# Prevention and therapy of periodontal diseases and oral malodour

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# 7

# Can chemical mouthwash agents achieve plaque/gingivitis control? A meta-review

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# Key points

- Oral health is important since the mouth is the gateway to the human body. Bacteria are always present in the oral cavity and when not frequently removed the dental plaque biofilm leads to the development of oral disease.

- Over the past decades, the use of mouthwashes has become customary, usually following mechanical plaque biofilm control.

- Although people in industrialized countries use various oral hygiene products with the expectation of an oral health benefit, it is important that sufficient scientific evidence exists to support such claims.

- This meta-review summarized and appraised the current state of evidence that was based on systematic reviews, with respect to the efficacy of various active ingredients of over the counter chemotherapeutic mouthwash formulations for plaque control and managing gingivitis.

- Evidence suggests that a mouthwash containing chlorhexidine (CHX) is the first choice. The most reliable alternative for plaque control is essential oil (EO). No difference between CHX and EO with respect to gingivitis was observed.

# Introduction

The need to prevent human disease is well recognized and is related to making the occurrence or progression of a disease process unlikely or impossible. Oral health is important because the mouth is the gateway to the human body. Bacteria are always present in the oral cavity and when not frequently removed, the dental plaque biofilm leads to the development of oral disease. The merits of daily oral hygiene to oral health have long been understood (1). Studies of tooth cleaning suggest that despite technological innovations, the level of mechanical oral hygiene practice is inadequate (2–4).

The principle that plaque biofilm is the major etiologic factor causing gingivitis provides the justification for the use of antimicrobial mouth rinses (5). The practice of mouth rinsing has been in use by humans for more than 2000 years. The first mouthwash advocated for dental plaque reduction seems to be urine from a child or, even better, from a newborn baby (6). In the 1880s, Willoughby D. Miller (a dentist trained in microbiology) was the first to suggest the use of an anti- microbial mouthwash containing phenolic compounds to combat gingival inflammation (7). Over the past decades, the use of mouthwashes has become customary, usually following mechanical plaque biofilm control. Mouthwashes are an ideal vehicle in which to incorporate chemicals and are appreciated by the public because of their ease of use, reduction of plaque biofilm, and breath-freshening effect (8–10).

With keen competition between individual manufacturers vying for a percentage of this market, various claims for efficacy have been made, using numerous terms to describe efficacy. Although people in industrialized countries use various oral hygiene products with the expectation of an oral health benefit, it is important that sufficient scientific evidence exists to support such claims. Dental professionals have choices and make decisions every day as they advise their patients (11). An evidence-based clinical decision integrates and concisely summarizes all relevant and important research evidence of acceptable quality that examines the same therapeutic question. The model to guide clinical decisions begins with original single random controlled clinical studies at its foundation. Syntheses (systematic reviews) build up from these to integrate the best available evidence from these original studies (12). At the next level, a synopsis summarizes the findings of high-quality systematic reviews (13,14). Meta-analyses (meta-review) in particular are appropriate for describing whether the current evidence base is complete or incomplete. The quantitative evidence is synthesized from relevant previous systematic reviews. The reason for including only systematic reviews is because this kind of research generally provides more evidence than separate empirical studies. Also in the presence of a significant increase in systematic reviews, meta-reviews give the dental community better guidance. From this perspective, it is a step forward in the direction of a clinical guideline (15,16). Meta-reviews are a tool, a form of information, and guidance based on research evidence that assists the clinician in formulating the answer appropriate for each individual patient (11).

Recently, 2 meta-reviews have been published that evaluate the efficacy of home-care regimens for mechanical plaque removal (toothbrushes and interdental cleaning devices) on plaque and gingivitis in adults (2,3).

The purpose of this article was to prepare a meta-review that summarizes the contemporary synthesized evidence with respect to the efficacy and safety of home-care self-support activities focusing on chemical agents in mouthwashes to manage plaque and gingivitis.

## Materials and methods

The protocol of this meta-review detailing the evaluation method was developed using the AMSTAR (17) (a measurement tool to assess systematic reviews) tool to ensure the methodological quality of the review process.

### Focused Question

What is the effect of mouthwashes and their various chemical ingredients for plaque biofilm control in managing gingivitis in adults based on evidence gathered from existing systematic reviews?

### Search Strategy

For the comprehensive search strategy, several electronic databases were queried. Three Internet sources were used to search for appropriate articles that satisfied the study purpose. These sources included the National Library of Medicine, Washington, DC (MEDLINE-PubMed), the Cochrane Library, which also includes the DARE database of systematic reviews, and the evidence database of the American Dental Association (ADA) Center for Evidence-based Dentistry. All 3 databases were searched for eligible studies up to and including February 2015. The structured search strategy was designed to include any systematic review published on mouthwash products. For details regarding the search terms used, see Box 1. All of the reference lists of the selected studies were hand-searched for additional published work that could possibly meet the eligibility criteria of the study. The PROSPERO (2014) database, an international database of prospectively registered systematic reviews, was checked for reviews in progress. Further unpublished work was not sought.

### Screening and Selection

Two reviewers (DES and EvdS) independently screened the titles and abstracts for eligible articles. If eligibility aspects were present in the title, the article was selected for further reading. If none of the eligibility aspects were mentioned in the title, the abstract was read in detail to screen for suitability. Inclusion of titles, abstracts, and ultimately full texts was based initially on full agreement between the 2 reviewers (DES and EvdS). In case of discrepancies, the final decision was made following discussion with GAW. No attempt was made to blind the reviewers to names of authors or institutions and journals while making the assessment. Hand searching of reference lists of reviews was conducted to ensure inclusion of additional published and potentially relevant articles. When updates of systematic reviews were published, the latest version was selected. At the outset of this meta-review, no attempt was made to separate specific variables associated with mouthwashes.

**Box 1**
Search terms used for PubMed-MEDLINE, Cochrane Library and ADA Center for Evidence based Dentistry. The search strategy was customized appropriately according to the database being searched taking into account differences in controlled vocabulary and syntax rules.

The following strategy was used in the search mouthwashes:

{ [MeSH Terms] Mouthwashes OR [text words] Mouthwashes OR Mouthwash OR mouthwash* OR mouthrinses OR mouthrinse }

Used filter/limits: systematic review OR meta-analysis

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

## Inclusion and Exclusion Criteria

The inclusion criteria were as follows:

- Systematic reviews (with or without a meta-analysis)
- Articles written in the English or Dutch language
- Reviews evaluating studies conducted on humans
  - o ≥18 years old
  - o In good general health
- Intervention: mouthwashes and their various chemical ingredients for plaque control and reducing gingivitis

## The exclusion criteria were as follows:

- Orthodontic patients
- Dental implants

## Data Extraction and Assessment of Heterogeneity

The articles that fulfilled all of the selection criteria were processed for data extraction. Information extracted from the studies included publication details, focused questions, search results, descriptive or meta-analysis outcomes, and conclusions. Systematic reviews were categorized by 2 authors (DES and EvdS) according to various active ingredients of mouthwashes. Categorization was confirmed with a second author (GAW). Disagreements between the reviewers were resolved by discussion.

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

- Study and subject characteristics
- Methodological heterogeneity (variability in review approach and risk of bias)
- Analysis performed (descriptive or meta-analysis)

Heterogeneity within the meta-analysis was tested by $x^2$ test and the $I^2$ statistical. A $x2$ test resulting in a P<.1 was considered an indication of significant statistical heterogeneity. As a rough guide for assessing the possible magnitude of inconsistency across studies, an $I^2$ statistic of 0% to 40% was interpreted as not being important, and with an $I^2$ statistic higher than 40%, moderate (40%–80%) to considerable (>80%) heterogeneity may be present (18).

### Quality Assessment

Two reviewers (DES and EvdS) estimated the risk of bias by scoring the reporting and methodological quality of the included systematic reviews according to a combination of items described by the PRISMA (19) guideline for reporting systematic reviews and the (17) checklist for assessing the methodological quality of systematic reviews. A list of 27 items was assessed, and if all individual items were given a positive rating by summing these items, an overall score of 100% was obtained. Only systematic reviews including meta-analysis could achieve a full score of 100% (20). The estimated risk of bias was interpreted as follows: 0% to 40% may represent a high risk of bias, 40% to 60% may represent a substantial risk of bias, 60% to 80% may represent a moderate risk of bias, and 80%–100% may represent a low risk of bias (3).

### 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 meta-review of systematic reviews (21). Two reviewers (DES and GAW) rated the quality of the evidence as well as the strength of the recommendations according to the following aspects: study design, risk of bias, consistency and precision among outcomes, directness of results, detection of publication bias, and magnitude of the effect.

## Results

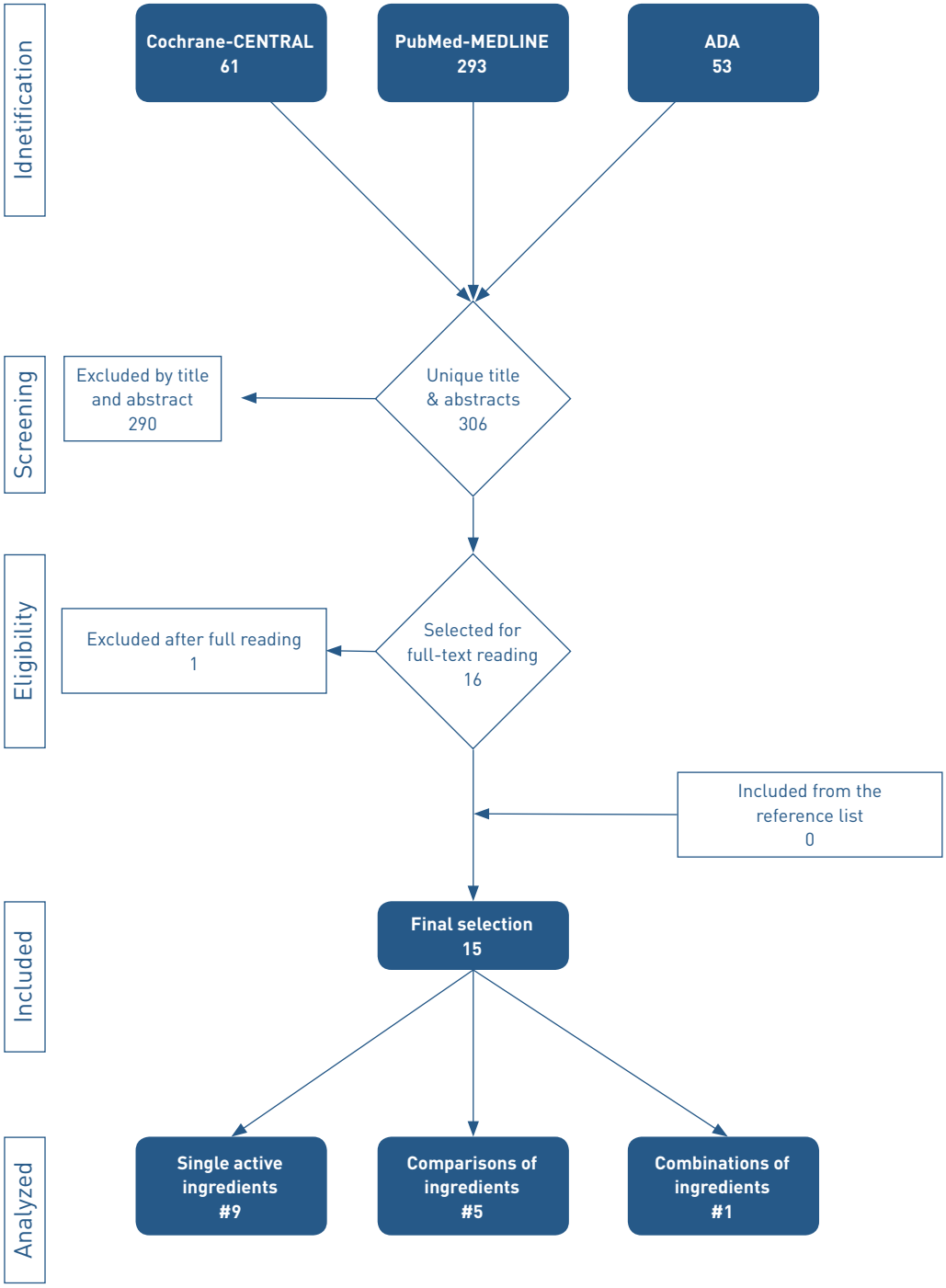
### Search and Selection Results

Fig. 1 describes the search process. A total of 306 unique articles were identified, from which 17 full-text articles were obtained and screened to confirm eligibility. One study was excluded because the data were summarized for a large variety of natural compounds and did not allow for an evaluation of individual ingredients (22). Hand searching of the reference lists from these articles did not reveal any additional suitable systematic reviews. Neither did a search of the PROSPERO (International Prospective Register of Systematic Reviews) database (2014). Two papers by Gunsolley(23,24) provided data on the same meta-analysis. As a result, a final 15 systematic reviews were identified as being eligible for inclusion in this synopsis. Nine articles were identified that evaluated the efficacy of single active ingredients, of which 2 reviewed more than 1 ingredient (23,24,26). Five studies compared active ingredients, of which 2 also contributed data for the singles active ingredients (27,28). In one publication, a combination of 2 active ingredients was systematically evaluated (29).

### Study Outcomes and Assessment of Heterogeneity

Considerable heterogeneity was observed in the 15 systematic reviews with respect to the data bases searched, study and subject characteristics of the original individual articles, description of inclusion and exclusion criteria, quality assessment scale used, reporting of effect scores, presence of meta-analysis, and conclusions made. Because of this hetero-

**Figure 1** Search and selection results.



geneity, a sophisticated level of data combination and analysis was neither possible nor indicated. A meta-analysis was therefore not undertaken. For the purpose of this synopsis, a summary of the selected systematic reviews was categorized and is presented by various chemical ingredients and ordered by common characteristics in Table 1.

## Quality Assessment

Most reviews were considered to have a low to moderate estimated risk of bias (Table 2). Two studies were estimated to have a substantial risk of bias (23–25). Critical items in this evaluation were the development of a protocol *a priori* and its registration, including non-English literature, contacting authors for additional information, grading obtained evidence, and the assessment of publication bias.

## Active Ingredients

For details regarding the extracted data of the meta-analysis, difference of means, P values, 95% confidence intervals, and test of heterogeneity, please see Table 3 for Plaque Index scores and Table 4 for Gingival Index scores.

## Single Active Ingredients

### *Alexidine*

Alexidine (ALX) is an antimicrobial of the biguanide class, and contains ethylhexyl end groups. This structure favors hydrophobic penetration into membrane lipids and electrostatic adhesion to the negative sites of cell membranes resulting in bactericidal activity. The systematic review by Serrano and colleagues (26). identified 2 articles and evaluated the adjunctive effect of ALX to toothbrushing in the prevention of plaque accumulation and gingival inflammation in studies with duration of 6 months or longer. The study outcome with respect to the Quigley and Hein (36). Plaque Index (PI) scores at the conclusion of the individual studies demonstrated a significant difference of means (DiffM) of -0.16, with nonsignificant heterogeneity ($I^2$ = 39.5%). Data with respect to the Gingival Index (GI) (37) were based on one study and showed a nonsignificant mean difference of -0.09 as compared with the control group.

### *Cetylpyridinium chloride*

Cetylpyridinium chloride (CPC) is a cationic quaternary ammonium compound with surface-active properties. Its mechanism of action relies on the hydrophilic part of the CPC molecule interacting with the bacterial cell membrane leading to loss of cell components, disruption of cell metabolism, inhibition of cell growth, and finally cell death. It has a broad antimicrobial spectrum, with rapid killing of gram-positive pathogens and yeast in particular. CPC may cause brown staining of teeth. The search retrieved 3 systematic reviews concerning the efficacy of CPC evaluating the adjunctive effect to toothbrushing in the prevention of plaque accumulation and gingival inflammation. The systematic review by Gunsolley (23,24) identified 7 articles in studies with a duration of 6 months or longer. The study outcome with respect to the PI at the finish of the individual studies demonstrated a weighted mean percentage reduction of 15.4% (SD 7.6). Data with respect to the GI showed

weighted mean percentage reduction of 13.4% (SD 8.7).
The systematic review by Haps and colleagues (33) identified 8 articles in studies of 4 or more weeks' duration. The meta-analysis of PI scores at the end of the individual studies demonstrated a significant DiffM of -0.35, with moderate heterogeneity ($I^2$ = 71.6%). Data with respect to the GI showed a significant DiffM of -0.15 in favor of CPC as compared with the control group (considerable heterogeneity, $I^2$ = 87%). The most recent systematic review by Serrano and colleagues (26) identified 10 articles in studies of 6 or more months' duration. The study outcome with respect to the PI scores at the finish of the individual studies demonstrated a significant DiffM of -0.39, with considerable heterogeneity ($I^2$ = 93.9%). Data with respect to the GI showed a significant DiffM of -0.33 in favor of CPC as compared with the control group (considerable heterogeneity, $I^2$ = 95.3%).

### *Chlorhexidine*

Chlorhexidine (CHX) is a cationic bisbiguanide that is active against gram-positive and gram-negative organisms, facultative anaerobes, aerobes, and yeasts. CHX lasts longer in the mouth than other mouthwashes (substantivity) and can cause stains on teeth, tongue, gingiva, and resin restorations. Prolonged use also can reduce bitter and salty taste sensations. CHX was first investigated more than 50 years ago and is currently one of the most widely used and thoroughly evaluated oral topical antiseptics.
The search retrieved 3 systematic reviews concerning the efficacy of CHX evaluating the adjunctive effect against toothbrushing in the prevention of plaque accumulation and gingival inflammation. The systematic review by Gunsolley (23,24) identified 6 articles in studies of 6 or more months' duration. The study outcome with respect to the PI at the finish of the individual studies demonstrated a weighted mean percentage reduction of 40.4% (SD 11.5). Data with respect to the GI (37) showed weighted mean percentage reduction of 28.7% (SD 6.5).
The systematic review by Van Strydonck and colleagues (18) identified 30 articles and evaluated the adjunctive effect of CHX to toothbrushing in the prevention of plaque accumulation and gingival inflammation in patients with gingivitis, including studies of 4 or more weeks' duration.
The meta-analysis of PI scores at the finish of the individual studies considered by the authors to be at 'low risk' demonstrated a DiffM of -0.68, heterogeneity was not significant ($I^2$ = 60%). Data with respect to the GI showed a DiffM of -0.24, in favor of CHX as compared with the control rinse (considerable heterogeneity, $I^2$ = 87%). Relative to control, the reduction with CHX for plaque was calculated to be 33% and for gingivitis 26%. The CHX rinsing groups demonstrated significantly more staining.
The most recent systematic review by Serrano and colleagues (26) identified 14 articles in studies of 6 or more months' duration. The study outcome with respect to the PI scores at the finish of the individual studies demonstrated a significant DiffM of -0.64, with nonsignificant heterogeneity ($I^2$ = 47.4%). Data with respect to the GI showed a significant DiffM of -0.17, in favor of CHX as compared with the control group (considerable heterogeneity, $I^2$ = 95.3%).

**Table 1** Overview of the characteristics of the included systematic reviews processed for data extraction.

| Author (year)<br>Ingredient | Data bases searched | Number of included studies/trails, No. involved participants base (end) | Leading mode of analysis |
|---|---|---|---|
| Serrano et al. 2015 (26)<br>Multiple ingredients | • PubMed | ? studies<br>? (?) | Meta-analysis |
| Van Leeuwen et al. 2014 (30)<br>EO | • PubMed-Medline<br>• Cochrane-CENTRAL<br>• EMBASE | 5 studies<br>605 (534) | Meta-analysis |
| Van Maanen-Schakel et al. 2012 (29)<br>CHX + $H_20_2$ | • PubMed-Medline<br>• Cochrane-CENTRAL<br>• EMBASE<br>• Trial registers<br>• Others | 4 studies<br>252 (229) | Meta-analysis |
| Van Strydonck et al. 2012 (18)<br>CHX | • PubMed-Medline<br>• Cochrane-CENTRAL<br>• EMBASE | 30 studies<br>34 experiments<br>3554 (2965) | Meta-analysis |
| Van Leeuwen et al. 2011 (31)<br>EO vs CHX | • PubMed-Medline<br>• Cochrane | 19 studies<br>827 (?) | Meta-analysis |
| Hossainian et al 2011 (28)<br>$H_2O_2$ | • PubMed-Medline<br>• Cochrane-CENTRAL<br>• EMBASE | 10 studies<br>12 experiments<br>384 (363) | Descriptive analysis |
| Gunsolley<br>2006/2010 (23,24)<br>Multiple ingredients | • Medline<br>• Unpublished studies | ? studies<br>? (?) | Meta-analysis |
| Afennich et al. 2010 (27)<br>Hexitidine | • PubMed-Medline<br>• Cochrane- CENTRAL<br>• EMBASE | 6 studies<br>357 (336) | Descriptive analysis |
| Berchier et al 2010 (32)<br>CHX<br>0.12% vs 0.2% | • PubMed-Medline<br>• Cochrane | 8 studies<br>10 experiments<br>803 (?) | Meta-analysis |
| Haps et al. 2008 (33)<br>CPC | • PubMed-Medline<br>• Cochrane | 8 studies<br>867 (?) | Meta-analysis |
| Addy et al. 2007 (25)<br>Delmopinol | • Unknown | 8 studies<br>913 (?) | Pooled weighted point estimate |
| Stoeken et al. 2007 (34)<br>EO | • PubMed-Medline<br>• Cochrane | 11 studies<br>2810 (2515) | Meta-analysis |
| Paraskevas et al. 2006 (35)<br>$SnF_2$ | • PubMed-Medline<br>• Cochrane-CENTRAL<br>• EMBASE | 3 studies concerning mouthwashes<br>781 (500) | Descriptive analysis |

ALX = alexidine
CPC = cetylpyridinium chloride
CHX = chlorhexidine
DEL = delmopinol
EO = essential oils
HEX = hexetidine
$H_20_2$ = hydrogen peroxide
OA = oxygenating agents
$SnF_2$ = Stannous fluoride

| | Original review authors' conclusions | Comments of the meta- review authors |
|---|---|---|
| | Formulations with specific agents for chemical plaque control provide statistically significant improvements in terms of gingival bleeding and plaque indices. | Triclosan was assessed in the meta-analysis as a 'pre-rinse' to toothbrushing which is considered to provide an 'indirect' effect because this is not a common daily oral hygiene habit. |
| | EO produce an effect on plaque and gingivitis that extends beyond the vehicle solution. | Comparisons to vehicle control are frequently done to 5% hydro-alcohol while a true placebo would contain 21.6% - 26.9% alcohol. |
| | There is moderate evidence that a combination of CHX and an oxygenating agent reduces tooth staining without interfering with plaque growth inhibition. | Tooth discoloration was considered as the primary outcome variable and plaque and gingivitis as secondary. |
| | There is strong evidence for the anti-plaque and anti-gingivitis effects of a CHX rinse as an adjunct to regular oral hygiene in gingivitis patients. But a significant increase in staining score was seen by CHX mouthrinse. | Staining as a side effects of CHX can affect patient compliance. |
| | Long term studies showed that CHX mouthwash was statistically more effective than EO with respect to plaque control. However, there was no significant difference with respect to reduction of gingival inflammation. Also, significantly more staining was observed with CHX compared to EO. | The evidence suggests that EO acts primarily through anti-inflammatory process and is a reliable alternative to CHX for long term control of gingival inflammation. |
| | $H_2O_2$ mouthwashes do not consistently prevent plaque accumulation when used as a short-term mono-therapy. When used as a long-term adjunct to daily oral hygiene, the results of one study indicate that oxygenating mouthwashes reduce gingival redness. | As side effect painful sensation in the mouth and/ or erosive changes of the oral mucosa may occur. |
| | The studies provide strong evidence of the anti plaque and anti gingivititis effects of multiple agents. It supports the use of mouthwashes as part of a daily oral hygiene. | The used review methodology is unclear. |
| | Hexitidine mouthwashes provide better effects regarding plaque reduction than placebo mouthwashes. They are less effective than CHX. | Higher Hexitidine concentrations cause more side effects compared with lower concentrations. |
| | In the comparison 0.12% and 0.2% CHX information concerning the effect on gingival inflammation was sparse. With respect to plaque inhibition, the results showed a small but significant difference in favour of the 0.2% CHX concentration. | The clinical relevance of the difference between the 2 concentrations was considered negligible.<br>Several sub analysis are performed such as rinsing duration, mouthwash solution with/without alcohol, manufacturer. |
| | When used as adjunct to either supervised or unsupervised oral hygiene, CPC-containing mouth rinses, provide a small but significant additional benefit in reducing plaque accumulation and gingival inflammation. | The bioavailability and concentration of the active ingredient may influence it clinical efficacy. |
| | Delmopinol is effective as an adjunct measure for reducing plaque burden and indices of gingivitis, whether or not it is used under supervision. | No common method for meta-analysis was used. |
| | EO provides an additional benefit to unsupervised oral hygiene with regard to plaque and gingivitis reduction as compared to a placebo or control | Comparisons are also made to 5% hydro-alcohol, CHX and a group that uses floss. |
| | With regard to $SnF_2$ there is insufficient information on gingivitis and plaque in order to make any conclusions. | The effect of the combined use of $SnF_2$ dentifrice + $SnF_2$ mouthwash would be of interest. |

SLS = Sodium Lauryl Sulphate
TCL = triclosan

**Table 2** Estimated the risk of bias by scoring a list of items related to the reporting and methodological quality of

| Criteria \ Author | Addy et al. 2007 (25) | Afennich et al. 2010 (27) | Berchier et al. 2010 (32) | Gunsolley 2006/2010 (23,24) | Haps et al. 2008 (33) |
|---|---|---|---|---|---|
| Defined outcome criteria of interest | + | + | + | + | + |
| Describes the rationale | + | + | + | + | + |
| Describes the focused (PICO)[S] question / hypothesis | + | + | + | + | + |
| Describes if a protocol was developed 'a pirori'. | - | - | - | - | - |
| Protocol registration/publication | - | - | - | - | - |
| Presented eligibility criteria (in/exclusion criteria) | + | + | + | + | + |
| Presents the full search strategy | - | + | + | + | + |
| Various databases searched | ? | + | + | - | + |
| Performed (hand) search in additional sources (f.i. grey literature or trial registers) | ? | + | + | - | + |
| Review selection by more than 1 reviewer | - | + | + | + | + |
| Non-English papers included | ? | - | - | - | - |
| Provide details on the performed study selection process/flow chart | - | + | + | - | + |
| Report included study characteristics | - | + | + | + | + |
| Provide data of the selected studies on the outcome measures of interest | + | + | + | + | + |
| Data were extracted by more than 1 reviewer | ? | + | + | - | + |
| Contacted authors for additional information | + | ? | + | + | ? |
| Report heterogeneity of the included studies | - | + | + | + | + |
| Estimated risk of bias in individual studies | - | + | + | - | + |
| Performed a meta analysis | + | - | + | + | + |
| Performed a descriptive analysis | - | + | + | + | + |
| Describe additional sub analysis | + | + | + | - | + |
| Grading of the obtained evidence | - | - | - | - | - |
| Present limitations of the systematic review | - | - | - | - | - |
| Provide a conclusion that respond to the objective | + | + | + | + | + |
| Publication bias assessed | - | - | - | - | - |
| Funding source | - | + | + | + | - |
| Conflict of interest statement | + | + | + | - | - |
| Original authors estimated level of evidence | NR | NR | NR | NR | NR |
| Current authors estimated quality score | 52% | 74% | 78% | 52% | 70% |
| Current authors estimated risk of bias | **Substantial** | **Moderate** | **Moderate** | **Substantial** | **Moderate** |

Each aspect of the reporting and methodological quality item score list was given a rating of a plus '+' for informative description of the item at issue and a study design meeting the quality standard, was assigned, plus-minus (±) was assigned if the item was incompletely described, ? when unknown and minus '-' was used if the item was not

the included systematic reviews.

| | Hossainian et al. 2011 (28) | Paraskevas et al. 2006 (35) | Serrano et al. 2015 (26) | Stoeken et al. 2007 (34) | Van Leeuwen et al. 2011 (31) | Van Leeuwen et al. 2014 (30) | Van Maanen-Schakel et al. 2012 (29) | Van Strydonck et al. 2012 (18) |
|---|---|---|---|---|---|---|---|---|
| | + | + | + | + | + | + | + | + |
| | + | + | + | + | + | + | + | + |
| | + | + | + | + | + | + | + | + |
| | - | - | + | - | - | - | - | - |
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| | + | - | + | + | + | + | + | + |
| | NR | NR | NR | NR | NR | Moderate | Moderate | Strong |
| | 78% | 63% | 85% | 81% | 78% | 85% | 93% | 89% |
| | **Moderate** | **Moderate** | **Low** | **Low** | **Moderate** | **Low** | **Low** | **Low** |

described (20). NR= not reported

For the quality assessment score individual items with a positive rating were summed to obtain an overall percentage score.

**Table 3** Overview of data extraction of the included systematic reviews regarding Plaque Index scores.

| **Source** | | | **Outcomes** |
|---|---|---|---|
| **Ingredient** | Systematic Reviews | # Experiments included in MA | Difference of Means |
| **ALX** | Serrano et al. 2015 (26) | 2 | -0.16 |
| **CPC** | Gunsolley 2006 (24) | 7 | -15.4% |
| | Haps et al. 2008 (33) | 7 | -0.35 |
| | Serrano et al. 2015 (26) | 10 | -0.39 |
| **CHX** | Gunsolley 2006 (24) | 6 | -40.4% |
| | Van Strydonck et al. 2012 (18) | 5 | -0.68 |
| | Serrano et al. 2015 (26) | 3 | -0.64 |
| **DEL** | Addy et al. 2007 (25) | 8 | -0.34 |
| | Serrano et al. 2015 (26) | 3 | -0.14 |
| **EO** | Gunsolley 2006 (24) | 25 | -27.0% |
| | Stoeken et al. 2007 (34) | 7 | -0.83 |
| | Serrano et al. 2015 (26) | 9 | -0.83 |
| **HEX** | Affenich et al. 2011 (27) | □ | □ |
| **OA** | Hossainian et al. 2011 (28) | □ | □ |
| **SAN** | Serrano et al. 2015 (26) | 1 | -12.1% |
| **$SnF_2$** | Paraskevas & Van der Weijden 2006 (35) | □ | □ |
| | Serrano et al. 2015 (26) | 2 | -0.08 |
| **TCL** | Serrano et al. 2015 (26) | 3 | -0.68 |
| **0.12% CHX versus 0.2% CHX** | Berchier et al. 2010 (32) | 9 | -0.10 |
| **EO versus CHX** | Van Leeuwen et al. 2011 (31) | 5 | -0.19 |
| **OA plus CHX** | Van Maanen-Schakel et al. 2012 (29) | 3 | -0.10 |

* P-value >0.1 not significant (ns)
MA = meta analysis
□ = no data available
ns = not significant

ALX = alexidine
CPC = cetylpyridinium chloride
CHX = chlorhexidine
DEL = delmopinol
EO = essential oils
HEX = hexetidine
OA = oxygenating agents
SAN = sanguinarine
$SnF_2$ = Stannous fluoride
TCL = triclosan

| | | | Heterogeneity | |
|---|---|---|---|---|
| | 95% CI | P-value | $I^2$ | P-value* |
| | -0.25; -0.08 | P<0.0001 | 39,5% | ns |
| | □ | □ | □ | □ |
| | -0.47; -0.24 | P<0.00001 | 71.6% | P=0.002 |
| | -0.54;-0.24 | P<0.0001 | 93.9% | P=0.000 |
| | □ | □ | □ | □ |
| | -0.85; -0.51 | P<0.00001 | 60% | P=0.06 |
| | -0.76; -0.52 | P<0.0001 | 47.4% | ns |
| | -0.39; -0.29 | P<0.00001 | □ | □ |
| | -0.23; -0.06 | P=0.001 | 0% | ns |
| | □ | □ | □ | □ |
| | -1.13; -0.53 | P<0.00001 | 96.1% | P<0.00001 |
| | -1.05; -0.60 | P=0.000 | 97% | P=0.000 |
| | □ | □ | □ | □ |
| | □ | □ | □ | □ |
| | □ | □ | □ | □ |
| | □ | □ | □ | □ |
| | -0.26; 0.10 | ns | 60.9% | ns |
| | -0.85; -0.51 | P<0.0001 | 68% | P=0.04 |
| | -0.17; -0.03 | P=0.008 | 0% | ns |
| | -0.30; -0.08 | P<0.0009 | 0% | ns |
| | -0.17; -0.04 | P=0.003 | 0% | P=0.97 |

**Table 4** Overview of data extraction of the included systematic reviews regarding the Gingival Index scores.

| Source | | | Outcomes | | | Heterogeneity | |
|---|---|---|---|---|---|---|---|
| **Ingredient** | **Systematic Reviews** | **# Experiments included In MA** | **Difference of Means** | **95% CI** | **P-value** | **$I^2$** | **P-value** |
| **ALX** | Serrano et al. 2015 (26) | 1 | -0.09 | -024; 0.07 | ns | □ | □ |
| **CPC** | Gunsolley 2006 (23) | 6 | -13.4% | □ | □ | □ | □ |
| | Haps et al. 2008 (33) | 7 | -0.15 | -0.23; -0.07 | P=0.0003 | 87% | P<0.0001 |
| | Serrano et al. 2015 (26) | 4 | -0.33 | -0.53;-0.12 | P=0.002 | 95.3% | P=0.000 |
| **CHX** | Gunsolley 2006 (23) | 6 | -28.7% | □ | □ | □ | □ |
| | Van Strydonck et al. 2012 (18) | 3 | -0.24 | -0.29; -0.20 | P<0.00001 | 87% | P=0.0005 |
| | Serrano et al. 2015 (26) | 6 | -0.17 | -0.25; -0.08 | P<0.0001 | 59.5% | P=0.03 |
| **DEL** | □ | □ | □ | □ | □ | □ | □ |
| **EO** | Gunsolley 2006 (23) | 24 | -18.2% | □ | □ | □ | □ |
| | Stoeken et al. 2007 (34) | 8 | -0.14 | -0.25; -0.03 | P<0.00001 | 75.4% | P=0.02 |
| | Serrano et al. 2015 (26) | 2 | -0.13 | -0.19; -0.07 | P<0.0001 | 45.1% | ns |
| **HEX** | Affenich et al. 2011 (27) | □ | □ | □ | □ | □ | □ |
| **OA** | Hossainian et al. 2011 (28) | □ | □ | □ | □ | □ | □ |
| **SAN** | Serrano et al. 2015 (26) | 1 | -2.8% | □ | □ | □ | □ |
| **$SnF_2$** | Paraskevas & Van der Weijden 2006 (35) | □ | □ | □ | □ | □ | □ |
| | Serrano et al. 2015 (26) | 2 | -0.25 | -0.43; -0.07 | P=0.007 | 54.2% | ns |
| **TCL** | Serrano et al. 2015 (26) | 3 | -0.27 | -0.31; -0.24 | P<0.0001 | 41% | ns |
| **0.12% CHX versus 0.2% CHX** | Berchier et al. 2010 (32) | □ | □ | □ | □ | □ | □ |
| **EO versus CHX** | Van Leeuwen et al. 2011 (31) | 4 | -0.03 | -0.16; 0.09 | ns | 62% | P=0.05 |
| **OA plus CHX** | Van Maanen-Schakel et al. 2012 (29) | □ | □ | □ | □ | □ | □ |

* P-value >0.1 not significant (ns)
MA = meta analyses
□ = no data available

ALX = alexidine
CPC = cetylpyridinium chloride
CHX = chlorhexidine
DEL = delmopinol
EO = essential oils
HEX = hexetidine
OA = oxygenating agents
SAN = sanguinarine
$SnF_2$ = Stannous fluoride
TCL = triclosan

### *Delmopinol*

Delmopinol, an amino alcohol, is a third-generation antiplaque agent used as a mouthwash to reduce plaque and alleviate gingivitis. It has surface-active properties and creates an environment that will not allow plaque biofilm and bacteria to adhere.

The search retrieved 2 systematic reviews concerning the efficacy of CHX evaluating the adjunctive effect to toothbrushing in the prevention of plaque accumulation and gingival inflammation. The systematic review by Addy and colleagues (25) identified 8 studies with durations ranging from 8 to 24 weeks. Analyses for plaque and gingivitis based on aggregated data confirm the efficacy of delmopinol 0.2% over the placebo for PI scores, demonstrating a significant DiffM of -0.34. Data with respect to the GI were not available. Modified gingival index (38) scores and bleeding on probing (BOP) scores also showed a significant effect on gingivitis. Analysis also revealed no sustained heterogeneity of outcome, although the variable of BOP ranged considerably across the studies from less than 10% to greater than 30% (DiffM -2.8%).

The most recent systematic review by Serrano and colleagues (26) identified 3 articles in studies of 6 or more months' duration. The study outcome with respect to the PI scores at the finish of the individual studies demonstrated a significant DiffM of -0.14, with nonsignificant heterogeneity ($I^2$ = 0%). Data with respect to the GI were not available. Modified GI (38) scores and BOP scores indicate a nonsignificant effect on gingivitis.

### *Essential oils*

Essential oils (EO) are used in an over-the-counter mouthwash containing a fixed formula of 2 phenol-related EO, thymol 0.064% and eucalyptol 0.092%, mixed with menthol 0.042% and methyl salicylate 0.060% in a 22% alcohol vehicle. The anti- microbial mechanisms of action of EO against bacteria are complex. At high concentrations, there is disruption of the cell wall and precipitation of cell proteins, whereas at lower concentrations, there is inactivation of essential enzymes. Also, anti- inflammatory action has been proposed based on antioxidant activity. EO also may cause staining of teeth (39,40). The search retrieved 3 systematic reviews concerning the efficacy of EO evaluating the adjunctive effect to toothbrushing in the prevention of plaque accumulation and gingival inflammation. The systematic review by Gunsolley (23,24) identified 20 articles with a study duration of 6 or more months including unpublished data. The study outcome with respect to the PI at the finish of the individual studies demonstrated a weighted mean percentage reduction of 27% (SD 11.0). Data with respect to the GI showed weighted mean percentage reduction of 18.2% (SD 9.0).

The systematic review by Stoeken and colleagues (34) identified 11 studies with durations of 6 or more months. The study outcome with respect to the PI scores at the finish of the individual studies demonstrated a significant DiffM of -0.83, with considerable heterogeneity ($I^2$ = 96.1%). Data with respect to the (modified) GI showed a significant DiffM of -0.14 in favor of CHX as compared with the control group (moderate heterogeneity, $I^2$ = 75.4%).

The most recent systematic review by Serrano and colleagues (26) identified 15 articles including studies of 6 or more months' duration. The study outcome with respect to the PI scores at the finish of the individual studies demonstrated a significant DiffM of -0.14, with nonsignificant heterogeneity ($I^2$ = 0%). Data with respect to the GI showed a significant

(P<.0001) DiffM of -0.13 in favor of CHX as compared with the control group (nonsignificant heterogeneity, $I^2$ = 45.1%). Differences in modified GI scores also were significant and more pronounced (DiffM -0.54, 95% CI -0.76 to -0.31).

### *Hexetidine*

Hexetidine (HEX) belongs to the group of pyrimidine derivatives. It is a broad-spectrum antiseptic, active in vitro and in vivo against gram-positive and gram-negative bacteria as well as yeast. However, oral retention appears to be limited so that the antimicrobial activity does not last long. The systematic review by Afennich and colleagues (27) identified 6 articles and evaluated the adjunctive effect of HEX to toothbrushing in the prevention of plaque accumulation and gingival inflammation in short-term (≤4 weeks) and long-term (≥4 weeks) study designs. The data that were retrieved did not allow for a meta-analysis. Therefore, a descriptive analysis was presented that showed that both in the short and long term, antiplaque effects can be expected; however, no concomitant effect on GI scores was observed.

### *Oxygenating agents*

Oxygenating agents (OA), such as hydrogen peroxide ($H_2O_2$), buffered sodium peroxyborate, and peroxycarbonate, have been recommended for short-term use as disinfectants. They exert antimicrobial effects through the release of oxygen. The systematic review by Hossainian and colleagues (28) identified 10 articles and evaluated the adjunctive effect of OA to toothbrushing in the prevention of plaque accumulation and gingival inflammation in short-term (≤4 weeks) and long-term (≥4 weeks) study designs. The data that were retrieved did not allow for a meta-analysis. Therefore, a descriptive analysis was presented that showed that OA mouthwashes do not consistently prevent plaque accumulation when used as a short-term monotherapy. When used as a long-term adjunct to daily oral hygiene, the results of one study indicate that OA mouthwash reduces gingival redness.

### *Sanguinarine*

Sanguinarine (SAN) is a (toxic) quaternary ammonium salt from the group of benzylisoquinoline alkaloids. It is extracted from some plants, including bloodroot (Sanguinaria canadensis). It is also found in the root, stem, and leaves of the opium poppy. The systematic review by Serrano and colleagues (26) identified 1 article evaluating the adjunctive effect of SAN to toothbrushing in the prevention of plaque accumulation and gingival inflammation with 6 months' duration. The study outcome with respect to the PI at the finish of the study demonstrated a significant mean difference of 12.1% versus placebo and data with respect to the GI showed a nonsignificant mean difference of 2.8%.

### *Stannous fluoride*

Tin fluoride, commonly referred to commercially as stannous fluoride ($SnF_2$) is a well-known agent that has been used in dentifrice formulations as early as the beginning of the 1940s. Apart from reducing the incidence of dental caries, it has antimicrobial effects and as such has been formulated in mouthwashes. The combination of tin and fluoride is

difficult to formulate because of limited stability in an aqueous solution. $SnF_2$ may cause a yellowish-brown staining of teeth. The search retrieved 2 systematic reviews concerning the efficacy of $SnF_2$ evaluating the adjunctive effect to toothbrushing in the prevention of plaque accumulation and gingival inflammation. The systematic review by Paraskevas and van der Weijden (35) identified 2 articles evaluating mouthwashes in studies with a duration of 6 or more months. The data that were retrieved did not allow for a meta-analysis. Therefore, a descriptive analysis was presented that showed that $SnF_2$ mouthwashes do not consistently prevent plaque accumulation or prevent gingivitis. The most recent systematic review by Serrano and colleagues (26) identified 3 articles in studies of 6 or more months' duration. The study outcome with respect to the PI scores at the finish of the individual studies demonstrated a nonsignificant DiffM of -0.08, with nonsignificant heterogeneity ($I^2$ = 60.9%). Data with respect to the GI showed a significant DiffM of -0.25 in favor of CHX as compared with the control group (nonsignificant heterogeneity, $I^2$ = 54.2%).

### *Triclosan*

Triclosan (TCL) is a nonionic chlorinated aromatic compound that has functional groups representative of both ethers and phenols. It has antibacterial and antifungal properties and is applied in consumer products, including soaps and detergents. In mouthwash products it is combined with either zinc sulfate or a copolymer. The systematic review by Serrano and colleagues (26) identified 4 articles that evaluated the adjunctive effect of TCL as pre-rinse to toothbrushing in the prevention of plaque accumulation and gingival inflammation in studies of 6 or more months' duration. The study outcome with respect to the PI scores at the finish of the individual studies demonstrated a significant DiffM of -0.68, with moderate heterogeneity ($I^2$ = 68%). Data with respect to GI showed a significant DiffM of -0.27 in favor of TCL as compared with the control group (nonsignificant heterogeneity, $I^2$ = 41.0%).

## Comparisons of Active Ingredients

### *Chlorhexidine 0.12% versus chlorhexidine 0.2%*

In their systematic review, Berchier and colleagues (32) identified 8 articles evaluating the 2 CHX concentrations in relation to the prevention of plaque accumulation and gingival inflammation with no limits to study duration. With respect to the PI scores at the finish of the individual studies demonstrated a significant (P = 0.008) DiffM of -0.10 (95% CI -0.17 to -0.03), in favor of 0.2% CHX with nonsignificant heterogeneity ($I^2$ = 0%). The investigators considered the clinical relevance of this difference likely to be negligible. Information concerning the effect on gingival inflammation was sparse. Descriptive analysis tended to show that there was no difference.

### *Essential oils versus chlorhexidine*

The systematic review by Van Leeuwen and colleagues (31) identified 19 articles that evaluated the adjunctive effect of EO mouthwash against CHX in short-term (≤4 weeks) and long-term (≥4 weeks) study designs. Long-term studies evaluating the adjunctive effect to toothbrushing showed that, at the end of the studies, PI scores were reduced significantly

(P<.0009) with DiffM of -0.19 (95% CI -0.30 to -0.08), in favor of CHX as compared with the EO group with nonsignificant heterogeneity ($I^2$ = 0%). Data with respect to GI showed a nonsignificant DiffM of -0.03 (95% CI -0.16–0.09) with moderate heterogeneity ($I^2$ = 62%, P 5 .05).

*Essential oil versus alcohol solution*

The systematic review by Van Leeuwen and colleagues30 identified 5 articles that evaluated the adjunctive effect of EO mouthwash against an alcohol vehicle solution of 21.6 or 26.9% hydro-alcohol (V-Sol) in short-term (≤4 weeks) and long-term (2:4 weeks) study designs. Long-term studies evaluating the adjunctive effect to toothbrushing showed with respect to the PI scores at the finish of the individual studies a significant (P<.00001) DiffM of -0.39 (95% CI -0.47 to -0.30), in favor of EO with nonsignificant heterogeneity ($I^2$ = 0%). Data with respect to GI showed, in favor of EO, a significant (P<.00001) DiffM of -0.36 (95% CI -0.62 to -0.26), with considerable heterogeneity ($I^2$ = 92%, P<.00004).

*Hexetidine versus chlorhexidine*

In their systematic review Afennich and colleagues (27) (see earlier in this article) showed in their descriptive analysis that HEX is consistently less effective in plaque reduction than a CHX mouthwash and also less effective in reducing gingival inflammation than a CHX mouthwash.

*Oxygenating agents versus chlorhexidine*

In their systematic review, Hossainian and colleagues (28) (see earlier in this article) showed in their descriptive analysis that OAs are consistently less effective in plaque reduction than a CHX mouthwash.

## Combination of Active Ingredients

*Chlorhexidine and oxygenating agents*

In their systematic review, Van Maanen-Schakel and colleagues (29) identified 4 articles that evaluated the adjunctive effect of OA in combination with CHX in relation to the prevention of plaque accumulation and gingival inflammation with no limits to study duration. In their descriptive analysis, CHX in combination with OA showed no consistent difference in plaque or gingivitis reduction as compared with CHX mouthwash alone. Meta-analysis concerning the Silness and Löe PI (1964) showed a significant DiffM in favor of the combination (DiffM -0.10, 95% CI -0.17 to -0.04) with nonsignificant heterogeneity ($I^2$ = 0%). However, a significant (P = 0.02) reduction in staining was observed in the combination with OA (DiffM -0.27, 95% CI -0.49 to -0.05]), with nonsignificant heterogeneity ($I^2$ = 38%, P = 0.20).

*Evidence Profile*

Table 5 shows a summary of the various factors used to rate the body of evidence and strength of recommendations according to GRADE. There is strong evidence in support of the efficacy of both CHX and EO that have a large beneficial effect on plaque reduction and a moderate effect on gingivitis. There is also strong evidence in support of the efficacy

of CPC, which has a moderate beneficial effect on both plaque and gingivitis scores. There is moderate evidence for a small effect of ALX and for a large effect of TCL when used as pre-rinse before toothbrushing. Weak evidence emerged for small or indistinct effects of HEX, OA, SAN, and $SnF_2$.

# Discussion

This meta-review summarized the available evidence as was present in the form of systematic reviews with respect to the efficacy of mouthwash for plaque control in managing gingivitis. We included only systematic reviews because there are many such reviews available and this type of research generally provides more evidence than separate empirical studies taken alone (15). There was strong consistent evidence emerging from 3 systematic reviews that evaluated CHX and EO showing that these ingredients are effective in plaque reduction. However, the evidence also shows moderate to considerable heterogeneity in the meta-analysis. In cases in which heterogeneity is obvious, readers should exercise caution, as the DiffM may not provide an exact measure of the results. It is therefore difficult to compare these 2 chemical agents based on the DiffM or make inferences that one ingredient would be more effective than the other. Only one review emerged that compared mouthwash ingredients (31) with a moderate estimated risk of bias and a quality score of 78%. It showed that in comparison to EO, CHX provided better results for plaque control. For the long-term control of gingival inflammation, EO was not different from CHX.

### Grading

The steps toward guideline development involve formulating recommendations that clinicians and their patients should follow (41). A variety of systems are used to rate the quality of the evidence underlying their recommendations. The GRADE working group has developed a common, sensible, and transparent approach to grading quality of evidence and strength of recommendations. Many international organizations have provided input into the development of the approach and have started using it. The strength of a recommendation indicates the extent to which one can be confident that the desirable effects of an intervention outweigh its undesirable effects. When a recommendation is weak, clinicians and other health care providers need to devote more time to the process of shared decision-making by which they ensure that the informed choice reflects individual values and preferences. This is likely to involve ensuring patients understand the implications of the choices they are making, possibly by using a formal decision aid. When recommendations are strong, clinicians may spend less time on the process of making a decision, and focus efforts on overcoming barriers to implementation or adherence. However, the strength of a recommendation may not be directly correlated with its priority for implementation (42).

Alternatively, in considering 2 or more possible management strategies, a recommendation's strength represents the confidence that the net benefit clearly favors one alternative or another. From this meta-review, 2 chemical agents emerged for which strong evidence with a large effect was available to recommend their use in mouthwash products. These were CHX and EO.

**Table 5** Estimated evidence profile (21) for the effect of various active ingredients of mouthwashes on dental plaque and gingival health.

| GRADE | ALX | CPC | CHX | DEL |
|---|---|---|---|---|
| **Study designs** | Systematic review N=1 | Systematic review N=3 | Systematic review N=3 | Systematic review N=2 |
| **Reporting and methodological estimated potential risk of bias** | Low | Low to Substantial | Low to Substantial | Substantial |
| **Consistency** | Inconsistent | Consistent | Consistent | Fairly consistent |
| **Heterogeneity** | ND | Considerable | Considerable | ND |
| **Directness** | Direct | Direct | Direct | Direct |
| **Precision** | Precise | Precise | Precise | Imprecise |
| **Publication bias** | Possible | Possible | Possible | Possible |
| **Magnitude of the effect** | Small | Moderate | Large | Small |
| **Body of evidence** | **Moderate** | **Strong** | **Strong** | **Weak** |

ALX = alexidine
CPC = cetylpyridinium chloride
CHX = chlorhexidine
DEL = delmopinol
EO = essential oils
HEX = hexetidine

## Side Effects

Various side effects have been reported for mouthwash products of which staining is a more common complaint following use of CHX, CPC, delmopinol (DEL) EO, and $SnF_2$. The staining can become worse when other products that are known to cause staining, such as tea, coffee, wine, and cigarettes, are consumed at the same time. One systematic review included in this meta-analysis showed that there is moderate evidence that a combination of CHX and an OA reduces tooth staining and also showed that it slightly but significantly increases inhibition of plaque growth (29). Another issue is taste disturbance, which has been attributed to CHX, CPC, DEL EO, SAN, and HEX. For instance CHX, which tastes bitter, greatly reduces the perceived intensity of the salt (43). The development of taste disturbance and tooth staining and the promotion of calculus formation does not permit the widespread long-term use of CHX as a daily adjunct to normal oral hygiene procedures (18). CHX is therefore rather restricted to short-term to moderate-term use and in special clinical situations. A rare side effect that can be disturbing to the patient is parotid swelling, which has been reported after the use of both HEX and CHX (44). The investigators of this case report concluded that parotid swelling may not be related to the type of mouthwash used, but may instead be a consequence of the rinsing action itself. Another potential adverse effect is a shift in the type or quantity of oral commensals. Virtually all of the main chemical plaque-control agents do not produce major shifts or development of resistant strains. When, on rare occasion, adverse effects on the oral microflora emerge, these effects quickly disappear when the chemical is discontinued (8,45). Tissue disturbance has been reported for SAN, which is suspect for causing the formation of white lesions (46). Although the available clinical and animal data provide no support that the use of a SAN mouthwash is causally associated (47), its production has been discontinued (48).

| | EO | HEX | OA | SAN | $SnF_2$ | TCL |
|---|---|---|---|---|---|---|
| | Systematic review N=3 | Systematic review N=1 | Systematic review N=1 | Systematic review N=1 | Systematic review N=2 | Systematic review N=1 |
| | Low to Substantial | Moderate | Moderate | Low | Low to Moderate | Low |
| | Consistent | Inconsistent | Inconsistent | Inconsistent | Inconsistent | Consistent |
| | Considerable | ND | ND | ND | Moderate | Moderate |
| | Direct | Indirect | Indirect | Direct | Direct | Indirect |
| | Precise | Imprecise | Imprecise | Imprecise | Imprecise | Precise |
| | Possible | Possible | Possible | Possible | Possible | Possible |
| | Large | Indistinct | Indistinct | Small | Small | large |
| | **Strong** | **Weak** | **Weak** | **Weak** | **Weak** | **Moderate** |

OA = oxygenating agents
$SnF_2$ = Stannous fluoride
SAN = sanguinarine
TCL = triclosan
ND = not determinable

## Chlorhexidine and sodium lauryl sulfate

Chemicals in mouthwash and dentifrice formulations can result in antagonism with reduction or negation of activity of one or both chemicals. In the broad search, 2 systematic reviews surfaced concerning the negative impact dentifrices containing sodium lauryl sulfate (SLS) may have on the efficacy of CHX mouthwash on the prevention of plaque accumulation and gingival inflammation. This interaction is not restricted to just CHX but any cationic antiseptic-containing mouthwash, such as CPC, making it essential that active mouthwash ingredients are evaluated for bioavailability under normal use. SLS is the most commonly used surfactant in dentifrices that, in addition to other properties, enhance the dentifrice foaming action. In their systematic review Kolahi and Soolari (49) identified an unclear number of articles that evaluated the effect of SLS in combination with CHX in relation to the prevention of plaque accumulation and gingival inflammation with no limits to study duration. There was not sufficient similarity between the included trails to combine them in a formal meta-analysis. Hence, the investigators declare that they used best evidence synthesis as an intelligent alternative for meta-analysis. They concluded that there are adequate reasons to believe CHX and SLS dentifrices are not compatible. Also, besides SLS, CHX may not be compatible with many anionic compounds found in dentifrices (50).
More recently, Elkerbout and colleagues (51) also evaluated the effect of SLS in combination with CHX in relation to the prevention of plaque accumulation and gingival inflammation with no limits to study duration and identified 4 articles. The study outcome with respect to the PI scores at the finish of the individual studies demonstrated a nonsignificant DiffM of -0.08 (95% CI -0.26–0.11), with nonsignificant heterogeneity ($I^2$ = 0%). No analysis with respect to gingivitis scores could be performed. The investigators concluded that there is moderate evidence to state that SLS dentifrice can be freely used in combination with CHX.

Van Strydonck and colleagues (18) also noted that in most of the studies in their review CHX was always combined with regular oral hygiene procedures. However, this usage still showed a beneficial effect on oral health, which indicates that the impact of SLS may not be clinically relevant.

### Substantivity and bioavailability

Mouthwashes are simply a means for delivery of active substances in the oral cavity where, after 20 to 30 s of rinsing, all surfaces of the dentition have come into contact with the mouthwash (52). Most are composed of a water or water-alcohol base, with flavor, surfactant, and humectant added for their cosmetic properties. Mouthwashes and their active ingredients are exposed to the mouth for a relatively short period of time before expectoration from the mouth. In addition, the proteins present in saliva may reduce the activity of some substances (53). The property of substantivity ensures that, at least for some chemicals (such as CHX), possible antibacterial effects are sustained for much longer periods of time (45). Substantivity refers to the ability of an agent to be retained in the oral cavity and to be released over an extended period of time with retention of potency. The overall oral retention of an antiplaque agent is determined by the strength and rate of association of the agent with its receptor sites and the accessibility of these sites. The substantivity of an antiplaque agent and its clearance from the oral cavity are determined by the rate of dissociation of the agent from the receptor sites and the salivary composition and flow rate (9). CHX is well known for its substantivity being retained in supragingival plaque, the tooth pellicle, and the oral soft tissues from where it exerts a plaque inhibitory effect that, within the oral cavity, may last up to 12 hours (54).

It is noteworthy that the inclusion of a known active agent in a formulation does not guarantee efficacy, although it is often used to make piggy-back claims for new products. For instance, 2 recent systematic reviews have shown that CHX can be successfully formulated into a dentifrice/gel and will inhibit plaque growth to some degree, but not to the same extent as CHX incorporated into a mouthwash (55,56). Many oral hygiene products are complex formulations, and the potential for ingredient interactions is great. Bioavailability is an issue that deserves attention when formulating a mouthwash. Formulations with high bioavailable CPC are associated with greater biological activity and therefore suggest an increased probability for clinical efficiency (57).

### Alcohol

Alcohol in mouthwashes is used to enhance flavor impact, to solubilize the flavor and some active ingredients, to provide some preservative power, and improve the transport of active ingredients into the dental plaque biofilm. The systematic review by Van Leeuwen and colleagues (30) indicated that the alcohol vehicle solution does not contribute to the efficacy of the mouthwash. Although the accumulated effects of mouthrinse usage with a high percentage of alcohol and ingestion of alcohol could theoretically predispose toward oral or pharyngeal carcinoma, the contributory effects of alcohol in these rinses are unclear and not considered proven (58) by most national regulatory organizations, including the US Food and Drug Administration (59).

More recently, for various reasons, there has been an increase in the demand for alcohol-free mouthwashes (60). An important determination is whether the inclusion or exclusion of alcohol could affect the activity of the mouthwashes. In the meta-analysis of Serrano and colleagues (26), 10 studies evaluating EO included 9 mouthwash products that contained alcohol and 1 that did not. Based on this limited evidence, no major difference was observed (DiffM for alcohol -0.827 and mean difference alcohol free -0.746). Berchier and colleagues (32) in their 0.12% versus 0.2% CHX article, performed a subanalysis on 0.12% CHX with/without alcohol as compared with 0.2% CHX with alcohol. The data show a trend that the nonalcohol product was slightly less effective.

There has been concern that alcohol from mouthwash products is being converted to acetaldehyde in the oral cavity, which then may cause DNA damage and lead to mutations. A meta-analysis of epidemiologic studies concerning mouthwash and oral cancer also specifically evaluating mouthwash products containing greater than 25% alcohol was performed by Gandini and colleagues (61). The meta-analysis included 18 studies. No statistically significant associations (relative risk [RR]) were found between regular use of mouthwash and risk of oral cancer (RR 1.13; 95% CI 0.95– 1.35). There was also no association reported use of mouthwash specifically containing alcohol and risk of oral cancer (RR 1.16; 95% CI 0.44–3.08). Based on their observations, the investigators came to the conclusion that based on the quantitative analysis of mouthwash use and oral malignancy, no statistically significant associations were revealed between mouthwash use and risk of oral cancer, nor was any significant trend observed in risk with increasing daily use, nor association between use of mouthwash containing alcohol and oral cancer risk.

### Rinse Duration and Volume

The manufacturers of mouthwash products recommend different durations for the rinsing procedure. Keijser and colleagues (62) compared mouthwashes with various rinsing times. Results of the questionnaire indicated that the subjects preferred the shorter rinsing time, which raises the question of whether shorter rinsing times can be sufficient for effective plaque control. Another study assessed the plaque inhibiting effect of a 0.2% CHX solution with 3 different rinsing times following a 72-hour nonbrushing period, this being 60 s as proposed by the manufacturer, and 2 shorter rinsing times of 30 s and 15 s (63). The outcome did not reveal a significant difference in plaque development whether the subjects rinsed for 60, 30, or 15 s, which suggests that even 15 s may be long enough to reduce plaque levels. Berchier and colleagues (32) also showed that there is minimal difference between rinsing for 30 or 60 s on plaque scores. Further studies are needed to establish whether shorter rinsing times will be sufficient for effective gingivitis control. A consideration is that a shorter rinsing time could have a positive effect on compliance. Manufacturers also recommend different volumes, ranging from 10 to 20 ml. It seems relevant to have information about the mouthwash volume that is understood by the patient to ensure optimal compliance. One study assessed the volume of mouthwash with respect to patients' perceptions of comfort (64). This study investigated volunteers' subjective perceptions to different volumes of mouthwash (volumes of 5, 10, 15, 20, and 30 ml) to establish the most comfortable volume of mouthwash with which to rinse. Based on the results of this expe-

riment with a nonfoaming mouthwash, it was concluded that the most pleasant volume of mouthwash is 15 ml. This volume had a mean visual analogue scale (VAS) score that was closest to the optimal score. The differences between the mean VAS scores of rinsing with 15 ml and other volumes were statistically significant (P<.001).

### Limitations of mouthwashes in the prevention of dental plaque formation

- The oral biofilm produces an encased and highly protective community of cells that acts as a barrier and as a result is much less influenced by its environment, including the introduction of chemical agents (65). This aspect has received little attention in mouthwash studies.
- There appears to be a consensus that mouthwashes with antiplaque agents are not designed to be used in isolation and should be used in combination with mechanical cleaning (8).
- For individuals with existing disease with frank periodontal pocketing, the use of vehicles such as mouthwash or dentifrice to deliver antimicrobial and antiplaque agents has only limited or no effects on the subgingival flora (8,45). In these cases, chemical agents need to be placed directly into the subgingival environment by subgingival irrigation or by some alternative drug-release device. However, within minutes, gingival crevicular fluid outflow will dilute subgingivally applied antiseptics (66).
- Only sparse information is available with respect to the efficacy of chemotherapeutic agents on biofilm-contaminated titanium surfaces (67).
- Mouthwashes can also act as a vehicle in which to incorporate chemicals that promote fresh breath and help alleviate the problem of oral malodor. This aspect was not addressed by this meta-analysis. Systematic reviews have shown that due to very limited evidence, the potential effect of a specifically formulated mouthwash for treating oral malodor is, in general, unclear (68,69).
- Publication bias cannot be ruled out. The results as presented in this meta-review may therefore provide a biased estimate of the true effect (overestimation) because there is a tendency to publish mainly positive studies.

### Cost-effectiveness

The long-term adjunctive use of antiplaque agents in any vehicle other than dentifrice would have significant cost implications to the average family. At present prices, the cost of mouthwashes would be far greater than that of toothbrushes and dentifrice. This may be prohibitive for many individuals, and dentifrice is thus still the best vehicle for delivering antiplaque agents. Nonetheless, if a mouthwash is highly effective in terms of oral health gain, the additional cost of its use may be a price worth paying (8). As emerged out of this review, this would apply particularly to CHX and EO mouthwashes.

## Summary

This meta-review summarized and appraised the current state of evidence based on systematic reviews, with respect to the efficacy of various active ingredients of over-the-counter chemotherapeutic mouthwash formulations for plaque control in managing gingivitis. Evidence suggests that a mouthwash containing CHX is the first choice. The most reliable alternative for plaque control is EO. No difference between CHX and EO with respect to gingivitis was observed.

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Authors contributions

Conception or design of the study: GAW, DES

Analysis and/or interpretation of the data: GAW, EVDS, SGC, DES

Drafted the manuscript: GAW, DES

Critically revised the manuscript: EVDS, SGC

All authors gave their final approval and agreed to be accountable for all aspects of the work

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