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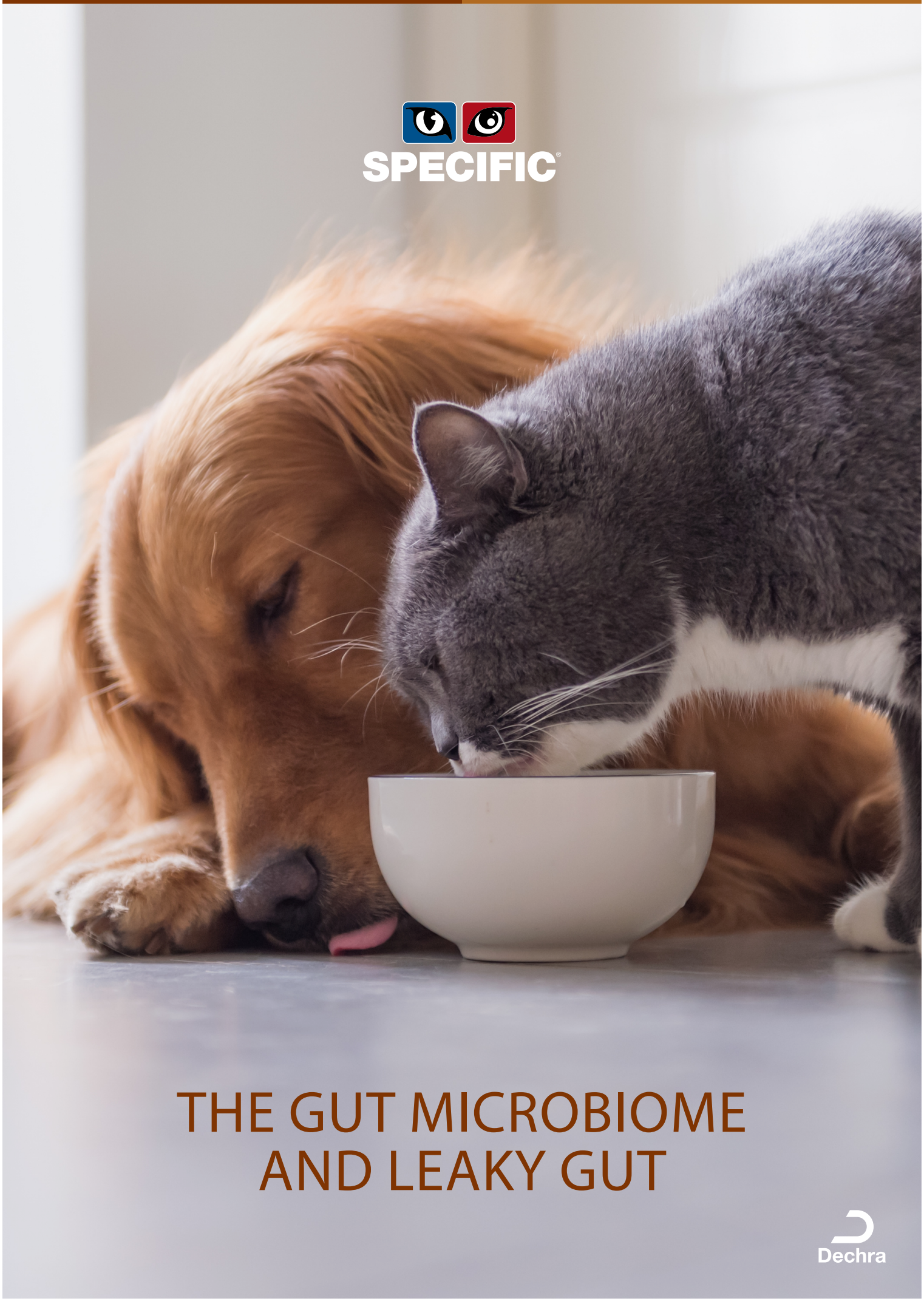

THE GUT MICROBIOME AND LEAKY GUT

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ROLE OF MICROBIOTA AND GUT BARRIER FUNCTION IN INTESTINAL AND GENERAL HEALTH

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INTRODUCTION

At first sight, the most obvious function of the intestinal tract is digestion of food and absorption of nutrients.

However, the surface of the intestinal tract is one of the largest interfaces between the environment and the internal milieu of the body. The gut is therefore not only responsible for digestion and absorption of nutrients, but has also an essential role as intestinal barrier as first line of defense against potential harmful bacteria, toxins and food-derived allergens (Barbara et al. 2021, Jergens et al. 2021). The gut-associated lymphoid tissue (GALT) makes up about 70% of the body's immune system. There is a close interplay between the intestinal barrier, intestinal microbiota and the immune response. A disruption in the interaction can lead to intestinal but also systemic diseases.

INTESTINAL BARRIER

The intestinal barrier is composed of three major elements: a mucus layer, a columnar monolayer of epithelial cells and the underlying lamina propria (Figure 1). The most prevalent cells in the epithelium are enterocytes, which are responsible for the absorption of nutrients. The epithelium contains also some specialized types of cells such as mucus producing goblet cells, Paneth cells which produce lysozymes and antimicrobial peptides (defensins, Reg3-peptides), and immune cells such as intra epithelial lymphocytes and dendric cells. Intra epithelial lymphocytes are responsible for immune surveillance and can immediately kill invading cells. Dendric cells can sample antigens at the surface of the epithelium layer and present them to immune cells in the lamina propria to trigger a further response of the immune system (Barbara et al. 2021, Jergens et al. 2021).

The transport of nutrients, water and other components from the intestinal lumen through the epithelial barrier into the lamina propria can go via two routes: through the epithelial cells (transcellular pathway) or through the small space between the epithelial cells (paracellular pathway). Nutrients and larger compounds such as proteins are absorbed and transported through the enterocytes by means of receptor-mediated endocytosis and phagocytosis or by carrier-dependent transport. The epithelial cells of the mucosal barrier are held together by tight junctions, composed of transmembrane proteins such as occludin and claudin, which interact with intracellular proteins, zonula occludins (ZO). These tight junctions are responsible for the regulation of transport of luminal substances into the lamina propria through the space between the epithelial cells (paracellular pathway).

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They allow the transport of water and ions but prevent the passage of larger molecules (proteins, antigens) and microbes (Sturgeon & Fasano 2016, Martini et al. 2017).

The luminal surface of epithelial cells is covered with a layer of mucus, produced by the goblet cells, which protects epithelial cells against digestive enzymes, antigens, toxins and bacteria. Mucus contains primarily mucins, gel-forming glycoproteins, but also antimicrobial peptides and immunoglobulin-A which can kill or immobilize bacteria (Barbara et al. 2021, Pickard et al. 2017). The high content of polysaccharides in mucus offers also a source of nutrition and adhesion receptors for several types of microbes. The production of mucus is affected by intestinal microbiota and their metabolites.

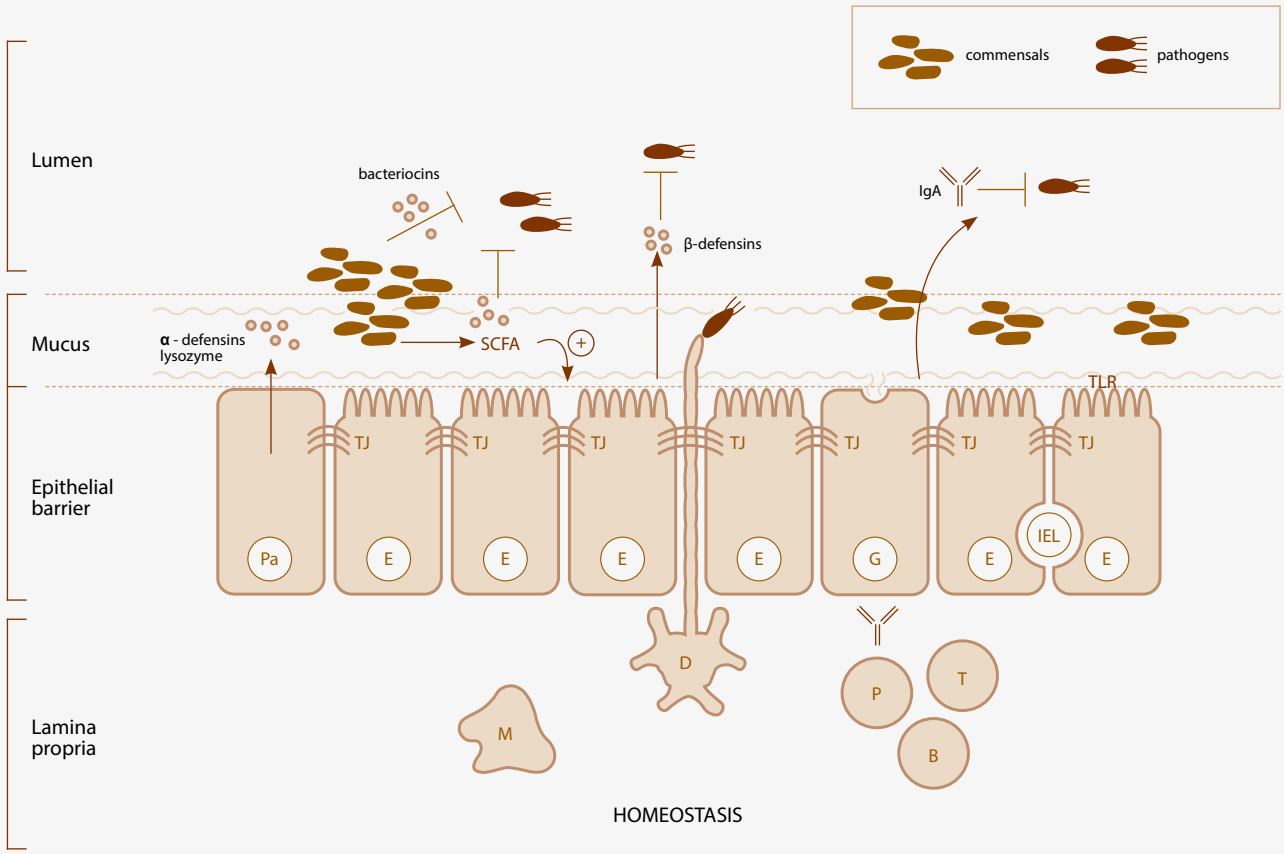


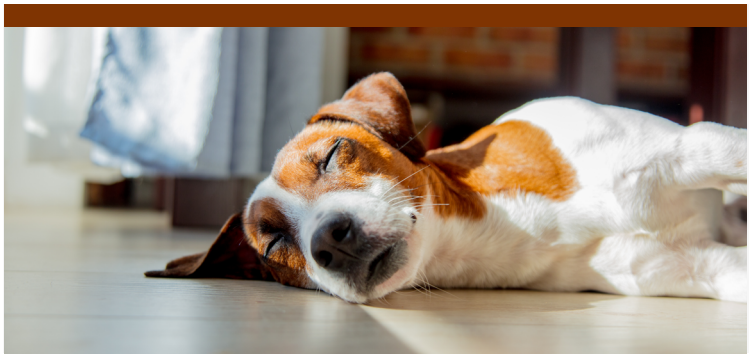
Figure 1. Simplified schematic representation of the gut barrier during the healthy homeostatic state. The intestinal barrier is formed by a monolayer of epithelial cells (E), closely connected by means of tight junctions (TJ), and covered by a layer of mucus, produced by goblet cells (G). Paneth cells (Pa) and intra epithelial cells (IEL) play a role in the defense against harmful bacteria. Commensal bacteria are important for development of colonic resistance by direct competition with pathogens and through production of bacteriocins or metabolites as SCFAs. SCFAs also support tight junctions and production of mucus. Binding of commensals to toll-like receptors (TLR) promotes tolerance to commensals, whereas recognition of pathogenic bacteria by dendric cells (D) can alert other immune cells in the lamina propria such as macrophages (M), plasma cells (P), T cells (T) and B cells (B) for defense against pathogens (Adapted from Sturgeon & Fasano 2016, Pickard et al. 2017, Jergens et al. 2021).

INTESTINAL MICROBIOTA

Although there has been a time that microbes where especially regarded as harmful and pathogenic organisms, nowadays it is known that the intestinal microbes play a crucial role in the host health.

The gastrointestinal tract of dogs and cats is populated by approximately 10^{10} to 10^{14} micro-organisms (bacteria, viruses, fungi and protozoa): the microbiota. The number of microbiota in the gut is much greater than the total number of host cells and the microbiome, the collective genomes of the microbiota, is about 150 times larger than the dog's or cat's own genome (Mondo et al. 2019). Thousands of years of co-evolution has resulted in a symbiosis of microbiota and host which provides mutual benefits. The host provides the microbiota with nutrition and an environment to live in, and in turn microbiota provide the host with enzymes and biochemical pathways that the host itself does not own, thereby providing support in digestive function, nutrient and drug metabolism, regulation of the immune system, protection against pathogenic bacteria and maintenance of the gut barrier.

Unborn puppies and kittens are sterile, but immediately after birth they get populated by bacteria from the birth canal and the environment. After several weeks the gut is fully colonized by primarily anaerobic bacteria, with number and type of bacteria varying along the gut depending on environmental conditions such as pH and type of available substrate. In the stomach the number of bacteria is relatively low and the bacteria are primarily aerobic or facultative anaerobic, whereas the colon is populated with the highest number of bacteria, which are almost exclusively anaerobic. Almost all microbiota found in the intestinal tract of cats and dogs belong to the phyla Firmicutes, Bacteroidetes, Proteobacteria, Fusobacteria and Actinobacteria (Suchodolski 2011).



IMMUNE RESPONSE

Studies with germ-free animals have shown that microbiota are essential for the development and structure of the gut mucosal barrier and intestinal immune response. Germ-free animals have a thinner lamina propria and less developed GALT-system, decreased concentration of immunoglobulins, thinner villi and a reduced mucosal surface area (Suchodolski 2011).

The early presence of intestinal microbiota in life of puppies and kittens is essential for the development of oral tolerance to commensal bacteria and food antigens (Suchodolski 2011). Recognition of microbial fractions by Toll-like receptors on membranes of immune and epithelial cells improves the function of the intestinal epithelial barrier, secretion of mucus and antimicrobial peptides and promotes the tolerance towards the commensal gut microbiota (Barbara et al. 2021). The microbiome educates the immune system to respond to pathogens and at the same time to develop tolerance to commensal microbiota and harmless antigens.

Microbial activity yields energy and metabolites which can be used by the microbiota but also by the host. Examples of microbial metabolites are ammonia, vitamins (K, B12, biotine and folate), short chain fatty acids (SCFAs), lactate, secondary bile acids, indoles, amines, phenols, hydrogen sulfate, methane and neurotransmitters GABA and serotonin (Pilla & Suchodolski 2020, Barbara et al. 2021, Suchodolski 2011). Especially fermentation by specific microbiota of non-digestible dietary fibres and intestinal mucus into SCFAs has beneficial effects on the mucosal barrier and the immune system. The major SCFAs which are produced are acetate, propionate and butyrate. They can be used as energy source for bacterial growth but can also be absorbed and provide energy to the dog or cat. Butyrate is important as the main source of energy for colonocytes. SCFAs can enhance mucus production, epithelial proliferation, barrier function, host immunity, anti-inflammatory reactions and release of chemokines and cytokines. Also other metabolites as indole derivatives, bile acid metabolites, polyamines and polyphenolic derivates can improve the gut barrier integrity or induce an anti-inflammatory response (Barbara et al. 2021, Ziese & Suchodolski 2021).

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IMMUNE RESPONSE continued

A healthy balanced microbiota forms a stable community that resists invasion by foreign or pathogenic bacteria. This colonization resistance is obtained by competition for space and nutrients, killing of other bacteria by means of bacteriocins, production of metabolites which create an environment which is not suitable for other types of bacteria or inhibits their growth and by enhancement of the host's immune response (Pickard et al. 2017) (Figure 1). The healthy homeostatic state is maintained by a close interaction between microbiome, intestinal epithelial barrier and immune response (Figure 2).

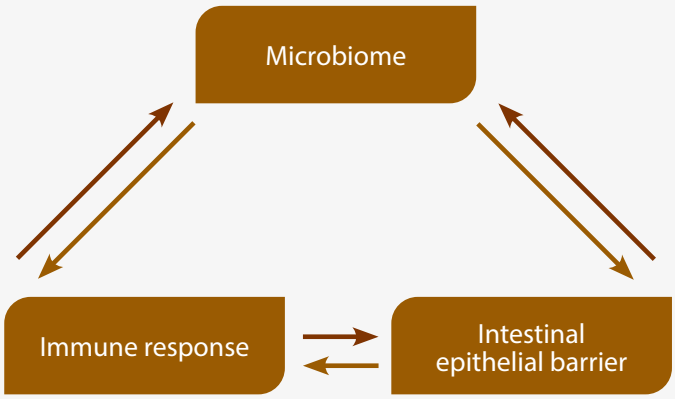
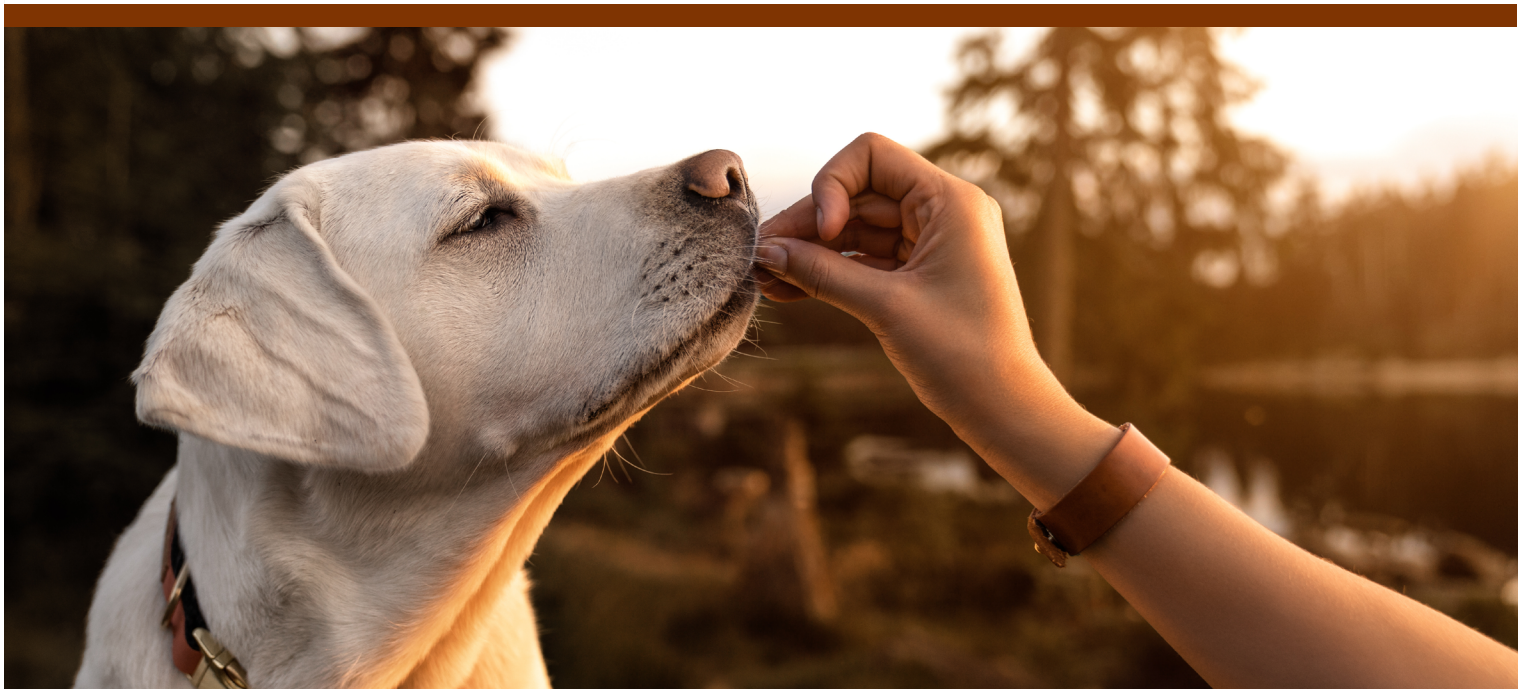


Figure 2. Homeostasis in the healthy state: a close interaction between microbiome, intestinal epithelial barrier and immune response.



THE CONSEQUENCES OF A DISTURBED INTESTINAL HOMEOSTASIS

DYSBIOSIS, INCREASED INTESTINAL PERMEABILITY AND INFLAMMATION

During intestinal disease the equilibrium between microbiota, epithelial barrier and immune response is often disturbed.

Many acute and chronic gastrointestinal disorders in dogs and cats are associated with dysbiosis, a change in the composition of the microbiota that impacts its function. In case of dysbiosis the diversity of the microbiome is reduced, with a decrease in beneficial bacteria and an increase in pathogens. A change in microbiota can be induced by several factors such as a change in available substrate (e.g. more undigested food in case of maldigestion or malabsorption, or a change in dietary composition), use of antibiotics, loss of colonization resistance, change in environmental conditions, invasion of pathogenic bacteria or altered immune response. Changes in the type or number of bacteria and their metabolites can have a direct effect on the integrity of the intestinal barrier and the intestinal immune response.

Comparison of fecal samples of healthy dogs and dogs with various gastrointestinal disorders showed bacterial dysbiosis in the dogs with intestinal disorders, with especially a reduction in bacterial groups which produce SCFAs (Suchodolski et al. 2012). In dogs with inflammatory bowel disease, there was a negative association between fecal SCFA concentration and clinical score (Xu et al. 2016). SCFAs play an important role in the maintenance of tight junctions (Suzuki 2020). SCFAs as butyrate can lower the oxygen level in the intestinal lumen by stimulating epithelial cell metabolism. A lower oxygen level is less favorable for growth of pathogenic bacteria. During inflammation luminal oxygen levels rise due to increased blood flow, which promotes the growth of facultative anaerobic bacteria like Enterobacteriaceae (Pickard et al. 2017).

Dysbiosis is associated with increased epithelial permeability and inflammation. While the presence of commensal microbiota, their metabolites or certain dietary components protect the tight junction barrier function (Bron et al. 2017, Hiippala et al. 2018), cytokines, endotoxins or pathogen adherence to enterocytes disrupt the tight junction structure and cause epithelial permeability (Sturgeon & Fasano 2016). Impairment of the tight junctions allows bacteria, toxins and allergens to pass through the paracellular space into the lamia propria where they trigger an immune reaction by activating macrophages, T-helper, T-regulatory and B-cells, thereby inducing the release of cytokines such as TNF-α, IFN-γ and IL-6 or immunoglobulins. The provoked inflammatory response induces epithelial cell damage and TNF-α and IFN-γ further destroy tight junction function, exacerbating the increased gut permeability causing more passage of bacteria into the lamina propria, resulting in further enhanced immune response, reduced mucosal tolerance and dysbiosis, eventually leading to a self-perpetuating process of dysbiosis, reduced intestinal barrier function and inflammation (Barbara et al. 2021, Sturgeon & Fasano 2016) (Figure 3 and Figure 4).

A majority of chronic intestinal diseases is indeed associated with inflammation. In a study with dogs with chronic diarrhoea, 71% of the dogs had non-infectious inflammatory enteropathies (Volkmann et al. 2017).

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DYSBIOSIS, INCREASED INTESTINAL PERMEABILITY AND INFLAMMATION

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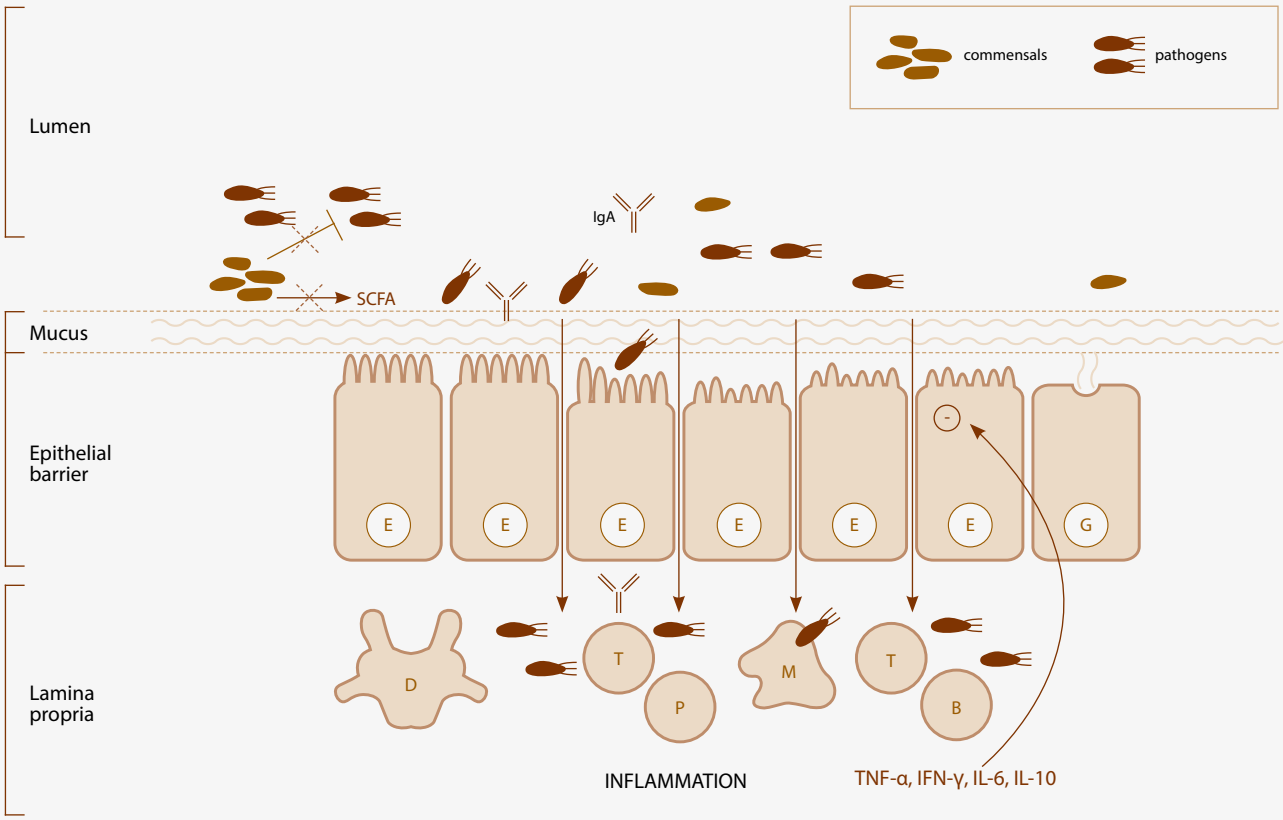

Figure 3. Simplified schematic representation of an impaired gut barrier during dysbiosis and inflammation. Dysbiosis is associated with reduced colonization resistance and reduced production of SCFAs by commensals and increased production of endotoxins and adherence by pathogens, which will impair tight junctions and reduce mucus production. The reduced gut barrier integrity allows bacteria to pass through the paracellular space into the lamina propria, where they trigger an immune response from macrophages (M), plasma cells (P),T-cells (T), B-cells (B) and release from inflammatory mediators. TNF-α and IFN-γ further destroy tight junctions, resulting in more passage of bacteria into the lamina propria, and further enhanced immune response, epithelial permeability, dysbiosis and inflammation (Adapted from Sturgeon & Fasano 2016, Pickard et al. 2017).

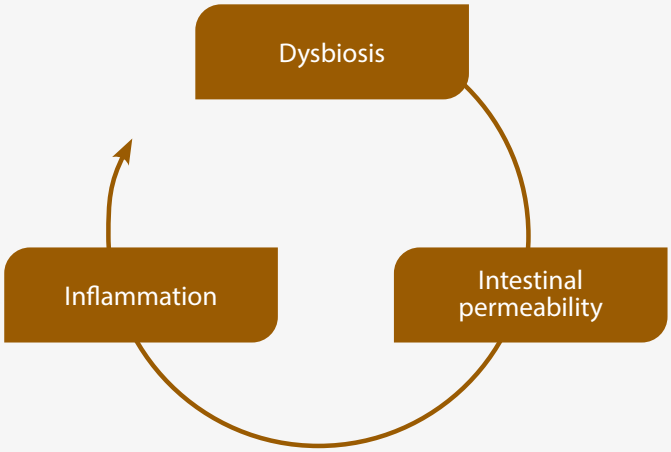

Figure 4. Self-perpetuating process of inflammation, intestinal permeability and dysbiosis.

ASSOCIATION OF INTESTINAL DYSBIOSIS AND DISFUNCTION OF OTHER ORGANS

Dysbiosis of the gut microbiota and severe intestinal permeability with translocation of microbes and allergens into the lamina propria does not always result in an inflammatory immune response which remains restricted to the intestinal tract. Bacterial translocation can induce a widespread immune response, extending to a systemic immunological response that affects other organs and tissues.

Dysbiosis of the gut microbiota has also been associated with other clinical conditions than gastrointestinal disorders, such as obesity, kidney and liver failure, diabetes, atopy, cancer, rheumatic disease and neurological disfunction (Pilla & Suchodolski 2021, Mondo et al. 2019, Sturgeon & Fasano 2016). Although it may not always be clear whether intestinal dysbiosis is a cause or a symptom of the disease, several studies in humans and animals models showed that intestinal dysbiosis and increased intestinal permeability precede the development of some of these diseases (Sturgeon & Fasano 2016).

MANAGEMENT OF GASTROINTESTINAL DISEASE AND INTESTINAL MICROBIOME

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MANAGEMENT OF GASTROINTESTINAL DISEASE

The management of intestinal disorders depends on the underlying cause and can include nutritional management, antibiotics and/or anti-inflammatory/ immunosuppressive drugs.

In dogs with chronic diarrhoea, the major causes were inflammatory enteropathies (71%), infectious causes (13%) and exocrine pancreas insufficiency (6%). From the dogs with inflammatory enteropathies, 66% were diet-responsive and 11% antibiotic-responsive; the remaining 23% that did not respond to an elimination diet or antibiotics were diagnosed as idiopathic inflammatory bowel disease (IBD) and treated with anti-inflammatory or immune suppressive drugs (Volkmann et al. 2017). The pathogenesis of IBD is not completely known, but studies with germ-free animals showed that IBD can only develop in the presence of intestinal microbiota. The proposed pathogenesis involves an abnormal immune reaction towards commensal intestinal microbiota in genetically predisposed individuals (Pickard et al. 2017).

Although antibiotics are useful in case of pathogenic infections and antibiotic-responsive chronic inflammatory enteropathies, just routine use of antibiotics in case of gastrointestinal diseases is discouraged. In dogs with chronic inflammatory enteropathies antibiotics should only be started if other therapeutic approaches failed. Abundant use of antibiotics can reduce the beneficial gut microbiota and also contribute to antimicrobial resistance (Ziese & Suchodolski 2019).

Nutrition is an essential part of the management of all gastro-intestinal disorders. Nutritional management should be tailored to the type of intestinal disorder, underlying causes and the condition of the individual dog or cat. Contrary to old advice, it is generally not recommended to fast dogs or cats with diarrhoea or vomiting. Supply of nutrients via the intestinal tract is important to preserve villi length, required for maintenance of an extended surface area for absorption, and mucosal barrier function in order to decrease the risk of bacterial translocation (Qin et al. 2002).

For almost all intestinal patients it is recommended to provide a highly digestible diet to compensate for maldigestion and malabsorption and to reduce the amount of undigested food in the lower intestinal tract, as this might induce bacterial overgrowth or bring potential harmful allergens in the intestinal lumen. Despite the use of a highly digestible diet, patients with exocrine pancreas insufficiency will benefit from additional management with pancreatic enzymes. Highly digestible hypoallergenic diets based on novel or hydrolysed proteins are specially indicated for dogs and cats with adverse food reactions or food-responsive chronic enteropathy. In case of damaged intestinal mucosa, hypoallergenic diets can be used preventively to minimize the risk of developing an allergy towards commonly used proteins in the pet's habitual diet (Guilford 1994).

The optimal level of dietary fat is dependent on the type of intestinal disease. In most intestinal patients the digestion and absorption of fat is not impaired and especially cats with intestinal disorders can tolerate higher levels of fat in the diet (Laflamme et al. 2011). However, intestinal problems related to pancreatitis, cholestasis, protein-losing enteropathy and lymphangiectasia require nutritional support with a diet with a restricted fat content.

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MANAGEMENT OF GASTROINTESTINAL DISEASE

continued

Not only the level, but also the type of fat is relevant, especially in case of inflammatory enteropathies. Omega-3 fatty acids EPA and DHA are precursors of anti-inflammatory mediators. Increased intake of EPA and DHA supports the body's anti-inflammatory response (Calder 2006). Already in older studies in human patients and animal models of colitis is was found that increased intake of fish oil reduced the severity of clinical symptoms, the required dose of corticosteroids and levels of inflammatory mediators, and improved the histological appearance of the colon (Vilaseco et al. 1990, Hawthorne et al. 1992, Stenson et al. 1992).

The fibre level in intestinal diets is generally low to moderate, since high fibre levels can reduce digestibility of the diet. High-fibre diets are however useful for management of certain gastrointestinal conditions like constipation and fibre-responsive colitis. The use of dietary fibres in intestinal disease has received special interest, because some fibre types, especially fermentable fibres, can influence the composition of the intestinal microbiome.

MANIPULATION OF THE INTESTINAL MICROBIOME

Strategies to influence the composition of the intestinal bacterial population can successfully be implemented as part of the treatment of gastrointestinal diseases. Antibiotics have already been used for a long time to eliminate pathogenic microbes and bacterial overgrowth in dogs and cats with intestinal disorders, but approaches to promote the growth of beneficial enteral bacteria populations or restore a healthy microbiome by means of prebiotics, probiotics, postbiotics or fecal microbiota transplantation in dogs and cats are more recent.

Prebiotics are already frequently used in intestinal diets and are defined as 'non-digestible compounds that, through its metabolization by microorganisms in the gut, modulates composition and/or activity of the gut microbiota, thus conferring a beneficial physiological effect on the host' (Bindels et al. 2015). Fermentable fibres, which are most commonly used as prebiotics in pet food include beet pulp, FOS (fructo-oligosaccharides), chicory (inulin), MOS (mannan-oligosaccharides), XOS (xylo-oligosaccharides) and pectin. These fibres cannot be digested by the pet's digestive enzymes, but can be fermented by specific bacteria types. The use of prebiotic fibres in dogs and cats is associated with increased numbers of SCFAs-producing bacteria like Bifidobacterium and Firmicutes, reduced numbers of Fusobacterium, E.coli and Clostridium, a reduction in intestinal pH and increased production of SCFAs (Mondo et al. 2019, Pilla & Suchodolski 2021). SCFAs are well known for their beneficial effect on gut barrier integrity and the immune response.

Probiotics are living, viable micro-organisms that, when digested in adequate amounts, provide health benefits to the host. In human research and animal studies positive effects of probiotica have been found, for instance through the support of the intestinal barrier function (Bron et al. 2017, Makielski et al. 2018). In a systematic review of studies on the clinical effect of probiotics in the prevention or treatment of gastrointestinal disease in dogs, there was no sufficient proof for a beneficial effect on clinical outcome yet, but this conclusion was based on a limited number of studies with a small number of dogs (Jensen & Bjørnvad 2019).

Studies investigating other health benefits of probiotics showed an increase in T-cell markers and a more balanced microbiome (Rossi et al. 2014) and an upregulation of tight junction proteins in dogs with idiopathic IBD (White et al. 2017). Probiotics do not colonize in the intestinal tract, meaning that they have to be used long-term. Even though they do not colonize, the presence of these microbials or their metabolites provide benefits (Mondo et al. 2019,

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MANIPULATION OF THE INTESTINAL MICROBIOME continued

Ziese & Suchodolski 2021). Probiotics can be supplied as powder, gel or capsules, and can also be added to petfood. Evaluation of commercial diets claimed to contain probiotics indicated that 26% of the diets showed no relevant growth, meaning that most likely the bacteria which were added to the pet food had not survived commercial food processing and storage (Weese & Arroyo 2003).

Another way to modify the composition of the microbiome and promote health benefits is by means of postbiotics, preparations of inanimate microorganisms and/or their components that confer a health benefit on the host. Postbiotics may thus contain intact animate microbial cells, and/or microbial cell fragments or structures (cell walls, membranes, exopolysaccharides, cell-wall anchored proteins etc.) with or without metabolites and end products (short-chain fatty acids, vitamins, organic acids, amino acids, secreted proteins, bacteriocins, neurotransmitters etc.). Postbiotics can exert effect by modulation of microbiota, enhancement of epithelial barrier function, modulation of local or systemic immune response or metabolic response or systemic signaling via the nervous system (Salminen et al. 2021). Since composition of various postbiotics can vary a lot, depending on the type of microorganism which are used, formed metabolites, presence of cell fragments and inactivation process, the efficacy will vary and should be evaluated for each specific postbiotic product.

Fecal microbiota transplantation (FMT) is another method to modulate the intestinal microbiota by transfer of intestinal content from a healthy donor to a diseased recipient. FMT has been successfully used in human patients with Clostridium difficile infections or IBD (Mondo et al. 2019). There is still limited data available on the use of FTM in dogs. However in a recent study on dogs with acute diarrhoea and associated dysbiosis, which received either FTM as a single enema or antibiotic treatment for 7 days, all dogs had improved fecal consistency after 7 and 28 days. However, the dogs which received antibiotics kept altered fecal microbial and metabolic profiles, whereas dogs receiving FMT had improved microbiota and metabolome profiles close to those of healthy dogs (Chaitman et al. 2020).

REGULATION OF INTESTINAL BARRIER BY NUTRITION

The intestinal barrier can be affected by microbiota (Bron et al. 2017; Hiippala et al 2018), but also dietary components (others than fibres as described above) can affect the intestinal barrier function directly or indirectly by affecting the microbiota.

Amino acids as glutamine and tryptophan play a protective role and are associated with increased levels of occludin, claudin and ZO-1. High-fat diets are found to impair tight junction structure and cause hyperpermeability, which is assumed to be related to down regulation of tight junction proteins, increased bile excretion and/or changes in the microflora. For nutrients as zinc, vitamin D and vitamin A a protective effect on the tight junction barrier was found. The presence of polyphenols in the diet can improve tight junction function through increased expression of tight junction proteins and improved assembly of these proteins in the tight junction structure (Suzuki 2020).

CONCLUSION

There is a close interplay between the intestinal microbiota, intestinal barrier function and immune response.

Disturbances in the healthy equilibrium between microbiota, intestinal barrier and immune response can lead to dysbiosis, gut permeability and inflammation, not only causing gastrointestinal diseases, but potentially also involving other organs and a systemic response. Nutritional management can play an important role in restoring a healthy balance between microbiota, gut integrity and a controlled immune response.

SPECIFIC DIETS FOR THE MANAGEMENT OF GASTROINTESTINAL DISORDERS

OPTIMISATION OF SPECIFIC DIGESTIVE SUPPORT DIETS

SPECIFIC Digestive Support diets for nutritional support of gastrointestinal conditions associated with malabsorption and intestinal absorptive disorders are optimized with two new natural ingredients to support the integrity of the intestinal barrier, a healthy microbiome and immune response in the gut:

- Postbiotic (a yeast – Saccharomyces cerevisae – fermentation product)
- Auraguard, a mixture of natural polyphenol-containing plant extracts and natural antimicrobials

The postbiotic is a Saccharomyces cerevisiae fermentation product (SCFP), a dry product produced via yeast (S. cerevisiae) fermentation which includes residual yeast cells, yeast cell wall fragments, fermentation metabolites and media used during fermentation, which can provide health benefits. Studies in various species have shown its effectiveness in health, performance and support of immune response. In humans with allergic rhinitis, supplementation with SCFP reduced severity of clinal signs of rhinitis (Moyad et al. 2009). In pigs, yeast culture supplementation improved growth performance, jejunal villus height and villus height:crypt depth ratio and gut immune response (Shen et al. 2009). Also in broilers, a yeast culture improved villus height to crypt depth ratio and increased antibody titers after vaccination (Gao et al. 2008). Weaning calves showed reduced Salmonella colonization after SCFP supplementation (Brewer et al. 2014). In a recent study in dogs (Lin et al. 2019), supplementation of SCFP modulated the gut microbiota, increasing the relative abundance of Bifidobacterium, which is generally associated with a healthy gut and enhanced immune function.

Dogs supplemented with SCFP had a higher number of MHC class-II presenting B-cells, suggesting an increased capacity of the immune cells to react to antigens. Stimulated immune cells of dogs supplemented with SCFP produced less pro-inflammatory cytokine TNF-α, which suggests a potential effect of SCFP to support a balanced immune response.

AuraGuard, a mixture of natural polyphenol-containing plant extracts and natural antimicrobials, has been investigated in in-vitro and in-vivo studies which showed that the product can increase microbiome diversity, production of short chain fatty acids, integrity of tight junctions, and local immunity and has antioxidant properties.

In an in-vitro study, the antimicrobial mix showed an antimicrobial effect against C.coli by reduced biofilm forming capacity, motility and exopolysaccharide production (Stratakos et al. 2019). The natural antimicrobials decreased colonisation of pathogenic bacteria (Sima et al. 2018) and reduced virus-load
and clinical signs of infection in an in-vivo chicken infection model. These effects were accompanied by a reduction in the level of pro-inflammatory cytokines and an increase in IgA and SCFAs (Balta et al. 2020).

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OPTIMISATION OF SPECIFIC DIGESTIVE SUPPORT DIETS continued

In an in-vitro study (Balta et al. 2021), investigating the underlying mechanism of the effect of AuraGuard on canine cells infected with pathogenic bacteria (Campylobacter jejuni, Salmonella enterica perfrigens and Clostridium perfrigens), it was found that supplementation with AuraGuard:

- Reduced the virulence from pathogenic bacteria by reducing adhesion to and invasion of cells
- Improved the integrity of tight junctions for maintenance of gut barrier function by increased production of tight junction related proteins, as occludin and ZO-1
- Reduced the production of pro-inflammatory cytokines in challenged cells
- Decreased the production of reactive oxygen species (ROS) in challenged cells

INTRODUCTION OF SPECIFIC DIGESTIVE SUPPORT LOW FAT

SPECIFIC Digestive Support Low Fat for nutritional support of gastrointestinal conditions that benefit from a low level of dietary fat such as pancreatitis, EPI, inflammatory enteropathies, protein-losing enteropathy, lymphangiectasia, cholestasis and hyperlipidemia.

CID-LF

CIW-LF

DIETARY CHARACTERISTICS:

- High digestibility to ensure optimal intake of nutrients
- Low dietary level of fat to support dogs with low-fat responsive disorders
- With beneficial fibres (beet pulp, MOS, psyllium husk, FOS), beta-glucans, fish oil, AuraGuard (natural phenol-containing plant-based antimicrobial mixture) and nucleotides to support a healthy gut microbiome, immune response and barrier function of the gut
- Low allergenicity for support of gastrointestinal disorders with potential involvement of adverse reactions and for feeding during periods of reduced intestinal gut barrier. The diet is based on tapioca, hydrolysed salmon protein, rice protein and potato protein.

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