Nutrition

Food Ingredients Promoting Oral Health
Guest Editor: Stefan Zimmer

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Since the oral cavity is the entrance for food and the commencement of the digestive tract, it is obvious that there is some local interaction between food consumption and the status of oral tissues. In modern nutrition, the most important influence of food on oral health is the metabolism of fermentable carbohydrates to organic acids by acidogenic bacteria, which are organized in oral biofilms at the tooth surface. These acids dissolve the inorganic components of enamel and dentine, and if the healing potential of saliva is overstrained, dental caries is the consequence. This happens if fermentable carbohydrates are consumed too frequently. Consequently, caries could potentially be prevented by a reduction in the frequency of sugar intake. However, from a public health perspective, this has been shown to be a more theoretical possibility than a practical option. On the other hand, specific food ingredients/constituents can substantially contribute to healthy teeth since they can be delivered simultaneously or replace the harmful agent. As an example, fluoride-containing table salt has been proven to be an effective public health measure and has contributed to the considerable caries decline in Switzerland and Germany. Not only fluoride but also other substances influencing the balance of de- and remineralization of dental hard tissues as well as non-fermentable carbohydrates or substances affecting the composition of the oral microflora or the adherence of cariogenic microorganisms are options in caries prevention. In contrast to oral hygiene measures and preventive programmes offered in the dental office, they have the potential to reach the whole population.

Another food-related disease affecting oral hard tissues is dental erosion. It is also a consequence of the misbalance of de- and remineralization at the tooth surface, but in contrast to caries without involving microorganisms. Dental erosions are developing by the direct detrimental effect of dietary acids such as citric or phosphoric acid. Since the usage of these acids in foods and drinks is considerably increasing within the last decade, the incidence of dental erosions is rising as well in developed countries. This becomes a noteworthy challenge to the dental profession. Due to the fact that both diseases, dental caries and erosion, can be positively influenced by measures reducing demineralization and promoting remineralization of enamel and dentine and that this can be provided by certain food ingredients, there is a large research field for functional food, and some scientific findings have already found their way into daily practice.

In contrast to caries and erosion, the aetiology of other diseases affecting the oral cavity is hardly locally influenced by food properties. However, diseases of the oral mucosa can be positively and negatively influenced by food characteristics. For example, dry mouth can be alleviated by chewing fibrous or acidic food, both stimulating saliva flow. But since acidic food may cause dental erosions, it can only be recommended if the patient has no natural teeth in his mouth. This example makes clear that diet counselling with the perspective of diseases of the oral mucosa is not a public health topic, but belongs to the individualized consultation in the dental office.

The last interaction between food and oral health, which is discussed in the present supplement of the European Journal of Nutrition, is dealing with the periodontium. Inflammatory periodontal diseases are the second most
prevalent disease of the oral cavity and are the number one reason of tooth loss in the second half of life. Apart from severe malnutrition like scurvy, which is no longer prevalent in developed countries, periodontitis is not caused by food habits. In fact, there is a strong relationship between the presence of specific bacteria and periodontitis. On the other hand, nutritional components could locally act against these bacteria and potentially prevent or slacken the development of periodontitis. Some food components and probiotics have shown some activity against periodontal pathogens, but there is still a long way of research to go until clinically relevant results may come up.

In conclusion, food plays an important role in oral health, both in causing and preventing oral diseases. The current status of knowledge in this field is summarized by excellent scientists in the present supplement of the European Journal of Nutrition.
The health of oral tissues and organs are, more or less, inevitably related to the chemical, physical and physiological properties of foods and diets. It is recognized that various dietary components may impair oral health; for example, a high frequency of consumption of fermentable carbohydrates such as sugars and starches are considered a risk factor for dental caries when a frequent intake is associated with low oral hygiene. Food acids (phosphoric and citric acid, to name a few) are risk factors for dental erosion.

Already several decades ago, research aimed to identify the role of non-fermentable bulk sweeteners such as polyols in the prevention of dental caries. The tooth-friendliness of polyols, such as erythritol, isomalt, lactitol, mannitol, sorbitol and xylitol, has meanwhile been well established and has led to sugar-free confectionary and chewing gums in which they replace fermentable ingredients.

More recent interests have been focussed on the active potential of foods and diets on oral health and disease prevention. This has led to the development of foods and beverages with ‘functional ingredients’ that provide added benefit to certain oral health conditions or may help to prevent the development or progression of impaired and disease states.

Both passive and active roles of certain functional ingredients on specific oral health functions have been recognized by the European Food Safety Authority in their positive assessments on the role of sugar-free chewing gums on plaque acid neutralization, maintenance and reduction in tooth demineralisation and reduction in oral dryness. The EFSA also acknowledged the role of these markers to reduce the risk of tooth decay and dental caries.

The purpose of this review is to provide a more extensive and intensive information on the variety of types of functional foodstuffs and drinks, and dietary supplements with perspective on oral aspects. Their effect on various oral health conditions and diseases are summarized, respectively; their characteristic targets and the practical release methodology are assessed; and the possible functional mechanisms are discussed.

Part 1 focuses on whether the prevention of dental caries could benefit substantially from the regular diets or functional supplements. It encapsulates a variety of foodstuffs and beverages, food constituents and functional supplements, for example, trace elements, fruits, plant extracts, food preservatives, as well as the addition of bio-active peptides and probiotic.

Part 2 deals with periodontal disease. The evidence for the beneficial contribution of the diets to the prevention of periodontal problems seems scant, despite wealthy information indicating the relationship between nutrition deficiency and periodontitis. A quite limited numbers of studies on the ‘topical protective effect’ of antioxidants, tea, polyphenols, probiotics and dairy products on periodontal diseases are included, and obviously more scientific evidence is essential.

Part 3 is about the major mucosal disease, for example, yeast and viral infections, oral lichen planus and aphthous stomatitis, and non-specific symptoms of mouth mucosa, for example, xerostomia, burning syndrome and glossodynia, and halitosis. In theory, all these mucosal diseases and symptoms can be modified by selecting healthy
nutrients and by avoiding foodstuffs or beverages that irritate mucosal surfaces. Practically, it should be made aware that the individual-dependent risk factors and the unidentified etiology for some mucosal problems make many strategies principle rather than practical.

The last part is about dental erosion, which is highly associated with the consumption of acidic foods and drinks. Through comprehensively analyzing the etiology of erosion, it is manifest that the dietary modification and the supplementation of functional ingredients are practical and promising strategies for preventing erosive tooth wear. A vast literature is introduced to explore the effect of different physical, for example, adhesive abilities and displacement abilities, and chemical properties, for example, pH, buffering capacity and degree of saturation with respect to tooth mineral, on the erosive potential of foods and beverages.

To conclude, this report compiles and highlights the potential of functional food ingredients on oral and dental health for future research and development.

Acknowledgments. This publication was commissioned by the Functional Foods Task Force of the European branch of the International Life Sciences Institute (ILSI Europe). Industry members of the task force are Abbott Nutrition, Barilla G. & R. Fratelli, BASF, Bionov, Biosearch Life, Cargill, Chiquita Brands International, Coca-Cola Europe, Danone, Dow Europe, DSM, DuPont Nutrition & Health, Institut Merieux, International Nutrition Company, Kellogg Europe, Kraft Foods Europe, Mars, Martek Biosciences Corporation, McNeil Nutritional, Naturex, Nestlé, PepsiCo International, Pfizer Consumer Healthcare, Red Bull, Rudolf Wild, Schwabegroup, Royal FrieslandCampina, Soremartec Italia—Ferrero Group, Südzucker/BENEÖ Group, Tate & Lyle Ingredients, Tereos-Syr al, Unilever and Yakult Europe. This publication was coordinated by Dr. Alessandro Chiodini, Scientific Project Manager at ILSI Europe. For further information about ILSI Europe, please email info@ilsieurope.be or call +32 2 771 00 14. The opinions expressed herein and the conclusions of this publication are those of the authors and do not necessarily represent the views of ILSI Europe nor those of its member companies.

Declaration of interest X. Wang and A. Lussi received a honorarium from ILSI Europe for their participation in this publication and reimbursement of their travel and accommodation costs for attending the related meetings.
Introduction

In dentistry, there is a well-established practice of fluoridating water, salt and milk for the prevention of dental caries. The use of other foods to promote oral health is another step in the same direction, and the development of research into adding therapeutic benefit to food is welcome. As the mouth is at the beginning of the gastrointestinal tract, the potential to capture oral health benefits from the emerging developments in functional foods is considerable. This chapter will consider whether the prevention of dental caries could benefit substantially from the development of functional foods. ‘Functional Foods’ are foods or foods with components that may provide a health benefit beyond basic nutrition. Examples can include fruits and vegetables, whole grains, fortified or enhanced foods and beverages, and some dietary supplements. Functional attributes of many traditional foods are being discovered, while new food products are being developed with beneficial components. This chapter will present an overview of the possible role of functional foods in caries prevention.

Caries process

Tooth, plaque and substrate (diet) are the three prerequisites for a caries lesion to develop as first postulated by Keyes [37] (see the inner three circles in Fig. 1). Teeth may vary in susceptibility to caries according to composition, morphology, location and position, which may promote plaque retention. The greater the tooth’s susceptibility to disease, the greater the chance that caries will occur, although it will not develop without the presence of both bacteria and substrate. The bacteria circle indicates the need for the presence of acidogenic species for caries to develop. Caries will not develop in the absence of bacteria. Streptococcus mutans, a Gram-positive acidophilic bacterium, is usually associated with the initiation of caries. In addition to producing lactic acid when it ferments dietary saccharides, S. mutans produces by glycosyl tranferase (GTF) activity extracellular glucans, which adhere to enamel, allowing the bacterium to colonise the smooth enamel surface. In addition to the extracellular sticky glucans, S. mutans produces also intracellular polysaccharides that can be splitted to acidic end products when sugar food is not present in the oral cavity. Other acid-producing microorganisms such as Lactobacillus species contribute to the caries process once the initial demineralisation has taken place and a niche for non-adhesive bacteria is created.

The key to the third circle is that microorganisms need substrate to produce acid. Monosaccharides, disaccharides and fermentable carbohydrates can be used for bacterial plaque metabolism. The fourth circle encompassing the other three signifies the importance of time, as caries takes time to develop and the importance of other modifying factors like quantity and quality of saliva, variation in the availability of the substrate and protective factors like the...
use of fluorides. The length of time the bacteria have access to substrate at the plaque enamel interface plays a major role in the progress of caries.

The tooth minerals, enamel, dentine and root cement consist of an inorganic component (approximately 86, 55 and 45 vol%, respectively), an organic component (approximately 4, 25 and 30 vol%, respectively) and water. The inorganic component is hydroxyapatite, \( \text{Ca}_{10}\text{PO}_4\text{(OH)}_2 \). The oral and dental plaque fluids contain calcium and phosphate ions, and it depends on the pH whether the environment of the tooth is saturated, under- or supersaturated with respect to the mineral. When the environment is undersaturated, demineralisation will occur, and when the environment is supersaturated, remineralisation will take place. The critical pH for tooth mineral to dissolve varies between pH 5.0–5.7. The pH in dental plaque, physiologically around pH 7, will drop after the intake of fermentable carbohydrates to around or just below the critical value. The pH drop will be counteracted by the clearing and buffering effect of saliva. Furthermore, saliva will bring minerals to the dental plaque. Because caries develops not too far below the point of saturation, it can be assumed that relatively small changes in either factor involved in the caries process may shift the circumstances from being demineralising to remineralising or the other way around. So it may be assumed that the addition of minerals increasing the degree of saturation is beneficial, it may be assumed that factors reducing the acid formation in dental plaque (e.g. antimicrobial agents) are beneficial, and it may be assumed that gustatory, mechanical and psychological stimulation of salivary flow can be beneficial. All these incentives could be incorporated in a food making a functional food (Table 1). It should thereby be realised that any induced change in the oral conditions will be counteracted by the oral homoeostasis.

**Methodology to assess the effect of functional food/active ingredients in dental caries control**

Food claims towards reducing cariogenicity can be tested in vitro, in animal experiments, in situ and in vivo. In vitro studies mainly comprise the effect of food ingredients on growth, acid production and adherence of oral bacteria or mixed cultures of oral bacteria either in suspension or in biofilm. It is however difficult to validly recreate intra-oral conditions with in vitro systems, and therefore, the predictive value for cariogenicity is low. In animal experiments (usually with the laboratory rat), the animals can be orally infected with oral human bacteria and the feeding can be programmed to simulate diet patterns. In order to score caries, the animals have to be killed. In many countries, there is a move away from the use of animals in research for regulatory purposes and consumer attitudes.

Relatively simple human studies are plaque pH measurements. There are three methods: the plaque sampling (post in vivo), the touch electrode and the interproximal telemetry method. Each of the three types of the methods can satisfactorily identify non-acidogenic foods when used properly with appropriate positive (10% sucrose) and negative (10% sorbitol) controls [45, 73]. It is important to realise that plaque pH methods can indicate acidogenic potential and only possibly the cariogenic potential of a product. If the plaque pH profile of a product is not

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**Table 1** Key targets of functional food in cariogenic attack and components of functional food

<table>
<thead>
<tr>
<th>Cariogenic bacteria (as such)</th>
<th>Probiotics, polyphenols and plant extracts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial adherence, co-aggregation, glycosyltransferase (GTF) activity</td>
<td>Sugar polyols, bioactive peptides, polyphenols</td>
</tr>
<tr>
<td>Bacterial fermentation of carbohydrates</td>
<td>Artificial sweeteners, sugar polyols</td>
</tr>
<tr>
<td>Saliva secretion, composition and buffering capacity</td>
<td>Chewing gum as such sugar polyols</td>
</tr>
<tr>
<td>Availability of calcium and fluorides</td>
<td>Dairy products, other mineral sources</td>
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statistically significantly different from that of the 10% sorbitol rinse, then the food can effectively be considered as non-cariogenic. When the plaque pH profile falls below that of sorbitol but not to pH 5.7, an in situ cariogenicity test is required to further study the foodstuff. As the critical pH is higher for dentine than for enamel, the level of safety ‘not below pH 5.7’ may not be safe for exposed roots comprising dentine and cementum. The ‘critical pH’ of dentine and cementum has yet to be preconceived.

In situ caries models involve the use of appliances or other devices that carries enamel or dentine samples and are worn intra-orally by participants [82]. The strength of these models is that all the multifactorial aspects of natural dental caries are generally included. Foods and beverages can be tested under clinically relevant conditions, and very sensitive laboratory methods can be applied to measure changes in mineral status of the tooth substrate.

Finally foods can be tested in clinical experiments including randomised controlled trials. Clinical studies with appropriate controls allow assessing local caries risk factors and clinical assessment of caries increment. Prospective clinical studies should continue at least 36 months in subjects of school age and at least 72 months in adult subjects.

Although there may be a substantial amount of research on a product and its health benefits, it may be difficult to compare in vitro and in vivo data across laboratories due to lack of standardised experimental procedures. Improvement in these aspects and the design of controlled clinical and multidisciplinary research studies is warranted.

**Micronutrients and trace elements**

During tooth formation, impurities may be incorporated in the tooth mineral making the mineral either more [e.g. incorporation of \((CO_3)^{2−}\) and \((HPO_4)^{2−}\)] or less (e.g. incorporation of \(F^{−}\)) soluble. The impurities that promote enamel solubility will be washed out during de- and remineralisation cycles, while impurities that reduce enamel solubility continue to be incorporated further increasing the resistance against the caries process. A comparison of the (trace) element concentration in caries-affected and healthy teeth suggests that caries associates lower concentrations of fluoride, zinc, iron, copper, nickel, selenium and strontium and higher concentrations of chromium, cobalt, lead and cadmium [22]. The caries reducing effect of fluoride is indisputable. Zinc compounds are added to oral hygiene products to prevent the mineralisation of calculus. There is, however, no indication that this application of zinc would interfere with remineralisation or would adversely affect the anticaries effects of fluoride [30]. The association of copper (\(Cu^{2+}\)) with lower caries prevalence has been reported by various authors [18, 19]. Also, the ability of \(Cu^{2+}\) to inhibit cariogenesis in animals has been documented [47, 71, 72]. \(Cu^{2+}\) co-crystallised with sugar during manufacturing reduces the cariogenic potential of sugar [71, 72]. The mechanism involved has been attributed to a combination of its antimicrobial effects and to its ability to inhibit demineralisation directly [8]. In situ evidence showed a beneficial effect on dental enamel in response to a cariogenic challenge of a combination of \(Cu^{2+}\) and amine fluoride [1]. For the other trace elements, there is no strong evidence to reduce cariogenicity when incorporated in food or oral hygiene products.

**Natural anticaries properties of (non-milk) food constituents and plant extracts**

Some fruits and plants of human nutrition (e.g. tea, cocoa, coffee and raisins) contain polyphenols as phenolic acids or flavonoids that may suppress by antioxidant activity oral pathogens associated with caries and are thus hypothesised to benefit oral health (Table 2). Further substances identified with antimicrobial activity against oral pathogens are oleanolic acid, oleanolic aldehyde, linoleic acid, linolenic acid, betulin, betulinic acid, 5-(hydroxymethyl)-2-furfural, rutin, beta-sitosterol and beta-sitosterol glucoside.

**Tea**

Tea is an aqueous infusion of dried leaves of the plant *Camellia sinensis* L. (family Theaceae). The chemical composition of tea is complex: polyphenols, catechins, caffeine, amino acids, carbohydrates, protein, chlorophyll, volatile compounds, fluoride, minerals and other undefined compounds [23]. Black tea has many more components than green tea, including bisflavanols, theaflavins, thearubigins, epiflavic acids, and thearubigins. The most interesting components of tea leaves, in relation to oral health, are epigallocatechin gallate, epicatechin gallate, epigallocatechin, epicatechin, galloatechin and (+)-catechins [23, 53]. These oxidised polyphenols are often collectively called tannins, which are chemically very different from the commercial tannic acid or the plant tannins [92]. It is estimated that a cup of green tea (2.5 g of green tea leaves/200 mL of water) may contain 90 mg of epigallocatechin gallate.

Specific pathogen-free rats infected with *S. mutans* and fed a cariogenic diet containing green tea polyphenols had significantly lower caries scores than control animals [63]. Drinking tea (without added sugar) has been associated with lower caries levels in humans [60, 61]. Although tea is also a source of fluoride, studies have demonstrated that tea
polyphenols rather than fluoride contributed to the anti-cariogenic potential [35, 96]. Several mechanisms have been proposed for the observed anticariogenic properties of teas. These include tea’s inhibitory effect on bacterial growth, bacterial viability, glycosyltransferase activity, adherence and salivary amylase activities [34, 50, 53, 94].

Cranberry

Cranberry components are potential anticaries agents since they inhibit acid production, attachment and biofilm formation by *S. mutans*. Glucan-binding proteins, extracellular enzymes, carbohydrate production and bacterial hydrophobicity are all affected by cranberry components.

It is often suggested that cranberry components, especially those with high molecular weight, could serve as bioactive molecules for the prevention and/or treatment of oral diseases [5]. After 42 days of using a mouthwash enriched with a high molecular weight polyphenols cranberry fraction, total bacterial and *S. mutans* counts in saliva were reduced [90].

Cocoa

Cocoa polyphenol pentamers significantly reduce biofilm formation and acid production by *S. mutans* and *Streptococcus sanguinis* [77]. Extracts from cocoa mass have been shown to have anticariogenic potential but not strong enough to suppress the cariogenicity of sucrose [62]. Cacao bean husk extract (CBH) has been shown to possess antibacterial and antiglycosyltransferase activities. The number of mutans streptococci in dental plaque was significantly reduced when human dental plaque was exposed to CBH extract for 1 h. A mouth rinse with CBH extract in ethanol, before and after each intake of food and before sleeping at night for 4 days without using other oral hygiene procedures, reduced plaque depositions and the numbers of mutans streptococci, compared with rinsing with 1% ethanol alone [50].
Coffee

Trigonelline, caffeine and chlorogenic acid occurring in green and roasted coffee interfere with \( S.\mathbf{mutans} \) adsorption to saliva-coated hydroxyapatite beads. The anti-cariogenic effects against alpha-haemolytic streptococci showed by polyphenols from coffee suggest further studies to a possible application of this beverage in the prevention of pathogenesis of dental caries [21].

Apple

The inhibitory effects of apple polyphenols on the synthesis of water-insoluble glucans by glycosyltransferases (GTF) of the mutans streptococci and on the sucrose-dependent adherence of the bacterial cells were examined in vitro. Apple-derived polyphenols markedly inhibited the activity of GTF purified from the cariogenic bacterial cells; however, they showed no significant effect on the growth of the cariogenic bacteria [95].

Raisins

When the effect of raisins and raisin-containing bran cereal on in vivo plaque acidogenicity was examined in 7–11-year-old children, it was found that raisins did not lower the plaque pH below pH 6 over the 30-min test period [41]. Compared with commercial bran flakes or raisin bran cereal, a smaller plaque pH drop was noted in children who consumed a raisin and bran flake mixture when no sugar was added [93].

Grapes and wine

When the minimally inhibitory concentration of plant polyphenols was tested in \( S.\mathbf{mutans} \) cultures and in the cultures of other microorganisms, the lowest MICs were found for the extracts of red grape skin 0.5 mg/mL. Grape seed extract, high in proanthocyanidins, positively affected found for the extracts of red grape skin 0.5 mg/mL. Grape cultures of other microorganisms, the lowest MICs were [93]. In another study, the maximum permitted use levels of sorbic and benzoic acid was shown to inhibit the growth of oral streptococci but not the in vitro glycolysis at tested concentrations [42]. The combination of benzoate and fluoride reduced caries activity more effectively in rodents fed a cariogenic diet ad libitum than fluoride alone [17]. In a double-blind, controlled crossover study, Arweiler et al. [4] evaluated the influence of food preservatives (0.1% benzoate, BA, and 0.1% sorbate, SA) on in situ dental biofilm growth in comparison with 0.2% chlorhexidine (CHX) and saline. After 5 days, the developed biofilms were scanned after staining by confocal laser scanning microscopy for biofilm thickness and bacterial vitality. The use of SA, BA and

Propolis

Propolis is a resinous mixture that honeybees collect from tree buds, sap flows or other botanical sources and contains numerous flavonoids. It is used as a sealant for unwanted open spaces in the hive. Propolis has been shown to exhibit good antimicrobial activity against a range of oral bacteria and inhibit the adherence of \( S.\mathbf{mutans} \) and \( S.\mathbf{sobrinus} \) to glass [39]. It was also shown to be a potent inhibitor of water-soluble glucan synthesis (GTF-activity inhibitor). The activity of propolis against a number of microorganisms, including \( S.\mathbf{mutans} \) and \( \text{Streptococcus sobrinus} \), was demonstrated [85]. Ethanol extracts of four samples of propolis collected from different geographical regions in Anatolia exhibited MIC values of 2–64 \( \mu\)g/mL. Propolis showed antimicrobial activity similar to chlorhexidine and greater than clove or sage extracts in a study investigating the ability of these chemicals to inhibit the growth of microbes obtained from the saliva of periodontally healthy subjects and those with chronic periodontitis [20].

\( \text{Nidus vespae} \), the honeycomb of \( \text{Polistes olivaceous} \) (De Geer), \( \text{P. japonicus} \) de Saussure and \( \text{P. Parapolybiavaria fabricius} \), is a traditional Chinese medicine that has a number of pharmacological properties. While \( N.\mathbf{vespae} \) is similar to propolis, it contains additional material including waxes and aromatic oils. Like propolis, extracts and fractions of \( N.\mathbf{vespae} \) have been shown to exert antimicrobial activity towards a number of oral microorganisms, in particular \( S.\mathbf{mutans} \) [94]. In addition, the extracts showed significant anti-acidogenic activity.

Food preservatives

There has been a large increase in the use of food preservatives over the last few decades. For instance, in the last decades of the previous century, the use of preservatives in the USA increased over 20-fold and it is estimated that the average ingestion of benzoate in the USA is currently 2.3 mg/kg bw per person per day. Manufactured foods and soft drinks are the primary sources of preservatives. Many toothpastes and mouthwashes also contain benzoate.

Sodium benzoate, potassium sorbate and sodium nitrite are commonly used food preservatives. Food preservatives behave like weak acids and can dissipate the \( \Delta\mathbf{pH} \) across the bacterial cell membrane causing acidification of the cytoplasm. In an in vitro study, food preservatives inhibited \( S.\mathbf{mutans} \) biofilm formation [3]. In another study, the maximum permitted use levels of sorbic and benzoic acid was shown to inhibit the growth of oral streptococci but not the in vitro glycolysis at tested concentrations [42]. The combination of benzoate and fluoride reduced caries activity more effectively in rodents fed a cariogenic diet ad libitum than fluoride alone [17]. In a double-blind, controlled crossover study, Arweiler et al. [4] evaluated the influence of food preservatives (0.1% benzoate, BA, and 0.1% sorbate, SA) on in situ dental biofilm growth in comparison with 0.2% chlorhexidine (CHX) and saline. After 5 days, the developed biofilms were scanned after staining by confocal laser scanning microscopy for biofilm thickness and bacterial vitality. The use of SA, BA and
CHX resulted in a significantly reduced biofilm thickness and bacterial vitality compared to saline ($p < 0.001$). Differences between SA and BA were not statistically significant, while CHX showed significantly lower values. Thus, both preservatives showed antibacterial and plaque-inhibiting properties, but not to the extent of 0.2% CHX.

**Alternative sweeteners**

Sugar-free sweets, confectionery, chewing gum and drinks are formulated with sugar alcohols, intense sweeteners, non-cariogenic disaccharides and non-cariogenic bulking agents. The relevant alternative sweeteners, sugar replacers and bulking agents currently used are described in Table 3.

The most widely used sugar alcohols are xylitol (pentitol), sorbitol, mannitol (both hexitols), maltitol, lactitol (both glucosyl-hexitols) and hydrogenated starch hydrolysates (6–8% sorbitol, 50–55% maltitol, 1,4-glucosyl-sorbitol), 20–25% maltotriitol (di-glucosyl-sorbitol) and 10–20% poly glucosyl alcohols) and isomalt (1:1 mixture of 1,6-glucosyl-sorbitol and 1,1-glucosyl-mannitol, two glucosyl-polyols). Other sugar alcohols such as erythritol are emerging with promising results [7]. Erythritol may reduce the numbers of mutants streptococci and the amount of dental plaque to the same extent as xylitol [36, 46]. The relative sweetness of the sugar alcohols compared to sucrose varies from 0.5 to 1. All sugar alcohols have been tested in vitro for fermentation by oral microorganisms and can be classified as hypo- or non-acidogenic. There is a reduced or virtually no extracellular polysaccharide production from sugar alcohols. Hypo- and non-acidogenicity of the sugar alcohols is confirmed by plaque pH measurements. From animal experiments and intra-oral cariogenicity tests (ICT), it is concluded that sugar alcohols are (extremely) low or non-cariogenic. In vitro, adaptation of mutants streptococci by frequent subculturing in sorbitol, maltitol, lactitol and hydrogenated starch hydrolysates occur, but this is not likely to be important in vivo when the sugar alcohols are given in combination with a diet rich in sucrose. In all these experiments, xylitol stands out. With rare exceptions, xylitol is not fermented by oral microorganisms. Xylitol inhibits the growth of mutants streptococci [86] even selectively in mixed chemostat cultures [6]. It interferes with the glycolysis when glucose is used as energy source [89] although this may not be a stable phenomenon in vivo [74]. In vivo, there was also no reduction of the acidogenic response of dental plaque to sucrose after periods of using xylitol chewing gums [91] or xylitol mouth rinses [44]. It has been proposed that xylitol weakens the caries-inductive properties of dental plaque colonising newly erupting tooth surfaces [31] and that such a caries protective effect might persist several years after the cessation of use of xylitol products [28]. From animal experiments, it has been concluded that xylitol is antarcigenic [26]. Recently, it has been demonstrated that children of mothers who frequently use xylitol-sweetened chewing gum were less colonised with mutants streptococci. For all this, it is widely believed that xylitol is superior to the other sugar alcohols for potential caries control (for reviews: [81, 83]), although the clinical evidence for this superiority has been challenged and classified as weak [29, 74, 84, 88]. For all sugar alcohols, there is a limited use due to laxative effects in particular in beverages.

Meanwhile, novel disaccharides of very low acidogenicity and with good gastrointestinal tolerance for manufacturing tooth-friendly sweets have been developed and are on the market (isomaltulose and leucrose).

**Table 3** Commonly used sugar substitutes (sugar alcohols, bulking agent, novel disaccharides and intense sweeteners) for the manufacture of tooth-friendly confectionery and for use in oral care products.

<table>
<thead>
<tr>
<th>Category</th>
<th>Structure</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sugar alcohols</td>
<td>Hydrogenated monosaccharides</td>
<td>Sorbitol, mannitol, xylitol, erythritol</td>
</tr>
<tr>
<td>hydrogenated carbohydrates</td>
<td>Hydrogenated disaccharides</td>
<td>Isomalt, lactitol, maltitol</td>
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<tr>
<td></td>
<td>Hydrogenated oligosaccharides</td>
<td>Maltitol syrups, hydrogenated starch hydrolysates</td>
</tr>
<tr>
<td>Bulking agent</td>
<td>Polymer</td>
<td>Polydextrose</td>
</tr>
<tr>
<td>Novel disaccharides</td>
<td>Disaccharide (isomers to sucrose)</td>
<td>Leucrose, isomaltulose (Palatinose™)</td>
</tr>
<tr>
<td>Non-caloric, intense sweeteners</td>
<td>Acesulfame K</td>
<td></td>
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<tr>
<td></td>
<td>Aspartame</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cyclamate</td>
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<tr>
<td></td>
<td>Saccharin</td>
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<td></td>
<td>Sucralose</td>
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</table>

All substances are non-cariogenic, and some of the intense sweeteners can interfere with microbial fermentation.
coffee and tea. Although the light or diet soft drinks may not cause caries, they may contain high amounts of acids that could cause tooth erosion.

**Bioactive peptides in dairy products**

Dairy products were recognised in the late 1950s as a food group that is effective in preventing dental caries. Shaw et al. [76] observed that milk, ice cream and cheese lowered incidence of dental caries in rats. Desalivated rats given 2% milk or lactose-reduced milk remained essentially caries-free [6]. Epidemiological studies in recent years indicate that children [65, 66] and adolescents [67] with low incidence of dental caries drank more milk than those with high caries incidence. Elderly people who eat cheese several times per week had a lower incidence of root surface caries development [64]. Several reviews describe the role of milk and dairy products in dental caries prevention [33, 35, 54].

The dairy components that have anticariogenic properties are calcium, phosphate, casein and lipids. Casein added to food (e.g. chocolate) reduced cariogenicity, but casein’s adverse organoleptic properties and the large amount required for efficacy precluded its use in a food. Digestion of casein did not destroy the proteins’ ability to prevent enamel demineralisation in a human oral caries model. Two casein digestives, caseinophosphopeptides (CPP) and glycomacropeptide (GMP), have been patented for use in common personal hygiene products to prevent dental caries. Research has shown CPP and GMP to be growth inhibitory to the cariogenic bacteria *S. mutans* and other species [32, 56, 57]. Additionally, CPP forms nanoclusters with amorphous calcium phosphate at the tooth surface to provide a reservoir of calcium and phosphate ions to maintain a state of super saturation with respect to tooth enamel.

Caseinophosphopeptides (CPP) can be produced forming colloidal complexes with calcium and phosphate in solution (CPP–ACP). The use of CPP–ACP would increase the level of amorphous calcium phosphate in plaque increasing the degree of saturation. Specific pathogen-free rats orally infected with *S. sobrinus* had a reduced incidence of smooth surface caries after CPP–ACP solutions were applied to the animal’s teeth twice daily. The in situ caries model has shown the ability of CPP–ACP to prevent enamel demineralisation and promote remineralisation. Clinical experiments have been conducted with CCP–ACP in chewing gum (for overview see: [70]).

Schupbach et al. [75] demonstrated that GMP could prevent cariogenic bacterial adhesion in an in vitro model. The researchers speculate that GMP reduces dental caries by changing the microbial population of dental plaque from being predominated by *S. mutans* and *S. sanguis* to a less cariogenic population predominated by *Actinomyces viscosus*. In vitro experiments, Reynolds et al. [69] showed GMP to have an inhibitory activity to enamel demineralisation.

Other bioactive components of milk that might play a role in prevention of dental caries include lactoferrin, lysozyme, lactoperoxidase, folate-binding protein, immunoglobulin proteins, growth factors and others (Table 4). For example, lactoferrin inhibits adherence of *S. mutans* to saliva-coated hydroxyapatite beads. Lactoperoxidase and lysozyme synergistically inhibit glucose metabolism by *S. mutans* [43]. Protease peptone fractions 3 and 5 were shown to inhibit demineralisation of hydroxyapatite in vitro [24].

**Probiotics**

The idea to use bacteria to modify plaque virulence has been a topic of dental research for many years. There have been several approaches. It has been investigated how the resident oral flora associated with health could be favoured over the species associated with disease. Many early studies concentrated on utilising bacteria that were known to compete with or that expressed bacteriocins or bacteriocin-like inhibitory substances against cariogenic bacteria [27, 80, 87]. Another approach was to replace for instance

<table>
<thead>
<tr>
<th>Table 4 Bioactive proteins secreted in bovine milk [3]</th>
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<tbody>
<tr>
<td><strong>Protective proteins</strong></td>
</tr>
<tr>
<td>Lactoferrin</td>
</tr>
<tr>
<td>Transferrin</td>
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<tr>
<td><strong>Growth factors</strong></td>
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<tr>
<td>Tissue growth factor β (TGFβ)</td>
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<tr>
<td><strong>Enzymes</strong></td>
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<td>Lysozyme</td>
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<td>Plasmin</td>
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<td>Xanthine oxidase</td>
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<td>Glucose oxidase</td>
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<td><strong>Hormones</strong></td>
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<td>Somatostatin (SIH)</td>
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<td>Insulin</td>
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<tr>
<td>Relaxin</td>
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<tr>
<td>Luteinising-releasing hormone (LRH)</td>
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<tr>
<td>Adrenocorticotropic hormone (ACTH)</td>
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</table>
The probiotic approach needed to identify food grade and probiotic bacteria that may have potential in caries prevention. These have been selected because of their likely ability to colonise teeth and influence the supragingival plaque; in vitro models for this selection have included adhesion to hydroxyapatite and mixed species biofilm models [16, 25]. Also, strains have been screened for suitable antagonistic activity against relevant oral bacteria [66]. In vitro studies of the antibacterial activity of live yoghurts showed inhibition of \textit{S. mutans} but not of some other oral streptococci, including \textit{S. sobrinus}; this activity was heat-sensitive implying that the effect was not simply due to acid [66].

Recently, oral lactobacilli have also been screened for their utility as potential probiotic strains [79], and strains of oral lactobacilli have been isolated that are inhibitory against \textit{S. mutans}, \textit{Aggregatibacter actinomycetemcomitans}, \textit{Porphyromonas gingivalis} and \textit{Prevotella intermedia}, as well as being tolerant of relevant environmental stresses [38].

Recently, a probiotic mouthwash product containing three selected species of naturally occurring oral streptococci strains, \textit{S. oralis KJ3sm}, \textit{S. uberis KJ2sm} and \textit{S. rattus JHI45}, successfully affected the levels of dental pathogens (\textit{S. mutans}) in saliva and periodontal pathogens in subgingival plaque (\textit{P. gingivalis} and \textit{Campylobacter rectus}) [97].

Genetically modified probiotics with enhanced properties can be developed (‘designer probiotics’). For example, a recombinant strain of \textit{Lactobacillus} that expressed antibodies targeting one of the major adhesins of \textit{S. mutans} (antigen I/II) was able to reduce both the viable counts of \textit{S. mutans} and the caries score in a rat model [40].

Clinical studies have indicated that bacteria with established probiotic effects (lactobacilli and bifidobacteria) have some promise for the prevention of caries. LGG ingested in dairy products (milk and cheese) reduced salivary mutants streptococcal counts in adults and protected against caries in children [2, 55]. Other lactobacilli have also been shown to reduce mutants streptococcal counts in saliva. \textit{Lactobacillus reuteri}, when delivered by yoghurt [58], straw or tablet [11], by chewing gum [12] or as a lozenge [13], significantly reduced the counts of mutants streptococci in saliva ($p < 0.05$). The short-term consumption of yoghurt [9, 10] or ice cream [14] containing \textit{Bifidobacterium} spp. resulted in a significant reduction in salivary mutants streptococci ($p < 0.05$) but not in lactobacilli. Other studies have reported reductions in mutants streptococci levels in saliva following use of probiotic-containing yoghurts [65].

Despite the fact that some products have reached the market, there remains a paucity of clinical evidence to support the effectiveness of probiotics to prevent or treat caries [51, 52].

**Conclusions**

Caries is the result of an interaction of microbes (plaque), dietary factors and their fermentation on teeth. The effect of dietary components on microbial fermentation can be studied in situ and in vitro. Many dietary factors have been identified that enhance or reduce the formation of cariogenic lesions. Together with improved oral hygiene and fluoridated toothpaste, functional food ingredients/constituents that inhibit oral microflora and/or their fermentation thus contribute to a reduction of dental caries. Some products such as sugar alcohols are already on the market for a long time. Research has also identified the beneficial effects of certain phytochemicals. For other concepts such as probiotics, evidence is just starting to emerge.

**Acknowledgments** This publication was commissioned by the Functional Foods Task Force of the European branch of the International Life Sciences Institute (ILSI Europe). Industry members of the task force are Abbott Nutrition, Barilla G. & R. Fratelli, BASF, Bio-nov, Biosearch Life, Cargill, Chiquita Brands International, Coca-Cola Europe, Danone, Dow Europe, DSM, DuPont Nutrition & Health, Institut Mérieux, International Nutrition Company, Kellogg Europe, Kraft Foods Europe, Mars, Martek Biosciences Corporation, McNeil Nutritional, Naturex, Nestlé, PepsiCo International, Pfizer Consumer Healthcare, Red Bull, Rudolf Wild, Schwabegroup, Royal Friesland-Campina, Soremar-tec Italia—Ferrero Group, Südzucker/BENEO Group, Tate & Lyle Ingredients, Tereos-Syral, Unilever and Yakult Europe. This publication was coordinated by Dr. Alessandro Chiodini, Scientific Project Manager at ILSI Europe. For further information about ILSI Europe, please email info@ilsieurope.be or call +32 2 771 00 14. The opinions expressed herein and the conclusions of this publication are those of the authors and do not necessarily represent the views of ILSI Europe nor those of its member companies.
Declarations of interest  C. van Loveren and Z. Broukal received an honorarium from ILSI Europe for their participation in this publication and reimbursement of their travel and accommodation costs for attending the related meetings.

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Periodontal diseases are a collection of inflammatory processes that affect the periodontium, that is, the teeth supporting tissues. Gingivitis (infected red swollen and easily bleeding gums) is a mild reversible form of periodontal disease. Almost 100% of the population suffers from time to time from gingivitis. Gingivitis can develop into periodontitis, which is a chronic inflammatory disease of the supporting tissues of the teeth [34]. In conjunction with red, swollen gums that easily bleed as a result of the disease, teeth may show exposed root surfaces and often dental radiographs reveal periodontal (alveolar) bone loss around the teeth due to the inflammation process; teeth will become mobile and migrate and will eventually exfoliate.

Patients with periodontitis may have bad breath, suffer from important subjective and objective esthetic problems and experience problems with chewing due to tooth mobility and loss of teeth. Dental professionals provide labor-intensive treatment to periodontitis patients, including periodontal surgery.

Like gingivitis, also periodontitis has a relative high prevalence in the population. About 10% of the total adult population and about 30% of individuals over the age of 50 years have been estimated to suffer from severe periodontitis [9]. Chronic, adult form of periodontitis progresses at a relative slow rate and is diagnosed during middle age. However, in some individuals, the disease manifests itself at adolescent or post-adolescent age in a rapidly progressive manner, and this form of disease is diagnosed as early onset periodontitis or aggressive periodontitis [42].

Periodontitis may be considered as a model for the other inflammatory diseases, with a pathogenesis that is multifactorial, involving complex interactions between multiple genetic traits, infectious agents and lifestyle factors such as diet and smoking.

Several lines of data suggest that periodontitis may be associated with systemic diseases. For example, periodontitis has been associated with increased risk for cardiovascular diseases (for a recent review see [46]), possibly through the elevation of the acute-phase reactant C-reactive protein or other systemic markers of inflammation [24]. Oral bacteria may play an important role in the systemic reactions to periodontitis. There are strong indications that the inflamed and ulcerated subgingival pocket epithelium forms an easy port of entry for oral bacteria. Short moments of bacteremia occur most likely several times a day. Like any other inflammatory condition, untreated chronic periodontitis may pose a risk for the overall health of the subject [23].

The etiology of periodontitis is multifactorial, involving the following.

1. **Microbial factors**

   Many oral bacteria are able to colonize the subgingival pocket, that is, the area directly around the teeth below the gum line. These bacteria form dental plaque, which is attached to the surfaces of the teeth. It is recognized that in the subgingival pocket, bacteria are organized in a complex microbial biofilm. This biofilm consists mainly of Gram-negative strict anaerobic bacteria [11]. Of the several hundreds of oral bacterial species, a limited number of species is recognized as periodontal pathogens and have
been identified as important markers of progressive disease. These include: Porphyromonas gingivalis, Aggregatibacter actinomycetemcomitans, Tannerella forsythia, Treponema denticola, Prevotella intermedia and Fusobacterium nucleatum [45]. It has been proposed that the bacteria in the subgingival biofilm are organized in complexes and interplay with various species associated with periodontitis [39].

It is important to note that not the same periodontal pathogens and not all the periodontal pathogens are infecting all patients with periodontitis. The microbiological factors of periodontitis differ considerably among different patients, which make periodontitis polymicrobial.

2. Genetic factors

It is recognized that siblings of patients with early onset aggressive periodontitis also suffer from periodontitis [7]. Evidence for genetic susceptibility for chronic adult periodontitis is deduced from family studies and studies in twins [43]. From the twin studies, it has been estimated that 38–82% of population variance in periodontal disease expression may be attributed to genetic factors [31]. Further chronic adult periodontitis was estimated to have 50% heritability, which was unaltered following adjustments for lifestyle variables including smoking [30].

In the last years, the search for genetic markers and candidate disease-modifying genes in periodontitis has received great attention. Especially, genetic variation (single nucleotide polymorphisms = SNPs) of genes encoding for host defense system molecules has been targeted [23]. Parallel to other complex inflammatory diseases, periodontitis is a polygenic disorder. Possible modifying disease genes have been identified in the interleukin (IL) -1 gene cluster [16, 19, 20] and Fc gamma receptor loci [25, 28, 47]. Moreover, there is growing evidence that SNPs in the IL-10, vitamin-D, CD14 and Toll-like receptor (TLR) genes may be associated with periodontitis [3, 12, 13, 20, 35, 40].

3. Lifestyle factors

Smoking is currently accepted as the most significant lifestyle factor in periodontitis [22]. Smokers are more susceptible to periodontitis, suffer from a more progressive disease and have more severe periodontal breakdown than non-smoker patients. Smoking has also been shown to be a predictor for the recurrence of periodontitis [26]. Moreover, smoking periodontitis patients show a less favorable response to non-surgical and surgical periodontal treatments.

The exact role of smoking in periodontitis is still unknown. Smoking and non-smoking periodontitis patients have been suggested to differ in their subgingival microflora [44]; however, others studies did not report this relation [5]. In smokers, the host resistance and immunological functions may be hampered, for example, by reduced phagocytosis, altered T-cell function, lack of immunoglobulin production and reduced local blood supply in comparison with non-smoker periodontitis patients [6, 14, 26].

4. Topical effects of “Ingredients”

Other factors that have been proposed as environmental risk factors for periodontitis include diet and stress [2, 8]. A recent review by Schifferle [36] makes clear that good nutrition (proteins, carbohydrates, lipids, vitamins and (trace) minerals) is essential for general health, and therefore, a nutritional adequate diet is also helpful in preventing periodontal problems. And although there is a wealth of information on the relationship between vitamin/mineral deficiency and periodontitis, it was nevertheless concluded that there is insufficient evidence to justify treatment with supplementation in adequately nourished individuals. Also, no “topical” effects were described.

In a recent review on the relationship between diet-derived antioxidants and the control/prevention of periodontal disease, a similar conclusion was drawn: although antioxidants are important in the control/prevention of periodontal diseases, the effects are systemical, via modulation of the host’s inflammatory response [10].

The effects of tea (derived ingredients) on periodontal health have also received a lot of attention in the last years. Very recently, it was shown that production of a chemokine ligand (CXCL10), which plays an important role in the development of the diseases, was inhibited by the green tea-derived polyphenols, catechins [15]. Green tea catechin also inhibits lipopolysaccharide-induced bone resorption in vivo [32]. A recent clinical study on green tea (polyphenols; [18]), where the epidemiologic relationship between the intake of green tea and periodontal disease was investigated by following periodontal parameters in 940 Japanese men, showed that there was a modest inverse association between the intake of green tea and periodontal disease. Studies that could reveal whether the effects of polyphenols are topical or systemic are scarce. Two studies on local (oral) applications of polyphenols [17, 21] have to conclude that green tea catechins and polyphenols might have a positive influence on the inflammatory reaction of periodontal structures, but larger scale studies would be necessary to determine the efficacy and oral health benefits of oral administration.

Topical effects of polyphenols (like those derived from cranberries) have been shown to have an inhibitory effect on periodontal pathogenic bacteria in vitro. These effects have recently been reviewed by Bodet et al. [4] and Petti and Scully [33] who list inhibitory effects of cranberry fractions on biofilm formation, and adherence of P.
gingivalis and \textit{F. nucleatum}, and proteolytic activities (\textit{P. gingivalis}) and coaggregation of periodontal pathogens. Also wine catechins were shown to have a strong antimicrobial activity against \textit{P. gingivalis} and \textit{P. intermedia}. This indicates that the plant-derived polyphenols could serve as topical bioactive molecules for the prevention and/or treatment of oral diseases.

Some promising “topical effects” can be concluded from several studies on the application of probiotics for the management of periodontal diseases: It was shown that colonization of \textit{Lactobacillus reuteri} in the oral cavity leads to decreased gum bleeding and reduced gingivitis [18], and also effects of this bacterium on inflammatory mediators were reported [41]. Improvement of periodontal health was also reported after colonization of \textit{Lactobacillus salivarius} [37], possibly via reduction/replacement of pathogenic bacteria [27]. Several in vitro studies on possible positive effects of probiotic bacteria in relation to periodontal diseases have been recently reviewed by Meurman and Stamatova [29], who recommended more investigations before conclusions could be drawn.

There are several publications on the positive effects of dairy products [1, 38], but it is not at all clear whether these effects are topical or systemic.

Acknowledgments This publication was commissioned by the Functional Foods Task Force of the European branch of the International Life Sciences Institute (ILSI Europe). Industry members of the task force are Abbott Nutrition, Barilla G. & R. Fratelli, BASF, Bionov, Biosearch Life, Cargill, Chiquita Brands International, Coca-Cola Europe, Danone, Dow Europe, DSM, DuPont Nutrition & Health, Institut Mérieux, International Nutrition Company, Kellogg Europe, Kraft Foods Europe, Mars, Martek Biosciences Corporation, McNeil Nutritionalis, Naturex, Nestlé, PepsiCo International, Pfizer Consumer Healthcare, Red Bull, Rudolf Wild, Schwabegroup, Royal FrieslandCampina, Soremartec Italia—Ferrero Group, Südzucker/BENEOS Group, Tate & Lyle Ingredients, Tereos-Syrup, Unilever and Yakult Europe. This publication was coordinated by Dr. Alessandro Chioldi, Scientific Project Manager at ILSI Europe. For further information about ILSI Europe, please email info@ilsieurope.be or call +32 2 771 00 14. The opinions expressed herein and the conclusions of this publication are those of the authors and do not necessarily represent the views of ILSI Europe nor those of its member companies.

Declaration of interest W. Crielard and M. L. Laine received a honorarium from ILSI Europe for their participation in this publication and reimbursement of their travel and accommodation costs for attending the related meetings.

References

Functional foods/ingredients and oral mucosal diseases

Jukka H. Meurman

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Introduction

Diseases and symptoms of mouth mucosa are prevalent in particular in the ageing populations. For example, a nationwide representative examination in the US revealed approximately 28% prevalence of all oral mucosal lesions in subjects 17 years of age and older with distinct differences between age groups and whether or not the subject smoked [27]. There are no comprehensive epidemiological data on the respective incidence and prevalence figures from Europe. In this review, the following chapters first outline the defensive mechanisms of the oral cavity followed by brief description of the most important oral mucosal diseases and symptoms. Finally, possibilities for intervention and the known effects of foods constituents, including functional food on oral mucosal diseases and symptoms, are summarized although research for most substances is in its infancies too early for conclusions.

Defensive mechanisms of the mouth

Healthy oral mucosa is the most essential defensive mechanism of the mouth. Disrupted epithelial integrity opens up deeper tissue layers for oral micro-organisms to invade with potential systemic complications. For example, in immunosuppressed patients, the mouth has been shown to be a major source of septicaemia in 25–75% of cases undergoing treatment for cancer [17] and, similarly, among organ transplant patients [24]. Mouth ulcerations in mucositis and gingivitis are thought to be the major portals of entry of these severe infections. But also in healthy humans, oral bacteraemia is highly prevalent and results from normal daily activities such as chewing food and tooth brushing [11]. The examples demonstrate the importance for health of the well-functioning defensive mechanisms of the mouth.

Oral surfaces are bathed in saliva, which flushes down micro-organisms to be swallowed and subsequently destroyed in the high acidity in the stomach. Normal salivary flow in adults, stimulated by chewing, is approximately 1–2 ml/min while flow rates below 0.7 ml/min are regarded as reduced flow. For unstimulated resting salivary flow, the respective lower threshold value is 0.1 ml/min. Hence, hyposalivation is diagnosed if the patient’s measured flow rate values are below these reference limits. However, subjective dry mouth or xerostomia does not necessarily follow clinical hyposalivation since the feeling of how much saliva is enough is highly subjective. An individual with objectively measured satisfactory salivary flow may still report subjective feeling of dry mouth. It should be further noted that the clinically measured saliva values only assess the secretion from major salivary glands while there are hundreds of minor glands in the mucosa, which are thought to play a major role in the feeling of dry mouth [7]. To measure their output is complicated and not performed as routine diagnosis.

Saliva is a ‘chemical cocktail’ containing a variety of specific and non-specific defensive mechanisms of its own. Saliva contains, for example, high concentrations of calcium and phosphates, which are essential elements of the dental hard tissues. Saliva also contains lubricating mucopolysaccharides, proteolytic enzymes, immunoglobulins...
and other components of the defensive systems. Further, there are effective buffering mechanisms in saliva. In addition, the ‘oral fluid’ contains detached epithelial cells, bacteria and other micro-organisms, and food remnants [6].

Secretory immunoglobulins (Ig) are originated from immune cells, which reside in the salivary glands, after they are produced as response to antigenic stimulus, for example, by oral bacteria. Secretory IgA is the major immunoglobulin in saliva that specifically prevents microbial attachment to oral surfaces. The secretory component in the IgA molecule protects it from the innate proteolytic enzymes of saliva. Saliva also contains lesser amounts of serum-derived IgG and IgM. The Igs aggregate bacteria and may activate the complement system in the gingival crevice but do not cause bacterial lysis in saliva [6]. Igs can be measured with validated methods but are seldom performed in clinical practice.

Of the non-specific defensive mechanisms, saliva contains lysozyme that disrupts the peptidoglycan layer of bacterial cell walls causing lysis and cell death. Salivary lysozyme also seems to link with systemic sugar metabolism [14], so this partly from saliva and partly from white blood cells–derived enzyme may have several functions. Of the numerous other non-specific salivary defensive systems, the reader is advised to consult special texts beyond the topic of this review [6]. The several unspecific salivary defensive proteins can be also measured with validated methods.

In general, however, normal salivary flow is essential for healthy mouth. Hence, reduced salivary flow directly affects oral microbiota causing microbial shift towards colonization of more pathogenic species. This is particularly seen in medicated patients. There are hundreds of pharmacological agents, which affect salivary glands causing reduction in saliva secretion. Drugs with anticholinergic effect are particularly harmful in this regard since salivary secretion is regulated by the autonomic nervous system. However, it has been shown that in practice the number of drugs taken daily is more important than the exact chemical nature of the medicine so that the more daily drugs a patient needs to take the less is there saliva in the mouth [22]. Thus, in particular, the elderly are patient–at-risk also in this regard, and reduced salivary flow and function explains why these individuals often harbour oral Candida, for example. Further, an extremely problematic group of patients are those who have received radiotherapy to the head and neck. Irradiation may irreversibly damage salivary glands and thus render the patient highly liable to oral infections due to total lack of saliva.

Mastication is of pivotal importance in stimulating salivary flow but also the taste of food is a strong stimulus. For example, citric acid is commonly used to artificially stimulate salivary secretion for flow rate measurements. Consequently, acidic foods and drinks effectively cause an increase in salivary flow, which then counteracts by buffering the harmful effects of acidity on dental hard tissues. Hence both the consistency and taste of foods (and drinks) are of importance in regulation of salivary flow and need to be taken into account when evaluating the effect of diet on oral health. Understandably, foods that call for chewing are beneficial to the mouth in contrast to liquid nutrition.

To sum up, functioning defensive mechanisms of the oral cavity usually maintain homoeostasis and prevent overgrowth of micro-organisms. If the balance is disturbed from one reason or another, the result may be colonization and emergence of potentially pathogenic microbiota that detrimentally affects not only oral and dental health but also has systemic health consequences. Patients with hyposalivation are particularly at risk also in this regard. Factors affecting oral health are illustrated in Fig. 1. So far there are no possibilities for improving the contents of saliva or the function of the defensive systems of an individual. Gene therapy may offer unforeseen means in the future in this respect, however. Until then, stimulating salivary secretion by mastication or with pharmacological means is the only method to improve salivary defence.

Diseases of mouth mucosa

Yeast infections

Oral mucosal infections are mainly caused by Candida albicans [25]. Concomitant use of several drugs, including antimicrobial agents, causes selective suppression of resident bacteria in the oral cavity leading to yeast overgrowth. Particularly elderly individuals and patients in long-term care facilities harbour Candida species in the mouth. Wearing dentures has long been known to contribute to yeast infection, and good oral hygiene has been shown to decrease the colonization of Candida [10]. Diet modifies the colonization, and consumption of fermentable carbohydrates enhances yeast growth. As said, dry mouth increases the risk for oral Candida infections.

Systemic, invasive yeast infections are rare and mainly encountered in high-risk patients. Mortality in Candida blood-stream infections is of the magnitude of 40%, however. These potentially fatal infections are seen in intensive care units and in patients with severe and prolonged neutropenia, and often with multi-organ failure [25].

Oral yeast infections are diagnosed by cultivating samples taken directly from the affected sites (mucosal lesions) with cotton swabs, or from saliva. In saliva, high yeast counts represent colony forming units >10^5/ml. In clinical practice, however, also semi-quantitative scales are used (0—++). Merely positive yeast count (+) does not indicate infection because yeasts belong to the normal microbiota of the mouth. Histological biopsy specimens
Yeast infections are treated with special antifungal drugs. For oral health purposes, there are both topical and systemic preparations on the market. Usually, locally applied preparations are prescribed for milder infections while severe infections call for administration of systemic drugs. The emergence of antibacterial and antifungal drug resistance is a growing global problem, and there is a reason for concern also in oral health care in this respect. In a study on cancer patients receiving palliative care, oral colonization with non-albicans yeasts was observed in more than 40% of the isolates with a high percentage of resistance to the commonly used antifungal drugs fluconazole and itraconazole [1]. There are data showing that probiotics may be of help in controlling oral yeast infections. In the study by Hatakka et al. [12], a combination of probiotic bacteria twice daily in cheese significantly reduced salivary high yeast counts in the elderly in a 16-week placebo controlled trial. High salivary yeast count as such does not indicate an infection, and thus the result needs to be verified among patients with diagnosed yeast infection before further conclusion. In general, however, frequent consumption of acidic foods is risk for oral Candida infections while stimulating the salivary flow by chewing tends to reduce the risk. Nevertheless, evidence-based data do not exist on these interactions.

Viral infections

Several contagious viral infections may cause localized skin and mucosal affections in addition to general symptoms. Viral infections of the mouth can be diagnosed based on clinical symptoms and signs or, more specifically, by cultures for samples taken from the infected area. Blood tests to check for antibodies to viruses or for the antigens themselves are also available. Polymerase chain reaction methods are used to accurately identify the virus. Thus, eventual efficacy of intervention can be measured.

Herpes viruses (HSV) are traditionally suggested to associate with gingivostomatitis and genital lesions. Herpetic lesions in the mouth characteristically present as painful blisters and ulcers with prodromal itching symptoms. HSVs have been detected more frequently in skin cancer than in control individuals [15]. The risk of presenting basal cell carcinomas was more than 3 times higher for HSV-6-infected patients, whereas the risk was 8.1 times higher for HSV-1. Moreover, HSV-1 seropositivity has also been reported to associate with oropharyngeal squamous cell carcinoma. After adjusting for sex, cigarette smoking, alcohol consumption, age and income, HSV-1 positivity was associated with a slightly increased risk of oral cancer (OR 1.3). However, the adjusted association between HSV-1 antibody positivity and oral cancer risk among those who were current cigarette smokers had been stronger (OR 4.2) than would have been predicted based on the additive combination of smoking alone (OR 2.3) and HSV-1 seropositivity alone (OR 1.0). HSV-1 may thus enhance the development of oral cancer in individuals who are already at increased risk of the disease because of cigarette smoking or human papilloma virus (HPV) infection [15]. HPV causes papillomatous lesions also in the mouth mucosa, and some strains are carcinogenic.

Herpes or varicella zoster virus (VZV) is known to cause chickenpox (varicella) and then remains latent for decades in cranial nerve, dorsal root and autonomic nervous system ganglia along the entire neuraxis. The virus may reactivate, most often after age 60, produce shingles
(zoster), which are characterized by pain and rash. The overall incidence of VZV is approximately 3/1,000 of the population per year rising to 10/1,000 per year by 80 years of age. Approximately 50% of individuals reaching 90 years of age will have had the infection [9].

There are studies indicating that the intake of certain foods may modify the risk for herpetic infections. For example, fruits and vegetables may maintain immune health and prevent zoster [30]. Malnutrition in general affects the susceptibility for HSV-1 in the rat model [3]. However, there are no population studies in humans in this regard.

Oral lichen planus

Lichen is a disease of unknown aetiology. It affects approximately 1–2% of the adult population [5]. The symptoms are white striations and papules, erythema and erosions or blisters. The lesions are often bilateral and seen on the buccal mucosa. The patients experience mucosal sensitivity and pain particularly when eating spicy food. Oral mucosa is often very sensitive to oral hygiene products, too, and then the patients cannot use toothpaste or mouthwash preparations in particular if these contain sodium lauryl sulphate. Corticosteroids are of help in the treatment of lichen planus, and the preparations are used either topically or in severe cases systemically. However, there are no evidence-based data for the best treatment of oral lichen planus. Ameliorating the symptoms is often possible by simply abstaining from all known irritants. Regular use of sour milk products may also help subjectively the patient, but no randomized trials have been published in this area. Similarly, lubricating mouth mucosa with olive oil or other vegetable oil may be of help to the patient. These recommendations are based on clinical experience only.

Lichen planus is diagnosed based on the appearance of the lesion and by histological examination of biopsy specimens to confirm the diagnosis. Assessing the efficacy of treatment can thus be made by monitoring the amelioration of the lesions.

Aphthous stomatitis

Aphthous stomatitis or recurrent aphthous ulcers are of unknown aetiology presenting as painful ulcers, one or several, commonly on the unattached oral mucosa. The condition is self-limiting typically lasting 7–10 days. Similar ulcers can, however, be found in several disease conditions such as herpetic lesions, inflammatory bowel diseases, Behcet’s syndrome and lupus erythematosus. Aphthous stomatitis is estimated to affect 20% of the population, and typically onsets after puberty and subsides at older age. There are several triggering factors for aphthous stomatitis. These include, for example, stress, characteristically among women of the premenstrual phase as well as a genetic predisposition.

The diagnosis of aphthous stomatitis is based on characteristic clinical picture and symptoms. Mucosal biopsy specimens can be used to confirm the diagnosis although the histological finding is unspecific ulceration.

Numerous topical agents and medications have been introduced for the treatment of aphthous ulcers. These include antimicrobial and coagulating agents, among others. Corticosteroids seem effective, and there are several topical preparations on the market. In the most severe cases, steroids are orally administered. As treatment efficacy can only be monitored by measuring the subsiding of the lesions and amelioration of clinical symptoms, the efficacy of different treatment methods can so far not be evaluated.

Manifestations of systemic and skin diseases on mouth mucosa

In general, several systemic diseases and particularly skin diseases may also manifest in the mouth with highly non-specific symptoms and signs [26].

Diabetes and rheumatic diseases need to be specifically mentioned as examples of diseases often linked with dry mouth with subsequent complications such as yeast overgrowth. Little data exist on the efficiency of treating oral symptoms associated with these diseases. Nevertheless, clinical practice has shown that maintaining good oral hygiene and use of saline as mouth rinse may help the patients by ameliorating the symptoms. Regardless of the underlying disease, the patients with oral lesions often suffer from mucosal pain and burning sensation in the mouth. Controlling the underlying systemic disease is therefore essential in the treatment of patients with symptoms and signs of the mouth, too. So far, there are no data of whether the use of specific diet is of benefit in this area.

Non-specific symptoms of the mouth

Xerostomia

Xerostomia or subjective feeling of dry mouth is highly prevalent in elderly populations [21]. The estimates of the percentage of older individuals with xerostomia range from 10 to 40%. Medications are believed to be responsible for a significant proportion of cases with xerostomia, and the list of drugs that are believed to affect saliva secretion includes more than 400 pharmacological agents [22]. Several studies indicate that the risk of xerostomia increases with increasing numbers of medications used. However, the
most severe cases of dry mouth and xerostomia are seen in patients irradiated for head and neck cancer. These patients also present a number of dental and oral health problems [19].

Dry mouth also predisposes the patients to mucosal irritation by other ingredients, such as sodium lauryl sulphate in oral health care products. In this regard, betaine or trimethylglycine has been successfully used instead of sodium lauryl sulphate [28]. In a randomized controlled 6-week trial, 44% of patients with dry mouth reported relief of the symptom in the betaine group in comparison with 18% of patients receiving sodium lauryl sulphate-containing toothpaste [23]. The difference was statistically significant, but no further evidence can be found in the literature.

Dry mouth, xerostomia and the sensation of burning mouth are particularly prevalent in menopause-age women. Wardrop et al. [32] studied the relationship between oral discomfort and menopause in 149 women and observed that the prevalence of oral discomfort was significantly higher in perimenopausal and postmenopausal women (43%) than in pre-menopausal women (6%). Their results also showed an association between oral discomfort and psychosocial symptoms in menopausal women. Approximately two-thirds of the menopausal women with oral discomfort, but without oral clinical signs, found that this symptom was relieved by hormone replacement therapy (HRT). Ben Aryeh et al. [2] reported a high prevalence of oral discomfort in women attending a menopause clinic with highly significant odds ratio (up to 8.03) between systemic and oral complaints of menopause. They also observed a significantly altered salivary composition in the women pointing to sympathetic activation due to psychological stress. Sympathetic nervous system also regulates salivary gland output. In our study group, we observed in type 2 diabetic patients with polyneuropathy decreased secretion, which supports the concept above [18]. Volpe et al. [31] have also suggested that oestrogen deficiency can be considered a possible cause of oral discomfort in some postmenopausal patients and that HRT indeed may improve subjective symptoms.

As discussed earlier, reduced saliva flow inevitably also reduces defensive mechanisms in the oral cavity. Consequently, dry mouth should be treated. But apart from drinking water and using local oral gels and other preparations for dry mouth, pharmacological means for ameliorating xerostomia are sparse. Pilocarpine (5-mg tablets taken several times daily) has been used in cases with severe hyposalivation in patients with no systemic contraindications for using cholinergic drugs. Of the topical agents used for ameliorating dry mouth feeling, olive oil, betaine and xylitol-containing products have been shown beneficial for patients with xerostomia [26]. In this context, it must be re-emphasized that subjective xerostomia does not necessarily reflect reduced salivary flow rates because the feeling of ‘how much saliva is enough’ is highly subjective.

Xerostomia and/or dry mouth are diagnosed based on the patient’s history using structured questionnaire. The questions enquire, for example, the diurnal variation of the symptom and assess the harm caused by xerostomia/dry mouth to the patient. This may include, for example, the need to drink water at night and difficulties in swallowing dry food stuffs.

Measuring salivary secretion rates is an objective measure to assess dry mouth as described earlier. Xerostomia assessment, however, is based on patient history. The efficacy of treatment is measured by monitoring the improvement in the secretion values and amelioration of subjective symptoms of the patient recorded by a structured questionnaire.

Burning mouth syndrome and glossodynia

These symptom entities comprise dull pain or feeling of burn in mouth mucosa and tongue among patients where no clinical pathology can be seen in the symptomatic areas. Burning mouth can be a mere nuisance to the patient while in severe cases the symptom is intolerable. The prevalence of the sensation of burning mouth is estimated to be of the magnitude of 10% in elderly (+60 years old) populations [4]. Women are more often affected than men, and the symptom is particularly prevalent at menopause. Burning mouth mostly affects the tongue, hence the name glossodynia. The symptom very often presents itself simultaneously with dry mouth. The aetiology is not known but psychological factors play an important role as is the case with all patients with chronic pain. In women, hormonal changes have been thought to associate with the symptom but the data are controversial in this regard [29, 33]. Because the cause for burning mouth is unknown, there are no specific treatments available. Many patients subjectively benefit from using soothing oral gels, and mouth rinses but severe cases of burning mouth need antidepressants (e.g. amitriptyline, milnacipran, mocclobemide and paroxetine) or antiepileptic drugs (e.g. clonazepam, lamotrigine, topiramate, gabapentin and pregabalin) targeted for chronic pain. Other agents investigated in burning mouth syndrome include alpha lipoic acid, an antioxidant, and capsaicin, the active component in chilli peppers. However, the results from the studies investigating the drugs or other agents here mentioned have mostly shown no statistically significant effect when compared with treatment with placebo. Hence, properly conducted randomized trials are needed also in this area. The effect of diet on burning mouth and
glossodynia is not known but similar to other symptoms of mouth mucosa soothing milk products may be of subjective help.

Burning mouth and glossodynia are diagnosed based on the patient’s subjective complaints together with clinical oral examination showing the lack of any mucosal pathology. Treatment efficacy is thus based on recording change in the same parameters.

Halitosis

Bad breath or halitosis usually originates in the oral cavity. Approximately 30–40% of halitosis patients have no underlying organic disease, and up to 30% of the population may present with this condition [13]. Hence, usually the process of developing bad breath is similar to that noted in the progression of periodontal disease [20]. The three species of micro-organisms associated with both periodontal disease and bad breath are *Treponema denticola*, *Porphyromonas gingivalis* and *Tannerella forsythia*. These bacteria produce volatile sulphur compounds (VSC) as end products of metabolism [16]. VSCs are a family of gases such as hydrogen sulphide, methylmercaptan and dimethylsulphide that arise from bacterial metabolism of amino acids which primarily are responsible for oral malodour [20]. Fermentable carbohydrates in diet which in general increase oral microbial colonization should be avoided in cases with bad breath. However, no controlled studies exist on the effect of dietary regimens on halitosis, which in effect is mostly due to putrescence in deep periodontal pockets or tonsillar crypts. Indeed, a recent Cochrane review on this topic concluded that the scientific evidence is still weak regarding the treatment of halitosis with the commonly used mouth rinses [8].

Diagnosing bad breath calls for careful dental examination and also examining the throat, larynx and nasal cavity. Occasionally, gastroenterological examinations are needed to rule out reasons such as gastric regurgitation. Sulphur emissions in the mouth air can be measured with special instruments (halimeters), which give oral malodour scores. Furthermore, gas chromatography tests have been introduced to measure the molecular levels of VSCs in mouth air. To analyse malodour-related bacteria, various tests are also available. BANA- and β-galactosidase-tests can be used to monitor salivary levels of enzymes indicating the presence of certain bacteria [31]. Finally, organoleptic measures are used to score the intensity of halitosis using, for example, the visual analogue scale. The same methods listed here can then be used to assess the effect of treatment of halitosis.

Finally, it should be noted that many patients suffer from halitosis without any objective measures of bad breath. There often is a strong psychic component involved among such individuals, and the condition is then termed pseudohalitosis or in severe cases halitosis phobia.

Conclusion

The oral cavity with its unique anatomical structures and physiology is greatly affected by foodstuffs and drinks both directly and indirectly as illustrated in Fig. 2. Hence,

Fig. 2 Foodstuffs and drinks affect oral tissues both directly and indirectly

<table>
<thead>
<tr>
<th>Method</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual analogue scale</td>
<td>Subjective and objective assessment (e.g. pain scale)</td>
</tr>
<tr>
<td>Biopsy specimens</td>
<td>Confirming diagnosis (e.g. lichen planus)</td>
</tr>
<tr>
<td>Microbial culture</td>
<td>Setting specific diagnosis (e.g. oral yeast infection)</td>
</tr>
<tr>
<td>Clinical oral examination</td>
<td>Recording signs of disease (e.g. mucosal lesions)</td>
</tr>
<tr>
<td>Blood tests</td>
<td>Confirmation of infection and for diagnosing specific diseases (e.g. viral infections)</td>
</tr>
<tr>
<td>Salivary tests</td>
<td>Setting diagnosis and monitoring treatment effect (e.g. dry mouth)</td>
</tr>
<tr>
<td>Structured questionnaire</td>
<td>Recording patient’s symptoms and history (e.g. xerostomia)</td>
</tr>
</tbody>
</table>
practically all oral diseases and symptoms can be modified by selecting healthy nutrients and by avoiding foods or drinks that irritate mucosal surfaces. However, the eventual irritate substances are highly individual, and thus intervention for the general public is difficult to assess. Furthermore, because the aetiology of many oral diseases and symptoms still remains open, there is a need for in-depth studies in the field. Randomized controlled trials are particularly needed for comparing different treatment modes. Table 1 summarizes the monitoring methods for assessing treatment efficacy on oral mucosal diseases.

Acknowledgments
This publication was commissioned by the Functional Foods Task Force of the European branch of the International Life Sciences Institute (ILSI Europe). Industry members of the task force are Abbott Nutrition, Barilla G. & R. Fratelli, BASF, Bionov, Biosearch Life, Cargill, Chiquita Brands International, Coca-Cola Europe, Danone, Dow Europe, DSM, DuPont Nutrition & Health, Institut Mérieux, International Nutrition Company, Kellogg Europe, Kraft Foods Europe, Mars, Martek Biosciences Corporation, McNeil Nutritionalis, Naturex, Nestlé, PepsiCo International, Pfizer Consumer Healthcare, Red Bull, Rudolf Wild, Schwabegroup, Royal FrieslandCampina, Soremartec Italia—Ferrero Group, Südzcuker/BENEQ Group, Tate & Lyle Ingredients, Tereos-Syral, Unilever and Yakult Europe. This publication was coordinated by Dr. Alessandro Chiodini, Scientific Project Manager at ILSI Europe. For further information about ILSI Europe, please email info@ilsieurope.be or call +32 2 771 00 14. The opinions expressed herein and the conclusions of this publication are those of the authors and do not necessarily represent the views of ILSI Europe nor those of its member companies.

Declaration of interest
J.H. Meurman received a honorarium from ILSI Europe for his participation in this publication and reimbursement of his travel and accommodation costs for attending the related meetings.

References


**Introduction**

Dental erosion is defined as the loss of tooth substance by a chemical process (acid exposure) that does not involve bacteria [91]. With the decline of the prevalence of caries, considerable attention has been focused on tooth erosion. Dental erosion is a multifactorial condition: the interplay of chemical, biological and behavioural factors, which is crucial and helps to explain why some individuals exhibit more erosion than others. Erosive tooth wear can be caused by intrinsic or extrinsic acid, or the combination of both. There is some evidence that the presence of dental erosion is growing steadily. In the United Kingdom, the prevalence of erosion was shown to have increased from the time of the children’s dental health survey in year 1993 compared with 1996/1997 [76]. In another UK study, the progression of erosion was investigated: 1,308 children were examined at the age of 12 and again 2 years later. In this study, 4.9% of the subjects at baseline and 13.1% 2 years later had deep enamel or dentine lesions. Twelve per cent of erosion-free children at 12 years developed the condition over the subsequent 2 years. New or more advanced lesions were seen in 27% of the children over the study period [26]. The progression of erosion seems to be greater in older adults (52–56 years) compared with younger (32–36 years) and has a skewed distribution [66].

Currently, increased tooth erosion has been largely linked to the increased consumption of acidic foods and drinks. To reduce or prevent erosive demineralization, strategies have been performed in the laboratory and clinic that are directed at the modification of the chemical, biological and behavioural factors involved in the aetiology of erosion. As dietary modifications are less patient-dependent, more interest has been paid to the erosion-decreasing potential of foods or beverages by various additives. The objective of this overview is to summarize the effective strategies for dietary modification to prevent dental erosion.

**Diagnosis**

To diagnose erosion, dental professionals have to rely on clinical appearance, as there is no device available for its detection. The teeth should be dried thoroughly and be well illuminated to reveal minor surface changes. The appearance of smooth, silky-glazed, sometimes dull, enamel with the absence of perikymata and intact enamel along the gingival margin are typical signs. It has been hypothesized that the preserved enamel band along the oral and facial gingival margin could be due to some plaque remnants, which could act as a diffusion barrier for acids. This phenomenon could also be due to an acid neutralizing effect of the sulcular fluid [67]. The clinical examination should be carried out systematically using a simple but accurate index. This is a difficult task to achieve, as an index with a too fine grading shows a small inter- and intraexaminer reliability [62], and vice versa an index with a too rough grading is not able to assess small changes. The initial features of erosion on the occlusal and incisal surfaces are the same as previously described. Further progression of occlusal erosion leads to rounding of the cusps and restorations rising above the level of the adjacent tooth surfaces. In severe cases, the entire occlusal morphology disappears.

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The Basic Erosive Wear Examination (BEWE) provides a simple scoring system that can be used with the diagnostic criteria of all current indices [8]. The most severely affected surface in a sextant is recorded with a four level score (Table 1). The maximum score per subject is 18. It is sometimes challenging to distinguish between the influences of erosion, attrition and abrasion during a clinical examination. Attrition-affected areas are often flat, have glossy areas with distinct margins and corresponding features at the antagonistic teeth. Facial erosion should be distinguished from wedge-shaped defects that are located at, or apical to, the enamel–cementum junction. The coronal part of wedge-shaped defects ideally has a sharp margin and cuts at a right angle into the enamel surface, whereas the apical part bottoms out to the root surface. Thereby, the depth of the defect exceeds its width.

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
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<tbody>
<tr>
<td>0</td>
<td>No erosive tooth wear</td>
</tr>
<tr>
<td>1</td>
<td>Initial loss of surface texture</td>
</tr>
<tr>
<td>2*</td>
<td>Distinct defect, hard tissue loss &lt; 50% of the surface area</td>
</tr>
<tr>
<td>3*</td>
<td>Hard tissue loss ≥ 50% of the surface area</td>
</tr>
</tbody>
</table>

* In scores 2 and 3, dentine is often involved

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**Risk, preventing and modifying factors**

There are many factors involved in the erosive tooth wear process. Figure 1 shows the different predisposing factors and aetiologies of the erosive condition. The interplay of all these factors is crucial and helps to explain why some individuals exhibit more erosion than others do, even if they are exposed to exactly the same acid challenges in their diets.

**Biological factors**

Biological factors such as tooth structure and positioning in relation to soft tissues and the tongue are related to dental erosion development. A very important biological parameter is saliva. The acquired pellicle may protect against erosion by acting as a diffusion barrier or a perm-selective membrane that prevents direct contact between the acids and the tooth surface, thereby reducing the dissolution rate of dental hard tissue. When an acidic solution comes in contact with enamel, it must first diffuse through the acquired pellicle, and only thereafter can it interact with the enamel. The acquired pellicle is an organic film that is free of bacteria and covers oral hard and soft tissues. It is composed of mucins, glycoproteins and proteins, including several enzymes [36]. On the surface of the enamel, the hydrogen ion component of the acid will start to dissolve the enamel crystal. The prism sheath area is dissolved first, followed by the prism core are, leaving the well-known honeycomb appearance [72]. Thereafter, fresh unionized acid will eventually diffuse into the interprismatic areas of the enamel and further dissolve mineral in the region underneath the surface [27, 30, 67]. This will lead to an outflow of ions (dissolution) and to a subsequent rise in the local pH in the tooth substance immediately below and in the liquid surface layer adjacent to the enamel surface [67]. The events in the dentine are the same in principle, but are even more complex.

Studies have shown that erosion may be associated with low salivary flow or/and low buffering capacity [49, 66, 93]. Dry mouth condition is usually related to ageing [24, 74, 84], even though some other studies have not found this correlation [9, 40]. It is well established that patients taking medications can also present with decreased saliva output [101], as well as those who have received radiation therapy for neck and head cancer [25]. It has been shown that sour foodstuffs have a strong influence on the anticipatory salivary flow [17, 58], which can be significantly increased when compared to the normal unstimulated flow rate [28]. Hypersalivation also occurs in advance of vomiting as a response from the ‘vomiting centre’ of the brain [59], as seen in individuals suffering from anorexia to bulimia nervosa, rumination or chronic alcoholism [68, 94]. The influence of saliva on the remineralization/rehardening of erosive damaged dental hard tissue is a controversial issue. It seems that in vitro, some rehardening could be expected if a
and act as a buffer to maintain the hardness of the tooth and can diffuse into the hard tissue of the tooth in beverages. Undissociated acid is the primary determinant of the dissociation rate of a solution’s ability to maintain its pH value. The primary determinant of the dissolution rate is the pH value, while buffering capacity has been accepted as a better indicator for the erosive potential of a beverage [29, 79]. Buffering capacity is associated with the undissociated acid in beverages. Undissociated acid is not charged and can diffuse into the hard tissue of the tooth and act as a buffer to maintain the H⁺ concentration. Consequently, the driving force for demineralization at the site of dissolution is maintained [30, 34]. Therefore, the greater the buffering capacity of the drink, the longer it will take for saliva to neutralize the acid. However, dilution will also reduce concentrations of Ca and P (if present), which have a protective effect [15, 63, 64].

The pH value and the Ca, P and F content of a drink or foodstuff determine the degree of saturation (DS) with respect to the tooth mineral, which is the driving force for dissolution. The DS is defined as the ratio of the mean ionic activity product (Ip) for HAP in solution to its solubility product constant (Ksp). When the tooth is in contact with acidic solutions, the following reaction occurs:

\[ \text{Precipitation} \leftrightarrow \text{Dissolution} \]

\[ \text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2 \rightarrow 10\text{Ca}^{2+} + 6\text{PO}_4^{3-} + 2\text{OH}^- \]

A small amount of tooth mineral dissolves, releasing Ca, P and OH ions. This process continues until the solution is saturated with respect to HAP. At that point, the rate of the mineral dissolution is equal to the rate of the mineral precipitation. This equilibrium constant for this saturated solution and solid formation (precipitate) is called Ksp. For a solution saturated with respect to HAP, the Ksp is \([\text{Ca}]^{10}[\text{PO}_4]^6[\text{OH}]^2\). Strictly speaking, the values within brackets represent the chemical activities of the component ions rather than their actual concentrations. It is noteworthy that when analysing the erosive potential of drinks or foods the chemical activity of a substance is the characteristic property that indicates the free available ions, although concentration is often used in practice instead. Chemical activity is a term used to describe the thermodynamical ‘effective concentration’ of a species in a mixture. For extremely dilute solutions, the chemical activity is approximately equal to the concentration. However, because activity is dependent on the temperature, pressure and composition of the mixture, the activity and the concentration are significantly different in most circumstances. For undersaturated and supersaturated solutions, the system is not at equilibrium, and Ip that has the same expression as Ksp is used. If Ip = Ksp, then the solution is just saturated with respect to HA. If Ip > Ksp, the solution is supersaturated with respect to dental hard tissue and will not dissolve it. If Ip < Ksp, the solution is undersaturated and leads to initial surface demineralization that is followed by a local rise in pH and increased mineral content in the liquid surface layer adjacent to the tooth surface. This layer will then become saturated with respect to the enamel (or dentine) and will not demineralize further [22, 30].

Acids, such as citric acid, exist in water as a mixture of H⁺, acid anions (e.g. citrate) and undissociated acid molecules, with the amounts of each determined by the acid dissociation constant and the pH of the solution. The H⁺ directly attack the crystal surface. Over and above the effect of the H⁺, the citrate anions may complex with Ca when the pH is high enough. Consequently, acids such as citric acid have double actions and may be highly damaging to the tooth surface [30]. Up to 32% of the Ca in saliva can be complexed by citrate at concentrations common in fruit juices, thus reducing the supersaturation of saliva and increasing the driving force for dissolution with respect to tooth minerals [73].

In summary, the two often-cited parameters, the pH and the titratable acidity, do not readily explain the extent of the erosive potential of food and drink. The mineral content is also an important parameter, as is the ability of any of the components to complex calcium and to remove it from the mineral surface.

### Behavioural factors

The manner in which dietary acids are introduced into the mouth will affect which teeth are contacted by the erosive challenge and, possibly, the clearance pattern. As lifestyles have changed throughout the decades, the total amount and frequency of consumption of acidic foods and drinks have also increased [16]. Soft drink consumption in the United States increased by 300% in 20 years [16], and serving sizes increased from 185 gr (6.6 oz) in the 1950s to 340 gr (12 oz) in the 1960s and to 570 gr (20 oz) in the late 1990s. Around the year 1995, between 56 and 85% of school children in the USA...
consumed at least one soft drink daily, with the highest amounts ingested by adolescent men. Of this group, 20% consumed four or more servings daily [32]. In 2007, the worldwide annual consumption of soft drink reached 552 billion litres, the equivalent of just under 83 l per person per year, and this is projected to increase to 95 l per person per year by 2012. However, the figure has already reached an average of 212 l per person per year in the United States in 2009 [81]. Studies in children and adults have shown that this number of servings per day is associated with the presence and the progression of erosion when other risk factors exist [66, 78].

Studies in children and adults have shown that the number of servings per day is associated with the presence and the progression of erosion when other risk factors such as swishing drinks are present [66, 78]. High erosion was associated with a method of drinking whereby the drink was kept in the mouth for a longer period of time [53]. Considerable risk of erosion was found with the frequent consumption of citrus fruits (more than twice a day) as well as the daily consumption of soft drink [49]. On the other hand, other studies were not able to find an association between dental erosion and behavioural factors [48], or they found only a weak association [75]. One can only speculate about the reasons. A possible explanation is the mode of questioning (oral vs. written questionnaire), the statistics employed (multivariate vs. univariate) and the population group under study (selected vs. randomly).

Excessive consumption of acidic candies combined with a low salivary buffering capacity or hyposalivation may aggravate erosive lesions [23, 51, 65]. The high intake of herbal teas, widely perceived as a healthy drink, may have an erosive potential exceeding that of orange juice [85].

A healthier lifestyle, paradoxically, can lead to dental health problems in the form of dental erosion, as it often involves a considered healthy diet with more fruits and vegetables. Health-conscious individuals also tend to have better than average oral hygiene. While good oral hygiene is of proven value in the prevention of periodontal disease and dental caries, frequent tooth brushing with abrasive oral hygiene products may enhance erosive tooth wear. At the other end of the spectrum, an unhealthy lifestyle may also be associated with dental erosion [102]. Wine has properties such as low pH and low calcium and phosphate content, which result in erosive potential. Alcoholics may be at particular risk for dental erosion and tooth wear as they often suffer from regurgitation.

The role of fluoride, calcium and phosphate in the prevention of erosion

Efforts have been taken to modify drinks or beverages with fluoride due to the previous findings that fluoride successfully inhibits tooth caries [71, 96]. Fluoride supplementation was found to reduce the erosive potential of a series of beverages, for example soft drinks and sports drinks [31, 35, 95]. It was also demonstrated that fluoride levels in beverages were statistically correlated with their potential erosive capability when no other aggressive factors were present [63]. However, the fluoride concentrations to be used to reduce tooth erosion have a risk of toxicity. Hence, the widespread use of fluoride is limited.

The modification of drinks and foods with calcium and phosphate compounds is a feasible and promising strategy against tooth erosion, especially with calcium, because of the increasing demand for a higher intake of this salt to satisfy the nutritional needs and to prevent osteoporosis [38]. The addition of calcium and/or phosphate to a beverage will increase its degree of saturation with respect to tooth mineral. Additionally, calcium can bind to citrate and prevent citrate from chelating calcium from enamel [30].

One of the earliest studies to report that the addition of calcium ions to acid solutions had an effect on the appearance of acid attack on human enamel was in 1953 by Besic [10]. Afterwards, many in vitro [6, 39, 50, 90] and in situ [45, 99] studies were performed and proved that calcium and/or phosphate additives increased the acid resistance of teeth. In a study by Hooper et al. [43], the erosive potential of sports drinks was reduced due to the addition of a calcium compound. A significant variation in the carbohydrate composition did not influence this outcome. In fact, many calcium-fortified beverages, such as pure juices and other drinks, have been introduced into European and United States markets. The addition of calcium into these commercial beverages was originally aimed to increase dietary calcium intakes for bone accretion and osteoporosis prevention [21, 38]. These commercially applied calcium concentrations were proven to cause less enamel demineralization [21, 38]. A recent study by Jensdottir et al. [52] demonstrated that after adding 15 mM calcium the erosive potential of an acidic candy was also significantly reduced.

In theory, a range of different calcium salts can be used to supply calcium ions, such as calcium gluconate, calcium lactate, calcium malate, calcium chloride and calcium citrate [4, 38, 50]. The challenge for beverage manufacturers is to select an appropriate calcium source that can provide a high ionic calcium concentration and decrease the erosive potential of a specific beverage without altering the taste. The first successfully modified ‘tooth-friendly’ soft drink was a blackcurrant drink with a low pH value calcium fortification. It has been shown to reduce the erosive demineralization compared with conventional blackcurrant drinks and orange juice during a period of 20 days [45, 46, 99].

Phosphate is usually applied in combination with calcium and/or fluoride. The presence of both calcium and
phosphorus in the same beverage is assumed to have a tandem effect on erosion prevention and be associated with a lower erosive potential of soft drink or orange juice [4, 50]. With a low level of mineral ions (0.5 mM Ca, 0.5 mM P and 0.037 mM F), some modified soft drink induced less dental loss and only exerted a minimal effect on the taste of the test beverages [4]. When the added Ca (42.9 mM) and P (31.2 mM) saturated an orange juice (pH = 4.0) with respect to apatite, Larsen and Nyvad [57] found no significant enamel erosion caused by this modified soft drink after immersion for 7 days.

Recently, much attention has been directed towards the effect of polymer phosphates, such as pyrophosphate, polyphosphate and tripolyphosphate, on tooth erosion. These polymer phosphates are usually used as preservatives in meat products [19] or in non-alcoholic flavoured drinks [7]. In a study by Barbour et al. [7], these food-approved polymer phosphates were observed to significantly reduce the dissolution rate of hydroxyapatite in a citric acid solution representative of soft drink. A subsequent in situ study found that the modifications of acidic soft drink with polyphosphate alone or combined with calcium or xanthan gum are all effective at reducing enamel erosion compared with the unmodified soft acidic drink [44]. The preventive effect of polymer phosphates might be due to the chemical nature of the polymer that it can be adsorbed onto the enamel surface. Phosphate groups in the polyphosphate may bind to the tooth surface and substitute for phosphate groups in the hydroxyapatite. Consequently, the detachment of ions is prevented and the surface area available for dissolution is reduced [6].

Modification of beverages with calcium or calcium phosphate has been generally accepted as an effective anti-erosion strategy, while the stability of the solution is still problematic and phase transformations may occur. To stabilize calcium and phosphate ions, casein phosphopeptides (CPP) were introduced. CPP, heavily phosphorylated peptides derived from milk casein proteins, contain amino acid sequences and strongly bind calcium ions to form soluble complexes [42, 77]. Therefore, CPP can localize ACP to form CPP-ACP nanocomplexes and provide a reservoir of calcium and phosphate ions to maintain a state of supersaturation in close proximity of dental hard tissues and induce possible remineralization [86]. After a number of in the clinic and laboratory experiments, CPP-ACP have been incorporated into dental care products to inhibit caries [1]. Recent evidence has also shown that CPP-ACP may protect teeth against erosion [80, 83, 89]. However, there are also a number of reports that show no protection of CPP-ACP against erosion [60, 75, 99]. As a functional ingredient, CPP-ACP was added to sports drinks by Reynolds et al. [97] and Ramalingam et al. [87] to raise the Ca-concentration in the drinks. The modified sports drinks reduced enamel demineralization and increased remineralization. Moreover, the incorporation of CPP-ACP did not affect the product’s taste [87]. In fact, casein alone has also been supplied in some sport drinks. A recent experimental study by Barbour et al. [7] found that casein protein itself, in the absence of any calcium phosphate particles, might provide significant protection against hydroxyapatite dissolution in acids. The inhibition of hydroxyapatite dissolution by casein was ascribed to the binding of casein to the hydroxyapatite surface.

The role of other ingredients in the prevention of erosion

The erosion-inhibiting potential of other metal ions, such as iron and copper, has also been investigated. An in vitro study by Brookes et al. [11], which originally aimed to investigate the effect of the copper ion on caries, showed that 10 mM CuSO_4·5H_2O in 10 mM acetic acid (pH = 3.2) reduced erosive tooth mineral loss by 49%. The mechanism of this might involve the formation of an acid-insoluble copper phosphate layer on the tooth surface [11]. A follow-up study by the same group indicated that 10 mM FeSO_4·7H_2O reduced synthetic hydroxyapatite loss by 51% [12]. Using bovine enamel powder, Buzalaf et al. [14] came to the same conclusion and demonstrated a reduction in tooth loss by iron ions in acids. Subsequently, a series study by Kato et al. [54–56] provided insight into the erosion resistance capability of iron in soft drink. It was shown that iron could interfere with the enamel dissolution in acidic drinks, where the prevention ability depended on the concentration of iron and the type of acid in the drinks. The mechanism responsible for the erosion-inhibiting of iron is not completely understood. Several possible explanations were suggested, such as forming an acid-resistant coating of hydroxy iron oxide on the tooth surface [98], participating in the remineralization of human enamel and in the nucleation of apatite [5, 88], replacing calcium in apatite [69, 88] and inhibiting demineralization [5]. However, Magalhaes et al. [69] found that the addition of low concentrations of Fe (0.047 mM) in combination with Ca (1 mM), F (1 mM) and P (1 mM) into a soft drink did not reduce the enamel loss compared with the pure beverage. Additionally, the supplemented iron might deteriorate the taste of beverages and affect tooth colour [14, 54, 55].

Amaechi et al. [2] found that the supplementation of an orange juice with xylitol (25% w/v) and fluoride (0.5 ppm) had a protective effect on dental erosion in vitro, while xylitol alone did not reduce erosion by orange juice. Xylitol has been approved for use in foods as a non-sugar sweetener for many years and can be found naturally in...
small quantities in fruits (including berries) and vegetables [33]. It might form complexes with calcium, penetrate into demineralized enamel and interfere with the transport of dissolved ions from the lesion to the demineralizing solution by lowering the diffusion coefficient of the calcium and phosphate ions [70]. More recently, Chunmuang et al. [18] showed that the addition of xylitol (25% w/v) alone or a xylitol (25% w/v)/fluoride (1.0 ppm) combination to orange juice could reduce enamel erosion. The conflicting conclusion was assumed to be due to the different experimental conditions [18].

In a study by Barbour et al. [6], xanthan and carboxymethylcellulose, which are often used in foods and drinks as thickening and gelling agents, were added to citric acid solutions and demonstrated some protection against hydroxyapatite dissolution. The two polymers are presumed to adsorb and form a preventing layer at the hydroxyapatite surface. This layer could inhibit dissolution by reducing diffusion at the hydroxyapatite surface and hence reduce the exchange of hydrogen ions and calcium and phosphate ions between the hydroxyapatite and the solution [6].

Rios et al. [92] found that the light cola drink is less erosive than the regular one. This lower erosive potential is possibly related to the presence of the amino acid phenylalanine. The erosion-preventing action of phenylalanine might be due to two reasons. First, the amino acid could act as a buffer system, increasing the neutralization and buffering the acids from the cola drink. Another possibility is the formation of an amino acid-based layer on dental surfaces. This layer might reduce dental erosion by acting as a diffusion barrier or a perm-selective membrane, thereby preventing the direct contact between the acids and the tooth surface.

Ovalbumin is the main protein found in the white of hens’ eggs. It is a complex protein and is used as an additive in many foods [20]. Ovalbumin was observed to adsorb to bovine enamel [82] and inhibit bovine enamel demineralization in vitro [3]. Hemingway et al. [41] added 0.02 and 0.2% w/v ovalbumin to citric acid solutions and found a lower hydroxyapatite dissolution rate under conditions within a range of pH values and calcium concentrations that represent dental erosion by citrus-based soft drink. Therefore, ovalbumin was regarded as a potential additive to reduce tooth erosion by citrus-based drinks. The adsorption of ovalbumin molecules onto the hydroxyapatite surface might be responsible for the protective effect. The adsorbed molecules can form a semi-permeable barrier, hindering the transport of proteins and/or calcium and phosphate ions. In this context, it has to be kept in mind that these strategies need a long enough contact time to the tooth in order to work properly. This contact time may be too short when a beverage is drunk quickly.

The role of the chemical and physical properties of diet in the prevention of erosion

Besides the modification of foods and beverages with a variety of functional ingredients, the optimization of the chemical and physical properties of foods or beverages may be a feasible and promising approach to inhibit tooth erosion and should be given consideration.

It is thought that the erosive potential of citric acid-containing beverages can be also decreased by replacing citric acid with hydrochloric and phosphoric acids, because citric acid is known to exhibit a greater erosive capacity [100]. The greater erosive potential of citric acid might be related to its ability to form chelating complexes. The titratable acidity, or buffering capacity, is a good indicator for the erosive potential of a beverage, even though pH has been used to measure acidity. The high buffering capacity of drinks or beverages resists the ability of saliva to alter pH and maintains the low pH status for a comparatively longer time [29, 79].

Ireland et al. [47] investigated the ability of soft drink to adhere to enamel. Two properties of a variety of drinks, including the contact angle (the angle a droplet of the liquid will make on the surface) and surface tension, were analysed to determine the degree to which a liquid will adhere to a surface. The results showed a ranking of the drinks indicating that the relative stickiness of beverages to enamel might be associated with the tooth erosion. The greater the adherence of an acidic substance is, the longer the contact time with the tooth surface and, therefore, the greater the likelihood of erosion will be. Busscher et al. [13] showed that the displacement of saliva by Cola required 14 ml/m², and the displacement of saliva by Diet Cola required 5 ml/m². However, displacement of Cola film by saliva required 45 ml/m², of Diet Cola by saliva 52 ml/m². It seems to be more difficult to displace a soft drink film by saliva than it is to displace a salivary film by a soft drink [13]. Further research is required to quantify the impact of these factors.

Conclusion

In this paper, the possible risk factors for tooth erosion and their interplay are discussed. Special attention is paid to various modifications of foods or beverages aimed at reducing tooth erosion (Tables 2, 3). Dietary modifications have been developed with varying success, while great efforts are still required to better prevent tooth erosion due to the complicated relationship between diet and erosion. The efficacy of aforementioned supplementation with various functional ingredients depends not only on their type and, but also on a series of factors, such as the pH
value, the amount of titratable acidity (or buffering capacity) and the chemical and physical properties of foods or beverages. At the same time, an appealing taste is another important criterion for the successful dietary modification.

Acknowledgments

This publication was commissioned by the Functional Foods Task Force of the European branch of the International Life Sciences Institute (ILSI Europe). Industry members of the task force are Abbott Nutrition, Barilla G. & R. Fratelli, BASF, Bionov, Biosearch Life, Cargill, Chiquita Brands International, Coca-Cola Europe, Danone, Dow Europe, DSM, DuPont Nutrition & Health, Institut Merieux, International Nutrition Company, Kellogg Europe, Kraft Foods Europe, Mars, Martek Biosciences Corporation, McNeil Nutritionals, Naturex, Nestlé, PepsiCo International, Pfizer Consumer Healthcare, Red Bull, Rudolf Wild, Schwabegroup, Royal Friesland-Campina, Soremartec Italia—Ferrero Group, Sudzucker/BENEO Group, Tate & Lyle Ingredients, Tereos-Syral, Unilever and Yakult Europe. This publication was coordinated by Dr. Alessandro Chiodini, Scientific Project Manager at ILSI Europe. For further information about ILSI Europe, please email info@ilsieurope.be or call +32 2 771 00 14. The opinions expressed herein and the conclusions of this publication are those of the authors and do not necessarily represent the views of ILSI Europe nor those of its member companies.

Declaration of interest

X. Wang and A. Lussi received a honorarium from ILSI Europe for their participation in this publication and reimbursement of their travel and accommodation costs for attending the related meetings.

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