Eur J Nutr (2012) 51 (Suppl 2):S31–S38
DOI 10.1007/s00394-012-0324-6

SUPPLEMENT

Functional foods/ingredients and oral mucosal diseases

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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

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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 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 patients-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

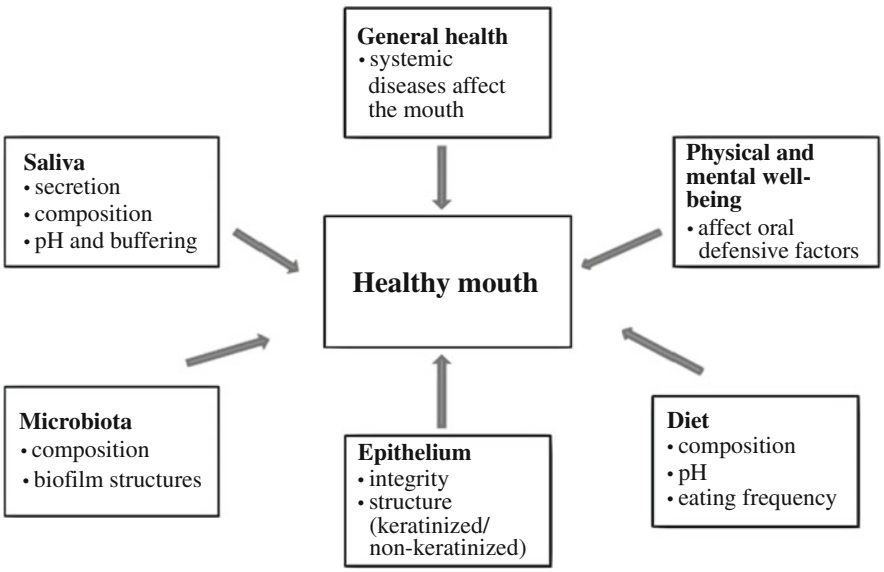

Fig. 1 Principal factors affecting health of the oral cavity. Several these factors offer possibilities for intervention

can also be used in diagnosis and in particular in the assessment of invasive yeast infections. Thus, there are validated methods for assessing the efficacy of intervention also regarding oral yeast infections.

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.

Aphtous stomatitis

Aphtous stomatitis or recurrent aphtous 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. Aphtous 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 aphtous stomatitis. These include, for example, stress, characteristically among women of the premenstrual phase as well as a genetic predisposition.

The diagnosis of aphtous 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 aphtous 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 psychological 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 contexts, 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, moclobemide 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 dimethylsulfide 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,

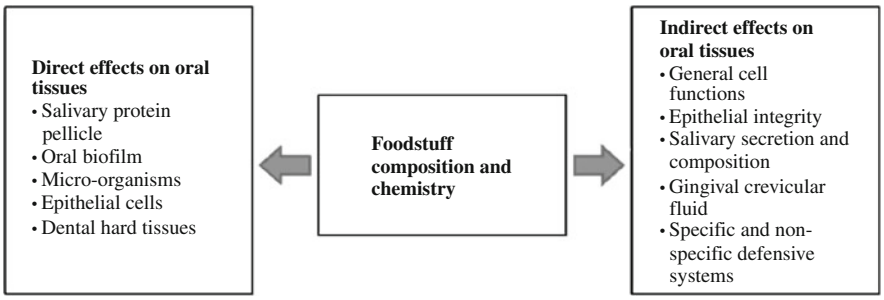

Fig. 2 Foodstuffs and drinks affect oral tissues both directly and indirectly

Table 1 Methods for monitoring the efficacy of treatment for oral mucosal diseases and symptoms

Method	Purpose
Visual analogue scale	Subjective and objective assessment (e.g. pain scale)
Biopsy specimens	Confirming diagnosis (e.g. lichen planus)
Microbial culture	Setting specific diagnosis (e.g. oral yeast infection)
Clinical oral examination	Recording signs of disease (e.g. mucosal lesions)
Blood tests	Confirmation of infection and for diagnosing specific diseases (e.g. viral infections)
Salivary tests	Setting diagnosis and monitoring treatment effect (e.g. dry mouth)
Structured questionnaire	Recording patient's symptoms and history (e.g. xerostomia)

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 Nutritionals, Naturex, Nestlé, PepsiCo International, Pfizer Consumer Healthcare, Red Bull, Rudolf Wild, Schwabegroup, Royal FrieslandCampina, Soremartec 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.

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.

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