of fluoride-free hydroxyapatite toothpastes across children, adolescents, and adults; one trial evaluated the caries-preventive efficacy of fluoride-free arginine toothpaste in children.

Conclusion: Caries prevention relies on reducing sugar intake and thorough daily oral care, with toothpaste, containing evolving combinations of remineralizing agents, antibacterials, and abrasives, playing a central role. With growing global interest in fluoride-free options, this literature review shows that clinically proven fluoride alternatives are already in use.

Clinical Significance: This review provides evidence-based guidance for dentists when recommending fluoride-free toothpastes to patients.

Keywords: fluoride-free toothpaste, caries prevention, randomized clinical trials

Introduction

Caries remains highly prevalent worldwide.[1] The primary cause of caries is dental plaque, where bacteria metabolize sugars into acids that demineralize the mineral phase of the tooth structure. Therefore, reducing sugar intake and maintaining effective preventive oral care are two key strategies to lower caries risk.[2]

Toothpastes play an important role in preventive oral health care and caries prevention.[3] In toothpastes, effective plaque removal is essential and can be achieved with cleaning abrasives; antibacterial agents can also be included.[2] However, there is a general trend away from using strong antibacterials such as chlorhexidine in oral care products due to concerns about resistance development as well as due to negative impact on the oral microbiome.[4,5] To strengthen and remineralize enamel, toothpastes can incorporate remineralizing agents.[2] Overall, toothpaste formulations, ingredients, and efficacy have continually evolved and improved.[6]

While fluoride compounds have been used in toothpaste for decades,[4] various fluoride alternatives have been introduced in recent years, many of which are already used in commercial toothpaste products.[5] One rationale behind fluoride-free concepts for toothpastes is that, although fluorides are frequently used around the globe, still caries remains highly prevalent globally,[1] so new approaches are needed. Additionally, there are ongoing discussions about potential

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side effects of fluoride, especially in children.[6] These concerns include not only dental fluorosis,[7] but also possible negative effects on the developing brain.[6,8,9] Although studies were conducted with fluoride in drinking water, it is important to note that, on one hand, infants and toddlers often swallow relatively large amounts of toothpaste,[10] and on the other, dosing of fluoridated toothpastes for children is frequently excessive.[11–13]

Taken together, there is a need for fluoride-free caries-preventing agents for the use in toothpastes. Several reviews have been published on fluoride-free anti-caries agents. A review titled "Non-Fluoride Anticaries Agents" published as early as 1994 classified fluoride-free active ingredients into several categories:[14] phosphorus-containing agents, calcium-containing agents, antimicrobials and antibiotics, metals, and miscellaneous agents. While studies back then were mainly performed under in vitro conditions, the field of fluoride-free anti-caries agents has been shown to be highly dynamic, and the clinical evidence has grown significantly in recent years.

Recent review articles in this field focus on calcium phosphates including hydroxyapatite (HAP), casein phosphopeptide-amorphous calcium phosphate (CPP-ACP), calcium sodium phosphosilicate (CSPS), and β-tricalcium phosphate (β-TCP),[15] as well as general reviews on agents specifically intended to prevent caries in primary dentition.[16] There are also reviews focusing solely on single active ingredients, such as, hydroxyapatite,[17,18] arginine,[19,20] and xylitol,[21] with in-depth literature analysis. Fluoride-free caries-preventing agents may differ between their modes of action, eg., some agents such as calcium-containing agents promote remineralization of early caries lesions, while others exert antibacterial/biofilm reducing effects.[14]

For patient-centered recommendations, it is important to know which fluoride-free anti-caries agents have been described in the dental literature and, most importantly, what the clinical evidence for these agents in caries prevention is. As toothpastes are the most widely used vehicle for daily caries prevention, this systematic review focuses exclusively on fluoride-free toothpastes. As outlined above, there are articles that have addressed fluoride-free agents; however, to our knowledge, a more recent and comprehensive overview that also considers newly published clinical trials is still not fully available.

The aim of this systematic review was to present a current overview on fluoride-free agents used in toothpastes for caries prevention and to summarize the clinical evidence in comparison to fluoride toothpastes. Additionally, the modes of action of those agents in caries prevention are presented. While the main focus of the present review was on in vivo studies, some findings from the past years were included to capture the latest developments in toothpaste technology regarding caries prevention.

Methods

The PICO Framework

For the literature search the following PICO framework was used:

P (Population): participants of all ages, with primary, mixed, or permanent dentition.

I (Intervention): the use of a toothpaste with an active ingredient that is not fluoride.

C (Comparison): a fluoride-containing toothpaste as control.

O (Outcome): a measurable oral health effect that is based on a caries estimation in vivo.

Databases

Informed by, but not fully sticked to the PRISMA guidelines for literature reviews (Supplemental Table S1), MEDLINE (via PubMed), and EMBASE (via Scopus) were screened for literature.[22] Full texts and supplementary information were extracted for each publication. The search was limited to English-language publications and conducted on the 17th of October 2025 using the following inclusion and exclusion criteria. All studies conducted in vivo in humans as clinical trial, using a fluoride-free toothpaste, focusing on caries and were written in English were included in the synthesis. Studies on animals or in vitro studies, studies not directly focusing on caries (eg., plaque studies etc.), studies only comparing fluoride products, and studies comparing other products than toothpastes were excluded from the review.

The search terms, following the inclusion and exclusion criteria were as follows:

("fluoride-free":ti,ab OR "fluoride free":ti,ab OR "non-fluoride":ti,ab OR "non-fluoridated":ti,ab OR nonfluoride:ti,ab OR "without fluoride":ti,ab) AND (toothpaste:ti,ab OR dentifrice*:ti,ab) AND (caries:ti,ab OR "dental caries":ti,ab OR cavit*:ti,ab) AND ("clinical trial"/de OR "randomized controlled trial"/de OR randomized:ti,ab OR "in vivo":ti,ab) NOT

("in vitro":ti,ab OR "in situ":ti,ab OR mouthwash:ti,ab OR "mouth rinse":ti,ab) NOT ("review"/de OR "systematic review":ti,ab OR "meta-analysis"/de) (for EMBASE), where "ti,ab" refers to title and abstract search. The same terms were used for PubMed with adaptation to the requirements.

Qualitative Synthesis

Qualitative synthesis was conducted on the included studies, demonstrating caries-preventive efficacy of fluoride-free toothpaste agents. The randomized clinical trials were suitable for Cochrane Risk of bias (RoB) analysis.[23] For the RoB analysis, study authors used the Cochrane RoB 2 tool.

Results

According to the inclusion and exclusion criteria, the search was conducted on both databases, as described above (Figure 1). The search resulted in 59 publications of which 51 remained after de-duplication. Titles and abstracts were screened using Rayyan software by two authors (JE and PU). 17 studies were excluded because they lacked caries-specific endpoints, 6 that only investigated fluoride-containing products, 6 that did not investigate toothpastes, 4 were not clinical trials, and one could not be fully read due to non-English language (Chinese) [the English abstract states that the tested fluoride-free toothpaste was inferior to fluoride toothpastes in terms of remineralization]. After full text screening, two more studies were excluded due to a non-caries-related focus.

Thus, in total 15 studies were included for qualitative synthesis (Table 1). Those 15 publications can be divided into two different groups, comparing a fluoride toothpaste with either 1) an abrasive non-therapeutic placebo toothpaste, or 2) with a toothpaste containing an active ingredient for caries prevention. Four studies are part of the latter group showing toothpastes with either hydroxyapatite or arginine as active ingredients in different concentrations. All other 11 studies are comparing fluoride toothpaste with an abrasive comparator. All study details are presented in Table 1. The results of the 4 studies investigating the caries-preventing effect of an active ingredient will be briefly summarized as follows.

Three studies analyzed the caries preventing effects of fluoride-free hydroxyapatite toothpastes: Paszynska et al reported in a 1-year trial using the International Caries Detection and Assessment System (ICDAS) that a fluoride-free toothpaste was non-inferior to a 500 ppm fluoride toothpaste in children with primary dentition.[32] Schlagenhauf et al demonstrated the non-inferiority of a fluoride-free hydroxyapatite toothpaste compared with a 1400 ppm fluoride toothpaste in adolescents undergoing orthodontic treatment, in a 6-month study using ICDAS.[34] In adults, Paszynska et al showed that in a 18-month trial that a fluoride-free hydroxyapatite toothpaste was non-inferior to a 1450 ppm fluoride toothpaste based on Decayed, Missing, and Filled Surfaces (DMFS) outcomes.[39] One study investigated the caries-preventive effect of fluoride-free arginine toothpaste: In a large 2-year Phase 3 trial, Yin et al showed that arginine was an alternative to a 1450 ppm fluoride toothpaste in children with permanent dentition.[37]

The RoB analysis based on the Cochrane RoB2 tool of the 4 included clinical trials, indicated low RoB for all four considering all five domains (Figure 2).

Discussion

Discussion of Results

Sugar reduction is essential to prevent caries.[2] Besides that, toothpastes are used worldwide for caries prevention,[3] and both toothpaste formulation and selection of ingredients have been significantly improved over recent decades.[40] Various toothpaste ingredients such as remineralizing agents, cleaning abrasives, and antibacterial agents can contribute to caries prevention.[2] Consequently, it is important not to focus on single ingredients, but rather on the caries-preventive efficacy of the entire toothpaste formulation.

While fluoride was the sole caries-preventing agent for many decades, this has changed.[17,18,37] Mainly due to ongoing discussions addressing potential side effects of fluorides,[6–9,41,42] and, despite its widespread use, caries remains prevalent globally.[1]

In the past, many additives in toothpastes were evaluated only in combination with fluoride (eg., 1.5% arginine with 1450 ppm fluoride,[43] or 10% xylitol with 1100 ppm fluoride).[44] Consequently, the caries-preventive effect of the fluoride-

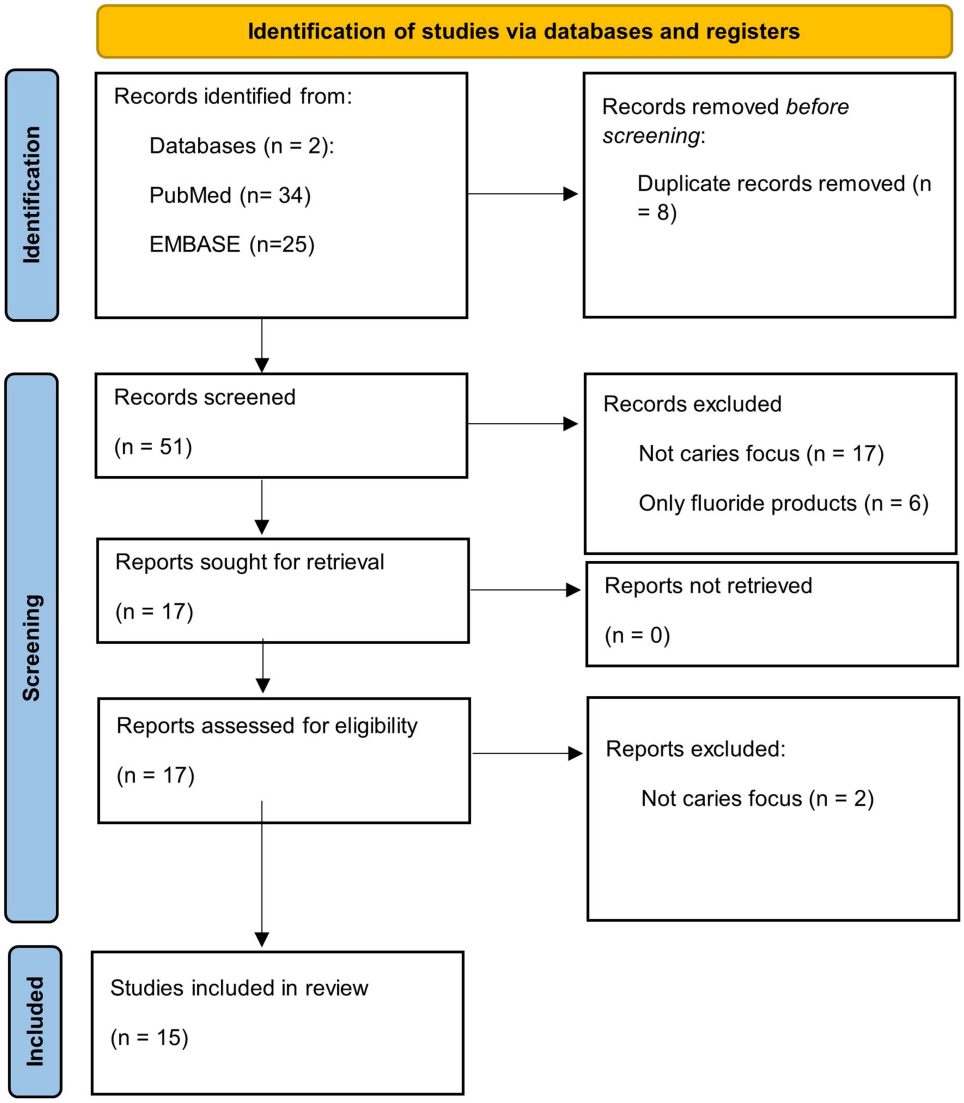

Figure 1 PRISMA flow chart depicting the selection of studies according to Page et al 2021.[21]

free active ingredient itself could not be determined. Recent clinical trials have addressed this by analyzing fluoride-free toothpaste formulations for caries prevention as well (Table 1).

Arginine and hydroxyapatite have been evaluated as fluoride-free alternative in caries prevention (see Table 1 for all study details). The caries-preventing efficacy of arginine at two concentrations (1.5% and 8.0%) was analyzed in a multicenter two year, phase 3, trial in China among children aged 10–14 years.[37] However, regarding toothpaste formulations used in this study, it is noteworthy that the arginine toothpastes used a calcium carbonate base, whereas the fluoride control toothpaste used a silica base. Therefore, future studies analyzing the caries preventing effect of arginine could also include head-to-head comparisons using identical toothpaste bases. On the other hand, the hydroxyapatite study by Paszynska et al used identical toothpaste bases that differed only in their active ingredients: 10% hydroxyapatite versus sodium fluoride (1450 ppm fluoride).[39] Another significant limitation of the arginine study is the difference in baseline caries scores (DMFS [Decayed, Missing, and Filled Surfaces] and DMFT [Decayed, Missing, and Filled Teeth]) between participants in the arginine groups and the fluoride control group.[42]

The caries-preventing efficacy of hydroxyapatite toothpaste has been evaluated across different age groups, ie., children,[32] adolescents,[34] and adults,[39] in Germany and Poland. The non-inferiority of hydroxyapatite compared to fluoride in caries prevention was consistent across all three clinical trials. Building on this evidence, a fluoride-free

Table 1 Overview of Selected Studies

Author, Year [Ref.]	Study Design, Duration	Population: Number of Participants per Group	Method of Caries Detection	Test Products	Comparator Product	Main Results	Main Conclusions	Active Substance
Biesbrock et al, 1998[24]	Randomized, double-blind, placebo-controlled clinical trial, 3 years	Placebo: n=224; Sodium fluoride: n=584; Stannous fluoride: n=603 (1,411 subjects total who completed all examinations)	Visual-tactile examination (Radike criteria, differentiating incipient vs. frank lesions) and bitewing radiographic examination	1) 0.243% sodium fluoride/silica dentifrice (Crest); 2) 0.4% stannous fluoride/ calcium pyrophosphate dentifrice (Original Crest)	Non-fluoridated placebo/calcium pyrophosphate dentifrice	At Year 3, sodium fluoride showed statistically significantly greater caries reversals vs. placebo for total caries (p=0.006) and radiographic caries (p=0.008). Stannous fluoride showed greater reversals than placebo but differences were not statistically significant in all subjects. In "at risk" subjects (those with ≥1 lesion at baseline), both fluoride	Both 0.243% sodium fluoride/silica and 0.4% stannous fluoride/calcium pyrophosphate dentifrices can clinically reverse caries. Sodium fluoride may deliver a greater frequency of caries reversals than stannous fluoride, although the difference between fluoride treatments was not statistically significant	Fluoride-free placebo toothpaste
Damle et al, 2012[25]	Randomized controlled trial (blind study), 18 months (semiannual follow-up)	Test group: 302 children; Control group: 293 children (total 595 school children aged 12–15 years)	WHO Oral Health Assessment Form (1997) criteria for DMFT and DMFS	Dentifrice containing sodium monofluorophosphate (1000 ppm) + calcium glycerophosphate	Placebo dentifrice (non-fluoridated, with all characteristics similar except fluoride content)	DMFT increased from 4.67±2.25 to 5.13±2.30 (test) vs. 4.43±2.03 to 5.84±2.29 (control) (p=0.001 at 18 months). DMFS increased from 7.06±4.77 to 7.92±5.07 (test) vs. 6.42±4.10 to 8.64±4.51 (control) (p=0.095 at 18 months). Plaque scores reduced from 2.91±0.72 to 0.91 ±0.38 (test) vs. 2.94±0.72 to 1.33±0.46 (control) (p<0.001 at 18 months).	The test dentifrice was effective in inhibiting the progression of dental caries. Mean DMFT and DMFS values increased in both groups, but the increase was significantly less in the test group compared to control. The test dentifrice also showed significantly better plaque reduction efficacy.	Fluoride-free placebo toothpaste

(*Continued*)

Table 1 (Continued).

Author, Year [Ref.]	Study Design, Duration	Population: Number of Participants per Group	Method of Caries Detection	Test Products	Comparator Product	Main Results	Main Conclusions	Active Substance
Fan et al, 2008[26]	Double-blind, parallel-group, randomized clinical trial, 2 years	Test (1.14% SMFP calcium carbonate): n=329; Positive control (1.14% SMFP silica): n=341; Negative control (non-fluoride): n=328	Visual and probe examination using dfs (decayed and filled tooth surfaces) index according to US National Institute of Dental Research criteria	1) 1.14% SMFP calcium carbonate-based dentifrice (Colgate Anticavity Toothpaste); 2) 1.14% SMFP silica-based dentifrice (Colgate Fluoride Toothpaste)	Non-fluoride calcium carbonate-based dentifrice (ZhongHua Toothpaste)	After 1 year: Mean dfs increment was 1.53 (test), 1.69 (positive control), 2.19 (negative control), representing 30% and 23% caries reduction vs. negative control ($p<0.05$). After 2 years: Mean dfs increment was 2.75 (test), 2.98 (positive control), 4.73 (negative control), representing 42% and 37% caries reduction vs. negative control ($p<0.05$). No significant difference between the two fluoride dentifrices	Both 1.14% SMFP calcium carbonate-based and silica-based dentifrices provide clinically superior anticaries efficacy compared to non-fluoride dentifrice. The calcium carbonate-based formulation is equivalent in efficacy to the silica-based formulation	Fluoride-free placebo toothpaste
Feng et al, 2007[27]	Single-blind cluster randomized controlled trial (schools as unit of randomization), 6 months	MFP group: 100 subjects (383 lesions); NaF group: 99 subjects (319 lesions); Non-F group: 106 subjects (342 lesions). Total: 296 subjects completed	Quantitative light-induced fluorescence (QLF) measuring enamel autofluorescence. Primary outcome: ΔQ (product of fluorescence loss and area) at 5% threshold.	(1) Sodium fluoride dentifrice (NaF, 1,450 ppm F; Crest Regular); (2) Sodium monofluorophosphate dentifrice (MFP, 1,450 ppm F; Colgate Ultra Cavity Protection)	Herbal non-fluoride dentifrice (Tianqi Toothpaste, 0 ppm F)	At 3 months: significant difference between MFP and placebo ($p=0.02$), but not NaF vs. placebo. At 6 months: significant differences for both NaF vs. placebo ($p=0.002$) and MFP vs. placebo ($p<0.001$) for all QLF metrics (area, ΔF, ΔQ). All groups showed lesion improvement, but fluoride groups demonstrated more rapid and substantial remineralization.	QLF methodology can detect differences in remineralization between fluoride-containing and non-fluoride dentifrices within 3- and 6-month periods of supervised brushing. Fluoride groups experienced more rapid and substantial remineralization than placebo. The abbreviated trial design combining supervised brushing and QLF can discriminate between fluoride and non-fluoride products.	Herbs

Fogels et al, 1979[28]	Randomized, double-blind, parallel-group clinical trial (2×3 factorial design with two examiners), 3 years (baseline + 3 annual follow-ups)	A: 451; B: 449; C: 439 (completers); Initially enrolled: A: 731; B: 752; C: 735	Clinical examination using no. 23 sharp explorer and no. 4 dental mirror; bitewing radiographs	A: 0.4% stannous fluoride dentifrice in silica gel base; C: 0.4% stannous fluoride dentifrice in calcium pyrophosphate base (commercially available, positive control)	B: Nonfluoride dentifrice in silica gel base	After covariance adjustment for age and initial DFS: Net DFS whole mouth: A vs B: −15% reduction ($p<0.01$); Net DFS interproximal: A vs B: −25% reduction ($p<0.01$); DFS on new eruptions: A vs B: −16% reduction ($p<0.05$); New DMFT: A vs B: −7% reduction (not significant). No significant difference between A and C	The test dentifrice (0.4% stannous fluoride in silica gel base) significantly reduced caries (15–25% reduction for whole mouth and interproximal surfaces) compared to nonfluoride control. Performance was comparable to the commercially available 0.4% stannous fluoride in calcium pyrophosphate base. Larger reduction on interproximal surfaces attributed to therapeutic fluoride action	Fluoride-free placebo toothpaste
Hu et al, 2013[29]	Randomized, controlled, double-blind clinical trial, 6 months	Experimental: 141; Positive control: 134; Negative control: 137; Total: 412 subjects aged 50–70 years, mean 64 ±4.1 years, 53.6% female	1) Clinical hardness assessment (visual/tactile with sharp probe); 2) Electrical Caries Monitor (ECM IV)	1) Experimental: 1.5% arginine + 1450 ppm F as sodium monofluorophosphate in calcium base; 2) Positive control: 1450 ppm F as sodium fluoride in silica base	Negative control: Non-fluoride toothpaste in calcium base	At 6 months (clinical hardness): Improved: 61.7% (experimental), 56.0% (positive), 27.0% (negative); Worse: 0.7% (experimental), 9.0% (positive), 18.2% (negative); ECM at 6 months: End values: 7.9 MΩ (experimental), 1.9 MΩ (positive), 387 kΩ (negative); Differences between experimental vs. negative ($p<0.001$), positive vs. negative ($p<0.001$), and experimental vs. positive ($p=0.03$) were statistically significant	Both fluoride-containing dentifrices were significantly better than non-fluoride at arresting and reversing primary root caries lesions. The arginine-containing dentifrice (1.5% arginine + 1450 ppm F) provided significantly greater root caries benefit than fluoride alone (1450 ppm F), as demonstrated by both clinical hardness measures and ECM assessments	Fluoride-free placebo toothpaste

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Table 1 (Continued).

Author, Year [Ref.]	Study Design, Duration	Population: Number of Participants per Group	Method of Caries Detection	Test Products	Comparator Product	Main Results	Main Conclusions	Active Substance
Murray et al, 1980[30]	Double-blind, randomized controlled clinical trial with three parallel groups, 3 years	Group 1: n=367; Group 2: n=356; Group 3: n=383 (children present at all examinations)	Clinical examination (Ash No. 6 probe, plane mouth mirror, compressed air drying) and bitewing radiographs (taken annually)	Group 1: Low abrasivity paste (RDA 60) containing 0.8% sodium monofluorophosphate; Group 2: Conventional abrasivity paste (RDA ~110) containing 0.8% sodium monofluorophosphate	Group 3: Low abrasivity (RDA 60) non-fluoride paste (placebo)	3-year net DMFS increments (clinical and radiographic combined): Group 1: 4.22; Group 2: 4.72; Group 3: 6.43. Differences between Groups 1 vs 3 and Groups 2 vs 3 were highly significant (P<0.001). Group 1 vs Group 2 difference (11%) was not statistically significant	Both fluoride dentifrices (0.8% sodium monofluorophosphate) significantly reduced caries compared to placebo (34% and 27% reduction respectively). Reducing abrasivity had no statistically significant effect on caries inhibition, though numerical superiority was observed. Reducing abrasivity had no meaningful effect on oral hygiene or gingivitis	Fluoride-free placebo toothpaste
Obersztyn, et al, 1984[31]	Randomized controlled trial, non-blind, 18 months	Test group: n=787; Control group: n=499	Visual examination using sharp explorers and dental mirrors, without radiographs; sticky fissures regarded as carious lesions; teeth dried with compressed air	Amine fluoride gel (Elmex gel containing amine fluorides 297 and 335 and NaF at concentrations 0.231% F^-, 0.019% F^- and 1% F^-, respectively); used once weekly for 5 min, unsupervised.	Fluoride-free dentifrice (Nivea) used twice daily	Mean DMFS increments over 18 months: Test group: 2.9; Control group: 4.9. DMFS increment reduction: 41%. At 6 months: Test 1.2 vs Control 1.9; At 12 months: Test 2.1 vs Control 3.5	The unsupervised, once weekly use of amine fluoride gel in Polish cadets reduced the mean DMFS increment over 18 months when tested against a fluoride-free dentifrice. Amine fluoride gel was an effective caries prophylactic agent, required less time and was not as personnel-dependent as previously described SnF_2-caries prophylaxis programs	Fluoride-free placebo toothpaste

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Paszynska et al, 2021[32]	Double-blinded randomized controlled trial (RCT), non-inferiority design, 1 year	ITT analysis: n=207 total (test group n=88, control group n=89); Per protocol: n=177 total	ICDAS (International Caries Detection and Assessment System) ≥ code 1 on primary dentition	Fluoride-free toothpaste with microcrystalline hydroxyapatite, used three times daily	Toothpaste with fluoride	Increase in caries ICDAS ≥ code 1 per tooth observed in 72.7% of hydroxyapatite group vs. 74.2% of fluoride group (difference: −1.4%). One-sided upper 95% CI for difference was 9.8%, below the non-inferiority margin of 20%	Daily use of toothpaste with microcrystalline hydroxyapatite is not inferior to fluoride toothpaste for enamel caries progression prevention in primary dentition of children. This was the first RCT to demonstrate this finding	Hydroxyapatite
Paszynska et al, 2023[33]	Two-centered, double-blinded, randomized, active-controlled parallel-group study (non-inferiority trial), 18 months	PP population: Test n=84, Control n=87; ITT population: Test n=94, Control n=95	DMFS index (Decayed Missing Filled Surfaces); DIAGNOcam (laser diode near-infrared light transillumination); Plaque Control Record (PCR)	Fluoride-free hydroxyapatite toothpaste (10% hydroxyapatite)	Sodium fluoride toothpaste (1,450 ppm fluoride)	PP analysis: No increase in DMFS in 89.3% (test) vs. 87.4% (control). Upper limit of one-sided 95% CI for difference = 6.84%, below non-inferiority margin of 20%. No significant difference in NCL or PCR between groups.	Hydroxyapatite toothpaste was non-inferior to fluoride toothpaste for caries prevention. Hydroxyapatite proven to be a safe and efficient anticaries agent in oral care for adults aged 18–45 years	Hydroxyapatite
Schlagenhauf et al, 2019[34]	Randomized controlled trial, double-blind, multi-center, non-inferiority design, 24 weeks	ITT: 74 HAP group, 73 fluoride control group; PP: 64 HAP group, 69 fluoride control group	ICDAS-II (International Caries Detection and Assessment System) on vestibular surfaces of teeth 15–25	Fluoride-free dentifrice containing 10% microcrystalline hydroxyapatite (HAP) (Karex GmbH, Bielefeld, Germany)	Commercially available fluoridated toothpaste containing 1400 ppm fluoride (amine fluoride/ stannous fluoride - meridol Zahnpasta; CP GABA GmbH, Hamburg, Germany)	Primary outcome (ICDAS ≥code 1): HAP group 56.8% (ITT) and 54.7% (PP) vs fluoride control 60.9% (ITT) and 61.6% (PP). Non-inferiority demonstrated (upper 95% CI limits: PP 8%, ITT 9%, both ≤20%). Secondary outcome (ICDAS ≥code 2): HAP 25.7% (ITT) and 23.4% (PP) vs fluoride 32.9% (ITT) and 34.8% (PP). No significant differences in plaque index or gingival index between groups	The impact of regular use of a fluoride-free microcrystalline HAP dentifrice on caries progression is not significantly different from the use of a 1400 ppm fluoride toothpaste. HAP dentifrice was non-inferior to fluoride control for preventing enamel caries lesions in orthodontic patients	Hydroxyapatite

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Table 1 (Continued).

Author, Year [Ref.]	Study Design, Duration	Population: Number of Participants per Group	Method of Caries Detection	Test Products	Comparator Product	Main Results	Main Conclusions	Active Substance
Stookey et al, 1975[35]	Randomized controlled trial, 2×2 factorial design (dentifrice type × prophylaxis), 27 months	Group 1 (NaF + prophylaxis): N=162 baseline, 105 at 27 months; Group 2 (Control + prophylaxis): N=162 baseline, 102 at 27 months; Group 3 (NaF, no prophylaxis): N=166 baseline, 118 at 27 months; Group 4 (Control, no prophylaxis): N=165 baseline, 116 at 27 months	Clinical examination (visual and tactile criteria with portable lights, compressed air, mouth mirrors, sharp explorers) + 7-film bitewing radiographs; combined clinical and radiographic findings	Sodium fluoride dentifrice (0.9% NaF = 1,000 ppm F) with zirconium silicate and high beta-phase calcium pyrophosphate as cleaning/polishing agent	Nonfluoride dentifrice with dicalcium phosphate as abrasive system	Examiner 1: 24.3% DMFT reduction, 24% DMFS reduction (combined groups); Examiner 2: 21% DMFT reduction, 26.4% DMFS reduction (combined groups). With prophylaxis: 35.1–37.2% DMFS reduction; without prophylaxis: 12.3–13.8% DMFS reduction	Sodium fluoride dentifrice resulted in significant dental caries reductions of approximately 24–26% (DMFS). Initial prophylaxis enhanced the effectiveness of the NaF dentifrice (36–37% reduction) but had no effect on caries incidence per se	Fluoride-free placebo toothpaste
Yin et al, 2013[36]	Randomized, controlled, double-blind clinical trial, 6 months	Experimental: N=141; Positive control: N=134; Negative control: N=137 (Total: 412 subjects completed; aged 50–70 years, mean 64±4.1 years; 53.6% female)	1) Visual/tactile assessment of lesion hardness using sharp probe (No. 5 Sharp Explorer); 2) Electrical Caries Monitor (ECM IV) measuring electrical resistance	1) Experimental: 1.5% arginine + 1450 ppm F as sodium monofluorophosphate in calcium base; 2) Positive control: 1450 ppm F as sodium fluoride in silica base	Negative control: Non-fluoride toothpaste in calcium base	At 6 months (hardness): 61.7%, 56.0%, 27.0% improved; 0.7%, 9.0%, 18.2% worsened ($p<0.001$ for both fluoride groups vs. negative; $p=0.006$ for experimental vs. positive). At 6 months (ECM): Mean resistance values 7.9 MΩ, 1.9 MΩ, 387 kΩ for experimental, positive, negative groups ($p<0.001$ for both fluoride groups vs. negative; $p=0.033$ for experimental vs. positive)	Both fluoride dentifrices significantly better than non-fluoride at arresting and reversing root caries. The arginine-containing dentifrice provides significantly greater root caries benefit than 1450 ppm fluoride alone	1.5% Arginine

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Yin et al, 2025[37]	Randomized controlled trial based, double blind, 3-arm, parallel group design, 2 years	1.5% Arginine: N=2002, 8% Arginine: N=1998, 0.32% SF: 2000 (total= 6000 children 10–14 years≥ 2 active caries lesions with scores ≥ 2 ICDAS)	Examination by trained personnel, primary efficacy outcome was incremental DMFS and DMFT caries indices scores after 2y	1.5% arginine and 8% arginine toothpaste	0.32% fluoride toothpaste	After 2 y, the 8.0% arginine– containing dentifrice demonstrated a statistically significant reduction of 26.0% in DMFS scores (−0.16; 95% CI, −0.22 to −0.10; P <0.001) and 25.3% in DMFT scores (−0.17; 95% CI, −0.24 to −0.11; P <0.001) versus control. No statistical difference was measured between the 1.5% arginine–containing dentifrice and control in DMFS (−0.01; 95% CI, −0.07 to 0.05; P =0.819) and DMFT (−0.01; 95% CI, −0.07 to 0.05; P =0.739).	Dentifrice containing 8.0% arginine showed a statistically significant reduction in caries incidence versus the NaF control, while the 1.5% arginine dentifrice showed equivalence to the NaF control regarding caries reduction. This clinical trial confirms that arginine dentifrices are effective alternatives to fluoride in providing anticaries protection.	1.5% and 8% Arginine
Zacherl, 1981[38]	Double-blind, randomized, placebo-controlled clinical trial (3:3:1 allocation ratio), 3 years	Baseline: Placebo n=438; Stannous fluoride n=1,328; Sodium fluoride n=1,327. Completing 3 years: Placebo n=254; Stannous fluoride n=760; Sodium fluoride n=740	Visual-tactile clinical examination using Radike criteria with artificial light, mouth mirrors, compressed air, and explorers; bitewing radiographs (0–7 films per subject)	0.243% sodium fluoride dentifrice with silica abrasive (1,100 ppm total fluoride, 95–100% available fluoride compatibility)	Positive control: 0.4% stannous fluoride dentifrice with calcium pyrophosphate abrasive (1,000 ppm total fluoride); Placebo: nonfluoride calcium pyrophosphate dentifrice	After 3 years: Sodium fluoride vs. stannous fluoride: 24.2% reduction in DMFT, 22.6% reduction in DMFS (both p<0.05). Sodium fluoride vs. placebo: 40.5% reduction in DMFT, 40.7% reduction in DMFS (both p<0.05). Stannous fluoride vs. placebo: 21.5% reduction in DMFT, 23.4% reduction in DMFS (both p<0.05)	The sodium fluoride-silica abrasive dentifrice is superior to the stannous fluoride-calcium pyrophosphate dentifrice in preventing dental caries. Both fluoride dentifrices showed significant caries reduction compared to placebo	Fluoride-free placebo toothpaste

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hydroxyapatite toothpaste for children (Health Canada; Natural Product Number: 80117093) offers the following oral health effects, as validated by the *Canadian Dental Association*: "Cavity protection" and "Helps rebuild tooth enamel". Two recent systematic reviews and meta-analyses on the clinical evidence for fluoride-free hydroxyapatite toothpastes in caries prevention have been published.[17,18] Both reviews conclude that hydroxyapatite prevents caries and remineralizes early lesions, indicating that it is a safe and effective alternative to fluoride across all age groups.

For a recent comprehensive meta-analysis that includes all three clinical trials on hydroxyapatite identified in the present review, we refer to Pawinska et al[18] To the best of the authors' knowledge, the clinical trial on arginine has not yet been included in a meta-analysis, presumably due to its recent publication (August 2025).

The risk-of-bias analysis was performed for the four clinical trials that demonstrated caries-preventive efficacy of fluoride-free actives. The risk-of-bias analysis demonstrates an overall low risk of bias for the arginine trial and the three hydroxyapatite trials (Figure 2), supporting the methodological quality of these studies.

Arginine and hydroxyapatite have different modes of action in caries prevention.

Arginine contributes to caries prevention because it is metabolized by arginolytic bacteria via the arginine deiminase system to produce ammonia (NH_3), which increases plaque pH and thus reduces its acidity and demineralizing potential.[20,45,46] However, because arginine provides neither calcium nor phosphate, it cannot directly remineralize early caries lesions. Arginine has a high safety profile, as it is a naturally occurring amino acid in the human body.[47]

Hydroxyapatite, on the other hand, directly remineralizes early caries lesions and forms a protective layer on the enamel surface.[48–53] Additionally, hydroxyapatite acts as a calcium and phosphate reservoir within dental plaque and can increase plaque pH due to its buffering properties.[54] The overall safety of calcium phosphates, including hydroxyapatite, has been demonstrated, as shown in a comprehensive review article.[55]

The present review also identified 11 studies in which fluoride-free toothpastes were used as placebo controls (Table 1). It is important to note that the inferior caries prevention observed in these studies, compared with fluoridated toothpastes, can likely be attributed to the use of simple abrasive formulations devoid of active anti-caries agents. The rationale for the use of these placebo toothpastes was to isolate and evaluate the purely mechanical effects of the toothpaste; accordingly, the formulations were intentionally not designed as anti-caries toothpastes and did not include caries-preventive ingredients. This contrasts with other studies that investigated active alternatives (arginine or hydroxyapatite), which were formulated to deliver anti-caries benefits (Table 1).

In general, children, in particular, have advantages when using fluoride-free toothpastes, because swallowing does not pose a fluorosis risk.[7,8] Moreover, fluoridated toothpastes for children must be used in very small amounts (up to two years: a grain-of-rice amount; ages 2–6: a pea-sized amount),[56] which significantly limits tooth-cleaning efficacy and might diminish caries prevention.[57] Fluoride-free toothpastes, on the other hand, can be applied in larger amounts, significantly increasing their cleaning efficacy.[57] Another group that may benefit from fluoride-free oral care products is pregnant women, since fluoride in drinking water has been reported to show neurotoxic effects on offspring.[6] Beyond these groups, people of all ages may benefit from fluoride-free oral care products. Fluoride has been shown to be cytotoxic to gingival fibroblasts in an in vitro study, leading to the conclusion that fluoride concentration should be reduced (though this would likely diminish its efficacy) or that suitable substitutes for fluoride should be considered.[42]

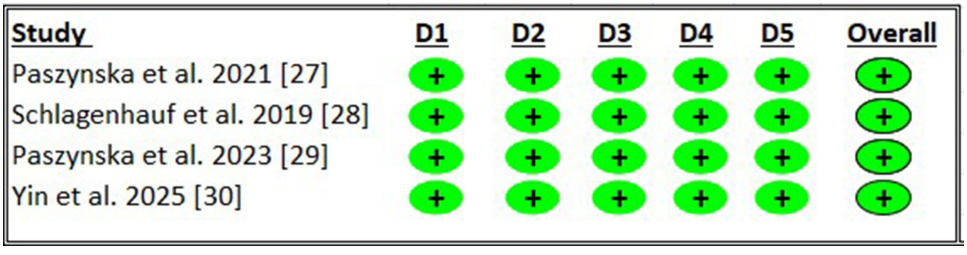

Figure 2 Risk of Bias (RoB) analysis of the included clinical trials according to Cochrane RoB 2.[23] Green plus indicating low risk of bias. D1= Randomisation process, D2 = Deviations from the intended interventions, D3= Missing outcome data, D4 = Measurement of the outcome and D5= Selection of the reported result.

Another important consideration is the publication date of the trials on hydroxyapatite and arginine (Table 1). Because these studies were published recently, they were conducted according to contemporary clinical trial standards. By contrast, most trials evaluating the caries-preventive effect of fluoridated toothpastes versus placebo toothpastes are considerably older (see Walsh et al for details).[4]

Strengths and Limitations

The literature search included only clinical toothpaste trials that mentioned "fluoride-free" or similar terms in the title or abstract (see Section 2.2 for details), which avoids preselecting specific active ingredients and ensures an objective literature search. On the other hand, studies describing toothpastes solely by their active ingredients without explicitly stating they are fluoride-free could have been overlooked. Furthermore, studies that note the absence of fluoride only in the full text may have been missed. Also, the PRISMA checklist was not followed completely eg. no protocol was prepared in advance. The risk-of-bias analysis was performed only for clinical trials demonstrating caries-preventive efficacy of fluoride-free toothpaste agents, and no meta-analysis was conducted. For meta-analyses on fluoride-free hydroxyapatite toothpastes, we refer to.[17]

Outlook – New Approaches in Caries Prevention

In general, there has been a well-documented improvement and evolution of toothpaste technology.[40] Due to the increased global interest in fluoride-free toothpastes, there is a lot of ongoing research in the field of fluoride-free anti-caries agents. Recent clinical trials have analyzed fluoride-free hydroxyapatite toothpastes[32,34,39] and fluoride-fee arginine toothpastes[37] in the field of caries prevention. Besides these two agents, there are various other promising agents, including calcium compounds such as calcium hypophosphite,[58] antimicrobial peptides,[59] self-assembling peptides such as P11-4,[60] and probiotics.[61] These approaches, as well as others, are promising for use in toothpastes and are candidates for further investigation in future clinical trials.

Conclusions

This review shows that clinical studies have demonstrated the caries-preventive efficacy of certain fluoride-free active ingredients in toothpastes. Furthermore, recent research has identified additional promising fluoride-free agents that could be incorporated into toothpaste formulations and merit evaluation in future clinical trials.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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