

# Alleviation of halitosis by use of probiotics and their protective mechanisms in the oral cavity

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## Abstract

Regarding the relation of halitosis with oral infections and its effects on social relations between humans, the present study investigated the positive effects of probiotics on prevention or treatment of halitosis. The causative agents of halitosis are volatile sulphur compounds (VSCs), and halitosis is divided into oral and non-oral types according to the source of the VSCs. H<sub>2</sub>S and CH<sub>3</sub>SH are two main halitosis metabolites—produced following the degradation of proteins by bacteria in the mouth—however, CH<sub>3</sub>SCH<sub>3</sub> has a non-oral origin, and is a blood neutral molecule. Just as much as halitosis is important in medicine, its psychological aspects are also considered, which can even lead to suicide. Today, the use of probiotics as a new therapeutic in many roles is in progress. Most probiotics are used for the treatment of gastrointestinal tract disorders, but various studies on the alleviation of halitosis by use of probiotics have reported satisfactory results. The genera *Lactobacillus*, *Streptococcus* and *Weissella* are among the most useful probiotics for the prevention or treatment of halitosis in the oral cavity.

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## Introduction

Halitosis or bad breath, can have a variety of causes, such as poor oral hygiene, dental caries, periodontal diseases (periodontitis and gingivitis), corruption of residual food between teeth and tongue debris [1]. The term halitosis consists of two parts: *halitus* (a Latin word) meaning breath, and *osis* (a Greek suffix) meaning abnormal or diseased [2]. Gaseous compounds such as volatile sulphur compounds (VSCs) are responsible for

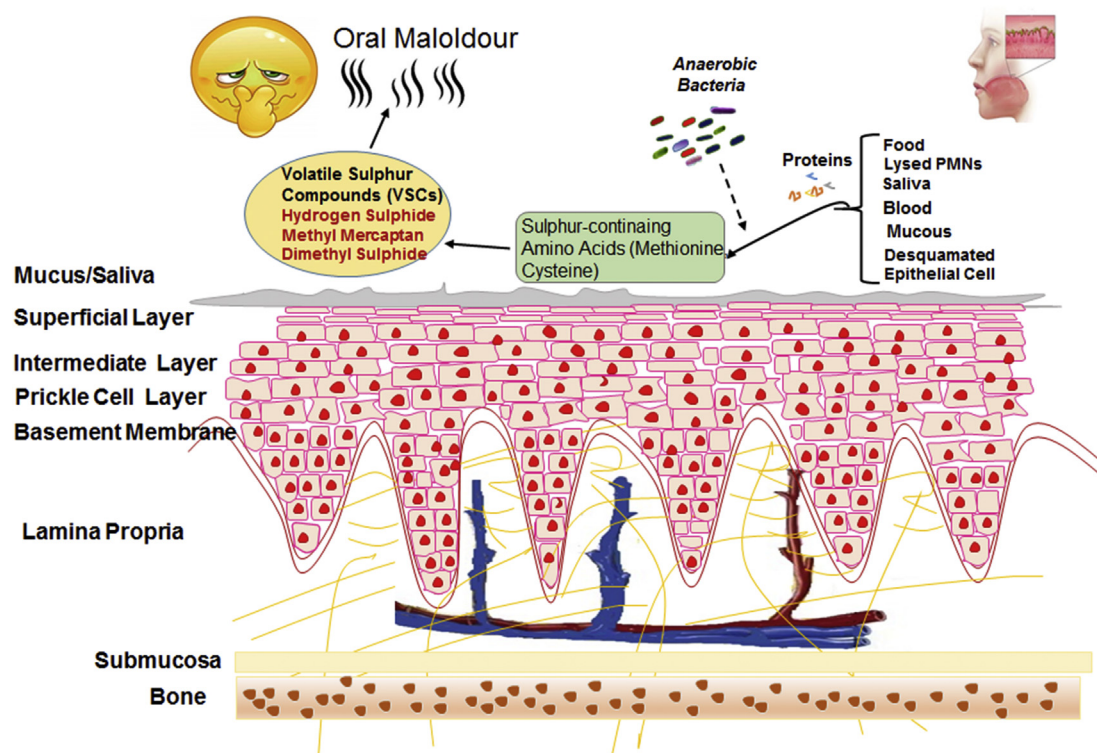
mouth malodour, and their sources are divided into oral and non-oral. VSCs are derived metabolites of the bacterial putrefaction process [3]. The majority of VSCs are produced following degradation of food and salivary proteins by oral bacteria, and the use of amino acids by VSC-producing bacteria. Most bacteria involved in periodontitis such as *Porphyromonas gingivalis*, *Treponema denticola*, *Prevotella intermedia* and *Fusobacterium nucleatum*, can produce VSCs. These compounds include hydrogen sulphide (H<sub>2</sub>S) and methyl mercaptan (CH<sub>3</sub>SH) [4,5]. Overall, halitosis classification consists of three categories—genuine halitosis, pseudo-halitosis and halitophobia (or psychological halitosis). Genuine halitosis is considered a pathological condition, as it is caused by oral bacterial infections and leads to periodontal diseases such as dental plaque (a bacterial biofilm), periodontitis and gingivitis. In such cases, treatment of the infections is urgent, and leads to amelioration and reduction in malodour. Pseudo-halitosis is associated with the absence of any pathological symptoms, but the person

believes in the presence of malodour in the mouth. Halitophobia occurs after treatment of genuine halitosis or pseudo-halitosis in patients who still think about and fear halitosis. Patients with halitophobia maintain an illusion about other people's hate for them [6]. Among all halitosis states, halitophobia is probably the worst, because it can gradually be exchanged for a social anxiety disorder or a state of social phobia. Individuals with halitophobia must be under the supervision of a psychological specialist, as they may progress to suicide [7]. Scientifically, probiotics encompass the viable bacteria and yeasts that, when consumed in adequate amounts, have benefits for humans (or animals) [8]. According to WHO, the Food and Agriculture Organization of the United Nations and the European Food Safety Authority, the acceptable conditions for probiotics include safety for humans, and persistence against acid and bile [9]. Eli Metchnikoff, the Russian scientist and Nobel laureate, was the first researcher to demonstrate the benefits of consumption of a yogurt probiotic on the gastrointestinal tract of Bulgarian peasants [10]. Today, studies have demonstrated the positive effects of probiotic products (especially fermented dairy products) in the treatment of many chronic gastrointestinal disorders such as diarrhoeal diseases, *Helicobacter pylori* infection, irritable bowel syndrome, non-alcoholic fatty liver disease and inadequate lactase digestion, as well as in immunosuppressive states, paediatric allergies, growth retardation,

hyperlipidaemia, halitosis and cancer prevention [11–18]. Probiotic microorganisms contain both bacteria and yeasts. The most usable bacterial genera include *Lactobacillus*, *Bifidobacterium*, *Enterococcus*, *Streptococcus*, *Pediococcus*, *Leuconostoc*, *Bacillus* and *Escherichia coli*; the only yeast is *Saccharomyces* [19]. Through science-based studies, consumption of probiotic products (e.g. yogurt, milk, cheese, butter, or even gum) can significantly mitigate or treat oral and dental diseases, such as caries, gingivitis and periodontitis [20–24]. In the present study, we critically summarize the relationship between the causative microorganisms of halitosis and probiotics effects (Fig. 1).

## Epidemiology of halitosis

Millions of people have halitosis worldwide; some studies on its prevalence report values between 22% and 50%, and others give 6% and 23% [25]. The American Dental Association, the largest dental association in the USA, reported that globally, approximately 50% of adults have had occasional halitosis, but 25% are affected by chronic halitosis. In general, oral hygiene is a very effective factor for the prevention of halitosis, because 80%–90% of halitosis is the result of long-term and untreated oral cavity disorders (caries and periodontal diseases), and is directly associated with poor oral hygiene [25]. Based on a



**FIG. 1.** General pattern of sulphur amino acid degradation and aetiopathogenesis of halitosis.

meta-analysis reported by Silva et al. [26], it was demonstrated that the incidence of halitosis in low- to middle-income countries (39.8%) is higher than in high-income countries (29%), which indicates the close relationship between halitosis and economic conditions. Poor cultural and economic conditions can be considered as two major factors for creating periodontal diseases and, consequently, halitosis; in low-income countries, conditions such as unhealthy diet and poor nutrition, physical inactivity, tobacco use, as well as excessive use of alcohol are more visible [27].

### Oral and non-oral halitosis

#### Oral halitosis

Based on the source of VSC production, halitosis is divided into extra-oral (or non-oral) halitosis and intra-oral (or oral) halitosis. The composition of the orally resident microbiota is over 700 species, and the physicochemical properties of saliva play a significant role in microbial equilibrium. One millilitre of saliva contains about 10<sup>8</sup> microorganisms. Poor oral hygiene and restoration defects lead to accumulation of food debris and dental bacterial plaque on the teeth and tongue; degradation of this retained debris by bacteria causes oral halitosis [28,29]. Therefore, 90% of halitosis is related to intra-oral halitosis, and only about 10% of cases are related to extra-oral [30–32]. However, no obvious association exists between halitosis and any specific bacterial infection, suggesting that bad breath reflects complex interactions between several oral bacterial species. It is generally believed that Gram-negative anaerobic bacteria digest proteins from food residues, desquamated cells from oral mucosa leucocytes and other saliva debris into amino acids that accumulate in the oral cavity and originate oral halitosis [33].

These bacteria can be isolated from the subgingival plaque in individuals with gingivitis or periodontitis, and the saliva and the dorsum of the tongue in healthy individuals. Several microorganisms recovered from periodontal lesions of gingivitis and periodontitis can produce large amounts of VSCs. Odour outcomes are significantly correlated with total counts of bacteria and the diversity of each type. As desquamating epithelial cells and remnants are available, putrefaction occurs. During the process of bacterial putrefaction, however, compounds other than sulphur compounds are also formed. Peptides are hydrolysed to amino acids, which can be metabolized further to amines or polyamines. The researchers concluded that halitosis is a result of multifaceted interactions between diverse species of bacteria [34].

In this regard, cleavage of certain amino acids led to bacterial metabolism production, principally of VSCs (H<sub>2</sub>S, CH<sub>3</sub>SH and

dimethyl sulphide [CH<sub>3</sub>]<sub>2</sub>S), organic acids (butyric acid), aromatic complexes (indole, skatole) and amines (putrescine, cadaverine). Studies *in vitro* and *in vivo* have demonstrated that oral surfaces are colonized by several bacterial species associated with oral malodour and responsible for the production of the malodorous compounds known as VSCs [35]. (Table 1).

Oral halitosis is caused by resident bacteria in the mouth. VSCs such as H<sub>2</sub>S and methyl mercaptan, are oral halitosis metabolites produced by oral cavity bacteria, especially tongue-coating areas [36]. The majority of cases of halitosis are related to oral halitosis, which is caused by different oral bacteria species. In the oral cavity, tongue coating, in particular, its dorsal surface, is considered the main area for halitosis production. This area is the best residential location for the accumulation of various bacteria. The studies show that the dorsal tongue has a peculiar capacity for binding to various bacteria. In this region, each epithelial cell can bind more than 100 bacteria—for comparison, the binding capacity of other types of oral epithelium is about 25 bacteria per cell. In addition, the existence of fissures in the dorsal tongue surface provides a hypoxic environment for the growth of VSC-producing anaerobic bacteria [37]. Usually, the VSCs and other odoriferous compounds are derived from the interaction of bacteria with specific amino acids. In general, the interaction of anaerobic bacteria with cysteine, methionine, tryptophan, arginine and lysine, leads to biotransformation of these amino acids to H<sub>2</sub>S, CH<sub>3</sub>SH, indole, putrescine and cadaverine, respectively [38,39].

#### Non-oral halitosis

As noted above, 10% of halitosis cases are related to non-oral halitosis. Several extra-oral conditions have been proposed that account for extra-oral halitosis, and can be divided into

**TABLE 1. Malodorous compounds known as volatile sulphur compounds (VSCs), source and bacterial species**

VSCs	Source	Bacterial species
H <sub>2</sub> S	Serum	<i>Prevotella intermedia</i> <i>Prevotella loescheii</i> <i>Porphyromonas gingivalis</i>
	Cysteine	<i>Peptostreptococcus anaerobius</i> <i>Micros prevotii</i> <i>Eubacterium limosum</i> <i>Bacteroides</i> spp. <i>Centipedia periodontii</i> <i>Selenomonas artemidis</i>
CH <sub>3</sub> SH	Serum	<i>Porphyromonas gingivalis</i> <i>Treponema denticola</i> <i>Porphyromonas endodontalis</i>
	Methionine	<i>Fusobacterium nucleatum</i> <i>Fusobacterium periodonticum</i> <i>Eubacterium</i> spp. <i>Bacteroides</i> spp.

halitosis from the ear, nose, and throat region, pulmonary pathology, gastrointestinal tract and blood-borne halitosis. In blood-borne halitosis, malodorous compounds in the bloodstream are carried to the lungs where they volatilize and enter the breath. Some systemic diseases are the basis of blood-borne halitosis, including liver pathology and endocrinological diseases, metabolic disorders, medications, and certain foods. Acute tonsillitis is the most significant reason for halitosis from the ear, nose, and throat region. Respiratory disorders such as bronchiectasis, lung abscesses or necrotizing lung neoplasia can produce an unpleasant odour. Several digestive diseases like gastro-oesophageal reflux or *Helicobacter pylori* infection may be associated with halitosis. Several well-recognized aetiologies for extra-oral malodour include renal failure, cirrhosis of the liver and diabetes [40–42]. The main microorganisms associated with oral halitosis and non-oral halitosis are listed in Table 2.

## Claimed beneficial probiotic bacteria

### Probiotics as endogenous microflora

Some bacteria and viruses are toxic and lethal for humans, including *Yersinia pestis*, *Bordetella pertussis*, *Clostridium tetani*, *Mycobacterium tuberculosis* and *Vibrio cholerae*, as well as influenza virus and human immunodeficiency virus. However, scientific findings are scarce concerning the endogenous microflora that live with humans and are in a symbiotic state. Human microbiome describes a beneficial relationship between human and endogenous microorganisms [19,43].

**TABLE 2. Main microorganisms associated with oral halitosis and non-oral halitosis**

Potential microorganisms associated with halitosis (in alphabetical order)	Cause of non-oral halitosis
<i>Atopobium parvulum</i>	Respiratory system problems
<i>Campylobacter rectus</i>	- upper respiratory tract problems
<i>Centipeda periodontii</i>	- lower respiratory tract problems
<i>Eikenella corrodens</i>	Sinusitis
Enterobacteriaceae	Antral malignancy
<i>Eubacterium sulci</i>	Foreign bodies in the nose or lung
<i>Fusobacterium nucleatum</i> subsp. <i>nucleatum</i>	Nasal malignancy and nasal sepsis
<i>Fusobacterium nucleatum</i> subsp. <i>polymorphum</i>	Subphrenic abscess
<i>Fusobacterium nucleatum</i> subsp. <i>vincentii</i>	Tonsilloliths and tonsillitis
<i>Fusobacterium periodonticum</i>	Pharyngeal malignancy
<i>Micromonas micros</i>	Lung infections, bronchitis and bronchiectasis
<i>Porphyromonas endodontalis</i>	Lung malignancy
<i>Porphyromonas gingivalis</i>	Gastrointestinal disease
<i>Prevotella (Bacteroides) melaninogenica</i>	Hepatic disease
<i>Prevotella intermedia</i>	Haematological disorders
<i>Solobacterium moorei</i>	Endocrine system disorders
<i>Tannerella forsythia (Bacteroides forsythus)</i>	Metabolic conditions
<i>Treponema denticola</i>	Leukaemias and renal failure

### Commensal probiotics in the oral cavity

Although many factors such as food debris, metabolic disorders and respiratory tract infections can contribute to the halitosis phenomenon, the main causative factor for halitosis is an imbalance (dysbiosis) in oral commensal flora composition [44]. *Streptococcus salivarius* is a non-pathogenic and predominant oral species that is one of the most important commensal probiotics, and most frequently isolated from people without halitosis. *Streptococcus salivarius* K12 can produce two lantibiotics—salivaricin A2 (SalA2) and salivaricin B (SboB). Clinical trials show that antimicrobial mouthwash containing *Streptococcus salivarius* K12 significantly reduced the levels of VSC-producing bacteria [45]. Burton *et al.* [46] concluded that the use of *Streptococcus salivarius* K12 as a probiotic, originally sourced from oral commensal bacteria, can play a pivotal role in the treatment of halitosis.

## Protective mechanisms of probiotics in the oral cavity

The presence of beneficial microbiota or so-called probiotics in or on the human body has advantages, such as increased resistance against infections through antimicrobial activities (to produce organic acids and hydrogen peroxide and bacteriocins); creation of biolayers as a protective lining for oral tissues against infectious bacteria, competitive adhesion to dental surfaces with pathogenic bacteria; modulation of the pH and oxidation–reduction potential conditions; and differentiation and enhancing of the host cellular and humoral immune system (*Lactobacillus rhamnosus* GG can prevent allergy in susceptible individuals) [41,47,48]. Enrichment of food products with probiotic strains (e.g. yogurt, butter, milk, kefir and cheese) can produce substances such as vitamins B6 and B12, riboflavin, folic acid, niacin and short-chain fatty acids (lactic acid, propionic acid). Collectively, these nutritional mixtures can assist in the improvement of gastrointestinal tract function or even halitosis [49]. About 70% of people worldwide are lactose intolerant and develop diarrhoea following consumption of milk. Probiotics *Streptococcus thermophilus* and *Lactobacillus bulgaricus* possess lactase enzymes, and their addition to milk can alleviate the clinical symptoms of lactose intolerance [50].

## Probiotics and prophylaxis of dental caries

One of the causative factors of oral halitosis is dental caries. Dental caries (or tooth decay) is one of most common oral

disease worldwide, and as a multifactorial disease is caused by oral pathogenic bacteria, which lead to acidic demineralization of enamel [51]. Different genera of bacteria can be used as probiotics. Nevertheless, the genera *Lactobacillus* and *Bifidobacterium* are most frequently used as probiotic products. The useful *Lactobacillus* strains include *L. acidophilus*, *L. johnsonii*, *L. casei*, *L. rhamnosus*, *L. gasseri* and *L. reuteri* and the *Bifidobacterium* strains are represented by *B. bifidum*, *B. longum* and *B. infantis* [52]. Following oral consumption, these bacteria can be used as cariostatic probiotics in the prevention of dental caries. Based on dentistry studies, it has been demonstrated that consumption of bovine milk containing *L. rhamnosus* GG (LGG), and *L. reuteri* bacteria, significantly reduced the number of *Streptococcus mutans* and *Streptococcus sobrinus*, two of the main causative pathogens for dental caries. Fermentation of carbohydrates in the diet by *Streptococcus* spp. and decreased pH (from 7.0 to 4.0) of dental plaque lead to enamel demineralization. Hence, probiotic bacteria can be used as preventive bacteria in dairy products [53]. Conversely, some species of lactobacilli, such as *L. salivarius* LS1952R, show potentially cariogenic activity in animal (rat) models. Firm adherence to the hydroxylapatite on the tooth surface is an inherent ability of the probiotic bacterium *L. salivarius* LS1952R strain for cariogenic activity [54]. More recently, based on *in vitro* and *in vivo* experiments, it has been proved that *Weissella cibaria* (previously classified in the genus *Lactobacillus*) as a new probiotic strain can prevent dental caries and significantly inhibits the formation of biofilm by *S. mutans*. This bacterium produces a remarkable amount of hydrogen peroxide, and can congregate with *F. nucleatum* and inhibits the production of VSCs by these pathogens in the oral cavity [55–57] (Fig. 2). Briefly, many studies that were performed on the effectiveness of probiotics on cariogenic pathogens are listed in Table 3 [58–64].

## Probiotics as immunomodulators in periodontal diseases

Periodontal diseases (or gum diseases) are caused by bacteria, in particular, Gram-negative bacteria in dental plaque, and comprise the destructive inflammation of the gingiva (gingivitis) and supporting structures of the teeth (periodontitis). Periodontal lesions are only a consequence of morphological defects but are not a direct consequence of bacteria found in dental plaque [65]. Although at the onset of periodontal disease the bacterial infection is not responsible for true halitosis, if the periodontal disease is not treated, then persistent infections maintain oral conditions leading to halitosis [66]. Pro-inflammatory cytokines such as tumour necrosis factor- $\alpha$  and interleukin-1 $\beta$  play a pivotal role in periodontal diseases, and it is demonstrated that commensal probiotics such as *Lactobacillus bulgaricus*, *Streptococcus thermophiles* and *Lactobacillus casei* DN 114 001 enhance the production of pro-inflammatory cytokines in blood culture [67]. On the other hand, various studies have shown that the genus *Lactobacillus* (*L. paracasei*, *L. plantarum*, *L. rhamnosus* and *L. salivarius*) can inhibit the growth of periodontal pathogens such as *Porphyromonas gingivalis*, *Prevotella intermedia*, *Aggregatibacter actinomycetemcomitans* and *Tannerella forsythia* [68]. Schmitter et al. [69] showed that the positive potential anti-inflammatory effects of probiotic strains *L. paracasei* LPc-G110 (SYBIO-15) and *L. plantarum* GOS42 (SYBIO-41) on periodontal diseases were significantly dose-dependent and independent of their viability. In another study, which was performed by Twetman et al. [70], consumption of chewing gum containing *L. reuteri* as a probiotic could have an impressive effect on the reduction of the pro-inflammatory cytokines tumour necrosis factor- $\alpha$  and

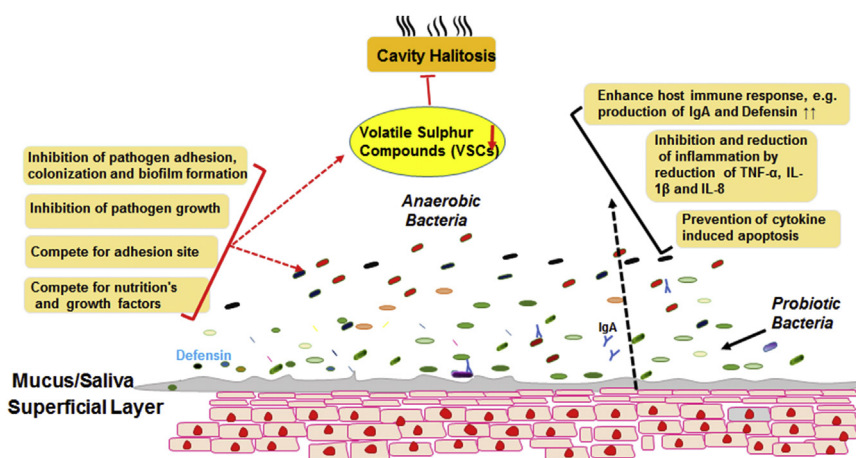


FIG. 2. Possible mechanisms of probiotics in prevention of halitosis.

**TABLE 3.** Effective probiotics against oral cariogenic pathogens

Probiotic species (or strain)	Cariogenic pathogens	Ref.
<i>Lactobacillus lactis</i> NCC2211	<i>Streptococcus sobrinus</i> OMZ176	[58]
<i>Lactobacillus fermentum</i>	<i>Streptococcus mutans</i>	[59]
<i>Lactobacillus rhamnosus</i> GG	<i>S. mutans</i>	[60]
<i>Lactobacillus reuteri</i> ATCC 55730	<i>S. mutans</i>	[61]
<i>Lactobacillus salivarius</i> BGHO1	<i>S. mutans</i>	[62]
<i>L. rhamnosus</i> GG and <i>Lactobacillus bulgaricus</i>	<i>Porphyromonas gingivalis</i> , <i>Fusobacterium nucleatum</i> and streptococcal species	[63]
<i>Lactobacillus</i> strains	<i>S. mutans</i> and <i>P. gingivalis</i>	[64]

interleukin-8 in the gingival crevicular fluid of volunteers with moderate levels of gingivitis and bacterial plaque. There are three possibilities for the protective effects of *L. reuteri* in periodontal diseases: first, the existence of two strong bacteriocins, reuterin and reutericyclin, which inhibit the growth of a wide range of pathogenic bacteria; second, the strong ability of *L. reuteri* to adhere to host tissues and compete with pathogens; and third, the known previous anti-inflammatory effects of this bacterium as an immunomodulator in gastrointestinal tract infections as an acceptable document for beneficial effects of *L. reuteri* in periodontal diseases [70]. The special defensive and immunomodulatory mechanisms of each oral probiotic against pathogens are listed in Table 4.

**TABLE 4.** Defensive and immunomodulatory mechanisms of probiotics against oral pathogens

Probiotic species	Protective mechanism(s)	Ref.
<i>Lactobacillus reuteri</i>	Production of reuterin, reutericyclin Reduction of TNF- $\alpha$ , IL-1, IL-8 and IL-17	[71]
<i>Weissella cibaria</i>	Inhibition of formation of biofilm by <i>Streptococcus mutans</i>	[72]
<i>Streptococcus salivarius</i> K12	Inhibition of production of VSCs by <i>Fusobacterium nucleatum</i>	[45]
<i>Lactobacillus rhamnosus</i> GG	Secretion of salivarin A2 and B	[63]
<i>Bifidobacterium animalis</i> ssp. <i>lactis</i>	Adhesion to saliva-coated hydroxyapatite	[73]
<i>Bacillus subtilis</i>	Inhibition of bone loss	[74]
<i>Bacillus licheniformis</i>	Inhibition of bone loss	[74]
<i>Lactobacillus brevis</i> CD2	Inhibition of bone loss	[75]
<i>Lactobacillus rhamnosus</i> ATCC 9595	Inhibition of CXCL8 attenuation by <i>Porphyromonas gingivalis</i>	[76]
<i>Lactobacillus casei</i> Shirota	Promote T helper type 1 and type 17 responses	[77]
<i>Lactobacillus delbrueckii</i> subsp. <i>bulgaricus</i>	Augmentation of natural killer cells activity through the induction of IL-12 production by monocytes/macrophages (anti-cancer)	[78]
<i>Enterococcus durans</i>	Inhibition of IL-6	[78]
<i>Pediococcus acidilactici</i> UL5	Anti-bacterial and anti-adherence effects	[78]
<i>Leuconostoc mesenteroides</i> B7	Reduction of TNF- $\alpha$ and IL-1 $\beta$	[79]
	Production of pediocin PA-I	[80]
	Production of leucocin B	[81]

Abbreviations: IL-1 interleukin-1; TNF- $\alpha$ , tumour necrosis factor- $\alpha$ .

## Conclusion

Today, the emergence of bacteria resistant to a wide range of antibiotics has become one of the main concerns of humans in combatting infectious diseases. For this reason, using an alternative method for the prevention and treatment of infectious diseases is considered urgent. As noted previously, the occurrence of dysbiosis in the population of resident oral bacteria and the domination of pathogens over commensal flora lead to the development of pathological states such as periodontal diseases, dental plaque, caries and eventually oral halitosis. Based on many scientific studies, it is concluded that consumption of probiotics can be a better alternative to antibiotics for the alleviation of gastrointestinal disorders. Probably the best strategy for the prevention or even treatment of oral cavity diseases by probiotics is the identification and selection of probiotic bacteria according to the source of commensal microflora in the mouth. Probiotics have various advantages such as antimicrobial activities, powerful binding capacity, the formation of protective biolayers, neutralization of acidic pH, modulation of oxidation–reduction potential, augmentation of the immune system and reduction of pro-inflammatory cytokines. These qualities combined lead to the improvement of oral cavity disorders, and also to the prevention or amelioration of oral halitosis. Less than 10% of halitosis cases are related to extra-oral halitosis. This type of halitosis is derived from the blood and respiratory tract. The main factors of extra-oral halitosis are dimethyl sulphide and tuberculosis respectively from blood and lungs. The source of dimethyl sulphide is unknown, but the likely complete treatment of patients affected by tuberculosis has an impressive effect on the alleviation of extra-oral halitosis. However, before the use of probiotic therapy for periodontal diseases, several aspects of this type of treatment must be considered. These include (a) evaluation of length and mode of therapy for the prevention of reverting to dysbiotic status after treatment; (b) careful investigation of cariogenic probiotic strains during the treatment of periodontal diseases; and (c) complete supervision of the administration of probiotics in patients with mild to moderate immune suppression.

## Conflict of interest

The authors have none to declare.

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