

# Therapeutic oral rinsing with non-commercially available products: Position paper and statement from the Canadian Dental Hygienists Association, part 2

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## ABSTRACT

**Background:** To control biofilm and prevent gingival inflammation and disease, mechanical methods of oral hygiene can be complemented with a therapeutic oral rinse. Much research has been conducted on commercially available oral rinse products, and there is also considerable research being conducted on formulations not yet available to the Canadian market, of which many are natural or herbal products. This comprehensive review focuses on non-commercially available therapeutic oral rinse products and is the second part of a 2-part position paper and statement that replaces the 2006 Canadian Dental Hygienists Association position paper on oral rinsing. **Methods:** Based on a PICO question, a literature search using MEDLINE-PubMed, Cochrane Central Register of Controlled Trials, and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) databases was conducted in stages. The search was limited to English-language articles published between 2006 and 2016. Articles were selected if they focused on predetermined variables, and each article was reviewed utilizing an analysis table to identify the study parameters. **Results:** The search returned 452 studies, and initial screening of titles and abstracts identified 20 papers for full review. An additional 25 articles identified through hand searching resulted in 45 full-text articles retrieved. Of these, 26 studies were included in the final review. Studies were categorized and reviewed according to a research-stage taxonomy. **Discussion and Conclusions:** Because no long-term ( $\geq 6$  months) clinical trials have been conducted on any non-commercial oral rinse formulations, statements about these rinse products' effectiveness or safety cannot be made at this time. Several products did show efficacy in lower level research, indicating that further study of these specific formulations may be warranted. There is a need for more well-conducted studies using standardized research designs to produce findings that dental hygienists and other oral health professionals can use to guide their client recommendations for appropriate oral biofilm control.

## RÉSUMÉ:

**Contexte :** Les rince-bouche thérapeutiques peuvent être un complément aux méthodes mécaniques d'hygiène buccale pour contrôler la formation de biofilm et prévenir l'inflammation et l'affection des gencives. Plusieurs recherches ont été effectuées sur les rince-bouche offerts en vente libre et il existe aussi de nombreuses études qui sont menées sur des formulations qui ne sont pas encore offertes sur le marché canadien, dont plusieurs sont des produits naturels ou à base d'herbes. Cette analyse approfondie est axée sur les rince-bouche thérapeutiques qui ne sont pas offerts sur le marché et représente la deuxième partie d'un exposé de position et d'une déclaration à 2 volets qui remplace l'exposé de position de 2006 de l'Association canadienne des hygiénistes dentaires sur le rinçage buccal. **Méthodes :** D'après une question PICO, une recherche documentaire a été effectuée en étapes à l'aide des bases de données de MEDLINE-PubMed, Cochrane Central Register of Controlled Trials, et le Cumulative Index to Nursing and Allied Health Literature (CINAHL). La recherche était limitée aux articles de langue anglaise publiés entre 2006 et 2016. Les articles étaient sélectionnés s'ils étaient axés sur des variables prédéterminées et chaque article a été examiné au moyen d'un tableau d'analyse pour cerner les paramètres de l'étude. **Résultats :** La recherche a produit 452 études et la vérification initiale des titres et des résumés a répertorié 20 articles pour examen complet. Grâce à une recherche manuelle, 25 articles supplémentaires ont été trouvés, ce qui a permis de repérer le texte intégral de 45 articles. Parmi ces articles, 26 études ont été ajoutées à l'examen final. Les études ont été classées et révisées en fonction de la taxonomie par phase de recherche. **Discussion et conclusions :** Comme aucun essai clinique à long terme ( $\geq 6$  mois) n'a été effectué sur des formulations de rince-bouche non commerciaux, des déclarations sur l'efficacité ou la sécurité de ces rince-bouche ne peuvent être faites en ce moment. Lors des recherches à bas niveau, plusieurs produits ont fait preuve d'efficacité, démontrant que des études complémentaires sur ces formulations particulières pourraient être justifiées. Il est nécessaire d'effectuer d'autres études bien menées en utilisant des modèles de recherche standardisés pour produire des résultats qui permettront d'orienter les hygiénistes dentaires et autres professionnels de la santé buccodentaire lorsqu'ils formulent des recommandations aux clients pour le contrôle approprié du biofilm buccal.

## CANADIAN DENTAL HYGIENISTS ASSOCIATION POSITION STATEMENT

Dental hygienists are encouraged to recommend a demonstrated effective and safe therapeutic oral rinse to their adult clients to complement home care routines for the reduction of plaque and gingival inflammation. Based on the research reviewed, there is no evidence from rigorous, long-term ( $\geq 6$  months) studies to show that non-commercially available oral rinse formulations are as effective as commercially available prescription or over-the-counter oral rinses in reducing plaque and gingivitis. Consequently, dental hygienists should continue to recommend the use of commercially available oral rinse products that have been proven effective and safe, taking into account specific client needs, to promote optimal oral health.

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**Key words:** dental plaque, mouth rinse, mouthwash, oral antiseptic, oral biofilm, oral chemotherapeutic, oral hygiene, oral rinse

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## BACKGROUND

It is recognized that people have persistent challenges in achieving satisfactory oral hygiene and controlling gingival inflammation through mechanical methods alone.<sup>1,2</sup> Oral biofilm is the primary etiology for gingivitis, periodontitis, and caries and also contributes to halitosis and systemic well-being.<sup>3</sup> Therapeutic oral rinsing has been advanced, most recently in the updated Canadian Dental Hygienists Association's (CDHA) position statement on oral rinsing, as an important component of home care routines to optimize oral hygiene.<sup>4</sup> While research conclusively demonstrates the therapeutic effectiveness of some commercially available oral rinses,<sup>4</sup> there are numerous formulations not yet commercially available that are in development and undergoing study. Many of these non-commercial formulations are made with synthetic products; others contain what are commonly referred to as “natural” compounds, which are of interest not only to Canadian dental hygienists and their clients, but also to those concerned with improving the oral health of vulnerable populations globally, who may be better able to access natural, locally derived products.<sup>5</sup>

This position paper, endorsed by CDHA, represents a comprehensive review of the research on non-commercially available oral rinse products currently in development. Commercially available over-the-counter and prescription oral therapeutic rinsing agents were reviewed in part 1 of the position paper.<sup>4</sup> The findings of both reviews have been used to update CDHA's position statement on the use of home oral rinses as a preventive oral health strategy particularly as it relates to periodontal disease initiation and progression. The author of the 2006 CDHA position paper was contracted by CDHA to research and write the present position paper.

## INTRODUCTION

While studies testing the efficacy and effectiveness of oral rinse agents have been extensively conducted, readers will note a wide variety of study designs and protocols, particularly with non-commercially available products, making the research difficult to compare and interpret, which can subsequently complicate evidence-based decision making in clinical practice. Oral rinse studies can be placed on a continuum from early- to late-stage research (Table 1), which was discussed in detail in part 1 of this review.<sup>4</sup> New product formulations, often testing active ingredients before commercial products are developed, are typically initially studied using short-term in vitro and in

vivo studies and, if found to be effective, may proceed to longer term studies ultimately including home use clinical trials, which are more expensive and involve ethical considerations.<sup>6</sup> If a formulation is found to lack efficacy in the early stages of research, it is unlikely to be effective in later stage trials; these trials are therefore unwarranted.<sup>6</sup> There has been a call from some investigators in the field to apply a more standardized and systematic approach to therapeutic oral rinse studies.<sup>6</sup>

Many not yet commercially available oral rinse products undergoing testing are natural or herbal products and fall within the scope of traditional medicine, which is a field of health that has expanded globally both in developing and developed countries.<sup>5</sup> With this expansion comes the need to examine the safety and efficacy of such products. Quality control is increasingly important to health authorities, researchers, and the public.<sup>5,7</sup> There may be an inherent belief that these products are safe, consistently formulated, and offer benefits to one's health.<sup>5</sup> As regulated health care providers, dental hygienists must maintain a critical eye as part of competent and ethical practice, and make client recommendations based on the best available research. According to the World Health Organization (WHO), the safety and efficacy data on herbal medicines are generally insufficient to support worldwide use, thus substantiating the need for well-conducted clinical trials to confirm the efficacy demonstrated in some early-stage research.<sup>7</sup>

This second part of the position paper aims to summarize, interpret, and make recommendations based on non-commercially available oral rinse research published in the last decade. This review is framed according to research design stages in order to situate products on an evidence continuum and clarify for dental hygienists and other readers the practical relevance of non-commercially available oral rinse products.<sup>4,6</sup>

## MATERIALS AND METHODS

Along with the author and CDHA staff, a committee was convened to oversee the development of the position paper and assist in defining the scope of the review. Committee members were selected based on their content and/or research expertise. Committee members and CDHA staff communicated with the author via teleconference throughout the review process.

The first step in the investigation was to develop a PICO question to guide the literature search and the writing of this review. The initial PICO question was limited to commercially available products:

Do healthy adults who have plaque or biofilm or gingivitis or early periodontitis [Population] who use home mouth rinse or mouthwash or oral rinse according to manufacturers' directions with a commercially available, non-prescription or prescription formulation as an adjunct to mechanical cleansing including toothbrushing alone or toothbrushing and flossing or interdental cleansing [Intervention] compared to not using oral rinse [Comparison] have improved plaque or biofilm or inflammation or gingivitis scores [Outcome]?

Because of the substantial quantity of research on non-commercially available products that emerged through the search, it was determined that a separate review would be undertaken to examine these products specifically. The PICO question was adjusted by removing the term "commercially available" in order to broaden the scope of the review. The literature search for both parts of the review was conducted simultaneously in stages from

January 4, 2016, to April 30, 2016, using the following electronic databases: MEDLINE-PubMed, Cochrane Central Register of Controlled Trials, and the Cumulative Index to Nursing and Allied Health Literature (CINAHL).

The initial part of the search focused on primary research studies and excluded reviews. The search was limited to articles written in English and published between 2006 (when the first CDHA position paper was released) and April 30, 2016. For the second part of the review, papers were selected for retrieval if they focused on:

- *Independent variables:* non-commercially available home oral rinsing product
- *Outcome variables:* impact on bacteria/plaque/biofilm, inflammation/gingivitis

The second phase involved a manual search of references from papers retrieved in the first phase. Systematic reviews, meta-analyses, reports, and grey literature were also hand searched to ensure that no original research meeting the inclusion criteria was missed in the initial review.

To ensure consistency and minimize researcher bias, the author reviewed each paper utilizing an analysis table to identify the study parameters, including the study authors/researchers, date of study publication, stage of research, proposed active ingredients, outcome measures and results (effect sizes; *p* values), and any other notes regarding the study.

Table 1. Stages of therapeutic oral rinse research<sup>a</sup>

Stage	Classic design	Measured outcomes	Comments
Stage 1	In vitro kill ability; 8-hour in vivo substantivity	Bacterial vitality (vital fluorescence technique), minimal inhibitory concentrations (MIC), colony forming units (CFU)	Measures bactericidal activity and plaque inhibitory effects in cleaned surfaces after single rinse over 8± hours; other oral hygiene suspended; MIC: the lowest concentration of a formulation that will inhibit bacterial growth after a period of incubation; crossover designs suitable
Stage 2	4-day plaque regrowth in vivo	Plaque indices, gravimetry, planimetry	Plaque inhibitory effects in cleaned surfaces while rinsing daily (1x to 3x/day); other oral hygiene suspended; crossover designs suitable
Stage 3	21-day experimental gingivitis study in vivo	Plaque and gingivitis indices, bleeding indices	Plaque and gingivitis inhibitory effects in cleaned surfaces while rinsing daily (1x to 3x/day); other oral hygiene suspended; shorter than 21 days insufficient time for gingivitis to occur in all study subjects; should use parallel groups to minimize number of times experiencing gingivitis
Stage 4	Home use studies; long term; in vivo; requirements for safety records	Plaque (i.e., plaque index [PI]) and gingivitis indices (i.e., modified gingival Index [MGI]); bleeding indices (i.e., bleeding index [BI]); side effects; favourability	Typically 6 months; plaque and gingivitis inhibitory effectiveness in real-life conditions while rinsing daily (1x to 3x) and while using other mechanical methods; parallel groups

<sup>a</sup>Source: Asadoorian J. Therapeutic oral rinsing with commercially available products: Position paper and statement from the Canadian Dental Hygienists Association. *Can J Dent Hyg.* 2016;50(3):126–39.

## RESULTS

The initial electronic search of the databases returned 452 research papers (relevant to either part of the review), of which 20 articles on non-commercially available products were selected for full review. An additional 25 studies were identified through the hand search, which resulted in 45 full-text articles retrieved. Of these, 26 studies were found to:

- focus on the research question
- be original research
- include a non-commercially available oral rinse formulation
- include a relevant outcome measure
- be available in English

and were, thus, included in the review. Studies were excluded if they focused on a commercially available product, lacked a suitable study population, comparison group or outcome measure. As with the first part of the position paper, the non-commercially available oral rinse studies were reviewed and presented within the study stages framework (Table 1) and were summarized according to this taxonomy.<sup>4,6</sup> The 2006 CDHA position paper did not consider non-commercial formulations.

### Non-commercially available products

#### Stage 1 summary

Stage 1 studies are primarily aimed at determining the efficacy of a formulation under controlled laboratory conditions and, if so, for how long and if the outcomes sufficiently warrant studying the formulation in higher stage research designs. In addition, some of these studies examine new methods of preventing biofilm formation at different stages of the disease process, such as adherence and co-aggregation, without having actual bactericidal activity.

Five stage 1 studies examining a variety of experimental, non-commercial rinse formulations were located and included minimum inhibitory concentrations (MIC), plaque vitality, adherence, bacterial counts, and colony forming units (CFU) as the outcome measures. These experimental products consisted of a wide variety of primarily natural compounds, and almost all of these studies included chlorhexidine gluconate (CHG) as a positive control rinse, although some used an established commercially available essential oil (EO) rinse or other comparison group. Several studies included negative controls along with or without a positive control group. The research design parameters, including the formulation and outcome measures, of these stage 1 studies varied widely.

An early-stage 2012 study was conducted on a 2% taurolidine rinse, which is a chemical antimicrobial pharmaceutical product with limited application and is not currently used as an oral rinse. This 24-hour study measured the effects of the test rinse compared to 0.2% CHG and a placebo on the vitality of the plaque flora under the fluorescence microscope (VF%). The VF was reduced with the CHG rinse, which demonstrated statistically significantly better outcomes than the placebo ( $p < 0.001$ )

and the taurolidine rinse ( $p < 0.05$ ). However, the taurolidine also reduced the VF significantly when compared to the control rinse ( $p < 0.0001$ ).<sup>8</sup>

A 2013 in situ study evaluated the effect of 3 edible oils (safflower, linseed, and olive oil) compared to CHG (0.2%). The study required participants to hold these oils intraorally for 10 minutes to simulate the practice of “oil pulling,” a controversial practice of current interest as an oral hygiene activity. The CHG had considerable effects on the adherent bacteria, whereas none of the oils had a significant effect ( $p > 0.05$ ). Similarly, the CHG statistically significantly reduced quantities of CFU while the oil rinses had no effect. Overall, no reduction of the microbial colonization of the enamel was observed with the oil groups.<sup>9</sup>

Chitosan is a naturally occurring and abundant polysaccharide that has been used in diverse industries. In a 2014 laboratory study, a 0.4% chitosan-based rinse was compared to EO and CHG rinses (0% not reported) with regard to the MIC of 5 microorganisms. The MIC was determined by observation of the lowest concentration of rinse inhibiting visible bacterial growth. The MIC of the chitosan rinse was comparable to the EO rinse, whereas the chitosan rinse resulted in even lower MIC values than the CHG rinse. The chitosan rinse was also significantly superior ( $p < 0.05$ ) in preventing adherence of microorganisms compared to the EO and the CHG. Further, the chitosan had significantly better ( $p < 0.05$ ) anti-biofilm activity compared to the 2 positive controls. The researchers concluded that chitosan, although likely not compatible within other formulations, has potential as a therapeutic oral rinse.<sup>10</sup>

In the Middle East and Africa, the *Salvadora persica* plant, a small tree growing wild, is most commonly used as a wooden dental cleaner and has been used for centuries as an oral hygiene aid. A recent study compared a persica-based mouthwash to 0.2% CHG, a commercially available EO mouthwash, and a negative control. Plaque samples were incubated and the zone of bacterial inhibition (ZOI) was measured along with CFU. Bacterial counts were reduced in all test groups, but the CHG performed the best followed by the EO and then the persica-based rinse. The difference between CHG and EO was not significant ( $p > 0.05$ ), but CHG was found to be significantly better ( $p < 0.05$ ) when compared to the persica group. All 3 test groups were significantly superior ( $p < 0.05$ ) to the negative control. For the ZOI test, there was no demonstrated inhibition of bacterial growth by the EO, persica, and placebo, whereas the CHG prevented the growth of bacteria. This discrepancy between the CFU and ZOI outcomes was explained by the researchers as follows: the ZOI was measured 24 hours after the last exposure to the rinses and the products were presumed to have lost their effectiveness.<sup>11</sup>

Although only marginally applicable to this review, an earlier but unique study examined a MPC-polymer solution

in comparison with a negative control to determine its effect on streptococcal adherence in vitro (initial colonizers) and fusobacterial adherence to streptococcal biofilm in vitro (co-adhesion). Results showed that the MPC-polymer treatment significantly ( $p < 0.05$ ) inhibited the adherence of *Streptococcus mutans* to saliva-coated hydroxyapatite, and the MPC-polymer treatment also significantly ( $p < 0.05$ ) inhibited the co-adherence of *Fusobacterium nucleatum* to both saliva-treated streptococcal biofilms.<sup>12</sup>

#### Stage 2 summary

Five stage 2 plaque regrowth studies were reviewed and all, with one exception, were either a 4- or 5-day model, of which the former is considered the classic timeframe.<sup>6</sup> Plaque regrowth study designs examine the degree to which a product suppresses plaque on cleaned surfaces in vivo in the absence of other oral hygiene methods.<sup>6</sup> An additional 24-hour study was included in this section although it was of shorter duration, because it used a similar protocol. The studies compared various non-commercial formulations to CHG and in some cases used other commercial products for comparison. Test formulations in these studies included a polyherbal, two propolis (natural bee) products, pomegranate extract, and an aloe vera extract-based product.

Triphala, meaning “three fruits,” is a traditional herbal formulation composed of 3 native fruits to India: amalaki (*Emblia officinalis*), bibhitaki (*Terminalia bellerica*), and haritaki (*Terminalia chebula*). A crossover study was designed to compare de novo plaque formation 24 hours after the use of triphala in comparison to HiOra® (a commercially available herbal rinse), CHG (% not provided), and a CPC rinse (Colgate® Plax®; % not provided), but no negative control group. The study demonstrated no statistically significant difference in plaque suppression between the groups, with the exception of the CPC rinse, which was significantly outperformed by all of the other rinses ( $p < 0.05$ ). The study was limited by the fact that concentrations of positive controls were not provided, there was no negative control group included for comparison, the dosages were not consistent across groups, and rinsing was carried out for an unconventionally long period (3 minutes).<sup>13</sup>

An alternative branch of health care referred to as “apitherapy” offers unconventional treatments for various health conditions and illnesses using honey and other bee products.<sup>14</sup> A novel 2012 4-day plaque regrowth study was designed to examine a honey rinse compared to 0.2% CHG and a placebo with regard to MIC and inhibition of several strains of micro-organisms, but the study did not measure actual plaque scores, which is customary in this design.<sup>6</sup> Although the MIC was lowest in the CHG group, the honey rinse did inhibit growth of all 6 bacterial test species, while the placebo rinse did not.<sup>14</sup> A 2011 5-day plaque regrowth study compared a propolis-based rinse with 0.2% CHG and a placebo and demonstrated the CHG rinse to significantly

reduce plaque ( $p < 0.05$ ) compared to both the propolis-based rinse and the placebo. Although the propolis rinse was better at suppressing plaque than the placebo, the results were not statistically significant.<sup>15</sup>

A 4-day plaque regrowth study compared a pomegranate extract-based rinse to 0.2% CHG and a placebo. Both the pomegranate and CHG rinses significantly reduced ( $p < 0.05$ ) plaque and bacteria as compared to placebo; however, no significant difference was demonstrated between the 2 groups.<sup>16</sup> More recently a large ( $n = 300$ ) 4-day plaque regrowth study comparing an aloe vera extract rinse to 0.2% CHG and a placebo rinse showed both the test group and positive control to significantly ( $p < 0.05$ ) reduce plaque compared to the placebo, while no statistically significant difference was demonstrated between them.<sup>17</sup>

#### Stage 3 summary

Stage 3 experimental gingivitis studies are designed to measure the ability of a test rinse to inhibit plaque and suppress gingival inflammation in vivo over a 3-week period with other oral hygiene suspended. Five non-commercial stage 3 experimental gingivitis studies of sodium hypochlorite, turmeric extract, propolis, green tea, and polyherbal rinse products were included in the review and, overall, the studies showed mixed results. Of these suspended oral hygiene in vivo studies, 3 were 21 days in duration and were therefore conducive to analysing gingival inflammation suppression.

A 21-day study evaluating the twice daily, 60-second use of 0.05% sodium hypochlorite (household bleach) in comparison to a negative control rinse with all other oral hygiene methods suspended demonstrated statistically significant ( $p < 0.05$ ) suppression of plaque, gingival inflammation, and bleeding in the test group as compared to the control. However, significantly higher levels ( $p < 0.05$ ) of extrinsic brown tooth stain appeared (100%) in the test subjects versus the control group (35%). In addition, a (mostly) tolerable bleach taste, red tongue, and burning sensation were reported side effects in the experimental group.<sup>18</sup>

A 21-day equivalence study of a 2% propolis-based rinse compared to a positive control rinse containing 0.05% NaF plus 0.05% CPC in 21 pairs of twins demonstrated no difference ( $p > 0.05$ ) between the groups in suppressing gingival inflammatory values through papillary bleeding scores and standard digital imaging of the gingival tissue, referred to as a G parameter.<sup>19</sup> No negative control group was included in the study for comparison, and plaque suppression was not evaluated.

A larger ( $n = 100$ ) 21-day study that included adults ages 25 to 35 using a turmeric extract rinse in comparison to CHG (0.2%) demonstrated significant reductions ( $p < 0.05$ ) in plaque, gingival inflammation, and microbial counts for both groups when compared to baseline measures. When comparing the CHG rinse to the turmeric extract group,

the CHG was found to be statistically significantly superior in reducing plaque scores compared to the turmeric rinse ( $p < 0.05$ ). However, there was no significant difference between groups in inflammation scores or microbial counts. The study lacked a negative control group.<sup>20</sup>

A small ( $n = 30$ ), 1-week study investigating green tea catechin rinse (0.25%), the major component of green tea extract, compared to 0.12% CHG rinse was conducted with young adults (ages 18 to 25 years). Although the study was short and did not include an assessment of the gingiva, it was included in this section of the review because the protocol was similar to 21-day experimental gingivitis studies; participants rinsed 2 times daily while all other oral hygiene methods were suspended. The study demonstrated no statistically significant difference in plaque reductions between the 2 groups over the 1-week period ( $p > 0.05$ ). It should also be noted that study subjects rinsed for a full minute and there was no negative control group included.<sup>21</sup>

Although only 2 weeks long, an experimental gingivitis study compared a polyherbal non-commercial rinse (HM-302) containing traditional herbal medicines *Centella asiatica*, *Echinacea purpurea*, and *Sambucus nigra* to a CPC rinse (% not reported), EO rinse, and a negative placebo control (15 mL each). This combination of herbal components was selected following pretesting that demonstrated this specific mixture to have the best anti-inflammatory profile. While all rinses resulted in increased plaque scores, only the placebo ( $p < 0.008$ ) and EO ( $p < 0.04$ ) rinses were found to be significantly increased from baseline measures, albeit only marginally in the case of the EO. While the study was not long enough to make definitive conclusions about inflammatory findings, the results showed only the placebo rinse had a statistically significant increase in inflammation ( $p < 0.05$ ) compared to baseline. The herbal test rinse group had a very small improvement in inflammation scores from baseline, but this was not shown to be significant ( $p = 0.66$ ).<sup>22</sup>

#### Stage 4 summary

Positive outcomes in home use long-term ( $\geq 6$  month) clinical trials are considered to be the hallmark for demonstrating effectiveness and safety in real-life conditions.<sup>4,23,24</sup> In non-commercial home use clinical trials, the majority of studies were short term (1 week to 1 month), which in many cases precludes measurement of visible changes to gingiva, although gingival parameters were often included as outcome measures. These short-term home use studies are differentiated from stage 3 experimental gingivitis studies in that home use trials do not suspend other oral hygiene methods and are, therefore, aimed at measuring effectiveness under more realistic conditions. At the time of this review, no long-term ( $\geq 6$  month) home use clinical trials of non-commercially available oral rinse products were found, although there was one 3-month home use study, which was reviewed.

Eleven home use studies testing non-commercial

formulations were located, many of which focused on derivatives of natural compounds such as essential oils from plants, teas, neem (*Azadirachta indica*), cinnamon, algae (*Enteromorpha linza*), witch-hazel (*Hammelis virginiana*), while others involved several products in combination referred to as polyherbals. In most cases, these short-term home use studies compared the experimental formulation to CHG, commercially available EO and/or placebo. Virtually all of these studies demonstrated plaque reductions in test groups compared to baseline.

A short-term early study was conducted with a rinse made from the essential oil of leaves from a shrub native to northeast Brazil called *Lippia sidoides*, which is more commonly known as pepper-rosmarin. Although the study was only 1 week long, it was included in this section of the review because participants continued to use their usual home care aids in addition to the test or positive control rinse. This study compared the test formulation to 0.12% CHG and measured both plaque and gingivitis, although measurements at 1 week is considerably early to detect a gingival response in many subjects. The study found a significant decrease ( $p < 0.001$ ) in plaque and gingivitis from baseline for both groups and, while there was no difference found between groups, 44% of the test rinse group experienced a mild burning sensation, whereas only 14% of the CHG group reported such a side effect. The study did not include a negative control group.<sup>25</sup>

A 6-week home use study examined a rinse derived from *Enteromorpha linza* extract, a green algae found on European, Mediterranean, South Korean, and Japanese coastlines, which attaches to solid bedrock, mobile boulders, mud banks or sandy shores where it rapidly colonizes. The test formulation was compared to a commercially available EO rinse and measured plaque, gingival inflammation, and bleeding. The study found statistically significant reductions from baseline in both groups ( $p < 0.05$ ). No difference was reported between the groups, but the researchers did not include this data in the report. The study was limited in that it lacked a sufficient number of participants to include a negative control group and the dose of the positive control rinse was half (10 mL) of what is recommended by the manufacturer.<sup>26</sup> In addition, there was a disproportionate number of tobacco smokers in the positive control group (33%) as compared to the experimental group (17%), which was not controlled for. Despite the unlikelihood of a home oral rinse penetrating into the sulcus or pocket, the study also examined the reduction of specific periodontal pathogens (*Porphyromonas gingivalis* and *Prevotella intermedia*) within “the deepest pockets” in each quadrant of study subjects. The reductions found in both groups were statistically significant.<sup>27</sup>

Another home use study examined a neem-based (*Azadirachta indica*) mouthrinse, which is derived from the leaves of a tree indigenous to India and considered to have

medicinal properties. The test rinse (0.19%) was compared to 0.2% CHG and a negative control, all using a 2 times daily regimen with 15 mL for 1 minute over 21 days. Both the test and positive control groups significantly reduced ( $p < 0.05$ ) plaque and gingivitis measures. The study demonstrated no difference with the negative control group as compared to baseline or between the groups.<sup>28</sup>

A small study conducted with young adults also examined a rinse derived from neem stick powder (2%) (*A indica*) to tea leaves (0.5%) (*Camellia sinensis*) and a positive control, CHG (0.2%). Over both a 2- (all groups) and 3-week period (neem and tea only), anti-plaque effectiveness was observed from baseline in all groups ( $p < 0.05$ ), with the highest reductions observed in the tea group. The CHG group was only tested over 2 weeks as planned a priori because of anticipated side effects, which precludes comparisons regarding inflammation given that it can take a full 3 weeks to observe such effects.<sup>6</sup> While all 3 groups reduced inflammation over 2 weeks, there was no significant difference between the groups ( $p > 0.05$ ). The study also lacked a negative control group.<sup>29</sup>

A small study conducted in 2015 also included a rinse made from green tea leaves (*C sinensis*) (0.5%) compared to CHG (% not reported), and demonstrated significant improvements ( $p < 0.05$ ) in both plaque and gingival outcome measures in both the test and positive control groups compared to baseline over 1 month. No significant difference between groups was observed. The green tea rinse resulted in a statistically significant decrease in bleeding index compared to the chlorhexidine group. The study did not include a negative control, and the rinsing time, rinsing amount, and concentration (positive control only) were not reported.<sup>30</sup>

Cinnamon is derived from the inner bark of several species of trees largely grown and cultivated in South Asia. Research supporting cinnamon as a medicinal ingredient is limited. A recent 30-day study was conducted with young adults comparing a cinnamon extract rinse to 0.2% CHG and a negative control rinse. Both the test and positive control groups showed significant reductions ( $p < 0.05$ ) in plaque and gingival inflammation compared to baseline and to the placebo. However, in this study, the CHG rinse had a significantly better ( $p < 0.05$ ) effect than the test product.<sup>31</sup>

Witch-hazel (*Hamamelis virginiana*) is a shrub grown in North America, China, and Japan, and its bark and leaves have a history of use as a medicinal ingredient. Another recent 21-day 5-block study compared a witch-hazel-based rinse to several well-established commercially available oral rinses: CHG 0.12%, EO, CPC, and triclosan, but no placebo group was included. Results demonstrated the non-commercial product to significantly reduce mean plaque scores over the 3-week period ( $p < 0.01$ ), but it was shown to be statistically significantly the least effective of all of the products compared.<sup>32</sup>

Another 21-day study ( $n = 40$ ) examined a polyherbal

rinse consisting of tea tree oil (0.2% to 0.3%) (*Melaleuca alternifolia*) plus oils of clove (0.2% to 0.3%) (*Syzygium aromaticum*) and basil (0.2% to 0.3%) (*Ocimum sanctum*) compared to an established, commercially available EO rinse measuring plaque and gingival inflammation. Both the test and commercial EO groups significantly reduced both outcome parameters from baseline ( $p < 0.0001$ ), while there was no significant difference demonstrated between groups. Of note, the study did not include a negative control group and used only 10 mL of the positive control rinse, which is half the recommended dosage.<sup>33</sup>

A 2016 study also investigated a polyherbal rinse, in this case derived from coarsely powdered ginger (*Zingiber officinale*), rosemary extract (*Rosmarinus officinalis*), and marigold (*Calendula officinalis*) (5% v/w), in comparison to 0.2% CHG and a negative control. The study demonstrated significant improvements ( $p < 0.05$ ) in both plaque and gingival outcome measures in both the test and positive control group compared to baseline, but no significant difference between them. The negative control group demonstrated no significant effects. The study was only 2 weeks in length, which, therefore, precludes definitive conclusions about the anti-inflammatory benefits of the tested products.<sup>34</sup>

A recent study conducted with young adults (20 to 30 years of age) compared 0.2% CHG to a commercially available probiotic-derived rinse (Sporlac Plus®) and a negative control, but the study is included in this part of the review because the product is commercially indicated for diarrhoea of varied etiology and was used experimentally in the study for oral application. Probiotics are ingested live microorganisms believed to offer human health benefits, although research demonstrating such benefits is limited. The test product, Sporlac Plus®, contains *Lactobacillus acidophilus*, *Lactobacillus rhamnosus*, *Lactobacillus sporogenes*, *Bifidobacterium longum*, and *Saccharomyces boulardii*.

The participants rinsed for 15 days with their assigned rinse, but the study did not indicate what other oral hygiene aids were permitted during the rinse period. Outcome measures were taken at 14 days and 28 days, but it is unclear from the report what oral hygiene regimen was followed after the test period (day 15) until the final measure (day 28). The study demonstrated significant effectiveness for both the CHG and the probiotic rinse in reducing both plaque and gingivitis scores compared to baseline and the placebo ( $p < 0.05$ ), while there was no difference between them. The study did not indicate the dosage of the CHG. It was also not clear from the report what outcome measure time period (day 14 or day 28) was used in the statistical analysis and results, as only 1 set of data was presented.<sup>35</sup>

The longest of the home use studies was conducted over 3 months and compared a rinse containing African basil (*Ocimum gratissimum*) to CHG (0.12%) and a negative

control rinse. *O. gratissimum* is a tropical aromatic plant whose essential oil has shown some antibacterial effect. This study had a small sample size—only 10 subjects in each group—but demonstrated significant ( $p < 0.05$ ) plaque and gingivitis reductions in the test and CHG groups, but no significant difference between them. The participants used their assigned rinse (10 mL) for a full minute along with toothbrushing 3 times per day.<sup>36</sup> While there was good compliance among test rinse users, there was evidence of staining and taste alterations in the CHG group.

### Systematic reviews

While only primary research studies were included in this review, it is helpful to survey previously conducted systematic reviews in order to ensure that no primary studies have been overlooked and to compare findings. The search strategy for this position paper failed to locate any systematic reviews specifically conducted on non-commercially available products. However, 1 systematic review targeting natural compound-containing rinses has been conducted.<sup>37</sup> Less than half of the test formulations included in that systematic review were commercially available.<sup>37</sup> Although the reviewers considered commercially available EO rinse LISTERINE® to be a natural compound-containing rinse, it was not included in the review because it had been included in several previously conducted systematic reviews and meta-analyses.<sup>37-40</sup>

The systematic review of natural compound-containing products yielded 2236 titles and abstracts; 11 clinical trials were included in the final review.<sup>37</sup> Substantial heterogeneity of the study parameters prevented the researchers from conducting a meta-analysis.<sup>37</sup> Of the 11 studies that met inclusion criteria, 5 were considered to be of low quality. All of the studies included had small sample sizes and low-level study design. All but 3 of the included studies were published prior to 2006 and were, therefore, not considered for the present review. The systematic review categorized natural compounds into 3 groups: those containing a single natural product, those containing compounds from several natural products, and those containing both natural and synthetic products. This categorization highlights the challenge inherent in examining the specific benefits of individual products included in polyherbals. Of course, some therapeutic products like commercially available EO rinses have demonstrated effectiveness within a combination formulation.<sup>4</sup> The researchers of the systematic review concluded that the evidence demonstrating effectiveness of natural compound-containing rinses was insufficient and that further study is required.<sup>37</sup>

### DISCUSSION

The American Dental Association (ADA) has stringent guidelines for awarding its seal of acceptance for oral rinses, including a study period of at least 6 months to evaluate both efficacy and safety of chemical agents as well

as client compliance along with an intermediate evaluation at 3 months.<sup>23,24</sup> Because no long-term ( $\geq 6$ -month) home use studies of non-commercial products were located at the time of this review, it is not possible to confirm the effectiveness of any non-commercial oral rinse products reviewed. Therefore, with just over half of the studies reviewed here being in stages 1 to 3 and the remaining being short-term home use studies, this position paper can only identify products that are most promising and may warrant further research, ideally at the appropriate stage and with the use of standardized parameters.

Of the studies included in this review, most demonstrated positive effects compared to baseline and/or placebo controls of a wide variety of compounds. However, there were some important weaknesses in study designs and methods, which may mitigate the merits of conducting additional, especially higher level, research that involves ethical considerations for human study subjects.

Of the 5 products studied in stage 1 research designs, 2 formulations showed positive effects. The chitosan rinse was shown to be superior to both CHG and EO rinses with regard to MIC and adherence qualities. The study of MPC-polymer also produced interesting findings with regard to preventing adherence and colonization of pathogenic microbes. While persica and taurolidine rinses performed better than placebo, the effect was significantly less than positive controls. Edible oil-based rinses simulating the practice of “oil pulling” were found to have no effect. In the stage 2 plaque regrowth studies, both the pomegranate and aloe vera extract-based rinses demonstrated positive outcomes as compared to placebo rinse, while no significant differences were demonstrated compared to the positive control (CHG). Two studies showed bee products (propolis) to inhibit plaque compared to the negative control, though only one had statistically significant results, but neither was as effective as CHG, the positive control rinse. A further study was conducted with a traditional herbal rinse, but had major limitations in methodology making its interpretations erroneous.

In the stage 3 experimental gingivitis studies, none of the test formulations demonstrated significantly favourable effects over both positive and placebo controls. One study with sodium hypochlorite suppressed inflammation significantly better than the placebo although it did result in statistically significant increases in brown dental stain. The turmeric extract rinse showed similar inflammatory reductions to CHG, but there was no placebo control in that study. The remaining studies did not demonstrate significant results with regard to positive controls and had other design flaws including a lack of placebo groups, short duration ( $< 21$  days), and unconventional rinse times.

All of the home use studies were less than 6 months in duration, and only 1 was greater than 1 month long. None of the test formulations was shown to have statistically significant superior effects when compared to positive

controls, but many demonstrated no difference between the test and positive controls (CHG, EO). Of these, several studies did not include a placebo control rinse, were very short in duration thus precluding inflammatory measures, lacked reporting of treatment regimens, used less than recommended dosages in positive control groups, or had other poor design features. However, one 3-week neem rinse (0.19%) study and the 3-month African basil study both showed no statistically significant differences between test formulation outcomes, including plaque and inflammatory measures, and the positive control rinse (CHG), although they were shown to have significantly superior effects compared to placebo.

### Limitations

Inadequacies in research designs or methods and voids in reporting limit the conclusions that can be drawn about many of these non-commercial products. An important consideration for these studies is the inclusion or exclusion of active or positive controls and placebo or negative control rinses. The lack of a negative control was the norm for all 4 of the stages of research reviewed. The problem with not including a placebo group is that the study is unable to demonstrate internal evidence of efficacy or effectiveness.<sup>41</sup> The inclusion of a placebo rinse allows for absolute measures of efficacy and safety versus relative measures taken when using active controls.<sup>41</sup> Furthermore, if proper blinding and randomization occur, a negative control group controls for a placebo effect and all other potential influences on study outcomes.<sup>41</sup>

Active or positive controls can reveal differences between a test and a known product that has established effectiveness or efficacy. These differences are important in oral rinse research because identifying products that are more accessible or of lower cost may benefit populations in developing countries and other vulnerable population groups. The use of control groups helps to determine the superiority, equivalency or non-inferiority of a new formulation in comparison to established products. Depending on the focus of the study, how the research hypothesis is stated and measured and how samples are calculated are affected.

In addition, where the aim is to study a test product in relation to its equivalence to a known active control, the acceptable equivalence margin must be determined prior to the start of a study. The equivalence margin is the range of values that is described as being “close enough” to be deemed equivalent.<sup>41</sup> Furthermore, studies including an active control are affected by compliance and placebo response and may require larger sample sizes.<sup>41</sup> In studies including a positive control, a key point is ensuring that the study is “fair” in that the dose and regimen of the active rinse are consistent with the demonstrated effectiveness in previous research.<sup>41</sup>

Only 1 of the studies reviewed here was referred to as an equivalence study.<sup>19</sup> While no equivalence margin was

stated in the study, there was no significant difference demonstrated between the test rinse and what was deemed the positive control.<sup>19</sup> Interestingly, however, the positive control used in the study—a NaF/CPC rinse—has not been demonstrated to be equivalent to the gold standard, CHG, or to other well-established oral rinse products like commercially available EO in plaque and inflammation studies. While many studies did include a positive control group, these were often not used according to manufacturer instructions. In commercially available rinse studies,<sup>4</sup> many studies include both an active control group, sometimes multiple groups, and a negative control group to determine both absolute and relative effectiveness. Likely reflecting the relative infancy of non-commercial oral rinse research, the failure to include negative placebo groups and/or appropriate active control treatment regimens makes it difficult to draw conclusions and identify products warranting further research.

In addition, other methodological weaknesses in these studies limit the ability to make comparisons. For example, many of the stage 1 and 2 studies conducted with non-commercial products measured gingival changes, which is inappropriate given the short duration of these studies and their design.<sup>6</sup> In addition, in some studies, the confounding effect of smokers was not taken into account. For example, in 1 study 50% of the positive control group smoked versus 25% of the experimental group, which may affect gingival outcome measures particularly in shorter studies.<sup>27</sup> In short-term home use clinical trials there was substantial heterogeneity across study designs making it difficult to compare and interpret results. Inconsistencies among active ingredients, the concentration of active ingredient, inclusion and exclusion criteria for study participants, study duration, outcomes measures, rinse amounts (dosages) and rinse times, control groups, blinding, ambiguity in reporting, and the lack of repeated studies all make it difficult to compare findings and draw conclusions. Such inferences have been made by other review authors.<sup>37</sup> Interestingly, there has been a lack of replication research conducted where earlier studies, which show significance, are repeated in some way to explore or verify earlier findings.<sup>42</sup> Much of the research conducted in the field of non-commercial formulations appears to be unique rather than conceived as part of a larger, systematic research agenda.<sup>42</sup> Such an approach will limit or slow the expansion of the body of knowledge on this topic.

### Rationale for natural compound-containing products and research

Many of the active ingredients in non-commercial oral rinse products are natural compounds and are of particular interest to researchers and others attempting to find low-cost alternatives to established commercially available rinses, particularly for populations in developing countries where formulations with demonstrated effectiveness cannot be as readily accessed.<sup>5,7,22,41</sup> In addition, it has been

suggested that some natural compounds may not require the inclusion of alcohol in their preparations, which may present advantages to some population groups.<sup>43</sup> Other factors stimulating research on natural compounds include the negative side effects attributed to some commercial products, such as staining, poor or burning taste, potential systemic effects, antibiotic resistance, and other concerns.<sup>4,41</sup>

In addition, there is great interest among the general public for natural products because of the perception that they are healthier and safer than synthetic compounds.<sup>5,44</sup> However, there is a need for increased public awareness of what a “natural” product actually is. There is considerable ambiguity surrounding the nomenclature of natural products and herbal remedies. The *WHO Guidelines for Research on Traditional Medicine* provide definitions for terminology associated with herbal products<sup>7</sup>; some of these are provided in Table 2 and, for consistency, should be more widely utilized in discussions. In addition, it should be recognized that holism is an important element of traditional medicine. Herbal remedies may be used as part of a holistic approach to health rather than as a singular intervention outside of their intended context, which has been suggested as likely to occur in western health care approaches.<sup>7</sup>

Natural compounds are generally derived from plant extracts. Plants are rich in a wide variety of secondary metabolites which have been found in vitro to have antimicrobial properties.<sup>37</sup> Polyphenolic plant derivatives are a part of plants’ natural defence mechanisms, which are effective against both viral and bacterial pathogens, and these have been the main focus of research on natural compounds so far.<sup>43</sup> India, among other less developed countries, is a rich source of natural herbal products, which have been used both topically and systemically for disease treatment. Often, research emanating from these regions is aimed at substantiating locally available natural products that can be developed and made consistently into rinses for these populations. While the utility of these natural products is limited due to scant research testing product effectiveness,<sup>29</sup> WHO has developed guidelines and strategies for enhancing natural and herbal product research and development.<sup>5,7</sup>

There has been extensive research conducted on commercially available products and, while research continues, a concomitant focus should also be on new products showing similar or enhanced outcomes to established products. Beyond their therapeutic benefits, these products have potential because they may prove to have fewer side effects, be more accessible, cost less, and have easier and more pleasant applications.<sup>41</sup>

### Recommendations

Well-established randomized controlled clinical trials provide the highest level of evidence for efficacy and effectiveness and would lend credibility to natural

Table 2: Selected terminology for natural products and herbal remedies<sup>7,45</sup>

Term	Definition
Herbal medicine	<p>“Plant-derived material or preparation with therapeutic or other health benefits which contains either raw or processed ingredients from one or more plants.”<sup>7, Annex II, p27</sup></p> <p>Note: Plant materials include juices, gums, fatty oils, essential oils, and other similar substances. Herbal medicines may contain some type of binding ingredient in addition to the active ingredients. Formulations containing additional “chemically defined active substances” are not considered to be herbal medicines. In some countries, traditional herbal medicines may also contain non-plant natural organic or inorganic active ingredients.<sup>7</sup></p>
Processed plant materials	<p>“Plant materials treated according to their traditional procedures to improve their safety and/or efficacy, to facilitate their clinical use, or to make medicinal preparations”<sup>7, Annex II, p27</sup></p>
Natural products	<p>“A small molecule produced naturally by any organism including primary and secondary metabolites...include very small molecules...and complex structures; they may only be isolable in small quantities”<sup>45</sup></p>

products and herbal medicines in different regions and among people with different cultural traditions.<sup>7</sup> The *ADA Acceptance Program Product Guidelines* require that products follow good and consistent manufacturing procedures,<sup>37</sup> and, therefore, virtually all of these products are not yet suitable for mass production. While making recommendations for the home use of these products by Canadian populations is premature, given the research reviewed here and elsewhere,<sup>37</sup> replication with more high-quality studies (i.e., those with standardized parameters including design, samples, outcome measures, safety) and in some cases at higher stages appears to be warranted.

### CONCLUSION

At this time, while several non-commercial oral rinse formulations have shown possible benefits, their effectiveness and safety have not been proven consistently under the methodological demands of experimental procedure, particularly in long-term clinical trials. The research conducted on these products would benefit from a standardized protocol and systematic research agenda, which together have the potential to advance the field over the next several years. Based on both parts of this comprehensive review, dental hygienists should continue to recommend a commercially available therapeutic oral rinse that has been consistently shown to be effective and safe in numerous rigorous clinical trials.

## CONFLICT OF INTEREST

Joanna Asadoorian was paid as a consultant by the Canadian Dental Hygienists Association for the design, research, and writing of this position paper. She has also done short-term contractual work with Johnson & Johnson in the past.

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Introduction It is well-known that hygienic methods for oral cavity care and caries prevention induce changes in the molecular composition of fluids within the oral cavity, thereby affecting teeth health [1-3]. The significance of the changes in the molecular composition of mixed saliva has been previously shown in diabetes, oncology and pathologies of the oral cavity [4-9]. Canadian Dental Hygienists Association Position Statement. Based on current research, dental hygienists are strongly encouraged to make recommendations to clients supporting mechanical interdental cleansing as an adjunct to toothbrushing in order to control plaque accumulation and to pre-vent and/or control periodontal diseases. Conversely, flossing has been shown to be effective in cleaning interproximal surfaces of teeth from the contact point to the sulcus<sup>7,10,24</sup> and has not been shown to produce unfavourable consequences.<sup>25</sup> The ADA has reported that flossing is capable of removing up to 80% of plaque interdentally in a "normal" dentition, meaning that "the interdental space is filled with. Therapeutic oral rinsing with non-commercially available products: Position paper and statement from. Canadian dental hygienists association position statement." the Canadian Dental Hygienists Association, part 2. a demonstrated effective and safe therapeutic oral rinse to their adult clients to complement home care routines for the reduction of plaque and gingival inflammation. Based on the research reviewed, there is no evidence from rigorous, Joanna Asadoorian\*, PhD, RDH. commercially available oral rinse products that have been proven effective and safe, taking into account specific client needs, to promote optimal oral health. rinse products and is the second part of a 2-part position paper and statement that.