Review

Essential Oils Compared to Chlorhexidine With Respect to Plaque and Parameters of Gingival Inflammation: A Systematic Review

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Background: The purpose of this review is to systematically evaluate the effects of an essential-oil mouthwash (EOMW) compared to a chlorhexidine mouthwash with respect to plaque and parameters of gingival inflammation.

Methods: PubMed/MEDLINE and Cochrane CENTRAL databases were searched for studies up to and including September 2010 to identify appropriate articles. A comprehensive search was designed, and the articles were independently screened for eligibility by two reviewers. Articles that evaluated the effects of the EOMW compared to chlorhexidine mouthwash were included. Where appropriate, a meta-analysis was performed, and weighted mean differences (WMDs) were calculated.

Results: A total of 390 unique articles were found, of which 19 articles met the eligibility criteria. A meta-analysis of long-term studies (duration ≥4 weeks) showed that the chlorhexidine mouthwash provided significantly better effects regarding plaque control than EOMW (WMD: 0.19; P = 0.0009). No significant difference with respect to reduction of gingival inflammation was found between EOMW and chlorhexidine mouthwash (WMD: 0.03; P = 0.58).

Conclusion: In long-term use, the standardized formulation of EOMW appeared to be a reliable alternative to chlorhexidine mouthwash with respect to parameters of gingival inflammation. *J Periodontol 2011;82:174-194.*

KEY WORDS

Chlorhexidine; control; essential oils; gingivitis; meta-analysis; plaque.

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Systematic reviews have rapidly gained an important place in aiding clinical decision making in medicine, although dentistry has been somewhat slower to adopt this approach. The objective of a systematic review is to provide a comprehensive and contemporary appraisal of research using transparent methods while aiming to minimize bias. If such conditions are met, there should be greater confidence in the conclusions of the review than in other summaries of clinical evidence.[1]

Mouthrinses have been used for centuries for medicinal and cosmetic purposes, but it is only in recent years that the rationale behind the use of chemical ingredients has been subject to scientific research and clinical trials.[2] One essential-oil mouthwash (EOMW)§ has the longest history of use, dating back to the 19th century. It has been used as a mouthwash for the prevention of dental and periodontal diseases.[2] In a recent systematic review,[3] an antigingivitis potential was established when this EOMW was used as an adjunct to unsupervised oral hygiene compared to a placebo or control. The first official approval of this EOMW dates back to 1987 and was based on clinical studies that satisfied the American Dental Association (ADA) criteria.[4-8] Currently, seven flavors of this EOMW have

§ Listerine, Johnson & Johnson, Skillman, NJ.

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been approved for the control of supragingival plaque and gingivitis by the ADA.[9] Another mouthrinse product approved by the ADA is chlorhexidine (CHX), which is a cationic bisbiguanide with a very broad antimicrobial spectrum. It was proven many times over as the most effective agent against plaque. It is used as an adjunct to mechanical cleaning procedures as well as used alone. Its effectiveness was also shown for control of gingivitis in long-term studies. The major advantage of CHX over most other compounds lies in its substantivity. It binds to soft and hard tissues in the mouth, enabling it to act over a long period after application of a formulation.[2] Bacterial counts in saliva consistently drop to between 10% and 20% of baseline after single rinses and remain at this level for ≥7 hours[10] and probably >12 hours.[11] Therefore, CHX is used as a positive control in many clinical trials of new mouthrinse formulations and is considered the gold standard. To our knowledge, there is no systematic review available that has evaluated comparisons of EOMW to a CHX mouthwash (CHX-MW).

Therefore, the aim of this review is to gather and evaluate, in a systematic manner, available data on the effect of a standardized EOMW formulation compared to a CHX-MW with respect to plaque, parameters of gingival inflammation, stains, and calculus when the products were used as an adjunct to self-performed, daily, oral hygiene procedures or as a monotherapy.

MATERIALS AND METHODS

Focused Question

For patients with gingivitis, what is the effect of a standardized EOMW compared to a CHX-MW with respect to the clinical parameters of gingival inflammation?

Search Strategy

Two internet sources were used to search for appropriate articles that satisfied the study purpose: the PubMed/MEDLINE and Cochrane Central Register of Controlled Trials (CENTRAL) databases. Both databases were searched for studies conducted during the period up to and including September 2010. This comprehensive search was designed to include any published articles that evaluated the effects of EOMW compared to CHX-MW. Detailed search strategies are shown in Figures 1 and 2.

The eligibility criteria for articles were as follows: randomized controlled clinical trials (RCTs) or controlled clinical trials; trials conducted in humans with subjects ≥16 years of age and in good general health (no systemic disorders); intervention: an EOMW‖ as a standardized formulation of essential-oil technology; comparison: a CHX-MW; mouthwashes either used as a monotherapy or as an adjunct to self-performed daily oral hygiene; parameters mentioned in short-term studies (duration <4 weeks): plaque; parameters mentioned in long-term studies (duration ≥4 weeks): plaque, stain, calculus, bleeding, and gingivitis.

<Intervention AND comparison>

Intervention:
<([text words] Listerine *or* essential oils *or* essential oil *or* Phenol *or* Phenols
or
[MeSH terms /all subheadings] "Oils, Volatile" *or* "Phenol" *or* "Phenols"
or
[Substance Name] "Listerine " *or* "tartar control Listerine")

AND

Comparison:
([text words] chlorhexidine *or* chlorhexidine phosphanilate *or* chlorhexidine di-gluconate *or* chlorhexidine gluconate *or* zinc-chlorhexidine *or* chlorhexidine gluconate lidocaine hydrochloride *or* CHX *or* CHX formulations
or
[MeSH terms /all subheadings] " chlorhexidine ")>

Figure 1.
PubMed/MEDLINE search strategy and terms.

<Intervention AND comparison>

Intervention:
<([text words] Listerine *or* essential oils *or* essential oil *or* Phenol *or* Phenols
or
[MeSH terms /all subheadings] "Oils, Volatile" *or* "Phenol" *or* "Phenols")

AND

Comparison:
([text words] chlorhexidine *or* chlorhexidine phosphanilate *or* chlorhexidine di-gluconate *or* chlorhexidine gluconate *or* zinc-chlorhexidine *or* chlorhexidine gluconate lidocaine hydrochloride *or* CHX *or* CHX formulations
or
[MeSH terms /all subheadings] " chlorhexidine ")>

Figure 2.
Cochrane CENTRAL search strategy and terms.

Screening and Selection

Only articles written in the English language were accepted. Case reports, letters, and narrative or historical reviews were not included in the search. First, the articles were independently screened by title and abstract by two reviewers (GAVdW and MPCVL). If the search key words were present in the title, the article was selected. If none of the key words were mentioned in the title, the abstract was read in detail to search for key words. When the abstract was not clear, but the title seemed to be relevant, the article was selected for full-text reading. If no abstract was available, but the title contained the key words, the article was also selected for full-text reading. After

‖ Listerine, Johnson & Johnson.

selection, full-text articles were read in detail by two reviewers (DES and MPCVL). Articles that fulfilled all selection criteria were processed for data extraction. Disagreements were resolved by a discussion. If the disagreement persisted, the judgment of a third reviewer (GAVdW) was decisive. All reference lists of the selected studies were hand searched by two reviewers (DES and MPCVL) for additional published work that could possibly meet the eligibility criteria of the review.

Assessment of heterogeneity. Factors used to evaluate the heterogeneity of the outcomes of the different studies were as follows: study design and subject characteristics; comparison and regimen; and industry funding.

Quality assessment. Two reviewers (DES and MPCVL) individually scored the methodologic quality of the included studies. The assessment of methodologic quality was performed by combining the proposed criteria of the RCT checklist of the Dutch Cochrane Center[12] with the quality criteria obtained from the Consolidated Standards of Reporting Trials statement[13] by Moher et al.,[14-17] Esposito et al.,[18] Needleman et al.,[19] the Delphi List,[20] and the Jadad scale.[21] This combination resulted in a quality-criterion list.

Criteria were designed to address external validity, internal validity, and statistical methods. An aspect of the score list was given a plus (+) for an informative description of the item at issue for a study design meeting the quality standard, a minus (–) for an informative description but a study design that did not meet the quality standard, and a question mark (?) for a lack of sufficient information.

When random allocation, defined inclusion and exclusion criteria, masking of patients and examiners, balanced experimental groups, identical treatment between groups except for intervention, and reporting of follow-up criteria were present, the study was classified as having a low risk of bias. Studies that were missing one of these six criteria were considered to have a moderate risk of bias. Studies missing two or more of these criteria were considered to have a high risk of bias. To assess the methodologic quality, the Center for Evidence-Based Medicine (CEBM) Levels of Evidence[22] resource was used. In this system, the level of evidence was scored as follows: score 1a was given to a systematic review (with homogeneity) of RCTs, score 1b was given to individual RCTs with a narrow confidence interval (CI), and score 1b– was given to individual RCTs with a wide CI. According to the CEBM, there are four grades of recommendation (A through D), where grade A denotes consistent level-1 studies.

Data extraction. From the collection of articles that met the inclusion criteria, data were extracted with regard to the effectiveness of EOMW compared to CHX-MW as a monotherapy or as an adjunct to self-performed oral hygiene. Mean values and SDs were extracted for baseline, end, and difference with respect to the parameters of interest (DES and MPCVL). The authors of this review specifically used only the data concerning the results of essential oils and CHX from the selected articles. Some of the studies provided SEs of the mean. Where possible, the authors calculated the SD based on the sample size ($SE = SD/\sqrt{N}$). Studies were categorized as non-brushing studies (*de novo* plaque accumulation and experimental gingivitis) and brushing studies (<4- and ≥4-week durations).

Data analyses. With the exception of one article (XIV),[23] only baseline data and end-of-trial assessments were available. Consequently, it was not possible to perform a meta-analysis of the differences because the SDs of the differences were not available and could not be calculated. Therefore, data for baselines and ends of trials were presented separately. An analysis was performed for both time points. A meta-analysis was performed for plaque parameters for studies ≥4 weeks of duration and for the *de novo* plaque accumulation studies. Because the non-brushing studies started with a thorough prophylaxis, the meta-analysis was performed using only available data from the end-of-trial assessments. Weighted mean differences (WMDs) were calculated with software¶ using a random-effect model. Not all studies were included in the meta-analysis (i.e., cases of non-comparable indices, inappropriate date presentation, or unknown SDs were excluded). Therefore, data were summarized in a descriptive manner.

RESULTS

Search and Selection

The PubMed/MEDLINE and Cochrane CENTRAL searches identified 383 and 66 articles, respectively (Table 1). In total, 390 unique articles were found. Screening of titles and abstracts initially identified 25 full-text articles. The reasons for exclusion of seven papers[24-30] are shown in Table 1. Hand searching of reference lists of selected studies identified one additional article for exclusion (XIX).[31] Ultimately, 19 articles were processed for data extraction.

Assessment of Heterogeneity

Considerable heterogeneity was observed in the study design, evaluation period, oral prophylaxis, intervention, industry funding, comparisons, and regimens used in the 19 selected articles. Furthermore, the numbers, ages, age ranges, and sex of

¶ Review Manager, version 4.2 for Windows, The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark.

Table 1.

Search and Selection Results

Selection	Results
Search	383 studies from PubMed/MEDLINE, 66 studies from Cochrane CENTRAL, and 59 identical studies
Unique articles	390
Articles excluded by title and abstract	365
Selected articles for full reading	25
Articles excluded after full reading	7 (reasons for exclusion: no Listerine, [24]*, [25]* no outcome parameter of interest,[26]†, [27]†, [28]‡ and non-eligible subject selection [29]§, [30]‡)
Articles included after full reading	18
Articles excluded for insufficient data presentation	0
Articles included from reference list	1
Articles included in final selection for data extraction	19

* Essential oils from *Lippia sidoides* were obtained from hydrodistillation of fresh leaves.
† McNeil, Stockholm, Sweden.
‡ Warner Lambert, Morris Plains, NJ.
§ Davis (India), Hyderabad, India.

participants also varied among studies. Table 2 [4,23,31-47] presents information regarding study characteristics.

Study Design and Subject Characteristics

All studies but one (XVI) were conducted as RCTs. Fourteen studies were double-masked, and five studies were single-masked. Eight studies were performed using a crossover design, whereas 11 studies had parallel designs. In all studies, subjects received an oral prophylaxis before the experiment. The study populations in 12 selected studies were subjects with gingivitis without periodontitis, whereas study I included successfully treated periodontal patients who received professional periodontal maintenance care with a mean probing depth at baseline of 2.43 mm. Six studies (IV, V, VII, XII, XIII, and XVI) provided no specific information about the periodontal status of included subjects. Evaluation periods varied among the selected studies. When intermediate assessments regarding the use of CHX and essential oils were presented, baseline and final evaluations were used in this review.

Comparison and Regimen

Six studies (I, IV, XII, XV, XVII, and XVIII) used the EOMW or CHX-MW as adjuncts to self-performed, daily oral hygiene procedures. The other 13 studies used mouthrinses as a monotherapy with no other oral hygiene procedure permitted during the experimental periods. Two studies (I and VIII) specifically mentioned that a particular version# of EOMW was used. No specific description of the EOMW product was provided in the other 17 studies.

The CHX-MW used in the selected studies included several brands. Peridex**,†† was used in six studies (I,** IV,** VIII,†† XIII,†† XV,** and XVII††), Corsodyl‡‡ was used in two studies (X and XIV), and Eburos,§§ Hexident,|||| Chlorhexamed,¶¶ and Hibitane## were each used in a single study (studies II, III, VII, and XVIII, respectively). In eight studies (V, VI, VIII, IX, XI, XII, XVI, and XIX), the brand name was not specified. Consequently, different concentrations of CHX-MW were used in different studies ranging from 0.09% to 0.2%. The study by Axelsson and Lindhe[47] (XVIII) evaluated two different concentrations of CHX-MW: 0.1% and 0.2%. In 14 studies, the CHX-MW contained alcohol. In one study (V), the CHX rinse was alcohol free, and in three other studies (III, XII, and XVI), it was unclear whether the CHX-MW contained alcohol. Both 0.12% alcohol-free and 0.12% alcohol-containing CHX rinse were used in a study by Eldridge et al.[39] (VIII). The rinsing time of essential oils and CHX varied, ranging from 30 to 60 seconds with 10, 15, or 20 ml. The study by Eldridge et al.[39] (VIII) is presented in Table 2 in the 15-ml group, in which patients rinsed for precisely 60 seconds with 0.5 oz ± 14 ml. In a study by Haffajee et al.,[32] the rinse volume was not mentioned.

Industry Funding

Funding was mentioned in 10 articles, including grants from two commercial companies (studies VII,*** XIII,††† and XV***), a grant from the University of Palermo (study II), and an educational grant (study I‡‡‡).

\# Cool Mint Listerine, Johnson & Johnson.
** Peridex, Zila Pharmaceuticals, Phoenix, AZ.
†† Peridex, Procter & Gamble, Cincinnati, OH.
‡‡ Corsodyl, ICI Pharmaceuticals, Macclesfield, Cheshire, UK.
§§ Eburos, Betafarma, Cesano Boscona, Italy.
|||| Hexident, Ipex AB, Solna, Sweden.
¶¶ Chlorhexamed, Procter & Gamble, Schwalback, Germany.
Hibitane, ICI Pharmaceuticals.
*** Warner-Lambert, Freiburg, Germany.
††† Glenbrook Laboratories, a division of Sterling Drug, New York, NY.
‡‡‡ Natural Dentist, Medford, MA.

Table 2.

Overview of the Studies Processed for Data Extraction

Study Number and Reference, Evaluation Period and Design	Subjects (n) at Baseline (end of study), Age in Years (range), Sex of Subjects, and Prophylaxis	Inclusion and Exclusion Criteria	Groups, Regimen, and Supervision	Conclusion
I. Haffajee et al., 2009[32] 3 months RCT, parallel and double-masked	59◇ (59◇) Mean age: 49◇; (range: ?) Male: 26◇ Female: 33◇ OP	Good general health. ≥20 years of age. ≥20 natural teeth and ≥4 teeth with pocket depths >4 mm and AL >3 mm before therapy. Perio maintenance.	EOMW; ? ml, 60 seconds CHX 0.12%; ? ml, 60 seconds Twice daily Brushing Unsupervised	The use of antibacterial mouthrinses reduced supragingival plaque levels and affected the composition of the adjacent subgingival biofilm.
II. Pizzo et al., 2008[33] 4 days RCT, crossover and double-masked	15 (15) Mean age: 23.2; (range: 19 to 30) Male: 9 Female: 6 OP	Good general health. ≥22 natural teeth with two scorable surfaces. No recession ≥2 mm, and no other signs of periodontitis. No subject received mouthrinses, gels, or chewing gums containing antimicrobial agents ≤3 months before the trial. Non-perio.	EOMW; 20 ml, 30 seconds CHX 0.12%; 15 ml, 30 seconds Twice daily Non-Brushing Semi-supervised (compliance assessed by measuring the bottle weight at the end of the study)	EOMW rinses may represent effective alternatives to CHX-MW as adjuncts to oral hygiene.
III. Sekino and Ramberg, 2005[34] 2 weeks RCT, crossover and single-masked	21 (?) Mean age: 27; (range: 20 to 42) Male: ? Female: ? OP	Good general health. No sign of destructive periodontal disease. ≥24 teeth (six teeth in each quadrant). No antibiotic treatment ≤3 month before the trial. No regular use of oral antiseptics. Non-perio.	EOMW; 10 ml, 60 seconds CHX 0.1%; 10 ml, 60 seconds Twice daily Non-brushing Unsupervised	The effect of the EOMW on gingivitis was more pronounced than on plaque formation. This indicated that the phenolic compound may have anti-inflammatory effects.
IV. Charles et al., 2004[35] 6 months RCT, parallel and double-masked	70◇ (70◇) Mean age: 31.7; (range: 20 to 57) Male: 25◇ Female: 45◇ OP	≥20 sound, natural teeth. Minimal criteria PI (≥1.95) and GI (≥0.95). Non-perio: ?	EOMW; 20 ml, 30 seconds CHX 0.12%; 15 ml, 30 seconds Twice daily Brushing One of two daily rinses was supervised.	The EOMW and CHX-MW had comparable antiplaque and antigingivitis activities and can have a distinct role in the management of patients with periodontal diseases.

Table 2. (continued)

Overview of the Studies Processed for Data Extraction

Study Number and Reference, Evaluation Period and Design	Subjects (n) at Baseline (end of study), Age in Years (range), Sex of Subjects, and Prophylaxis	Inclusion and Exclusion Criteria	Groups, Regimen, and Supervision	Conclusion
V. Rosin et al., 2002[36] 4 days RCT, crossover and double-masked	16 (16) Mean age: 23.4; (range: ?) Male: 6 Female: 10 OP	Good general health. High standard of oral health and gingival health. ≥25 scorable teeth. Non-perio: ?	EOMW; 20 ml, 60 seconds CHX 0.12%; 20 ml, 60 seconds Twice daily Non-brushing Semi-supervised (compliance assessed by measuring the bottles)	Plaque inhibition with the EOMW was essentially the same as with the CH-MW.
VI. Claydon et al., 2001[37] 24 hours RCT, crossover and single-masked	42 (42) Mean age: 33; (range: 20 to 60) Male: 11 Female: 31 OP	Good general health. High standard of oral hygiene and gingival health. Non-perio.	EOMW; 20 ml, 30 seconds CHX 0.09%; 15 ml, 60 seconds Twice daily Non-brushing Semi-supervised (morning rinses)	The EOMW resulted in significantly greater plaque areas compared to the CHX rinses.
VII. Riep et al., 1999[38] 4 days RCT, crossover and double-masked	24 (23◇) Mean: ?; (range: 20 to 34) Male: 14 Female: 9 OP	Good general health. ≥20 natural teeth with two scorable surfaces. Minimal criteria PI (≥1.95). Non-perio: ?	EOMW; 10 ml, 30 seconds CHX 0.1%; 20 ml, 30 seconds Twice daily Non-brushing Supervised	The plaque reductions seen in the EOMW and CHX-MW groups were statistically significant.
VIII. Eldridge et al., 1998[39] 21 days RCT, parallel and double-masked	32 (?/32) Mean age: 24.5; (range: ?) Male: 24 Female: 8 OP	Good general health. Non-perio.	EOMW; 15◇ ml, 60 seconds CHX 0.12% (Alc+); 15◇ ml, 60 seconds CHX 0.12% (Alc-); 15◇ ml, 60 seconds Twice daily Non-brushing Semi-supervised	Mean plaque scores for both CHX-MW products decreased after 21 days, whereas the mean for the EOMW increased. Bleeding and GI scores for all 3 groups increased, which may have been due to the initially healthy tissues of the participants.

Table 2. (continued)

Overview of the Studies Processed for Data Extraction

Study Number and Reference, Evaluation Period and Design	Subjects (n) at Baseline (end of study), Age in Years (range), Sex of Subjects, and Prophylaxis	Inclusion and Exclusion Criteria	Groups, Regimen, and Supervision	Conclusion
IX. Netuschil et al., 1995[40] 3 days RCT, parallel and double-masked	20◇ (?/20◇) Mean age: ?; (range: 16 to 31) Male: ? Female: ? OP	All selected teeth displayed clinically sound vestibular enamel surfaces. Non-perio.	EOMW; 10 ml, 60 seconds CHX 0.2%; 10 ml, 60 seconds Twice daily Non-brushing Semi-supervised (compliance assessed by checking remaining solution)	The EOMW showed no difference compared to the control rinse. Because of the strong antibacterial action of CHX during use, only a thin plaque developed. As a clinical consequence, CHX showed retardation of plaque development as reflected by significantly reduced plaque indices.
X. Moran et al., 1995[41] 4 days RCT, crossover and single-masked	15 (15) Mean age: ?; (range: ?) Male: 15 Female: 0 OP	Good general health. High standard of oral hygiene and gingival health. ≥15 anterior teeth. No recession ≥2 mm. Non-perio.	EOMW; 20 ml, 30 seconds CHX 0.2%; 10 ml, 60 seconds Twice daily Non-brushing Supervised	The CHX-MW was significantly more effective than EOMW.
XI. Ramberg et al., 1992[42] 4 days RCT, crossover and double-masked	10 (10) Mean: 29.5; (range: 24 to 40) Male: ? Female: ? OP	No third molars. Non-perio.	EOMW; 10 ml, 60 seconds CHX 0.12%; 10 ml, 60 seconds Twice daily Non-brushing Unsupervised	The EOMW was significantly less effective than the CHX-MW.
XII. Brecx et al., 1992[43] 3 weeks RCT, parallel and double-masked	20◇ (20◇) Mean age: ?; (range: 20 to 35) Male: ? Female: ? OP	Good general health. Fair, but not optimal oral hygiene. Non-perio: ?	EOMW; 10 ml, 60 seconds CHX 0.2%; 10 ml, 60 seconds Twice daily Brushing Semi-supervised (compliance assessed by measuring the bottles)	When mouthrinses were used to supplement habitual mechanical oral hygiene, CHX remained the most powerful solution.
XIII. Maruniak et al., 1992[44] 2 weeks RCT, parallel and double-masked	44◇ (44◇) Mean age: ?; (range: 18 to 55) Male: 21◇ Female: 23◇ OP	Good general health with preexisting plaque and gingivitis. ≥20 sound natural teeth. Minimal criteria PI (≥1.95) and papillary BI (≥1.95). Non-perio: ?	EOMW; 20 ml, 30 seconds CHX 0.12%; 15 ml, 30 seconds Twice daily Non-brushing Supervised	CHX-MW was superior for reducing plaque and gingivitis compared to EOMW.

Table 2. (continued)

Overview of the Studies Processed for Data Extraction

Study Number and Reference, Evaluation Period and Design	Subjects (n) at Baseline (end of study), Age in Years (range), Sex of Subjects, and Prophylaxis	Inclusion and Exclusion Criteria	Groups, Regimen, and Supervision	Conclusion
XIV. Moran et al., 1991[23] 19 days RCT, crossover and single-masked	15 (15) Mean age: ?; (range: 20 to 28) Male: 7 Female: 8 OP	Good general health. High standard of oral hygiene. ≥22 permanent teeth. No PDs >2 mm. Non-perio.	EOMW; 20 ml, 60 seconds CHX 0.2%; 10 ml, 30 seconds Twice daily Non-brushing Unsupervised	Both CHX-MW and EOMW significantly reduced plaque regrowth; however, the CHX-MW was more effective.
XV. Overholser et al., 1990[4] 6 months RCT, parallel and double-masked	? (82◇) Mean age: ?; (range: 21 to 62) Male: 32◇ Female: 50◇ OP	Subjects with preexisting plaque and gingivitis. ≥20 sound natural teeth. Minimal criteria PI (≥1.95) and GI (≥1.95). No third molars. Non-perio.	EOMW; 20 ml, 30 seconds CHX 0.12%; 15 ml, 30 seconds Twice daily Brushing Semi-supervised (weekdays)	CHX-MW was more effective in inhibiting plaque formation, and the EOMW and CHX-MW were comparable in inhibiting the development of gingivitis when used as adjuncts to routine oral hygiene after professional prophylaxis.
XVI. Brecx et al., 1990[45] 3 weeks CCT, parallel and double-masked	17◇ (17◇) Mean: ?; (range: 20 to 34) Male: ? Female: ? OP	Good general health. Non-perio: ?	EOMW; 10 ml, 60 seconds CHX 0.2%; 10 ml, 60 seconds Twice daily Non-brushing Unsupervised	The CHX-MW was superior to the EOMW in its ability to maintain low plaque scores and gingival health during a 3-week period of no mechanical oral hygiene.
XVII. Grossman et al., 1989[46] 6 months RCT, parallel and double-masked	242◇ (242◇) Mean age: 37.0◇; (range: ?) Male: 81◇ Female: 161◇ OP	Subjects with preexisting gingivitis. ≥16 natural teeth (incl. four molars). Non-perio.	EOMW; 15 ml, 30 seconds CHX 0.12%; 20 ml, 30 seconds Brushing Unsupervised	When used unsupervised as a part of regular oral hygiene and professional care, the CHX-MW provided significantly greater plaque and gingivitis reductions when compared to the EOMW.

Table 2. (continued)

Overview of the Studies Processed for Data Extraction

Study Number and Reference, Evaluation Period and Design	Subjects (n) at Baseline (end of study), Age in Years (range), Sex of Subjects, and Prophylaxis	Inclusion and Exclusion Criteria	Groups, Regimen, and Supervision	Conclusion
XVIII. Axelsson and Lindhe, 1987[47] 6 weeks RCT, parallel and double-masked	72◇ (66◇) Mean age: ?; (range: 16 to 50) Mean: ? Female: ? OP	All subjects had signs of varying degrees of gingivitis. Non-perio.	EOMW; 20 ml, 30 seconds CHX 0.1%; 10 ml, 60 seconds CHX 0.2%; 10 ml, 60 seconds Brushing Twice daily Semi-supervised (weekdays)	CHX-containing mouth rinses are equally or more effective in reducing plaque than the EOMW but not as effective in enhancing gingivitis resolution.
XIX. Siegrist et al., 1986[31] 3 weeks RCT, parallel and single-masked	18◇ (17◇) Mean age: ?; (range: 19 to 28) Male: ? Female: ? OP	Good general health. High standard of oral hygiene. Maximal criteria PI (<2.0) and GI (<2.0). Non-perio.	EOMW; 20 ml, 30 seconds CHX 0.12%; 15 ml, 30 seconds Twice daily Non-brushing Semi-supervised (weekdays)	The 0.12% CHX-MW was superior to the EOMW in its ability to maintain optimal gingival health during the entire 3 weeks of mouthrinse use.

OP = professional prophylaxis at baseline; ? = not specified/unclear; ◇ = calculated by the authors; PI = plaque index; GI = gingival index; BI = bleeding index; CCT = controlled clinical trial; Alc+ = alcohol containing; Alc- = alcohol free; perio maintenance = history of periodontitis; non-perio = no history of periodontitis.

Several other articles received funding from commercial companies (studies IX,§§§ XII,§§§ XIII,‖‖‖ XVI,§§§ and XVIII¶¶¶). Some articles included authors who were employed by various companies (studies VI,### VII,**** X,†††† XI,‡‡‡‡ and XVII§§§§). Of the studies funded by industry, two studies had affiliations with essential oil mouthwash‖‖‖ products, whereas seven other studies had connections with CHX products, and one study was supported with an educational grant.

Quality Assessment

Quality assessment parameters, including external, internal, and statistical validity, are presented in Table 3. Based on a summary of these criteria, the estimated risk of bias was low in 12 of 19 studies. The risk was considered moderate for five studies and high for two studies. One study (IV) received a score of 1b, and the other 18 studies received a score of 1b– because they did not present CIs. All studies consistently had a score of level 1 according to the CEBM,[22] which allowed a grade-A recommendation to emerge from this review. Furthermore, all studies ≥4 weeks of duration also had a low level of potential bias, which suggested that this review presented a high level of evidence.

Study Outcomes

Differences between baseline and end-of-trial scores for parameters of interest are shown in Tables 4 through 8.[48-64] Outcomes are presented for non-brushing and brushing studies. The short-term non-brushing studies are subdivided into *de novo* plaque accumulation and experimental gingivitis. The brushing studies are subdivided into short-term (<4 weeks) and long-term (≥4 weeks) studies.

Within Groups

Only a few included data presented baseline and end-of-trial scores with respect to changes in time within each group (Tables 4 through 8). From studies that did provide data, the general trend was that, with two exceptions (studies I and XVIII), the CHX-MW showed a significant change between baseline and end-of-trial scores for all evaluated parameters.

Between Groups

Differences between the EOMW and CHX-MW are presented in a descriptive manner in Table 9.

Plaque scores. In the seven studies that evaluated *de novo* plaque accumulation, five studies (II, V, VI,

§§§ GABA International, Therwil, Switzerland.
‖‖‖ ICI Pharmaceuticals.
¶¶¶ Procter & Gamble.
SmithKline Beecham Consumer Healthcare, Weybridge, U.K.
**** Warner-Lambert.
†††† ICI Pharmaceuticals.
‡‡‡‡ Colgate-Palmolive Technology Center, Piscataway, NJ.
§§§§ Procter & Gamble.
‖‖‖ Listerine, Johnson & Johnson.

X, and XI) provided statistical data, of which four studies (II, VI, X, and XI) showed that a CHX-MW was more effective than the EOMW with respect to plaque scores. The studies (III, VIII, XIII, XIV, XVI, and XIX) that used the experimental gingivitis model all provided statistical data that a CHX-MW was more effective than the EOMW with respect to plaque scores. In the five long-term brushing studies, four studies (I, IV, XV and XVII) provided statistical data, of which three studies (I, XV, and XVII) showed that a CHX-MW was more effective for plaque inhibition.

Gingivitis scores. Five studies (III, VIII, XIV, XVI, and XIX) used the experimental gingivitis model. Two (XVI and XIX) of four studies that provided statistical data reported that CHX-MW was more effective than EOMW with respect to the gingival index (GI). Two other studies (VIII and XIV) showed no differences. The CHX-MW was found to be more effective than the EOMW in only one (XVII) of the long-term brushing studies, whereas the other four studies (I, IV, XV, and XVIII) did not show a difference between the two products with respect to GI.

Bleeding scores. With respect to bleeding scores, only one (XIX) of five short-term experimental gingivitis studies that provided statistical analyses showed a significant effect in favor of a CHX-MW. The four other studies (III, VIII, XIII, and XIV) did not detect a significant difference. Three (I, IV, and XV) of four long-term brushing studies also showed no difference between the EOMW and CHX-MW with respect to bleeding.

Stain and calculus scores. Five long-term brushing studies (IV, XII, XV, XVII, and XVIII) evaluated stain development, of which three studies (IV, XV, and XVII) showed that rinsing with CHX resulted in more stain. In two studies (IV and XV) in which calculus scores were also assessed, more calculus formation was found with CHX-MW compared to EOMW.

Meta-analysis. A meta-analysis was performed to compare the effects of the EOMW and CHX-MW as monotherapies or as adjuncts to self-performed daily oral hygiene procedures. A summary is presented in Table 10. Data from study XVIII concerning the EOMW were used twice, once each for the comparison of the EOMW to a 0.1% and 0.2% CHX-MW. The non-brushing designs (*de novo* plaque) evaluating plaque scores at the end of the trial (Quigley and Hein[48] modified by Turesky et al.[49]) showed a significant effect in favor of a CHX-MW with a WMD of 0.46 (P = 0.01). In long-term studies that included self-performed, daily oral hygiene procedures, the WMD for plaque scores was 0.19 (P = 0.0009).

However, the long-term studies that allowed a meta-analysis of GI (Löe and Silness[53]) did not show a significant difference between the two products with a WMD of –0.03 (P = 0.58). The WMD for staining (Lobene extrinsic tooth stain index[60]) in studies with durations ≥4 weeks was –0.42, which was not statistically significant (P = 0.12).

DISCUSSION

The effective control of supragingival plaque is a critical factor for preventing and treating periodontal disease.[65-67] However, most adults do not properly control dental plaque because of problems with motivation and compliance.[68-70] The adjunctive use of antimicrobial mouthrinses has been shown to be of value in inhibiting or reducing supragingival plaque formation. Therefore, mouthrinses are recommended when mechanical oral hygiene is difficult, compromised, or impossible.[33,68,71-73] In most countries, there is a variety of mouthwash formulas available for the general public.[74]

Evaluation Period

The clinical evaluation of chemical agents included short-term studies (durations of 4 days to 2 weeks) used to investigate antiplaque effects. Intermediate-length trials (durations of 2 weeks to 2 months) evaluated both antiplaque and antigingivitis efficacy.[75] Clinical trials using experimental gingivitis models[76] were frequently used as a short-term model to evaluate the antiplaque and antigingivitis efficacy of mouthrinses containing antimicrobial agents[77] and were accepted as a valid model to determine and compare the efficacy of antiseptic mouthrinses.[23] However, this model allows the estimation of the effect of the mouthrinse without the influence of mechanical plaque control.[77] Therefore, it is not an accurate reflection of the patient's actual habitual use of the product.[75] The ADA requires long-term studies (≥6 months) for a seal of acceptance, with an intermediate evaluation at 3 months to evaluate the efficacy and safety of chemical agents and patient compliance.[78] Because mouthrinses are also used and prescribed for short periods, their short-term efficacy is also of interest.[79] Therefore, besides experimental gingivitis studies, studies with an evaluation period ≥4 weeks were also included in this review with respect to gingivitis.[71] This is in accordance with the ADA requirements concerning adjunctive dental therapies for the reduction of plaque and gingivitis.[80]

Effect Size

This review is part of a series of reviews[3,71,81-85] that have addressed the efficacy of various chemical agents in oral health care products for patients with gingivitis. These include the use of stannous-fluoride, essential oils, cetylpyridinium chloride (CPC), hexetidine, hydrogen peroxide (H_2O_2), triclosan, and CHX. Addy et al.[86] also evaluated the effect of delmopinol. The review of hexetidine and hydrogen peroxide did not provide sufficient data to calculate WMD. The two

Table 3.

Methodologic Quality Scores of Included Studies

Quality Criteria	Study																		
	I[32]	II[33]	III[34]	IV[35]	V[36]	VI[37]	VII[38]	VIII[39]	IX[40]	X[41]	XI[42]	XII[43]	XIII[44]	XIV[23]	XV[4]	XVI[45]	XVII[46]	XVIII[47]	XIX[31]
Internal validity																			
Random allocation	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+
Allocation concealment	?	?	?	?	+	?	?	?	?	?	+	?	?	?	+	?	?	?	?
Masked to patient	+	+	?	+	+	–	+	+	+	?	+	+	+	–	+	+	+	+	+
Masked to examiner	+	+	?	+	+	+	+	+	+	?	+	+	+	+	+	+	+	+	?
Masking during statistical analysis	?	?	?	?	+	?	?	?	?	?	+	?	?	?	+	?	?	?	?
Balanced experimental groups	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	?	+	+	+
Reported loss to follow up	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Dropouts (n [%])	?	0 (0)	0 (0)	0◇ (0◇)	0 (0)	0 (0)	1 (4.17◇)	0 (0)	0 (0)	0 (0)	0 (0)	0◇ (0◇)	0 (0)	0 (0)	?	0 (0)	0 (0)	6◇ (12.50◇)	1◇ (5.56◇)
Treatment identical except for intervention	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
External validity																			
Representative population group	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	?	+	+	+
Eligibility criteria defined	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	–	+	+	+
Statistical validity																			
Sample-size calculation and power	+	?	?	+	?	?	?	?	?	?	?	?	?	?	+	?	?	+	?
Point estimates	+	+	+	+	–	+	+	–	–	–	+	–	+	+	+	–	+	+	–
Measures of variability presented for the primary outcome parameter	+	+	–	+	–	+	+	–	–	–	+	–	–	+	+	–	–	+	–
Include an intention-to-treat analysis	–	?	?	?	?	?	?	?	?	?	?	?	?	?	–	?	?	–	?
Authors' estimated risk of bias	Low	Low	High	Low	Low	Mod	Low	Low	Low	Mod	Low	Mod	Low	Mod	Low	High	Low	Low	Mod
Levels of evidence (Center for Evidence-Based Medicine 2009)[22]*	1b–	1b–	1b–	1b	1b–	1b–	1b–	1b–	1b–	1b–	1b–	1b–	1b–	1b–	1b–	1b–	1b–	1b–	1b–

+ = yes, – = no; ? = not specified/unclear; ◇ = calculated by the authors; Mod = moderate.
* A minus sign after 1b denotes a wide or unknown CI.

Table 4.

Effects on the Plaque Index (mean ± SD)

Study	Index	Intervention/Groups	Baseline*	End	Difference	Significant Baseline-End
Non-brushing						
De novo model						
II[33]	Quigley and Hein, 1962[48] modified by Turesky et al., 1970[49]	EOMW	–	1.91 (0.62)	–	–
		CHX (0.12%)	–	1.21 (0.53)	–	–
V[36]	Quigley and Hein, 1962[48] modified by Turesky et al., 1970[49]	EOMW	–	•	–	–
		CHX (0.12%)	–	•	–	–
VII[38]	Quigley and Hein, 1962[48] modified by Turesky et al., 1970[49]	EOMW	–	1.96 (0.35)	–	–
		CHX (0.1%)	–	1.65 (0.41)	–	–
IX[40]	Silness and Löe, 1964[50]	EOMW	–	?	–	–
		CHX (0.2%)	–	?	–	–
XI[42]	Silness and Löe, 1964[50]	EOMW	–	0.88 (0.16)	–	–
		CHX (0.12%)	–	0.53 (0.17)	–	–
VI[37]	Shaw and Murray stain index, 1977[51] modified by Addy et al., 1983[52]	EOMW	–	238.88 (111.68)	–	–
		CHX (0.09%)	–	204.06 (109.62)	–	–
Experimental gingivitis model						
III[34]	Quigley and Hein, 1962[48] modified by Turesky et al., 1970[49]	EOMW	–	2.08	–	–
		CHX (0.1%)	–	1.36	–	–
VIII[39]	Quigley and Hein, 1962[48] modified by Turesky et al., 1970[49]	EOMW	–	4.15	–	–
		CHX (0.12%) (Alc+)	–	3.83	–	–
		CHX (0.12%) (Alc–)	–	3.63	–	–
XIV[23]	Quigley and Hein, 1962[48] modified by Turesky et al., 1970[49]	EOMW	–	4.86 (1.06)	–	–
		CHX (0.2%)	–	2.72 (1.31)	–	–
XIII[44]	Quigley and Hein, 1962[48]	EOMW	–	2.87	–	–
		CHX (0.12%)	–	2.20	–	–
XVI[45]	Silness and Löe, 1964[50]	EOMW	–	1.44	–	–
		CHX (0.2%)	–	•	–	–
XIX[31]	Silness and Löe, 1964[50]	EOMW	–	•	–	–
		CHX (0.12%)	–	0.51	–	–
Brushing						
Study duration <4 weeks						
XII[43]	Silness and Löe, 1964[50]	EOMW	•	•	?	No
		CHX (0.2%)	•	•	?	Yes
Study duration ≥4 weeks						
I[32]	Quigley and Hein, 1962[48] modified by Turesky et al., 1970[49]	EOMW	0.91 (0.61)	0.84 (0.64)	–0.07◇	No
		CHX (0.12%)	1.09 (0.71)	0.55 (0.43)	–0.54◇	Yes
IV[35]	Quigley and Hein, 1962[48] modified by Turesky et al., 1970[49]	EOMW	2.50 (0.41◇)	1.77 (0.41◇)	–0.73◇	?
		CHX (0.12%)	2.64 (0.42◇)	1.71 (0.48◇)	–0.93◇	?
XV[4]	Quigley and Hein, 1962[48] modified by Turesky et al., 1970[49]	EOMW	2.492 (0.27◇)	1.048 (0.52◇)	–1.444◇	?
		CHX (0.12%)	2.378 (0.23◇)	0.815 (0.51◇)	–1.563◇	?

Table 4. (continued)

Effects on the Plaque Index (mean ± SD)

Study	Index	Intervention/Groups	Baseline*	End	Difference	Significant Baseline-End
XVII[46]	Quigley and Hein, 1962[48] modified by Turesky et al., 1970[49]	EOMW	1.48	1.13	–0.35◇	Yes
		CHX (0.12%)	1.41	0.76	–0.65◇	Yes
XVIII[47]	Quigley and Hein, 1962[48] modified by Turesky et al., 1970[49]	EOMW	1.2 (0.5◇)	0.6 (0.5◇)	–0.6◇	Yes
		CHX (0.1%)	1.2 (0.5◇)	0.5 (0.5◇)	–0.7◇	Yes
		CHX (0.2%)	1.4 (0.4◇)	0.3 (0.4◇)	–1.1◇	Yes

Significant Baseline-End = significant change between baseline and end of trial; – = not applicable; ● = insufficient data presented; ? = not specified/unclear; Alc+ = alcohol containing; Alc– = alcohol free; ◇ = calculated by the authors.
* Professional prophylaxis at baseline rendering zero visible plaque.

Table 5.

Effects on the Gingival Index (mean ± SD)

Study	Index	Intervention/Groups	Baseline	End	Difference	Significant Baseline-End
Non-brushing						
Experimental gingivitis model						
VIII[39]	Löe and Silness, 1963[53]	EOMW	●	●	?	?
		CHX (0.12%) (Alc+)	●	●	?	?
		CHX (0.12%) (Alc–)	●	●	?	?
XIV[23]	Löe and Silness, 1963[53]	EOMW	0.19 (0.13)	0.37 (0.16)	+0.18 (0.24)	?
		CHX (0.2%)	0.20 (0.14)	0.31 (0.16)	+0.11 (0.15)	?
XVI[45]	Löe and Silness, 1963[53]	EOMW	●	●	?	?
		CHX (0.2%)	●	0.48	?	?
XIX[31]	Löe and Silness, 1963[53]	EOMW	●	●	?	?
		CHX (0.12%)	●	●	?	?
III[34]	Löe, 1967[54]	EOMW	0.43	●	?	?
		CHX (0.1%)	0.47	●	?	?
Brushing						
Study duration ≥4 weeks						
I[32]	Löe and Silness, 1963[53]	EOMW	0.78 (0.36)	0.65 (0.42)	–0.13◇	No
		CHX (0.12%)	0.81 (0.39)	0.56 (0.43)	–0.25◇	Yes
IV[35]	Löe and Silness, 1963[53]	EOMW	1.31 (0.23◇)	1.04 (0.17◇)	–0.27◇	?
		CHX (0.12%)	1.35 (0.24◇)	0.99 (0.18◇)	–0.36◇	?
XVIII[47]	Löe and Silness, 1963[53]	EOMW	1.19 (0.34◇)	0.48 (0.29◇)	–0.71◇	Yes
		CHX (0.1%)	1.26 (0.34◇)	0.61 (0.29◇)	–0.65◇	Yes
		CHX (0.2%)	1.18 (0.34◇)	0.65 (0.30◇)	–0.53◇	Yes
XVII[46]	Löe, 1967[54]	EOMW	0.5227	0.3308	–0.1919◇	No
		CHX (0.12%)	0.5332	0.2514	–0.2818◇	Yes
XV[4]	Modified gingival index[55]	EOMW	2.234 (0.14◇)	0.748 (0.41◇)	–1.486◇	?
		CHX (0.12%)	2.281 (0.20◇)	0.810 (0.42◇)	–1.471◇	?

Significant Baseline-End = significant change between baseline and end of trial; Alc+ = alcohol containing; Alc– = alcohol free; ◇ = calculated by the authors; ? = not specified/unclear; and ● = insufficient data presented.

Table 6.

Effects on the Bleeding Index (mean ± SD)

Study	Index	Intervention/Groups	Baseline	End	Difference	Significant Baseline-End
Non-brushing Experimental gingivitis model						
XIV[23]	Bleeding aspect of the Löe and Silness index, 1963[53]	EOMW	0.93 (1.39)	1.27 (1.33)	+0.33 (2.26)	?
		CHX (0.2%)	0.80 (1.10)	1.00 (1.25)	+0.20 (1.32)	?
XIX[31]	Bleeding aspect of the Löe and Silness index, 1963[53]	EOMW	●	36%	?	?
		CHX (0.12%)	●	●	?	?
III[34]	Bleeding aspect of the Löe index, 1967[54]	EOMW	?	10.7%	?	?
		CHX (0.1%)	?	13.5%	?	?
XIII[44]	Papillary bleeding score (Loesche, 1979[56])	EOMW	2.71	2.51	–0.20◇	?
		CHX (0.12%)	2.35	1.94	–0.41◇	?
VIII[39]	Bleeding on probing	EOMW	●	●	?	?
		CHX (0.12%) (Alc+)	●	●	?	?
		CHX (0.12%) (Alc–)	●	●	?	?
Brushing Study duration ≥4 weeks						
IV[35]	Bleeding aspect of the Löe and Silness index, 1963[53]	EOMW	33.29%	12.72%	–20.57%	?
		CHX (0.12%)	35.60%	11.01%	–24.59%	?
XVII[46]	Bleeding aspect of the Löe index, 1967[54]	EOMW	0.1225	0.0678	–0.0547◇	?
		CHX (0.12%)	0.1273	0.0493	–0.0780◇	?
XV[4]	Interdental bleeding index (Caton and Polson, 1985[57])	EOMW	0.71 (0.31◇)	0.29 (0.27◇)	–0.42◇	Yes
		CHX (0.12%)	0.72 (0.36◇)	0.25 (0.29◇)	–0.47◇	Yes
I[32]	Bleeding on probing	EOMW	15.37% (9.21)	17.87% (11.82)	+2.5◇	No
		CHX (0.12%)	20.16% (14.47)	18.65% (15.05)	–1.5◇	No

Significant Baseline-End = significant change between baseline and end of trial; ? = not specified/unclear; ● = insufficient data presented; Alc+ = alcohol containing; Alc– = alcohol free; ◇ = calculated by the authors.

reviews that addressed stannous-fluoride and triclosan included a meta-analysis of these chemical agents incorporated in a dentifrice. The WMDs compared to a control product in terms of GI were 0.21 (95% CI: 0.14 to 0.27) and 0.24 (95% CI: 0.13 to 0.35), respectively. Haps et al.[71] evaluated the effect of a CPC mouthrinse. Their meta-analysis revealed a WMD of 0.15 (95% CI: 0.24 to 0.47) with respect to GI.[54] In a meta-analysis of a 0.2% delmopinol mouthrinse, Addy et al.[86] established a WMD of 0.10 (95% CI: 0.06 to 0.14) with respect to the modified GI.[55] In the light of these results, the largest effect has been established for essential oils in mouthrinses. The WMD reported by Stoeken et al.[3] was 0.32 (95% CI: 0.15 to 0.46). However, the test for heterogeneity was also significant, suggesting that the exact measure of the outcome should be interpreted cautiously. A recent review by Van Strydonck et al.[85] on CHX established a WMD of 0.31 (95% CI: 0.40 to 0.22) for GI,[53,54] which is similar to the effect observed with essential oils; these data also tested positive for heterogeneity. For plaque,[48] the WMDs were 0.83 (95% CI: 0.53 to 1.13)[3] and 0.67 (95% CI: 0.53 to 0.87)[85] for essential oils and CHX, respectively. Thus, for this parameter, it can also be concluded that the effect of essential oils was the largest; however, the test for heterogeneity was significant in both studies. Heterogeneity in the meta-analysis reflected different behaviors of the study populations with respect to the study product as well as differences in study designs and all other factors that may influence outcomes. In such a circumstance, we should be cautious when interpreting WMD as the exact measure for the effect. The observations of Stoeken et al.[3] with respect to EOMW and of Van Strydonck et al.[85] with respect to CHX-MW were the main reasons for the present review, which presents a direct comparison of CHX-MW and EOMW. This present

Table 7.

Effects on the Stain Index (mean ± SD)

Study	Index	Intervention/Groups	Baseline	End	Difference	Significant Baseline-End
Non-brushing						
Experimental gingivitis model						
XIV[23]	Shaw and Murray, 1977[51]	EOMW	0◇	0.06 (0.05)	+0.06 (0.05)◇	Yes
	modified by Addy et al., 1983[52]	CHX (0.2%)	0◇	0.04 (0.05)	+0.04 (0.05)◇	Yes
	Self-developed stain index	EMOMW	0◇	1.33 (0.72)	+1.33 (0.72)◇	Yes
	(Moran et al.,1991[23])	CHX (0.2%)	0◇	1.47 (0.52)	+1.47 (0.52)◇	Yes
XIX[31]	Meckel stain index described	EOMW	0◇	35.63	+35.63◇	?
	by Lang et al., 1982[58]	CHX (0.12%)	0◇	56.86	+56.86◇	?
		EOMW	0◇	0.93	+0.93◇	?
	Discoloration index system[59]	CHX (0.12%)	0◇	1.28	+1.28◇	?
Brushing						
Study duration ≥4 weeks						
XVIII[47]	Lobene extrinsic tooth-stain	EOMW	0.13 (0.44)	0.09 (0.24)	–0.04◇	No
	index, 1968[60]	CHX (0.1%)	0.13 (0.44)	0.10 (0.29)	–0.03◇	No
		CHX (0.2%)	0.00 (0)	0.14 (0.30)	+0.14◇	No
IV[35]	Lobene extrinsic tooth-stain	EOMW	0.29	0.33	+0.04◇	?
	index, 1968[60]	CHX (0.12%)	0.30	2.08	+1.78◇	?
XV[4]	Lobene extrinsic tooth-stain	EOMW	0.07 (0.15◇)	0.13 (0.24◇)	+0.06◇	?
	index, 1968[60]	CHX (0.12%)	0.11 (0.21◇)	1.45 (1.27◇)	+1.34◇	Yes
XVII[46]	Self-developed stain index	EOMW	3.34	3.48	+0.14◇	Yes
	(Grossman et al., 1989[46])	CHX (0.12%)	2.94	5.15	+2.21◇	Yes

Significant Baseline-End = significant change between baseline and end of trial; ◇ = calculated by the authors; ? = not specified/unclear.

Table 8.

Effects on the Calculus Index (mean ± SD)

Study	Index	Intervention/Groups	Baseline	End	Difference	Significant Baseline-End
Brushing						
Study duration ≥4 weeks						
IV[35]	Volpe-Manhold calculus	EOMW	0.30	0.24	–0.06◇	?
	index, 1965[61-64]	CHX (0.12%)	0.26	0.45	+0.19◇	?
XV[4]	Volpe-Manhold calculus	EOMW	0.19 (0.33◇)	0.14 (0.22◇)	–0.05◇	?
	index, 1965[61-63]	CHX (0.12%)	0.21 (0.31◇)	0.36 (0.37◇)	+0.15◇	Yes

Significant Baseline-End = significant change between baseline and end of trial; ◇ = calculated by the authors; ? = not specified/unclear.

review found that the CHX-MW was more effective in terms of plaque scores; however, a difference is not established with respect to parameters of gingival inflammation.

Anti-Inflammation

It is generally accepted that there is a correlation between plaque scores and parameters of gingival inflammation.[87] However, this does not agree with the observations in the present review. The CHX-MW was found to be more effective with respect to plaque scores but failed to show a similar difference in parameters of gingival inflammation. The most likely explanation for this observation is that the CHX-MW acts through an antiplaque effect on the level of gingival inflammation, whereas the effect of the EOMW occurs more predominantly through an anti-inflammatory process. This presumption is in agreement with in vitro observations of Dewhirst,[88] who observed that phenolic compounds have anti-inflammatory and

Table 9.

Summary of Significant Differences in Favor of the EOMW Compared to a CHX-MW as an Adjunct to Daily Brushing or Rinsing Alone

Study	PI	GI	BI	SI	CI	Comparison
Non-brushing						
De novo model						
IX[40]	?	NA	NA	NA	NA	0.2% CHX
X[41]	–	NA	NA	NA	NA	0.2% CHX
II[33]	–	NA	NA	NA	NA	0.12% CHX
V[36]	○	NA	NA	NA	NA	0.12% CHX
XI[42]	–	NA	NA	NA	NA	0.12% CHX
VII[38]	?	NA	NA	NA	NA	0.1% CHX
VI[37]	–	NA	NA	NA	NA	0.09% CHX
Experimental gingivitis model						
XIV[23]	–	○	○	+	■	0.2% CHX
XVI[45]	–	–	■	■	■	0.2% CHX
VIII[39]	?	○	○	■	■	0.12% CHX (Alc+)
	?	○	○	■	■	0.12% CHX (Alc–)
XIII[44]	–	■	○	■	■	0.12% CHX
III[34]	–	?	○	■	■	0.1% CHX
XIX[31]	–	–	–	○	■	0.12% CHX
Brushing						
Study duration <4 weeks						
XII[43]	–	NA	NA	NA	NA	0.2% CHX
Study duration ≥4 weeks						
XVIII[47]	?	○	■	○	■	0.2% CHX
	?	○	■	○	■	0.1% CHX
I[32]	–	○	○	■	■	0.12% CHX
IV[35]	○	○	○	+	+	0.12% CHX
XV[4]	–	○	○	+	+	0.12% CHX
XVII[46]	–	–	–	+	■	0.12% CHX

PI = plaque index; GI = gingival index; BI = bleeding index; SI = stain index; CI = calculus index; ? = not specified/unclear; NA = not applicable; – = comparison was significantly more effective; ○ = no difference; + = intervention was significantly more effective; ■ = no data available; Alc+ = alcohol containing; Alc– = alcohol free.

prostaglandin synthetase-inhibiting activity. In a neutrophil chemotaxis assay, Azuma et al.[89] demonstrated that phenolic compounds act as scavengers of free oxygen radicals and, hence, affect leukocyte activity. Further, in an in vitro study, Firatli et al.[90] showed that the antioxidative effect of EOMW expressed as the percentage inhibition of spontaneous oxidation was greater than that of CHX and CPC. Hence, the anti-inflammatory potential of essential oils may explain the absence of a pronounced effect on plaque in conjunction with a significant effect on gingival inflammation.[34]

Periodontal Inflammation

The goal of antiplaque and antigingivitis agents is to decrease gingival inflammation so that destructive periodontal disease will not develop. The evidence demonstrates that mouthrinses containing CHX or essential oils reduce the level of gingival inflammation. It is not clear what level of reduction is necessary to decrease or prevent periodontal disease. However, gingival inflammation is a necessary, but insufficient, condition for the initiation and progression of periodontal disease.[75] Still, there are limitations of this review, which predominantly addresses the effect of the two mouthwashes in subjects with gingivitis.

Formulations

The proper formulation of active agents in mouthrinses is important for maintaining bioavailability and, in some cases, improving substantivity. Thus, different formulations of the same active agents may have different levels of efficacy.[75] The authors of this review chose the fixed and controlled formula of EOMW[¶¶¶¶] as representative of essential oil-based mouthwashes; this brand also has an ADA seal. After

¶¶¶¶ Listerine, Johnson & Johnson.

Table 10.

Meta-Analysis Comparing EOMW and CHX-MW as Monotherapies or as Adjuncts to Self-Performed Oral Hygiene Procedures

Model	Index	Included Study		WMD (random)	95% CI	Test for Overall Effect (*P* value)	Test for Heterogeneity (I^2 value [%])	Test for Heterogeneity (*P* value)
De novo	Plaque index[48,49]	II[33] VII[38]	End	0.46	0.09 to 0.84	0.01	62.5	0.10
≥4 weeks	Plaque index[48,49]	I[32] IV[35]	Base	–0.05	–0.20 to 0.09	0.48	56.0	0.06
		XV[4] XVIII[47]*	End	0.19	0.08 to 0.30	0.0009	0	0.53
≥4 weeks	Gingival index[53]	I[32] IV[35]	Base	–0.04	–0.12 to 0.04	0.37	0	0.96
		XVIII[47]*	End	–0.03	–0.16 to 0.09	0.58	62.0	0.05
≥4 weeks	Stain index[60]	XV[4]	Base	0.01	–0.10 to 0.11	0.86	33.3	0.22
		XVIII[47]*	End	–0.42	–0.94 to 0.10	0.12	94.7	<0.000001

* EOMW data were used twice, once each for 0.1% and 0.2% CHX.

full-text reading, two articles by Botelho et al.[24,25] were excluded because they provided data on essential oils other than the EOMW selected for this review. These authors demonstrated that the essential oil *Lippia sidoides*–based mouthrinse was relatively safe and effective in reducing the plaque index, gingival index, and gingival bleeding index scores. Compared to 0.12% CHX-MW, no statistical significant difference in the observed effect was established. Therefore, the data of the studies by Botelho et al.[24,25] are in support of the findings for the EOMW and CHX-MW determined in this systematic review.

Safety of Alcohol-Containing Mouthwashes

Alcohol is used in mouthwashes as a solvent for other ingredients and as a preservative of the preparation. For years, different formulas of mouthwashes have been used; however, the question of whether the alcohol content is a threat for health is raised at regular intervals. The high quantity of alcohol in EOMW combined with the fact that these rinses are kept in contact with the oral mucosa for much more time than alcoholic drinks could induce a harmful effect from a local mechanism.[74]

Over the last 3 decades, ≥10 case-control studies have been published assessing the possible relationship between alcohol-containing mouthrinses and oral cancer.[91] Epidemiologic findings on mouthwashes and oral cancer were not consistent across the various studies, populations, and strata of major risk factors considered, including smokers and non-smokers.[92] More specifically, the pattern of risk is not different with reference to alcohol-containing mouthwashes and other types of non-alcohol containing mouthwashes. This absence of an association is also consistent with our knowledge of the dose-risk relationship between alcohol consumption and risk of upper digestive tract cancers, which show no excess risk for low doses of ethanol.[91,93] A review by Silverman and Wilder[94] concluded that abundant clinical data have demonstrated the safety of alcohol-containing mouthrinses and failed to find any evidence for a relationship with increased risk of developing oral cancer, xerostomia, burning, or irritation. There have been some reports of alcoholics drinking alcohol-containing mouthwashes. These non-beverage alcoholics may cause symptoms such as severe gastritis.[95]

Staining and Calculus

Stains are generally recognized as an esthetic problem. They may interfere with patient compliance in long-term treatment regimes. Staining is not currently a recognized side effect of EOMW, although few, if any, studies have actively recorded this parameter. Mandel[96] alluded in a review to the possibility of tooth staining by EOMW but offered no evidence. However, in an experimental gingivitis study,[23] greater extrinsic staining was observed with EOMW compared to the control rinse. In the latter study[23] and a study by Addy et al.,[27] the masked nature of scoring left little doubt that increased staining did occur with EOMW. The design of both of these studies, in which normal toothbrushing was suspended, makes it difficult to extrapolate the findings to normal home usage of EOMW.[27]

Even so, these short-term results do not seem to translate into long-term actual use. One (XVII) of the selected four long-term studies (IV, XV, XVII, and XVIII) reported a significant increase in staining for the EOMW; however, the magnitude of this increase (0.14) was negligible compared to the increase observed with a CHX-MW (2.21). Results for staining in the present review were as expected for the CHX-MW.[97] The lack of significance of WMD (0.42) (Table 10) may be due to the wide CI and the observed heterogeneity. In Table 9, all but one (XVIII) of the four studies (IV, XV, XVII, and XVIII) shows significantly more staining with the CHX-MW compared to the EOMW, suggesting that the CHX-MW has a pronounced effect on extrinsic tooth stain.

Also, calculus scores seemed higher with CHX-MW compared to EOMW, which is confusing in the context of the higher plaque control with CHX-MW. The explanation for this enhanced supragingival calculus formation has been provided by Addy and Moran[98] who suggested that this side effect of CHX is due to the precipitation of salivary proteins on the tooth surface, pellicle thickness, and/or the increased precipitation or inorganic salts on or in the pellicle layer.

Costs

Before any preventive measure is implemented, even one as conceptually simple as the control of plaque, a decision has to be made about its benefits and disadvantages. The costs of implementing the measures and any side effects that are seen with the use of a mouthwash are important considerations in this respect. Over a period of 1 year, the costs of twice daily rinsing with the EOMW would be $220 for an individual according to the regimens of use recommended by the manufacturer.#### Twice daily rinsing with CHX would cost approximately $234. This is comparable to the cost of two to three extensive visits to a dental hygienist in The Netherlands. The dental professional has to consider the benefits of both daily rinsing and a professional prophylaxis and weigh the advantages of one against the other.[3]

CONCLUSIONS

This review demonstrates that, compared to EOMW, CHX-MW provided better results for plaque. For the long-term control of gingival inflammation, the standardized essential-oil formulation is not different from CHX. Furthermore, CHX caused considerably more staining and calculus.

Considering the potential benefits in the light of the observed side effects, EOMW appears to be a reliable alternative to CHX-MW with respect to gingival inflammation in those cases where the dental professional has judged that long-term anti-inflammatory oral care may be beneficial. However, for indications where plaque control is the main focus such as post-surgery wound-healing, a CHX-MW remains the first choice. Further research could study the potential anti-inflammatory effect of essential oils in greater depth.

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