Intestinal Microbiome and impact of probiotics on digestive health of dogs and cats

Literature Review

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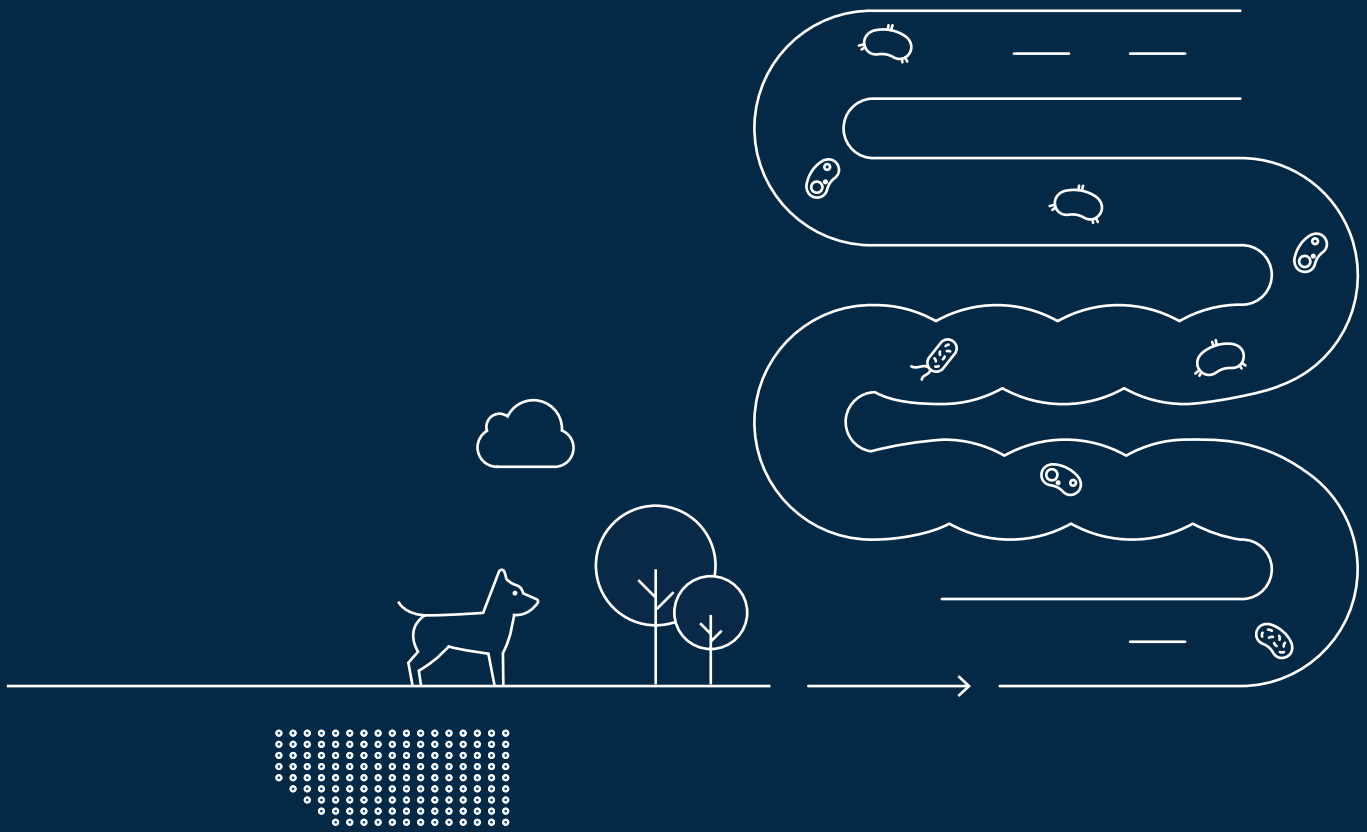
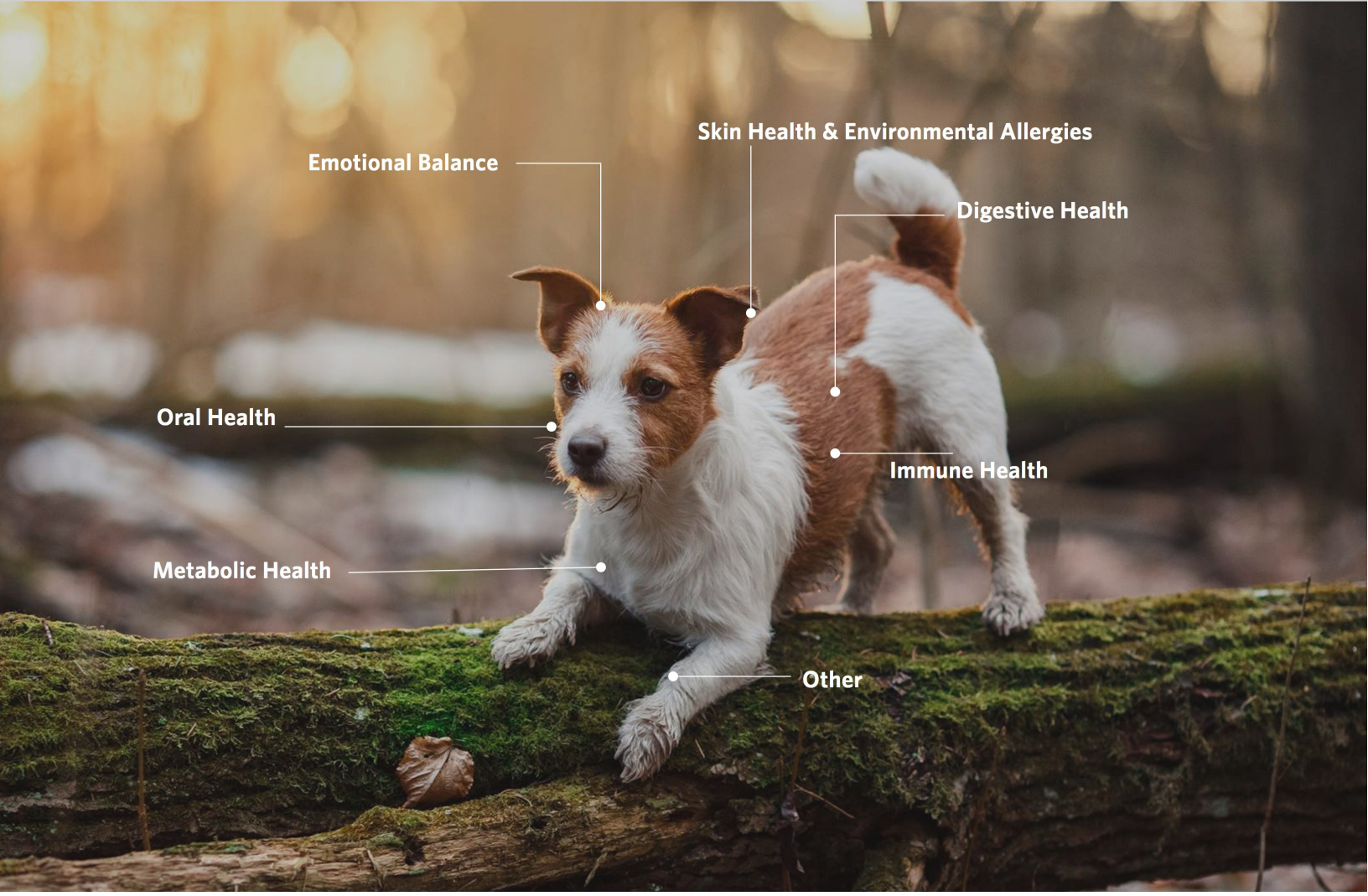


Introduction

The gastrointestinal tract harbors a complex ecosystem consisting of various microbes such as viruses, bacteria, fungi, and protozoa. This system is termed ***microbiota*** when referring which microbes are present (***"who is there"***), and ***microbiome*** when referring to their entire gene content and function (***"what are they doing"***).

The total number of microbes in the intestine is approx. 100 trillion cells, representing approximately 100 times more microbial genes than the host genome. Bacteria are the largest component, representing >90% of all intestinal microbes.[1,2]

The dog and cat intestine harbors a large number of different bacterial strains. Each animal possess a unique bacterial composition. The microbiota differs in complexity and numbers along the length of the gastrointestinal tract. Most intestinal bacteria are strict anaerobes, especially in the highly populated large intestine, with the predominant phyla in dogs and cats being Firmicutes, Fusobacteria, and Bacteroidetes.[3,4] These interact with the host in a mutualistic relationship, providing many immune and metabolic functions.[5] Therefore, a balanced intestinal microbiota provides various benefits for health. Examples are the production of nutrients, modulation of the immune system, and protection from enteropathogens.



Gut microbiome plays a key role in pet health and well-being.

Microbiome function

The gut microbiome is an important immune and metabolic organ, as bacteria metabolize dietary components into bacterial-derived metabolites, so called postbiotics. In a healthy state with a balanced microbiota, these metabolites provide important health properties.

For example, bacteria ferment dietary carbohydrates into short-chain fatty acids (SCFA). These provide energy for intestinal epithelial cells, modulate gut motility, and are anti-inflammatory.[6] Other beneficial metabolites are indole compounds, which are produced by bacterial degradation of the dietary amino acid tryptophan.[7,8] Some metabolites improve gut barrier function and increase mucin production.

Primary bile acids (BA) are secreted by the liver and are converted to secondary BA by bacteria in the large intestine. In dogs and cats, *Clostridium hiranonis* is the main BA-converting bacterium.[9]

Secondary BA, when in balanced amounts, have beneficial effects. They act on receptors across multiple organs, and have anti-inflammatory and glucose-lowering effects, and suppress enteropathogens.[10]

These microbial effects reach beyond the GI tract. Various studies performed in dogs and cats show that disturbances in the intestinal microbiome are not only present in GI disease,[11,12] but are also associated with chronic kidney disease,[13] heart disease,[14,15] neurological disorders,[16] diabetes mellitus,[17] and obesity.[18]

Assessment of the microbiome

While still used by many veterinarians for the diagnosis of dysbiosis, bacterial culture of feces is not useful to assess the microbiome, as the majority of intestinal bacteria are strict anaerobes requiring special growth media. Consequently, only a small percentage of bacterial species can be cultured as performed by diagnostic laboratories.

Molecular methods based on sequencing of bacterial 16S rRNA genes provide information on the microbial composition in a sample, and are used in research settings.

The **dysbiosis index** (*DI*) is a quantitative PCR based test that is commercially available in North America and Europe (https://tx.ag/DysbiosisGI). It can be used to assess the canine fecal microbiome.[9,19] The DI quantifies seven bacteria, which are often altered in dogs with intestinal disease and after antibiotic use.[20,21] The assay provides reference intervals for these bacterial groups. Furthermore, the assay combines data into a single number that expresses the extent of intestinal dysbiosis.

A DI above 2 indicates dysbiosis with high specificity, while a DI in the 0-2 range indicates a mild-moderate shift in the fecal microbiome. Some dogs with chronic enteropathy may have a DI below 0, but with some bacterial taxa outside the reference intervals, and this represents a milder form of dysbiosis.

The microbiome across different life stages

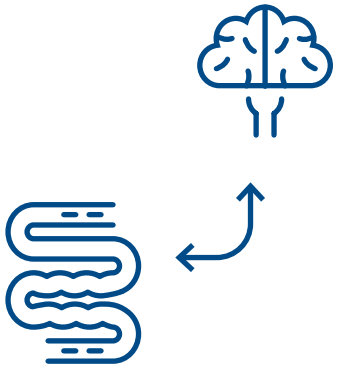
The intestinal microbiome plays an important role in the development and homeostasis of gut structure and function. The microbiota in early life is important for establishing oral tolerance, and thereby prevents inappropriate immune responses against bacterial and food antigens.[22]

Immediately after birth, the intestine is colonized by bacteria from the birth canal and the environment. Therefore, the initial microbiota differs from the adult microbiota and is composed of mainly aerobic bacteria such as ***E. coli.*** In dogs and cats, the intestinal microbiota undergoes major changes over the first 3-4 months. As the intestinal tract matures in response to weaning and the immune system develops, the normal microbiota becomes established, with increases in normal anaerobic bacteria.[23] Within 4-6 months, the puppy microbiota resembles those of adult dogs.[23] During adulthood, the microbiota remains stable in healthy animals. In humans, the microbial diversity decreases in older age.[24] There are various lifestyle factors (dietary changes, chronic diseases, antibiotics, reduced mobility, weakened immunity) that have been associated with a decreased diversity and increase in ***E. coli*** with aging. Less is known in dogs and cats.

A study showed that lactic acid bacteria change with age in cats.[25] Ageing in cats is associated with impaired nutrient digestibility, and likely this will have an influence of microbial populations in the intestine. Cats fed a prebiotic/antioxidant/ fatty acid-supplemented enriched diet lived significantly longer than a control group.[26,27]

This effect is thought to be in part by modulation of the intestinal microbiota.

Gut-brain axis



Changes in gut microbiota are associated with changes in cognition and behavior. Pathways include interactions between the enteric nervous and/or immune system, and secretion of endocrine metabolites by the intestinal microbiota that stimulate the nervous system. Some bacteria produce neurotransmitters, such as gamma-aminobutyric acid (*GABA*) or acetylcholine[28,29].

In stress situations, the host can also produce neuroendocrine substances, which may modulate the virulence of some enteropathogens[30,31, 32].

Dogs with meningoencephalomyelitis of unknown origin (*MUO*), an immune-mediated condition, show decreases in specific bacterial taxa that are associated with immune-mediated brain disease.[16]

Microbiome in intestinal disease

Shifts in the bacterial populations in intestinal disease are called dysbiosis. Dysbiosis can be a reduction in the number of different bacterial species, changes in the total quantities of bacteria, and functional changes (***e.g., altered production of bacteria-derived metabolites***). Dysbiosis occurs often secondary to underlying pathologies within the intestine and can contribute to clinical signs.

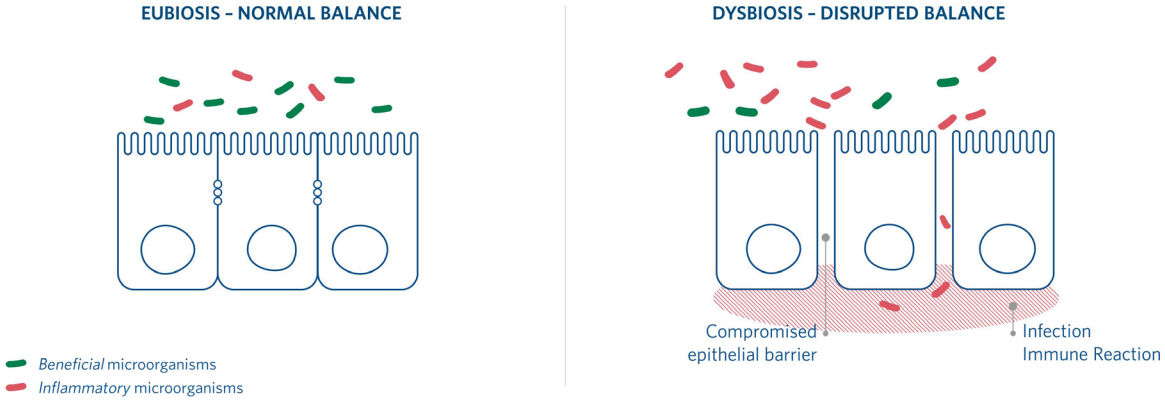
Dogs with chronic diarrhea often have increased numbers of ***E. coli*** and decreased numbers of beneficial bacterial such as ***Fusobacterium***, ***Faecalibacterium***, and ***Clostridium hiranonis***. Dogs with acute diarrhea have often transient and self-limiting increases in ***C. perfringens***. A key feature of intestinal dysbiosis is also a decrease in microbiota function. In some patients, dysbiosis may be the cause of diarrhea, whereas in others, it may be the consequence of underlying intestinal disease. For example, dysbiosis occurs in most patients with GI disease, either along the entire GI tract or more localized to the small or large intestine. The extent of clinical signs varies between patients.

Table 1 summarizes intestinal disorders that are often associated with changes in the microbiota. A dysbiosis is often present in patients with exocrine pancreatic insufficiency (***EPI***),[33] after broad-spectrum antibiotic treatment, and in chronic enteropathy (***CE***).[20,21] CE is accompanied by inflammation and destruction of the mucus layer and mucosal structure, resulting in more oxygen at the mucosal surface and increase in aerobic bacteria (***E. coli***), and decrease in normal anaerobic flora. In CE, loss of mucosal architecture leads to a decrease of transporters for carbohydrates, amino acids, fatty acids and bile acids, resulting in malabsorption of these compounds[34]. Increased luminal amounts of these substrates can directly lead to osmotic or secretory diarrhea, and to overgrowth of bacteria.

Table 1: Intestinal disorders associated with intestinal dysbiosis

Exocrine pancreatic insufficiency (EPI) – due to undigested food in lumen
Chronic enteropathies – intestinal inflammation creates aerobic conditions, and there is unabsorbed food due to damage of transporters. This leads to overgrowth of bacteria
Broad-spectrum antibiotics – decrease the normal bacterial populations
Decreased gastric acid output due to acid suppressing drugs (e.g., omeprazole)
Motility disorders

Therapeutic approaches to dysbiosis



Dysbiosis causes a disturbance in the metabolic and immunologic homeostasis in the intestine.[35] Therefore, treatment strategies aimed at modulating microbial populations can be of therapeutic benefit.[36] Several clinical studies have demonstrated that administration of specific probiotic strains can be useful in the prevention and/or treatment in patients with specific intestinal disorders *(Table 2 – page 13)*.

However, dysbiosis is often one component of the intestinal disease, and it is important to highlight that a multi-modal therapy addressing the underlying disease is required. For example, in animals with maldigestion due to EPI, treatment with pancreatic enzyme supplementation leads to improvement in clinical signs and often the intestinal microbiome will normalize after several weeks.[32] In CE, stepwise treatment trials are typically employed.[37]. Therapies include dietary modulation, addition of pre- and probiotics, antimicrobials, and fecal microbiota transplantation (*FMT*). Each of these approaches address a different mechanism, and often treatments are combined for best success.

Dietary changes should always be the first treatment option in patients with chronic intestinal disease. Various studies have shown that between 50-70% of dogs with CE respond to dietary changes.[37] Most commonly used diets are hydrolyzed protein and novel protein, which are typically highly digestible. These are hypoallergenic and reduce undigested nutrients in the GI lumen, reducing the potential for bacterial overgrowth. In most cases of food-responsive enteropathy, the dietary change is sufficient to achieve clinical remission, leading to gradual improvement of intestinal inflammation and dysbiosis over several months.[38,39]

Probiotics are often administered alone in mild cases of intestinal disease or together with dietary modulation in CE. They can exert beneficial effects, like shortening the duration of acute diarrhea and reducing antibiotic-associated gastrointestinal side effects such as vomiting or diarrhea.[40] High potency multi-strain probiotics reduced *C. perfringens* in dogs with acute hemorrhagic diarrhea [41] and strengthened the intestinal barrier in dogs with CE.[42]

Antibiotics have been often used for treatment of acute and chronic intestinal disease, but their first-line use is now debated.[37] While antibiotics can lead to improvement of clinical signs, often patients relapse after treatment. This is likely because antibiotics can lead to a reduction of bacterial numbers [43,44], but bacteria populations will often rebound after therapy. Furthermore, it is now recognized that antibiotics often induce secondary intestinal dysbiosis, which can last for weeks to months in some dogs.[20,21,40] Also, antibiotics promoted an increase in antimicrobial resistance, a major concern for health care in humans and animals.[46] Because studies have shown that only 10-16% of CE dogs are antibiotic-responsive, most relapse after treatment, and due to the negative effects on the microbiome, antibiotics are currently not recommended as first line treatment in CE.[37]

Probiotics, Prebiotics, Synbiotics, and Postbiotics

Probiotics are defined as live microorganisms, which when administered in adequate amounts confer a health benefit on the host.

This definition stresses that health benefits need to be demonstrated before a bacterial strain can be designated as a probiotic.

In the USA, the Food and Drug Administration (FDA) does not regulate probiotics and, therefore, there is currently no governing agency overseeing the label claims of probiotic products.

Most commonly used probiotic strains in commercial products are lactic acid bacteria (***i.e., Lactobacillus, Enterococcus, Streptococcus***) and ***Bifidobacterium spp***., as these have traditionally been associated with health benefits. However, other microorganisms, including specific strains of E. coli,[47] ***Bacillus*** spores, and yeasts (***e.g., Saccharomyces boulardii***)[48] have also shown health benefits in clinical studies, and are therefore used as commercially available probiotics.

Prebiotics are non-digestible food ingredients that are either added to diets or to supplements with the intent to modulate the growth or metabolic function of resident intestinal bacteria.

They are primarily dietary fiber sources, such as fructooligosaccharides, cellulose, pectins, inulins, resistant starches, beta-glucans, and various others.[49] The aim of using prebiotics is to promote the growth of the already present beneficial bacteria in the gut.

Many commercial GI diets contain prebiotics. For animals with colitis, high fiber diets can be beneficial.

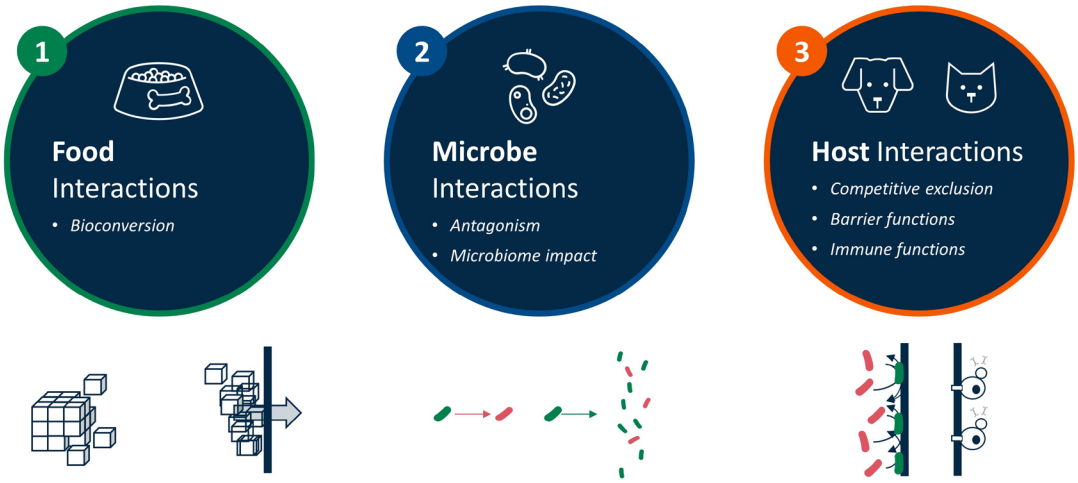
Addition of psyllium husk, a soluble and fermentable fiber, to the diet can improve stool quality in animals with large bowel disease.

Administering probiotics and prebiotics together may enhance the potential for eliciting health benefits. Some commercially available products contain both probiotics and prebiotics, and these combinations are called **synbiotics**.

Postbiotics are defined* as a "preparation of inanimate microorganisms and/or their components that confers a health benefit on the host". Postbiotics are deliberately inactivated microbial cells with or without metabolites or cell components that contribute to demonstrated health benefits. Purified microbial metabolites and vaccines are not postbiotics. A postbiotic does not have to be derived from a probiotic for the inactivated version to be accepted as a postbiotic.

The beneficial effects of a postbiotic on health must be confirmed in the target host (***species and subpopulation***). The site of action for postbiotics is not limited to the gut. Postbiotics must be administered at a host surface, such as the oral cavity, gut, skin, urogenital tract or nasopharynx. Injections are outside the scope of postbiotics. Implicit in the definition of a postbiotic is the requirement that the postbiotic is safe for the intended use.

Mechanism of actions of probiotics



Health effects of probiotics are **strain specific**, and every probiotic strain may have unique functional and immunological characteristics, and therefore potentially a different mechanism of action.[50]

Combining different bacterial strains into a multi-strain formulation can enhance synergistic benefits, but depending on the mode of action, a combination of strains can also hinder probiotic effects.

Ultimately, it is recommended that only probiotic products that have shown effects in clinical studies for specific applications should be used. Therefore, to select a probiotic product for individual patients, it is important to understand the strain-specific mechanisms, which probiotic strain is contained in a commercial product, and whether there is scientific evidence that the particular probiotic strain has been evaluated for the targeted disorder (*e.g., acute diarrhea, chronic enteropathy*).[41,42,48,51,52]

Most studies have evaluated mechanisms of action of probiotics *in vitro*, and therefore, a direct comparison cannot be made to clinical settings, but they can suggest a potentially underlying clinical benefit.

1. **Reduction of intestinal pathogens**

   Some probiotic strains reduce intestinal colonization by pathogens. For example, *in-vitro* studies reported that some bacterial strains produce compounds that act as antimicrobial peptides (*i.e., bacteriocins, lactic acid*). Some probiotic strains produce anti-fungal substances (*e.g., benzoic acid, methylhydantoin, mevalonolactone*).

   Some probiotic bacteria ferment carbohydrates from the diet and thereby produce short chain fatty acids (*SCFAs*), such as butyrate, propionate, lactate, or acetate. Those SCFAs lower the pH in the intestine, which makes the intestinal environment hostile for pathogens. Some probiotic strains (*e.g., Bacillus subtilis*) are also able to compete with pathogens for substrates

and, therefore, limit the growth of pathogens such as *Clostridium perfringens.*[53,54]

Other probiotic strains are able to inhibit intestinal epithelial cell invasion of pathogens *in vitro*. Several probiotic bacteria are also able to directly compete for receptor sites on host cells, which share carbohydrate-binding specificities with enteropathogens. Furthermore, the expression of bacterial toxins can be inhibited by probiotic strains. *Bacillus subtilis, Lactobacillus plantarum, L. rhamnosus,* and *Bifidobacterium lactis* were shown to induce mucin production[55] and, therefore, indirectly inhibit the adhesion of enteropathogens on intestinal cells.[56]

2. **Immunomodulation, enhancement of intestinal barrier function, and anti-inflammatory effects**

Probiotic strains, as well as any other bacteria, are recognized by the host immune system.

Some probiotic strains induce expression of heat shock proteins, mucus layer and SCFA, which help maintain intestinal barrier function.

Some *Enterococcus faecium* and *Lactobacillus* strains have been shown to induce T-helper-1 cytokines and natural killer cells, improving cellular immunity.[57,58] Specific strains of *Bifidobacteria* (*i.e., B. lactis, B. bifidum*) and *Lactobacillus* (i.*e., L. delbrueckii subsp bulgaricus, L. casei*), and *Streptococcus thermophilus* were shown to have anti-inflammatory effects in the intestine.

They also promote antibody production such as IgA from plasma cells, which protect the host by binding several antigens from microorganisms. Studies also reported a response of the gut associated lymphoid tissue (*GALT*) following the administration of *L. plantarum* and *L. acidophilus*.[59,60]

One probiotic strain used was shown to enhance immunoglobulin A (*IgA*) production in dogs.[61]

A high potency multi-strain product improved intestinal mucosal barrier function by increased expression of tight junction proteins.[37]

3. **Modulation of the commensal microbiota**

A common indication for probiotics is to modulate the intestinal microbiota. The effects of different probiotics on intestinal microbiota is not consistent across studies. It may depend on the administered strain(s), the dose, and the composition of the microbiota at baseline. Some studies have shown no major global changes in intestinal microbiota,[62] others an increase in the administered probiotic species with only minor impact on the overall structure of the gut microbiota,[63] while other studies have shown major changes are induced through probiotics.[64]

More studies are needed to better predict the impact of probiotic strains on the gut microbiota diversity.

4. **Nutritional effects**

Probiotics produce metabolites that confer nutritional benefit to the host. Probiotics produce a variety of other beneficial metabolites, e.g., vitamins B, K and folate. Additionally, SCFAs such as acetate serve as an energy source.

5. **Neuromodulatory effects**

The gut-brain-axis enables communication between the gut and the central nervous system.

A study reported that probiotic administration (*L. rhamnosus*) led to altered patterns of GABA receptors in the central nervous system.

A commercially available strain in the USA of the *Bifidobacterium longum* is used for the management of anxiety in dogs.

Safety of probiotics

Probiotics are generally considered safe for use in dogs and cats. Some animals may initially experience flatulence and/or looser stools for the first few days, especially when receiving high-dose multi-strain probiotics. In such cases, dose adjustment by reduction of the amount for the first few days is generally sufficient to stop these clinical signs. After that, the amount of probiotic can be increased again to the full dose.

Major side effects of probiotics are very rarely noted. In humans, only in a very small number of cases probiotics were reported to translocate and cause septicemia in hospitalized patients.[60] No serious side effects have been reported in veterinary patients to date.

While it is prudent to use probiotics with caution in immunocompromised patients, clinical studies have used probiotics in dogs with parvovirosis[61] and acute hemorrhagic diarrhea without reported complications.[36]

Quality of commercially available probiotics

Several studies have reported that the majority of commercially available probiotic products marketed for human and veterinary use lack proper product quality.[67,68]

The majority of commercial products did not provide sufficient information about the probiotic strain and amount. Many products also stated incorrect scientific names, with incorrect spelling of bacterial organisms.

In addition, several products contained a smaller number of probiotic organisms than was listed on the label. [67,68]

Therefore, many specialists currently recommend that only probiotic formulations from reputable manufacturers should be used, especially those formulations that have demonstrated a clinical benefit in clinical studies.

Considerations when using probiotics

Table 2 summarizes clinical studies performed with commercially available probiotic products. Promising conditions for probiotics are the treatment of acute uncomplicated diarrhea, prevention of stress diarrhea, prevention of antibiotic-associated gastrointestinal signs, and as adjunct therapy in chronic enteropathies.

For prevention of stress-related diarrhea (for example during periods of weaning, boarding, traveling, or in working dogs), a prophylactic administration a few days to weeks ahead of the event may increase success as probiotics need 1-2 days to colonize in the intestine.

Similarly, for prevention of antibiotic-associated gastrointestinal signs (e.g., diarrhea and vomiting), starting probiotics a few days ahead of an elective procedure may increase the success rate.[64]

Like any other bacteria, probiotics can be either susceptible or resistant to concurrently administered antibiotics. To prevent antibiotic-associated diarrhea, antibiotics and probiotics should be prescribed together. The manufacturer should be able to provide information about the susceptibility patterns of their strains. If this is not available, probiotics and antibiotics should be administered at least 1 to 4 hours apart to avoid inactivation of the probiotic by the antibiotic. An important property of yeast probiotics is the natural resistance to antibiotics; therefore, administration of yeast does not promote antimicrobial resistance and they can also be administered at the same time with antibiotics.

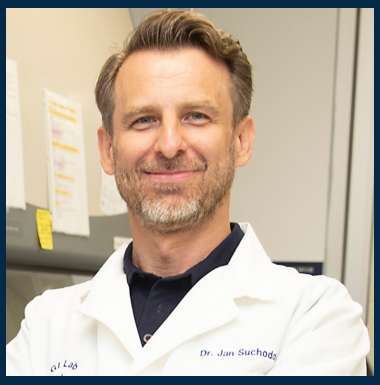
For proper immune stimulation, long-term administration over weeks to months is likely preferable.[61] In dogs and cats with chronic enteropathy, long-term administration over several months is recommended to elicit optimal benefits on intestinal barrier function and immune regulation.[42,70,71]

Table 2: Clinical studies reporting beneficial effects of commercially available probiotics

GASTROINTESTINAL DISORDER	PROBIOTIC ADMINISTRATION	EFFECTS
Chronic enteropathies in dogs [42]	High potency multi-strain probiotic, adjunct to prednisone therapy	Improved intestinal barrier function
Acute uncomplicated diarrhea in sheltered cats[51]	Single-strain probiotic	Significantly lower percentage of cats having diarrhea lasting longer than 2 days
Acute hemorrhagic diarrhea in dogs[36]	High potency multi-strain probiotic	Decreased fecal abundances of *C. perfringens*, quicker normalization of intestinal microbiota
Chronic diarrhea in cats [71]	Synbiotic	Significantly firmer stool character after synbiotic use
Antibiotic-associated gastrointestinal signs [72]	Synbiotic	Decreased hyporexia and vomiting in healthy cats
Chronic enteropathy in dogs [47]	Yeast probiotic	Improved clinical activity index, stool frequency, stool consistency compared to standard treatment

Conclusion

The intestinal microbiome plays a crucial role in host health. Many animals with GI disease or older animals have dysbiosis, resulting in abnormal microbial function, and the dysbiosis can contribute to clinical signs. As intestinal dysbiosis can have different underlying causes, multimodal and often long-term therapeutic approaches are necessary to improve microbiota composition. Therefore, probiotics are often used as part of these treatment approaches.



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* Definition of Postbiotics: https://www.nature.com/articles/s41575-021-00440-6

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