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REVIEW ARTICLE

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The effect of medicated, sugar-free chewing gum on plaque and clinical parameters of gingival inflammation: *a systematic review*

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Abstract: *Objective:* This study aimed to systematically review the present literature to establish the clinical effect of *medicated*, sugar-free chewing gum on plaque indices and parameters of gingival inflammation. *Materials and methods:* MEDLINE–PubMed, Cochrane CENTRAL and EMBASE databases were searched up to April 2012 to identify appropriate studies. Included studies used an intervention of *medicated,* sugar-free chewing gum containing antimicrobial agents or herbal extracts compared with a control gum. Plaque and gingivitis scores were selected as outcome variables. *Results:* Independent screening of 594 unique titles and abstracts identified 10 *non-brushing* and four *brushing* studies that met the eligibility criteria. Means and standard deviations were extracted. A sufficient number of studies evaluated chlorhexidine gum to perform a meta-analysis. Although this review provides evidence for the comparative effectiveness of chewing gums containing various ingredients, the results must be weighed carefully against the methods that were used to assess their outcomes. *Conclusion:* Most of the chewing gums with antimicrobial agents or herbal extracts were shown to have a positive effect with respect to plaque and gingivitis scores. The most compelling evidence was provided for chewing gum containing chlorhexidine. Meta-analysis and individual results indicate a beneficial effect of chlorhexidine on plaque inhibition. However, GRADE evidence profile shows that the recommendation to use CHX-gum to reduce plaque scores in the absence of brushing is considered to be 'weak'. Other ingredients with positive outcomes on plaque scores are eucalyptus, acacia, funoran, Pycnogenol and mastic. Limited data with respect to gingivitis scores were available, and the following agents showed a positive effect: magnolia, eucalyptus and CHX.

Key words: chewing gum; gingival inflammation; meta-analysis; plaque; systematic review

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Introduction

Chewing gum is a worldwide multibillion-dollar industry, with more than a half million tons chewed annually. There are two chewing gum categories with different potential benefits. There are the so-called 'fun and pleasure gums', sugar-based or sugar-free, and there are the so-called 'functional chewing gums', such as *medicated* chewing gums (1). Chewing gum consists of a gum base, sweetener, flavouring and an aromatic agent.

In a recent systematic review (2), it has been observed that the use of sugar-free chewing gum as an adjunct to toothbrushing provides a small but significant reduction in plaque scores.

Chewing gum is one of many potential vehicles for establishing sufficient concentrations of antibacterial agents in the oral environment to reduce the growth of plaque (1). The advantage with chewing gum is that it is usually kept in the mouth for a longer time than rinses and toothpastes. Medicated chewing gums have been studied and used as delivery vehicles for a host of dental substances, such as calcium, bicarbonate, carbamide, chlorhexidine, fluoride and polyol sweeteners, as well as medicinal substances and vitamins (3). Antibacterial agents including chemical inhibitors have been successfully used to maintain supragingival cleanliness as an aid for mechanical oral hygiene measures. Certain plant extracts can also serve as sources of therapeutic agents. Some of these natural extracts, for example magnolia bark extract, possess antibacterial activity against cariogenic and periodontopathic bacteria (4–6).

Thus far, no systematic quantitative evaluation has been performed concerning the clinical effects of *medicated*, sugar-free chewing gum containing antimicrobial agents or herbal extracts on plaque indices and parameters of gingival inflammation. Therefore, this paper systematically evaluates the current literature to add 'evidence-based' knowledge concerning the impact of sugar-free chewing gum containing different antimicrobial agents or herbal extracts on oral health compared with regular, sugar-free gum or gum base.

Materials and methods

This systematic review was conducted in accordance with the guidelines of Transparent Reporting of Systematic Reviews and Meta-analyses (PRISMA-statement) (7).

Search strategy

Three Internet sources were used to search for appropriate papers that satisfied the study purpose. These sources included the National Library of Medicine, Washington, DC (MEDLINE–PubMed), the Cochrane Central Register of Controlled Trials (CENTRAL) and EMBASE (Excerpta Medical Database by Elsevier). For this comprehensive search, all three databases were searched for eligible studies up to 20 April 2012. The structured search strategy was designed to include any published paper that evaluated the effect of sugar-free chewing gum on plaque and parameters of gingival health. No attempt was made to access the grey (non-published) literature. For details regarding the search terms used, see Box 1.

The eligibility criteria were as follows:

- Randomized controlled clinical trials (RCTs) or controlled clinical trials (CCTs);
- Manuscripts written in the English language;
- Conducted in humans;
- Participants $\geq$18 years of age and without orthodontic appliances or (partial) dentures [ADA, Guideline Sugar-Free Chewing Gums 2010 (8)];
- Intervention group: *medicated*, sugar-free chewing gum containing antimicrobial agents or herbal extracts;
- Control group: placebo and/or negative control and/or sugar-free control (without antimicrobial agents or herbal extracts);
- Clinical parameters: plaque scores and gingivitis scores.

Box 1

Search terms used for PubMed–MEDLINE, Cochrane CENTRAL and EMBASE. The search strategy was customized according to the database been searched

The following strategy was used in the search:

[{intervention} AND {outcome/disease}]

[*Intervention:*<[MeSH terms/all subheadings] Chewing Gum OR [text words] Chewinggum OR Chewinggums OR Chewing-gum OR Chewing-gums OR Gum-chewing OR Bubblegum OR Bubblegums OR Bubble-gum OR Bubble-gums>

OR

<(Chewing OR chew OR bubble) AND (Gum OR gums)>}

AND

{*Outcome/disease:* [MeSH terms/all subheadings] Gingival Pocket OR Periodontal Pocket OR Periodontal Diseases OR gingival hemorrhage OR gingivitis OR [text words] gingivitis OR gingivit* OR gingival bleeding OR gingival hemorrhage OR gingival diseas* OR gingival index OR gingival inflammation OR bleeding on probing OR papillary bleeding OR bleeding index OR sulcus bleeding index OR Periodontitis OR pocket depth OR Gingival Pocket OR Periodontal Pocket OR Periodontal Diseas* OR pockets OR probing depth OR probing-depth OR probing-pocket-depth OR probing pocket depth OR pocket-depth OR periodontal attachment loss OR plaque index OR dental plaque OR plaque OR interdental plaque OR interproximal plaque OR dental deposit* OR stain OR discoloration OR calculus OR tartar]

The asterisk (*) was used as a truncation symbol.

Screening and selection

Two reviewers (GAW and RSK) independently screened all titles and abstracts for eligible papers. If the eligibility aspects were present in the title, the paper was selected. If none of the eligibility aspects was mentioned in the title, the abstract was read in detail to screen for suitability. When the abstract was not clear, but the title appeared to be relevant, the paper was selected for full-text reading. If no abstract was available, but the title met the eligibility criteria, the paper was also selected for full-text reading. After selection, the full-text papers were read in detail by two reviewers (DES and RSK). Any disagreement between the two reviewers was resolved after additional discussion. If a disagreement persisted, the judgment of a third reviewer (GAW) was decisive. The papers that fulfilled all of the selection criteria were processed for data extraction. All of the reference lists of the selected studies were hand-searched by two reviewers (DES and RSK) for additional published work that could possibly meet the eligibility criteria of the study.

Assessment of heterogeneity

The heterogeneity across the studies was determined according to the following factors:

- Study design;
- Participant characteristics;
- Intervention, control and regimen;
- Clinical indices;
- Funding source.

Quality assessment

Two reviewers (DES and RSK) scored the methodological qualities of the included studies. The methodological study quality was assessed according to the method described by Keukenmeester *et al.* (2). In short, when random allocation, defined eligibility criteria, blinding of examiners, blinding of patients, balanced experimental groups, identical treatment between groups (except for the intervention) and reporting of follow-up were present, the study was classified as having a low risk of bias. When one of these seven criteria was missing, the study was considered to have a moderate risk of bias. When two or more of these criteria were missing, the study was considered to have a high risk of bias, as proposed by Van der Weijden *et al.* (9).

Data extraction

The data from the papers that met the selection criteria were processed for further analysis. Data were extracted with regard to medicated, sugar-free chewing gum in comparison with a placebo gum. For studies that presented an intermediate assessment, the baseline and final evaluations were used. The baseline, end and incremental mean values and standard deviation (SD) values were extracted by DES and RSK. Disagreements were resolved by discussion, and if the disagreement persisted, the judgment of a third reviewer (GAW) was decisive.

Data analysis

Studies were categorized as *non-brushing* studies (i.e. examining the use of chewing gum in the absence of daily toothbrushing focusing on plaque parameters, duration <4 weeks) and *brushing* studies (i.e. examining the use of chewing gum in addition to daily oral self-care focusing on plaque and gingivitis parameters, duration $\geq$4 weeks). When appropriate, a meta-analysis was performed, and the differences in the means (DiffM) were calculated using the Review Manager 5.1 software with the 'fixed-effects' model [RevMan version 5.1 for Windows, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration (10)]. Only two studies met the criteria for this quantitative analysis of the total body of evidence. Therefore, the collective data were summarized using vote counting and presented in a descriptive manner (Table 5).

Grading the 'body of evidence'

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system as proposed by the GRADE working group was used to grade the evidence emerging from this review (11,12). Two reviewers (DES and RSK) rated the quality of the evidence and the strength of the recommendations according to the following aspects: risk of bias of the individual studies; consistency and precision among the study outcomes; directness of the study results; and detection of publication bias. Any disagreement between the two reviewers was resolved after additional discussion.

Results

Search and selection results

The search resulted in 594 unique papers (for more details, see Fig. 1). The screening of titles and abstracts initially identified 25 full-text articles. In total, 11 papers were excluded after full-text reading based on the eligibility criteria; see Table 1 for the reasons for exclusion. No additional papers were retrieved from the reference lists. Consequently, 14 papers were identified as eligible for inclusion in this review according to the defined criteria for the study design, participants, intervention and outcome. Of these 14 papers, 10 *non-brushing* studies and four *brushing* studies were assessed for heterogeneity, quality assessment and data extraction.

Assessment of heterogeneity

Considerable heterogeneity was observed in the 14 clinical trials regarding study design, evaluation period, oral prophylaxis, intervention, control and regimen. Information regarding the study characteristics, including study population (number, gender and age of participants) and funding source, is displayed in

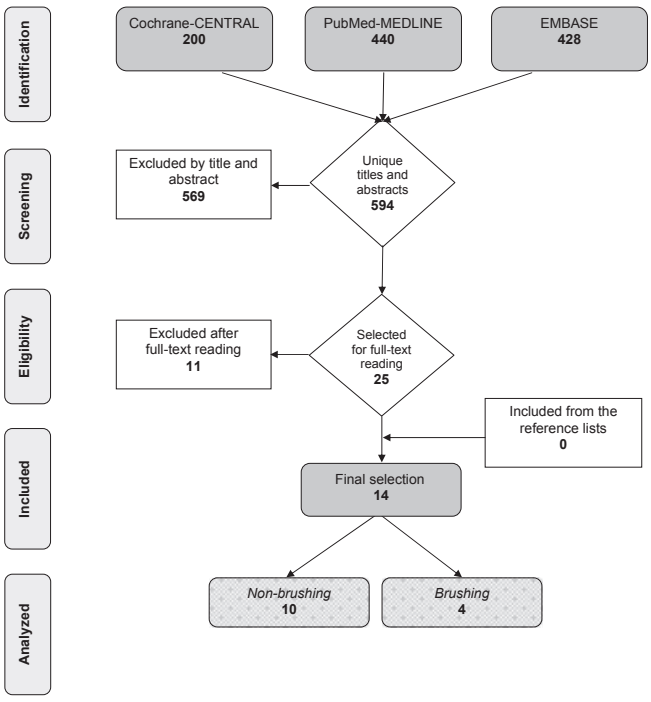

Fig. 1. Search and selection results.

Table 1. **Overview of the studies that were excluded after full-text reading**

Author(s) (reference)	Reason for rejection
Cochrane *et al.* (13)	No clinical data
Sofrata *et al.* (14)	Intervention of *Salvadora persica* (miswak) chewing sticks, no chewing gum
Amoian *et al.* (15)	Participants < 18 years old
Twetman *et al.* (16)	Intervention gum was a probiotic chewing gum containing *Lactobacillus reuteri* and ATCC, no antimicrobial agents or herbal extracts
Hellgren (17)	Intervention gum was a chewing gum containing Krillase, no antimicrobial agent or herbal extract
Lingström *et al.* (18)	Intervention gum was a chewing gum containing vitamin C, no antimicrobial agent or herbal extract
Kleber *et al.* (19)	No control gum; the control group used breath mints
Simons *et al.* (20)	Elderly volunteers with (partial) dentures
Sharma *et al.* (21)	No control gum; the control group used breath mints
Simons *et al.* (22)	Three subjects wore partial dentures, and four had fixed prostheses
Nuuja *et al.* (23)	Chewable preparations/tablets, but no chewing gums

Table 2. In this review, different indices and their modifications are used.

Study design and participant characteristics

Eleven studies were double blind. Of the nine studies using a crossover design, the washout periods varied from 2 to 10 days (for the *non-brushing* studies, the participants resumed their normal oral hygiene habits). The *non-brushing* studies had smaller subject populations (range 6–40) than the *brushing* studies (range 29–119).

All of the *non-brushing* studies included dental care professionals as participants for the experiment. *Brushing* study XIII used dental staff and students. The other three studies, which evaluated the effect of chewing gum on gingivitis scores, used gingivitis patients (XII) with a minimum mean gingival index of 1.2 (49) (XIV) or >25% bleeding on probing (XI). In eight experiments (I, II, III, V, VI, XII, XIII and XIV), the participants received oral prophylaxis before each test period.

Intervention, control and regimen

For this review, *medicated*, sugar-free chewing gum was used as the intervention. Three types of control gums were included:
1 Placebo gum: identical to the medicated gum in the experiment but without the antimicrobial agent or herbal extract.
2 A sugar-free control gum: a sugar-free gum containing xylitol or sorbitol.
3 A negative control gum consisting only of gum base.

In one *non-brushing* study (IV), the participants wore acrylic stints placed in one quadrant. The acrylic stent covering three teeth was worn only when the participants brushed their teeth. The three teeth covered by the stent, which were not subjected to brushing, were used for evaluation. In three of the *brushing* studies (XI, XII and XIV), the study participants used the same toothpaste that had been provided at the start of the experiment. Certain studies specifically mentioned that the participants had to abstain from using any other chewing gums (II) or products containing xylitol or sorbitol (XI). Six studies (II, VI, VII, IX, X and XI) mentioned that the participants were requested to maintain their customary dietary habits. In two *brushing* studies (XI and XIV), it was specifically mentioned that toothbrushing was not allowed for 30–60 min before or after the use of the chewing gum. In study II, the participants were requested to avoid eating and drinking during the first hour after using the chewing gum. Moreover, in study XIII, the participants were not allowed to consume any food or drinks for 1 h after chewing and were not allowed to eat, smoke or brush their teeth for 2 h before each visit.

Study quality

Quality assessment values, including the internal, external and statistical validity, are presented in Table 3. Based on a summary of these criteria, the estimated potential risk of bias is low for four studies (I, III, XI and XII), moderate for seven studies (II, IV, V, VI, VII, XIII and XIV) and high for the remaining three studies (VIII, IX and X).

Study XII was commissioned and financially supported by Lotte Central Laboratory, Saitama, Japan. Drs. Osawa and Shimizu, coauthors of this study, are employed full time as researchers with Lotte.

Study outcomes

Information regarding the changes within each intervention group for the various indices is presented in Table 4A–C. The outcomes are presented separately for the *non-brushing* and *brushing* studies. Analyses of within-group changes are not commonly reported.

Table 5 presents a summary of the descriptive data concerning significant differences between the intervention groups (*medicated*, sugar-free chewing gums and control gums).

Plaque score

In the *non-brushing* studies, there are six comparisons of CHX-containing gum versus a control gum, as reported in four studies (I, VI, IX and X). All of these six comparisons showed that the CHX-medicated chewing gum was significantly more

Table 2. **Overview of the included *non-brushing* and *brushing* studies processed for data extraction**

No. Authors (reference)	Study design, duration	No. of subjects baseline (end), gender, age	Groups *Products supplied by...*	Regimen: Use and instruction *Financially supported by...*	Authors' orginal conclusions
I. Kolahi *et al.* (24)	RCT Crossover Double blind 5 days	18 (18) ♀: 10 ♂: 8 Mean age: 22 Age range: 19–28	Med-gum (CHX 10 mg, mannitol, aspartame) Placebo	1 gum/2 × daily/20 min Non-brushing *The Research Funds of the Isfahan University of Medical Sciences*	CHX can be successfully incorporated in a chewing gum-based delivery system for use as an adjunct to mechanical plaque control
II. Pizzo *et al.* (25)	RCT Crossover Single blind 4 days	12 (12) ♀: 4 ♂: 8 Mean age: 23 Age range: 21–28	Med-gum (Golia relief: zinc gluconate) SFC-gum	1 gum/4 × daily/30 min Non-brushing	Chewing gum containing zinc gluconate provides no plaque inhibitory effects on smooth surfaces and should not be recommended as an adjunct to mechanical oral hygiene
III. Takahashi *et al.* (26)	RCT Parallel Double blind 7 days	20 (20) ♀: 4 ♂: 16 Mean age: 25.9 Age range: ?	Med-gum (Mastic (Pistacia lentiscus)) Placebo *Maubeni Company, Tokyo, Japan, and Nakamura Kairo Corporation, Japan*	1 gum/3 × daily/20 min Non-brushing *The Marubeni Company and Ministry of Education, Science, and Culture of Japan*	Mastic chewing gum is a useful antiplaque agent in reducing plaque formation on teeth
IV. Kimbrough *et al.* (27)	RCT Parallel Double blind 14 days	40 (40) ♀: 20 ♂: 20 Mean age:? Age range: 22–35	Med-gum (Pycnogenol 5 mg) SFC-gum (Trident Advantage gum)	1 gum/6 × daily/15 min Non-brushing *Horphag Research, Geneva, Switzerland*	Pycnogenol-containing chewing gums can minimize gingival bleeding and plaque accumulation
V. Sato *et al.* (28)	RCT Crossover Double blind 4 days	15 (?) ♀: 4 ♂: 11 Mean age: 25 Age range: 23–30	Med-gum (Funoran) Med-gum (Eucalyptus extract) Placebo	1 gum/3 × daily/10 min Non-brushing	Funoran-containing chewing gum and eucalyptus extract-containing chewing gum may be useful in inhibiting dental plaque formation
VI. Tellefsen *et al.* (29)	RCT Crossover Double blind 6 days	14 (?) ♀: 7 ♂: 7 Mean age: 25 Age range: 21–35	Med-gum (CHX 5.0 mg) SFC-gum1 (Xylitol 0.8 g) SFC-gum2 (Sorbitol 1.0 g) *Fertin A/S, Vejle, Denmark (Med-gum)*	1–2 gums/3 × daily/20 min (2 in the morning, 2 after the midday meal and 1 in the afternoon) Non-brushing	Regular use of CHX-containing chewing gum appears to be useful in controlling dental plaque formation
VII. Etemadzadeh (30)	RCT Crossover Double blind 4 days	12 (?) ♀: ? ♂: ? Mean age: ? Age range: ?	Med-gum (Urea hydrogen peroxide 18.5 mg, sorbitol 0.4 g) Placebo NC-gum *Fertin Laboratories, Vejle, Denmark*	2 gums/5 × daily/10 min Non-brushing	The observed plaque-growth-inhibiting effect of the hydrogen peroxide-releasing chewing gum was found to be of limited clinical significance
VIII. Gazi (31)	RCT Crossover Single blind 7 days	10 (?) ♀: 10 ♂: 0 Mean age: ? Age range: ?	Med-gum (Acacia) SFC-gum	?/5 × daily/10 min Non-brushing	Acacia gum appeared to have the potential to inhibit early plaque formation
	RCT Crossover Single blind 5 days	10 (?) ♀: 0 ♂: 10 Mean age: ? Age range: ?	Med-gum (Acacia) SFC-gum	?/5 × daily/10 min Non-brushing	

(Continued)

Table 2. **(Continued)**

No. Authors (reference)	Study design, duration	No. of subjects baseline (end), gender, age	Groups *Products supplied by...*	Regimen: Use and instruction *Financially supported by...*	Authors' orginal conclusions
IX. Ainamo *et al.* (32)	RCT Crossover Double blind 5 days	6 (?) ♀: ? ♂: ? Mean age: ? Age range: ?	Med-gum (CHX 5 mg, sorbitol 447 mg) NC-gum	2 gums/2 × daily/10 min Non-brushing	CHX acetate, when released from chewing gum, has an antiplaque effect.
X. Ainamo & Etemadzadeh (33)	RCT Crossover Double blind 4 days	12 (?) ♀: ? ♂: ? Mean age: ? Age range: ?	Med-gum (CHX 5 mg, urea hydrogen peroxide 20 mg, sorbitol 427 mg) Med-gum (CHX 5 mg, sorbitol 447 mg) NC-gum (gum base with flavouring agents (without sweetener))	2 gums/5 × daily/10 min Non-brushing	The CHX + hydrogen peroxide-containing gum and the CHX-gum had an excellent plaque-growth-inhibiting effect during the 4-day test periods
XI. Campus *et al.* (34)	RCT Parallel Double blind 4 weeks	120 (119) ♀: 65 ♂: 55 Mean age: 24.3 Age range: 18–30	Med-gum (magnolol, xylitol) Placebo SFC-gum (sorbitol) *Perfetti Van Melle SpA (Lainate, Italy)*	1–2 gums/3 × daily/5 min (2 in the morning, 2 after the midday meal and 1 in the afternoon) Normal oral hygiene habits. Toothpaste containing 1,450 ppm NaF was provided.	A chewing gum containing magnolia bark extract and xylitol showed an effect on the reduction in bleeding on probing, thereby increasing oral health
XII. Nagata *et al.* (35)	RCT Parallel Double blind 12 weeks	100 (97) ♀: 49◊ ♂: 48◊ Mean age: 34◊ Age range: 20–49	Med-gum (0.6% eucalyptus extract) Med-gum (0.4% eucalyptus extract) Placebo	2 gums/5 × daily/5 min No toothbrushing instruction was given *Lotte Central Laboratory, Saitama, Japan*	Chewing gum containing eucalyptus extract had a significant effect on plaque accumulation, gingival index and bleeding on probing, and may promote periodontal health
XIII. Fure *et al.* (36)	RCT Crossover Double blind 12 weeks	30 (29) ♀: 16 ♂: 13 Mean age: 40 Age range: 22–75	Med-gum (urea, sorbitol, xylitol) Placebo *Fertin Laboratories*	5 pieces daily/10–20 min Normal toothbrushing Toothpaste containing 0.055% sodium fluoride (ACTA®) *Patentmedelsfonden för-rOdontologisk Profylaxforskning*	The frequent use of sugar-free chewing gum, with or without urea, can be considered to be beneficial from an overall oral health point of view
XIV. Smith *et al.* (37)	RCT Parallel Single blind 8 weeks	90 (90) ♀: ? ♂: ? Mean age: ? Age range: ?	Med-gum (CHX 5 mg) Placebo *Fertin A/S, Vejle, Denmark (Med-gum)* *Corsodyl, ICI Pharmaceuticals,* Macclesfield, England (Placebo)	2 gums/2 × daily/10 min Oral hygiene with fluoride toothpaste and multitufted toothbrushes	Chlorhexidine chewing gum used with normal tooth cleaning provides similar adjunctive benefits to oral hygiene and gingival health as a 0.2% chlorhexidine rinse

Med-gum, medicated gum (sugar-free chewing gum with an active/therapeutic ingredient); Placebo, placebo chewing gum (identical to the medicated gum but without the active ingredient); SFC-gum, sugar-free control gum; NC-gum, negative control gum: gum base.
◊ = calculated by the authors of this review based on the presented data in the selected paper.
? = unknown.

Table 3. **Methodological, validity and quality scores of the included non-brushing and brushing studies**

Model	Non-brushing									
	Study									
Quality criteria	I	II	III	IV	V	VI	VII	VIII	IX	X
Internal validity										
Random allocation*	+	+	+	+	+	+	+	+	+	+
Allocation concealment	?	?	?	?	?	?	?	?	?	?
Blinded to patient*	+	–	+	+	+	+	+	–	+	+
Blinded to examiner*	+	+	+	+	+	+	+	+	+	+
Blinding during statistical analysis	+	?	?	?	?	?	?	?	?	?
Balanced experimental groups*	+	+	+	+	+	+	+	+	+	+
Reported loss to follow-up*	+	+	+	+	–	–	–	–	–	–
No. (%) of dropouts	0	0	0	0	?	?	?	?	?	?
Treatment identical, except for intervention*	+	+	+	+	+	+	+	+	+	+
External validity										
Representative population group	+	+	+	+	+	+	+	+	+	+
Eligibility criteria defined*	+	+	+	–	+	+	+	–	–	–
Statistical validity										
Sample size calculation and power	+	?	?	?	?	?	?	?	?	?
n sufficient for ADA + guideline ($n \geq 15$) (8)	+	–	–	+	?	–	–	–	–	–
Point estimates	+	+	+	+	+	+	–	+	–	–
Measures of variability presented for the primary outcome	+	+	+	+	+	+	–	+	–	–
Per protocol analysis	–	+	?	?	?	?	?	?	?	?
Include an intention-to-treat analysis	+	–	?	?	?	?	?	?	?	?
Authors' estimated risk of bias	**Low**	**Mod**	**Low**	**Mod**	**Mod**	**Mod**	**Mod**	**High**	**High**	**High**

Model	Brushing			
	Study			
Quality criteria	XI	XII	XIII	XIV
Internal validity				
Random allocation*	+	+	+	+
Allocation concealment	+	?	?	?
Blinded to patient*	+	+	+	–
Blinded to examiner*	+	+	+	+
Blinding during statistical analysis	+	?	?	?
Balanced experimental groups*	+	+	+	+
Reported loss to follow-up*	+	+	+	+
No. (%) of dropouts	0.8%◊	3%◊	3.3%◊	0
Treatment identical, except for intervention*	+	+	+	+
External validity				
Representative population group	+	+	–	?
Eligibility criteria defined*	+	+	–	+
Statistical validity				
Sample size calculation and power	+	?	?	?
n sufficient for ADA + guideline ($n \geq 15$) (8)	+	+	+	+
Point estimates	+	+	+	+
Measures of variability presented for the primaryoutcome	+	+	+	+
Per protocol analysis	?	–	–	–
Include an intention-to-treat analysis	–	+	+	+
Authors' estimated risk of bias	**Low**	**Low**	**Mod**	**High**

Criteria were designated for each domain of internal validity, external validity and statistical methods. Each aspect of the score list was given a rating of '+' for an informative description of the item at issue and a study design meeting the quality standard, '–' for an informative description without a study design that met the quality standard and '?' for lacking or insufficient information.
+ = Yes.
– = No.
? = Not specified/unclear.
◊ = Calculated by the authors.
NA = Not Applicable.
*Reporting criteria for estimating the potential risk of bias.

Table 4. **Mean (SD) scores for the different intervention groups are presented separately for non-brushing and brushing studies, with various indices and their modifications. Within-group analyses are presented**

Model	No.	Index	Intervention groups	Mean (SD)			Statistically significant within groups
				Baseline	End	Difference	
(A) Plaque score							
Non-brushing	I.	Quigley & Hein (38)	Med-gum (CHX)	1.0911 (0.4093)	0.9322 (0.4208)	−0.1589 (0.3940)	?
		Turesky *et al.* (39) Δ†	Placebo	1.1178 (0.4268)	4.1172 (0.4570)	+2.9994 (0.6669)	?
	II.	Quigley & Hein (38)	Med-gum (Zinc gluconate)	$\bar{x}$ 0◊	3.00◊ (0.31◊)	+3.00 (0.31)	?
		Turesky *et al.* (39) †	SFC-gum		2.77◊ (0.47◊)	+2.77 (0.47)	?
	III.	Quigley & Hein (38)	Med-gum [Mastic (*Pistacia lentiscus*)]	1.06 (0.29)	2.69 (0.29)	+1.63◊	Yes
		†	Placebo	1.19 (0.19)	3.15 (0.24)	+1.96◊	Yes
	IV.	Quigley & Hein (38)	Med-gum (Pycnogenol)	2.95 (1.03◊)	2.93 (1.48◊)	−0.02◊	No
		Turesky *et al.* (39) ∏	SFC-gum (Trident Advantage gum)	3.01 (0.85◊)	3.82 (1.03◊)	+0.81◊	Yes
	V.	Quigley & Hein (38)	Med-gum (Funoran)	$\bar{x}$ 0◊	1.83 (1.1)	+1.83◊	?
		Δ†	Med-gum (Eucalyptus extract)		1.97 (1.1)	+1.97◊	?
			Placebo		2.57 (1.2)	+2.57◊	?
	VI.	Quigley & Hein (38)	Med-gum (CHX)		0.7 (0.4)	−0.6◊	Yes
		Δ†	SFC-gum1 (Xylitol)	$\bar{x}$ 1.3 (0.4)	1.7 (0.3)	+0.4◊	?
			SFC-gum2 (Sorbitol)		2.7 (0.4)	+1.4◊	Yes
	VII.	Silness & Löe (41) ■‡	Med-gum (Urea hydrogen peroxide)	?	?	?	Yes*
		Ainamo & Bay (42)	Placebo	?	?	?	Yes*
		■‡	NC-gum	?	?	?	Yes*
	VIII.	Silness & Löe (41)	Med-gum (Acacia)	?	1.41 (0.43)	?	?
		Podshadley & Haley (43) Δ	SFC-gum	?	1.60 (0.32)	?	?
		Photographs	Med-gum (Acacia)	?	?	?	?
		Gazi (44)	SFC-gum	?	?	?	?
	IX.	Silness & Löe (41)	Med-gum (CHX)	?	?	?	?
		■ ‡	NC-gum (Gum base)	0.18	0.85	+0.67◊	Yes
	X.	Silness & Löe (41) ■‡	Med-gum (CHX + Urea hydrogen peroxide)	?	?	?	?
			Med-gum (CHX)	?	?	?	?
			NC-gum (Gum base with flavouring agents)	0.1	1.3	+1.2◊	Yes
Brushing	XIII.	Ainamo & Bay (42) ▲₪	Med-gum (Urea)	$\bar{x}$ 16.9% (14.4%)	11.5% (8.2%)	−5.4%◊	?
			Placebo		12.6% (12.4%)	−4.3%◊	?
	XIV.	Quigley & Hein (38)	Med-gum (CHX)	3.05 (0.34◊)	1.42 (0.47◊)	−1.63◊	?
		Turesky *et al.* (39) †	Placebo	3.15 (0.34◊)	2.09 (0.47◊)	−1.06◊	?
	XII.	Suzuki *et al.* (45) ●₪	Med-gum (Eucalyptus 0.6%)	1.86 (0.66)	1.43◊	−0.43 (0.33)	Yes
			Med-gum (Eucalyptus 0.4%)	1.90 (0.62)	1.55◊	−0.35 (0.37)	Yes
			Placebo	1.69 (0.80)	1.84◊	+0.15 (0.41)	No

(Continued)

Table 4. **(Continued)**

Model	No.	Index	Intervention groups	Mean (SD) Baseline	End	Difference	Statistically significant within groups
(B) Bleeding score							
Brushing	XI.	BOP%	Med-gum (magnolol)	32.1%	21.6%	−10.5%◊	Yes
			Placebo	33.4%	25.3%	−8.1%◊	Yes
			SFC-gum (sorbitol)	33.0%	29.4%	−3.6%◊	No
	XIII.	Ainamo & Bay (42) ▲₪	Med-gum (Urea)	$\bar{x}$ 7.2% (7.0%)	2.6% (3.7%)	−4.6%◊	?
			Placebo		4.1% (5.2%)	−3.1%◊	?
	XII.	Chaves *et al.* (46) BOP% ‡	Med-gum (Eucalyptus 0.6%)	48.54% (25.55%)	29.53%◊	−19.01% (16.46%)	Yes
			Med-gum (Eucalyptus 0.4%)	42.86% (22.80%)	28.81%◊	−14.05% (16.11%)	Yes
			Placebo	38.57% (26.25%)	42.59%◊	+4.02% (16.01%)	No
	XIV.	Bleeding aspect of GI Löe & Silness (47) ‡	Med-gum (CHX)	?	?	22.7 (9.4◊)	?
			Placebo	?	?	17.00 (9.4◊)	?
(C) Gingival index							
Brushing	XII.	Löe & Silness (47) ‡	Med-gum (Eucalyptus 0.6%)	0.83 (0.31)	0.54◊	−0.29 (0.29)	Yes
			Med-gum (Eucalyptus 0.4%)	0.85 (0.36)	0.60◊	−0.25 (0.29)	Yes
			Placebo	0.80 (0.34)	0.79◊	−0.01 (0.24)	No
	XIV.	Löe & Silness (47) ‡	Med-gum (CHX)	1.50 (0.27◊)	0.98 (0.13◊)	−0.52 (0.13◊)	?
			Placebo	1.53 (0.27◊)	1.13 (0.13◊)	−0.40 (0.13◊)	?

Δ = only the six Ramfjord teeth (40) were scored or only six teeth.
■ = only the teeth on the left side of the jaw were scored.
▲ = only the teeth in the upper right quadrant were scored.
∏ = only the 3 teeth covered by the stint were used for evaluation.
● = measured according to the method described by (45): upper right and lower left molars, upper left and lower right premolars, and upper left and lower right incisors were selected.
† = only the smooth surfaces (facial and lingual sites) were measured.
‡ = the mesial, distal, buccal and lingual surfaces were measured.
₪ = 6 sites per tooth were measured.
◊ = calculated by the authors of this review based on the presented data in the selected paper.
? = unknown/not reported.
* = 2 different plaque indices were scored.

effective than the control gum. Two studies (VII and X) investigated the effect of urea-containing chewing gum. In study VII, the urea gum was significantly more effective than the gum base (NC-gum), but there was no significant difference compared with the placebo. The urea gum in study X, contained CHX, was significantly more effective than the gum base. In study II, analysis of variance did not show significant differences in antiplaque activity in the zinc gluconate gum compared with the placebo. The mastic-containing chewing gum, in study III, showed a significant difference in plaque scores ($P < 0.001$). In study IV, the Pycnogenol-containing chewing gum was significantly more effective than the sugar-free control gum. In study V, both funoran-containing and eucalyptus-containing gums were significantly more effective than the placebo gum. Two trials in study VIII evaluated the effect of acacia gum, and one of these trials showed a significant difference between the acacia gum and the SFC-gum ($P < 0.05$). In the *brushing* studies, eucalyptus-containing chewing gums were investigated in study XII, and both medicated gums in this study were significantly more effective than the placebo. The urea-containing gum (XIII) showed no significant effect on plaque scores compared with the placebo. The CHX-containing gum in study XIV also showed a significant difference compared with the placebo.

Gingivitis scores

The studies XII and XIV, which evaluated the gingival index, showed that the intervention gums were significantly more effective compared with the placebo gum. These studies also showed a significant difference in bleeding scores in favour of the medicated gums. Study XI did not investigate plaque scores but focused on bleeding scores and showed that the magnolia-containing gum was significantly more effective than

Table 5. **A summary of the descriptive data on whether there are significant differences between the medicated, sugar-free chewing gums and the control gums**

Model	No.	Frequency of use	Gum medication	Plaque score	Comparison
(A) Non-brushing studies					
Non-brushing	I.	1 gum/2 × daily/20 min	CHX	+	Placebo
	VI.	1–2 gums/3 × daily/20 min	CHX	+	SFC-gum1
			CHX	+	SFC-gum2
	IX.	2 gums/2 × daily/10 min	CHX	+	NC-gum
	X.	2 gums/5 × daily/10 min	Urea, CHX	+	NC-gum
			CHX	+	NC-gum
	VII.	2 gums/5 × daily/10 min	Urea	○*	Placebo
			Urea	+*	NC-gum
	II.	1 gum/4 × daily/30 min	Zinc gluconate	○	SFC-gum
	III.	1 gum/3 × daily/20 min	Mastic (Pistacia lentiscus)	+	Placebo
	IV.	1 gum/6 × daily/15 min	Pycnogenol	+	SFC-gum
	V.	1 gum/3 × daily/10 min	Funoran	+	Placebo
			Eucalyptus extract	+	Placebo
	VIII.	? gum/5 × daily/10 min	Acacia exp1	○	SFC-gum
			Acacia exp2	+	SFC-gum

Model	No.	Frequency of use	Gum medication	Plaque score	Bleeding score	Gingival index	Comparison
(B) Brushing studies							
Brushing	XI.	2 gums/3 × daily/5 min	Magnolia	□	+	□	SFC-gum
			Magnolia	□	+	□	Placebo
	XII.	2 gums/5 × daily/5 min	Eucalyptus extract 0.6%	+	+	+	Placebo
			Eucalyptus extract 0.4%	+	+	+	Placebo
	XIII.	5 pieces daily/10–20 min	Urea	○	○	□	Placebo
	XIV.	2 gums/2 × daily/10 min	CHX	+	+	+	Placebo

SFC-gum, sugar-free control gum (containing xylitol or sorbitol); NC-gum, negative control gum (gum base); CHX, chlorhexidine.
+ = Intervention was significantly more effective.
○ = No significant difference.
* = 2 different plaque indices were scored.
Exp = experiment.
□ = This aspect was not assessed in this study.

both SFC-gum ($P = 0.04$) and the placebo ($P = 0.01$). No significant differences in the bleeding scores between urea gum and the placebo were observed in study XIII.

Meta-analysis

A meta-analysis was performed to assess the effects of CHX-containing chewing gum as a monotherapy (*non-brushing*). The forest plot is presented in Fig. 2. This meta-analysis was performed for the plaque index of (38) and based on the studies I and VI. The analysis showed a significant effect ($P < 0.00001$) in favour of the CHX-containing gum with a difference in means (DiffM) of −2.19 and a 95% confidence interval (CI) of [−2.38; −2.01]. Other meta-analyses were not feasible due to the large variation in active ingredients, the use of different indices and the limited number of included studies in support of these ingredients.

Grading the 'body of evidence'

Table 6 shows a summary of the various aspects that were used to rate the quality of evidence and strength of recommendations according to GRADE (11,12). Sufficient support for this assessment was present only for CHX-containing chewing gum in *non-brushing* studies. Because the data are consistent, with a moderate estimated risk of bias, the precision is moderate, and the study results are not generalizable, the recommendation to use CHX-containing chewing gum to reduce the presence of plaque in the absence of brushing is considered to be 'weak'.

Discussion

Medicated chewing gum

Medicated chewing gum generally consists of a masticatory gum core that is composed of an insoluble gum base that can be mixed with sweeteners and flavours. In medicated chewing gum, active agents may be present in the core or in the coat or in both. The proportion of active agents can vary from 0.5% to 30% of the final gum weight. The coating can be applied as a film of polymers, waxes, sweeteners, flavours and colours (48). To succeed in the market, the gum formulation must have a pleasant taste and texture. One of the major challenges for medicated chewing gum product developers is that any small adjustment in the amount of active substances,

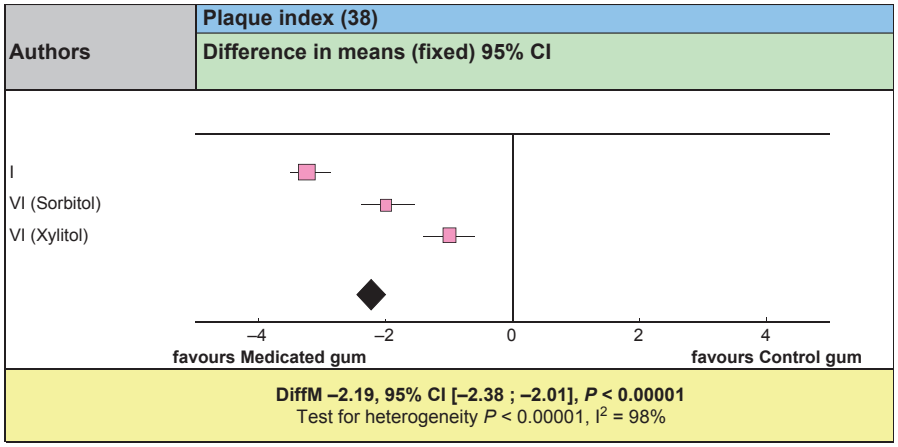

Fig. 2. Meta-analysis comparing the use of CHX-containing chewing gum with the use of a control gum in non-brushing studies.

Table 6. **GRADE evidence profile for the impact of the use of CHX-containing chewing gum on plaque scores in comparison with a control gum**

Follow-up	Outcome	Risk of bias	Consistency	Directness	Precision	Publication bias	**Strength of recommendation**
Non-brushing	**CHX-gum**	Moderate	Consistent	Not generalizable	Moderate	Possible	**Weak**

flavours or sweeteners often changes the gum base texture, which requires adjustments to customize the gum base for a specific active substance (48). There are different advantages of chewing gum as a carrier for antimicrobials. Chewing gum can be used at any time and everywhere (1,48). It is typically kept in the mouth longer than mouth rinses and toothpastes, which implies that the active agent, if successfully released into the saliva, would have ample time to be retained at a variety of reception sites (49–51). However, others claim that the ingredients released from chewing gum into the saliva disappear rapidly from the oral cavity because of involuntary swallowing and that the concentration in the oral cavity tends to decrease as a result of salivary dilution (52). The stability of medicated chewing gum is good because the incorporated therapeutic agents are protected from oxygen, light and water. Chewing gum can produce both local effects in the mouth (local delivery) and systemic effects after the active agents have been swallowed or (preferably) absorbed through the oral mucosa (1).

CHX-containing chewing gum

It is well established that chlorhexidine has a great influence on parameters of gingival health (53). In this review, there are five studies (I, VI, IX, X and XIV) that investigated the effect of CHX-containing gum. Study I used a chewing gum containing CHX gluconate, whereas the other studies used CHX acetate as an active ingredient. All of these five studies showed a significant difference in comparison with the control gum, and four of these studies assessed the gum in the absence of toothbrushing. The results of the included studies suggest that CHX-containing chewing gum may be useful for short-term plaque control, for instance, to support the oral health of hospitalized and geriatric patients. Although the body of evidence is consistent with respect to a positive effect of CHX-gum, this statement is merely based on non-brushing studies, which limits generalization of this recommendation. Subsequently, the GRADE evidence profile was considered to be 'weak'. Observation periods need to be extended if this product is anticipated for longer-term use. Recent narrative reviews also suggest that CHX chewing gum can be used to treat gingivitis and periodontitis and to inhibit plaque growth (48,54,55). CHX in a chewing gum formulation is more convenient to use than a CHX mouth rinse, and the bitter taste of CHX can be masked quite well in the gum formulation (54). However, in the studies published by Ainamo (IX and X), the subjective evaluations of taste were poor. The stain extent and intensity with CHX-containing gum are significantly lower than with CHX mouthwash (XIV), which may be related to its low dosage. Despite this low dosage of CHX, the stain intensity and extent recorded from the placebo gum were significantly less than with the CHX-gum (XIV). The optimal dosage of CHX in chewing gum has been shown to be a total of 20 mg daily (IX), whereas the total daily dose of CHX in mouthwash is often 40 mg (XIV). The RCTs in this review that include CHX-containing chewing gum primarily used a total daily dose of 20 mg (I, IX and XIV) or 25 mg (VI) of CHX. One study (X) used a total of 50 mg of CHX in chewing gum per day. A pilot study shows that the release of CHX acetate from chewing gum is, on average, 40% after 5 min and approximately 67% after 15 min of chewing (X). The participants in the studies including CHX-containing gum in this review chewed for 10 min (IX, X and XIV) or 20 min (I and VI). This chewing time and dose do not cause any pain or fatigue in the jaw muscles that might affect patient compliance (56).

Crossover studies

Although this review provides evidence for the effectiveness of various chewing gums containing antimicrobial agents or herbal extracts, the results must be weighed carefully against the methods that were used to assess their outcomes. Of the 14 studies included in this systematic review, five studies used a parallel-arm design (III, IV, XI, XII and XIV), whereas the other nine studies used a crossover design with washout periods varying from 2 to 10 days. The parallel-arm design is the simplest type of randomized trial. When the treatment assignment for each patient is made independently of all other patients, this design is sometimes called the completely randomized design to denote the fact that there are no constraints on the random assignments and that one patient's assignment does not influence the assignment of another patient (57). Crossover studies are often used with small numbers of participants because, with the parallel-arm design, a large imbalance in sample sizes between treatment groups is possible with small studies. An advantage of a crossover design is that each participant acts as his or her own control, eliminating between-participant variation. However, statistically, crossover trials are not appropriate due to the likelihood of a carry-over effect. There are concerns that the effect of the active ingredient in the chewing gum, for example CHX, might be prolonged. Crossover studies using therapeutic agents are at risk of showing a period effect that is greater than the effect of interest. A washout period from 2 to 10 days may not be sufficient, and longer washout periods are preferable (58). The two studies that were used for the meta-analysis were both crossover studies, which, based on the above, indicates that the results should be interpreted with caution. Moreover, both were short-term studies.

Acceptance Programme Guidelines

The American Dental Association® (ADA) has established several Acceptance Programme Guidelines, such as Adjunctive Dental Therapies for the Reduction of Plaque and Gingivitis (59) and Chemotherapeutic Products for Control of Gingivitis (60). A guideline discussing sugar-free chewing gums to help reduce/prevent cavities (8) is also available. At present, there is no guideline concerning chewing gum and plaque/gingivitis; therefore, we used the guidelines mentioned above.

If a company wishes to make an anticaries claim for its sugar-free gum with one or more active/therapeutic agents, the council requires at least two clinical studies showing that the gum provides a statistically significantly better caries reduction than the ADA-accepted, clinically tested, standard, sugar-free gum, when used in the same clinical study (8). If this requirement is also applied to plaque reduction, a claim can be made regarding the efficacy of CHX-gum. In this systematic review, more than two clinical studies show that CHX-containing chewing gum provides statistically significantly better short-term plaque reduction than the sugar-free control gums. However, it is not clear whether the CHX-gum used in the different clinical trials is exactly the same.

A sample size of at least 15 subjects is deemed necessary for claim support studies (8). In this review, six of ten *non-brushing* studies did not meet this criterion. The limited number of participants may have negatively impacted the outcome and power of the *non-brushing* studies. Furthermore, masked studies are required, and the populations selected for the studies must be representative of the individuals for whom the product is intended, which, in most cases, would be individuals with mild to moderate gingivitis (59). All of the included studies in this review are masked; however, the subject populations are not representative in all studies because all of the *non-brushing* studies included dental care professionals as participants. Another *brushing* study used dental staff and students. The periodontal condition and the oral cleaning habits of these participants are likely to be better than those of the general population. For the *non-brushing* studies, the inclusion of dental professionals or dental students was not deemed to be a critical item. However, the *non-brushing* aspect of these studies has a negative impact on their generalizability. Three other studies, which evaluated the effect of chewing gum on gingivitis scores, used a representative group of gingivitis patients with a minimum mean gingival index of 1.2 (47) or >25% bleeding on probing.

In accordance with the ADA guideline for Adjunctive Dental Therapies for the Reduction of Plaque and Gingivitis (59), the product must show clinical significance in gingivitis reduction compared with placebo controls in at least two well-designed clinical studies (minimum 4 weeks). All of the *brushing* studies were longer than 4 weeks, but only one study is available for each of the various ingredients, so there is insufficient evidence to make a firm, evidence-based statement. For chemotherapeutic products, product efficacy must be demonstrated by two clinical studies over 6 months (60). None of the studies included in this review meet this criterion.

Limitations

- A small number of papers is available evaluating the effect of chewing gum containing potential active ingredients other than CHX.
- The use of studies that were exclusively written in the English language may be a limitation. Although the potential impact of studies that have been published in languages other than English in a meta-analysis may be minimal, it is difficult to predict in which cases this exclusion may bias a systematic review (61).
- Another limitation may be the use of published research papers only. The authors of this review did not have the resources to obtain data that are kept 'on file' by the various chewing gum manufacturers. This is known as the 'file drawer problem' (62), as a form of publication bias.

• The formal testing for publication bias (63) could not be used owing to insufficient statistical power because <10 studies were included in the meta-analysis (61).

Conclusion

In this review, nearly all of the chewing gums with antimicrobial agents or herbal extracts were shown to have a positive effect with respect to plaque indices and parameters of gingival inflammation. The most compelling evidence was provided for chewing gum containing chlorhexidine. There were a sufficient number of studies that evaluated CHX-containing gum to perform a meta-analysis. The meta-analysis and the vote-counting results of the individual studies indicate a beneficial effect on plaque inhibition. However, the GRADE evidence profile shows that the recommendation to use CHX-containing chewing gum to reduce the presence of plaque in the absence of brushing is considered to be 'weak'. Other ingredients with positive outcomes on plaque scores are eucalyptus, acacia, funoran, Pycnogenol and mastic. Limited data with respect to gingivitis scores were available, but the following agents showed a positive effect: magnolia, eucalyptus and CHX.

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Directions for further research

Quality assessment values are presented in Table 3. The estimated risk of bias for those *non-brushing* studies evaluating CHX-containing chewing gum is low for one of these studies, moderate for one and high for two studies. Furthermore, these studies have very small subject populations (6–18 subjects). The *non-brushing* studies evaluating the effect of CHX chewing gum showed a reduction in plaque scores. However, the inadequate power and a moderate-high risk of bias of these study designs indicate improvements that could be a direction for further research. Additionally, further research investigating the effect of chewing gum containing anti-microbial agents or herbal extracts other than CHX is recommended.

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