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Gianluca M. Tartaglia, Santhosh Kumar, Claudia Debora Fornari, Eleonora Corti & Stephen Thaddeus Connelly

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REVIEW

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Mouthwashes in the 21st century: a narrative review about active molecules and effectiveness on the periodontal outcomes

Gianluca M. Tartaglia[a,b], Santhosh Kumar[c], Claudia Debora Fornari[b], Eleonora Corti[d] and Stephen Thaddeus Connelly[e]

[a]Department of Biomedical Sciences for Health, Functional Anatomy Research Center (FARC), Università degli Studi di Milano, Milano, Italy; [b]SST Dental Clinic, Segrate, Italy; [c]Population and Social Health Research Programme, Menzies Health Institute Queensland and School of Dentistry and Oral Health, Griffith University, Gold Coast, Australia; [d]Department of Regulatory Affairs, Biokosmes srl, Bosisio Parini, Italy; [e]Department of Veterans Affairs Medical Center, San Francisco, CA, USA

ABSTRACT

Introduction: Poor oral hygiene is a major risk factor for oral diseases. Regular home-based care is essential to maintain good oral hygiene. In particular, mouthrinses can support conventional tooth brushing in reducing accumulation of oral plaque.

Areas covered: The most common molecules contained in mouthrinses (chlorhexidine, essential oils, cetyl pyridinium chloride, triclosan, octeneidine, delmopinol, polyvinylpyrrolidone, hyaluronic acid, natural compounds) are discussed, together with relevant clinical and *in vitro* studies, focusing on their effects on periodontal health. Currently, chlorhexidine is the most efficacious compound, with both antiplaque and antibacterial activities. Similar results are reported for essential oils and cetyl pyridinium chloride, although with a somewhat reduced efficacy. Considering the adverse effects of chlorhexidine and its time-related characteristics, this molecule may best be indicated for acute/short-term use, while essential oils and cetyl pyridinium chloride may be appropriate for long-term, maintenance treatment.

Expert opinion: The literature has not clearly demonstrated which compound is the best for mouthrinses that combine good efficacy and acceptable side effects. Research should focus on substances with progressive antibacterial activity, prompting a gradual change in the composition of oral biofilm and mouthrinses that combine two or more molecules acting synergistically in the mouth.

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1. Introduction

According to World Health Organization (WHO), 'oral health is a state of being free from chronic mouth and facial pain, oral and throat cancer, oral sores, birth defects such as cleft lip and palate, periodontal (gum) disease, tooth decay and tooth loss, and other diseases and disorders that affect the oral cavity. Risk factors for oral diseases include unhealthy diet, tobacco use, harmful alcohol use, and poor oral hygiene' [1]. The maintenance of healthy oral soft and hard tissues is a cornerstone of current dentistry, as oral health contributes to total health and is an essential component of the quality of life.

Evidence from the research during the recent decades on periodontal medicine also demonstrates that poor oral hygiene induces dysbiosis in certain susceptible individuals which results in a general status of inflammation that may be among the causes of systemic diseases (cardiovascular disease, rheumatoid arthritis, Alzheimer's disease, pulmonary disease, pre-term delivery of low birth weight infants and metabolic disease) [2]. Waiting for prospective case studies with higher level of evidence, we can assume that poor oral hygiene is a major risk factor for oral diseases and can also contribute to bacteremia [3]. Current data indicate that periodontal disease is much more prevalent than previously thought, and an increasing number of patients require the services of a dental professional [4,5]. In the United States, it is estimated that 47.2% of adult people (64.7 million American adults) have periodontitis [6]. Similar percentages were reported for Europe [7]. According to the Global Burden of Disease study, severe periodontitis affects 11% of the global population and is thesixth most prevalent condition in the world, provoking a reduced quality of life, and leading to tooth loss [8].

Indeed, healthy oral tissues require the maintenance of good oral hygiene which can be achieved by regular home-based oral hygiene practices. Tooth brushing, interproximal toothbrushes, dental floss, dentifrices, gels, mouthrinses, chewing gums have all been described as efficacious in home maintenance programs [5,9–13]. In particular, mouthrinses are usually used to support conventional tooth brushing in an attempt to reduce accumulation of oral plaque [5,9,10,14–20]. They even can be used as the only oral care for patients unable to brush either after surgery or because of the motor or cognitive limitations (elderly or special needs patients). One additional use of mouthrinses is to prevent or treat oral malodor [11,14,21–23].

Apart from the mechanical action of brushing, the effect of selected chemicals on oral tissues and their action against microorganisms have been intensively studied both *in vitro, ex vivo* and *in vivo* [5,9,10,14,15,17,18]. Ideally, the substances

CONTACT Gianluca M. Tartaglia farc@unimi.it Department of Biomedical Sciences for Health, Via Luigi Mangiagalli 31, 20133 Milano, Italy

Article highlights

- At the moment, the best effects for the maintenance of oral health are provided by chlorhexidine that couples antiplaque and antibacterial effects, and promotes gingival health.
- Essential oils and cetyl pyridinium chloride have effects similar to those reported for chlorhexidine, but with a somewhat reduced efficacy.
- Chlorhexidine could be suggested only for acute/short-term use, while essential oils and cetyl pyridinium chloride could be indicated for long-term, maintenance treatment.
- Research should focus on substances promoting a gradual change in the composition of oral biofilm, and on mouthrinses that combine two or more molecules that can with positive synergy in the mouth.
- Further research should be performed especially for long-term use, maintenance of a healthy oral microbiota, and special need patients.

This box summarizes key points contained in the article.

should respect dental and gingival tissues, help in their healing if damaged, reduce plaque formation, and block the activity of microorganisms without modifying the existing ratio between gram-positive and gram-negative anaerobic bacteria [9,15]. This normal ratio is important to avoid the proliferation of anerobic pathogens in protected oral niches (spaces where mechanical cleaning is more difficult), which may act as reservoir of aggressive bacteria in susceptible individuals [24].

The antibacterial activity should be obtained without using antibiotics and maintaining the native oral microflora to compete with disease-producing microorganisms. As a matter of fact, the reduction in the use of antibiotics should be one of the goals of current medical and dental therapy, considering the increased risk of developing resistant strains [25–27].

Several molecules and preparations have been devised and proposed to the market. In the current narrative review, some general information about the most common molecules contained in mouthrinses will be provided, and the most recent clinical and *in vitro* studies will be presented. This review will focus on the effects of the most common molecules contained in mouthrinses on periodontal health.

2. Molecules

Molecules included in the commercial mouthwashes are derived from antiseptic, disinfectant, and preservation research areas. The active chemical agents (biocides) are then differently combined to be used in mouthwash formulations that in general should have a combination of the following characteristics:

(1) Effective against disease-producing micro-organisms.
(2) Active against the local effects of disease-producing habits.
(3) Disrupt dental plaque effect without disturbing the normal, healthy oral flora.
(4) Safe for human and environmental use.
(5) Minimum and reversible side effects.
(6) Pleasant taste.

2.1. Chlorhexidine (CHX)

At the moment, the best antiseptic for the oral cavity is CHX. It is a biguanide; this substance couples both bactericidal and bacteriostatic effects [5,10,19,28]. It is not sporicidal, but prevents the development of spores. It was synthesized for the first time in 1950, and it is included by WHO in the list of essential medicines needed in a basic health system. Addy [9] reviewed its side effects for dental use: it can provoke a brown⁄black discoloration of the teeth and lingual mucosa with an increased formation of supragingival calculus; additionally, taste disturbances have been reported as well as discoloration of some restorative materials. Studies also suggest that CHX use is associated with increased roughness of restorations which favors plaque retention and this effect of the mouthrinse is pronounced when followed by toothbrushing. However, this adverse effect has also been found with other mouthrinses containing cetyl pyridinium chloride (CPC),triclosan, and alcohol [29].

CHX mouth rinses should be used at least 30 min after other dental products because its activity is pH dependent: mouth pH could be influenced from anionic surfactants commonly used as detergents in toothpastes and mouthwashes [30].

The standard concentration of CHX used throughout the world is 0.2% but few researchers have also observed that a concentration of 0.12% was also clinically effective. Data from a systematic review suggest that there are no differences in preventing gingivitis between these concentrations. However, some statistically significant differences, which might not be clinically significant, have been found in plaque prevention with 0.2% CHX exhibiting greater plaque prevention. It was also found that any duration of rinsing (30 s and 60 s) was effective in controlling plaque [31].

A recent systematic review ascertains the efficacy of CHX on plaque and gingivitis irrespective of the concentration, yet the dosage was found to be an important factor with an optimum dose of 20 mg twice daily [32]. On the contrary, antimicrobial efficacy of 0.12% CHX on salivary flora was unequivocally found to be significantly weaker than that of 0.2% [33–35].

2.2. Cetyl pyridinium chloride

CPC is an amphiphilic quaternary compound with an antimicrobial activity facilitated by its positive charge that promotes its binding to negatively charged bacterial surfaces. CPC also reduces bacterial adhesion on surfaces [14,18,20]. Longitudinal studies have demonstrated its favorable effectiveness in the reduction of dental plaque and gingivitis [15,18,20]. One limitation may be dental staining that seems to be dose-dependent and proportionately less of an issue than with CHX [9,15].

2.3. Essential oils

Mouthrinses formulated with essential oils (EO) contain a mix of thymol, eucalyptol, menthol, and methyl salicylate in an alcohol solution [12,19]. EO have antimicrobial and anti-inflammatory activities [4] and are considered the best alternative to CHX for plaque control. In addition, they are as efficacious as CHX for gingivitis [19]. According to the review by Addy [9], EO seems to have no local side effects, even if their strong taste may be a limitation in some patients.

2.4. Alcohol

Alcohol is one of the components of most mouthrinses because of its capacity to preserve the formula components and help to dissolve the active substances [11,19]. According to Lemos and Villoria [11], in the majority of adult patients, the alcohol content of mouthrinses does not have negative effects on general health when proper instructions and expert guidance are given. Of course, children, patients with mucosal injuries and alcohol addicts should refrain from preparations containing alcohol. At the moment, there is no sufficient information comparing mouthrinses with and without alcohol [19]. While there is no synthesized evidence on the comparative effectiveness of alcohol free with alcohol based mouthrinses, most of the studies observed that alcohol free mouthrinse have plaque inhibiting efficacy comparable to alcohol based mouthrinses [36–39].

Although unsubstantiated, there have been concerns about the possible association of alcohol to carcinogenesis during the recent times [38]. This might be the reason why some researchers recommend use of mouthwashes without alcohol.

2.5. Triclosan

Triclosan was synthesized around 1980. It is a bis-phenol antibacterial and antifungal agent with suggested anti-inflammatory activity. Its efficacy as an antimicrobial agent and its possible role to influence hormonal development remain controversial [30]. In the last decades of the past century, it was used to reduce the side effect of the sodium laurilsulfate contained in dentifrices and mouthwashes [40,41]. Its use together with zinc citrate is not associated with staining as observed with CHX usage. In general, it is considered not harmful to humans and the environment, but its utilization has been recently put under review by the US Food and Drug Administration [42] and limited from EU [43].

2.6. Octeneidine

Octeneidine was developed in the 1980s. It is active against bacteria, fungi and yeasts with similar effectiveness when compared with the most commonly utilized antiseptic agents [44]. Moreover, it interferes with the dental plaque microbial co-aggregation. The unpleasant taste of Octeneidine has not supported its use in mouthwash formulations [45].

2.7. Polyvinylpyrrolidone (PVP)

PVP is a hydrophilic polymer that forms a film over the mucosal surfaces, increasing tissue hydration and promoting wound healing [46]. Initial studies showed that PVP, when coupled with CHX, reduces the staining caused by CHX [47].

2.8. Hyaluronic acid (HA)

HA is the main component of the extracellular matrix of many tissues, and it is present in human saliva acting as a lubricant [48–50]. HA possesses a role in healing both acute and chronical oral lesions, especially periodontal alterations [25,27,49,51].

HA contributes to tissue protection by forming a superficial film over oral mucosa [46]. *In vitro* studies demonstrated that HA possesses good viscoelastic properties that can mimic those of human saliva [50]. *In vivo*, the plaque growth inhibition activity of HA in 4-day plaque regrowth model is comparable to CHX [52].

2.9. Delpmopinol

Delpmopinol is a surface active cationic agent developed in late 1980s. It is able to bind hard and soft oral tissues influencing different steps of the formation and consolidation of the dental plaque biofilm. It affects the acid production in oral bacteria shifting the microbial composition of dental plaque toward a microflora that appears to be more associated to gingival health [53].

2.10. Natural compounds

In the recent years, natural compounds (excluding EO) containing mouthrinses (NCCM) had shown an important growth demand from the markets and professional community. Plant, fungal, microorganism, animal, and marine extracts show a wide variety of metabolites with *in vitro* anti-microbial and anti-viral properties. Moreover, they possess anti-inflammatory and anti-oxidant activities that are beneficial to oral health. They act by reducing both bacterial adhesion to tooth and restorative materials surfaces and the oxidative burst from neutrophils. Initial studies on NCCM demonstrated promising antibacterial activity against gingival diseases [54,55].

2.11. Fluoride compounds (FC)

FC are extensively used in dentistry both against caries and oral bacteria since their discovery in the early 1940s. Their action against oral bacteria is derived from their capacity to reduce bacterial acid metabolism. NaF and more recently, SnF_2, are the main molecules used in mouthrinses formulations. In particular, SnF_2 long-term use is accompanied with a reduction of the total plaque virulence. Dental stains are reported as side effect, however, formulations with sodium hexametaphosphate supplementation seem to have a beneficial effect in controlling stain deposition. Formula stability in the air still remains a commodity-related problem: when the molecules are englobed inside a dentifrice, they seems to be more stable than in a fluid mouthrinse [56,57].

3. Evidence on the effectiveness of various molecules on periodontal outcomes

Table 1 summarizes the outcomes of the molecules mentioned in the narrative review. Findings from meta-analyses and systematic reviews were used to summarize the effectiveness of various molecules. For the molecules not mentioned in systematic reviews, we have considered first the outcomes from clinical trials, or, if not available, the *in vitro* or *ex vivo* efficacy.

Table 1. Principal molecules in mouthrinses that were effective on periodontal outcomes.

Molecules	References	FDA approval	EU approval	Groups		Outcomes					Authors' conclusion	Side effects	6 Months follow-up RCTs
				Placebo group	Control group	Bacterial counts	Plaque regrowth	Gingival index	Bleeding index	Plaque index			
CHX	[10,95]	Yes	Yes	Yes	Yes			*	*	*	+	Yes	Yes
EO	[10,95]	It depends on the active ingredient	It depends on the active ingredient	Yes	Yes			*	*	*	+	Yes	Yes
CPC	[10,95]	Yes	Yes		Yes			*	*	*	+	Yes	Yes
AmF/SnF$_2$	[89]	Yes	Yes	Yes				*	*	*	+	No	Yes
Triclosan	[65]	Yes	Yes	Yes				*		*	+		Yes
Octeneidine	[45,71]		Yes	Yes	Yes	*	*	*		*	+		
Delmopinol	[10,95]		Yes						*	*	+	Yes	
HA	[52]	Yes	Yes			*					+		
NCCM	[54]	It depends on the active ingredient	It depends on the active ingredient	Yes	Yes			*	*	*	+	Yes	
Associated molecules													
PVP + CHX	[47]							*	*	*	+	Yes	
CPC + CHX	[60]				Yes	*					+		
CHX + Alcohol	[60]				Yes	*					+		

Authors' conclusions: +, positive effect of the compound(s).
Asterisks (*) in a cell denotes that the molecule is effective on that periodontal outcome.

3.1. CHX, essential oils, CPC

These three compounds are often used together in clinical and laboratory studies, and they will be analyzed comparatively in the current chapter.

Gunsolley [10] performed an extensive review of published meta-analyses and systematic reviews and reported a significant anti-plaque and anti-gingivitis effect of both CHX and EO, while no conclusive evidence for CPC could be found due to the reduced number of studies and variety of formulations. On the contrary, other reviews reported a positive effect of CPC both with and without alcohol, stating that the compound possesses effective antibacterial, antiplaque, and antigingivitis potential [15,20]. CPC appears more effective in long term (6 months) rather than in intermediate (3 months) follow-up periods [15]. Recently, Kulik et al. [26] reported that prolonged *in vitro* exposure to CHX can lead to the development of resistance in some oral microbial strains, and suggested that CHX should be used only for limited periods of time [26]. A similar recommendation was provided by Wilder and Bray [5].

A different time dependent result was reported by Mouchrek Junior et al. [12]. These authors compared the anti-plaque effects of CHX, EO, and CPC during a 3-week *in vivo* trial, and found that the best results were given by CHX, followed by EO. CPC had effects comparable to those of the other molecules at7 days of observation, but the efficacy decreased in the subsequent weeks.

A superior effect of EOversus CPC was also reported by Cortelli et al. in a long-term investigation that included more than 300 subjects [58], while Charles et al. found that EO and CHX had equivalent antiplaque and antigingivitis activity, but CHX had more side effects [59].

The effects of these molecules were also assessed *in vitro*. Pan et al. [17] studied the antimicrobial activity of various mouthrinses using an *in vitro* model of plaque biofilms. Overall, CHX and EO had comparable efficacy, which was better than that obtained by CPC. More recently, the antibacterial effect of CPC combined with sodium fluoride was tested by Latimer et al. [16] in an *in vitro* and *ex vivo* study. The molecules had a significant effect against planktonic bacteria and reduced the formation of biofilm over hydroxyapatite.

Garcia-Godoy et al. [14] compared the *in vivo* and *in vitro* antimicrobial activity of several commercial mouthrinses containing CPC and found a variety of effects which were directly influenced by the bioavailability of the compound. Sreenivasan et al. [18] used a mixed *in vitro* and *ex vivo* protocol and found that mouthrinses containing CPC had a broad-spectrum activity against both laboratory strains and supragingival plaque bacteria.

CHX formulations with addition of CPC and essential oils have also been tested. Findings from an *in vivo* and *in vitro* study by Herrera et al. indicate that the combination of CHX and CPC had the highest antimicrobial potential followed by CHX and alcohol in comparison to CHX and CHX plus NaF. They have concluded that CPC acts synergistically with CHX to increase the antimicrobial potential of mouthrinses containing both molecules [60].

Very recently, CHX and CPC have also been tested for their effectiveness on the bacteria associated with peri-implantitis.

In an *in vitro* study, CPC was found to inhibit the growth of six bacterial strains that are associated with peri-implant disease [61]. Another study found 0.2% CHX to have antibacterial effects on a bacterial strain that was isolated from peri-implantitis sites [62].

The addition of mouthrinses (CPC or EO) to tooth brushing with a therapeutic paste significantly reduced oral plaque in an 8-week clinical study [63]. EO were used by Martin et al. [3] in a randomized controlled trial that assessed adolescent orthodontic patients with gingivitis. No significant reductions in inflammation and plaque indices were reported [4].

3.2. Triclosan

Evidence suggests that 6 months' use of triclosan mouthrinse is effective in reducing plaque and gingivitis when compared to a placebo [64,65]. However, data from a 3-weekstudy suggest that triclosan was less effective in preventing gingivitis and plaque than CHX [66]. Another clinical trial found that triclosan mouthrinse did not provide any additional antiplaque and antigingivitis advantage when daily used along with a fluoride dentifrice [67]. Currently, triclosan is mainly used in dentifrice preparation. Due to its broad spectrum antimicrobial efficacy which includes antifungal properties, triclosan has high anti-candida activity [68]. Hence, it is recommended in HIV-infected patients [69] and those using removable dentures, two patient populations who are susceptible to candidal overgrowth.

3.3. Octeneidine

The literature on the effectiveness of octeneidine in maintaining oral hygiene is limited, but a few initial studies suggest that this molecule significantly reduces plaque and gingivitis when compared to the regular use of dentifrice [70] or of a placebo mouthrinse [45,71]. Unfortunately, none of these studies had a follow-up longer than3 months. However, data from *in vitro* and *in vivo* studies suggest that mouthrinses containing octeneidine hydrochloride as an active ingredient had comparable [72] or greater effectiveness than CHX on cariogenic bacteria [73–75]. Further, a recent 4-day plaque-regrowth study found that octeneidine had antibacterial and antiplaque efficacy comparable to CHX. In spite of the promising findings, this molecule has not been widely used, the reasons used, which might be due to its bitter taste and also partly due to the lack of evidence from studies with longer follow-up periods [76].

3.4. Polyvinylpyrrolidone

Another mouthrinse component that has been less studied is PVP, which has been found to reduce the staining potential of CHX but at the expense of losing some plaque reduction potential when used along with CHX [47]. There is convincing evidence that the effectiveness of PVP + iodine (povidone-iodine) in preventing plaque and gingivitis is comparable to CHX [77,78] and placebo [79]. However, mouthrinses with octeneidine and PVP failed to be as popular as CHX, which might be partially due to the lack of robust evidence on their effectiveness from studies with longer follow-up periods. Contact dermatitis from this disinfectant is reported and iodine is considered the responsible antigen [80].

3.5. Delmopinol

Studies on delmopinol focused on its anti-plaque activity; when compared to CHX, delmopinol was found to be less effective in terms of antimicrobial activity but more tolerable and with less adverse effects [81].

3.6. HA

Dahiya and Kamal [49] recently reviewed the biological properties and clinical applications of HA, reporting its positive effect on periodontal disease, and its active role in periodontal wound healing. HA has been proposed as an adjuvant in the treatment of gingivitis [50]. The literature on the effectiveness of HA in the form on mouthrinse on periodontal outcomes is very limited. A 4-day plaque regrowth study from India found HA-based mouthrinses to be effective in reducing the growth of periodontal pathogens (*Aggregatibacter actinomycetemcomitans* and *Prevotella intermedia*) *in vitro* and had plaque inhibition potential similar to CHX *in vivo* [53]. de Araujo Nobre et al. [28] compared the effects of HA and CHX after the insertion of endosseous implants in two groups of edentulous patients. At short-term follow-up (2 months after surgery), healing of the peri-implant tissues was better in the HA group than in the CHX group, while the effect partially reversed at midterm follow-up (6 months). They concluded that HA had a favorable action during tissue healing [28]. Another study that compared the effectiveness of CHX + HA and CHX on the healing of implants found CHX + HA to have an additional anti-edematigenous effect after 15 days [82].

Its use during pregnancy and breast-feeding has not been sufficiently studied, so it is suggested to avoid its use.

Owing to the wide variety of periodontal outcomes, and follow-up periods used in the experimental studies, it is difficult to summarize or compare the findings across the studies. This calls for a uniform reporting system for the effectiveness of various molecules on periodontium.

3.7. Natural compounds

Since thepast decade, the research on clinical efficacy of NCCM has been rapidly growing. Market demand of natural compounds instead of synthetic products is mainly driven from the idea that natural products are intrinsically safer than the chemically synthetized active agents. NCCM are used alone, differently mixed or in combination with synthetic products.

This wide variety of combination formulations hamper the ability to identify whether or not a clinical outcome is related to the herbal or chemical agents. Research on the side effects of these formulations is still lacking. For example, Sanguinaria, which has been used as herbal additive in dentifrices and mouthrinses for many decades, was found to be associated with a unique form of leukoplakia with dysplastic changes similar to that of conventional leukoplakia [83].

Data from a systematic review suggests that NCCMs with *Echinacea, Chamomile, Salvadora persica, Folate, Myrrh, Rhatany* as main ingredients were effective in preventing gingivitis and plaque but, when using the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach [84], the relevant treatment outcomes were low excepting for EO [54]. Although the findings from more than half of the clinical studies on each of the above herbal compounds found positive results, the authors caution that the evidence is still insufficient to prescribe them as an adjunct to regular oral hygiene [54].

3.8. Fluoride compounds

FC comprise a family of products with evidence-based, proven beneficial activity that meet all the criteria approved from the Council of Dental Therapeutics in 1986. Studies onFC which focused on their anti-caries and anti-plaque activity found them to be more effective in terms of antimicrobial activity than placebo [85].

Few initial studies have found that the effectiveness of SnF_2 in preventing plaque was comparable to CHX [86] or better than a placebo mouthrinse [87]. Some researchers have proposed usage of Amine F (AmF) along with SnF_2 owing to their caries preventive effect and antimicrobial potential respectively [85]. Studies indicate that usage of AmF/SnF_2 mouthrinse along with AmF/SnF_2 toothpaste is more effective than using only amine F/SnF toothpaste in preventing plaque and gingivitis [88,89]. Similar findings were reported by Zimmerman et al. [90]. In their 7-month clinical trial, they observed that AmF/SnF_2 mouthrinse was more effective in preventing plaque and gingivitis than a placebo.

4. Conclusions

Oral health is integral to general health, and the general rules of good personal hygiene practices should also be followed for the tissues and organs of the mouth. This should be performed by all individuals, but especially in older or medically compromised patients due to the wider implications of poor oral hygiene on systemic conditions.

Generally speaking, the research in the field of mouthrinses, and more in general about chemical and mechanical tools that can help the patients in maintaining optimal oral health, has increased exponentially in the last years. For example, a PubMed search of 'oral health' retrieved 3557 papers in 2005 and 10,681 in 2015, with a threefold increment [91]. We can compare this increment with a general body benchmark like 'heart', where the increment of published papers was only 1.6 times (32,746 papers in 2005 and 52,468 in 2015).

At the moment, the best results for the maintenance of oral health are produced by mouth rinses that contain CHX, which couples antiplaque and antibacterial activity, and promotes gingival health. EO and CPC have effects similar to those reported for CHX, with a somewhat reduced efficacy [92]. Considering the adverse effects of CHX and its time dependent characteristics, this molecule should be indicated only for acute/short-term use, while EO and CPC could be proposed for long-term or maintenance treatment. Another interesting molecule is HA which has significant efficacy in treating periodontal disease and can actively promote wound healing. HA could be effectively combined with other substances that possess antimicrobial activity such as CPC, thus coupling mucosal protection and bacterial inactivation in a single compound with reduced side effects. Further studies are required on the effectiveness of HA mouthrinses on periodontal outcomes as the preliminary findings from few studies on the effectiveness of HA gels have been promising but not conclusive.

5. Expert opinion

Notwithstanding the exponential interest of the scientific community for the topics related to oral health and oral hygiene in particular, the literature has not produced a clear consensus regarding the best procedures and chemical compounds that may help patients to maintain their oral structures (teeth, periodontium, and oral mucosa) in good condition without suffering significant local or general side effects. There are several reasons which may explain this lack of guidance; such as the difficulty in translating the results of *in vitro* and *ex vivo* studies to *in vivo* situations, variable follow-up times (for instance, longer studies may be confounded by variations in oral health due to factors that are not controllable), and finally, the actual bioavailability of the compounds may be variable given different conditions of the oral environment [14]. This last factor may be dramatically altered through the course of performing oral hygiene. For example, CHX activity is pH dependent, and oral pH could be influenced by other compounds present in dentifrices [30]. Thus, a false reduced antiplaque and antimicrobial activity may be observed as a result of an incorrect protocol.

Furthermore, the combination of tooth brushing and mouthwash can contribute to the increase of roughness surface of restorative materials, which can be a factor favoring plaque retention, and therefore compromise the function of their use [29].

Another reason for the current lack of consensus is related to the ultimate goal of the treatment. Generally, mouthrinses are prescribed for two different conditions; one is maintenance of oral health in patients with good hygiene and no acute or chronic alterations of local and body immune defenses, and the other is to recover from diseased states including local (gingivitis, periodontitis, surgical treatments, radiotherapy) and systemic (alteration of the immune response, chemotherapy) disorders [93].

For the latter case, antimicrobials with a strong activitysuch as CHX are indicated, and the compromised situation of the patients may sufficiently balance the side effect considerations, in the former, a less aggressive but more persistent action should be proposed.

Indeed, one of the goals of oral hygiene is to reduce the amount of pathogenic bacteria, shifting the oral microbiome toward a less pathogenic one [13,53]. In this regard, active substances contained in the mouthrinses should ideally act progressively, with a gradual change in the composition of the oral biofilm [13]. One possible approach is the use of mouthrinses with antibacterial compounds which inhibit pathogenic bacteria and maintain bacteria associated with a healthy microbiota [2,13]. Among the various candidate molecules, HA and triclosan demonstrate the most promising results. HA for its capacity to create a protective layer over the oral tissues that could be used by antibacterial actives, while triclosan for its antibacterial and antifungal activity avoiding tooth stains. This last point has to be carefully evaluated considering the regulatory published guidelines on the active [41,53,64,65].

Another approach is the use of mouthrinses that combine two or more molecules that have positive synergistic activity in the mouth. For instance, molecules that promote wound healing and reduce periodontal disease could be coupled with molecules that possess antimicrobial activity. One such ideal coupling may be that of HA and CPC, where the mucosal protection of the former synergizes with the bacterial inactivation of the latter. Another potential is CHX and HA, this combination proved to enhance soft tissue healing after oral surgery reducing local edema [82].In addition, HA can mimic the viscoelastic properties of saliva, and its use could be proposed to be used in patients with dry mouth either medication-related or radiation-induced [50]. PVP can be coupled with CHX in order to reduce the dental staining produced by this molecule [47] or to iodine for a stronger anti-plaque and anti-gingivitis action [77–79], or to HA for its activity in oral mucositis and pain in immunodeficient patients [93]. The limited literature available on the moleculessuch as octeneidine and SnF_2 demonstrates that the effectiveness of these molecules on periodontal outcomes is also promising. Therefore, studies with longer follow-up periods are recommended to evaluate the long term effectiveness of these molecules against the gold standard, CHX. In addition to the molecules discussed in this paper, introduction and research of many more new molecules is anticipated in the near future. In particular, the interest of researchers to explore the synergistic effect of established gold standard molecules with the newer ones might lead to the development of newer formulations with superior effectiveness.

However, future *in vivo* studies should aim to adopt a uniform method of assessment for clinical effectiveness of mouthrinse on plaque, gingivitis, or other periodontal outcomes. Currently, the heterogeneity in the methods of evaluation between the studies is a major hindrance to developing synthesized evidence based on valid comparisons which can help in choosing the effective mouthrinses over the ineffective ones. Another matter of concern with the current literature is the lack of a uniform protocol for reporting the adverse events associated with the usage experimental molecules. This warrants development and proposal of guidelines for recording and reporting the adverse events.

To date, the oral health issues that arise due to pregnancy have been under appreciated in the literature [94,95]. Pregnancy produces hormonal fluctuations that have a significant effect on the oral tissues and leads to changes in tissue characteristics, which impedes adequate oral hygiene. Nausea and vomiting also contribute to a general alteration of the ecological characteristics of the mouth. Considering the relationship among poor oral health and an increased risk of adverse pregnancy outcomessuch as preterm birth and reduced birth weight, more investigations should be performed to develop mouthrinses specifically adapted for use in pregnant women, for instance without alcohol and with a pleasant taste [94,95].

In summary, the medical and dental communities have gained a clear consciousness of the importance of an effective oral health. Daily home-based care is an integral component of this, and the market offers a variety of mechanical and chemical tools that can greatly help patients. For mouthrinses, the current formulations seem to be generally effective however, not without side effect (staining, alteration of taste). But there is a lack of conclusive *in vitro* and clinical data to support the use of any of them. Further research should be performed especially in indications for long-term use and maintenance of a healthy oral microbiota as well as special need patients.

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