

A comprehensive list of research and clinical studies conducted with *Streptococcus salivarius* K12 (BLIS K12™). Clinical studies assessing the efficacy of daily delivery of BLIS K12 demonstrate its ability to promote good oral health through the reduction of recurrent strep throat and otitis media (ear infections) episodes, as well as its impact on halitosis.

Benefit of BLIS K12 in ORAL INFECTIONS (Clinical trials)

1. Di Pierro et al., Clinical evaluation of the oral probiotic *Streptococcus salivarius* K12 in the prevention of recurrent pharyngitis and/or tonsillitis caused by *Streptococcus pyogenes* in adults. *Expert Opin Biol Ther.* 2013; 13(3):339-43.
2. Di Pierro et al., Preliminary pediatric clinical evaluation of the oral probiotic *Streptococcus salivarius* K12 in preventing recurrent pharyngitis and/or tonsillitis caused by *Streptococcus pyogenes* and recurrent acute otitis media. *Int J Gen Med.* 2012; 5:991-97.
3. Guglielmetti et al., Oral bacteria as potential probiotics for the pharyngeal mucosa. *Appl Environ Microbiol.* 2010; 76(12):3948-58.
4. Horz et al., Distribution and persistence of probiotic *Streptococcus salivarius* K12 in the human oral cavity as determined by real-time quantitative polymerase chain reaction. *Oral Microbiol Immunol.* 2007; 22(2):126-30.
5. Tagg et al., Oral streptococcal BLIS: Heterogeneity of the effector molecules and potential role in the prevention of streptococcal infections. *Int. Cong. Series.* 2006; 128:347-50.
6. Wescombe et al., Production of the lantibiotic salivaricin A and its variants by oral streptococci and use of a specific induction assay to detect their presence in human saliva. *Appl. Environ. Microbiol.* 2006; 72(2):1459-66.
7. Tagg et al., Prevention of streptococcal pharyngitis by anti-*Streptococcus pyogenes* bacteriocin-like inhibitory substances (BLIS) produced by *Streptococcus salivarius*. *Indian J Med Res.* 2004;119 Suppl:13-6.
8. Dierksen et al., The influence of indigenous bacteriocin-producing *Streptococcus salivarius* on the acquisition of *Streptococcus pyogenes* by primary school children in Dunedin, New Zealand. In: *Streptococci and streptococcal diseases entering the new millennium.* 2000;81-85.
9. Di Pierro et al., Use of *Streptococcus salivarius* K12 in the prevention of streptococcal and viral pharyngotonsillitis in children. *Drug Healthc Patient Saf.* 2014, 13(6):15-20
10. Di Pierro., Assessment of efficacy of BLIS-Producing probiotic K12 for the prevention of Group A *Streptococcus* pharyngitis: a short communication. *Probiotics Antimicrob Proteins,* 2018; doi: 10.1007/s12602-018-9398-7.
11. Di Pierro et al., Use of *Streptococcus salivarius* K12 to reduce the incidence pharyngo-tonsillitis and acute otitis media in children: a retrospective analysis in not-recurrent pediatric subjects, 2018; *Minerva Pediatr.* doi: 10.23736/S0026-4946.18.05182-4

12. Doyle et al., The Effect of the oral probiotic *Streptococcus salivarius* (K12) on Group A *Streptococcus* pharyngitis: A pragmatic trial In schools. *Pediatr Infect Dis J,* 2017; doi: 10.1097/INF.0000000000001847
13. Taylan et al., Clinical evaluation of the therapeutic use of oral probiotic *Streptococcus salivarius* K12 for recurrent pharyngitis and/or tonsillitis. *Ind J Res.* 2017; 6(9) :633-634.

Benefit against UPPER RESPIRATORY INFECTIONS

1. Fiedler et al., Protective mechanisms of respiratory tract *Streptococci* against *Streptococcus pyogenes* biofilm formation and epithelial cell infection. *Appl Environ Microbiol.* 2013; 79(4):1265-76.
2. Di Pierro et al., Preliminary pediatric clinical evaluation of the oral probiotic *Streptococcus salivarius* K12 in preventing recurrent pharyngitis and/or tonsillitis caused by *Streptococcus pyogenes* and recurrent acute otitis media. *Int J Gen Med.* 2012; 5:991-97.
3. Santagati et al., Bacteriocin-producing oral streptococci and inhibition of respiratory pathogens. *FEMS Immunol Med Microbiol.* 2012; 65:23-31.
4. Power et al., Preliminary investigations of the colonisation of upper respiratory tract tissues of infants using a paediatric formulation of the oral probiotic *Streptococcus salivarius* K12. *Eur J Clin Microbiol Infect Dis.* 2008; 27(12):1261-63.
5. Di Pierro et al., Effect of administration of *Streptococcus salivarius* K12 on the occurrence of streptococcal pharyngo-tonsillitis, scarlet fever and acute otitis media in 3-year-old children. *Eur Rev Med Pharmacol Sci.* 2016; 20:4601-06.
6. Di Pierro et al., Positive clinical outcomes derived from using *Streptococcus salivarius* K12 to prevent streptococcal pharyngotonsillitis in children: a pilot investigation. *Drug Healthc Patient Saf.* 2016; 8:77-81.
7. Gregori et al., Reduction of group A beta-hemolytic streptococcus pharyngo-tonsillar infections associated with the use of the oral probiotic *Streptococcus salivarius* K12: a retrospective observational study. *Ther Clin Risk Manag.* 2016; 12: 87–92.



Benefit against HALITOSIS (Clinical trials)

1. Masdea et al., Antimicrobial activity of *Streptococcus salivarius* K12 on bacteria involved in oral malodour. *Arch Oral Biol.* 2012; 57(8):1041-47.
2. Burton et al., A preliminary study of the effect of probiotic *Streptococcus salivarius* K12 on oral malodour parameters. *J Appl Microbiol.* 2006; 100(4):754-64.
3. Kazor et al., Diversity of bacterial populations on the tongue dorsa of patients with halitosis and healthy patients. *J. Clin. Microbiol.* 2003; 41(2):558-63.
4. Moon et al. The effect of *Streptococcus salivarius* K12 against *Prevotella intermedia* on the reduction of oral malodor. 2016. *Int J Clin Prev Dent*;12(3):153-161.
5. Jamali et al. Impact of Chlorhexidine pretreatment followed by probiotic *Streptococcus salivarius* strain K12 on Halitosis in children: A randomised controlled clinical trial. *Oral Health Prev Dent.* 2016; 14(4): 305-16

IMMUNITY

1. Groeger et al., B7-H1 and B7-DC receptors of oral squamous carcinoma cells are upregulated by *Porphyromonas gingivalis*. *Immunobiology.* 2011; 216(12):1302-10.
2. Cosseau et al., The commensal *Streptococcus salivarius* K12 down-regulates the innate immune responses of human epithelial cells and promotes host-microbe homeostasis. *Infection and Immunity.* 2008; 4163–75.

Benefit against OTITIS MEDIA

1. Di Pierro et al., Preliminary pediatric clinical evaluation of the oral probiotic *Streptococcus salivarius* K12 in preventing recurrent pharyngitis and/or tonsillitis caused by *Streptococcus pyogenes* and recurrent acute otitis media. *Int J Gen Med.* 2012; 5:991-97.
2. Tagg et al., Bacteriocin-like inhibitory substance (BLIS) production by the normal flora of the nasopharynx: potential to protect against otitis media? *J Med Microbiol.* 2003; 52(9):829-33.
3. Wescombe et al., Megaplasmids encode differing combinations of lantibiotics in *Streptococcus salivarius*, *Antonie Van Leeuwenhoek.* 2006; 90(3):269-80.
4. Martin et al. Probiotics and prebiotics in the prevention of Acute Otitis Media in children: A Randomized, Double-Blind, Placebo-Controlled Study. 2011. Abstract: 51st ICAAC. Chicago, IL.

SAFETY

1. Barretto et al., Genome sequence of the lantibiotic bacteriocin producer *Streptococcus salivarius* strain K12. *J Bacteriol.* 2012; 194(21):5959-60.
2. Burton et al., Evaluation of safety and human tolerance of the oral probiotic *Streptococcus salivarius* K12: a randomized, placebo-controlled, double-blind study. *Food Chem Toxicol.* 2011; 49(9):2356-64.
3. Burton et al., Extended safety data for the oral cavity probiotic *Streptococcus salivarius* K12. *Probiotics and Antimicro. Prot.* 2010; 2:135-44.
4. Burton et al. Safety assessment of the oral cavity *Streptococcus salivarius* K12. *Appl. Environ Microbiol.* 2006; 72(4):3050-53

MECHANISM OF ACTION

1. Hyink et al., Salivaricin A2 and the novel antibiotic salivaricin B, are encoded by adjacent loci on a 190 kb transmissible megaplasmid in the oral probiotic strain *Streptococcus salivarius* K12. *Appl Environ Microbiol.* 73(4): 1107-13.
2. Ishijima et al., Effect of *Streptococcus salivarius* K12 on the in vitro growth of *Candida albicans* and its protective effect in an oral candidiasis model. *Appl Environ Microbiol.* 2012; 78(7):2190-99.
3. Barbour et al., New insights into the mode of action of the lantibiotic salivaricin B. *Sci Rep.* 2016; 6: 31749:1-14.
4. Manning et al., Investigation of salivarius mediated inhibition of pneumococcal adherence to pharyngeal epithelial cells. *BMC Microbiol.* 2016; 16:225:1-9.
5. Dierksen, et al. The effect of ingestion of milk supplemented with salivaricin A-producing *Streptococcus salivarius* on the bacteriocin-like inhibitory activity of streptococcal populations on the tongue. *FEMS Microbiol Ecol,* 2007, 59(3): 584-591.
6. Orrù et al. The selective interaction of Pistacia lentiscus Oil vs. human Streptococci, an old functional food revisited with new tools. 2017. *Front Microbiol,* 8:2067.

REVIEWS

1. Wescombe et al., Developing oral probiotics from *Streptococcus salivarius*. *Future Microbiol.* 2012 ; 7(12):1355-71.
2. Hale et al., BLIS-producing probiotics targeting the oral cavity. *Microbiol Aust.* 2012; 33(3):103-05.
3. Burton et al., Beneficial microbes for the oral cavity: time to harness the oral streptococci? *Benef Microbes.* 2011; 2(2):93-101.
4. Wescombe et al., Something old and something new: An update on the amazing repertoire of bacteriocins produced by *Streptococcus salivarius*. *Probiotics & Antimicro. Prot.* 2010; 2:37-45.
5. Tagg., Streptococcal bacteriocin-like inhibitory substances: some personal insights into the bacteriocin-like activities produced by *streptococci* good and bad. *Probiotics and Antimicro. Prot.* 2009; 1:60-66.
6. Wescombe et al., Streptococcal bacteriocins and the case for *Streptococcus salivarius* as model oral probiotics. *Future Microbial.* 2009; 4(7):819-35.
7. Tagg et al., Streptococci as effector organisms for probiotic and replacement therapy. In: *Therapeutic Microbiology: Probiotic and Related Strategies.* J. Versalovic and M. Wilson, American Society for Microbiology. p61-81.
8. Tagg., Application of bacterial pathogens in replacement therapy. In: *Patho-Biotechnology.* R. Sleator and C. Hill Landes Bioscience. 2008; p1-15.
9. Heng et al., The diversity of bacteriocins in gram-positive bacteria. In: *Ecology and Evolution.* M. Riley and M. Chavan. 2007; p45-92.
10. Tagg et al., Bacterial replacement therapy: adapting 'germ warfare' to infection prevention. *Trends Biotechnol.* 2003; 21 (5):217-23.
11. Di Pierro., Comment on: "Probiotics in addition to antibiotics for the treatment of acute tonsillitis: a randomized, placebo-controlled study" *Eur J Clin Microbiol Infect Dis.* 2015; 34(7):1485-86.
12. Patras et al., *Streptococcus salivarius* K12 limits Group B Streptococcus vaginal colonisation. *Infect. Immun.* 2015; 83(9):3438-44.
13. Stowik, T.A., Contribution of Probiotics *Streptococcus salivarius* Strains K12 and M18 to oral health in humans: A review. *Honors Scholar Theses.* University of Connecticut. 2016; 488.
14. Hale et al. Streptococcal bacteriocin-producing strains as oral probiotic agents. In *The Bacteriocins Current Knowledge and Future Prospects.* Robert L. Dorit, Sandra M. Roy and Margaret A. Riley. Caister Academic Press, U.K. 2016 (Chapter 6).p103-126.
15. Zupancic et al. Influence of Oral Probiotic *Streptococcus salivarius* K12 on Ear and Oral Cavity Health in Humans: Systematic Review. *Probiotics Antimicrob Proteins.* 2017 9(2): 102-110

***Streptococcus salivarius* M18 (BLIS M18™) is an advanced oral probiotic that has been identified for its unique set of beneficial properties with regards to the teeth and gums.**

BLIS M18 produces four potent antimicrobial proteins called bacteriocins with inhibitory activity against dental-caries (cariogenic), gingivitis and periodontal pathogens such as *Streptococcus mutans* and *Actinomyces viscosus*. In addition, BLIS M18 produces enzymes urease and dextranase that can counteract plaque formation and saliva acidity.

Clinical studies assessing the efficacy of daily delivery of BLIS M18 demonstrate its ability to promote good dental health through the reduction of dental carries and prevention of gingivitis and periodontal diseases.

Benefit in DENTAL HEALTH

1. Burton et al., Influence of the probiotic *Streptococcus salivarius* strain M18 on indices of dental health in children: a randomized double-blind, placebo-controlled trial. *J. Med. Microbiol.* 2013; 62(6):875-84.

randomised double-blinded placebo-controlled pilot study. *Eur Rev Med Pharmacol Sci.* 2018; 22:8034-8041.

Benefit against DENTAL CARIES

2. Di Pierro et al., Cariogram outcome after 90 days of oral treatment with *Streptococcus salivarius* M18 in children at high risk for dental caries: results of a randomized, controlled study. *Clin Cosmet Investig Dent.* 2015; 7: 107–13.
3. Dierksen et al., The influence of indigenous bacteriocin-producing *Streptococcus salivarius* on the acquisition of *Streptococcus pyogenes* by primary school children in Dunedin, New Zealand. In: *Streptococci and streptococcal diseases entering the new millennium.* 2000;81-85.
4. James & Tagg., The prevention of dental caries by BLIS-mediated inhibition of mutans streptococci. *N Z Dent J.* 1991; 87(389):80-3.
5. Mani et al. Efficacy of oral probiotics an adjunct to scaling and root planning in nonsurgical treatment outcome of generalised chronic periodontitis patients: A clinico-microbiological study *Int J Exper Dental Sci,* 2017: 6(1) 6-13.
6. Tandelin R.T. et al. The effect of oral probiotic consumption on the caries risk factors among high-risk caries population, 2018;10(3):132-137

MECHANISM OF ACTION

10. Burton et al., Persistence of the Oral Probiotic *Streptococcus salivarius* M18 is dose dependent and megaplasmid transfer can augment their bacteriocin production and adhesion characteristics. *PLoS One.* 2013; 8(6):e65991.
11. MacDonald, K.W., The role of *Streptococcus salivarius* as a modulator of homeostasis in the oral cavity. Electronic Thesis and Dissertation Repository. The University of Western Ontario. 2015; Paper 2816.

SAFETY

12. Heng et al., Genome sequence of the bacteriocin-producing oral probiotic *Streptococcus salivarius* strain M18. *J. Bact.* 2011; 193:6402-03.

REVIEWS

13. Hale et al. Streptococcal bacteriocin-producing strains as oral probiotic agents. In the Bacteriocins Current Knowledge and Future Prospects Edited by: Robert L. Dorit, Sandra M. Roy and Margaret A. Riley. Caister Academic Press, U.K. 2016 (Chapter 6). P:103-126.
14. Stowik, T.A., Contribution of Probiotics *Streptococcus salivarius* Strains K12 and M18 to oral health in humans: A review. Honors Scholar Theses. University of Connecticut. 2016; 488.
15. Wescombe et al., Developing oral probiotics from *Streptococcus salivarius*. *Future Microbiol.* 2012; 7(12):1355-71.

Benefit against GINGIVITIS AND PERIODONTAL DISEASES

7. Scariya et al., Probiotics in periodontal therapy. *Int. J. Pharm Bio Sci.* 2015; 6(1)242-50.

Benefit against HALITOSIS

8. Benic et al., Oral probiotics reduce halitosis in patients wearing orthodontic braces: A randomized, triple-blind, placebo-controlled trial *J. Breath Res.* 2019. <https://doi.org/10.1088/1752-7163/ab1c81>.

OTHER CLINICAL BENEFITS

9. Campanella et al., Oral probiotics influence oral and respiratory tract infections in pediatric population: a

