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Review article

Essential oils-containing mouthwashes for gingivitis and plaque: Meta-analyses and meta-regression

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ABSTRACT

Objectives: To evaluate the efficacy of EO as adjuncts to mechanical plaque control (MPC) on the reduction of plaque and gingivitis when compared to placebo or cetylpyridium chloride (CPC).
Data: Randomized controlled trials of at least 6 months of follow-up including systemically healthy individuals with gingivitis were included.
Sources: MEDLINE, EMBASE, Lilacs and SCOPUS were searched up to April 2016. From 3045 citations, 16 studies were included. 14 studies assessed the Quigley-Hein Plaque Index (QHI) and 11 studies assessed the Modified Gingival Index (MGI) and were included in meta-analyses and meta-regression.
Study selection: The analysis of risk of bias suggested that the quality of the studies ranged from moderate to low. Mean QHI (WMD = −0.86, 95%CI −1.05 to −0.66) and MGI (WMD = −0.52, 95%CI −0.67 to −0.37) were lower for EO + MPC than placebo + MPC. Reductions in plaque and gingivitis were, respectively, 32% and 24% larger for EO + MPC than placebo + MPC. The decreases in QHI (WMD = −0.95, 95%CI −1.26 to −0.63) and in MGI (WMD = −0.34, 95%CI −0.53 to −0.15) observed in the EO + MPC group, compared to placebo + MPC in interproximal areas, were significantly different and in favor to EO + MPC. EO + MPC compared to CPC + MPC resulted in clinically lower levels of plaque and gingivitis. High heterogeneity ($I^2 > 95\%$) was found and explained (MGI – $R^2 = 63.6\%$; QHI – $R^2 = 80.1\%$) by differences between studies in the percentage of males, supervision of the mouthwashes and provision of oral hygiene.
Conclusions: EO seems to be superior to placebo + MPC and CPC + MPC for reduction of plaque and gingival inflammation in patients with gingivitis. Expected benefits may be clinically relevant and may also reach the interproximal area.
Clinical significance: Mouthwashes containing essential oils should be considered the first choice for daily use as adjuvants to self-performed mechanical plaque control.

1. Introduction

Mouthwashes containing essential oils (EO) are among the most clinically studied and commercialized oral antiseptic solutions due to their antimicrobial activity [1,2], ability to penetrate the biofilm [3] and safety [4]. Previous systematic reviews have demonstrated the superiority of EO adjunctive to daily self-performed mechanical plaque control (MPC) compared to placebo solutions [5–9]. Nevertheless, important characteristics of these reviews were not reported according to consolidated standards currently disseminated and required, limiting their interpretation. Moreover, variations in EO effects may be due to relevant variations across reviews regarding methodology, number of included studies and analyses.

Although the results of previous meta-analyses indicate that EO and other antiseptics are more efficacious than mechanical plaque control alone, high heterogeneity has been reported [8,9]. This heterogeneity has not been explored using meta-regression commands, and to the best of the authors' knowledge, there has been no attempt to evaluate which factors may be associated with the variability of the results.

Regarding previous systematic reviews that explored the efficacy of EO, the first two meta-analyses were conducted in the mid 2000's and both included a small number of studies published until that moment [7,8]. More recently, Boyle et al. [6] revised the literature until 2010 for a broad range of antiseptics, with a total of 11 studies evaluating EO. Noteworthy, some of their

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included studies were designed to test not only the anti-plaque and anti-gingivitis effects of EO over MPC, and the samples of some studies were not restricted to individuals with gingivitis. In a similar fashion, Serrano et al. [9] conducted a systematic review for a variety of anti-plaque chemical agents searching only one database until May 2014. For the analysis of EO, only 8 studies were included and weighted mean differences were calculated as an overall summary estimate. Araujo et al. [5] conducted a meta-analysis including studies without a systematic search of the literature, including exclusively studies that were funded by Johnson & Johnson and its predecessors. Data from 11 of the 27 studies included was obtained for unpublished studies directly from the industry, precluding any methodological assessment.

Unfortunately, clinically relevant estimates of the effect of EO generated by meta-analytical commands are still lacking in the literature. Also, the additional benefit of EO over mechanical plaque control alone in specific dental sites of difficult access, such as the interproximal area, has not been addressed. There is also no combined data comparing the efficacy of EO and cetylpyridium chloride (CPC), which is another widely used oral antiseptic.

The primary aim of this systematic review was to assess randomized clinical trials (RCT) testing the efficacy of EO as adjuncts to daily mechanical plaque control in comparison to placebo mouthwashes or CPC in reducing dental plaque and gingivitis among adults with gingivitis. Secondary aims included the comparison of essential oils to flossing and to placebo for the reduction of dental plaque and gingivitis in interproximal surfaces. Also, causes of heterogeneity were explored by conducting meta-regression analyses.

2. Materials and methods

The present systematic review follows the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [10]. This systematic review was conducted to answer the following focused questions:

- Is there an additional anti-plaque and anti-gingivitis effect of EO containing mouthwashes as adjunct to daily oral hygiene when compared to placebo in patients with gingivitis?
- Is there an additional anti-plaque and anti-gingivitis effect of EO containing mouthwashes as adjunct to daily oral hygiene when compared to mouthwashes with cetylpyridium chloride (CPC) in patients with gingivitis?
- Is there an additional anti-plaque and anti-gingivitis effect on interproximal sites of EO containing mouthwashes as adjunct to daily oral hygiene when compared to placebo in patients with gingivitis?
- Is there an additional anti-plaque and anti-gingivitis effect on interproximal sites of EO containing mouthwashes as adjunct to daily oral hygiene when compared to flossing in patients with gingivitis?

2.1. Eligibility criteria

The following inclusion criteria were used:

- RCT of 6-months follow-up of daily use of EO, according to the recommendation of the American Dental Association.
- Patients included in the studies should have diagnosis of gingivitis and should be systemically healthy.
- The comparison group always comprised a placebo solution, flossing, or cetylpyridinium chloride as adjuncts to mechanical plaque control.
- The test group should include the use of mouthwash containing EO as adjuvant to mechanical oral hygiene.
- The outcomes should include at least one measure of plaque and/or gingivitis.

The studies were not included in the following situations:

- participants diagnosed with periodontitis.
- experimental gingivitis models.
- participants were orthodontic patients.

2.2. Search strategy

The search strategy was build based on PICOT framework to obtain a high sensitive group of descriptors, combining outcome (search #1) and intervention (search #2). Search strategy for control interventions was not included because more than one comparison intervention was intended. Patients, test intervention and study restrictions were applied during reading of abstracts and full text. In addition, we combined the intervention search (#2) with the vehicle used for EO (mouthwash OR mouthrinse). Full search was performed in MEDLINE-Pubmed, EMBASE, Lilacs, and Scopus databases. The literature was searched up to 1st April 2016 according to the following search strategy (built for MEDLINE-Pubmed and adapted for other databases). No language or publication date restrictions were applied.

#1 – ("mouthwash"[Title/Abstract]) OR "mouthrinse"[Title/Abstract]) OR "antiplaque"[Title/Abstract]) OR "antigingivitis"[Title/Abstract]) OR "Gingivitis"[Mesh]) OR "Periodontal Index"[Mesh]) OR "gingival inflammation"[Title/Abstract]) OR Bleed* [Title/Abstract]) OR "gingival index"[Title/Abstract]) OR "Oral Hygiene Index"[Mesh]) OR "Dental Plaque Index"[Mesh]) OR "Oral Hygiene"[Mesh]) OR plaque[Title/Abstract]) OR biofilm[Title/Abstract]) OR (("Quigley"[Title/Abstract]) OR "Hein"[Title/Abstract]) AND "index"[Title/Abstract])) OR (("silness"[Title/Abstract] OR "loe"[Title/Abstract]) AND "index"[Title/Abstract])))

#2 – ("Oils, Volatile"[Mesh] OR "Thymol"[Mesh]) OR "Menthol"[Mesh]) OR "Monoterpenes"[Mesh]) OR "Phenol"[Mesh]) OR "Listerine"[Supplementary Concept]) OR listerin*[Title/Abstract]) OR "essential oils"[Title/Abstract]) OR "menthol"[Title/Abstract]) OR "eucalyptol"[Title/Abstract]) OR "methyl salicylate"[Title/Abstract]) OR "thymol"[Title/Abstract]) OR "phenol"[Title/Abstract]))

#3 – #1 AND #2

2.3. Study selection and data collection

Titles and abstracts were independently screened by three reviewers (ANH, FWMGM, TPW). Studies without abstracts but whose titles were potentially related to the aim of this systematic review were also selected, so the full text could be screened for eligibility. Hand search included references of selected studies and related systematic reviews. Any discrepancies were solved by discussion among the three reviewers.

One reviewer (FWMGM) independently performed the data extraction in a spreadsheet developed specifically for this systematic review. Thereafter, data extraction was duplicated by another reviewer (ANH) and no disagreements were found. The data extraction included the following variables: authors, date of publication, country of patients, funding, source of participants, number of subjects in each group, mean age, percentage of male and smokers, mean plaque and gingivitis in its respective index (with standard error or standard deviation). Any discrepancies with regard to this process were solved by extensive discussion between the two reviewers.