Episode 63 – Probiotics & the Oral Microbiome June 24, 2022

Human microbiome[1]

- Community of commensal (normal nonpathogenic flora), symbiotic (both the body and microbes benefit), and pathogenic microorganisms that live on and in humans, including all their collective genomes and genetic material, as well as their produced metabolites (e.g., signaling molecules, toxins, organic [e.g., bacteriocins] and inorganic molecules).
- Consists of over 100 trillion microorganisms that colonize the gut, oral cavity, skin, and elsewhere in the body.
- Contains over one hundred times more genes than in the human genome.
- Diverse collection of microbes that includes bacteria, archaea (primitive single-celled organisms), fungi, protozoa, and viruses.
- Estimated the human microbiome consists of 900-1,000 different species of microorganisms.
- Consists of the core microbiome (common to all individuals) and variable microbiome (unique to individuals depending on lifestyle and physiological differences).
- Diversity also exists between an individual's various organs and their matching body parts (e.g., right and left hands of the same person).
- Majority of microbes live in the gut, especially the large intestine.
- Groups of microorganisms are dynamic and change in response to environmental factors, such as exercise, diet, medication, and other exposures.
- Bacteria are the most numerous members, estimated between 75-200 trillion individual organisms, compared to the entire human body, which consists of about 50-100 trillion somatic cells.[2]
- Human microbiome was not generally recognized to exist until the late 1990s. [1] [2] [3] [4] [5] [6]

Function of the human microbiome

Helps to maintain health by:

- Inhibiting pathogenic microorganism growth in the gastrointestinal tract via:
    - Providing colonization resistance (i.e., help to prevent pathogens from colonizing by competing for nutrition and attachment sites; producing antimicrobial substances [e.g., bacteriocins] which inhibit pathogen growth);
    - Improving intestinal transit;

[1] Microbiome: "micro" means small; "biome" from bios means life; from Ancient Greek origin. [2]
[2] Somatic cells are cells in the body other than sperm and egg cells, which are germ cells.

    - Helping normalize a perturbed microbiota;[3]
    - Producing inhibitory compounds (e.g., bacteriocins); and
    - Reducing substrate availability to other bacterial populations.
- Providing the ability to absorb nutrients.
- Producing additional energy otherwise inaccessible to the host. For example, fermentation of indigestible fibres causes the production of short chain fatty acids that the body can use as a nutrient source.
- Synthesizing essential and nonessential amino acids.
- Producing vitamins, such as vitamin K and group B vitamins (biotin [B7], cobalamin [B12], folate [B9], nicotinic acid [B3], pantothenic acid [B5], pyridoxine [B6], riboflavin [B2], thiamine [B1]). Key enzymes needed to form vitamin B12 are only found in bacteria, not in plants and animals.
- Metabolizing xenobiotics (e.g., drugs, pesticides, flavourings, food additives, industrial chemicals, environmental pollutants) to render them less toxic and readily excretable.
- Transforming prodrugs into active drugs (e.g., lovastatin).
- Providing resistance to tumour and cancer-inducing neoplasms.
- Assisting in developing a mature immune system.
- Maintaining skin and mucosa barrier function. [7] [8] [9] [10]

Dysbiosis

- Dysbiosis is a disruption in the homeostasis of the microbiome caused by:
    - An imbalance in the microflora;
    - Changes in their functional composition and metabolic activities; or
    - A shift in their local distribution.
- Three types of dysbiosis are:
    - Loss of beneficial bacteria;
    - Overgrowth of potentially pathogenic bacteria; and
    - Loss of overall bacterial diversity.
    - These types of dysbiosis mainly occur at the same time.
- Lower bacterial diversity is considered a marker of gut dysbiosis. Gut dysbiosis is believed to play a significant role in the pathogenesis of intestinal disorders (e.g., inflammatory bowel disease [IBD],[4] irritable bowel syndrome [IBS]), and extraintestinal disorders, such as allergies, asthma, cardiovascular disease (CVD),[5] metabolic syndrome, obesity, and autoimmune disorders.[6]
- Autoimmune disorders associated with microbiome dysfunction include diabetes, rheumatoid arthritis, and multiple sclerosis. Pathogenic microbes accumulate over time, altering gene activity and metabolic processes, resulting in an abnormal immune response against normal healthy cells. Some autoimmune disorders may be passed in families not via DNA inheritance but by inheriting the family's microbiome. [3] [4] [11] [12] [13] [14] [15] [16]

[3] Microbiota are the numerous living microorganisms which reside in a specific ecological niche.
[4] Refer to Episode 60 for additional information on IBD.
[5] Refer to Episode 37 for discussion on CVD and periodontal disease.
[6] Refer to Episode 45 for additional information on autoimmune disorders.

Oral microbiome

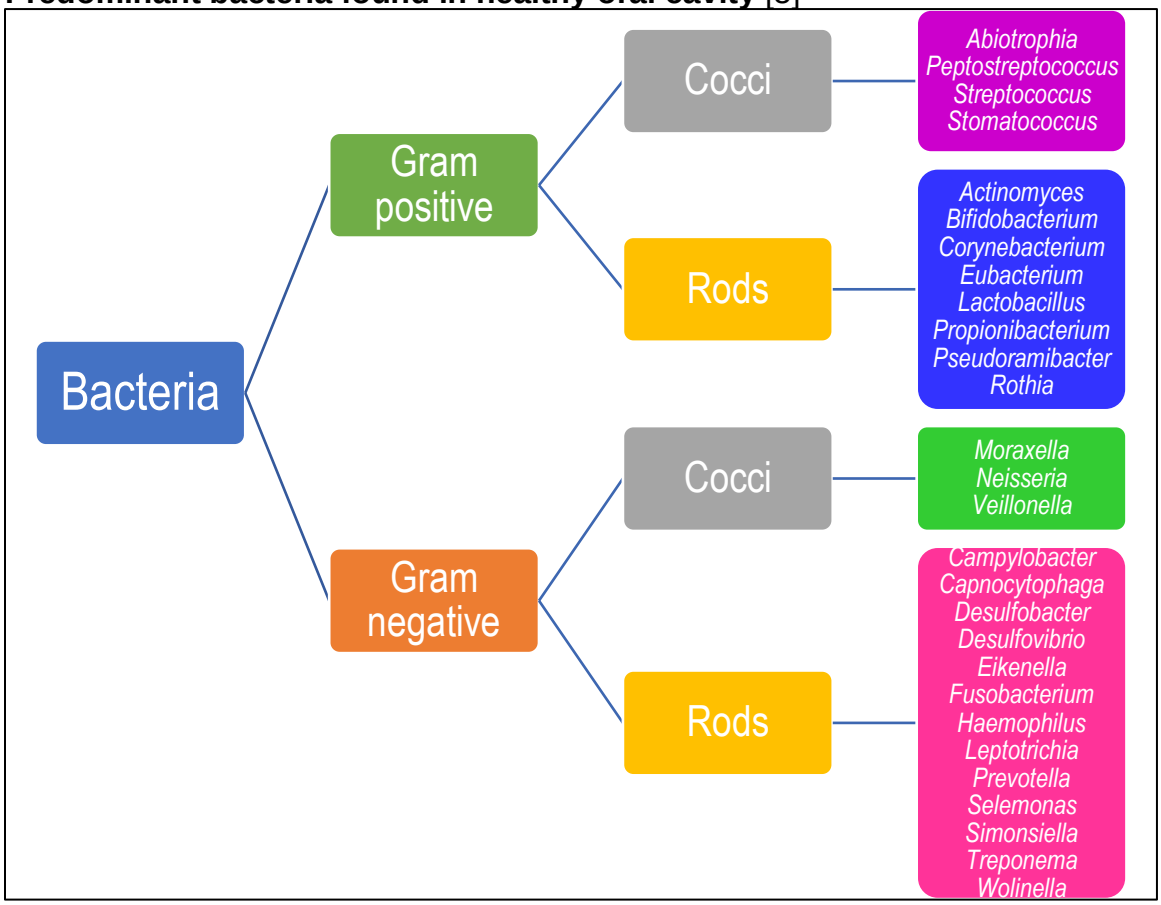
- Over 700 microbial species have been found in the oral cavity. Over 400 of these have been identified in periodontal pockets, the remainder from other sites (e.g., tongue, mucous membranes, carious lesions, endodontic infections). Each individual has approximately 100-200 of these 700 species demonstrating the diversity between individuals. [17] [18]
- Second largest and diverse microbiota after the gut. For example, one millilitre of saliva contains approximately 100 million microbial cells. [19]
- Consists of bacteria, fungi, archaea, viruses, and protozoa.
- Bacterial species belong to 185 genera and 12 phyla, of which approximately:
    - 54% are officially named;
    - 14% are unnamed (but cultivated); and
    - 32% are known only as uncultivated phylotypes. [5]
- The 12 phyla are *Firmicutes, Fusobacteria, Proteobacteria, Actinobacteria, Bacteroidetes, Chlamydiae, Chloroflexi, Spirochaetes, SR1, Synergistetes, Saccharibacteria*, and *Gracilibacteria.* [5]
- Dominant species in the oral cavity include *Streptococcus, Haemophilus, Actinomyces*, and *Prevotella.*
- Oral cavity contains several different niches of microorganisms (e.g., teeth, gingival sulcus, tongue, hard and soft palate, tonsils, saliva, buccal mucosa, floor of the mouth).
- Diversity is both individual and site specific. For example, the tongue harbours diverse microflora including anaerobes due to papillae creating anaerobic niches. Buccal and palatal mucosae have low microbial diversity.
- Initiates digestion and is crucial in maintaining oral and systemic health.
- Microbial dysbiosis contributes to oral diseases, such as dental caries, periodontal disease, peri-implant disease, mucosal diseases (e.g., oral candidiasis, “strawberry tongue” of scarlet fever, syphilis, hand, foot, and mouth disease),[7] and oral cancer.
- Factors contributing to oral dysbiosis include salivary gland dysfunction (e.g., changes in saliva flow and/or composition), poor oral hygiene, gingival inflammation, lifestyle choices [e.g., dietary habits, smoking], and certain drugs (e.g., antibiotics, chemotherapeutics, immunosuppressants). [5] [6] [13] [16] [17] [20]

Oral cavity is an ideal environment for bacterial growth due to:

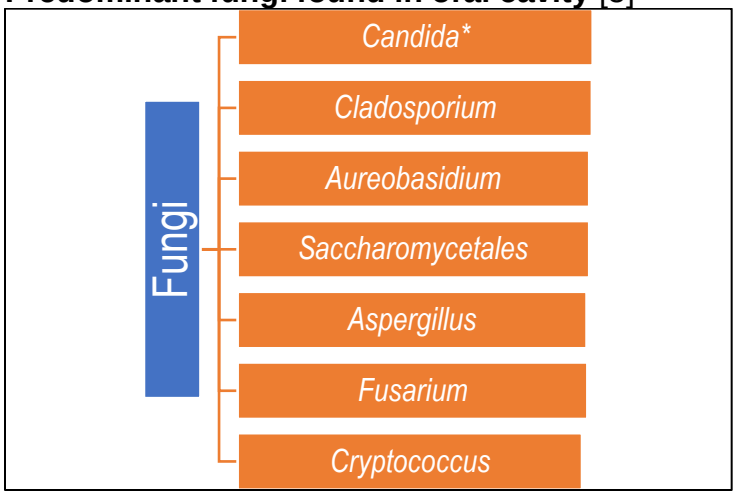
- Relatively stable average temperature of 37°C;
- Saliva has stable pH of 6.5-7 (favourable to most species);
- Provides host-derived nutrients (e.g., saliva proteins, glycoproteins, gingival crevicular fluid);
- Saliva keeps bacteria hydrated and serves as transportation medium of nutrients to microorganisms; and
- Teeth are natural non-shedding surfaces that provide opportunities for extensive biofilm formation and microbial persistence.[8] [5]

[7] Refer to Episode 61 for more information on oral manifestations of infectious diseases.
[8] Dental restorations, crown and bridgework, removable prostheses, and implants are additional non-shedding surfaces that influence biofilm formation and composition. [5]

Predominant bacteria found in healthy oral cavity [5]

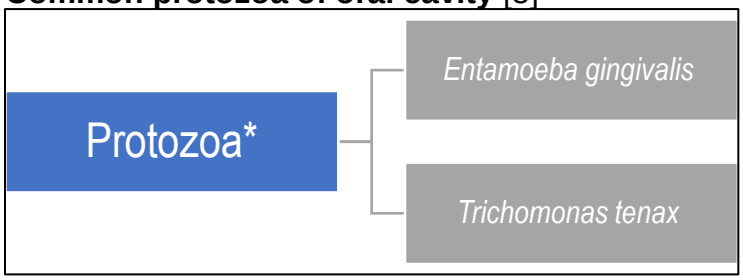


Predominant fungi found in oral cavity [5]



**Candida* species are the most prevalent fungi.*

Common protozoa of oral cavity [5]



*Mainly saprophytic (i.e., feeds on dead or decaying organic matter).

Microorganisms associated with oral disorders*

Disorder	Predominant bacterial pathogens	Fungi	Archaea	Viruses
Periodontal disease [5] [19] [21] [22] [23] [24] [25]	*Porphyromonas gingivalis* *Treponema denticola* *Tannerella forsythia* *Aggregatibacter actinomycetemcomitans* *Filifactor alocis* *Parvimonas micra*	*Candida albicans*	*Methanobrevibacter oralis* *Methanobacterium curvum/congolense* *Methanosarcina mazeii*	Human cytomegalovirus (HCMV) Epstein-Barr virus (EBV) Herpes simplex virus
Peri-implantitis [26] [27] [28]	*Aggregatibacter actinomycetemcomitans* *Prevotella intermedia* *P. gingivalis* *Tannerella forsythia*	*Candida albicans* *Candida boidinii* *Penicillum spp.* *Rhadotorula laryngis* *Paelicomyces spp.*		HCMV EBV
Dental caries [19]	*Streptococcus mutans* *Lactobacillus spp.*	*Candida albicans*		
Oral cancer [19]	*Capnocytophaga gingivalis* *Prevotella melaninogenica* *Streptococcus mitis*			Human papilloma virus (HPV)[9]
Esophageal cancer [19] [29]	*Tannerella forsythia* *P. gingivalis*			HPV
Candidiasis[10] [30]		*Candida albicans* *Candida glabrata* *Candida tropicalis* *Candida krusei*		
Halitosis [20]	*Fusobacterium nucleatum*			

[9] Refer to Episodes 7 & 53 for discussion on HPV and oral cancer.
[10] Refer to Episode 61 for discussion on candidiasis.

Disorder	Predominant bacterial pathogens	Fungi	Archaea	Viruses
	Porphyromonas gingivalis *Prevotella intermedia* *Treponema denticola*			

*Additional microbes may be associated with oral disorders.

History of probiotics

- History of probiotics is related to use of fermented foods, a centuries old practice.
- Approximately 10,000 years ago, humans began to produce fermented food and beverages.
- Nearly every civilization has developed some type of food fermentation (e.g., fermenting animal milk products).
- The modern history of probiotics started around the 1900s with the studies of Russian scientist Elie Metchnikoff working at the Pasteur Institute in Paris.
- Louis Pasteur identified the bacteria and yeast responsible for the fermentation process. Metchnikoff first introduced the concept of using probiotic microorganisms for health benefits in 1907. He proposed the gut flora could be modified and harmful microbes replaced with useful microbes.
- The word “probiotic” (from the Greek “pro bios” meaning for life) was introduced by German scientist Werner Kollath in 1953 to describe active substances essential for healthy development. [31] [32] [33]

Probiotics

- Probiotics are nonpathogenic live microorganisms when administered in appropriate amounts, are beneficial to human health. Many of these microorganisms are part of the normal human gut flora, where they live in a symbiotic relationship.
- Consist mainly of bacteria (e.g., *Lactobacillus*, *Bifidobacterium*) but also yeasts (e.g., *Saccharomyces*).
- Probiotics are naturally present in fermented foods, such as active-culture yogurts, certain cheeses (e.g., Swiss, gouda, typically cheeses that have been aged but not heated afterward), kefir (fermented milk beverage), kimchi (Korean fermented cabbage dish), kombucha (fermented tea), miso (fermented soybean-based paste), and sauerkraut (fermented cabbage). Some fermented foods (e.g., sourdough bread, most commercial pickles) are processed after fermentation and do not contain live cultures.
- Probiotics may also be added to other food products, and are available as dietary supplements.
- Genera of microbial organisms most often used in probiotic products include *Lactobacillus, Bifidobacterium, Saccharomyces, Streptococcus, Enterococcus, Escherichia,* and *Bacillus*.
- Not all foods and dietary supplements labelled as probiotics have proven health benefits.

- Research has shown a positive effect of probiotics on gastrointestinal conditions (e.g., antibiotic-associated diarrhea, *Clostridium difficile* diarrhea, constipation, IBS, IBD) and allergic diseases (e.g., atopic dermatitis).
- Recent studies suggest an active role of probiotics in prevention and treatment of oral diseases, including dental caries and periodontal disease. [20] [33] [34] [35] [36]

Probiotic supplements

- Available in various forms (e.g., capsules, powders, liquids) and a wide variety of strains and doses;
- Often contain mixed cultures of live microorganisms rather than single strains;
- Measured in colony forming units (CFU), which indicate the number of viable cells.
- Amounts may be noted, for example, as 1 x 10^9 for 1 billion CFU or 1 x 10^{10} for 10 billion CFU.
- Various probiotic supplements contain 1 to 10 billion CFU per dose, but some may contain up to 50 billion CFU or greater. However, higher CFU amounts do not necessarily improve the product's health effects. [35]

Probiotics commonly used in health conditions [15]

Type	Genus	Strain	Health condition
Bacteria	*Lactobacillus*	*L. acidophilus* *L. johnsonii* *L. casei* *L. rhamnosus* *L. gasseri* *L. reuteri* *L. fermentum* *L. plantarum* *L. salivarius*	Crohn's disease[11] Urogenital infection Acute diarrhea Cancer Oropharyngeal infection Allergy Cardiovascular disease Caries Gingivitis
	Bifidobacterium	*B. bifidum* *B. longum* *B. infantis*	Acute diarrhea Allergy Obesity Periodontal disease
	Streptococcus	*S. salivarius* *S. thermophilus* *S. oralis* *S. uberis* *S. rattus* *S. mitis* *S. sanguis*	Mucositis Caries Periodontal disease Halitosis
	Enterococcus	*E. faecalis*	Acute diarrhea
	Escherichia	*E. coli*	Crohn's disease Ulcerative colitis
	Bacillus	*B. cereus*	Acute diarrhea
Yeast	*Saccharomyces*	*S. boulardii* *S. cerevisiae*	Acute diarrhea Crohn's disease

[11] Refer to Episode 60 for additional information on Crohn's disease.

Health risks of probiotics

- Generally thought to be safe in healthy people, but some adverse effects such as bloating, flatulence, and diarrhea have been reported (effects usually temporary).
- Few studies have investigated the safety of probiotics in detail, so there is a lack of solid data on side effect frequency and severity.
- Risk of harmful effects is greater in individuals with serious infections, underlying health conditions, or compromised immune systems. For example, it has been reported patients in intensive care settings have developed bacteremia or fungemia after being administered probiotics.
- Other adverse effects may include production of harmful substances by the probiotic microorganisms, overactive immune function, and transfer of antibiotic resistance genes from probiotic microorganisms to other microorganisms* in the digestive tract.
- Individuals with cancer receiving immunotherapy with anti-PD-1 checkpoint inhibitors should avoid probiotic intake as they can reduce chances of cancer remission.
- Probiotic safety in infants (especially preterm) is not established because their immune systems are still developing.
- Some probiotic products have been reported to contain unlisted microorganisms, these contaminants may pose serious health risks.*
- Individuals with allergies or intolerances should read probiotic supplement labels carefully, since some products may contain allergens (e.g., dairy, egg, soy, gluten, lactose) that may cause an adverse reaction. [36] [37] [38] [39] [40]

*Important to purchase probiotics from reputable sources.

Prebiotics

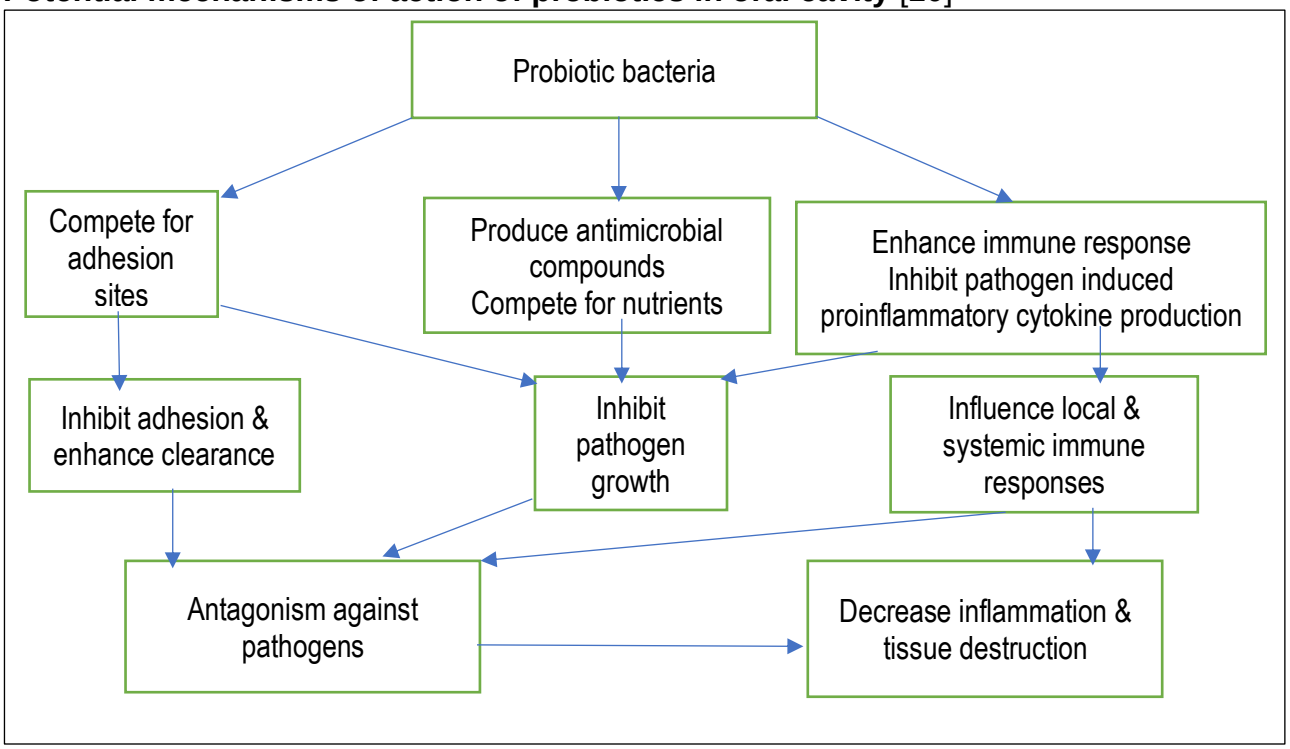
- Prebiotics are typically indigestible complex carbohydrates (e.g., inulin and other fructooligosaccharides[12]) that gut microbes use as metabolic fuel.
- Naturally present in a variety of foods.
- High amounts are found in raw versions of garlic, onions, leeks, asparagus, Jerusalem artichokes, dandelion greens, bananas, and seaweed. In general, fruits, vegetables, legumes, and whole grains (e.g., wheat, oats, barley) are good sources of prebiotic fibres.
- Commercial products containing both prebiotics and probiotics are often called synbiotics. [7] [35] [41]

Probiotics and oral health

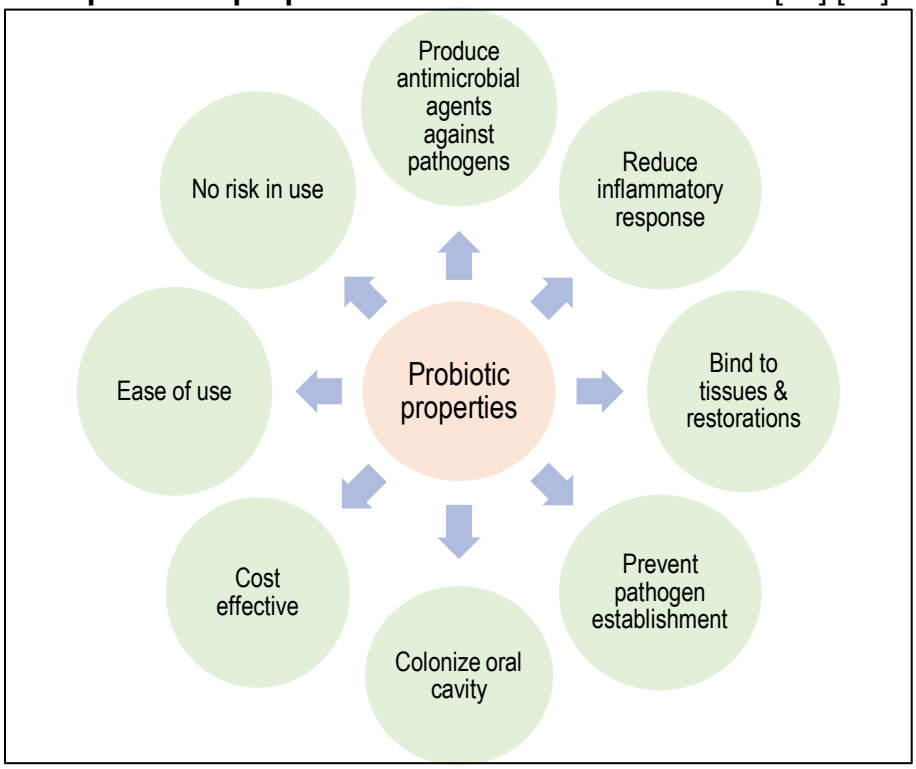
- Probiotics may play a role in the prevention and treatment of oral conditions, such as periodontal disease, dental caries, peri-implant disease, halitosis, and *Candida* infections.
- Commonly used species in oral probiotic preparations include *Lactobacillus bulgaricus, L. acidophilus, L. casei, L. helveticus, L. lactis, L. salivarius, L. plantarum, Streptococcus thermophilus, Enterococcus faecium, E. faecalis, Bifidobacterium*, and *Saccharomyces boulardii.* [20]

[12] Fructooligosaccharides (FOS) are a type of carbohydrate called oligosaccharides. They are composed of chains of fructose molecules. FOS occur naturally in many plants, such as garlic, onions, and leeks

Potential mechanisms of action of probiotics in oral cavity [20]



Ideal probiotic properties for use in oral disorders [42] [43]



Probiotics and oral disorders

Periodontal disease

- Many lactobacilli and streptococcal strains show antibacterial activity against *P. gingivalis*, *P. intermedia*, *A. actinomycetemcomitans*, and *F. nucleatum*.
- Research shows different lactobacilli strains can inhibit the ability of several microbial species (e.g., *L. gaseri* is active against anaerobes; *L. paracasei and L. acidophilus* inhibit the growth of *S. aureus*, a periodontal pathogen).
- Lactobacilli compete with *P. gingivalis* for adhesion to epithelial cells and also alter the interaction of epithelial cells with *P. gingivalis* by modulating the pathogen's ability to adhere to and invade epithelial cells.
- Streptococci inhibit anaerobes (e.g., *P. gingivalis*, *P. intermedia*) by producing lactic acid and other organic acids.
- Several studies found lactobacilli modulate the inflammatory response to periodontal pathogens. For example, *Lactobacillus* has shown the ability to reduce the inflammatory response to the pathogen, *P. gingivalis.*
- Several studies have shown probiotic treatment generally prevented alveolar bone loss. For example, reduced alveolar bone loss was observed in ligature-induced periodontal sites that received probiotic *Bacillus subtilis* treatment compared with those without. Lactobacilli also significantly inhibited inflammatory periodontal bone loss in animal studies.
- Research suggests mechanisms of action of probiotics on reducing alveolar bone loss and attachment loss or improving other clinical parameters are a combination of local and systemic effects, including modulation of local and systemic host immune response, antibacterial effects via different mechanisms, and stimulation of osteoblastic function. [44]

Peri-implant disease

- Studies suggest probiotics may be used during the treatment of peri-implant disease. However, the most appropriate form of probiotic administration and their effectiveness against peri-implant microbiota are still unclear. [45]

Dental caries

- Several studies have suggested short term consumption of some probiotics may reduce cariogenic bacteria counts, decrease dental plaque formation, and thus control dental caries progression. These effects appear to require temporary colonization of the oral cavity which may lead to decreased bacterial pathogens. However, probiotics were unable to definitively eliminate pathogenic bacteria. Future research is required to evaluate cariogenic bacteria counts as well as dental caries progression and incidence considering reduced salivary counts do not imply a reduction of bacterial plaque virulence. [46]

Halitosis

- Replacement of bacteria associated with halitosis by colonization with probiotic bacterial strains may have potential adjunctive application for the prevention and treatment of halitosis. [20]

Oral candidiasis

- Research has shown probiotics have a protective role against *Candida s*pp. infection, especially colonization via:
    - Coaggregation, modification of oral pH, and production of H_2O_2;
    - Releasing high amounts of lactic acid; and
    - Complete inhibition of fungal biofilms.
- However, these positive effects were highly linked to the administration method, type probiotic strains, and dosage. [47]

Bacteriocins

- Research has found bacteriocins (antimicrobial proteins or peptides secreted by bacteria as a defense mechanism) contribute greatly to antibacterial activities of many probiotics, including lactobacilli.
- Bacteriocins relevant to the oral cavity include salivaricin, reuterin, plantaricin, and nisin.
- Salivaricin, from *L. salivarius* and *S. salivarius*, suppresses oral bacteria related to malodour.
- Reuterin, from *L. reuteri*, has antibacterial effects against *T. forsythia*, a periodontal pathogen.
- Plantaricin, from *L. plantarum*, helps to prevent the growth of *P. gingivalis.*
- Nisin, from *L. lactis*, exhibits significant antibiofilm and antimicrobial effects against many gram-negative periodontal pathogens, such as *P. gingivalis, P. intermedia, A. actinomycetemcomitans, F. nucleatum,* and *T. denticola.* [44]

New research

The commensal bacteria, *S. salivarius*, produce a range of salivaricins (bacteriocins). Dr. Glogauer, Dr. Barbour,[13] and colleagues have discovered a novel salivaricin in healthy individuals, which they named salivaricin 10. Their research demonstrated salivaricin 10 conferred multi-level protection against bacterial infections via various mechanisms. For example, salivaricin 10 acted as an antibiotic and antibiofilm agent crowding out pathogens to help maintain homeostasis and by modulating anti-inflammatory responses. It also showed excellent bioactivity against selected multidrug-resistant bacteria and multispecies biofilms. Considering salivaricin 10 exhibited both immunomodulatory and antimicrobial effects, it is probable salivaricin 10 will offer protection against disease-causing pathogens and provide a promising approach to combat infectious diseases.

Take home messages

- Research has shown the balance between commensal and pathogenic bacteria is essential to maintain oral health.
- Probiotics may be a tool to change the oral ecology to restore microbial population associated with healthy oral status.
- Probiotics show promise for applications in the treatment and prevention of oral disorders. However, the effects of probiotics on long-term changes in microbiome composition requires further investigation.

[13] Refer to Episode 32 for discussion on the oral microbiome with Dr. A. Barbour.

- Individuals considering a probiotic dietary supplement should consult with their healthcare provider. Scientifically proven treatments should not be replaced with unproven products or practices.
- Collaborate with a registered dietitian for food sources of prebiotics and probiotics beneficial to general health.

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