Probiotics & Antimicro. Prot.
DOI 10.1007/s12602-017-9261-2

Influence of Oral Probiotic *Streptococcus salivarius* K12 on Ear and Oral Cavity Health in Humans: Systematic Review

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Abstract Traditionally, probiotics are linked to the good health of the intestine and most clinical studies focus on that field. Evidence of oral probiotic use for ear and oral cavity disease prevention with impact on human health is limited. This work reviews existing studies and literature on *Streptococcus salivarius* K12 as an oral probiotic and effects of *S. salivarius* K12 on human ear and oral cavity human health. The studies were accessed via database searches: MEDLINE, PubMed, and Elsevier. The search included/focused on/encompassed publications from 2003 to 2016 with keywords related to K12 *Streptococcus salivarius*, bacteriocin-like inhibitory substances (BLIS) K12, probiotic K12 *salivarius*, and K12 probiotic health effects. Only a small amount of studies was identified: the total of 68 studies was identified, 35 of which were relevant after screening, and 9 were included in the final analysis. Very little literature is available about the association/correlation between/connection/interrelation of *S. salivarius* K12 with/and human ear and oral cavity health. *S. salivarius* K12 may have a role in reducing the occurrence and/or severity of secretory otitis media (SOM) and also in prevention of streptococcal and viral pharyngotonsillitis in children. Research highlights that *S. salivarius* K12 has shown promising results in treatment of halitosis, but data are still deficient. Further studies need to be initiated to improve understanding of the association of oral probiotic *S. salivarius* K12 with human ear and oral cavity health.

Keywords *Streptococcus salivarius* K12 · BLIS K12 · *Otitis media* · Oral health

Introduction

In recent years, probiotics have become interesting for their beneficial role for the stomach, vaginal mucosa, urinary tract, skin, and oral cavity [1–4]. Probiotics are defined as microorganisms that, when administered in adequate amounts, confer a health benefit on the host [5]. So far, most probiotics to be investigated have been members of intestinal microbiota. Knowing that probiotics, in addition to their fermentation role in the gastrointestinal tract, can also influence the immune system, the knowledge has opened many possibilites in the development of probiotics for therapeutic purposes. Mechanisms that probiotics can use to interfere with the activity of pathogenic bacteria include (a) the production of antimicrobial substances (small molecules, bioactives peptides, bacteriocins), (b) the creation of a physiological environment that is unfavorable for the pathogen (competing with the nutrients, altering the pH), (c) the adherence to epithelial cells and thereby preventing pathogen interaction with surface molecules. Also, probiotics or their metabolites can interact with various receptors on epithelial cells and through different pro-inflammatory and anti-inflammatory signaling pathways balance homeostasis [6, 7]. *Streptococcus salivarius* is the primary and predominant colonizer of oral mucosal surfaces in humans and does not initiate infections in healthy individuals. In addition to the oral cavity, it also inhabits the stomach and jejunum. Originally, K12 was isolated from the throat of a healthy schoolchild in New Zealand [8]. The K12 strain became

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Published online: 24 February 2017

the first of *S. salivarius* species to be commercially developed as a probiotic. Strain K12 has been investigated for its ability to interfere with the growth of pathogens inhabiting the nasopharynx and/or oral cavity [9]. *S. salivarius* K12 produces bacteriocin-like inhibitory substances (BLIS): the lantibiotics salivaricin A2 and salivaricin B. These lantibiotics proved effective against *Streptococcus pyogenes* and various bacterial species in in vitro studies. In addition to bacteriocin production, K12 strain also has immunomodulatory properties and contributes actively to the host defense process: downregulating inflammatory responses by inhibiting the NF-kB pathway, interfering with IL-8 synthesis, and suppressing IL-8 secretion [10, 11]. *S. salivarius* K12 is a probiotic intended for use in the oral cavity [12].

K12 Health Effects—the Ear and Oral Cavity

Traditionally, probiotics are linked to the good health of the intestine and most clinical studies focus on the prevention or treatment of gastrointestinal infections and diseases. However, during the last decade, an increasing number of studies have investigated the health effects of probiotic bacteria in the treatment and/or prevention of urogenital and respiratory infections and in the prevention of allergies and atopic diseases in infants [13].

Otitis media is one of the most common problems encountered by pediatricians. Otitis media results in high consumption of drugs and considerable absenteeism from work and school [14]. About 80% of children have at least one episode of acute otitis media (AOM), and between 80 and 90% of preschool children have at least one episode of secretory otitis media (SOM) [15]. SOM, asymptomatic persistence of effusion in the middle ear cavity, is a possible sequel of AOM and is mainly characterized by persistent fluid in the middle ear cavity [16]. The most common bacterial pathogens causing AOM, such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and *S. pyogenes*, ascend through the eustachian tube from the nasopharynx to the middle ear, causing an inflammatory response. One third of bacterial infections are due to *S. pneumoniae*; one third to *H. influenzae*; one sixth to *M. catarrhalis*; and the rest to a mixture of species [17, 18].

Halitosis, bad breath, or oral malodor has a large social and economic impact. For patients suffering from bad breath, it causes embarrassment and affects their social communication and life. Moreover, halitosis can be indicative of underlying diseases [19]. Microbial proteolysis in the oral cavity is the main cause of oral malodor [19]. Halitosis can be classified either as genuine halitosis, pseudohalitosis, or halitophobia. Genuine halitosis is more common and usually related to an organic pathology such as periodontitis [20]. There is a positive correlation between halitosis and periodontitis [19]. Management of oral malodor is directed at managing and reducing the bacterial load both in periodontitis and in tongue coatings by proper oral hygiene measures, control of tongue flora by brushing or scraping, possibly the adjunctive use of antiseptic agents [21], and also use of oral probiotics [20].

Acute pharyngotonsillitis is one of the most frequent causes of visits to the primary care pediatrician's office. The incidence of pharyngotonsillitis is very high in children and is caused by bacteria in about 35% of cases and by respiratory viruses in about 65% of cases [22, 23]. Group A beta-hemolytic streptococci (GABHS) or *S. pyogenes* causes 15–30% of cases of acute pharyngotonsillitis in the pediatric age group [24]. *S. pyogenes*, *H. influenzae*, *S. pneumoniae*, and *M. catarrhalis* are responsible for almost all bacterial pharyngotonsillitis cases in children and adults [25]. The health benefit of *S. salivarius* K12 in control of pharyngeal infections could be attributed both to its effect in altering the host microbiota and to its potential antiinflammatory properties [10]. Due to the potential benefits of probiotics in pharyngotonsillitis treatment and prevention, it is important to do more research.

Methods

Data Sources

In May 2016, we searched the MEDLINE, PubMed, and Elsevier databases for studies about the probiotic *S. salivarius* K12 and its association with human ear and oral cavity health to provide a systematic review of the existing literature on the use of *S. salivarius* K12 and its effects on human ear and oral cavity health. We searched for publications between years 2003 and 2016 with keywords related to the K12 *Streptococcus salivarius*, BLIS K12, and K12 probiotic and health effects. A literature review was conducted with the aim of identifying *S. salivarius* K12 association with human ear and oral cavity health effect.

Rather, priority was given to the following studies that:

- were papers or reports of consensus opinions or
- have had a significant impact on the understanding of association between *S. salivarius* K12 and ear and oral cavity health.

Considered as relevant were clinical studies, retrospective observational analysis, and one in vitro study because they demonstrate *S. salivarius* K12 antimicrobial activity against bacteria involved in halitosis. Inclusion criteria: original publications describing the impact of *S. salivarus* K12 on ear and oral cavity health, published in English before May 2016. Considered were results for terms: BLIS, probiotic K12 *salivarius*, and K12 probiotic health effects. This report focused on the scientific important information and definition of *S. salivarius* K12 probiotic and avoided potential conflict of interest, and every commercial name or brand name was deleted and replaced by the name of the strain included in the product.

Results

In general, the scientific literature has detailed an increasing number of beneficial health effects of probiotics. Researchers have demonstrated an impact of probiotics on the adaptive immune system, prevention or alleviation of allergies and atopic diseases in infants, and treatment or prevention of urogenital and respiratory tract infections [26]. Much has been written about the potential benefits of probiotics, and there is a growing body of evidence for the role of probiotics in the gastrointestinal system (gastrointestinal infections, irritable bowel syndrome, inflammatory bowel disease) [27]. Only a relatively small number of studies have described the effects of probiotics on systems other than the human gastrointestinal tract, e.g., effects on the ear and oral cavity. Some research has examined the potential of *S. salivarius* K12 and applicability in the improvement of oral health. Beneficial organisms having the ability to adhere and colonize the oral cavity surfaces are referred to as "oral probiotics" [28].

Search Results

A flow diagram of the search strategy is provided in Fig. 1. This literature review for the period from 2003 to 2016 identified over 110 studies; over 68 relevant after screening; and 9 articles included. In 7 studies, the used research method is clinical trial; in 1, retrospective observation analysis; and in 1, in vitro. We decided to include that study in this paper because it represents research about antimicrobial activity against bacteria present in oral malodor and because of small amount of clinical studies that research impact of *S. salivarius* K12 on halitosis. The summary of studies is presented in Table 1, indicating the effects of *S. salivarius* K12 on human ear and oral health.

Discussion

Observed Effects on Oral Health

Acute pharyngitis and/or tonsillitis in children are among the most common recurrent diseases seen by general practitioners and pediatricians.

In a study from Italy conducted on 82 children, including 65 with and 17 without a recent diagnosis of recurrent oral streptococcal pathology, 45 were treated daily for 90 days with an oral slow-release tablet containing 5 billion colony forming units (CFU) of *S. salivarius* K12/tablet at manufacturing date and not less than 1 billion CFU/tablet at expiry date. Chlorhexidine (CHX) 0.2% mouthwash is recommended before administration of the first tablet in order to enhance the colonization process of the strain, reducing extreme competition from endogenous *S. salivarius* inhabiting the mouth. After 90 days of treatment, a 6-month follow-up period without treatment was included to evaluate a possible persistance of the protective role related to *S. salivarius* K12. The author's conclusion was that prophylactic administration of *S. salivarius* K12 to children with a history of recurrent oral streptococci pathology reduced episodes of streptococcal throat infection and/or angina as well as episodes of acute

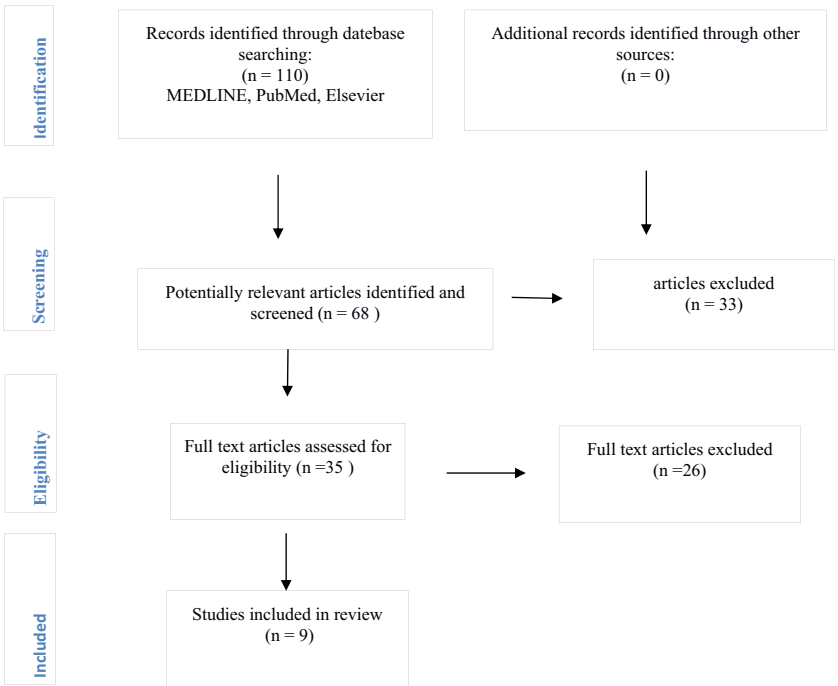

Figure 1 Prisma flow diagram of literature research for probiotic *S. salivarius* K12—association with ear and oral cavity human health effects. Overview of the geographic distribution of the studies indicates that the large majority of the studies reviewed to date have been conducted in New Zealand—3, Italy—5, and Switzerland—1.

Table 1 Probiotic *S. salivarius* K12—ear and oral cavity human health (studies: Europe, New Zealand)

References (location of study)	Type of epidemiological study	Probiotic *S.salivarius* K12	Population and period of observation	Observed health effects	Methods	Findings and conclusions	Health effect
Di Pierro et al., 2012 [29] Italy	Clinical trial	K12	82 children, including 65 with and 17 without a recent diagnosis of recurrent oral streptococcal pathology.	K12 efficacy in reducing the incidence of streptococcal pharyngitis and/or tonsillitis and episodes of acute otitis media.	45 children were treated daily for 90 days with an oral slow-release tablet (containing 5 billion UFC/tablet at manufacturing date and not less than 1 billion UFC/tablet at the expired date of *S. salivarius* K12) and the remaining 20 served as an untreated control group.	Prophylactic administration of *S. salivarius* K12 to children with a history of recurrent oral streptococcal pathology-reduced episodes of streptococcal pharyngeal infections and/or tonsillitis as well as episodes of acute otitis media.	Pharyngeal infections and/or tonsillitis
Di Pierro et al., 2014 [30] Italy	Multicenter, open, nonrandomized, controlled clinical trial	K12	61 children with a diagnosis of recurrent oral streptococcal disorders. 32 males (53.4%) and 29 females (46.6%).	Efficacy of *S. salivarius* K12 in the prevention of pharyngotonsillitis from group A *S. pyogenes* during the study period. Efficacy of *S. salivarius* K12 in reducing viral pharyngo-tonsillar infections in the same period, the onset of side.	The K12 strain was formulated in the form of slowly dissolving oral tablets. 31 children were enrolled to be treated daily for 90 days with a slow-release tablet for oral use, containing no less than 1 billion colony-forming units/tablet of *S. salivarius* K12 and the remaining 30 served as the untreated control group.	Prophylactic administration of *S. salivarius* K12 to children with a history of recurrent oral streptococcal disease resulted in a considerable reduction of episodes of both streptococcal and viral infections and reduced the number of days under antibiotic and/or antipyretic therapy and days of absence from school or work.	Pharyngotonsillar infections
Gregori et al., 2016 [31] Italy	Retrospective observational analysis	K12	12 primary care pediatritians, a total of 130 children who had experienced recurrent GABHS pharyngo-tonsillar infections	Study goal was to assess whether the administration of the oral probiotic, Streptococcus salivarius K12 (SsK12) could reduce the occurrence of GABHS pharyngo-tonsillar infections in children who had a recent history of recurrent episodes of these infections.	12 of 33 primary care pediatricians of the LHU of Piacenza participated in the study. Each pediatrician collected retrospective data of patients ranging from 3 to 7 years of age who had been diagnosed with GABHS RPTIs.	These observations are supportive of the use of probiotic *S. salivarius* K12 for the control of recurrent GABHS pharyngo-tonsillar infections in children, and as an associated benefit, the use of this probiotic could lead to reduced antibiotic consumption.	Pharyngo-tonsillar infection
Di Pierro et al., 2013 [32] Italy	Clinical evaluation	K12	40 adults with a diagnosis of recurrent oral streptococcal	Clinical evaluation of the oral probiotic *S. salivarius* K12 in the	20 subjects took a tablet containing *S. salivarius* K12 for/over the period	Prophylactic administration of *S. salivarius* K12 to	Pharyngitis and/or tonsillitiscaused by *S.*

Table 1 (continued)

			pharyngitis were included in the study.	prevention of recurrent pharyngitis and/or tonsillitis caused by *S. pyogenes* in adults.	of 90 days. The other 20 subjects served as untreated controls. A 6-month follow-up was included to evaluate any persistent protective role.	adults having a history of recurrent oral streptococcal pathology reduced the number of episodes of streptococcal pharyngeal infections and/or tonsillitis.	*pyogenes* in adults.
Burton and Chilcott et al., 2006 [33] New Zealand	Preliminary study	K12	23 subjects with halitosis,13 males, 10 females	Effect of probiotic *S. salivarius* K12 on oral malodor parameters	Subjects screened for the levels of VSC in their oral cavity air samples (breath scores) using a halimeter. Based on the average of three readings.	The outcome of this preliminary study indicates that the replacement of bacteria implicated in halitosis by colonization with competitive bacteria such as *S. salivarius* K12 may provide an effective strategy to reduce the severity of halitosis. Administration of bacteriocin-producing *S. salivarius* after an oral antimicrobial mouthwash reduces oral VSC levels.	Halitosis
Masdea et al., 2012 [34] Switzerland	In vitro	K12		Antimicrobial activity of *S. salivarius* K12 on bacteria involved in oral malodor. To investigate the antimicrobial activity of the bacteriocin-producing strain *S. salivarius* K12 against several bacteria involved in halitosis.	The inhibitory activity of *S. salivarius* K12 against *Solobacterium moorei* CCUG39336, four clinical *S. moorei* isolates.	Studies demonstrate that *S. salivarius* K12 has antimicrobial effects against bacteria involved in halitosis. This strain might be an interesting and valuable candidate for the development of an antimicrobial therapy for halitosis.	Halitosis
Power et al., 2008 [35] New Zealand	Preliminary clinical study	K12	19 young otitis media-prone children	Preliminary investigations of the colonization of the upper respiratory tract tissues of infants using a pediatric formulation of the oral probiotic *S. salivarius* K12.	Oral probiotic *S. salivarius* K12 has been given to 19 young otitis media-prone children following a 3-day course of amoxicillin administered as a preliminary to ventilation tube placement.	In two subjects, the use of K12 strain appeared to affect the expansion of an indigenous population of inhibitory *S. salivarius*. In other children, K12 strain colonization extended beyond the oral cavity to also	Otitis media

Table 1 (continued)

						include the nasopharynx oradenoid tissue. The relatively low proportion (33%) of subjects that colonized was attributed to failure of the amoxicillin pre-treatment to sufficiently reduce the indigenous *S. salivarius* populations prior to dosing with K12 strain powder.	
Walls et al., 2003 [36] New Zealand	Clinical study	K12	35 children (20 male and 15 female) were enrolled in the study. 20 children with recurrent AOM and 15 controls were tested.	This study investigated the production of bacteriocin-like inhibitory substances (BLIS) by streptococci isolated from the nasopharyngeal flora of children who either do or do not experience recurrent acute otitis media (AOM).	Nasopharyngeal swap was taken. A tongue swap was also taken at the time to provide a representative sample of the subject's oral streptococcal population.	The finding of *S. salivarius* with strong inhibitory activity against several AOM pathogens in the nasopharyngeal flora of children is unique. Although there is no clear evidence from the present study that these organisms protect against AOM, their low pathogenicity and strong in-vitro BLIS production capability indicate that they should be incorporated in future trials of bacterio therapy for recurrent AOM.	Acute otitis media
Di Pierro et al., 2015 [37] Italy	Preliminary uncontrolled study	K12	22 children (3–9 years old) having a recent history of recurrent AOM and with unilateral or bilateral fluid in the middle ear for at least 2 months were included.	Oral use of *S. salivarius* K12 in children with secretory otitis media.	*S. salivarius* K12 was administered to each subject every night, just before sleep. The possible evolution of SOM by using tone audiometry, tympanometry, endonasal endoscopy, otoscopy, and tonsillar examination is to follow.	Results indicate a good safety profile, a substantial reduction in AOM episodes, and a positive outcome of the treatment for all clinical outcomes tested. We conclude that the K12 strain may have a role in reducing the occurrence and/or severity of SOM in children.	Otitis media

otitis media [29]. The limitations of the study are that it was neither randomized, placebo-controlled, nor blinded. The subject numbers were relatively small. However, the results indicated that use of *S. salivarius* K12 can reduce the incidence of bacterial throat and ear infections in children with a history of recurrent oral streptococcal infection.

Two years later, the same author conducted a study, also in Italy, on 61 children with a diagnosis of recurrent oral streptococcal disorders. Thirty-one children were treated daily for 90 days with a slow-release tablet for oral use, containing no less than 1 billion colony-forming units/tablet of *S. salivarius* K12. All children were subsequently examined for occurrence of streptococcal infection. Twenty children (10 per group) were also assessed for viral infection. Importantly, the use of antipyretic and antibiotic therapy was reduced in both groups, as well as the number of days off school (children) and off work (parents). The 30 children who completed the 90-day trial with *S. salivarius* K12 treatment showed a significant reduction in their episodes of streptococcal pharyngeal infection (>90%), as calculated by comparing the infection rates of the previous year. The treated group also showed a significant decrease in the incidence (80%) of oral viral infections. In the study, the conclusion is that prophylactic administration of *S. salivarius* K12 to children with a history of recurrent oral streptococcal disease resulted in a considerable reduction of episodes of both streptococcal and viral infections and reduced the number of days under antibiotic and/or antipyretic therapy and days of absence from school or work [30]. The limits of the study were the absence of a placebo group, the absence of blind conditions, and the small size of the sample.

Recurrent pharyngo-tonsillar infection treatment contributes substantially to the total current requirement for antibiotic prescribing. The objective of one of the studies, also from Italy, was to evaluate the retrospective observation analysis of whether the application of *S. salivarius* K12 can reduce the incidence of GABHS pharyngotonsillitis in children who have had a recent history of recurrent episodes of these infections. In conclusion, on the basis of the results of this observational and retrospective study, it appears that oral preparations containing *S. salivarius* K12 may provide a beneficial option for prevention of pediatric GABHS infections, particularly in patients who would otherwise be forced to undergo frequent cycles of antibiotic therapy [31]. This observational study has less value than a double-blind, controlled, prospective, and randomized research.

S. salivarius K12 has been shown to inhibit the in vitro growth of *S. pyogenes*. In another clinical study from Italy, the researchers tested strain K12 for its efficacy in preventing streptococcal pharyngitis and/or tonsillitis in adults. Prophylactic administration of *S. salivarius* K12 to adults with a history of recurrent oral streptococcal pathology reduced the number of episodes of streptococcal pharyngeal infections and/or tonsillitis [32]. However, it was not a randomized, placebo-controlled, or blinded study, and it was based on a relatively small number of adult subjects.

Halitosis

Halitosis, more commonly known as oral malodor, afflicts up to half the adult human population to various degrees [38]. Different strategies have been developed to prevent or mitigate halitosis. A preliminary study from New Zealand was the first to report the use of a probiotic to aid the treatment of halitosis using volatile sulfur compounds as a clinical endpoint. Subjects with halitosis undertook a 3-day regimen of chlorhexidine (CHX) mouth rinsing, followed at intervals by the use of lozenges containing either *S. salivarius* K12 or placebo. This study found that replacement of bacteria implicated in halitosis by colonization with competitive bacteria such as *S. salivarius* K12 may provide an effective strategy to reduce the severity of halitosis [33]. The study was limited by a relatively small number of subjects in the active group having a favorable outcome.

Another study from Switzerland demonstrated that *S. salivarius* K12 has antimicrobial activity against bacteria involved in halitosis. *S salivarius* K12 suppressed the growth of all Gram-positive bacteria tested, but the extent to which the bacteria were inhibited varied [34]. Many of the reports on probiotic use for halitosis treatment are either in vitro studies or have been performed on a small number of subjects.

Otitis Media

Middle ear infections typically develop following the transmission of nasopharyngeal bacteria via the eustachian tube. A study of 19 children in New Zealand showed that strain K12 can ascend to the nasopharynx from oral cavity if it is well established there. The aim of this research was to determine whether K12 cells translocated to the nasopharynx following conventional oral administration [35]. Another study also from New Zealand, that included 20 children with acute otitis media (AOM) and 15 controls, compared the BLIS activities against potential AOM pathogens of streptococcal isolates from the nasopharyngeal microbiota of children who do or do not have recurrent AOM. The authors concluded that *S. salivarius* was present in the nasopharynx in some children and that some BLIS-producing strains act as strong inhibitors in vitro to AOM pathogens [36].

Secretory otitis media (SOM) is a common disease among children, and although its cause is not yet exactly defined, the pathology is often a sequel of AOM. Research from Italy demonstrated that K12 strain may have a role in reducing the occurrence and/or severity of SOM in children. Twenty-two children (3–9 years old) with a recent history of recurrent AOM and with unilateral or bilateral fluid in the middle ear for at least 2 months were included in this preliminary, uncontrolled study [37]. The results of the study indicated, that when compared with the corresponding incidence of AOM, calculated according to the number of episodes that occurred in the previous year, the AOM

incidence during the 3 months of treatment was reduced by approximately 40%.The study can be criticized for being uncontrolled and for utilizing subjective clinical examination.

Conclusion

Research into the impact of oral probiotics on human ear and oral cavity health is a relatively young but rapidly expanding field. The low pathogenicity and strong BLIS-producing capability of oral probiotic *S. salivarius* K12 indicate that this strain should be incorporated in future trials of the bacteriotherapy of recurrent AOM. Also, for pharyngitis, oral probiotics could have a role as prophylactic agents. Probiotic treatment of halitosis has already achieved promising outcomes, but despite the immense potential of probiotics, the supporting data are still deficient. It appears that K12 strain is well suited as a probiotic aid for human ear and oral cavity health. The current results mandate the need for further randomized clinical trials before any specific clinical recommendations can be defined.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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