Heliyon 5 (2019) e02850

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Review article

Effects of stabilized stannous fluoride dentifrice on dental calculus, dental plaque, gingivitis, halitosis and stain: A systematic review

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ARTICLE INFO

Keywords:
Dentistry
Stabilized stannous fluoride
Dental calculus
Dental plaque
Gingivitis
Halitosis
Stain

ABSTRACT

Objectives: The aim of the present systematic review was to examine the scientific evidence for the efficacy of stabilized stannous fluoride (SnF_2) dentifrice in relation to dental calculus, dental plaque, gingivitis, halitosis and staining.

Data and sources: Medline OVID, Embase.com, and the Cochrane Library were searched from database inception until June 2017. Six researchers independently selected studies, extracted data, and assessed methodological quality. A meta-analysis of the 6-month gingivitis studies was done. Risk of bias was estimated using a checklist from the Swedish Agency for Health Technology Assessment (SBU, 2018).

Study selection: Two studies on dental calculus, 21 on dental plaque and gingivitis, 4 on halitosis, and 5 on stain met the inclusion criteria. Risk of bias was high for the studies on dental calculus, halitosis, and stain, and varied for the dental plaque and gingivitis studies. Significant reductions in dental calculus and in halitosis were reported for the SnF_2 dentifrice; no differences in stain reduction were noted. A meta-analysis on gingivitis found better results for the SnF_2 dentifrice compared to other dentifrices, though the results of the individual trials in the meta-analyses showed a substantial heterogeneity.

Conclusions: The present review found that stabilized SnF_2 toothpaste had a positive effect on the reduction of dental calculus build-up, dental plaque, gingivitis, stain and halitosis. A tendency towards a more pronounced effect than using toothpastes not containing SnF2 was found. However, a new generation of well conducted randomized trials are needed to further support these findings.

Clinical relevance: Adding a SnF_2 toothpaste to the daily oral care routine is an easy strategy that may have multiple oral health benefits.

1. Introduction

In recent decades, awareness of the importance of oral health in relation to well-being and general health has grown [1]. Dental calculus, dental plaque, gingivitis, halitosis, and stain are all conditions of great concern in both objective and subjective perspectives. Gingivitis, inflammation of the gum, is one of the most common diseases in the world [2]. Prevalence is high and varies extensively due to assessment method, population, and age group [3, 4]. The primary causative factor of gingivitis is dental plaque, a biofilm formed by bacteria that have been colonizing on the teeth for a prolonged period of time [5, 6]. Plaque-induced gingivitis can be prevented with good oral hygiene, which includes regular tooth brushing and interproximal cleaning [7, 8]. Moreover, patient-administered mechanical plaque control is an effective preventive measure.

Tooth stain may be due to several factors, for example, coffee, tea, tobacco, and wine. If dental plaque is not removed, it may lead to calculus formation, halitosis, and eventually periodontal disease [9, 10]. Dental calculus forms when non-mineralized biofilms rich in oral bacteria become mineralized with calcium phosphate mineral salts [11, 12]. This mineralized biofilm may develop both supra- and sub-gingivally. The significance of dental calculus in the initiation and progression of periodontitis has been demonstrated [12]. Similar to gingivitis, bacterial plaque may also induce inflammation around dental implants, that is, peri-implant mucositis [13], which can develop into peri-implantitis.

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https://doi.org/10.1016/j.heliyon.2019.e02850
Received 8 May 2019; Received in revised form 23 July 2019; Accepted 8 November 2019
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Halitosis (bad breath, malodor) has a mean prevalence of 31.8 % [14] ranging from 1.5% to 100%, depending on how the condition has been assessed or defined [15]. The degree of halitosis varies throughout the day, with higher levels often occurring in morning breath. The etiological factors are primarily related to the bacterial degradation of proteins, which creates high concentrations of volatile sulphur compounds [16]. Halitosis may also originate from pathological conditions such as throat infections, tonsillitis, and lung disease [16]. Today, subjective and objective methods are available for assessing VSCs in exhaled air. Halitosis treatment is focused on oral hygiene, in particular tooth brushing, as well as tongue cleaning. Mouth rinses and dentifrices containing various active ingredients, such as metal salts, essential oils, and chlorhexidine have also been found to be effective in reducing VSC levels [17].

In home dental care, the most widely used method to clean teeth efficiently is tooth brushing with dentifrices [18, 19]. Today, numerous commercial dentifrices are available, and they are composed of different active ingredients, each with a special function, for example, anti-calculus agents, anti-bacterial agents, and anti-cavity agents. Fluorides have, in general, been considered the most important active ingredient in a toothpaste. Over the years, various fluoride formulations have been used, for example, sodium fluoride (NaF), sodium monofluorophosphate (SMFP), amine fluoride, and stannous fluoride (SnF_2). The first toothpaste with a clinically proven anti-cavity effect contained SnF_2 and was introduced in the 1950s [20]. However, the SnF_2 formula had some limitations, such as the potential to cause extrinsic tooth staining.

Aside from purported effects on gingivitis, caries, dental plaque, halitosis, and stain, dentifrices with an anti-calculus effect have been a focus of interest for many years. The first toothpaste to have a clinically proven anti-calculus effect was introduced in 1985 and contained sodium pyrophosphate as the anti-calculus ingredient [21].

A longer chain variant of pyrophosphate, sodium hexametaphosphate (SHMP) with increased anti-staining and anti-calculus effects, was added to dentifrice formulations [22, 23]. This addition overcame the staining problem caused by SnF_2.

Since SnF_2 is still considered to be superior compared to other fluoride compounds, a literature review for evidence of its effect on various oral conditions is valuable. The aim of this review was to systematically examine the scientific evidence for the efficacy of stabilized SnF_2 dentifrice in relation to dental calculus, dental plaque, gingivitis, halitosis, and stain.

2. Material and methods

2.1. Eligibility

A Population/Problems, Intervention, Comparison/Control, Outcome (PICO) process was used to develop the inclusion criteria: studies must be *in vivo* or *in situ*; the publication language, English; and publication year 1990 or later. Inclusion criteria concerning intervention, comparisons and outcome variables were specified for each category:

2.1.1. Population/problem

Individuals with, or at risk for, one or more of five dental problems: dental calculus, dental plaque, gingivitis, halitosis, and stain.

2.1.2. Intervention

Tooth cleaning with a manual or electric tooth brush and a stabilized SnF_2 dentifrice, or with experimental slurries containing stabilized SnF_2.

2.1.3. Comparison

Tooth brushing twice daily with another fluoridated or non-fluoridated dentifrice, a placebo, or no treatment.

2.1.4. Outcome

Dental calculus: the Volpe-Manhold Calculus Index [24]; dental plaque: various plaque indices [25, 26, 27]; gingivitis: the Gingival Index [28, 29], the Modified Gingival Index [30], the Gingival Bleeding Index [31], or the Bleeding Index [32]; halitosis: a reduction in volatile sulphur compounds [33]; and stain: the Lobene stain index [34].

Table 1. Inclusion and exclusion criteria.

Inclusion criteria
Randomized controlled trials (RCTs)
Controlled clinical trials (CCTs)
In the control group: no limitation
In the test group: stannous fluoride (SnF_2) or combinations: 0.454 % SnF2 0.454 % SnF2 + SHMP (sodium hexametaphosphate) 0.454 % SnF2 + 5% sodium polyphosphate 0.454 % SnF2 + calcium pyrophosphate 0.454 % SnF_2 + 350 ppm NaF (sodium fluoride)
Exclusion criteria
Articles published before 1990
Only abstract/Erratum
Reviews
Animal studies
In vitro studies
No control group
No relevant outcome variable
Mouth rinse or gel
Ionized toothbrush or laser in the treatment with SnF_2
SnF_2 + 5% KNO_3 (potassium nitrate)
SnF_2 + AmF (amine fluoride)
$SnCl_2$ (stannous chloride)

2.2. Exclusion criteria

Duplicates, reviews, *in vitro* studies, animal studies, and non-controlled studies were omitted. Other exclusion criteria were *(i)* the test dentifrice contained stannous chloride or SnF_2 in combination with potassium nitrate or amino fluorides, *(ii)* the SnF_2 formulation was applied in a gel, *(iii)* ionic or laser toothbrushes were used, *(iv)* a mouthwash was used (Table 1), *(v)* outcome data regarding dental plaque, gingivitis, stain, or halitosis were unclear.

2.3. Literature search strategy

We searched Medline OVID (including Epub Ahead of Print, In-Process & Other Non-Indexed Citations), Embase.com, and the Cochrane Library using medical subject headings (MeSH) associated with SnF_2, dentifrices, the dental problems being assessed in this review, and related dental problems. The MeSH terms identified in Medline were adapted to Embase and Cochrane. We also used free-text terms and, when appropriate, truncated and/or combined the search terms with proximity operators.

The following search terms were used: gingivitis, dental plaque, dental plaque index, plaque control, gingival hemorrhage, bleeding on probing, biofilms, inflammation, dental calculus, anti-calculus, calcificat, tartar, dental, tooth, teeth, tooth discolorations, stain, halitosis, malodor odor, breath, fetor oris, fetor ex, or foetor, periodontitis, aggressive periodontitis, chronic periodontitis, periodontal pocket, periapical abscess, periapical granuloma, peri-implantitis, tin fluorides, stannic, fluoride, difluoride, tetrafluoride, stannofluoride, snf, dentifrices, paste, and toothpaste; the free-text terms we used were crest pro health, crest gum care, and crest plus gum care.

Information specialists at the university library at Karolinska Institutet in Stockholm searched from database inception until January 2018 (dental calculus, dental plaque/gingivitis, stain, halitosis) according to the PRISMA flow chart (http://prisma-statement.org/). The authors also

conducted searches by hand after reading the reference lists of retrieved full-text papers to identify additional articles.

2.4. Study selection

The reviewers formed pairs. Each pair reviewed one of the problem categories: dental calculus, dental plaque, gingivitis, halitosis, and stain. Each of the reviewers in a pair independently screened all titles and abstracts for a category to identify potentially eligible studies. The reasons for excluding a study were noted (Table 1). Studies that met the inclusion criteria were obtained in full text and assessed for eligibility. When the two reviewers disagreed, consensus was reached by discussion. The reviewers were not blinded to authorship or journal. Figure 1 summarizes the literature search and article selection in a flow chart.

2.5. Data extraction

Data were extracted and tabularized from all studies meeting the inclusion and exclusion criteria (Table 1). The present review reports only baseline and final results. Mean values and standard deviations (SDs) or standard errors (SEs) were extracted from the studies.

2.6. Risk of bias assessment

Each reviewer in a pair independently scored the methodological quality of the included studies. Quality was rated using a risk bias assessment checklist developed by the Swedish Agency for Health Technology Assessment [35]. The SBU risk bias checklist is similar to the Cochrane checklist (http://www.cochrane.org/). In short, selection bias, performance bias, detection bias, attrition bias, and reporting bias were rated. Based on this information, risk of bias was judged as low, medium, or high.

2.7. Data analysis

The outcome of the intervention compared to placebo was of interest for estimating treatment efficacy. Since few studies were available to form the same pairwise comparisons, a random-effect meta-analysis was applied only for 6-month gingivitis studies. All SE values were recalculated into SD using the formula $SD = SE \times \sqrt{N}$. Since some studies used different indices to measure gingivitis the means and SDs of assessments of gingival inflammation reported at 6 months were used to estimate the standardized mean difference (SMD) and 95% confidence interval (95% CI).

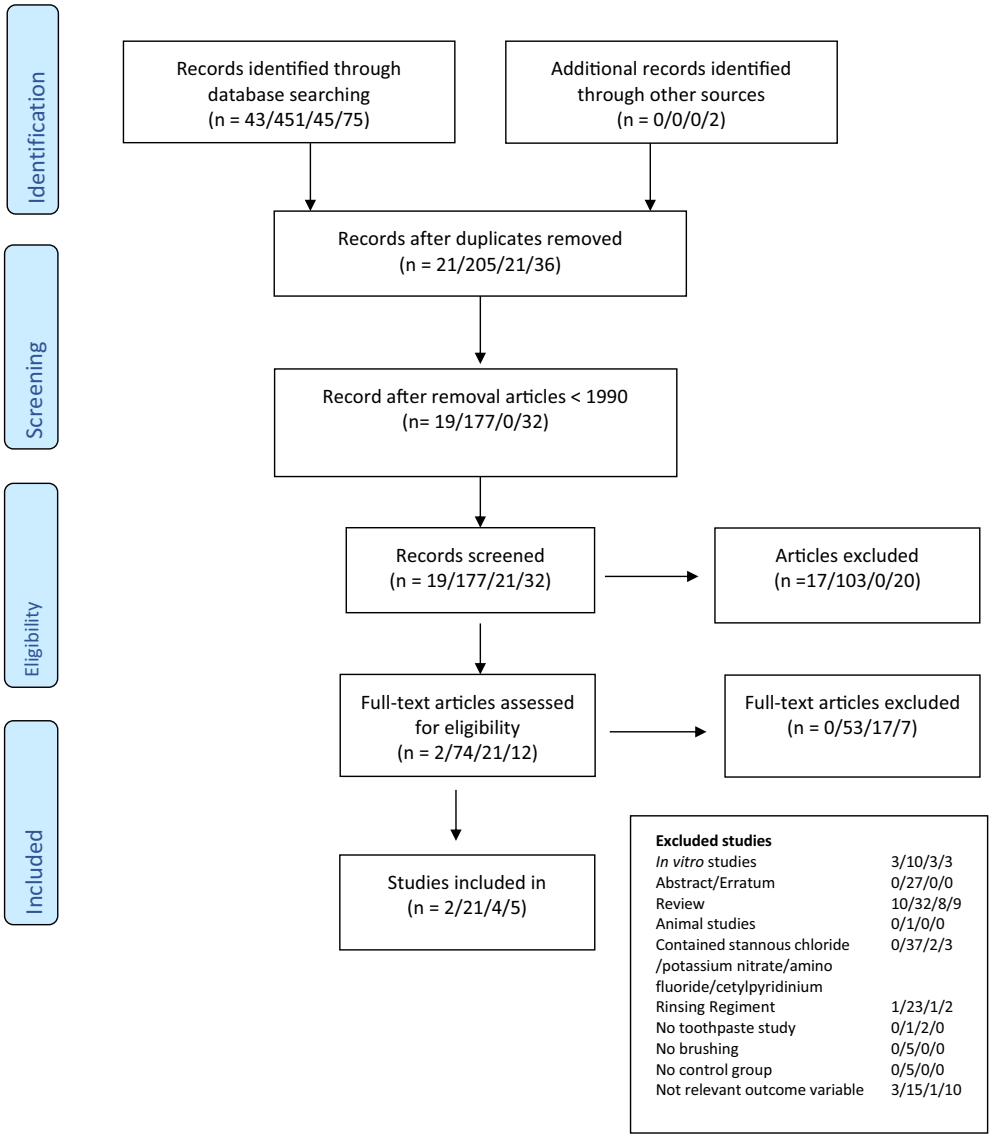

Figure 1. Flow chart presenting the literature search for dental calculus, dental plaque/gingivitis, halitosis and stain. (n = dental calculus/dental plaque + gingivitis/halitosis/stain).

Heterogeneity was quantified using I^2 and tested using Cochran's Q statistic. A probability level of $P < 0.05$ was considered significant.

3. Results

The literature search identified 42 articles referring to dental calculus, 451 to dental plaque and gingivitis, 45 to halitosis, and 75 to stain (Figure 1). After duplicates were excluded, 279 abstracts remained and were screened. Two papers on dental calculus, 21 on dental plaque/gingivitis, 4 on halitosis, and 5 on stain were reviewed in full text. Hand searching yielded no additional articles.

3.1. Dental calculus

The two included studies (Table 2) were published between 2005 and 2007. Both were double-blinded, randomized, and parallel-grouped 6-month trials representing 222 participants (age range 19–63 y) with 113 patients in test groups and 109 in control groups. The test toothpaste in both studies was 0.454% SnF_2 + SHMP. One study used a positive control (0.243% NaF +0.3% triclosan; [36], and one a negative (0.243% NaF; [37]. After 6 months, the Volpe-Manhold Calculus Index showed 55%–56% lower values for the test toothpaste than either of the positive or negative controls. The differences were statistically significant.

3.2. Dental plaque and gingivitis

Twenty-one full-text articles published between 1995 and 2013 met the inclusion criteria (Table 2). Table 3 presents the study design, characteristics, outcome variables, results, and risk of bias of the included studies in detail.

The studies included various study population such as patients, students, volunteers or subjects employed at dental product companies. The number of subjects varied greatly, ranging from 14 to 835 subjects. The 21 included studies comprised 3221 subjects. The duration of the studies ranged from 24 h to 2 years. One study had a duration of 2 years [38], 8 studies of 6 months [39, 40, 41, 42, 43, 44, 45, 46], one study of 4.5 months [47], five studies of 3–12 weeks [48, 49, 50, 51, 52], four studies of 14–17 days [53, 54, 55, 56], and two studies of 24 h [57, 58]. Most test products contained 0.454% SnF_2 + SHMP as the active ingredients. One study, however, contained sodium gluconate and two contained zinc citrate. The control dentifrices in 12 studies contained between 0.1% and 0.15% fluoride as sodium fluoride. Eight trials also included 0.3% Triclosan (TCN) one trial included phenolics (Listerine) and Baking soda + Hydrogen peroxide and one trial included Chlorhexidine as a positive control.

Various indices were used to assess the presence and/or amount of plaque at the examinations. Two studies measured the percentage of surfaces harboring plaque in relation to the total number of tooth surfaces. Four studies [40, 41, 51, 52], assessed plaque according to the plaque index [26]; these studies reported a mean percentage reduction of 6.2% (range 1.6%–12%) for the SnF_2 dentifrice compared to a negative control. Six studies [42, 43, 44, 45, 46]; used the modified Quigley and Hein Index [25, 27] and reported a mean reduction in plaque of 15.3% (range 3.9%–25.8%) for the SnF_2 dentifrice compared to a negative control.

Gingival inflammation was assessed in 15 of the 21 studies (Table 2). Some used more than one index to measure the level of gingival inflammation. The mean reduction in gingival inflammation, registered as mean GI change, was 17.2% (range 5.3%–25.8%) greater in the SnF_2 groups than in the sodium fluoride groups The reduction in percentages

Table 2. Characteristics of included studies on dental calculus.

Authors	Study design	Study population	Intervention (I)	Control (C)	Treatment/	Outcome	Comments	Risk
(year)	Methods	Number (gender)	Toothpaste	Positive/negative	brushing			of bias
	Duration	Age (range)						
		Country						
Schiff et al	randomized	n=80 (49 male/31 female)	I: 0.454% SnF2 + SHMP	C: 0.243% NaF + 0.3% TCN	Brushing twice	BL:	No drop outs	High
2005	double-blind	27.5 (19-45) yrs.		positive control	daily for for 1 min.	I: 16.66		
	parallel group					C: 15.88	Sponsored by	
		I=40					Procter & Gamble	
	V-MI	C=40				6M		
		USA				I: 5.41	Superior anti-calculus	
	6 M					C: 15.79	effect for SnF2	
						% treatment diff.		
						I vs C: 56% (p<0.0001)		
Winston et al	randomized	n=142 (70 male/72 female)	I: 0.454% SnF2 + SHMP	C: 0.243% NaF	Brushing twice	BL:	Drop-out=4	High
2007	double-blind				daily for for 1 min.	I: 27.21		
	parallel group	34 (19-63) yrs.		negative control		C: 27.84	Sponsored by	
							Procter & Gamble	
	V-MI	USA				6M:		
						I: 9.27	Superior anti-calculus	
	6 M					C: 20.78	effect for SnF2	
						% treatment diff.		
						I: vs C 55 (p<0.001)		

BL (baseline), I (intervention), C (control), NaF (Sodium fluoride), SnF2 (Stannous fluoride), TCN (Triclosan), SHMP (Sodium hexametaphosphate), V-MI (Volpe-Manhold index).

Table 3. Characteristics of included studies on dental plaque and gingivitis.

Authors (year)	Study design Methods Duration	Study population Number (gender) Age (range) Country	Intervention (I) Toothpaste	Control (C) Positive/negative	Treatment/ brushing	Outcome Plaque Index	Outcome Gingival Index	Outcome Gingival Bleeding	Comments	Risk of bias
Archila et al	randomized	n= 186	I: 0.454% SnF2 + SHMP	C: 0.234% NaF + 0.3% TCN	Baseline prophylaxis.		GI: (mean ±SD)	GB: (mean ±SD)	Drop out: n=11	Medium
2004	double-blind	I: n= 95 (33 male/ 63 female)		positive control	Brushing twice		BL:	BL:		
	parallel	30.7±10.0 (17-65) yrs.			daily for for 1 min.		I: 0.51±0.32	I: 40.0±25.7	Sponsored by	
	single center				Supervised twice-		C: 0.50±0.25	Cl: 39.8±20.3	Procter & Gamble	
		C: n= 91 (30 male/ 61 female)			daily 3 days/week					
	GI: (Löe & Silness 1963)	29.4±9.1 (30 male/ 61 female)					3M (mean ±SE)	3 M (mean ±SE)		
	GB: Gingival Bleeding						I: 0.18±0.01	I: 13.9±1.05		
	(no of sites)	USA					C: 0.31±0.01	C: 24.6±1.07		
	6 M						6M (mean ±SE)	6M (mean ±SE)		
							I: 0.27±0.02	I: 21.0±1.46		
							Cl: 0.37±0.02	C: 28.9±1.49		
							GI Reduction (%)	GB reduction (%)		
							3M: 42.6% p< 0.001	3M: 43.4% p=0.001		
							6M: 25.8% p=0.001	6M: 27.4% p=0.001		
Barnes et al	randomized	n=25	I: 0.454% SnF2 +	C: 0.234% NaF + 0.3% TCN	Baseline prophylaxis	MGMPI: (mean ±SD)			No drop outs	High
2010	double-blind	R: 18-65 yrs.	SHMP/ZN- lactate	positive control	Scaling and prophylaxis,	Study 1				
	cross-over				remove dental plaque	I: 22.05± 12.42			Sponsored by	
		3 studies – conducted with			and dental calculus	C: 14.14± 8.02			Procter & Gamble	
	Modified Gingival Margin	same clinical procedures.			before the study					
	Plaque index (MGMPI)					Study 2				
		USA			Washout period –use	I: 25.35± 10.48				
	24 H				Colgate 0.76 % SMFP	C: 12.95± 7.18				
						Study 3				
						I: 27.09± 11.95				

(*continued on next page*)

Table 3 (*continued*)

Authors (year)	Study design Methods Duration	Study population Number (gender) Age (range) Country	Intervention (I) Toothpaste	Control (C) Positive/negative	Treatment/ brushing	Outcome Plaque Index	Outcome Gingival Index	Outcome Gingival Bleeding	Comments	Risk of bias
						C: 9.65± 8.30				
						% treatment diff.				
						I vs. C: Advantage C.				
						Study 1: 7.91 p=0.05				
						Study 2: 12.4 p=0.05				
						Study 3: 17.44 p=0.05				
Beiswanger et al	randomized	n= 463	IA: 0.454% SnF2 +	C: 0.243% NaF	No instructions.	PLI: (mean ±SE)	GI: (mean ±SE)	GB: (mean ±SE) no of sites	Drop out: n=47	Medium
1995	double-blind	BL:	2.08% sodium gluconate	Negative control		BL:	BL:	BL:		
	parallel	IA: n=157 (50 male/ 107 female)				IA: 1.03±0.03	IA: 0.67±0.02	IA: 17.6±1.2	Sponsored by	
	single center	33.34 (18-68) yrs.	IB: 0.454% SnF2 +			IB: 0,97±0.04	IB: 0,70±0.02	IB: 18.2±1.3	Procter & Gamble	
			4.16% sodium gluconate			C: 0.95±0.03	IC: 0.70±0.02	C: 18.7±1.1		
	PLI: (Silness & Löe 1964)	IB: n=153 (50 male/ 103 female)								
	GI: (Löe 1967)	34.13 (19-67) yrs.				3M:	3M:	3M:		
	GB: Gingival bleeding					IA: 1.03±0.03	IA: 0.68±0.02	IA: 17.6±01.2		
	(no of sites)	C: n=153 (45 male/ 108 female)				IB: 0.96±0.03	IB: 0.70±0.02	IB: 18.2±1.3		
		32.34 (18-64) yrs.				C: 0.93±0.03	C: 0.69±0.02	C: 18.4±1.1		
	6 M									
		6M:				6M:	6M:	6M:		
		IA: n=140 (44 male/ 96 female)				IA: 1.03±0.03	IA: 0.68±0.02	IA: 17.6±1.2		
		33.79 (18-68) yrs.				IB: 0.96±0.04	IB: 0.69±0.02	IB: 18.2±1.3		
						C: 0.95±0.03	C: 0.71±0.02	C: 18.7±1.1		
		IB: n=140 (49 male/ 91 female)								
		34.55 (19-67) yrs.				6M reduction	6M reduction	6M reduction		
						IA and IB vs C:	IA and IB vs C:	IA and IB vs C:		
		C: n=136 (41 male/ 95 female)				IA: 2.6% NS	IA: 18.8% NS	IA: 30.5% NS		
		32.64 (19-64) yrs.				IB: 1.6% NS	IB: 18.0% NS	IB: 23.1% NS		
		USA								

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Table 3 (*continued*)

Authors (year)	Study design Methods Duration	Study population Number (gender) Age (range) Country	Intervention (I) Toothpaste	Control (C) Positive/negative	Treatment/ brushing	Outcome Plaque Index	Outcome Gingival Index	Outcome Gingival Bleeding	Comments	Risk of bias
Beiswanger et al	randomized	N= 835	I: 0.454% SnF2	C1: 0.243% NaF	Oral prophylaxis	PLI: (mean ±SE)	GI: (mean ±SE)	GB: (mean ±SE)	Drop out: n=83	Medium
1997	double-blind	BL:		Negative control		BL:	BL:	BL: (%)		
	parallel	I: n=278 (77 male/ 201 female)				I: 0.73±0.02	I: 0,86±0.02	I: 24.876±1.05	Sponsored by	
	single center	36.3 ±0.62		C2) 0.243% NaF + PHEN		C1: 0.67±0.03	C1: 0.84±0.02	C1: 23.36±1.37	Procter & Gamble	
				(Listerine®)		C2: 0.70±0.02	C2: 0.88±0.02	C2: 26.18±1.16		
	PLI: (Silness & Löe 1964)	C1: n= 144 (40 male/104 female)		Positive control		C3: 0.74±0.03	C3: 0.89±0.02	C3: 24.87±1.81		
		36.1 ± 0.90								
	GI: (Löe 1967)					3M:	3M:	3M: (%)		
		C2: n= 289 (71 male/218 female)		C3) 0.243% NaF + Baking		I: 0.51±0.02	I: 0.72±0.01	I: 18.05±0.56		
	GB: Gingival bleeding	35.7 ±0.59		soda + Hydrogen peroxide		C1: 0.50±0.02	C1: 0.79±0.01	C1: 22.02±01.77		
	(no of sites)			Positive control		C2: 0.44±0.02	C2: 0.73±0.01	C2: 20.33±0.55		
		C3: n=148 (40 male/ 108 female)				C3: 0.54±0.02	C3: 0.77±0.01	C3: 21.31±0.76		
	6M	36.5 ± 0.85								
						6M:	6M:	6M: (%)		
		6M				I: 0.55±0.02	I: 0.64±0.01	I: 16.13±0.65		
		I: 267				C1: 0.54±0.02	C1: 0.78±0.02	C1: 22.25±0.90		
		CI: n=140				C2: 0.48±0.02	C2: 0.73±0.02	C2: 20.95±0.63		
		C2: n= 281				C3: 0.58±0.02	C3: 0.74±0.02	C3: 21.82±1.1		
		C3: n= 147								
		No data regarding gender and				6M PLI (%)	6M GI (%)	6M GB (%)		
		mean age				I vs C3: 4.2	I vs C1: 17.5 p=0.05	I vs C1: 27.5 p=0.05		
						C2 vs C3: 16.2 p=0.05	I vs C2: 10.8 p=0.05	I vs C2: 23.0 p=0.05		
		USA				C2 vs I: 12.5 p=0.05	I vs C3: 13.8 p=0.05	I vs C3: 26.1 p=0.05		
						C2 vs C1: 10.8 p=0.05	C2 vs C1: 7.4 p=0.05	C2 vs C1: 5.9 NS		
						C2 vs I: 2.0 NS	C2 vs C3: 3.4 NS	C2 vs C3: 4.0 NS		
						C2 vs C4: 6.1 NS	C3 vs C1: 4.2 NS	C3 vs C1: 1.9 NS		
Bellamy et al	randomized	n=21	I: 0.454% SnF2 + SHMP	C: 0.76% SMFP + 2%	Brushing with	DPIA: mean ±SE, % plaque			No drop outs	High
2008	double-blind			Zn-Citrat	standardized fluoride	coverage				

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Table 3 (*continued*)

Authors	Study design	Study population	Intervention (I)	Control (C)	Treatment/	Outcome	Outcome	Outcome	Comments	Risk
(year)	Methods	Number (gender)	Toothpaste	Positive/negative	brushing	Plaque Index	Gingival Index	Gingival Bleeding		of bias
	Duration	Age (range)								
		Country								
	cross-over	R: 20-60 yrs.		Positive control	(non-antibacterial) TP for	A.M. Pre-brush			Sponsored by	
					two weeks.	I: 9.63±106			Procter & Gamble	
	Digital plaque imaging	England				C: 12.90±1.01				
	analysis (DPIA)									
						A.M. Post-brush				
	15 days					I: 4.89±0.36				
						C: 5.76±0.34				
						P.M.				
						I: 9.15±1.12				
						C: 11.92±1.06				
						% treatment diff.				
						A.M. Pre-brush 25.32 p=0.05				
						A.M. Post-brush 15.13 NS				
						P.M. 23.24 p=0.09				
Bellamy et al	randomized	n=25 (11 male/ 15 female)	I: 0.454% SnF2 + SHMP	C: 0.32% NaF	Pre-treatment with NaF TP	DPIA: (mean ±SE) % plaque			No drop outs	High
2009A	double-blind			Negative control	Brushing twice daily.					
	Two treatment and a	35.3 (25-57) yrs.			No other oral hygiene aids.	A.M. Pre-brush			Sponsored by	
	four-day washout period.					I. 12.5±1.63			Procter & Gamble	
		England				C. 16.24±1.63				
	Digital plaque imaging									
	analysis (DPIA)					A.M. Post-brush				
						I. 5.39±0.89				
	17 days					C. 6.52±0.89				
						P.M.				
						I. 9.46±1,26				
						C. 12.22±1.26				
						% treatment diff.				

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Table 3 (*continued*)

Authors	Study design	Study population	Intervention (I)	Control (C)	Treatment/	Outcome	Outcome	Outcome	Comments	Risk
(year)	Methods	Number (gender)	Toothpaste	Positive/negative	brushing	Plaque Index	Gingival Index	Gingival Bleeding		of bias
	Duration	Age (range)								
		Country								
						A.M. Pre-brush 23.03				
						p= 0.0001				
						A.M. Post-brush 17.33				
						p= 0.01				
						P.M. 22.59 p= 0.0004				
Bellamy et al	randomized	n=27 (14 male/ 13 female)	I: 0.454% SnF2 + SHMP	C: 1400 ppm AlF		DPIA: (mean ±SE) % plaque			Drop out: n=2	High
2009B	double-blind			0.05% chlorhexidine +		coverage:				
	crossover	35.2 (25-57) yrs.		0.08% aluminium lactate		A.M. Pre-brush			Sponsored by	
	Two treatment and a			(AlF3/Chx)		I: 13.08±1.46			Procter & Gamble	
	four-day washout period.	England				C: 16.16±1.46				
				Positive control						
	Digital plaque imaging					A.M. Post-brush				
	analysis (DPIA)					I: 5.31±0.87				
						C: 7.14±0.87				
	17 days									
						P.M.				
						I: 9.76±1.27				
						C: 12.17±1.27				
						% treatment diff.				
						A.M. Pre-brush 19.37				
						p=0.0043				
						A.M. Post-brush 25.63				
						p=0.0014				
						P.M. 19.80 p=0.0057				
Boneta et al	randomized	n=109	I: 0.454% SnF2 + SHMP	C: 0.234% NaF + 0.3% TCN	Brushing twice daily for	PLI: (mean ±SD)	GI: (mean ±SD)		Drop out: n=12	Medium
2010	double-blind			Positive control	1 min.	BL:	BL:			

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Table 3 (*continued*)

Authors	Study design	Study population	Intervention (I)	Control (C)	Treatment/	Outcome	Outcome	Outcome	Comments	Risk
(year)	Methods	Number (gender)	Toothpaste	Positive/negative	brushing	Plaque Index	Gingival Index	Gingival Bleeding		of bias
	Duration	Age (range)								
		Country								
	parallel	I: n=55 (14 male/41 female)				I: 3.19±0.64	I: 2.18±0.40		Sponsored by	
	single center	39 (21-68) yrs.				C: 3.16±0.64	C: 2.17±0.36		Colgate	
	PLI= Turesky modification of	C: n= 54 (18 male/ 36 female)				3M (mean ±SE)	3M (mean ±SE)			
	the Quigley and Hein	40 (21-63) yrs.				I: 2.46±0,51	I: 1.48±0.25			
	(Quigley & Hein 1962,					C: 1.95±0.61	C: 1.20±0.27			
	Turesky et al 1970)	USA								
						6M (mean ±SE)	6M (mean ±SE)			
	GI: (Löe & Silness 1963)					I: 2.36±0.55	I: 1.40±0.28			
						C: 1.75±0.65	C: 1.16±0.29			
	6M									
						6M Reduktion %	6M Reduktion %			
						I: 32.1	I: 35.8			
						C: 44.7	C: 46.5			
						6M: % treatment diff.	6M: % treatment diff.			
						I vs C: 18.9 p=0.05	I vs C: 17.1 p=0.05			
Gerlach & Amini	randomized	n= 97 (60% female)	I: 0.454% SnF2	C: 1000 ppm SMFP +			MGI: (mean ±SD)	GB: (mean ±SD)	Drop out: n=3	High
2012	controlled	33.6 ±11.1 (18-66) yrs.		450 ppm NaF			BL:	BL:		
	clinical trial			Negative control			I: 2.18 ± 0.10	I: 14.9± 8.89	Sponsored by	
		I: n=49					C: 2.19 ± 0.10	C: 16.1± 9.72	Procter & Gamble	
	MGI: Modified Gingivitis index	C: n=48								
	(Lobene 1986)						3M: no data in the article	3M: (adjusted mean)		
		USA						1: 4.2		
	GB: Gingival bleeding							2: 15.4		
	(no of sites)									
								Improvement GBI %:		
	3M							1. -74% p=0.001		
								2. 2% NS		

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Table 3 (*continued*)

Authors	Study design	Study population	Intervention (I)	Control (C)	Treatment/	Outcome	Outcome	Outcome	Comments	Risk
(year)	Methods	Number (gender)	Toothpaste	Positive/negative	brushing	Plaque Index	Gingival Index	Gingival Bleeding		of bias
	Duration	Age (range)								
		Country								
Mallatt et al	randomized	n= 128	I: 0.454 SnF2 + SHMP	C: SMFP		PLI: (mean ±SD)	MGI: (mean ±SD)		Drop out: n=12	Medium
2007	double-blind			Negative control		BL.	BL.			
	parallel, clinical study	Age: Range 18-65 yr.				I: 2.88±0.34	I: 2.00 ± 0.13		Sponsored by	
	single center					C: 2.79±0.42	C: 2.00 ± 0.13		Procter & Gamble	
		I: n=62 (25 male/ 37 female)								
	PLI: Turesky Modified Quigley-					6M:	6M:			
	Hein (Turesky et al 1970)	C: n=66 (23 male/37 female)				I: 2.20±0.40	T: 1.58±0.31			
						C: 2.34±0.49	C: 1.90 ±0.21			
	MGI: Modified gingival index	USA								
	(Lobene 1986)					PLI	MGI reduction %			
						I vs C: 8.5 % p=0.001	I vs C: 16.9 p=0.001			
	GBI: Gingival bleeding index									
	(Saxton & van der Ouderaa						GBI: mean ±SD			
	1989)						BL.			
							I: 10.86±4.93			
	6M						C: 10.90±3.92			
							6M:			
							I: 5.08±4.89			
							C: 8.53±4.48			
							GBI reduction %			
							I vs C: 40.8 p=0.001			
Mankodi et al	randomized	n= 130	I: 0.454% SnF2 + SHMP	C: 0.76% SMFP	Dental prophylaxis	PLI: (mean ±SD)	MGI: (mean ±SD)		Drop out: n=13	Medium
2005	double-blind			Negative control	Tooth brushing for 1 min	BL:	BL:			
	parallel	I: n=64 (20 male/44 female)			2 times/day	I: 2.73±0.41	I: 2.03±0.10		Sponsored by	
		37.1± 10.9 (18-65) yrs.				C: 2.91±0.35	C: 2.04±0.10		Procter & Gamble	
	PLI: Turesky Modified Quigley-									

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Table 3 (*continued*)

Authors (year)	Study design Methods Duration	Study population Number (gender) Age (range) Country	Intervention (I) Toothpaste	Control (C) Positive/negative	Treatment/ brushing	Outcome Plaque Index	Outcome Gingival Index	Outcome Gingival Bleeding	Comments	Risk of bias
	Hein (Turesky et al 1970)	C: n=66 (23 male/43 female)				3M (mean ±SE)	3M (mean ±SE)			
		38.5 ± 11.3 (18-64) yrs.				I: 2.24±0.05	I: 1.75±0.02			
	MGI: Modified Gingival Index					C: 2.38±0.05	C: 1.98±0.02			
	(Lobene 1986)	USA								
						6M (mean ±SE)	6M (mean ±SE)			
	GBI: Gingival Bleeding Index					I: 2.14±0.05	I: 1.57±0.03			
	(Saxton & van der Ouderaa					C: 2.30±0.05	C: 2.01±0.03			
	1989									
						6M % treatment diff.	6M % treatment diff.			
	6M					I vs C: 6.9 p=0.001	I vs C: 21.7% p=0.001			
							GBI: (mean ±SD)			
							BL			
							I: 9.39±3.22			
							C: 8.67±3.40			
							3M (mean ±SE)			
							I: 4.14±0.34			
							C: 7.92±0.34			
							6M (mean ±SE)			
							I: 3.81±0.40			
							C: 8.88±0.39			
							6M % treatment diff.			
							I vs C: 57.1% p=0.001			
Owens et al	randomized	n=138 (41 male/102 female)	I: 0.454% SnF2	C1: 0.1% NaF +	Dental prophylaxis,	PLI: (mean ±SD)	GI: (mean ±SD)		Drop out: n=5	Low
1997	single-blind			0.76% SMFP	remove plaque and	BL.	BL.			
	parallel, comparison	Age: 18-65 yr.		Negative control	calculus	I: 2.04±0.18	I: 1.45±0.28		No information	
					Brush 2 times a day for	C1: 2.04 ±0.24	C1: 1.38±0.20		regarding sponsor	

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Table 3 (*continued*)

Authors	Study design	Study population	Intervention (I)	Control (C)	Treatment/	Outcome	Outcome	Outcome	Comments	Risk
(year)	Methods	Number (gender)	Toothpaste	Positive/negative	brushing	Plaque Index	Gingival Index	Gingival Bleeding		of bias
	Duration	Age (range)								
		Country								
	PLI= Turesky modification of	I:n= 34		C2: 0.8% NaF + 0.3% TCN	18 weeks.	C2: 2.12±0.21	C2: 1.42±0.25			
	the Quigley and Hein	C1:n= 33		0.75% zn-citrate		C3: 2.13±0.25	C3: 1.41±0.21			
	(Quigley & Hein 1962,	C2:n= 35		Positive control						
	Turesky et al 1970)	C3:n= 36				18W	18W			
				C3: 0.32% NaF + 0.3% TCN		I: 1.91±0.03	I: 1.21±0.02			
	GI: Gingival index	England		Positive control		C1: 1.88±0.03	C1: 1.22±0.02			
	(Mandel-Chilton 1977					C2: 1.86±0.03	C2: 1.21±0.02			
	modification of the Loe &					C3: 1.83±0.03	C3: 1.24±0.02			
	Silness (1963)									
						% treatment diff.	% treatment diff.			
	4 Groups					I: 6.4	I: 16.6			
						C1:7.8	C1: 11.6			
	18 W					C2: 12.3	C2: 14.8			
						C3: 14.1	C3: 12.1			
						NS	NS			
Papas et al	randomized	N= 334	I: 0.454 SnF2	C: 0.234% NaF + 0.3% TCN	No treatment			BOP (mean ±SD)	Drop out: n=106	Medium
2007	double-blind			Positive control				BL:		
	parallel	I: n=163 (77 male/ 86 female)						I: 94.6±19.5	Sponsored by	
		626.2 ±9.36 (40-79) yrs.						C: 88.3±27.9	Procter & Gamble	
	Bleeding on probing (BOP)									
								1 Yrs.:		
	2 Yrs.	C: n=171 (76 male/ 95 female)						I: 7.4±20.8		
		66.3±9.31 SD (41-80) yrs.						C: 9.6±23.2		
		USA						2 Yrs.:		
								I: 33.5±35.2		
								C: 32.5±32.7		
								2 Yrs.		

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Table 3 (*continued*)

Authors	Study design	Study population	Intervention (I)	Control (C)	Treatment/	Outcome	Outcome	Outcome	Comments	Risk
(year)	Methods	Number (gender)	Toothpaste	Positive/negative	brushing	Plaque Index	Gingival Index	Gingival Bleeding		of bias
	Duration	Age (range)								
		Country								
								I vs C: 61.1% vs 55.8% NS		
Perlich et al	randomized	n= 328	I: 0.454% SnF2	C: 0.243% NaF	A 3-month pre-test period	PLI: (mean ±SE)	GI: (mean ±SE)	GB: (mean ±SE)	Drop out: n=55	High
1995	double-blind			Negative control	where all subjects brushed	BL:	BL:	BL		
	parallel	I: n=154 (51 male/ 103 female)			with 0.243% Sodium	I: 1.94±0.04	I: 0.68±0.02	I: 14.43±0.94	Sponsored by	
		37.3 (19-69) yrs.			fluoride TP.	C: 1.90±0.04	C: 0.68±0.02	C: 16.40±1.03	Procter & Gamble	
	PLI= Turesky modification of									
	the Quigley and Hein					3M	3M	3M	Identical data as	
	(Quigley & Hein 1962,	Cl: n=174 (60 male/ 114 female)				I: 1.99 ±0.12	I: 2 0.43±0.01	I: 7.23±0.32	presented in	
	Turesky et al 1970)	36.5 yr. (19-48) yrs.				C: 2.07±0.12	C: 0.53±0.01	C: 10.52±0.47	McClanahan et al	
									1997, but	
	GI: (Löe & Siless 1967)	USA				6M	6M	6M	exkluding TCN.	
						I: 2.16±0.13	I: 0.41±0.01	I: 5.71±0.39		
	GB: Gingival Bleeding					C: 2.23±0.13	C: 0.52±0.01	C: 8.57±0.43		
	(no of sites)									
						PLI (Increase)	GI	No of GBI sites:		
						I: -0.23 (11.9%)	I: 0.27 (39.7%)	I: 8.7% (60.4)		
						C: -0.43 (-22.6%)	C: 0.18 (25%)	C: 7.8% (47.7%)		
						6M - NS	6M p=0.05	6M p=0.05		
Sharma et al	randomized	n= 114 subjects	I : 0.454% SnF2	C: 0.234% NaF + 0.3% TCN	Dental prophylaxis, brush	RMNPI: (mean ±SD)			Drop out: n=8	High
2013	double-blind			Positive control	for at least 1 min 2	3W				
	parallel	I: n= 56 (21 male/39 female)			times/day	I: 0.39 ±0.01			Sponsored by	
		36.4 ±11.8 (21-71) yrs.				C:0.56±0.01			Procter & Gamble	
	RMNPI: Modification of the									
	Navy Plaque index	C: n= 58 (21 male/ 39 female)				6W				

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Table 3 (*continued*)

Authors	Study design	Study population	Intervention (I)	Control (C)	Treatment/	Outcome	Outcome	Outcome	Comments	Risk
(year)	Methods	Number (gender)	Toothpaste	Positive/negative	brushing	Plaque Index	Gingival Index	Gingival Bleeding		of bias
	Duration	Age (range)								
		Country								
	(Rustogi et al. 1992)	38.6 ±13.7 (20-82) yrs.				I: 0.27±0.01				
						C:0.50±0.01				
	6W	USA								
						% treatment diff.				
						I vs C:				
						3W: 29.7% p=0.0001				
						6W: 44.9% p=0.0001				
Shearer et al	randomized	n= 110 (male)	I: 0.454% SnF2	C1: 0.243% NaF + TCN	Scaling and rotplaning	PLI: (mean ±SD)	MGI: (mean ±SD)		Drop out: n=11	High
2005	double-blind	25-50 yrs.		+ Zn-citrate	and oral hygiene	3W	3W			
	3-arm parallel			Positive control	instruction	I: 1.04±0.03	I: 0.91 ±0.07		No baseline data	
		I: n= 39				C1: 1.08±0.03	C1: 1.07 ±0.09			
	PLI: (Löe 1967)	C1: n= 36		C2: 0.243% NaF		C2: 1.13±0.03	C2: 1.43 ±0.07		No sponser	
		C2: n = 35		Negative control						
	MGI: Modified Gingival Index					I vs CI: NS	I vs C2: p=0.0003			
	(Lobene 1986)	USA				I vs C2: NS	I vs CI: NS			
						C1 vs C2: NS	C1 vs C2: p=0.01			
	GBI: Gingival Bleeding Index									
	(Saxton 1989)						GBI (mean SD)			
							3W			
	21 Days						I: 0.33 ±0.03			
							C1: 0.3 ±0.03			
							C2: 0.51 ±0.03			
							I vs C2: p=0.0003			
							I vs C1: NS			
							C1 vs C2: p=0.0003			
White et al.	randomized	n= 16 (6 male/10 female)	I: 0.454% SnF2 + SHMP	C: 0.243% NaF	Treatment period (TP) 1:	DPIA: Plaque % mean ±SD			No drop outs	High
2006	blinded			Negative control	Including toothbrushing					
	3-arm cross-over study	33.2. (24-38) yrs.			with NaF TP	TP1: Plaque coverage:			Sponsored by	

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Table 3 (*continued*)

Authors (year)	Study design Methods Duration	Study population Number (gender) Age (range) Country	Intervention (I) Toothpaste	Control (C) Positive/negative	Treatment/ brushing	Outcome Plaque Index	Outcome Gingival Index	Outcome Gingival Bleeding	Comments	Risk of bias
	3-treatment period within the								Procter & Gamble	
	same group	USA			TP 2:	Pre-brushing: 13.3% ±4.27				
					Modified hygiene regimen	Post-brushing: 6.4% ±1.80				
	Digital plaque imaging				was applied using NaF TP					
	analysis (DPIA).				including a period of 24 H	TP2:				
					of non-brushing	Pre-brushing: 18.4 ±5.97				
	2W					Post-brushing: 7.3 ±3.64				
					TP 3:					
					24 H non-brushing	TP3:				
					regimen was continued	Pre-brushing: 15.2 ± 6.87				
					using SnF2 + SHMP TP	Post-brushing: 6.8 ±3.52				
						Reduction %:				
						TP3 vs TP1, TP2: 17%				
						Advantage TP3.				
White 2007	double-blind	n= 14	I: 0.454% SnF2	C.: 0.243% NaF	Dental prophylaxis	DPIA: Morning Pre-Bruch			No drop outs	High
	cross-over			Negative control	performed by subjects	Regrowth % ±SD				
		33 yrs.				I: 10.4 ±4.4			Sponsored by	
	Digital plaque imaging					Cl: 13.8 ± 5.5			Procter & Gamble	
	analysis (DPIA)	USA								
						Morning Post-Brushing				
						I: 6.2 ± 2.6				
						C: 6.3 ±3.3				
						Afternoon Regrowth				
						I: 8.1± 3.9				
						C: 11.2 ±5.1				

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Table 3 (*continued*)

Authors (year)	Study design Methods Duration	Study population Number (gender) Age (range) Country	Intervention (I) Toothpaste	Control (C) Positive/negative	Treatment/ brushing	Outcome Plaque Index	Outcome Gingival Index	Outcome Gingival Bleeding	Comments	Risk of bias
						% treatment diff.				
						Morning Pre-Brush				
						I vs C: 24.4 p=0.0002				
						Moring Post-Brush				
						I vs C 1.7 NS				
						Afternoon Regrowth				
						I vs C: 27.9 p=0.0003				
Willumsen et al	double-blind	n= 40	I: 0.4% SnF2	C: 0.2% NaF	Before the two periods,	PLI: (mean ±SD)	GI: (mean ±SD)		Excluded =4	Medium
2007	cross-over			Negative control	the subjects had their	BL: (all surfaces)	BL: (all surfaces)		Drop-out= 4	
		88.7 (82-98)			teeth professionally	I and C: 1.44 ± 0.48	I and C: 1.29 ± 0.38			
	PLI: (Silness & Löe 1964)				cleaned.				No sponsor	
		Norway				4W:	4W:			
	GI: (Löe & Silness 1963)					I: 1.14± 0.40	I:1.22± 0.30			
						C: 1.28± 0.34	Ctrl: 1.22± 0.27			
	4 W									
						% treatment diff.	% treatment diff.			
						I: 20.8 vs. C: 11.1	I: 7.0 vs. C: 7.0			
						p=0.001	NS			
Yates et al	randomized	n= 69 /21 days	I: 0.454% SnF2	C: 0.24% NaF	Professional prophylaxis,	PLI: (mean ±SE)	MGI: (mean ±SE)	GB: (mean ±SE)	Drop-out: n=6	Low
2003	double-blind	n= 67 /42 days		Negative control	allocated toothpaste and	For unshielded teeth	For unshielded teeth (that	For unshielded teeth (that	(42 days)	
	parallel				a standard toothbrush	(that have been shielded)	have been shielded)	have been shielded)	no data which	
		I: n=36 (7 male/ 29 female)			Oral hygiene Instructions	BL: 0	I: BL: 1.54±0.07	I: BL: 0.33±0.04	group	
	21 days experimental gingivitis	33.1 (20-60) yrs.				21 days:1.50±0.08	I: 21 days:1.74±0.05	I: 21 days: 0.62± 0.03		
	protocol and a 6 week (42 days)					42 days: 1.07± 0.08	I: 42 days: 1.17± 0.08	I: 42 days: 0.43± 0.03	No sponsor	
	home-use protocol	C: n=35 (7 male/ 28 female)								

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Table 3 (*continued*)

Authors (year)	Study design Methods Duration	Study population Number (gender) Age (range) Country	Intervention (I) Toothpaste	Control (C) Positive/negative	Treatment/ brushing	Outcome Plaque Index	Outcome Gingival Index	Outcome Gingival Bleeding	Comments	Risk of bias
		33.6 (21-63) yrs.				C: BL: 0	C: BL: 1.62±0.06	C: BL: 0.41±0.04		
	PLI: (Löe 1967)					21 days:1.73±0.06	C: 21 days:1.85±0.05	C: 21 days: 0.67± 0.04		
		United Kingdom				42 days: 1.05± 0.09	C: 42 days: 1.25± 0.07	C: 42 days: 0.49± 0.04		
	MGI: Modified gingival index									
	(Lobene et al. 1986)					Reduction: day 21 to day 42.	MGI reduction 21 – 42 day	GB reduction: 21 to 42days.		
						I: 0.43 vs C: 0.68	I: 0.57 vs C: 0.60	I: 0.19 vs C: 0.18		
	GB= Gingival bleeding					I vs C: NS	I vs C: NS	I vs C: NS		
	Teeth covered by tooth shield									
						For unshielded teeth	For unshielded teeth	For unshielded teeth		
	21 Days /42 Days					(mean ±SE)	(mean ±SE)	(mean ±SE)		
						I: BL: 0	I: BL: 1.43± 0.07	I: BL: 0.29± 0.03		
						21 days:0.78± 0.06	I: 21 days: 1.27± 0.07	I: 21 days: 0.34± 0.03		
						42 days: 0.81± 0.07	I: 42 days: 0.95± 0.08	I: 42 days: 0.37± 0.02		
						C: BL: 0	C: BL: 1.43± 0.07	C: BL: 0.34± 0.03		
						21 days:0.76± 0.07	C: 21 days: 1.25± 0.06	C: 21 days: 0.33± 0.03		
						42 days: 0.77 ± 0.07	C: 42 days: 1.02± 0.07	C: 42 days: 0.38± 0.03		
						PLI reduction: B to 42 days.	MGI reduction: B to 42 days.	GB reduction: B to 42 days.		
						I: -0.81 vs C: -0.77	I: 0.48 vs C: 0.41	I: -0.08 vs C: - 0.0		
						I vs C: NS	I vs C: NS	I vs C: NS		

AlF (aluminium fluoride) BL (baseline), I (intervention), C (control), H (Hour) NaF (Sodium fluoride), SnF2 (Stannous fluoride), SnCl (stannous chloride), STP (sodium tripolyphosphate), SHMP (Sodium hexametaphosphate), SMFP (Sodium monofluorophosphate), PHEN (Phenolic essential oils), TCN (Triclosan), TP (Toothpaste), NS (not significant), vs (versus) Zn- citrate (Zink citrate).

of sites showing gingival bleeding was 32.4% greater in the SnF_2 groups (range 11.6%–72%).

Figure 2 shows the results of the meta-analysis of gingival inflammation and the 6-month studies [39, 40, 41, 42, 43, 44, 46]. Brushing with SnF_2 toothpaste yielded significantly higher reductions in gingival inflammation. The SMD was -0.63 (95% CI: -1.11 to -0.15) with a significant reduction in the SnF_2 group ($P = 0.010$) compared with the controls. When compared with negative controls only, the anti-gingivitis effect of SnF_2 had a significant SMD of -0.93 (95% CI: -1.40 to -0.46; $P = 0.0001$) (see Figure 3).

3.3. Halitosis

Table 4 lists the four included studies on halitosis, which were published between 1998 and 2010. The studies were randomized and had a cross-over [59, 60, 61] or parallel design [33]. They evaluated the effect of either one-time [59] or repeated brushing [33, 60, 61]. The intervention was brushing with a toothpaste containing 0.454% SnF_2 alone [33, 59, 60], in combination with sodium fluoride [61], or in combination with tongue brushing [60]. Both single use and repeated exposure reduced breath malodor when using a SnF_2 toothpaste in comparison to control products. The studies reported a significant reduction in VSC after single use [33, 61] as well as after cumulative use and overnight readings [33, 59, 60, 61].

3.4. Stain

Table 5 presents the five included studies on stain, which were published between 2005 and 2013 [36,62-65]. The test period varied between 2 and 6 weeks. All studies were controlled, randomized, double-blinded, and parallel-grouped, and represented 488 patients (aged 19–74 yr) with 240 patients in the test groups and 248 in the control groups. In four studies, the test toothpastes contained 0.454% SnF_2 + SHMP [36, 62, 63, 65] and were compared with a positive control of 0.243% NaF +0.3% triclosan toothpaste. The fifth study [63] examined a stannous chloride and sodium fluoride toothpaste but had a positive control with only 0.454% SnF_2. The overall results showed that the 0.454% SnF_2 + SHMP toothpastes and the triclosan controls reduced the Lobene stain index, but at the end of the test periods, no significant differences in stain reducing effect were found. While there were no significant differences in mean Lobene scores between the stannous chloride and the triclosan dentifrices, the toothpaste with only SnF_2 had a higher stain score after 5 weeks than at baseline [63].

4. Discussion

In the present review, toothpastes containing SnF_2 have been proven to have preventive and therapeutic effects against dental calculus, dental plaque, gingivitis, halitosis and stain. Comparisons with the effects of other toothpastes on these conditions favored a toothpaste containing SnF_2. However, the meta-analyses on gingivitis showed a substantial heterogeneity in the results of the individual randomized trials.

4.1. Dental calculus

The significant reduction in calculus formation that occurred after 6 months of testing a toothpaste containing SnF_2 and a calcium phosphate-mineralization inhibitor (SHMP) compared with other toothpastes indicated a beneficial effect. Due to their hardness, calculus deposits can only be removed by scaling and polishing the teeth. SHMP acts by reducing the rate and extent of mineralization, thereby reducing calculus build-up. In the Winston et al. [37] study, home-based and unsupervised use of a SnF_2 dentifrice during normal hygiene

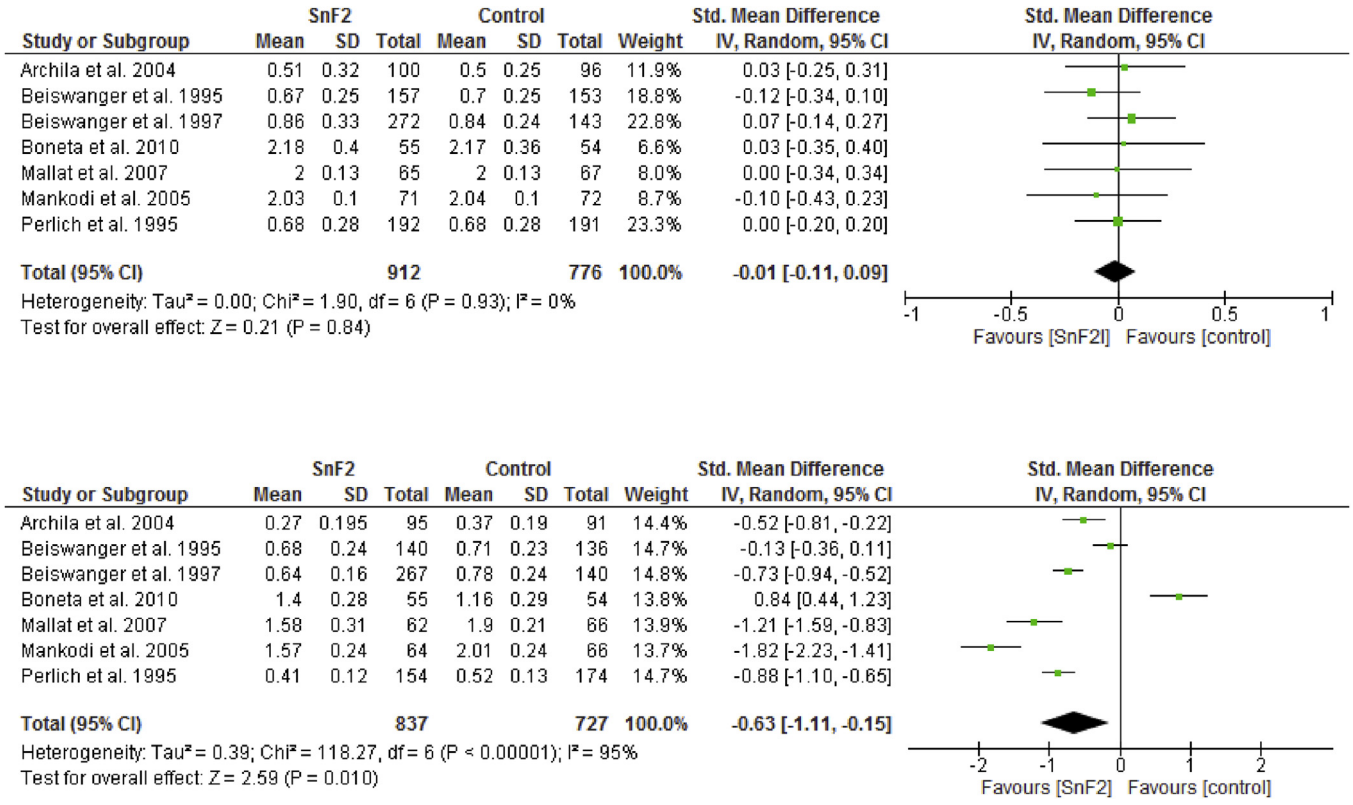

Figure 2. Forrest plot of baseline and after 6 month values (Standardized mean difference: SMD) of the gingivitis indices for the studies using a stannous fluoride (SnF_2) dentifrice compared to control dentifrice (positive and negative controls).

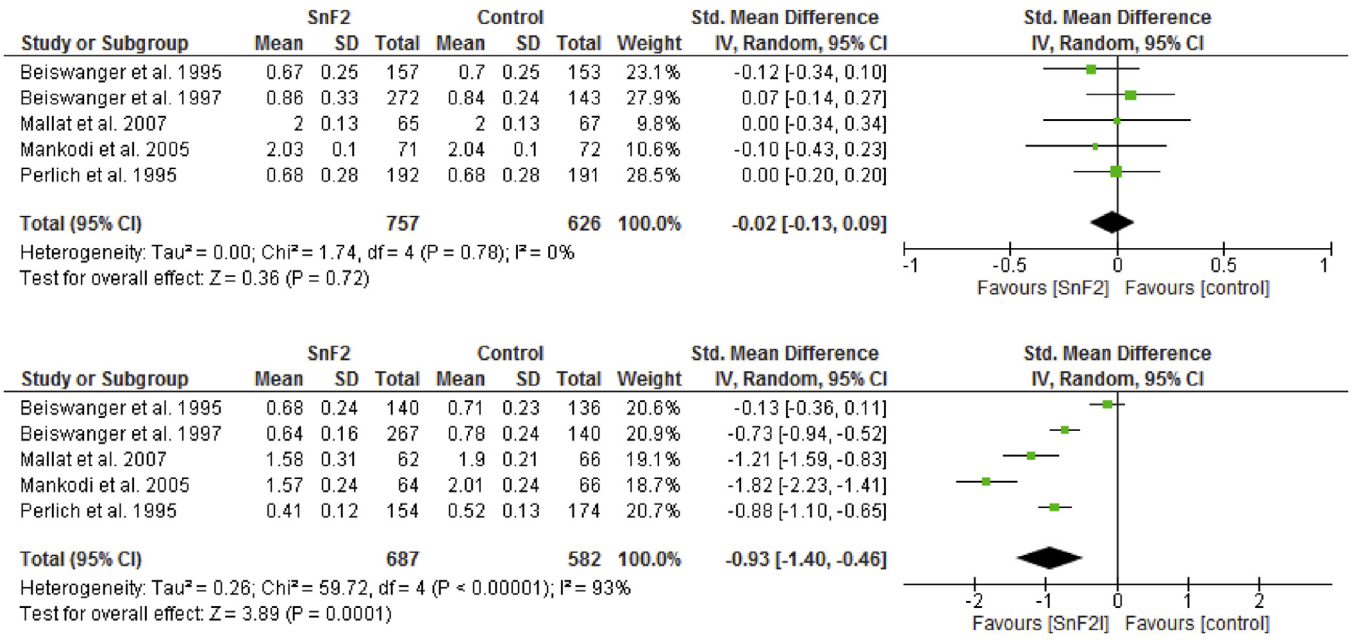

Figure 3. Forrest plot of baseline and after 6 month values (Standardized mean difference: SMD) of the gingivitis indices for the studies using a stannous fluoride (SnF_2) dentifrice compared to control dentifrice (negative control, NaF).

procedures effectively inhibited calculus regardless of the baseline levels of calculus. The significant anti-calculus efficacy that was observed is further evidence of the capacity of SHMP to interfere with calculus formation.

4.2. Dental plaque and gingivitis

A recent systematic review reported that use of a dentifrice with tooth brushing had a weak additional inhibitory effect on plaque regrowth when compared with tooth brushing alone [66]. The present systematic review demonstrated an increased plaque-reducing effect of a toothpaste containing SnF_2 compared with other toothpastes. Depending on the plaque index used and study duration, the reduction in dental plaque ranged from 1.6% to 25.8%. The effect was observed in both 24-hour as well as 6-month studies, indicating that both short- and long-term use of a SnF_2 dentifrice has a plaque inhibitory effect. Although long-term studies are desirable, studies of more than 6 months require a degree of compliance among participants that is sometimes difficult.

The present review found evidence for both direct and indirect effects on gingivitis development of brushing with a SnF_2 dentifrice. The indirect effect refers to the amelioration of gingivitis due to plaque reduction; the direct effect refers to a possible anti-inflammatory action, which both triclosan and SnF_2 have demonstrated, independent of how they affect bacteria [67]. The meta-analysis of the 6-month studies showed that stabilized SnF_2 significantly reduced gingival inflammation compared to positive and negative control dentifrices. The results of the present review are in line with the Paraskevas et al. [68] study, which reported that dentifrice containing SnF_2 reduced dental plaque as well as gingivitis.

4.3. Halitosis

The four papers [33, 59, 60, 61] evaluating the effect of a SnF_2 toothpaste on halitosis vary in number of exposures and in time point for measurement after exposure to the toothpaste. The overall picture, however, is that SnF_2 reduces the level of halitosis to a larger extent than comparative toothpaste products. The data are based on the combined level of hydrogen sulfide and methyl mercaptan, representing the VSCs produced by gram negative anaerobes most commonly found in bad breath. Other compounds, such as dimethyl sulfide and fatty acids, may also contribute [17]. The four papers reported limited information on the volunteers, but subjects with medical and oral conditions that could interfere with study measurements seem to have been excluded. The exact mechanism behind the positive findings is not fully known, but the antimicrobial effect of the SnF_2 compound is believed to play a significant role and also the effect of zinc in those toothpastes containing zinc citrate.

4.4. Stain

Several toothpastes on the market claim better stain-reducing capacities compared to conventional toothpastes. Historically, this effect has been due to the abrasive ingredient in the toothpastes. The studies in the present review have shown that a SnF_2 + SHMP toothpaste plays an important role in stain reduction. All studies demonstrated that the SnF_2 + SHMP toothpaste exhibited a stain-reducing effect equal to that of various control toothpastes. Clinical studies have shown that use of the polypyrophosphate formulation SHMP as the sole active ingredient in a toothpaste reduces the development of stain [69]. SHMP has the capacity to interact with stained pellicle films, remove the stain material, and then prevent adsorption of new chromogens by leaving a protective coating on the tooth surface [69].

4.5. Clinical relevance

Several aspects affect the clinical significance of the findings of the present review. For example, other ingredients in a toothpaste may contribute to the effects of a toothpaste on dental plaque, gingivitis, stains, and to some extent halitosis. An abrasive ingredient is necessary to remove plaque and biofilm [70, 71], so modern toothpastes often contain between 30% and 40% abrasives, which are usually various shapes and sizes of silica particles. Other aspects to be considered are the varying lengths and designs of the studies as well as the different indices used to measure results, which could well influence outcomes. This was especially obvious in the plaque and gingivitis studies; in the studies on stain and calculus, the small number of articles also potentially affected clinical significance.

Table 4. Characteristics of included studies on halitosis.

Authors (year)	Study design Methods Duration	Study population Number (gender) Age (range) Country	Intervention (I) Toothpaste	Control (C) Positive/negative	Treatment/ brushing	Outcome	Comments	Risk of bias
Chen et al 2010	randomized examiner-blind crossover	n=33 (14male/19 female) 25 yrs. USA	I1: 0.454% SnF2 I2: 0.454% SnF2 + tongue brushing	C1: 0.243% NaF negative control C2: 0.243% NaF + tongue brushing Positive control	Brushing three times during 24 H	24 H I1: 93.69 I2: 91.84 C1: 113.30 C2: 105.64	No drop out Sponsored by Procter & Gamble	High
	Breath measurement at 24 and 28 H					I1 + I2: 92.8 C1 + C2: 109.9		
	Halimeter (hydrogen sulfide, methyl mercaptan	ppb)"				28 H I1: 52.98 I2: 54.60 C1: 66.69 C2: 68.72		
						I1 + I2: 53 C1 + C2: 66.7		
Farrell et al 2007	Two RCTs cross-over double-blind Breath measurement at 24 H	Healthy adults with history of halitosis	I: 0.454% SnF2	C: 0.243% NaF negative control	Single day product use (2 brushings)	Study I (mean ± SD) I: 4.59 ± 0.14 C: 4.81 ± 0.14	No drop out Sponsored by Procter & Gamble	High
	Study 1 Halimeter (hydrogen sulfide, methyl mercaptan	Study 1 n=26 (13 male/13 female) 38.4 ± 6.7 yrs. ppb)"	Study II			Study II (mean ± SD) I: 5.72 ± 0.09 C: 5.94 ± 0.09		
	Study II Hedonic (9-point scale) 5 W	n=49 (14 male/35 female) 44.2 ± 12.7 yrs. USA						
Feng et al 2010	Randomized controlled single-blind crossover	n=100 (32 male/68 female) 34 (19-62) yrs. USA (Study I) China (Study II-IV)	I: 0.454% SnF2 + NaF	C I: 0.243% NaF (USA) C2: 0.321% NaF (China) negative control	Partly supervised brushing up to three times	3 H I: 88.3 C: 95.7 24 H I: 140.7 C: 157.3	No drop out Sponsored by Procter & Gamble	High
	Data presented as results from meta-analysis of four clinical trials. Halimeter VSC Readings after 3-4 H, 24 H and 27-28 H					27-28 H I: 75.2 C: 99.6		
Gerlach et al 1998	Randomized controlled parallell group	n=384 (79% female/21% male) 44.5 (18-77) yrs.	I: 0.454% SnF2	CI: 0.243% NaF +5% pyrophosphate positive control	Partly supervised on examination days	Organoleptic score 3/6/8 H I: 2.85/3.40/3.99 CI: 3.09/3.45/4.04	2% drop out Sponsored by Procter & Gamble	High

(*continued on next page*)

Table 4 (*continued*)

Authors	Study design	Study population	Intervention (I)	Control (C)	Treatment/	Outcome	Comments	Risk
(year)	Methods	Number (gender)	Toothpaste	Positive/negative	brushing			of bias
	Duration	Age (range)						
		Country						
	Fluoride groups			C2:0.24 NaF +		C2: 3.30/3.57/4.01		
	Five-day period	USA		0.30% TCN		C3: 3.23/3.42/4.01		
				positive control				
	Organoleptic scoring					99/102/104 H		
	Halimeter VSC (ppb)			C3: bottled distilled		I: 2.90/3.19/3.73		
				water		CI: 3.33/3.57/4.10		
	Readings after 3, 6			negative control		C2: 3.43/3.64/4.18		
	and 8 H (single use)					C3: 3.54/3.73/4.13		
	and 99, 102 and 104							
	H (cumulative use)					ppb		
						3/6/8 H		
						I: 4.39/3.97/4.09		
						CI: 4.51/3.99/4.19		
						C2: 4.50/4.02/4.18		
						C3: 4.56/4.04/4.20		
						99/102/104 H		
						I: 4.07/3.83/4.00		
						CI: 4.29/4.03/4.16		
						C2: 4.34/4.03/4.29		
						C3: 4.48/4.11/4.29		

BL (baseline), I (intervention), C (control), NaF (Sodium fluoride), SnF2 (Stannous fluoride), TCN (Triclosan), TP (Toothpaste), H (Hours).

Table 5. Characteristics of included studies on stain.

Authors	Study design	Study population	Intervention (I)	Control (C)	Treatment/	Outcome	Comments	Risk
(year)	Methods	Number (gender)	Toothpaste	Positive/negative	brushing			of bias
	Duration	Age (range)						
		Country						
He et al	randomized	Study 1:	I: 0.454% SnF2 + SHMP	C: 0.243% NaF + 0.3% TCN	Brushing twice	Study I:	Study I:	High
2007	double-blind	n=56 (26 male/26 female)		positive control	daily for for 1 min.	BL: I: 2.64, C: 2.45	Droup-outs= 4	
	parallel group					6 W: I: 1.05, C: 0.81		
		Study 2:				% treatment diff.	Study II:	
	Lobene stain index	n=58 (19 male/39 female)				I vs C= ns	Droup-outs= 2	
	6 W	30-70 yrs.				Study II:	Sponsored by	
						BL: I: 3.36, C: 3.17	Procter & Gamble	
		USA				6W: I: 0.31, C: 0.15		
						% treatment diff.	Equal effect between	
						I vs C= ns	test and control	
He et al	randomized	n=98 (32 male/66 female)	I: 0.454% SnF2	C1: 1450 ppm NaF+ SnCl	Brushing twice	BL: I: 0.42	Drop-out=2	High
2010	double-blind	19-63 yrs.		positive control	daily for for 1 min.	C1: 0.52, C2: 0.47,		
	parallel group					C3: 0.40	Sponsored by	
		I: n= 14		C2: 1450 ppm NaF+ SnCl			Procter & Gamble	
	Lobene stain index	C1: n= 28		positive control		5W: I: 0.80		
	1968	C2: n= 28				C1: 0.37, C2: 0.40	The I TP was less	
		C3: n= 28		C3: 1450 ppm NaF+0.3% TCN		C3: 0.30	effect	

(*continued on next page*)

Table 5 (*continued*)

Authors	Study design	Study population	Intervention (I)	Control (C)	Treatment/	Outcome	Comments	Risk
(year)	Methods	Number (gender)	Toothpaste	Positive/negative	brushing			of bias
	Duration	Age (range)						
		Country						
	5 W			negative control				
		USA				% treatment diff.		
						C1 vs C2 vs C3 = ns		
						I vs other 3 groups:		
						p<0.0001		
Nehme et al	randomized	n= 137	I1: 0.454% SnF2 + SHMP	C= 0.76% MFP	Brushing twice	BL: I1=0.36, I2= 0.32	Drop-out=6	High
2013	double-blind			negative cocntrol	daily for for 1 min.	C=0.30		
	parallel group	I1:= 21	I2: 0.454% SnF2 + STP				Sponsored by	
		I2:= 57				8W: I1=0.35, I2= 0.28	GlaxoSmithKline	
	Lobene stain index	C: n= 59				C=0.28		
	1968						Equal effect between	
		USA				No diff. I vs C	test and control	
	8 W							
Schiff et al	randomized	n= 80 (49 male/31 female)	I: 0.454% SnF2 + SHMP	C: 0.243% NaF + 0.3% TCN	Brushing twice	BL: I=0.0, C=0.0	No drop-out	High
2005	double-blind	27.5 (19-45) yrs.		positive control	daily for for 1 min.			
	parallel group					6M: I=0.02, C=0.0	Sponsored by	
		I= 40				No diff. BL vs 6M	Procter & Gamble	
	Lobene stain index	C= 40						
	1968						Equal effect between	
		USA					test and control	
	6 M							
Terézhalmy et al	randomized	Study 1:	Study I:	Study I:	Brushing twice	Study 1:	No drop-out	High
2007	double-blind	n=29 (12 male/17 female)	I: 0.454% SnF2 + SHMP	C: 0.243% NaF + 0.3% TCN	daily for for 1 min.	BL: I=1.06, C=1.05		
	parallel group	50.4 (21-62) yrs.		positive control		2W: I=0.57, C=0.53	Sponsored by	
			Study II			I vs C: ns	Procter & Gamble	
	Lobene stain index	Study 2:	I: 0.454% SnF2 + SHMP	Study II:				
	1968	n=30 (17 male/13 female)		C: 0.243% NaF + 0.3% TCN		Study 2:	Equal effect between	
		47.6 (33-59) yrs.		positive conrol		BL: I=1.68, C=1.48	test and control	
	2 W					2W: I=1.41, C=1.40		
		USA				I vs C: ns		

BL (baseline), I (intervention), C (control), NaF (Sodium fluoride), SnF2 (Stannous fluoride), SnCl (stannous chloride), STP (sodium tripolyphosphate), SHMP (Sodium hexametaphosphate), MFP (monofluorphosphate) TCN (Triclosan), TP (Toothpaste), NS (not significant), vs (versus).

To conclude that the favorable results that the present review found are exclusively related to SnF_2 content, identical toothpastes with and without SnF_2 must be compared. Other factors, such as the unique silica content of the SnF_2 toothpaste, may contribute to the positive findings.

4.6. Bias

Analysis of the included papers followed SBU recommendations for quality assessment. Many of the studies were sponsored by the manufacturers or had authors employed by a toothpaste manufacturer. Although the studies were carefully executed and presented evidence of good quality, the involvement or support of the manufacturers could be regarded as a factor in potential bias. Additional studies that are less dependent on commercial interests and performed by independent researchers are needed. Studies with similar designs including comparable test and control products are necessary for conclusive findings.

5. Conclusion

The present review found that stabilized SnF_2 toothpaste had a positive effect on the reduction of dental calculus build-up, dental plaque, gingivitis, stain and halitosis. A tendency towards a more pronounced

effect than using toothpastes not containing SnF_2 was found, though the results of the individual trials in the meta-analyses showed a substantial heterogeneity. However, a new generation of well conducted randomized trials are needed to further support these findings.

Declarations

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

Funding statement

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Competing interest statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

Acknowledgements

The authors thank Magdalena Svanberg and Klas Moberg, librarians at Karolinska Institutet, Huddinge, Sweden, for their assistance with the literature search. We also thank Helena Domeij, DDS, PhD, and the Swedish Agency for Health Technology Assessment and Assessment for Social Service for assistance with the meta-analyses.

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