

INPLASY

INPLASY2026100122

doi: 10.37766/inplasy2026.10.0122

Received: 29 October 2026

Published: 29 October 2026

Corresponding author:

Wensi Xiong

14780195010@163.com

Author Affiliation:

Meishan Center for Disease Control and Prevention.

Effects of low-fluoride toothpaste combined with natural active ingredients for preventing dental caries in children: a systematic review and network meta-analysis

Xiong, W; Xie, YK.

ADMINISTRATIVE INFORMATION**Support** - No support.**Review Stage at time of this submission** - Data analysis.**Conflicts of interest** - None declared.**INPLASY registration number:** INPLASY2026100122**Amendments** - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 29 October 2026 and was last updated on 29 October 2026.**INTRODUCTION**

Review question / Objective To compare the effectiveness and safety of low-fluoride toothpaste combined with natural active ingredients versus low-fluoride toothpaste alone, standard fluoride toothpaste, fluoride-free or placebo toothpaste, and other active toothpaste formulations for preventing dental caries in children. PICOS: P-children and adolescents aged 0-18 years; I-low-fluoride toothpaste plus a natural active ingredient; C-low-fluoride alone, standard fluoride, fluoride-free/placebo, natural-ingredient toothpaste without fluoride; O-carries increment (dmfs/DMFS or dmft/DMFT) at 12 months or longer; S-RCTs, cluster-RCTs, and quasi-RCTs..

Rationale Fluoride toothpaste is the cornerstone of caries prevention in children, but fluoride concentration must be balanced against dental fluorosis risk in younger children. Natural or biologically derived active ingredients (xylitol, arginine, CPP-ACP, hydroxyapatite, propolis, herbal extracts, tea polyphenols, chitosan) have

been proposed as adjuncts that may enhance remineralization or reduce cariogenic biofilm while allowing lower fluoride exposure. Existing reviews examine fluoride concentration, remineralizing agents, or individual additives separately. A network meta-analysis can compare multiple toothpaste formulations and estimate their relative effects when direct head-to-head trials are sparse..

Condition being studied Dental caries prevention in children and adolescents. Caries increment is measured as dmfs/DMFS or dmft/DMFT increment over a follow-up of at least 12 months..

METHODS

Search strategy Databases: PubMed/MEDLINE, Embase (Ovid), Cochrane CENTRAL, Web of Science, Scopus, CNKI, Wanfang, VIP, SinoMed, ClinicalTrials.gov, WHO ICTRP. Search terms combine: (child OR pediatric OR preschool OR adolescent OR infant) AND (caries OR dental caries OR tooth decay OR demineralization OR remineralization) AND (toothpaste OR dentifrice OR

tooth brushing) AND (fluoride OR low fluoride OR sodium fluoride OR monofluorophosphate OR amine fluoride) AND (xylitol OR arginine OR hydroxyapatite OR nano-hydroxyapatite OR CPP-ACP OR casein phosphopeptide OR propolis OR herbal OR neem OR clove OR tea polyphenol OR chitosan OR bioactive glass OR natural) AND (randomized OR randomised OR trial OR clinical trial)..

Participant or population Children and adolescents aged 0 to 18 years. The primary analysis focuses on children younger than 12 years; preschool children are analysed separately where the network permits, because fluoride ingestion and fluorosis risk differ by age..

Intervention Toothpaste or dentifrice formulations used for routine toothbrushing, including: low-fluoride toothpaste alone; low-fluoride toothpaste plus a natural active ingredient (xylitol, arginine, hydroxyapatite, CPP-ACP, propolis, herbal extracts, tea polyphenols, chitosan, bioactive glass); standard fluoride toothpaste; and standard fluoride toothpaste plus a natural active ingredient..

Comparator Low-fluoride toothpaste alone; standard fluoride toothpaste; fluoride-free or placebo toothpaste; natural active ingredient toothpaste without fluoride..

Study designs to be included Randomized controlled trials, cluster-randomized controlled trials, and quasi-randomized trials. Cluster trials are included only when the design effect can be accounted for or cluster-adjusted estimates are reported..

Eligibility criteria Inclusion: RCTs, cluster-RCTs, or quasi-RCTs comparing eligible toothpaste formulations in children and adolescents aged 0-18 years; caries increment reported at 12 months or longer (shorter follow-up accepted for secondary remineralization outcomes); any language, any country. Exclusion: non-randomized designs without a comparison arm; adults only; interventions not delivered as toothpaste/dentifrice; no extractable caries outcome data..

Information sources PubMed/MEDLINE, Embase (Ovid), Cochrane CENTRAL, Web of Science, Scopus, CNKI, Wanfang, VIP, SinoMed; trial registries (ClinicalTrials.gov, WHO ICTRP); reference lists of included studies and relevant reviews; contact with study authors for missing data..

Main outcome(s) Caries increment after at least 12 months of follow-up, expressed as dmfs/DMFS or dmft/DMFT increment; surface-level indices preferred over tooth-level indices. Effect measures: mean difference (same scale) or standardized mean difference (combined scales); risk ratio or odds ratio for binary caries incidence..

Additional outcome(s) Incidence of new caries lesions; change in non-cavitated or early caries lesions; caries arrest or regression; plaque index; mutans streptococci or salivary markers; adverse events; dental fluorosis; acceptability/adherence..

Data management Two reviewers independently screen titles/abstracts and full texts; disagreements are resolved by consensus or a third reviewer. Data are extracted into a standardized form (study characteristics, arm-level sample size, caries increment with SD/SE, new caries events, fluoride concentration, follow-up duration, cluster parameters). Records are managed in EndNote; extracted data are stored in structured spreadsheets..

Quality assessment / Risk of bias analysis RoB 2 for individually randomized trials; RoB 2 cluster-randomized extension for cluster trials. Two reviewers assess risk of bias independently; disagreements are resolved by consensus..

Strategy of data synthesis Random-effects network meta-analysis with treatment nodes defined by fluoride concentration and natural active ingredient class. Network geometry is inspected; disconnected interventions are summarised narratively or analysed pairwise. Ranking is presented via SUCRA/P-score but interpreted against effect estimates and certainty. Pairwise meta-analysis is used for direct comparisons. Inconsistency is assessed by node-splitting or loop-specific methods; design-by-treatment interaction where network size permits..

Subgroup analysis Age group and dentition (primary/mixed/permanent); baseline caries risk; water fluoride exposure; supervised versus unsupervised brushing; follow-up duration..

Sensitivity analysis Excluding quasi-randomized trials; excluding cluster trials; combining sparse nodes by mechanism of action; alternative effect measures; fixed-effects network meta-analysis..

Language restriction None.

Country(ies) involved China.

Other relevant information This protocol is registered retrospectively; screening and data extraction were completed before registration, following the transparency-oriented approach recommended by Canellas and Borges (<https://doi.org/10.1186/s13643-026-03278-8>). Search dates: PubMed 2026-06-05; Embase 2026-06-05; Cochrane CENTRAL 2026-06-05.

Keywords dental caries; children; toothpaste; fluoride; network meta-analysis.

Dissemination plans Publication in a peer-reviewed dental journal; reporting follows PRISMA 2020 and PRISMA-NMA..

Contributions of each author

Author 1 - Wensi Xiong - Conceived the review and drafted the manuscript.

Email: 14780195010@163.com

Author 2 - Yanke Xie - Performed screening, extraction, and risk of bias.

Email: x1562679419@163.com