ORALIS PLUS

Dental gel for the daily, brush-free oral hygiene in cats and dogs

ORALIS<O-RA-LIS
The name is inspired by the Latin word « oralis », which means « oral »
A Small Lexicon of Modern Latin: English-Latin Fundatio Melissa; 1988.

Dental disease is a common problem in dogs and cats. A study of North American pets showed a 20% incidence of calculus and/or gingivitis in dogs of all ages, while 24% and 13% of cats of all ages appeared with calculus and gingivitis, respectively[1]. Dental disease in older pets is more common, and during aging, the incidence of dental disease increases. One study identified periodontitis in 82% of dogs aged 6 -8 years and in 96% at the ages of 12- 14 years[2]. Dental plaque consists of salivary glycoproteins, food debris, and bacteria. As plaque ages and thickens, salivary calcium salts are deposited on the plaque layer, causing it to mineralize and become calculus, which allows further bacterial attachment. Production of bacterial toxins results in an inflammatory response (gingivitis and periodontitis). If allowed to become chronic, this process leads to local tissue destruction, including gingival recession and bone loss, and in severe cases root abscess, tooth loss, and even jaw fracture. In addition, entry of oral bacteria into the bloodstream can have negative consequences for the heart, liver, and kidneys[3].and their functions.

There have traditionally been two methods of preserving oral health, mechanical and chemical. For the latter, ingredients in products intended for oral health are mostly used either for reducing bacterial numbers (antimicrobials) or for impeding the formation of calculus (calcium chelators). Micronized silver exerts a natural, long-lasting antimicrobial effect, due to its unique high surface area and porous structure. Grapefruit seed extract contains large quantities of polyphenolic compounds and has a well-studied anti-biofilm effect. Silver has been known for its significant broad-spectrum antimicrobial activity and has widely been used as an antimicrobial agent in different fields of medicine. Sodium phosphate is used in a wide variety of pharmaceutical formulations as a buffering agent and a calcium chelating agent.

Lately, the modulation of oral microbiota by means of probiotics and postbiotics has been studied, and decrease of the dysbiotic rate in the oral cavity has emerged as the most important factor in maintaining oral health. Oral diseases (i.e., periodontitis, gingivitis, and dental caries) are an excellent example of infection associated with the formation of a highly pathogenic biofilm. Mechanical debridement and the use of antimicrobials are not enough to achieve long-term stability and regular maintenance care based on biofilm control is essential to

preserve the equilibrium of the oral microbiome. That is where the postbiotics - inactivated or dead intact cells and/or their cell structural components with or without metabolites- step in, representing a novel bio-therapeutic approach to biofilm-related oral diseases, favouring the formulation stability and safety.

Several studies have conclusively established that sugar alcohols, such as xylitol, inhibit the growth of pathogenic oral bacteria. However, in dogs, xylitol cannot be used because it results in life-threatening hypoglycemia and acute liver failure. Erythritol, a sugar alcohol similar to xylitol, is not metabolized and undergoes efficient renal excretion. The degree of periodontal-disease-associated bacteria growth inhibition by erythritol has been found to be comparable to that exhibited by xylitol, thus application of erythritol has been suggested as effective in the daily oral care for the management of PD in dogs.

Micronized silver (MicroSilver BG™)

Silver and its compounds have long been used, in one form or another, as antimicrobial agents[4]. Silver has been proven effective against streptococci of the human oral cavity and periodontal pathogens[5]. The microparticulate form has a high specific surface area capable of releasing reasonable amounts of silver. The *in vitro* antibacterial potential of a silver additive in resin composite materials was evaluated and the assessed materials with low concentrated microparticulate silver additives (0.3% and 0.6%) revealed anti-adherence activity and bactericidal effects against the oral pathogen *S. mutans*[6], considered as a major etiological agent of human dental caries[7]. *S. mutans* is also one of the primary colonizers in biofilm creation in cats and dogs, although caries in dogs have an occurrence of 5%[8] and in cats they are even more rare and not causing cavities[9]. From systemic exposure indicators (Ag in blood results), together with Ag in tissue data, it has been measured that the relative oral bioavailability of the various forms of silver evaluated was silver acetate = silver nitrate > nanosilver > > microparticulate silver, which confirms that micronized or bigger silver forms exhibit low toxicity potential[10].

MicroSilver BG™ is a trademarked pure elemental dry silver powder consisting of highly porous & micro-sized particles of pure silver, produced by physical process using highly refined medical grade pure silver (99.99%). It provides a pure silver deposit which liberates a continuous and lasting flow of silver ions over time even in complex environments (sweat, blood, wound drainage fluid, urine). It provides sustainable antimicrobial action on the surface of the skin or the mucosa against unwanted germs and without harming the resident skin flora (good resident bacteria). As a secondary benefit, it acts as a preservative booster in products. It has been used extensively since 2005 in cosmetics, skincare, oral & personal care, wound care, bone cement, dental fillers[11].

Grapefruit seed extract *(Citrus × paradisi)*

The antibacterial effect of GSE has been attributed to the citrus flavonoids, such as naringenin and hesperidin[12]. In an *in vitro* study aimed at comparing the effects of aqueous and ethanolic extracts of GS and to compare those effects to those of orally used antiseptics solutions of chlorhexidine gluconate (CHX) in 0.12% and 0.2% concentrations, aqueous GSE has a good antimicrobial effect against all the tested bacteria and yeast, albeit inferior to CHX solutions[13]. In a study evaluating the antifungal activity of grapefruit seed extract (GSE) against Candida species causing oral candidiasis, GSE showed high effectiveness against all tested Candida species and a fungicidal activity against *C. albicans* and non-albicans Candida species (NACS) and its activity was superior to miconazole[14]. Furthermore, the histopathological observation in the oral mucosa of rabbits treated with GSE showed no significant histopathological changes even at 1%[14]. In a previous study in rats, GSE exhibited an intense inflammatory response in the first few days after contact with conjunctive tissue even at 0,1%[15], so concentrations <0,1% are used for safety purposes.

POSTBIOTIC INNOVATION: Kalibiome oris (Lactobacillus Ferment, Mannitol)

The term postbiotic was defined by the International Scientific Association of Probiotics and Prebiotics (ISAPP) as "a preparation of inanimate microorganisms and/or their components that confers a health benefit on the host"[16]. A recent review discusses the underlying mechanisms of postbiotic action[17]. Studies conducted using postbiotics have demonstrated their ability to form eubiosis conditions and stabilize host homeostasis in the oral cavity either by competitively eliminating pathogens through competing for adhesion sites or by containing molecules with direct antimicrobial properties. Additionally, postbiotics have shown the ability to enhance mucosal barrier function through the alteration of secreted proteins. They have also exhibited anti-inflammatory (downregulation of IL-6, TNF- α and upregulation of IL-10) and anti-oxidative (removal of free radicals) properties in vitro and in vivo experimental animal models.

The impact of postbiotics on the growth and metabolism of periodontal pathogens, as well as on the progression of periodontitis in rodents and humans, is a subject of extended research[18]. Very recently, clinical data which support the effectiveness and safety of postbiotics in the modulation of human oral microbiota and oral health care have emerged. In a placebo-controlled study[19] using toothpaste with or without postbiotics (3×10^{10} CFU inactivated *Lactobacillus salivarius* LS97, *L. paracasei* LC86, and *L. acidophilus* LA85), saliva samples were collected at different time points and the immunoglobulin A (IgA) and short-chain fatty acid (SCFA) levels were determined, while the salivary microbiota was analyzed by 16S rRNA amplicon sequencing. The results showed that salivary IgA levels and acetic and propionic acid levels were notably higher in the postbiotic group ($P < 0.05$), accompanied by an

increase in the level of alpha diversity of the salivary microbiota, and these indexes remained high 1 month after discontinuation of the toothpaste. In conclusion, postbiotics dramatically and consistently improved oral immunity levels and SCFA content, effective in inhibiting the colonization of oral pathogenic bacteria, in the host. In addition, postbiotics were able to increase the level of microbial alpha diversity and down-regulate the abundance of some harmful microbes without significantly altering the structure of the host salivary microbiota.

Postbiotics display prolonged shelf life and good stability and, in this regard, can be potentially employed in oral therapy as a safer alternative to the use of viable cells (probiotics). Some Lactobacilli postbiotics with anti-biofilm properties toward oral pathogens are *L. reuteri*, *L. acidophilus*, *L. casei*, *L. paracasei*, *L. reuteri*, *L. Rhamnosus* etc.[20]

The oral microbiome of dogs and cats is composed of hundreds of different microbial species, that cover all mucosal and dental surfaces as a biofilm. Immune tolerance of the microbiome prevails in health and no inflammatory response is evoked, but if the equilibrium between the microbiome and host immune surveillance is disturbed, immune tolerance shifts to a proinflammatory response. The specific bacteria have which initiate the transition from health to inflammation have not been identified; however, the proportion of more virulent species is increased (dysbiosis) at sites of inflammation and tissue destruction. Systemic antimicrobial therapy neither prevents nor effectively resolves inflammation resulting from disrupted homeostasis between the microbiome and host[21].

Kalibiome oris is an innovative ingredient, which to our knowledge is used in a pet oral health product for the first time. It is a concentrated and reproducible postbiotics complex, obtained by controlled bio-fermentation, with maximum tolerability as it contains no culture broth or living bacteria and is preservatives free. Postbiotics were obtained from *Lactobacillus Paracasei*, a commensal microorganism that has been studied extensively for its beneficial properties in oral health[22,23].

Erythritol

Erythritol is a white, crystalline and odorless product widely used in food, beverages and personal care products. It is a natural sweetener approximately 60% as sweet as sugar. It can be considered natural because the production process is based on a non-genetically modified yeast fermentation of plant-based raw materials (glucose derived from corn).

Products to improve oral health in pets, such as dog chewing sticks containing erythritol, are becoming increasingly widely available. The literature shows that erythritol provides the same advantages for canines[24,25] as it does for human oral

health and – in contrast to xylitol[26]– erythritol is safe for use in animal care products, being non-toxic to dogs and cats[27].

References

1. Lund EM, Armstrong PJ, Kirk CA, Kolar LM, Klausner JS. 1999. Health status and population characteristics of dogs and cats examined at private veterinary practices in the United States. *J Am Vet Med Assoc.* 214(9):1336–41
2. Hamp S-E, Olsson S-E, Farsø-Madsen K, Viklands P, Fornell J. 1984. A macroscopic and radiologic investigation of dental diseases of the dog. *Vet Radiol*. 25(2):86–92
3. Larsen JA. 2010. Oral products and dental disease. *Compendium*. 32 9:E4
4. Russell AD, Hugo WB. 1994. 7 Antimicrobial Activity and Action of Silver. In *Progress in Medicinal Chemistry*. 31:351–70. Elsevier
5. Spacciapoli P, Buxton D, Rothstein D, Friden P. 2001. Antimicrobial activity of silver nitrate against periodontal pathogens. *J Periodont Res*. 36(2):108–13
6. Bürgers R, Eidt A, Frankenberger R, Rosentritt M, Schweikl H, et al. 2009. The anti-adherence activity and bactericidal effect of microparticulate silver additives in composite resin materials. *Arch Oral Biol*. 54(6):595–601
7. Loesche WJ. 1986. Role of *Streptococcus mutans* in human dental decay. *Microbiol Rev*. 50(4):353–80
8. Hale FA. 1998. Dental Caries in the Dog. *J Vet Dent*. 15(2):79–83
9. Percival S, Knottenbelt D, Cochrane C, eds. 2011. *Biofilms and Veterinary Medicine*, Vol. 6. Berlin, Heidelberg: Springer Berlin Heidelberg
10. Mertens J, Alami A, Arijs K. 2023. Comparative in vivo toxicokinetics of silver powder, nanosilver and soluble silver compounds after oral administration to rats. *Arch Toxicol*. 97(7):1859–72
11. *Technologies*. Bio-Gate AG. www.bio-gate.de
12. Cvetnić Z, Vladimir-Knezević S. 2004. Antimicrobial activity of grapefruit seed and pulp ethanolic extract. *Acta Pharm*. 54(3):243–50
13. Al–Âni W, Tawfik N, Shehab E. 2011. Antimicrobial Activity of Grapefruit Seeds Extracts *(In vitro* Study). *Al-Rafidain Dent J.* 11(2):341–45
14. Tsutsumi-Arai C, Terada-Ito C, Tatehara S, Imamura T, Takebe Y, et al. 2021. Fungicidal activity of grapefruit seed extract against the pathogenic *Candida* species causing oral candidiasis. *J Oral Maxillofac Surg, Med, Pathol*. 33(6):626–32
15. Martins MD. 2013. *In vitro* and *in vivo* toxicity of grapefruit seed extract. *Med Sci Tech*. 54:65–69
16. Vinderola G, Sanders ME, Cunningham M, Hill C. Frequently asked questions about the ISAPP postbiotic definition. *Front Microbiol.* 2024;14:1324565.
17. Ma L, Tu H, Chen T. Postbiotics in human health: a narrative review. *Nutrients*. 2023;15(2):291.

18. Moraes RM, Schlagenhauf U, Anbinder AL. Outside the limits of bacterial viability: Postbiotics in the management of periodontitis. *Biochemical Pharmacology*. 2022;201:115072.
19. Rui W, Zhong S, Li X, Tang X, Wang L, Yang J. Evaluating the role of postbiotics in the modulation of human oral microbiota: a randomized controlled clinical trial. *Probiotics & Antimicro Prot.* Published online March 19, 2024.
20. Giordani B, Parolin C, Vitali B. Lactobacilli as anti-biofilm strategy in oral infectious diseases: a mini-review. *Front Med Technol.* 2021;3:769172.
21. Davis EM, Weese JS. Oral microbiome in dogs and cats: dysbiosis and the utility of antimicrobial therapy in the treatment of periodontal disease. *Veterinary Clinics of North America: Small Animal Practice.* 2022;52(1):107-119.
22. Pahumunto N, Piwat S, Chankanka O, Akkarachaneeyakorn N, Rangsitsathian K, Teanpaisan R. Reducing mutans streptococci and caries development by *Lactobacillus paracasei* SD1 in preschool children: a randomized placebo-controlled trial. *Acta Odontologica Scandinavica.* 2018;76(5):331-337.
23. Teanpaisan R, Piwat S. *Lactobacillus paracasei* SD1, a novel probiotic, reduces mutans streptococci in human volunteers: a randomized placebo-controlled trial. *Clin Oral Investig.* 2014;18(3):857-862.
24. Shimizu M, Miyawaki S, Kuroda T, Umeta M, Kawabe M, Watanabe K. Erythritol inhibits the growth of periodontal-disease-associated bacteria isolated from canine oral cavity*. Heliyon.* 2022;8(8):e10224.
25. Tochio T, Makida R, Fujii T, et al. The bacteriostatic effect of erythritol on canine periodontal disease–related bacteria. *Polish Journal of Veterinary Sciences.* Published online March 11, 2022:75-82.
26. Murphy LA, Coleman AE. Xylitol toxicosis in dogs. Veterinary Clinics of North America: Small Animal Practice. 2012;42(2):307-312.
27. Eapen AK, De Cock P, Crincoli CM, Means C, Wismer T, Pappas C. Acute and sub-chronic oral toxicity studies of erythritol in Beagle dogs*. Food and Chemical Toxicology.* 2017;105:448-455.