Teresa Chanting Sun[1,2]

Chemical Oral, Dental, and Peri-Implant Biofilm Control

Authors' affiliations:
[1] Division of Periodontics, Department of Stomatology, Mackay Memorial Hospital, Taipei, Taiwan
[2] Division of Periodontics, Department of Dentistry, Tri-service General Hospital, Taipei, Taiwan

Correspondence to:
E-mail: Teresasun2015@gmail.com
Address: Taiwan Mackay Memorial Hospital, No. 92, Sec. 2, Zhongshan N. Rd., Taipei City 10449
Telephone: +886 921020316

Date:
Received: December 11, 2017;
Accepted: January 31, 2018

Keywords: chemical plaque control; gingivitis; peri-implant mucositis; mouth rinse; dentifrice; dental plaque; oral biofilm

Abstract: The mouths is the gateway to the human body. Appropriate oral health maintenance is not only vital for mastication, pronunciation, and esthetics, but it also plays a key role in the prevention of systemic diseases. Scientific evidence indicates that bacteria are constantly present in the oral cavity, serving as one of the main etiologies of many oral diseases. Removal of bacterial plaque and control of oral biofilm are essential for the prevention and treatment of those diseases. Mechanical plaque control has been proven as an effective way to reduce bacterial plaque. The use of chemical plaque control in conjunction with mechanical plaque control has become more frequent. This review article provides insight into the mechanisms of action and the delivery formats of chemical plaque control, and included detailed information on each individual active agent. Recent evidence on chemical oral, dental, and peri-implant chemical plaque control is summarized.

Introduction

Scientific evidence based on years of studies indicates that bacteria are the foremost cause of periodontitis[1,2,] and that effective dental plaque control is the most fundamental and critical approach to prevent and treat periodontitis. Since Dr. Brånemark's discovery of direct osseointegration in the 1950s, dental implants have been vigorously developed as treatment for restoring patients' function and esthetics[3]. Clinical studies have also identified peri-implant mucositis or peri-implantitis. Although the etiology and potential risk factors of peri-implant mucositis and peri-implantitis are widely discussed and remain debatable, the majority of studies emphasize that peri-implant plaque control is effective and a critical factor for maintaining healthy soft tissue around dental implants in the long-term[4].

Oral plaque control can be categorized into mechanical or chemical plaque control. Mechanical plaque control, which involves the use of toothbrushes, interdental brushes, and dental floss, is the most commonly used method to prevent and treat oral diseases[5]. Mechanical tools have proven effective in controlling dental plaque formation and reducing gingivitis; however, scholars[6,7] have reported that the use of mechanical tools alone in certain populations cannot completely prevent periodontitis, primarily because of the following factors: (1) Patients do not brush their teeth for long enough[8]. (2) Only < 10% of the population habitually use interdental cleaning tools[9]. (3) Encouraging patients to foster and maintain correct dental cleaning habits consistently for long periods is difficult10. (4) Except for toothbrushing, the general public does not habitually

clean the oral biofilm in other parts of the mouth (e.g., tongue and buccal mucosa)[11-13]. Patients may not be able to undergo mechanical oral hygiene under certain circumstances, such as patients who have recently undergone oral or periodontal surgery, patients experiencing acute inflammation that is painful to clean, or patients with physical and mental impairments who may be unable to perform mechanical plaque control on a daily basis. The use of chemical plaque control is suitable for these patients as an auxiliary to mechanical control.

Mechanisms of Action

Chemical plaque control is generally recommended as complementary to mechanical control. Except for chlorhexidine (CHX) and essential oil (EO)[17–19], most chemical agents work only on the outermost layer of the biofilm. To maximize the benefit of a chemical agent, mechanical tools play a role in reducing plaque count and disturbing the structure of dental plaque, which can improve the effects of chemical substances. Consequently, combined use of mechanical and chemical control is more effective than using a single approach alone[14,15]. Several systematic studies have verified the effect of several chemical substances on plaque control and gingivitis reduction (Tables 1 and 2). Chemical plaque control achieves quantitative control (i.e., reducing bacterial count) and/or qualitative control (i.e., reducing biofilm activity) through the following mechanisms of actions: (1) Preventing bacterial adhesion, (2) inhibiting bacterial growth or co-aggregation, (3) removing biofilms that have already formed, and (4) changing the pathogenicity of the biofilm[14,15].

Delivery Formats

Chemical substances for plaque control are delivered using different types of agents and formats, such as mouth rinses, dentifrice, gel, chewing gum, varnish, throat lozenges, oral rinses, oral sprays, or long-acting agents[20], among which mouth rinses and dentifrice are more commonly used to deliver chemical agents for plaque control[21].

Mouth rinses can easily achieve the ideal concentration of a chemical substance; it can be used when patients cannot brush their teeth and it can reach deeper areas such as the throat. Mouth rinses are convenient and highly accepted. The downside of mouth rinses is that the ingredients (e.g., alcohol) can induce side effects. Clinical reports have indicated the association between alcohol and oral cancer, although several literature reviews have obtained no evidence supporting this observation[22,23].

The benefit of dentifrice is that it can used together with a toothbrush, which is the most frequently used mechanical tool for plaque control. From a pharmacokinetic perspective, however, the concentration and stability of some chemical ingredients in dentifrices are unpredictable, and they cannot reach deeper areas such as the throat or tongue. Dentifrice is also unsuitable for patients who are unable to maintain oral hygiene mechanically (e.g., patients with physical or mental disabilities, those who have undergone oral surgery, and patients with intermaxillary fixation after surgery).

Chemical Biofilm Control: Introduction of a Single Active Ingredient

Antibiotics

Penicillins, tetracyclines, metronidazole, vancomycin, kanamycin, spiramycin

In contrast to localized antibiotics, systemic antibiotics facilitate maintain-

Table 1. Meta-analysis of literature reviews on the effects of chemical plaque control agents on plaque index scores.

Source			Outcomes			Heterogeneity	
Ingredient	Study	No. of studies included in MA	Difference of Means	95%CI	P value	$I^{2,\%}$	P value
CHX (chlorhexidine)	Gunsolley, 2006	6	-1.040	NA	<0.001	NA	NA
	Van strydonck et al, 2012	5	-0.68	-0.85 to -0.51	<.00001	60.0	0.06
	Serrano et al, 2015	3	-0.64	-0.76 to -0.52	<.0001	47.4	0.149
EO (essential oil)	Gunsolley, 2006	20	-0.852	NA	<0.0001	NA	NA
	Stoeken et al, 2007	7	-0.83	-1.13 to -0.53	0.00001	96.1	<.00001
	Serrano et al, 2015	9	-0.83	-1.05 to -0.60	.000	97.0	.000
CPC (cetylpyridinium)	Gunsolley, 2006	7	NA	NA	NA	NA	Sig.
	Haps et al, 2008	7	-0.35	-0.47 to -0.24	<.00001	71.6	.002
	Serrano et al, 2015	10	-0.39	-0.54 to -0.24	<.0001	93.9	.000
DEL (delmopinol)	Addy et al, 2007	8	-0.34	-0.39 to -0.29	<.00001	NA	NA
	Serrano et al, 2015	3	-0.14	-0.23 to -0.06	0.001	0	0.492
SnF_2 (stannous fluoride)	Paraskevas & van der Weijden, 2006	4	-0.31	-0.54 to -0.07	0.01	91.7	<.0001
	Gunsolley,2006	5	-0.168	NA	Sig.	<25	Low
	Serrano et al, 2015	2	-0.08	-0.26 to 0.10	0.338	60.9	0.110
TCL (triclosan)	Serrano et al, 2015	3	-0.68	-0.85 to -0.51	<.0001	68.9	0.04
TCL (triclosan)+ co-polymer	Gunsolley, 2006	17	-0.823	NA	<.0001	>75	High
	Hioe& ven der Weijden, 2005	9	-0.48	-0.73 to -0.24	<.0001	97.2	<0.00001
	Davies et al, 2004	11	-0.48	-0.64 to -0.32	<.00001	95.7	<0.00001
TCL (triclosan)+ zinc citrate	Gunsolley, 2006	NA	NA	NA	NA	NA	NA
	Hioe& ven der Weijden, 2005	6	-0.07	-0.10 to -0.05	<.00001	0	0.53
0.12% CHX vs. 0.2% CHX	Berchier et al, 2010	9	-0.1	-0.17 to -0.03	0.008	0	Ns.
EO vs CHX	Van Leeuwen et al, 2011	5	-0.19	-0.30 to -0.08	<0.0009	0	Ns.

缩写：MA- meta-analysis; NA- no data available; Ns.- non significant ;Sig.- significant; Heterogeneity P value: Non-significant if P> .1

ing stable effective concentration in the blood serum, which ensures increased persistence. Numerous studies have indicated that combined use of systemic antibiotics in periodontal phase I treatment generates a more favorable clinical effect in treating severe chronic periodontitis and aggressive periodontitis[24]. Except for treatment purposes, antibiotics should not be used solely for chemical plaque control because of the side effects of antibiotics and bacterial resistance resulting from a poor benefit-to-risk ratio, wherein the disadvantages have a greater bearing than all benefits combined[24].

Enzymes

Dextranase, mutanase, proteases, lipases

Enzymatic components interfere with bacterial adhesion to the surface of the teeth; however, enzymes are impractical and often accompanied by side effects. Only in vitro data are available on enzymes or their combined use, and clinical use remains limited[25,26]. The mechanisms of action of other enzymes, such as glucose oxidase and amyloglucosidase, rely on the catalyzation of thiocyanate by lactoperoxidase in the saliva to form hypothiocyanite, which interferes with bacterial metabolism. However, these enzymes have not yet been verified as absolutely effective, and longitudinal research data are lacking[27,28].

Amine Alcohols

Delmopinol, octapinol

The mechanisms of action of amine alcohols are not yet fully understood, except that they are neither bacteriostatic nor bactericidal. Amine alcohols inhibit or interfere with the formation of biofilms. Clinically, amine alcohols are used in commercial mouth rinses, at active concentrations of 0.1% and 0.2%. The plaque-resistant characteristics of amine alcohols and side effects, including dental staining and numbness or a burning sensation in the mucosa, have been verified[29].

Detergents/Surfactants (Active-Surface Compounds)

Sodium lauryl sulfate

The foaming property of sodium lauryl sulfate (SLS) may be effective for plaque removal; however, the reliability of this mechanism of action remains inconclusive. SLS has limited antimicrobial property, and it can inhibit plaque formation. SLS is found in numerous mouth rinse and dentifrice products, but it has not yet been used alone as a single agent[30].

Oxygenating Agents

Sodium peroxyborate, peroxycarbonate, hydrogen peroxide

Oxygenating agents exert a strong antimicrobial effect on obligate anaerobes[31]. Systematic studies have found no significant effect in the short term, but 6-month studies have demonstrated significant improvement in the gingival index. Hydrogen peroxide at a low concentration (< 1.5%) is not associated with any side effects, but hydrogen peroxide at a high concentration (>1.5%) causes oral pain, increased ulceration, or delayed tissue recovery[32,33].

Metal Salts

Zinc salts (zinc lactate, zinc citrate, zinc sulfate, zinc chloride)

Metal salts are ineffective when used alone; however, when used in conjunction with active agents (e.g., CHX, cetylpyridinium chloride, triclosan, hexetidine), metal salts can prolong their mechanism of action[34].

Stannous Fluoride

Stannous fluoride has long been used in dentifrice, mouth rinses, or gels, mostly at a concentration of 0.454%. Six-month follow-up studies and sys-

Table 2. Meta-analysis of literature reviews on the effects of chemical plaque control agents on gingival index scores.

Source			Outcomes			Heterogeneity	
Ingredient	Study	No. of studies included in MA	Difference of Means	95%CI	P value	$I^{2,\%}$	P value
CHX (chlorhexidine)	Gunsolley, 2006	6	-0.563	NA	<0.001	NA	0.013
	Van strydonck et al, 2012	3	-0.24	-0.29 to -0.20	<.00001	87.0	.0005
	Serrano et al, 2015	6	-0.17	-0.25 to -0.08	<.0001	59.5	.03
EO (essential oil)	Gunsolley, 2006	24	-0.306	NA	0.006	NA	<0.001
	Stoeken et al, 2007	8	-0.32	-0.46 to -0.19	<0.00001	96.7	<0.00001
	Serrano et al, 2015	2	-0.13	-0.19 to -0.07	<.0001	45.1	Ns.
CPC (cetylpyridinium)	Gunsolley, 2006	7	NA	NA	NA	NA	0.004
	Haps et al, 2008	7	-0.15	-0.23 to -0.07	.0003	87.0	<.0001
	Serrano et al, 2015	4	-0.33	-0.53 to -0.12	.002	95.3	.000
DEL(delmopinol)	Addy et al, 2007	8	-0.1	-0.14 to -0.06	<.00001	NA	NA
SnF_2 (stannous fluoride)	Paraskevas & van der Weijden, 2006	6	-0.15	-0.20 to -0.11	<0.00001	91.1	<.00001
	Gunsolley,2006	6	-0.441	NA	<0.001	0.010	NA
	Serrano et al, 2015	2	-0.25	-0.43 to 0.07	.007	54.2	0.140
TCL(triclosan)	Serrano et al, 2015	3	-0.27	-0.31 to -0.24	<.0001	41.0	0.184
TCL(triclosan)+ co-polymer	Gunsolley, 2006	16	-0.858	NA	<.001	NA	<0.001
	Hioe& ven der Weijden, 2005	8	-0.24	-0.35 to -0.13	<.0001	98.3	<0.00001
	Davies et al, 2004	14	-0.26	-0.34 to -0.18	<.00001	96.5	<0.00001
TCL(triclosan)+ zinc citrate	Gunsolley, 2006	1	NS	NA	NA	NA	NA
	Hioe& ven der Weijden, 2005	4	-10.81%	-12.69% to -8.93%	<.00001	0	0.48
0.12% CHX vs. 0.2% CHX	Berchier et al, 2010	NA	NA	NA	NA	NA	NA
EO vs CHX	Van Leeuwen et al, 2011	4	-0.03	-0.16 to -0.09	Ns.	62.0	0.48

缩写：MA- meta-analysis; NA- no data available; Ns.- non significant ;Sig.- significant; Heterogeneity P value: Non-significant if P> .1

tematic reviews have indicated that patients have a significantly improved gingival index and plaque index after using agents containing 0.454% stannous fluoride[40,41,94]. Stannous fluoride is also commonly used with amine fluoride. Both components are bactericidal and yield a synergistic effect when used together; they are the most effective among all dentifrice products[40,41]. The side effects of stannous fluoride include staining41.

Essential Oils

Eucalyptol (0.092%), menthol (0.042%), methyl salicylate (0.060%), thymol (0.064%), alcohol (26.9% in original formulation)

Multiple mechanisms of action have been proposed for EOs in chemical plaque control[42–44], including interference with the bacterial cell wall, inhibition of bacterial enzymes, reduction of the toxicity of lipopolysaccharide-producing endotoxins, and inhibition of inflammatory response (because of its antioxidant property). Six-month clinical studies and systematic reviews have proposed the effectiveness of EO in inhibiting plaque formation and reducing gingivitis[40,94,95]. Side effects include staining and a burning sensation in the oral mucosa. A wide variety of mouth rinse products are sold on the market, such as Listerine, which contains EO and ethanol. Excess intake of alcohol is considered a major risk factor for cancer; a clinical study reported the association of alcohol-containing mouth rinses and oral cancer[45] and a systematic review of three studies indicated that alcohol-containing mouth rinses are associated with higher carcinogenic risk. However, seven other studies did not support the ssociation[23]. Another study[22] contended that, except for several clinical reports, no rigorously designed study has proven the causal relationship between alcohol-containing mouth rinses and cancer. A well-designed prospective study is required in the future to determine whether alcohol-containing mouth rinses are a risk factor for cancer.

Triclosan

Triclosan can be used in mouth rinses or dentifrice, exhibiting bactericidal effects of different durations (5–8 h) in different forms[47]. It also exerts anti-inflammatory effects by inhibiting cyclooxygenase and the lipoxygenase pathway to reduce the secretion of prostaglandin and leukotrienes[49]. Dentifrices made of three different combinations comprising triclosan and other components have been extensively studied in clinical settings. The first combination is triclosan and zinc citrate; review studies have proposed different conclusions for this combination[51–54]. One review indicated that triclosan and zinc citrate are significantly more effective in controlling bleeding than they are in plaque reduction[57]. Another systematic review indicated a nonsignificant clinical effect[40]. The second combination is triclosan and copolymer. According to a literature review, multiple 6-month clinical studies have indicated that this combination statistical significantly controls dental plaque and gingivitis. However, the homogeneity of these studies differs, necessitating more homogeneous and comprehensive analysis to verify this result[57,40]. The third combination is triclosan and pyrophosphate. This combination is rarely investigated, and its efficacy therefore remains inconclusive[40]. A wide variety of triclosan products are available on the market, and their side effects are often discussed. In vitro studies and animal experiments have proposed that these products may produce carcinogens, but this assertion has not yet been verified in clinical usage[50]. Another possible side effect is the harmful effect of triclosan on the ecosystem. Waste water treatment facilities cannot effectively remove triclosan from water, and exposure to sunlight causes this component to produce dioxins as a byproduct, which is toxic and may contribute to environmental pollution, magnified by the natural biological food chain[58].

Bisbiguanides

Chlorhexidine, digluconate, alexidine dihydrochloride, octenidine dihydrochloride

This type of component, specifically CHX, is most frequently and extensively used because it achieves the best outcomes. CHX exhibits an optimal anti-plaque effect and has been studied for over half a century since the 1960s[59]. CHX is most commonly used in mouth rinses at a concentration of 0.1%–0.2%. A study reported that the optimal active concentration of CHX is [18–20] mg daily; therefore, the ideal clinical applications is three times per day at a dosage of 5–6 mg. A higher dose does not produce superior results but does increase side effects[60]. To achieve a 20-mg dosage with a 0.2% mouth rinse, using 10 mL of mouth rinse for 30 s is recommended, whereas using 15 mL of mouth rinse for 60 s is suggested for a 0.12% mouth rinse. CHX is active against Gram-positive and Gram-negative bacteria, yeasts, and viruses, including human immunodeficiency

virus and hepatitis B virus[61]. The mechanisms of action are as follows:

(1) Antimicrobial effect: At low concentrations, CHX increases the permeability of plasma membranes, achieving a bacteriostatic effect[62,63]. At high concentrations, CHX causes protein precipitation, thereby achieving a bactericidal effect. CHX not only acts on the surface of biofilms, but it can also penetrate these biofilms, extending its reach to kill or inhibit microbial growth[64,65].

(2) Inhibition of dental plaque: CHX molecules adhere to the tooth surface, subsequently interfering with bacterial adhesion. CHX also interacts with glycoproteins in the saliva to reduce the formation of salivary pellicles. CHX affects the activity of bacterial enzymes, such as glucan synthetase[66].

(3) Persistence: CHX molecules adhere to oral tissues, slowly and effectively providing a persistent antimicrobial environment (for up to 12 h) [67].

Regarding efficacy assessment, CHX as a component of dentifrice or mouth rinses has been assessed in 6-month clinical studies. The biggest problem with CHX-containing dentifrice is that the active ingredient is often deactivated by other components (e.g., stain-removing ingredients in toothpastes such, as SLS). CHX most commonly exists in mouth rinses at concentrations of 0.12% and 0.2%, both of which have demonstrated statistically significant anti-plaque and anti-inflammatory effects in 6-month clinical studies[68–73]. In systematic literature reviews and comprehensive analyses, CHX at 0.12% and 0.2% has exhibited nonsignificant differences in clinical efficacy[74].

CHX may cause side effects such as staining[75], increased calculus formation[76], change in taste quality[77], hypersensitivity[78], mucosal erosion[79], parotid gland swelling[75], and hearing impairment in the middle ear[80]. An in vitro study reported that CHX may influence wound healing because it affects fibroblast formation, although this side effect has not been proven in clinical studies[81].

Quaternary Ammonium Compounds

Benzylconium chloride, cetylpyridinium chloride

The mechanism of action of quaternary ammonium compounds (QAC) is as follows. The hydrophilic part of the molecule interacts with the bacterial cell membrane, causing the loss of cell components, interfering with cell metabolism and inhibiting cell growth, eventually leading to cell death[82]. This monocationic agent can quickly adhere to the oral surface, but it can also be easily desorbed, causing deactivation or neutralization of its structure. QACs have 3 to 5 h of persistence. The safe concentration of QAC is 0.045%–0.1%. Six-month clinical studies have reported a significant reduction in dental plaque and gingivitis[40,84].

Hexetidine

Hexetidine is a derivative of pyrimidine. It exhibits antimicrobial properties against Gram positive and Gram negative bacteria and yeast, but it cannot exist in the oral cavity for a long period. Therefore, the persistence of this compound in resisting microbial organisms is questionable[85]. An in vitro study revealed that hexetidine is bactericidal in the presence of biofilms. However, the reliability of this effect must be verified in clinical studies[86].

Future Approaches

Molecular Signaling

Dental plaque accumulates in a structural manner; therefore, signaling molecules play a crucial role throughout the process of dental plaque formation. Future studies can include inhibitors that reduce quorum-sensing processes, which may effectively reduce the pathogenicity[26].

Probiotics

Use of probiotics (e.g., Streptococcus salivaris, Lactobacillus reuteri, L. salivarius) may influence biofilm composition. For example, probiotics may compete with pathogenic bacteria or influence these bacteria through bacteriocin. A study reported that probiotics can effectively reduce pathogens, plaque formation, and gingivitis[88].

Inhibition of Transcription Genes

Formation of biofilms may be effectively inhibited if the sequence of activated or suppressed genes during biofilm formation can be identified and selected[26].

Chemical Plaque Control Around Natural Dentition: Current Evidence

Regarding the effectiveness of chemical plaque control, scientific studies have unanimously agreed that the safety and side effects chemical substances for plaque control must be verified in long-term, home-based, randomized clinical studies. Randomized clinical trials must be (1) double blind, (2) controlled, (3) at least 6 months

in duration, and (4) they must involve microbial analysis, in which (5) the microbial samples and clinical index to be tested are measured from start to end, including the mid-point of the trial (generally 3 months)[89,90].

The quality of clinical studies is also considered when assessing chemical control agents to determine whether the selected samples are representative and that homogeneity exists among different systematic analysis studies. To be recognized by the American Dental Association and the U.S. Food and Drug Administration, chemical substances must comply with at least two criteria to be verified as reliable anti-plaque control agent[s92].

Tables 1 and 2 summarize the meta-analyses of systematic reviews of clinical efficacy assessment of chemical plaque control agents published since 2004[40,41,57,74,84,93–98]. In 2015, Van der Weijden et al.[21] indicated in their review study that strong evidence (three systematic reviews) supports the high clinical efficacy of CHX and EO in controlling plaque formation and gingivitis. Strong evidence also supports the moderate clinical efficacy of CPC in resisting the formation of dental plaque and gingivitis, whereas only moderate evidence is available to substantiate the efficacy of triclosan as a mouth rinse agent, and only weak evidence has been obtained to support the clinical efficacy of hexetidine, oxygenating agent, and stannous fluoride.

Chemical Plaque Control Around Dental Implants: Current Evidence

Chemical control of dental plaques around dental implants and treatment of peri-implant mucositis or peri-implantitis remain a subject of dispute. Lang et al.[100] collectively proposed the cumulative interceptive supportive therapy (CIST) diagnosis and treatment guideline, which mentions the use of CHX in treating peri-implant mucositis. However, other studies have revealed that use of CHX gel or local irrigation with CHX is equally effective as mechanical debridement. Regarding treatment of peri-implantitis, evidences indicate the limited efficacy of combined used of CHX99. When accessing plaque control with different toothpastes, triclosan-containing dentifrice showed better effects on reduction of bleeding and gingivitis around dental implants compared with sodium fluoride toothpaste in a six-month assessment[35]. However, this finding was based on a six-month comparison of maintenance recall visits to prevent disease formation; the article did not mention the therapeutic effects of the tooth pastes on peri-implant mucositis or peri-implantitis. Regarding home-based CHX or EO-containing mouth rinse or CHX irrigation and gel products[36–39], some authors suggested that combined use of chemical agents and mechanical debridement is beneficial for reduction of plaque formation; however, majority of these studies did not have control group of mechanical plaque control alone as the base assessment and therefore could not draw a valid conclusion. In a two-year observational study, use of 0.12% CHX mouth rinse twice a day did not exhibit significant difference in implant related clinical parameters and success rate[38].

Conclusion

Chemical plaque control agents have proven effective in controlling plaque formation and reducing gingivitis, with the strongest and most complete evidence obtained for CHX and EO, as well as triclosan in terms of dentifrice agents. When selecting chemical substances, it is necessary to consider the inability of chemical control agents to completely replace mechanical plaque cleaning and the potential side effects of long-term use. Clinicians should carefully assess the advantages and disadvantages of each substance and provide patients with careful instructions before prescribing them. For patients who cannot perform mechanical oral hygiene practices effectively (e.g., patients with physical/mental disabilities or those who have undergone surgery), the benefits of chemical plaque control agents outweigh the potential side effects; however, for the general public, dosage must be controlled for long-term use, and the potential side effects must be considered. Regarding plaque control around implants, the current evidence suggests that the mechanical method is the most crucial approach to reduce plaque. The effects of chemical agents remain unknown. More long-term clinical studies are needed to verify the safety and efficacy of chemical plaque control agents, thereby providing physicians and patients with more options to prevent and treat oral and peri-implant diseases.

中文摘要

口腔健康的維護是十分重要的，我們的齒列不僅在咀嚼、發音及美觀上扮演重要角色，口腔疾病和全身疾病的關連性也是被醫學界日益重視的研究焦點。目前科學證據上已知口腔內存在許多細菌，某些特定菌也是造成各種口腔疾病最主要

的病因；而有效的牙菌斑控制是預防及治療口腔疾病最基本也是最重要的方法。除了機械式工具達成的牙菌斑控制已被證實為有效控制牙菌斑的方法之外，化學性的牙菌斑控制在使用上也是越來越頻繁，產品也越來越多樣化。此篇文章回顧化學性牙菌斑控制之相關重要文獻，重點於闡述其作用機轉、投遞時可使用的形式與介質，並且包含不同化學性製劑的詳細介紹以及目前與化學性牙菌斑控制劑相關及可知的證據與分析。另外有鑒於人工植牙的日益發展，此篇文章易回顧在植體周圍化學性牙菌斑控制之現階段證據。

References

1. Löe H, Theilade E, Jensen SB. Experimental gingivitis in man. *J Periodontol* 1965;36: 177-187.
2. Socransky SS, Haffajee AD, Cugini MA, Smith C, Kent RL Jr. Microbial complexes in subgingival plaque. *J Clin Periodontol* 1998;25:134-144.
3. Shulman LB, Driskell TD. Dental Implants: A Historical Perspective. In "Implants in Dentistry" Block M, Kent J, Guerra L eds, Philadelphia: W.B. Saunders; 1997:6.
4. Lindhe J, Meyle J. Peri-implant diseases: Consensus Report of the Sixth European Workshop on Periodontology. *J Clin Periodontol* 2008;35:282-285.
5. van der Weijden F, Slot DE. Oral hygiene in the prevention of periodontal diseases: the evidence. *Periodontol 2000* 2011;55:104-123.
6. van der Weijden GA, Hioe KP. A systematic review of the effectiveness of self-performed mechanical plaque removal in adults with gingivitis using a manual toothbrush. *J Clin Periodontol* 2005;32:214-228.
7. van der Weijden GA, Timmerman MF, Danser MM, van der Velden U. The role of electric toothbrushes: Advantages and limitations. In: "Proceedings of the European Workshop on Mechanical Plaque Control" Lang NP, Attström R, Löe H eds, London: Quintessence; 1998:138-155.
8. Beals D, Ngo T, Feng Y, Cook D, Grau DG, Weber DA. Development and laboratory evaluation of a new toothbrush with a novel brush head design. *Am J Dent* 2000;13:5-14.
9. Ronis DL, Lang WP, Farghaly MM, Ekdahl SM. Preventive oral health behaviors among Detroit area residents. *J Dent Hyg* 1994;68:123-130.
10. Stewart JE, Strack S, Graves P. Development of oral hygiene self-efficacy and outcome expectancy questionnaires. *Community Dent Oral Epidemiol* 1997;25:337-342.
11. Quirynen M, Bollen CM, Vandekerckhove BN, Dekeyser C, Papaioannou W, Eyssen H. Full- vs. partial-mouth disinfection in the treatment of periodontal infections: short-term clinical and microbiological observations. *J Dental Res* 1995;74:1459-1467.
12. Greenstein G. Full-mouth therapy versus individual quadrant root planing: a critical commentary. *J Periodontol* 2002;73:797- 812.
13. Greenstein G. Efficacy of full-mouth disinfection vs quadrant root planing. *Compend Contin Educ Dent* 2004:25:380-388.
14. FDI Commission. Mouth rinses and dental caries. *Int Dent J* 2002;52:337-345.
15. FDI Commission. Mouth rinses and periodontal disease. *Int Dent J* 2002;52:346-352.
16. Netuschil L, Weiger R, Preisler R, Brecx MC. Plaque bacteria counts and vitality during chlorhexidine, meridol and Listerine mouthrinses. *Eur J Oral Sci* 1995;103:355-361.
17. Pan PH, Finnegan MB, Sturdivant L, Barnett ML. Comparative antimicrobial activity of an essential oil and an amine fluoride/stannous fluoride mouthrinse in vitro. *J Clin Periodontol* 1999;26:474-476.
18. Pan PH, Barnett ML, Coelho J, Brogdon C, Finnegan MB. Determination of the in situ bactericidal activity of an essential oil mouthrinse using a vital stain method. *J Clin Periodontol* 2000;27:256-261.
19. Fine DH, Furgang D, Barnett ML. Comparative anti-microbial activities of antiseptic mouthrinses against isogenic planktonic and biofilm forms of Actinobacillus actinomycetemcomitans. *J Clin Periodontol* 2001;28:697-700.
20. Addy M, Renton-Harper P. Local and systemic chemotherapy in the management of periodontal disease: an opinion and review of the concept. *J Oral Rehabil* 1996;23: 219-231.
21. van der Weijden FA, van der Sluijs E, Ciancio SG, Slot DE. Can chemical mouthwash agents achieve plaque/gingivitis control? *Dent Clin N Am* 2015;59:799-829.

22. Ciancio SG. Alcohol in mouthrinse: lack of association with cancer. *Biol Ther Dent* 1993;9:1-2.
23. La Vecchia C. Mouthwash and oral cancer risk: An update. *Oral Oncol* 2009;45:198-200.
24. van Winkelhoff AJ, Herrera GD, Winkel EG, Dellemijm-Kippuw N, Vandenbroucke-Grauls CM, Sanz M. Antimicrobial resistance in the subgingival microflora in patients with adult periodontitis. A comparison between The Netherlands and Spain. *J Clin Periodontol* 2000;27:79-86.
25. Johansen C, Falholt P, Gram L. Enzymatic removal and disinfection of bacterial biofilms. *Appl Environ Microbiol* 1997;63:3724-3728.
26. Donlan RM, Costerton JW. Biofilms: Survival mechanisms of clinically relevant microorganisms. *Clin Microbiol Rev* 2002;15:167-193.
27. Kirstila V, Lenander-Lumikari M, Tenovuo J. Effects of a lactoperoxidase-system-containing toothpaste on dental plaque and whole saliva in vivo. *Acta Odontol Scand* 1994;52:346-353.
28. Moran J, Addy M, Newcombe R. Comparison of the effect of toothpastes containing enzymes or antimicrobial compounds with a conventional fluoride toothpaste on the development of plaque and gingivitis. *J Clin Periodontol* 1989;16:295-299.
29. Addy M, Moran J, Newcombe RG. Meta-analyses of studies of 0.2% delmopinol mouth rinse as an adjunct to gingival health and plaque control measures. *J Clin Periodontol* 2007;34:58-65.
30. Moran J, Addy M, Newcombe RG. The antibacterial effect of toothpastes on the salivary flora. *J Clin Periodontol* 1988;15:193-199.
31. Moran J, Addy M, Wade WG, Milson S. The effect of oxidising mouthrinses compared with chlorhexidine on salivary bacterial counts and plaque regrowth. *J Clin Periodontol* 1995;22:750-755.
32. Hossainian N, Slot DE, Afennich F, van der Weijden GA. The effects of hydrogen peroxide mouthwashes on the prevention of plaque and gingival inflammation: a systematic review. *Int J Dent Hyg* 2011;9:171-181.
33. Rees TD, Orth CF. Oral ulcerations with use of hydrogen peroxide. *J Periodontol* 1986;57:689-692.
34. Herrera D, Serrano J. Chemical Oral and Dental Biofilm Control. In "Clinical periodontology and implant dentistry" 6th ed, Lang NP, Lindhe J. Oxford: Blackwell Munksgaard; 2015:724.
35. Sreenivasan PK, Vered Y, Zini A, et al. A 6-month study of the effects of 0.3% triclosan/copolymer dentifrice on dental implants. *J Clin Periodontol* 2011;38:33-42.
36. Ciancio SG, Lauciello F, Shibly O, Vitello M, Mather ML. The effect of an antiseptic mouthrinse on implant maintenance: plaque and peri-implant gingival tissues. *J Periodontol* 1995;66:962-965.
37. Felo A, Shibly O, Ciancio SG, Lauciello FR, Ho A. Effects of sub-gingival chlorhexidine irrigation on peri-implant maintenance. *Am J Dent* 1997;10:107-110.
38. Truhlar RS, Morris HF, Ochi S. The efficacy of a counter-rotational powered toothbrush in the maintenance of endosseous dental implants. *J Am Dent Assoc* 2000;131**:**101-107.
39. De Siena F, Francetti L, Corbella S, Taschieri S, Del Fabbro M. Topical application of 1% chlorhexidine gel versus 0.2% mouthwash in the treatment of peri-implant mucositis. An observational study. *Int J Dent Hyg* 2013;11:41-47.
40. Gunsolley JC. A meta-analysis of six-month studies of antiplaque and antigingivitis agents. *J Am Dent Assoc* 2006;137**:**1649-1657.
41. Paraskevas S, van der Weijden GA. A review of the effects of stannous fluoride on gingivitis. *J Clin Periodontol* 2006;33:1-13.
42. Fine DH, Letizia J, Mandel ID. The effect of rinsing with Listerine antiseptic on the properties of developing plaque. *J Clin Periodontol* 1985;12:660-666.
43. Sekino S, Ramberg P. The effect of a mouth rinse containing phenolic compounds on plaque formation and developing gingivitis. *J Clin Periodontol* 2005;32:1083-1088.
44. Firatli E, Unal T, Onan U. Antioxidative activities of some chemotherapeutics: a possible mechanism of reducing inflammation. *J Clin Periodontol* 1994;21:680-683.
45. Blot WJ, Winn DM, Fraumeni JF Jr. Oral cancer and mouthwash. *J Natl Cancer Inst* 1983;70:251-253.
46. Arweiler NB, Auschill TM, Baguley N, Netuschil L, Sculean A. Efficacy of an amine fluoride-triclosan mouthrinse as compared to the individual active ingredients. *J Clin Periodontol* 2003;30:192-196.
47. Jenkins S, Addy M, Newcombe

RG. Triclosan and sodium lauryl suphate mouthrinses. I. Effects on salivary bacterial counts. *J Clin Periodontol* 1991;18:140-144.

48. Gilbert RJ, Williams PE. The oral retention and anti-plaque efficacy of triclosan in human volunteers. *Br J Clin Pharmacol* 1987;23:579-583.
49. Gaffar A, Scherl D, Afflitto J, Coleman EJ. The effect of triclosan on mediators of gingival inflammation. *J Clin Periodontol* 1995;22:480-484.
50. Dinwiddie MT, Terry PD, Chen J. Recent Evidence Regarding Triclosan and Cancer Risk. *Int J Environ Res Public Health* 2014;11:2209-2217.
51. Stephen KW, Saxton CA, Jones CL, Ritchie JA, Morrison T. Control of gingivitis and calculus by a dentifrice containing a zinc salt and triclosan. *J Periodontol* 1990;61:674-679.
52. Svatun B, Saxton CA, Rolla G. Six-month study of the effect of a dentifrice containing zinc citrate and triclosan on plaque, gingival health, and calculus. *Scand J Dent Res* 1990; 98:301-304.
53. Svatun B, Sadxton CA, Huntington E, Cummins D. The effects of three silica dentifrices containing Triclosan on supragingival plaque and calculus formation and on gingivitis. *Int Dent J* 1993;43:441-452.
54. Svatun B, Sadxton CA, Huntington E, Cummins D. The effects of a silica dentifrice containing Triclosan and zinc citrate on supragingival plaque and calculus formation and the control of gingivitis. *Int Dent J* 1993;43:431-439.
55. Palomo F, Wantland L, Sanchez A, Volpe AR, McCool J, DeVizio W. The effect of three commercially available dentifrices containing triclosan on supragingival plaque formation and gingivitis: a six-month clinical study. *Int Dent J* 1994;44:75-81.
56. Renvert S, Birkhed D. Comparison between 3 triclosan dentifrices on plaque, gingivitis and salivary microflora. *J Clin Periodontol* 1995;22:63-70.
57. Hioe KP, van der Weijden GA. The effectiveness of self-performed mechanical plaque control with triclosan-containing dentifrices. *Int J Dent Hyg* 2005;3:192-204.
58. Rule KL, Ebbett VR, Vikesland PJ. Formation of chloroform and chlorinated organics by free-chlorine-mediated oxidation of triclosan. *Environ Sci Technol* 2005;39:3176-3185.
59. Schroeder HE. Formation and Inhibition of Dental Calculus. Huber H ed, Berlin; 1969:145-172.
60. Cancro LP, Paulovich DB, Bolton S, Picozzi A. Dose response of chlorhexidine gluconate in a model in vivo plaque system. *J Dent Res* 1974;53:765.
61. Wade WG, Addy M. In vitro activity of a chlorhexidine-containing mouthwash against subgingival bacteria. *J Periodontol* 1989;60:521-525.
62. Hugo WB, Longworth AR. Some aspects of the mode of action of chlorhexidine. *J Pharm Pharmacol* 1964;16:655-662.
63. Hugo WB, Longworth AR. Cytological aspects of the mode of action of chlorhexidine diacetate. *J Pharm Pharmacol* 1965;17:28-32.
64. Arweiler NB, Netuschil L, Reich E. Alcohol-free mouthrinse solutions to reduce supragingival plaque regrowth and vitality. A controlled clinical study. *J Clin Periodontol* 2001;28:168-174.
65. Shapiro S, Giertsen E, Guggenheim B. An in vitro oral biofilm model for comparing the efficacy of antimicrobial mouthrinses. *Caries Res* 2002;36:93-100.
66. Vacca-Smith A, Bowen WH. Effects of some anti-plaque agents on the activity of glucosyltranferases of Streptococcus mutans adsorbed onto saliva-coated hydroxyapatite and in solution. *Biofilm J* 1996;1:1360-1365.
67. Schiøtt CR, Löe H, Jensen SB, Kilian M, Davies RM, Glavind K. The effect of chlorhexidine mouthrinses on the human oral flora. *J Periodontal Res* 1970;5:84-89.
68. Sanz M, Vallcorba N, Fabregues S, Muller I, Herkstroter F. The effect of a dentifrice containing chlorhexidine and zinc on plaque, gingivitis, calculus and tooth staining. *J Clin Periodontol* 1994;21:431-437.
69. Flemmig TF, Newman MG, Doherty FM, Grossman E, Meckel AH, Bakdash MB. Supragingival irrigation with 0.06% chlorhexidine in naturally occurring gingivitis. I. Six-month clinical observations. *J Periodontol* 1990;61:112-117.
70. Overholser CD, Meiller TF, DePaola LG, Minah GE, Niehaus C. Comparative effects of 2 chemotherapeutic mouthrinses on

the development of supragingival dental plaque and gingivitis. *J Clin Periodontol* 1990;17:575–579.

71. Hase JC, Attström R, Edwardsson S, Kelty E, Kisch, J. Six-month use of 0.2% delmopinol hydrochloride in comparison with 0.2% chlorhexidine digluconate and placebo. (I). Effect on plaque formation and gingivitis. *J Clin Periodontol* 1998;25: 746-753.
72. Lang NP, Hase JC, Grassi M, Hammerle CH, Weigel C, Kelty E, Frutig F. Plaque formation and gingivitis after supervised mouthrinsing with 0.2% delmopinol hydrochloride, 0.2% chlorhexidine digluconate and placebo for 6 months. *Oral Dis* 1998; 4:105-113.
73. Charles CH, Mostler KM, Bartels LL, Mankodi SM. Comparative antiplaque and antigingivitis effectiveness of a chlorhexidine and an essential oil mouthrinse: 6-month clinical trial. *J Clin Periodontol* 2004;31:878-884.
74. Berchier CE, Slot DE, van der Weijden GA. The efficacy of 0.12% chlorhexidine mouthrinse compared with 0.2% on plaque accumulation and periodontal parameters: a systematic review. *J Clin Periodontol* 2010;37:829-839.
75. Fløtra L, Gjermo P, Rølla G, Wærhaug J. Side effects of chlorhexidine mouth washes. *Scand J Dent Res* 1971;79:119-125.
76. Yates R, Jenkins S, Newcombe RG, Wade W, Moran J, Addy M. A 6-month home usage trial of a 1% chlorhexidine toothpaste (1). Effects on plaque, gingivitis, calculus and tooth staining. *J Clin Periodontol* 1993;20:130-138.
77. Marinone MG, Savoldi E. Chlorhexidine and taste. Influence of mouthwashes concentration and of rinsing time. *Minerva Stomatol* 2000;49:221-226.
78. Beaudouin E, Kanny G, Morisset M, et al. Immediate hypersensitivity to chlorhexidine: literature review. *Eur Ann Allergy Clin Immunol* 2004;36:123-126.
79. Almqvist H, Luthman J. Gingival and mucosal reactions after intensive chlorhexidine gel treatment with or without oral hygiene measures. *Scand J Dent Res* 1988;96:557-560.
80. Aursnes J. Ototoxic effect of iodine disinfectants. *Acta Otolaryngol* 1982;93:219-226.
81. Sanz M, Newman MG, Anderson L, Matoska W, Otomo-Corgel J, Saltini C. Clinical enhancement of post-periodontal surgical therapy by a 0.12% chlorhexidine gluconate mouthrinse. *J Periodontol* 1989;60:570-576.
82. Merianos JJ. Quaternary ammonium antimicrobial compounds. In: Block SS ed. Disinfection, Sterilization and Preservation. Philadelphia: Lea & Febiger Co,; 1991:225-255.
83. Porras R, Anderson GB, Caffesse RG, Narendran S, Trejo PM. Clinical response to 2 different therapeutic regimens to treat peri-implant mucositis. *J Periodontol* 2002;73:1118- 1125.
84. Haps S, Slot DE, Berchier CE, van der Weijden GA. The effect of cetylpyridinium-chloride-containing mouth rinses as adjuncts to toothbrushing on plaque and parameters of gingival inflammation: a systematic review. *Int J Dent Hyg* 2008;6:290-303.
85. Jones DS, McGovern JG, Woolfson AD, Gorman SP. The effects of hexetidine (Oraldene) on the adherence of Candida albicans to human buccal epithelial cells in vitro and ex vivo and on in vitro morphogenesis. *Pharm Res* 1997;14:1765-1771.
86. McCoy CP, Jones DS, McGovern JG, Gorman SP, Woolfson AD. Determination of the salivary retention of hexetidine in vivo by high-performance liquid chromatography. *J Pharm Pharmacol* 2000;52:1355-1359.
87. Heitz-Mayfield LJ, Salvi GE, Botticelli D, Mombelli A, Faddy M, Lang NP. Anti-infective treatment of peri-implant mucositis: a randomised controlled clinical trial. *Clin Oral Implants Res* 2011;22:237-241.
88. Teughels W, Loozen G, Quirynen M. Do probiotics offer opportunities to manipulate the periodontal oral microbiota? *J Clin Periodontol* 2011;38:159-177.
89. Council of Dental Therapeutics. Guidelines for acceptance of chemotherapeutic products for the control of supragingival dental plaque and gingivitis. *J Am Dent Assoc* 1986;112:529-532.
90. Overholser CD. Longitudinal clinical studies with antimicrobial mouthrinses. *J Clin Periodontol* 1988;15:517-519.
91. Thone-Muhling M, Swierkot K, Nonnenmacher C, Mutters R, Flores-de-Jacoby L, Mengel R. Comparison of two full-mouth approaches in the treatment of

peri-implant mucositis: a pilot study. *Clin Oral Implants Res* 2010;21:504-512.

92. Koch GG, Paquette DW. Design principles and statistical considerations in periodontal clinical trials. *Ann Periodontol* 1997;2:42-63.
93. van Strydonck DA, Slot DE, van der Velden U, van der Weijden F. Effect of a chlorhexidine mouthrinse on plaque, gingival inflammation and staining in gingivitis patients: a systematic review. *J Clin Periodontol* 2012;39:1042-1055.
94. Serrano J, Escribano M, Rolda´n S, Martin C, Herrera D. Efficacy of adjunctive anti-plaque chemical agents in managing gingivitis: a systematic review and meta-analysis. *J Clin Periodontol* 2015;42:S106–138.
95. Stoeken JE, Paraskevas S, van der Weijden GA. The long-term effect of a mouthrinse containing essential oils on dental plaque and gingivitis: a systematic review. *J Periodontol* 2007;78:1218-1228.
96. Addy M, Moran J, Newcombe RG. Meta-analyses of studies of 0.2% delmopinol mouth rinse as an adjunct to gingival health and plaque control measures. *J Clin Periodontol* 2007;34:58-65.
97. Davies RM, Ellwood RP, Davies GM. The effectiveness of a toothpaste containing triclosan and polyvinyl-methyl ether maleic acid copolymer in improving plaque control and gingival health: a systematic review. *J Clin Periodontol* 2004;3:1029-1033.
98. van Leeuwen MP, Slot DE, van der Weijden GA. Essential oils compared to chlorhexidine with respect to plaque and parameters of gingival inflammation: a systematic review. *J Periodontol* 2011;82:174-194.
99. Renvert S, Roos-Jansaker AM, Claffey N. Non-surgical treatment of peri-implant mucositis and peri-implantitis: a literature review. *J Clin Periodontol* 2008;35:305-315.
100. Lang NP, Berglundh T, Heitz-Mayfield LJ, Pjetursson BE, Salvi GE, Sanz M. Consensus statements and recommended clinical procedures regarding implant survival and complications. *Int J Oral Maxillofac Implants* 2004;19:150-154.