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Article

Intraoral administration of probiotics and postbiotics: An overview of microorganisms and formulation strategies

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The last decade provided significant advances in the understanding of microbiota and its role in human health. Probiotics are live microorganisms with proven benefits for the host and were mostly studied in the context of gut health, but they can also confer significant benefits for oral health, mainly in the treatment of gingivitis. Postbiotics are cell-free extracts and metabolites of microorganisms which can provide additional preventive and therapeutic value for human health. This opens opportunities for new preventive or therapeutic formulations for oral administration. The microorganisms that colonize the oral cavity, their role in oral health and disease, as well as the probiotics and postbiotics which could have beneficial effects in this complex environment were discussed. The aim of this study was to review, analyse and discuss novel probiotic and postbiotic formulations intended for oral administration that could be of great preventive and therapeutic importance. A special attention has been put on the formulation of the pharmaceutical dosage forms that are expected to provide new benefits for the patients and technological advantages relevant for industry. An adequate dosage form could significantly enhance the efficiency of these products.

Keywords: Postbiotics. Probiotics. Oral dosage forms. Oral microbiota. *Ligilactobacillus salivarius.*

INTRODUCTION

Fermented foods are one of the most common sources of beneficial microorganisms for humans. The process of food preservation by fermentation dates back to the Neolithic period (Arranz-Otaegui *et al.,* 2018). The generally accepted definition of fermented food and drink is: "Food made by desired microbial growth and enzymatic conversion of food components" (Marco *et al.,* 2021). Fermentation is described as "a process during which ATP is generated in which organic compounds play the role of electron donors and acceptors", from a biological perspective (Kim, Gadd, 2019). This definition is appropriate for anaerobic lactic acid and ethanol fermentations. In the first phase of anaerobic metabolism, glycolysis takes place, where two molecules of pyruvate are produced with the generation of two molecules of ATP, where glucose plays the role of an electron donor. In lactic acid fermentation, the second step is the reduction of pyruvate to lactic acid, where pyruvate plays the role of an electron acceptor (Wang *et al*., 2021). In alcoholic fermentation, the second step is the decarboxylation of pyruvate to acetaldehyde and the subsequent reduction of acetaldehyde to ethanol, where acetaldehyde plays the role of an electron acceptor (Moreno-Arribas, Polo, 2009). Simplified reaction mechanisms of these two fermentations are shown in Figure 1.

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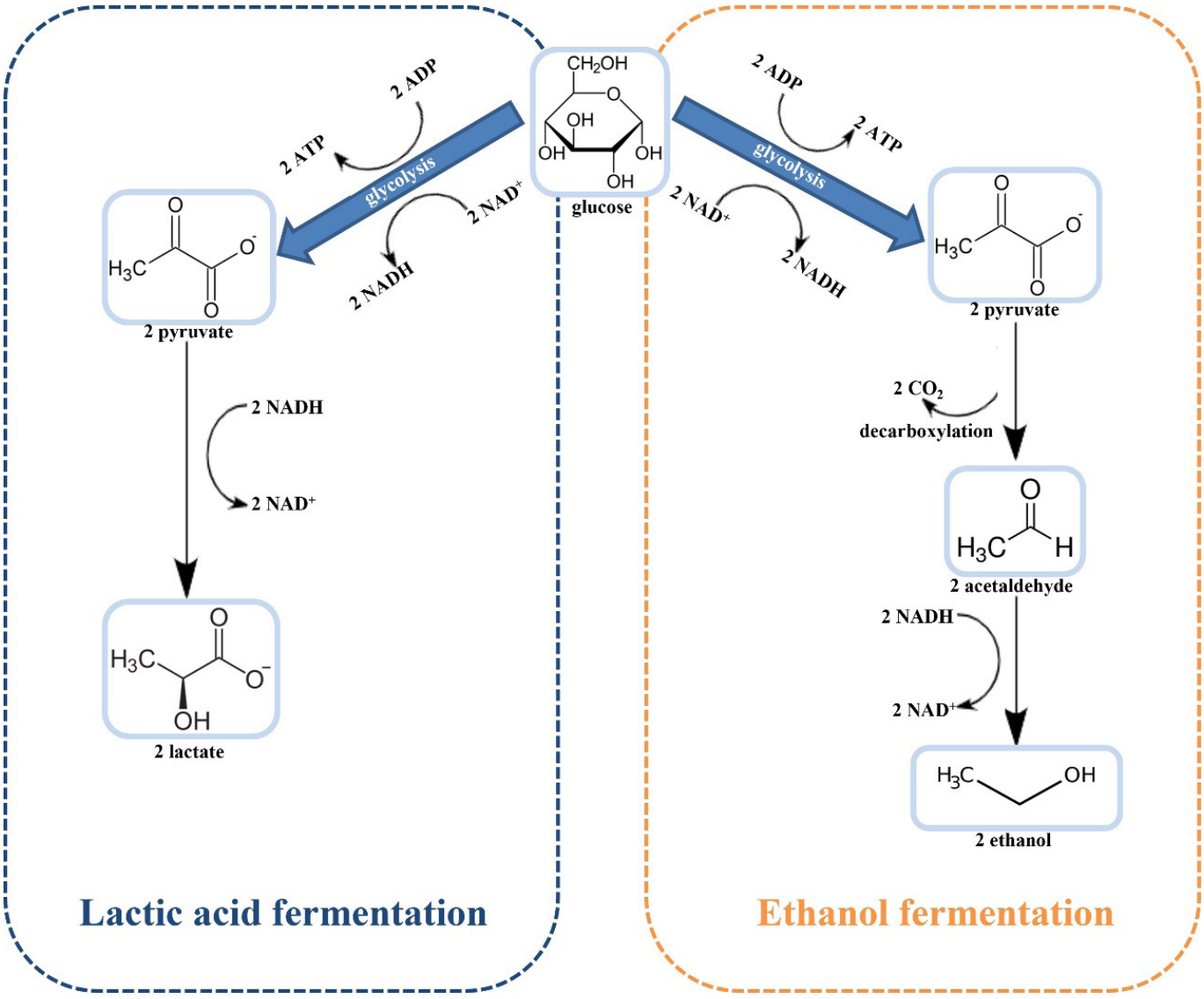

FIGURE 1 - Simplified reaction mechanisms of lactic acid and ethanol biosynthesis.

Fermented food contains antimicrobial compounds such as organic acids, ethanol and bacteriocins, products of the metabolism of fermentation microorganisms, which contribute to food safety and extend the shelf life of food. The term "fermented food" has been often synonymously used with terms such as "probiotics" or "probiotic-containing food", which is often wrong or sometimes partially true (Marco *et al.,* 2021). Therefore, the term "probiotic" or "probiotic food" should only be used when there is a scientifically proven health benefit provided by well-characterized live microorganisms.

The term "probiotic" has its roots in the Greek language "*pro bios* (προ βίος)" which means "for life". For medical purposes, the term probiotic was first mentioned in 1965 (Lilly, Stillwell, 1965). According to the definition of the World Health Organization (WHO) and the Food and Agriculture Organization of the United Nations, probiotics are "live microorganisms that, when dosed in an adequate amount, provide a health benefit to the host" (Hill *et al.,* 2014; Salminen *et al.,* 2021). From this definition, the difference between food microorganisms and probiotics can be derived. Microbial strains must also meet certain technological and safety criteria in order to be classified as a probiotic. The probiotic strain and its fermentation products must be non-toxic, non-pathogenic, neither to cause

allergic reactions, mutagenesis and/or carcinogenesis even in immunocompromised persons (Collins, Thornton, Sullivan, 1998). Some of the most common probiotic genera are *Lactobacillus, Bifidobacterium, Propionibacterium, Peptostreptococcus, Pediococcus, Leuconostoc, Enterococcus, Streptococcus, Bacillus, Saccharomyces* (Ranadheera *et al.,* 2017; George Kerry *et al.,* 2018; Ranjha *et al.,* 2021*).*

Probiotics achieve their biological activity by the production of biomolecules such as lactic acid, hydrogen peroxide, bacteriocins, vitamins, short-chain fatty acids, enzymes, cell membrane constituents such as exopolysaccharides, surface proteins, peptidoglycan, etc. (Benfreha *et al.,* 2022; Nataraj *et al*., 2020).

Postbiotic are defined as "a preparation of non-living microorganisms and/or their components that provide health benefits to the host", according to the International Scientific Association for Probiotics and Postbiotics (ISAPP) (Salminen *et al.,* 2021). They are fermentation products and cellular constituents of microorganisms, but not necessarily probiotics. They are sometimes mistakenly called probiotics and also terms such as parabiotics, paraprobiotics, inactivated probiotics, ghost probiotics, symbiotics, etc. can be found in the literature. All these terms have emerged in the literature with the aim to designate microbial products, including inactivated microbial biomass, which shows positive effects on human or animal health, but cannot be considered probiotics and postbiotic is a term currently accepted as a universal to cover all these terms.

The scientific community is becoming more and more interested in probiotic and postbiotic research because of its unique qualities. According to a Scopus database, there were 69,850 publications with the keyword "probiotics" between January 1, 2002, and January 1, 2023 (Figure 2) (Scopus, 2023). The official term postbiotic was defined only in 2021 and includes all previously used terms related to postbiotics (Salminen *et al.,* 2021). According to a Scopus database, the number of publications according to the key words "postbiotics", "paraprobiotics", "non-viable probiotics", "heat-killed probiotics", "ghost probiotics", which are the most frequently used terms on the given topic, amounted to 306 in the period between January 1, 2002, and January 1, 2023 (Figure 3) (Scopus, 2023). The graphs in Figures 1 and 2 illustrate a significant increase in the number of publications on the topic of probiotics and postbiotics in the past two decades. There is a noticeable increase in the number of publications observed in the last half-decade in both cases, especially in the postbiotics area.

A similar growth trend can be observed in the market for probiotics and postbiotics. The probiotics market is expected to reach USD 73.4 billion in 2023, with a compound annual growth rate (CAGR) of 8.6% until 2027, when it is expected to reach USD 101.89 billion (Probiotics Global Market Report 2023, 2023). As awareness of the importance of postbiotics is growing, the postbiotics market is expected to reach USD 24 million by 2029, with predicted CAGR of 10.1% during the period 2022-2029 (Postbiotics Market, 2023).

The aim of this work is to review, analyze and discuss new opportunities for probiotic and postbiotic formulations intended for intraoral application that could be of great preventive and therapeutic importance for the health of the oral cavity. An overview of the microorganisms comprising the oral microbiota, the health consequences of their imbalance and the possibility of improving these conditions with probiotics and postbiotics are presented. The formulations of the intraoral dosage forms of these products were also discussed with the aim to highlight gaps and opportunities for better exploitation of probiotics and postbiotics in the treatment of oral cavity disorders and diseases.

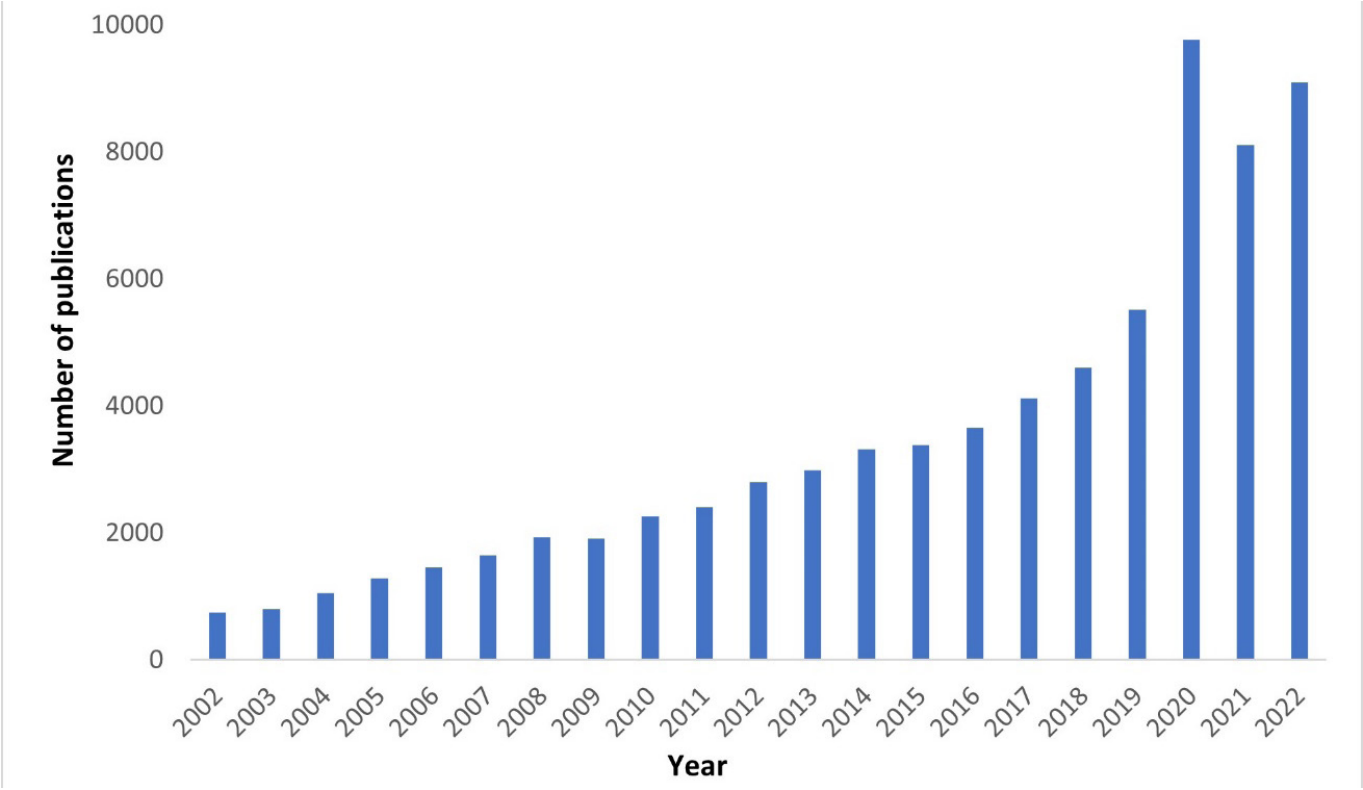

FIGURE 2 - The number of publications by year from January 1, 2002 to January 1, 2023, according to Scopus database, when the keyword "probiotics" was searched.

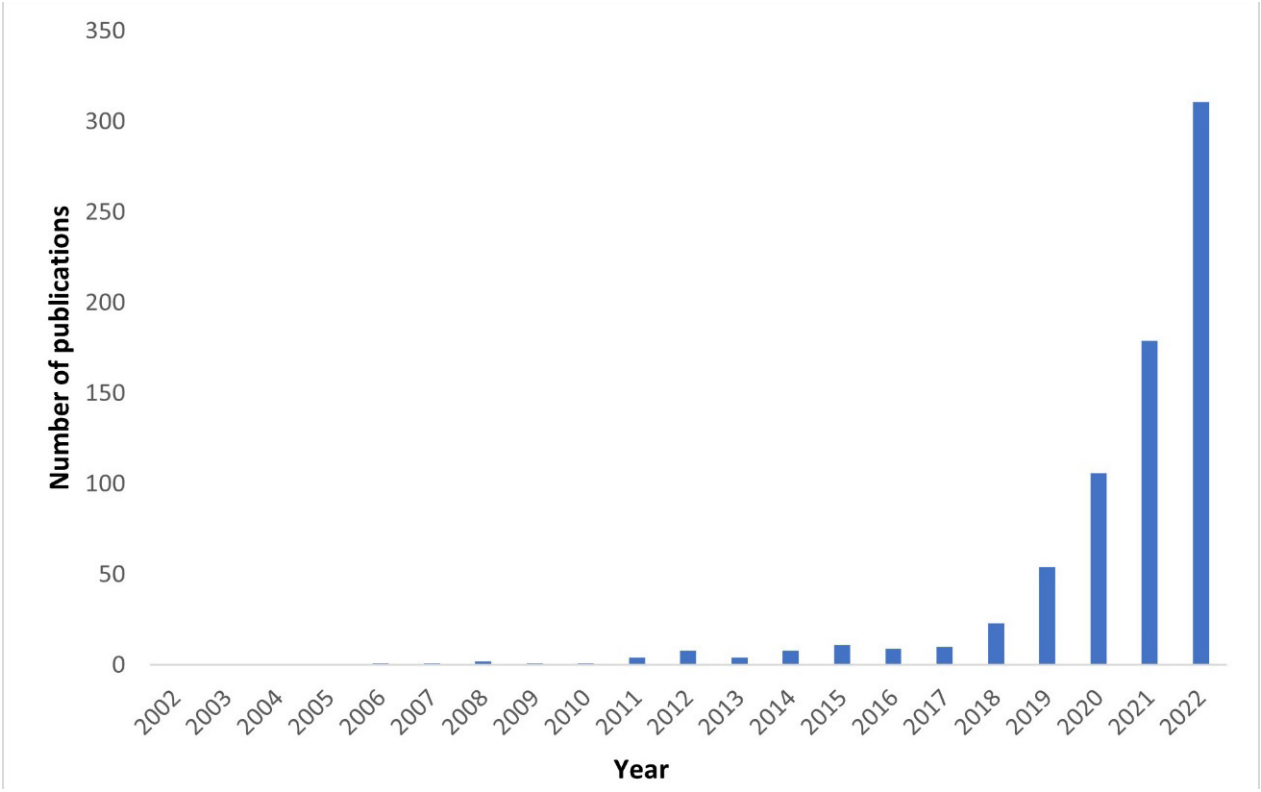

FIGURE 3 - The number of publications by year from January 1, 2002 to January 1, 2023, according to Scopus database, when the keywords "postbiotics", "paraprobiotics", "non-viable probiotics", "heat-killed probiotics", "ghost probiotics" were searched.

ORAL MICROBIOME

Numerous species of microorganisms, including bacteria, viruses, fungi, and others, make up the oral microbiota. It consists of a combination of roughly 700 different species of bacteria (Paster *et al.,* 2006). Not all species are present in the oral cavity at the same time. The microbial profile of the oral cavity differs in many ways in relation to the surface on which microbes adhere, so the microbial composition on the tongue, buccal mucosa, tooth surface, etc. is not identical. Most of the microbes that live in the oral cavity are harmless, but some can cause diseases such as periodontitis, gingivitis, dental caries or halitosis (Aas *et al.,* 2005). The microbial profile of the oral cavity says a lot about the state of the human health. Some authors have proven a close relationship between the microbial composition of the oral cavity and the occurrence of systemic diseases such as diabetes, cardiovascular diseases, rheumatic arthritis, Alzheimer's, oral cancer, etc. (Irfan, Delgado, Frias-Lopez, 2020; Willis, Gabaldón, 2020). The dynamic environment of the oral cavity, such as changes in pH, shear stress, oxygen content, temperature, and nutrient supply, forced the bacterial inhabitants of the oral cavity to evolve in a specific way (Cornejo, Van der Veen, Krom, 2019). In order to survive, they developed a mechanism of biofilm formation, whereby they aggregate and survive embedded in the extracellular matrix (Berger *et al.,* 2018) The bacterial genera that typically colonize the oral cavity are: *Streptococcus, Peptostreptococcus Actinomyces, Corynebacterium, Propionibacterium, Rothia, Lactobacillus, Veillonella, Neisseria, Selemonas, Eikenella, Fusobacterium, Hemophilus, Prevotella, Capnocytophaga and Treponema* (Marsh, 2000; Bik *et al.,* 2010; Almeida *et al.,* 2020).

Along with bacteria, the mouth also contains protozoa, the most common of which are *Entamoeba gingivalis* and *Trichomonas tenax* then fungi, archaea, and viruses (Santonocito *et al.,* 2022). *Candida, Cladosporium, Aureobasidium, Aspergillus, Saccharomycetales, Fusarium,* and *Cryptococcus* are the most frequent fungus genera in the oral cavity (Sharma *et al.,* 2018). The common archaea are *Thermoplasmatales, Methanobrevibacter, Methanobacterium, Methanosarcina,* and *Methanosphaera* (Dridi, Raoult, Drancourt, 2011). *Siphoviridae, Myoviridae* and *Podoviridae* are frequently present bacteriophages in a healthy human oral cavity (Ly *et al*., 2014; Pérez-Brocal, Moya, 2018).

In a large number of cases, an imbalance in the oral microbiota leads to the appearance of oral diseases (Radaic, Kapila, 2021). Dental caries is the most common disease that affects the oral cavity and is directly related to the decrease in pH value and the imbalance of the oral microbiota (Bowen *et al.,* 2018). Caries occur as a result of acidification in the oral cavity. Carbohydrates from food (sugars, starches) are fermented by oral microorganisms such as bacteria from genera previously classified as *Lactobacillus* whereby short-chain organic acids are formed as the final product. Increased acidity of the oral cavity increases the proliferation of acidophilic pathogenic bacteria such as *Streptococcus mutans*, which leads to dental caries (Mishra, Rath, Mohanty, 2020; Saïz, Taveira, Alves, 2021). *Prevotella, Dialister, Filifactor* and number of genera previously considered *Lactobacillus* are involved in the pathogenesis and progression of dental caries (Lu, Xuan , Wang, 2019). In addition to dental caries, common diseases of the oral cavity that occur as a result of an imbalance of the oral microbiota are periodontitis and halitosis. Periodontitis causes damage to the integrity of the paradental tissue and is an important factor in the development of certain systemic diseases (Hajishengallis, 2015) . The main factor for the occurrence of periodontal disease is the bacteria of the dental pulp. According to research, the number of bacteria from the genera *Carbachia, Clostridium, Micromonas, Eugenia, Porphyromonas, Helicobacter, Actinomycetes, Tannella, Carbachia, Hurdella, Micromonas, Streptococcus* is significantly higher in patients with periodontitis than in individuals with a healthy oral microbiome (Lu, Xuan, Wang, 2019). Halitosis or bad breath is also directly related to the bacteria present in the oral cavity. Patients with bad breath have an increased number of *Atopobium pavulum, Eubacterium sulci, Fusobacterium periodonticum, Dialister* spp., *Solobacterium moorei* and some undefined *Streptococcus* spp. (Kazor *et al.,* 2003). Probiotics can be a potential solution for diseases caused by an imbalance of the oral microbiota.

ORAL PROBIOTICS

A large number of scientific studies have proven the positive impact of probiotics on human health in general. Research has proven a positive impact of probiotics on the balance of intestinal microbiota, especially after antibiotic therapy and diarrhea (De Vrese, Marteau, 2010). It has also been proven that probiotics have a positive effect on reducing serum cholesterol levels by hydrolysis of bile salts which normally emulsify lip absorption of lipids in small intestines (Kumar *et al*., 2012). Positive impacts of probiotics on allergic reactions to food and lactose intolerance were also confirmed (Oak, Jha, 2019; Jin *et al.,* 2021). Research by some authors has proven the immunomodulatory and even anticancer abilities of probiotic strains (Elham *et al.,* 2022). Effects on the health of the oral cavity, reproductive organs, skin and nervous system have been observed, although these effects are much less studied (Allaker, Stephen, 2017; López, Aguilera, 2021; Le Morvan *et al*., 2022).

The oral cavity is the site of food entry and the first part of the gastrointestinal tract. It is known that probiotics have a positive effect on the microbiota of the intestine and a positive effect of probiotics on the oral health is also very likely. The most commonly used genera of probiotic bacteria for oral administration are *Lactobacillus, Streptococcus,* and *Bifidobacterium*. According to new scientific evidence, the *Lactobacillus* genus is genetically very diverse. Therefore, this genus is divided into genetically relevant 23 novel genera (Zheng *et al.,* 2020). The most commonly used strains from the genus previously classified as *Lactobacillus* genera are *Ligilactobacillus salivarius, Lactiplantibacillus plantarum, Lactobacillus acidophilus, Lacticaseibacillus casei, Lactobacillus delbrueckii* subsp. *lactis, Lactobacillus delbrueckii* subsp. *bulgaricus, Lacticaseibacillus rhamnosus, Lactobacillus helveticus, Lactobacillus johnsonii, Limosilactobacillus reuteri, Limosilactobacillus fermentum, Lactobacillus delbrueckii* subsp. *delbrueckii* (Chalas *et al*., 2016; Samot, Badet, 2013; Zheng *et al*., 2020). The most commonly used species from the *Bifidobacterium* genus are: *Bifidobacterium longum, Bifidobacterium bifidum* and *Bifidobacterium infantis* (Russell *et al.,* 2011; Chalas *et al*., 2016). Other oral used species include *Streptococcus salivarius, Streptococcus thermophilus, Enterococcus faecium, Enterococcus faecalis*, and *Saccharomyces boulardii* (Scannapieco, 2013; Chalas *et al.,* 2016).

The mechanisms by which probiotics have a positive effect on the oral microbiota have not yet been fully elucidated, but there are several potential mechanisms which are proposed. Probiotics are competitors in the consumption of nutrients and the colonization of the oral cavity with pathogenic microorganisms. They have an antagonistic effect on the oral biofilm, extracellular matrix, and pathogens.

Many scientific studies have shown the positive impact of probiotics in the treatment and prevention of dental caries, periodontal disease, and halitosis. Probiotics have proven to be a good tool in the fight against dental caries due to their bactericidal and antibiofilm effect on the cariogenic bacteria *Streptococcus mutans* (Nagarjuna *et al.,* 2020*).* A short-term, three-month study on children showed that supplementation with *Streptococcus salivarius* M18 at a dose of 3.6×10^9 CFU per day significantly reduced plaque formation and inhibited the growth of *Streptococcus mutans* compared to the placebo group (Burton *et al*., 2013). In the other study, 363 preschool children consumed 200 ml of fermented milk containing 5×10^6 CFU of *Lacticaseibacillus rhamnosus* and 3×10^6 CFU of *Bifidobacterium longum* for 9 months, while the placebo group consumed non-fermented milk. It was observed that fermented milk does not significantly inhibit the growth of *Streptococcus mutans,* but increases the buffering capacity of saliva (Villavicencio *et al*., 2018). Ovalgen® DC containing 6.7×10^8 CFU per tablet of *Ligilactobacillus salivarius* WB21, 2.8×10^8 CFU per tablet of *Ligilactobacillus salivarius* TI2711, or xylitol as a control were used in the two-week study on students. Study participants were directed to place the tablet on their tongues for a few minutes, in order to allow it to dissolve prior to swallowing. Tablets containing *Ligilactobacillus salivarius* WB21 reduced the amount of *Streptococcus mutans*, but without changing salivary pH. Tablets containing *Ligilactobacillus salivarius* TI2711 increased the buffering capacity of saliva (Nishihara *et al*., 2014).

Probiotics can be also beneficial in the treatment of periodontitis and halitosis. Sajedinejad *et al*., (2018)

investigated effects of *Ligilactobacillus salivarius* NK02 in treatment of patients suffering from chronic periodontitis. After 28 days, a significant improvement in clinical parameters of periodontitis, including periodontal pocket depth, gingival index and probing bleeding were observed. A decrease in the amount of *Aggregatibacter actinomycetemcomitans* was also observed in the tested group. In other study, *Ligilactobacillus salivarius* WB21 showed an improvement in clinical factors of periodontal disease in smokers after 8 weeks of use (Shimauchi *et al*., 2008). A combination of *Levilactobacillus brevis* CD2 and doxycycline, and the application of *Levilactobacillus brevis* CD2 alone contributed significantly in the alleviation of clinical signs of aggressive periodontitis as shown by Shah *et al*. (2017). These could imply a very promising role of probiotics in combination with antibiotics. Burton *et al*. (2006) report that lozenges containing *Streptococcus salivarius* K12 reduced 85% of the volatile sulfur compounds that are responsible for bad breath and, as such, could be significant for the treatment of halitosis.

ORAL POSTBIOTICS

Postbiotics, which are most commonly related to the bioactive compounds produced by the probiotic bacteria, show a great diversity of biological activities. Thus, the cell-free supernatant of *Lactobacillus acidophilus* showed anti-inflammatory properties on the epithelial cells of the fissures (De Marco *et al*., 2018). Wang *et al.* (2015) reported *in vitro* antitumor activity of exopolysaccharides produced by *Lactiplantibacillus plantarum* YW32 on the colon cancer cell line HT-29. Frequent components of postbiotic preparations are antioxidant enzymes such as superoxide dismutase, catalase and glutathione peroxidase, which are tools in the fight against free radicals (Żółkiewicz *et al.,* 2020). *Lactiplantibacillus plantarum* ATCC 14431 cultured under aerobic conditions produces manganese catalase which is highly sensitive in the presence of H_2O_2 (Peacock, Hassan, 2021). In the study of Kim *et al*. (2006), the lysate of *Lactobacillus acidophilus* KCTC 3111 had shown good antioxidant properties by the inhibition of lipid peroxidation (65.2%) and hydroxyl radical scavenging activity of 70.0%, *in vitro*.

Beneficial compounds with proven biological activity produced by probiotic bacteria or other microorganisms could be applied independently in oral postbiotic formulations, or combined with probiotic bacteria in formulations designed for oral administration. In the latter case, it is hard to strictly distinguish between microbial probiotic and postbiotic action because they are interrelated and synergistic.

A majority of oral postbiotics are based on the action of cytotoxic metabolites on the pathogen. The metabolites could be antimicrobial compounds such as bacteriocins, lactic acid and hydrogen peroxide, which inhibit the proliferation of pathogens (Djukić-Vuković *et al.,* 2015). They also activate T-lymphocytes, leading to an immune response (Mundula *et al*., 2019; Kaźmierczyk-Winciorek, Nędzi-Góra, Słotwińska, 2021). They maintain the microbial balance of the oral cavity by producing cytoprotective and antioxidative proteins (Soccol *et al*., 2010; George Kerry *et al*., 2018; Saïz, Taveira, Alves, 2021).

Bacteriocins play an important role in the fight against pathogenic microorganisms. Bacteriocins are compounds with a peptide structure that have bactericidal and bacteriostatic effects and are produced by many representatives of lactic acid bacteria. Therefore, they provide a potential therapeutic alternative or addition to antibiotics in multiresistant pathogenic microorganisms (Radaic *et al*., 2020). Bacteriocins produced by *Lacticaseibacillus paracasei* HL32 have bactericidal effects on *Porphyromonas gingivalis*, while bacteriocin Abp118, produced by *Ligilactobacillus salivarius* UCC118, showed antimicrobial properties against *Listeria monocytogenes* in a mouse model (Corr *et al*., 2014; Pangsomboon *et al*., 2006).

Exopolysaccharides (EPS) are compounds commonly produced by many bacteria, but particularly those produced by *Lactobacillus* spp. are well studied and reported as bioactive (Rajoka *et al.,*2020a). EPSs enable the adhesion of probiotics and have a protective role against both environmental stressors and pathogenic strains, playing a role in biofilm formation. Many microorganisms are producing EPS of different chemical composition, both homo- and hetero-polymers. They are an important component of biofilm with a significant effect

on antimicrobial resistance as a major treat in healthcare worldwide. EPS can be a very convenient component in pharmaceutical formulations with probiotics which are not natural EPS producers and can have a protective role during probiotic biomass drying and preparation, with effects which go beyond just technological advantages. Namely, some studies have shown antimicrobial and antibiofilm activities of EPS against the number of pathogenic microorganisms such as *Escherichia coli, Enterococcus faecalis, Staphylococcus aureus, Listeria monocytogenes* and *Pseudomonas aeruginosa*, as well as immunoprotective and antioxidant activity (Lebeer *et al*., 2011; Rajoka *et al*., 2020b; Abdalla *et al*., 2021).

Biosurfactants play an important role in the prevention of a pathogen's biofilm formation. Biosurfactants are secondary metabolites of probiotic bacteria with a glycopeptide or lipopeptide structure. They can be extracellular or bound to the cell membrane of the probiotic. The mechanism of action of biosurfactants is to emulsify pathogenic biofilms and support their removal, but also to prevent the formation of pathogenic biofilms. Some common biosurfactants are mannosylerythritol lipid, surfactin, rhamnolipid, emulsan, etc (Fakruddin, 2012). An *in vitro* study showed that biosurfactants produced by *Limosilactobacillus reuteri* DSM 17938, *Lactobacillus acidophilus* DDS-1, *Lacticaseibacillus rhamnosus* ATCC 53103, and *Lacticaseibacillus paracasei* B21060 were able to remove the biofilms of *Streptococcus mutans* ATCC 25175 and *Streptococcus oralis* ATCC 9811 (Ciandrini *et al*., 2016).

FORMULATION OF PROBIOTICS AND POSTBIOTICS IN DOSAGE FORMS FOR INTRAORAL ADMINISTRATION

Since probiotics are living organisms, many factors can limit their formulation, production and application in a specific dosage form. Microorganism can lose their viability under thermal and/or oxidative stress, mechanical force, humidity or pH change during preparation, storage or due to biological barriers such as enzymatic cleavage (Baral *et al*., 2021). In addition to the selection of the appropriate procedures for the production of pro/postbiotic products, sometimes the conditions (temperature, humidity, etc.) during the production need to be carefully monitored in addition to the suitable choice of the container and packaging material. Although numerous stabilization techniques are available, such as e.g. spray drying for microencapsulation, there is a need for special precautions regarding the probiotic products in order to ensure their viability in dried form. Short exposure of probiotics to high temperatures during spray drying qualifies it as a very suitable technique for the preparation of dried probiotics for pharmaceutical formulation (Huang *et al.* 2017). Spray drying is a versatile technique that can be additionally applied to mask the unpleasant taste and/or odor, controlled release, precise control of the dried particles size, as well as easier handling of formulations in solid form compared to the liquid form. Various dosage forms have been utilized for intraoral delivery of probiotics and/or postbiotics, including conventional tablets, chewable tablets, mucoadhesive (buccal) tablets and films, orally disintegrating tablets and films, wafers, lozenges, gels, mouthwashes, oral drops, oral sprays, etc. Currently, marketed dosage forms are predominantly chewable tablets and lozenges (Table I). In general, solid dosage forms provide better stability for probiotics and postbiotics, protecting them from potentially detrimental environmental factors, such as moisture, oxygen, and light. On the other hand, liquid formulations may exhibit a lower stability compared to solid forms, as they can be susceptible to microbial growth, chemical degradation, or loss of activity over time, which is particularly challenging in the case of live microorganisms or even postbiotics. Consequently, solid dosage forms typically have a longer shelf life when compared to liquid formulations. The dry environment and protective packaging of solid formulations may help to maintain the viability and functionality of probiotics and the stability of postbiotics for an extended period. Preservatives and proper storage conditions are usually necessary to maintain the stability of liquid dosage forms which is not acceptable in formulations with probiotics. Solid forms provide more accurate dosing uniformity, however liquid forms are more flexible in terms of adjustment of the specific dose, i.e. the quantity of bioactive ingredient. Liquid formulations may also facilitate a faster onset of action since the bioactive ingredients are readily available in

the oral cavity upon administration. Additionally, liquid forms can be more convenient for patients who have difficulty swallowing or prefer not to consume water or other liquids alongside the dosage form.

TABLE I - Selected examples of marketed probiotic products for intraoral administration

Name of the product	Composition in terms of probiotics and postbiotics	Formulation chemical composition
Prodegin™ (Klaire Labs), chewable tablets	Blend of 5 Lactobacillus species: *Lactobacillus acidophilus*, *Lactobacillus rhamnosus*, *Lactobacillus salivarius*, *Lactobacillus paracasei* and *Lactobacillus plantarum*	Freeze-dried Lactobacillus cultures in an inuline base with additional excipients: stearic acid, natural cherry flavor, silicon dioxide, magnesium stearate, licorice extract.
Oraldiet® Advanced Dental Hygiene, lozenges	*Lactobaccillus reuteri* with Aloe Vera gel.	Excipients: isomalt, xylitol, natural mint aroma, magnesium stearate, menthol.
ProlacSan® CMS Dental, gel	*Lactobacillus plantarum*, *Lactobacillus brevis*	Excipients: guar gum for gelation. Mixture in the syringe forms a gel-like mass with the sterile water
ProlacSan® CMS Dental, lozenges	*Lactobacillus plantarum*, *Lactobacillus brevis*	Excipients: sorbitol, guar gum, mint flavor, hydrogenated cottonseed oil
PRO-Dental® hyperbiotics®, chewable tablets	*Lactobacillus reuteri*, *Lactobacillus paracasei*, *Lactobacillus sakei*, *Lactobacillus salivarius* with Zinc (as amino acid chelate)	Excipients: isomalt, inulin, microcrystalline cellulose, glyceryl behenate, dicalcium phosphate, natural mint extract, stevia
Clinical Grade Oral Probiotics®, PUR Nutraceuticals®, dissolvable tablets	Mixture of two specific strains of *Streptococcus salivarius*: BLIS K12™ and BLIS M18™	Excipients: xylitol, witergreen and peppermint flavor, microcrystalline cellulose, stearic acid, silicon dioxide, stevia rebaudioside-A
Mycrobiome®, Solaray®, lozenges	Mixture of two specific strains of *Streptococcus salivarius*: BLIS K12™ and BLIS M18™; *Bacillus coagulans*	Excipients: xylitol, inulin, natural berry flavors, coconut oil powder, citric acid, silica, organic beet root powder, Lo Han Guo, stevia
ORAL HEALTH, Supersmart®, oral powder	*Lactobacillus rhamnosus*, *Bifidobacterium longum*, *Lactobacillus salivarius*, *Lactobacillus reuteri* with fructo-oligosaccharides	Excipients: sorbitol, maltodextrin (powder stick packaging)

Orally disintegrating dosage solid forms (films and tablets) are of special interest, due to their acceptance in a wide range of populations, including children, elderly and other patients that may have issues with swallowing;

as well as improved patients' compliance, since these dosage forms rapidly disintegrate in the mouth and do not require any liquid for administration. There are some potential hurdles in the development of orally disintegrating formulations, such as the achievement of fast disintegration, requirements for taste masking, and selection of the manufacturing method. Heinemann *et al.* (2013) have developed orally disintegrating films (ODF) for intraoral delivery of *Lactobacillus acidophilus* or *Bifidobacterium animalis* subsp. *lactis* entrapped in a matrix composed of carboxymethylcellulose, gelatin and starch. The formulation has demonstrated high viability of probiotics during 90 days of storage. Similarly, Lordello *et al.* (2021) have developed ODF for intraoral delivery of *Enterococcus faecium* CRL183, demonstrating its antifungal activity *in vitro* and 90 days storage stability. Dodoo *et al.* (2020) have utilized an inkjet printing approach to fabricate xylitol-based ODF for the delivery of *Streptococcus salivarius* for management of dental caries.

Mucoadhesive dosage forms provide a more intimate contact with the oral mucosa and often a prolonged release of the active ingredient (Kurćubić *et al*., 2021). Abruzzo *et al*. (2020) have formulated mucoadhesive buccal films for the local release and anti-inflammatory action of *Lactobacillus brevis* CD2. Authors have demonstrated a prolonged release of viable lactobacilli from the hydroxypropylmethylcellulose-based film, with better survival recorded for films stored at 2-8 °C. De Souza Ferreira *et al.* (2021) have used poloxamer 407 and Carbopol 974 P® to develop mucoadhesive wafer for delivery of anaerobic bacteria *Bifidobacterium bifidum* BB12. The wafers have suitable stability and mucoadhesive properties for 14 days. A combined approach to formulate probiotic orally disintegrating tablets (ODT) with excipients (polymers) that provide buccal mucoadhesion was exploited by (Hoffmann, Fischer, Daniels, 2020). Carbopol 971 P®, Metolose 65SH50 and chitosan were used to prepare tablets either by direct compression or wet granulation. Mucoadhesive ODTs were stable under refrigerated conditions over 30 months with *Lactobacillus plantarum* Lp299v as the model strain in the study (Hoffmann, Fischer, Daniels, 2020).

CONCLUSION

In the recent decade, an interest of the scientific community has turned to new interactions of beneficial microbes with xenobiotics, food or pathogens. New insights into the role of oral microbiota and its metabolic activity in the oral cavity offers new possibilities for the prevention or treatment of diseases, with a prominent role of postbiotics, a new class of microbial products. Solid dosage forms are more convenient for pro/postbiotics formulations because of low water content, which is a critical factor for the stability of probiotics. Evidence is piling up for the technological or pharmacological advantages of postbiotics, namely exopolysaccharides, enzymes, bacteriocins, cell lysates and other metabolites of probiotics or other non-pathogenic bacteria. Postbiotics could be more efficient than probiotics in oral dosage forms due to the short passage in oral cavity. It is clear that there is a great potential and need for further development of delivery systems and suitable dosage forms for intraoral administration of pro/postbiotics. In spite of the hurdles that need to be addressed, such as viability and stability issues, a number of novel technologies are indicating that many new products on the market can be expected in the future.

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