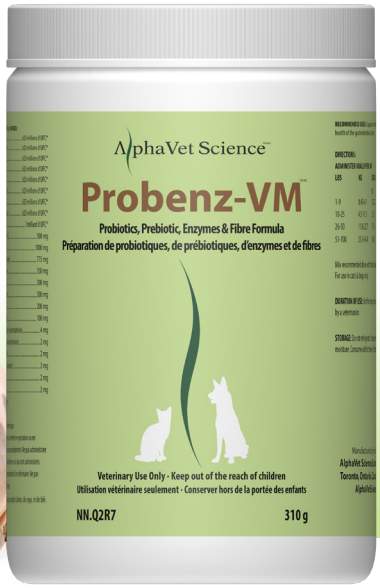
AlphaVet Science™

Probenz-VM™

Probiotics, Prebiotic, Enzymes & Fibre Formula NN.Q2R7

Probenz-VM™ is a synergistic blend of nine dynamic strains of probiotics, prebiotics, digestive enzymes, medicinal botanicals, citrus bioflavonoids, soluble fibre, and L-glutamine to aid optimal digestive system function. Entrapping probiotic bacteria in gels with ionic cross-linking is typically achieved with polysaccharides, such as pectin, which increases the viability when exposed to gastrointestinal conditions (Gebara et al., 2013).

Probenz-VM™ Advantage: Protects the probiotic living cells with a physical barrier against adverse conditions, which is critical for their survival. Probenz-VM™ encapsulates the probiotic cells with soluble fibres such as inulin, gums, and pectin, which protect the microorganisms and deliver them into the gut.



INDICATIONS

- Supports normal function and health of the gastrointestinal system.

INGREDIENTS ACTIONS

- Antimicrobial
- Demulcent
- Digestive
- Immunomodulator
- Nutritive
- Vulnerary

ADMINISTRATION

Mix recommended dose with food. Shake well before use. For use in cats & dogs only.

DOSAGE

ADMINISTER ORALLY PER DAY			
LBS	**KG**	**DOSAGE**	
		g	**Scoop(s)**
1-9	0.45-4.1	1.25-2.5	¼ - ½
10-25	4.5-11.3	2.5-5	½ - 1
26-50	11.8-22.7	7.5-10	1½ - 2
51-100	23.1-45.4	10-20	2-4
>100	45.4	25	5

STORAGE

Do not refrigerate. Store protected from light and moisture. Consume within three (3) months after opening.

PACKAGING

150 g, 310 g (unflavoured)

Probenz-VM™ FORMULA

Medicinal Ingredients Per 5 g (1 scoop)

Lactobacillus acidophilus	625 Million CFU*
Lactobacilus delbreuckii subsp. lactis	625 Million CFU
Lactobacillus casei	625 Million CFU
Lactobacillus plantarum	625 Million CFU
Lactobacillus rhamnosus	625 Million CFU
Bifidobacterium animalis subsp. lactis	625 Million CFU
Bifidobacterium bifidum	625 Million CFU
Bifidobacterium longum subsp. longum	625 Million CFU
Saccharomyces boulardii	1 Billion CFU
Inulin [Fructooligosaccharides (FOS)]	500 mg
Linum usitatissimum (Flax Seed/Semen Lini)	1000 mg
Laminaria digitata (Kelp Whole Plant/Thalli Laminariae)	775 mg
Althaea officinalis (Marshmallow Root/Radix Althaeae)	350 mg
L-Glutamine	300 mg
Spirulina platenis (Spirulina Whole)	300 mg
Citrus bioflavonoids	200 mg
Ulmus rubra (Slippery Elm Bark/Ulmi Rubrae Cortex)	100 mg
Cellulase (4-(1,3;1,4)-beta-D-Glucan 4-glucanohydrolase)	4 mg
alpha-Amylase (4-alpha-D-Glucan glucanohydrolase)	2 mg
Invertase (beta-Fructofuranosidase)	2 mg
Lactase (beta-D-galactoside galactohydrolase)	2 mg
Lipase (Triacylglycerol lipase)	2 mg
Protease	2 mg

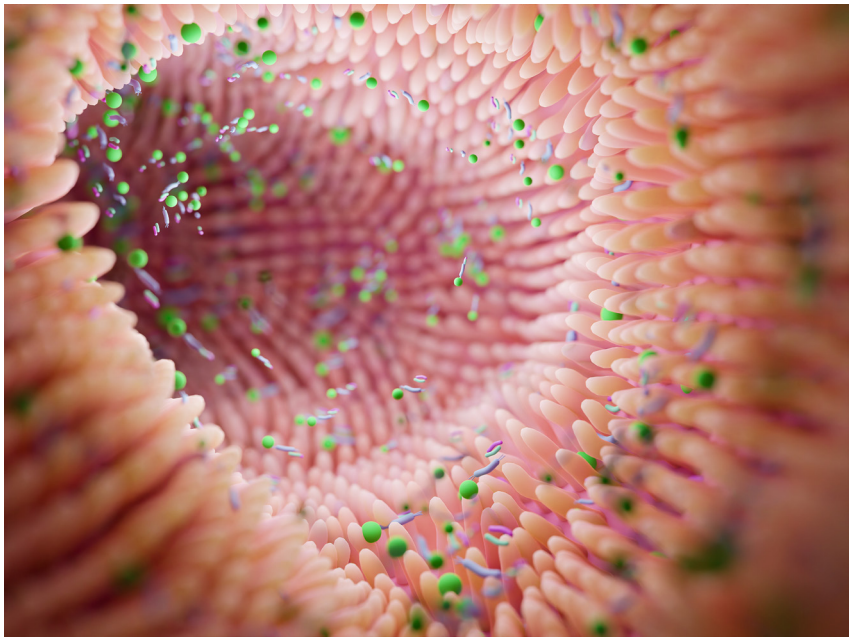
*CFU: Colony Forming Units

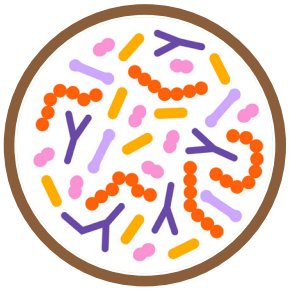
Non-Medicinal Ingredients

Malus pumila (Apple Fibre), *Cyamopsis tetragonoloba* (Guar Gum).

Probenz-VM™ is manufactured under strict GMP standards and contains no dairy, corn, gluten, wheat or soy. Does not contain animal by-products.

Probiotics





The Food and Agriculture Organization of the United Nations (FAQ) and World Health Organization (WHO) define probiotics as *"Live microorganisms which when administered in adequate amounts confer a health benefit on the host."* Maintenance of the bacterial flora and antagonism of pathogenic bacteria in the GI tract is crucial defence mechanisms. The defensive actions of the gut microbiota include:

- It prevents the adherence of the pathogens to mucosal cells by occupying the site or by steric hindrance (Reed *et al.*, 2004).
- Production of volatile fatty acids by normal microbial digestive processes creates an environment toxic to many bacterial populations, particularly the *Enterobacteriaceae* (Reed et al., 2004).
- Produces antibacterial factors that allow symbiosis rather than competition (Reed et al., 2004).

Several studies in dogs and cats have demonstrated that acute and chronic GI diseases, including inflammatory bowel disease (IBD), are associated with alterations in the small intestinal and fecal microbial communities. These alterations are generally similar to the dysbiosis observed in humans with IBD or animal models suggesting that microbial responses to inflammatory conditions are across mammalian host types (Honneffer et al., 2014). Probiotics colonize the alimentary tract in dogs and are beneficial for the clinical management of GI diseases such as chronic IBD (Chrzastowska et al., 2009).

Canine Studies of probiotics and synbiotics

Studies-Canine	Study Title	Study Summary
Baillon et al., 2004	Effects of Probiotic Lactobacillus Acidophilus Strain DSM13241 in Healthy Adult Dogs.	The study demonstrates that *Lactobacillus acidophilus* can be successfully incorporated into dry dog food. It survives transit through the canine gastrointestinal tract, populates the colon, and is associated with local and systemic changes. The study concluded that the probiotic bacterium has the potential to enhance intestinal health and improve immune function in dogs (n=15).
Aktas et al., 2007	Efficacy of Saccharomyces Boulardii as a Probiotic in Dogs with Lincomycin Induced Diarrhoea.	Lincomycin decreased total short-chain fatty acids causing diarrhea in the dogs (n=24) when given alone, and Saccharomyces boulardii was effective in treating lincomycin-induced diarrhea. It also prevents the occurrence of diarrhea when given together with lincomycin.
Pascher et al., 2008	Effects of a Probiotic Lactobacillus Acidophilus Strain on Feed Tolerance in Dogs With Non-Specific Dietary Sensitivity.	In canine patients (n=6) with non-specific dietary sensitivity (NSS), administration of *Lactobacillus acidophilus* improved fecal-dry matter, fecal consistency, and frequency. The study concluded that Lactobacillus acidophilus stabilizes the digestive processes in dogs with NSS.
Chung et al., 2009	Effect of Recombinant Lactobacillus Expressing Canine GM-CSF on Immune Function in Dogs.	Seven weeks old Beagle puppies (n=18) fed on a diet supplemented with *Lactobacillus casei* for seven consecutive weeks enhanced specific immune functions at both the mucosal and systemic levels.
Kelley et al., 2009	Clinical Benefits of Probiotic Canine-Derived Bifidobacterium Animalis Strain AHC7 in Dogs With Acute Idiopathic Diarrhea.	In canine patients with acute idiopathic diarrhea, nutritional management with the probiotic significantly reduced the time to resolution and the percentage of dogs (n=13) that were administered metronidazole compared with placebo (n=18).
Herstad et al., 2010	Effects of a Probiotic Intervention in Acute Canine Gastroenteritis--A Controlled Clinical Trial.	In a controlled clinical trial of 36 canine patients with acute diarrhea, administration of a mixture of probiotics reduced the convalescence time.
Arslan et al., 2012	Therapeutic effects of probiotic bacteria in parvoviral enteritis in dogs.	Probiotics may be beneficial in canine parvovirus (CPV) therapy, especially for shortening the recovery time under optimal care conditions.
Gagné et al., 2013	Effects of a Synbiotic on Fecal Quality, Short-Chain Fatty Acid Concentrations, and the Microbiome of Healthy Sled Dogs.	The use of synbiotics increases the beneficial bacterial flora of the host colon, which was associated with a decrease in the prevalence of diarrhea in 20 training sled dogs.

Rossi et al., 2014	Comparison of Microbiological, Histological, and Immunomodulatory Parameters in Response to Treatment With Either Combination Therapy With Prednisone and Metronidazole or Probiotic VSL#3 Strains in Dogs With Idiopathic Inflammatory Bowel Disease.	In an open-label study of canine subjects with IBD, a protective effect of probiotics was observed, with a decrease in clinical and histological scores and a decrease in T-cell infiltration. The protection was associated with an enhancement of regulatory T-cell markers in the probiotic-treated group but not in animals receiving combination therapy of prednisone and metronidazole.
Rose et al., 2017	Efficacy of a Probiotic-Prebiotic Supplement on Incidence of Diarrhea in a Dog Shelter: A Randomized, Double-Blind, Placebo-Controlled Trial.	In this randomized, double-blind, placebo-controlled trial of 773 dogs, supplementation of synbiotics significantly decreased the incidence of diarrhea.
Whittemore et al., 2019	Randomized, controlled, crossover trial of prevention of antibiotic□induced gastrointestinal signs using a synbiotic mixture in healthy research dogs.	Enrofloxacin/metronidazole administration is associated with a high frequency of antibiotic-associated gastrointestinal signs (AAGS). Synbiotic administration decreases food intake derangements. The presence of milder AAGS suggests that clinical effects of synbiotics persist >9 weeks after discontinuation, mitigating AAGS in dogs treated with antibiotics.
Tanprasertsuk et al., 2021	The microbiota of healthy dogs demonstrates individualized responses to synbiotic supplementation in a randomized controlled trial.	Synbiotic administration for four weeks caused a small but significant shift in the gut microbiota profile and predicted function in healthy dogs. It included an increase in the abundance of bacteria contained in the synbiotic and a decrease in potentially pathogenic bacteria, and gut microbiota composition largely returned to baseline two weeks after the termination of synbiotic supplementation.

Feline Studies of probiotics and synbiotics

Studies-Feline	Study Title	Study Summary
Stokes et al., 2017	Randomized, Controlled, Crossover Trial of Prevention of Clindamycin-Induced Gastrointestinal Signs Using a Synbiotic in Healthy Research Cats.	This randomized, double-blinded, placebo-controlled, 2-way, 2-period, crossover study in 16 cats found that synbiotic administration 1 hour after clindamycin therapy decreased hyporexia and vomiting. The beneficial effects of synbiotics lasted for at least six weeks after discontinuation. It also reduced the severity of antibiotic-associated GI signs in cats that subsequently received clindamycin.

PHARMACOLOGICAL ACTIVITIES - TOXICOLOGY - DRUG INTERACTIONS

Marshall-Jones et al., 2006	Effects of Lactobacillus Acidophilus DSM13241 as a Probiotic in Healthy Adult Cats.	*Lactobacillus acidophilus* feeding can alter the balance of GI microflora in healthy cats. Additionally, the administration of this probiotic results in beneficial systemic and immunomodulatory effects in cats (n=15).
Hart et al., 2012	Open-label Trial of a Multi-Strain Synbiotic in Cats With Chronic Diarrhea.	Adult cats with chronic diarrhea were treated with symbiotics for 21 days. The mean fecal score for the 53 cats completing the study decreased from 6.0 to 4.4, representing a significantly ($P < 0.001$) firmer stool character. Seventy-two percent of owners perceived an improvement in their cat's diarrhea.
Vientós-Plotts et al., 2017	Oral Probiotics Alter Healthy Feline Respiratory Microbiota.	Oral probiotics can serve as a tool to target dysbiosis that occurs in inflammatory airway diseases such as feline asthma.
Whittemore et al., 2018	Short and long-term effects of a symbiotic on clinical signs, the fecal microbiome, and metabolomics profiles in healthy research cats receiving clindamycin: a randomized, controlled trial.	Cats administered clindamycin commonly develop antibiotic-associated GI signs, short- and long-term dysbiosis and alterations in fecal metabolites. Significant differences between synbiotics and placebo groups were seen for metabolites that affect immunomodulation, intestinal permeability and barrier function, colonization resistance, and oxidative stress.

TOXICOLOGY

Toxicity of probiotics has not been documented in dogs and cats when administered orally in therapeutic doses.

The oral toxicity of three lactobacilli strains found a LD_{50} >50 g/kg (10^{11} cfu) in mice. Other reports include LD_{50} of 50g/kg for *Bifidobacterium longum,* LD_{50} of 6 g/kg for *Lactobacillus rhamnosus,* and LD_{50} of >5 g/kg for *Lactobacillus salivarius* (Watson & Preedy, 2010).

The equivalent toxic dose in a 20 kg dog: 1000 g PO of *Bifidobacterium longum*; 120 g PO of *Lactobacillus rhamnosus*; >100 g PO of *Lactobacillus salivarius.*

The equivalent toxic dose in a 5 kg cat: 250 g PO of *Bifidobacterium longum*; 30 g PO of *Lactobacillus rhamnosus*; >25 g PO of *Lactobacillus salivarius*.

DRUG INTERACTIONS

Validated interaction studies do not exist for probiotic preparations. Clinical interactions with other drugs have not been reported.

Inulin [Fructooligosaccharides (FOS)]

Helianthus tuberosus L. (Asteraceae), a perennial plant commonly known as the Jerusalem artichoke, is a sunflower species native to North America. Jerusalem artichoke tubers primarily contain two types of carbohydrates, inulin and sugars (fructose and glucose). Inulin and fructooligosaccharides (FOS) stimulate the immune system, increase absorption of calcium, and decrease triglycerides and fatty acids content in the blood serum. Besides, they modulate insulin and glucagon levels (Johansson et al., 2015). Inulin is considered a functional food ingredient since it affects physiological and biochemical processes in animals, resulting in better health and a reduction in the risk of many diseases (Kaur & Gupta, 2002).

Inulin and FOS are effective prebiotics. Inulin and FOS are hydrolyzed to their respective sugars on transit through the large bowel. The sugars are fermented to short-chain fatty acids (SCFAs) and biomass by the complex bacterial flora. SCFAs are the critical respiratory fuels for colonocytes, supplying up to 60 to 70% of their energy needs. Besides, SCFAs also stimulate the growth of colorectal mucosal cells, retard mucosal atrophy, and decrease the risk of malignant transformation in the colon. Butyrate is particularly effective in reducing the risk of malignant transformation of the colon (Rossi et al., 2005). Inulin supplementation can also reduce the malodor of cat and dog feces and may help prevent diseases such as colorectal cancer (Kays & Nottingham, 2008).

Canine and feline studies of inulin and fructooligosaccharides (FOS)

Studies-Canine	Study Title	Study Summary
Willard et al., 1994	Effects of dietary supplementation of fructo-oligosaccharides on small intestinal bacterial overgrowth in dogs.	The study concluded that dietary fructooligosaccharides affect small intestinal bacterial populations in dogs with small intestinal bacterial overgrowth.
Hussein et al., 1999	Petfood applications of inulin and oligofructose.	In canine subjects, dietary supplementation of inulin and fructooligosaccharides reduces the concentrations of ammonia and amines and increases the numbers of bifidobacteria.

PHARMACOLOGICAL ACTIVITIES - TOXICOLOGY - DRUG INTERACTIONS

Barry et al., 2009	Low-level fructan supplementation of dogs enhances nutrient digestion and modifies stool metabolite concentrations, but does not alter fecal microbiota populations.	In this study, supplementation of inulin and fructooligosaccharides in canine subjects enhanced nutrient digestion and modified stool concentrations of short-chain fatty acids and protein catabolites. High nutrient digestibility is critical when dogs are housed indoors for extended periods. Besides, a reduction in stool protein catabolites results in a less offensive stool odor and is also beneficial to intestinal health.
Bosch et al., 2009	The effects of dietary fibre type on satiety-related hormones and voluntary food intake in dogs.	The addition of fermentable fibre such as inulin in canine diets may contribute to the prevention or mitigation of obesity through its effects on satiety.
Verbrugghe A et al., 2010	Intestinal fermentation modulates postprandial acylcarnitine profile and nitrogen metabolism in a true carnivore: the domestic cat (Felis catus).	In healthy cats, adding inulin and fructooligosaccharides to a high-protein diet reduces postprandial amino acid-induced gluconeogenesis.
Garcia-Mazcorro et al., 2017	Molecular assessment of the fecal microbiota in healthy cats and dogs before and during supplementation with fructo-oligosaccharides (FOS) and inulin using high-throughput 454-pyrosequencing.	This study shows a high interindividual variation of fecal bacterial communities from pet cats and dogs, that these communities are relatively stable over time, and that some of this variation can be attributable to prebiotic administration, a phenomenon that may be affected by the amount of the prebiotic administered. Administration of inulin and FOS had no side effects (e.g., diarrhea) and was well accepted.

TOXICOLOGY

Toxicity for inulin and fructooligosaccharides have not been documented in dogs and cats when administered orally in therapeutic doses.

LD_{50} for inulin and fructooligosaccharides has not been determined.

DRUG INTERACTIONS

Validated interaction studies do not exist for inulin preparations. Clinical interactions with other drugs have not been reported.

Linum usitatissimum (Flax) [Seed]

Linum usitatissimum L. (Linaceae), commonly known as flax or linseed, is among the oldest crop plants cultivated for oil and fibre. Flaxseed (Semen Lini) provides a rich source of omega-3, digestible proteins, fibre, and lignans. It comprises 23-26% alpha-linolenic acid (ALA), making it the richest plant source. ALA is a precursor for the long-chain omega-3 fatty acids, docosapentaenoic acid (C20:4n-3; DPA) and eicosapentaenoic acid (C20:5n-3; EPA), and to some extent, it is also converted to docosahexaenoic acid (C22:6n-3; DHA). Increasing dietary intake of ALA from Semen Lini can help to guard against inflammation and associated chronic diseases such as obesity, diabetes, and cancer. Semen Lini increases ALA in mothers' milk in canines and felines and is an essential fatty acid to be transferred to their offspring (Adolphe & Fitzpatrick, 2016).

Semen Lini provides about 20 g protein per 100 g, making it a relatively rich source of protein compared to cereal grains. Complete proteins, also referred to as high-quality proteins, provide all essential amino acids in ratios required for protein synthesis by dogs and cats. Semen Lini protein is relatively high in arginine, aspartic acid, and glutamic acid, whereas lysine, methionine, and cysteine are the limiting amino acids (Adolphe & Fitzpatrick, 2016).

Semen Lini contains 28 g of total dietary fibre per 100 g, including 9 g of soluble dietary fibre. The insoluble fibre fraction in Semen Lini, consisting of cellulose, hemicellulose, and lignin, has a strong water binding capacity, thereby adding bulk to the diet and providing potential benefits for pets with digestive disorders. The fibre from Semen Lini may aid in weight control in pets (Adolphe & Fitzpatrick, 2016).

The main lignan in Semen Lini is secoisolariciresinol diglucoside, which is converted by mammalian microflora to enterodiol and enterolactone. Studies show that Semen Lini lignans support cardiovascular function, bone health, normal cell proliferation, hormone balance and are potent antioxidants (Jan et al., 2009). A study conducted at the University of Toronto concluded that Semen Lini ingestion produces potentially anticarcinogenic lignans in the colon and can decrease the risk for colon carcinogenesis (Serraino & Thompson, 1992).

PHARMACOLOGICAL ACTIVITIES - TOXICOLOGY - DRUG INTERACTIONS

Canine and feline studies of *Linum usitatissimum* and combinations

Studies-Canine	Study Title	Study Summary
Bauer et al., 1998	Dietary flaxseed in dogs results in differential transport and metabolism of (n-3) polyunsaturated fatty acids.	Dietary flax seed showed rapid accumulation of eicosapentaenoic acid (EPA) and certain other (n-3) fatty acids in plasma lipids in the canine model.
Rees et al., 2001	Effects of dietary flax seed and sunflower seed supplementation on normal canine serum polyunsaturated fatty acids and skin and hair coat condition scores.	A one-month supplementation with either flax seed or sunflower seed in dogs provided temporary improvement in skin and hair coat. These changes were associated with increased serum polyunsaturated fatty acids (PUFA) concentrations.
Kempe & Saastamoinen, 2007	Effect of linseed cake supplementation on digestibility and faecal and haematological parameters in dogs.	The study showed that working and racing dogs can utilize up to 4.2% linseed cake of diet dry matter as a fibre source without severe reductions in nutrient digestibility or feed consumption. Even higher levels of linseed cake, up to 8.5% of diet DM, can be used for healthy or obese dogs.
Jewell et al., 2022	Feeding Fiber-Bound Polyphenol Ingredients at Different Levels Modulates Colonic Postbiotics to Improve Gut Health in Cats.	The study findings indicate that bacteria in the large intestine of cats were able to digest the fibre bundle (flax seed, pecan shells, and powders from cranberry, citrus, and beet) to make compounds that may contribute to host health and also shifted to the digestion of carbohydrates instead of protein.
Jewell et al., 2022	Feeding Fiber-Bound Polyphenol Ingredients at Different Levels Modulates Colonic Postbiotics to Improve Gut Health in Dogs.	The study findings indicate that the fibre bundle (flax seed, pecan shells, and powders from cranberry, citrus, and beet) increases antioxidant and anti-inflammatory activity.

TOXICOLOGY

Toxicity for Semen Lini has not been documented in dogs and cats when administered orally in therapeutic doses.

LD_{50} for Semen Lini has not been determined.

DRUG INTERACTIONS

Validated interaction studies do not exist for Semen Lini preparations. Clinical interactions with other drugs have not been reported.

However, enteral absorption of concomitantly administered medicines may be delayed by bulk forming Semen Lini. For this reason, the product should not be taken ½ to 1 hour before or after intake of other medicinal products (EMEA, 2006).

Laminaria digitata (Kelp) [Whole Plant]

Seaweeds, also called macroalgae, are multicellular large-size marine organisms. Seaweeds are a source of antioxidants such as phenolic compounds, polysaccharides, pigments, vitamins, micro and macro-minerals, and proteins. Natural antioxidants applied as feed additives can improve animals' health and overall performance and increase their resistance to environmental stress (Michalak et al., 2022).

In animal models, dietary inclusion of laminarin derived from kelp thallus (Thallus Laminariae) reduces the Enterobacteriaceae population and increases total volatile fatty acid concentrations in the caecum (Smith et al., 2011).

Glucan-phycarine from Thallus Laminariae shows significant stimulation of phagocytic activity. It also potentiates the synthesis and release of interleukin-1, interleukin-6, and tumour necrosis factor-alpha (Vetvicka & Yvin, 2004). Thallus Laminariae is also a rich source of iodine, essential in the formation of thyroxine (T4) that regulates metabolism (Wolf & Lewter, 2017).

TOXICOLOGY

Toxicity for Thallus Laminariae has not been documented in dogs and cats when administered orally in therapeutic doses.

LD_{50} for Thallus Laminariae has not been determined.

DRUG INTERACTIONS

Validated interaction studies do not exist for Thallus Laminariae preparations. Clinical interactions with other drugs have not been reported.

However, the iodine content of seaweeds may affect the measurement of serum thyrotropin levels (Miyai et al., 2008).

Althaea officinalis (Marshmallow) [Root]

Roots of *Althaea officinalis* L. (Malvaceae), also called marshmallow roots (Radix Althaeae), are widely used for the treatment of irritated mucosa. Radix Althaeae contain water-soluble polysaccharides such as galacturonate, arabinans, glucans, and arabinogalactans (Deters et al., 2010).

Polysaccharides of Radix Althaeae are effective stimulators of cell physiology of epithelial cells that can be the rationale for its traditional use in the treatment of irritated mucous membranes (Deters et al., 2010). Traditionally Radix Althaeae is used in gastritis, peptic ulcers, enteritis, and colitis. Radix Althaeae mucilage stimulates phagocytosis and increases anti-inflammatory and hypoglycemic activity. It also demonstrates antimicrobial, spasmolytic, anti-secretory, diuretic, and wound healing effects (Jellin et al., 2002).

Feline studies of *Althaea officinalis* and combinations

Studies-Canine	Study Title	Study Summary
Nosál'ova et al., 1992	Antitussive action of extracts and polysaccharides of marsh mallow (Althea officinalis L., var. robusta).	Administration of marshmallow root extract or the polysaccharide fraction to cats demonstrated significant antitussive activity. It depressed the cough that resulted from irritation of laryngopharyngeal and tracheobronchial mucosa. Polysaccharide at a dose of 50 mg/kg was effective in suppressing the cough reflexes.
Sutovska et al., 2007	The antitussive activity of polysaccharides from Althaea officinalis l., var. Robusta, Arctium lappa L., var. Herkules, and Prunus persica L., Batsch.	The study results showed that the tested polysaccharides exhibited statistically significant cough-suppressing activity in adult cats of both sexes. Polysaccharides of Radix Althaeae exhibited potent antitussive activity.

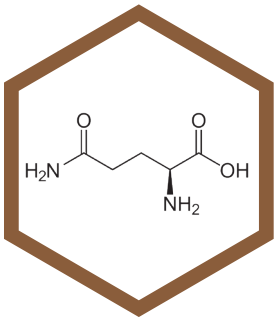
TOXICOLOGY

Toxicity for Radix Althaeae has not been documented in dogs and cats when administered orally in therapeutic doses.

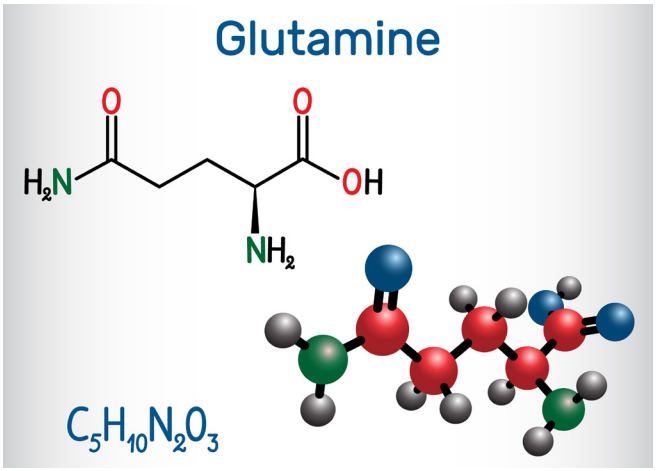
LD_{50} for Radix Althaeae has not been determined.

DRUG INTERACTIONS

Validated interaction studies do not exist for Radix Althaeae preparations. Clinical interactions with other drugs have not been reported.



L-Glutamine ($C_5H_{10}N_2O_3$)



L-glutamine is an amide of glutamic acid with amine as the functional group. L-glutamine has functions in the gastrointestinal tract such as attenuation of gut damage, support of intestinal barrier function and integrity, reduction in oxidative stress, restoration of mucosal immune homeostasis, and optimization of immune function by normalizing or reducing inflammatory cytokine secretion and increasing immune-regulatory cytokine concentrations (Rao & Samak, 2012).

Physiologically, L-glutamine plays a significant role in various metabolic processes. It is an intermediary in energy metabolism and a substrate in the synthesis of peptides and non-peptides such as nucleotide bases, glutathione, and neurotransmitters. Additionally, L-glutamine contributes to the detoxification of ammonia and systemic acid-base balance (Kim & Kim, 2017).

Experiments in animals with irritable bowel disease (IBD) have demonstrated that glutamine supplementation can protect the intestinal mucosa. Oral L-glutamine supplementation ameliorated abdominal radiation-induced mucosal injury and reduced bacterial translocation in the gut mucosa of rats (Souba et al., 1990). In dextran sulfate sodium-induced rats, oral administration of glutamine reduced bleeding and diarrhea (Xue et al., 2011).

Canine studies of L-glutamine and combinations

Studies-Canine	Study Title	Study Summary
Humbert et al., 2002	Does enteral glutamine modulate whole-body leucine kinetics in hypercatabolic dogs in a fed state?	In hypercatabolic canine subjects in the fed state, enteral glutamine supplementation acutely decreases leucine oxidation, improves net leucine balance, and preserves body protein.
Iwashita et al., 2005	Impact of glutamine supplementation on glucose homeostasis during and after exercise.	Glutamine availability modulates glucose homeostasis during and after exercise, which may have implications for postexercise recovery in canine subjects.
Humbert et al., 2007	Effect of glutamine on glutathione kinetics in vivo in dogs.	After a 3-day fast in dogs, supplementation of enteral feeding with glutamine declines glutathione utilization and significantly improves glutathione redox status. The study findings support the role of glutamine in preserving reduced glutathione in the gut under conditions mimicking decreased dietary intake accompanying severe illness.
Ohno et al., 2009	Glutamine decreases the duration of postoperative ileus after abdominal surgery: an experimental study of conscious dogs.	In canine subjects, glutamine can act as a motility-recovery agent after abdominal surgery and reduce the duration of postoperative ileus.

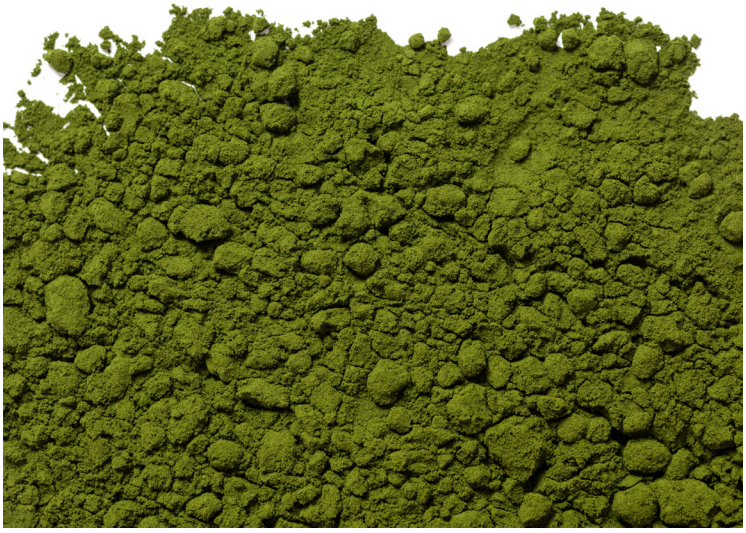
TOXICOLOGY

Toxicity for L-glutamine has not been documented in dogs and cats when administered orally in therapeutic doses.

DRUG INTERACTIONS

Validated interaction studies do not exist for oral L-glutamine preparations. Clinical interactions with other drugs have not been reported.

Spirulina platenis (Spirulina Whole)



Arthrospira platensis (Spirulina) is a photosynthetic, filamentous, spiral-shaped, multicellular and blue-green microalga. Spirulina has high nutritional value that provides a rich content of protein, polysaccharides, lipid, essential amino acids, fatty acids, minerals, and vitamins. The functional compounds include C-phycocyanin, allophycocyanin, phycobiliproteins, and polysaccharides. Pharmacological activities of spirulina include antimicrobial, metalloprotective, immunostimulant, and antioxidant effects (Hosseini et al., 2013; Finamore et al., 2017).

In animal studies, Spirulina has been shown to increase the population of lactic acid bacteria such as *Lactococcus lactis, Streptococcus thermophiles (Streptococcus salivarius), Lactobacillus casei, Lactobacillus acidophilus, and Lactobacillus bulgaricus* (Belay, 2002).

Canine and feline studies of Spirulina and combinations

Studies-Canine	Study Title	Study Summary
Qureshi & Ali, 1996	Spirulina Platensis Exposure Enhances Macrophage Phagocytic Function in Cats.	The study data showed that Spirulina platensis extract enhances macrophage phagocytic function and that dietary Spirulina supplementation may improve the disease resistance potential in cats.
Zhang et al., 2001	Chemo- and radio-protective effects of polysaccharide of Spirulina platensis on hemopoietic system of mice and dogs.	In gamma irradiation-induced hemopoietic system damage in dogs, feeding Spirulina increased the level of erythrocytes, leukocytes, hemoglobin, and nucleated cells in the bone marrow. The study concluded that polysaccharides of Spirulina have chemo-protective and radio-protective capability and may be a potential adjunct to cancer therapy.

Satyaraj et al., 2021	Supplementation of Diets With Spirulina Influences Immune and Gut Function in Dogs.	Dogs fed diets supplemented with Spirulina demonstrated enhanced immune status by showing significantly higher vaccine response and elevated levels of fecal IgA compared to the control group. Significant increase in gut microbiota stability in the test group was also observed.

TOXICOLOGY

Toxicity for *Spirulina platenis* has not been documented in dogs and cats when administered orally in therapeutic doses.

Oral LD_{50} of *Spirulina platenis* extract is > 6 g/kg in mice (Hutadilok et al., 2010). Oral LD50 of phycocyanin in rats and mice is >3 g/kg (Belay, 2002).

The equivalent toxic dose in a 20 kg dog: >120 g PO of S*pirulina platenis* extract.
The equivalent toxic dose in a 5 kg cat: >30 g PO of *Spirulina platenis* extract.

DRUG INTERACTIONS

Validated interaction studies do not exist for oral Spirulina platenis preparations. Clinical interactions with other drugs have not been reported.

Citrus bioflavonoids

Citrus bioflavonoids encompass diverse structures, including rutin, hesperidin, and quercetin. Several studies have shown that the anti-inflammatory properties of citrus flavonoids are due to their inhibition of the synthesis and biological activities of different pro-inflammatory mediators, mainly the arachidonic acid derivatives, prostaglandins E2, F2, and thromboxane A2 (Benavente-Garcia & Castillo, 2008).

The antioxidant and anti-inflammatory properties of citrus flavonoids can play a crucial role in their activity against several degenerative diseases (Benavente-Garcia & Castillo, 2008). Canine and feline obesity rates have reached pandemic proportions similar to those in humans, with approximately 30-40% of dogs and cats being overweight to obese (Loftus & Wakshlag, 2015), and citrus bioflavonoids have demonstrated anti-obesity activity.

Canine and feline studies of Citrus bioflavonoids and combinations

Studies-Canine	Study Title	Study Summary
Salas et al., 2009	Plant polyphenol intake alters gene expression in canine leukocytes.	Ingestion of citric extract in dogs modulates leukocyte functions through changes in gene expression.
Jeusette et al., 2010	Effects of consuming diets containing various fats or citrus flavanones on plasma lipid and urinary F2-isoprostane concentrations in overweight cats.	Supplementation of citrus flavanones in obese cats resulted in lower energy intake and a decrease in plasma lipids and oxidative stress.
Leray et al., 2011	Effect of citrus polyphenol- and curcumin-supplemented diet on inflammatory state in obese cats.	Obese cats supplemented with citrus bioflavonoids had decreased plasma haptoglobin and α1-acid glycoprotein after eight weeks.

TOXICOLOGY

Toxicity for citrus bioflavonoids has not been documented in dogs and cats when administered orally in therapeutic doses.

Oral LD_{50} for quercetin is 160 mg/kg in mice (IARC, 1999; Merck Index, 1983).
Subcutaneous LD_{50} for quercetin is 100 mg/kg in mice (IARC, 1999).
Intravenous $LD_{50}$for rutin is 950 mg/kg in mice (Merck Index, 1983).
Oral LD_{50} for rutin is 4,750 mg/kg in mice (Patil et al., 2012).
Oral LD_{50} for flavonoid mixture containing 90% diosmin and 10% hesperidin is >3g/kg (Meyer, 1994).

The equivalent toxic dose in a 20 kg dog: 3,200 mg PO of quercetin; 95,000 mg PO of rutin; 60 g of diosmin and hesperidin mixture.

The equivalent toxic dose in a 5 kg cat: 800 mg PO of quercetin; 23,750 mg PO of rutin; 15 g of diosmin and hesperidin mixture.

DRUG INTERACTIONS

Validated interaction studies do not exist for oral citrus bioflavonoids preparations. Clinical interactions with other drugs have not been reported.

Ulmus rubra (Slippery Elm) [Bark]

Ulmus rubra Muhl. (Ulmaceae), also called slippery elm, as identified by its "slippery" inner bark. Slippery elm bark (Ulmi Rubrae Cortex) mucilage contains residues of L-rhamnose, D-galactose, 3-O-methyl-D-galactose, and D-galacturonic acid (Beveridge et al., 1969). Ulmi Rubrae Cortex is a demulcent, an agent that forms a soothing film over mucous membranes, thus protecting irritated or inflamed tissue. Traditionally it has been used to soothe irritation or ulceration of the stomach and intestines (Lans et al., 2007).

Ulmi Rubrae Cortex has been used as an ethnoveterinary medicine to treat endoparasites and gastric problems in pigs and pets. It has mid- to high-level validity for its use in treating endoparasites in animals (Lans et al., 2007).

TOXICOLOGY

Toxicity for Ulmi Rubrae Cortex has not been documented in dogs and cats when administered orally in therapeutic doses.

LD_{50} for Ulmi Rubrae Cortex has not been determined.

DRUG INTERACTIONS

Validated interaction studies do not exist for oral Ulmi Rubrae Cortex preparations. Clinical interactions with other drugs have not been reported.

However, Ulmi Rubrae Cortex extract may slow the absorption of concomitantly administered oral medications (Brinker, 2001).

Cellulase (4-(1,3;1,4)-beta-D-glucan 4-glucanohydrolase) [E.C.3.2.1.4]

Cellulase does not exist in cat and dog digestive systems. Therefore, supplementation with enzymes which contain cellulose combined with protease, amylase, and lipase can be more advantageous to dogs and cats as it liberates nutrients such as zinc, selenium, and linoleic acid bound by fibre (Messonnier, 2001).

Cellulase can disrupt the cell wall and release carotenoids and anthocyanins (Kuhad et al., 2011; Lotfi et al., 2015). Evidence suggests that absorption of biologically active phytochemicals such as anthocyanins and carotenoids occurs in the stomach and small intestine (Yonekura & Nagao, 2007; He & Giusti, 2010). It also acts on cellodextrins, the intermediate products of cellulose hydrolysis, and converts them to cellobiase and glucose (Behera et al., 2017).

Bezoars, the accumulations of foreign material in the stomach, have been known to occur in animals and humans for centuries (Andrus & Ponsky, 1988). Phytobezoar, the most common type of bezoar, is composed of indigestible fruit and vegetable fibres, such as cellulose, hemicellulose, lignin, or tannins. The therapeutic options in phytobezoars include treatment with cellulase and proteolytic enzymes. In a study of patients with phytobezoar, treatment with cellulase was successful in 100% of the patients and 87% with proteolytic enzymes (Walker-Renard, 1993).

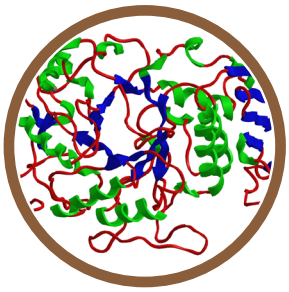
TOXICOLOGY

Toxicity for cellulase has not been documented in dogs and cats when administered orally in therapeutic doses.

DRUG INTERACTIONS

Validated interaction studies do not exist for oral cellulase preparations. Clinical interactions with other drugs have not been reported.

alpha-Amylase (4-alpha-D-Glucan glucanohydrolase) [EC.3.2.1.1]



α-Amylase catalyzes the first step in the digestion of starch, the principal carbohydrate (Butterworth et al., 2011). It is a hydrolase enzyme that catalyzes the hydrolysis of internal α-1, 4-glycosidic linkages in starch, resulting in the production of maltose, maltotriose, glucose, and α-limit dextrins as the main products (Gupta et al., 2003). Most amylases are metalloenzymes requiring Ca+2 for their activity, structural integrity, and stabilization (Rameshkumar & Sivasudha, 2011; Saha et al., 2014). Besides, chloride is also essential for amylase activation (Levitzki & Steer, 1974).

Dogs and cats only express amylase in the pancreas and not in the saliva. Dogs have a higher capacity to digest and absorb carbohydrates than cats (NRC, 2006; Batchelor et al., 2011), and dog amylase activity is more sensitive to dietary levels of starch (NRC, 2006). Cats possess only a small capacity for starch digestion by endogenous intestinal enzymes. They have 5% of the pancreatic amylase activity and 10% of the intestinal amylase activity of dogs (Scherk, 2008). In cats, high carbohydrate diets can induce diarrhea due to undigested carbohydrates in the lower small intestine and colon (Sturgess, 2008).

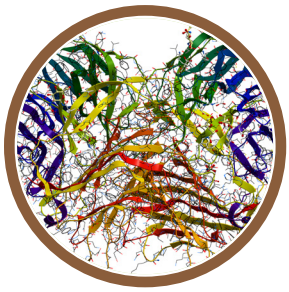
TOXICOLOGY

Toxicity for α-amylase has not been documented in dogs and cats when administered orally in therapeutic doses.

DRUG INTERACTIONS

Validated interaction studies do not exist for oral α-amylase preparations. Clinical interactions with other drugs have not been reported.

However, *in vitro,* α-amylase inhibitory effect of some clinically-used drugs include enalapril (99.9%), captopril (99.5%), tetracycline (97.9%), ketotifen (77.6%), naphazoline (13.6%), fluconazole (7.4%), diclofenac sodium (4.74%), ciprofloxacin (4.7%), Fluoxetine (4.7%), propranolol (4.6%), metronidazole (3.9%), timolol (3.9%), hydrochlorothiazide (3.8%), atenolol (3.5%), cloxacillin (3.5%), clarithromycin (3.13%), ampicillin (2.8%), azithromycin (2.75%), cephalexin (2.6%), orphinadrine citrate (2.6%), Astemizole (2.1%), and clindamycin (1.6%) [Hamdan II et al., 2004].



Invertase (beta-Fructofuranosidase) [EC 3.2.1.26]

Invertase, also called sucrase and saccharase, is present in the intestinal mucosa of animals. It catalyzes the hydrolysis of sucrose to glucose and fructose. Sucrase is beneficial in helping prevent gastrointestinal problems and discomfort. In animals, sucrase activity in the intestine increases as the need for and secretion of lactase decreases with age (Blood et al., 2007). Besides sucrose, invertase can also hydrolyze raffinose producing fructose, melibiose, and the polysaccharide inulin (Marques et al., 2016). Invertase is present in the feline small intestinal mucosa, but the activity in the intestinal brush border is low compared to other species (Verbrugghe & Hesta, 2017).

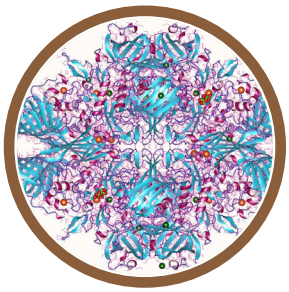
TOXICOLOGY

Toxicity for invertase has not been documented in dogs and cats when administered orally in therapeutic doses.

DRUG INTERACTIONS

Validated interaction studies do not exist for oral invertase preparations. Clinical interactions with other drugs have not been reported.

Lactase (beta-D-galactoside galactohydrolase) [EC 3.2.1.108]



Lactase is involved in the hydrolysis of disaccharide lactose into constituent galactose and glucose monomers (Sahi, 1994). Lactase activity is highest in weanling puppies and kittens, which decreases as the animal matures and can happen rapidly. Lactase activity peaks in the intestines of young dogs (5 days old) and slowly decreases to levels found in adults by 20 to 61 days of life (NRC, 2006).

Dogs have low lactase activity, and lactose remains undigested, causing diarrhea (Sahi, 1994). Lactose also causes diarrhea in some cats and significantly reduces the digestibility of crude protein in the total ration fed (Morris et al., 1977). Relative lactase deficiency occurs in dogs, particularly cats (Ettinger & Feldman, 2000).

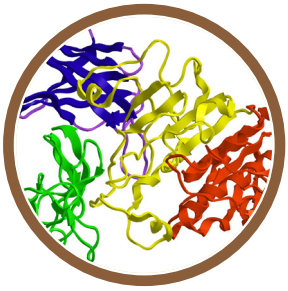
Consumption of a high amount of milk or milk products can cause digestive upsets in dogs. As in most mammals, the dog's intestinal mucosa decreases lactase activity as the dog reaches maturity. This change results in lactose maldigestion. Undigested lactose is fermented by bacteria in the large intestines, resulting in gas, loose stools, and diarrhea (Case, 2005).

TOXICOLOGY

Toxicity for lactase has not been documented in dogs and cats when administered orally in therapeutic doses.

DRUG INTERACTIONS

Validated interaction studies do not exist for oral lactase preparations. Clinical interactions with other drugs have not been reported.



Lipase (Triacylglycerol lipase) [EC 3.1.1.3]

Lipase is an enzyme that catalyzes the breakdown of fats into fatty acids and glycerol. Lipases are also involved in diverse biological processes such as cell signalling and inflammation (Spiegel et al., 1996; Tjoelker et al., 1995). Supplemental lipase enzyme therapy is beneficial in gastrointestinal disturbances, dyspepsia, cutaneous manifestations of digestive allergies, and malignant tumors (Gurung et al., 2013).

Pancreatitis is the most common disorder of the exocrine pancreas in dogs and cats (Xenoulis, 2015) and is less painful for cats than for dogs and humans (Schnauß et al., 2019). In a study, treatment of pancreatic deficiency steatorrhea in dogs with lipase showed a marked reduction in stool bulk and fat excretion and valuable therapy for dogs with pancreatic insufficiency (Griffin et al., 1989).

Oral digestive enzymes that contain triacylglycerol lipase should be taken with meals to ensure adequate mixing with chyme (Toouli et al., 2010). Supplementing with enzymes may improve nutrient malabsorption, which is often associated with inflammatory bowel disease. Treatment of steatorrhea by lipase supplementation therapy has become more successful in the last decade, and bacterial lipase products show promising potential and offer future therapeutic alternatives (Layer & Keller, 2003).

TOXICOLOGY

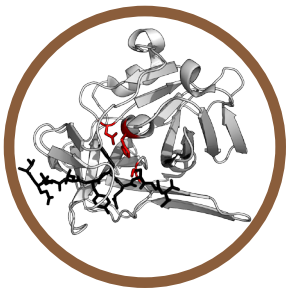
Toxicity for lipase has not been documented in dogs and cats when administered orally in therapeutic doses.

DRUG INTERACTIONS

Tetrahydrolipstatin (Orlistat), an anti-obesity drug, interferes with the activity of lipase (McNeely & Benfield, 1998). Tetrahydrolipstatin inhibits pancreatic lipase in several species, including humans (Hadváry et al., 1998).

Orlistat inhibits gastric and pancreatic lipases in the lumen of the gastrointestinal tract to decrease systemic absorption of dietary fat (Heck et al., 2000).

Protease (EC 3.4.23.18)



Protease performs proteolysis. Proteases regulate the fate, localization, and activity of many proteins, modulate protein-protein interactions, create new bioactive molecules, contribute to the processing of cellular information, and generate, transduce, and amplify molecular signals (López-Otín & Bond, 2008).

Proteolytic enzymes, such as bromelain, papain, pancreatin, trypsin, and chymotrypsin, are essential regulators and modulators of the inflammatory response. Proteolytic enzymes modulate the inflammatory process by a variety of mechanisms, including reducing the swelling of mucous membranes, decreasing capillary permeability, and dissolving blood clot-forming fibrin deposits and micro-thrombi (Lenard et al., 2013).

TOXICOLOGY

Toxicity for protease has not been documented in dogs and cats when administered orally in therapeutic doses.

DRUG INTERACTIONS

Validated interaction studies do not exist for oral protease preparations. Clinical interactions with other drugs have not been reported.

However, bromelain may affect the blood's ability to clot and could interfere with blood-thinning drugs (Penn State Hershey Medical Center, 2020).

Malus pumila (Apple) [Fibre]

In fresh apples, the soluble fibre fraction, mainly pectin, represents around 50-30% of the overall fibre content (Fotschki et al., 2014). Whereas apple pomace, a by-product of the apple juice industry, contains 51.1% dietary fibre (Sudha et al., 2007; Yangilar, 2013). Pectin is a water-soluble polysaccharide and is resistant to digestion in the small intestine but easily degraded by colonic bacteria (Otles & Ozgoz, 2014). Pectin is fermented in the colon to form acetate, propionate, and butyrate (Veldman et al., 1999). Besides, pectin provides resistance against GI juices for supplemented probiotics (Nazzaro et al., 2012).

Soluble fibre such as pectin results in more bulk, prolonged gastric emptying, and slowed transit through the small intestine of dogs. Both soluble and insoluble fibre is effective in the management of diarrhea in dogs. Additionally, consuming soluble fibre is more effective in improving glycemic control (Ettinger & Feldman, 2000; NRC, 2006).

TOXICOLOGY

Toxicity for apple fibre has not been documented in dogs and cats when administered orally in therapeutic doses.

DRUG INTERACTIONS

Chronic ingestions of pectin enhance the absorption of quercetin (Nishijima et al., 2009).

Co-administration of acetaminophen with pectin delays its absorption and onset (Bushra et al., 2011).

Consumption of pectin with lovastatin reduces the absorption of the drug (Bushra et al., 2011).

Cyamopsis tetragonoloba (Guar) [Gum]

Guar gum is a highly viscous soluble dietary fibre that has gel-forming effects in the stomach and small intestine, which is readily fermented to short-chain fatty acids (SCFA) in the large bowel by colonic bacteria. These actions lead to potentially beneficial effects in the gastrointestinal tract and systemically, such as lowering serum cholesterol and improving glycaemic control (James et al., 2003). The hypocholesterolemic activity associated with soluble fibre consumption is clear from the animal model and human clinical investigations (Rideout et al., 2008).

TOXICOLOGY

Toxicity for guar gum has not been documented in dogs and cats when administered orally in therapeutic doses.

DRUG INTERACTIONS

Guar Gum reduces the absorption of phenoxymethylpenicillin (Huupponen et al., 1984).

SAFETY INFORMATION

PRECAUTIONS

- An examination from a veterinarian is recommended prior to using this product.
- Do not use in pregnant, lactating, immature or immunosuppressed animals.
- Do not use in animals with thyroid disease or receiving other drugs, unless directed by a veterinarian.
- Consult your veterinarian before using in puppies and kittens.
- Absorption of drugs taken simultaneously may be delayed.
- Not to be used one week prior to surgery.
- Administer during or after the animal has eaten to reduce incidence of gastrointestinal upset.
- If animal's condition worsens or does not improve, stop product administration and consult your veterinarian.
- Off-label use of this product in ruminants is not recommended.
- Oral use only.
- Shake well before use.

WARNINGS

- To be used in dogs and cats only.
- Keep out of the reach of children and animals.
- In case of accidental overdose, contact a health professional immediately.

ADVERSE REACTIONS

- Mild gastrointestinal discomfort may occur which is dose dependent.

CONTRAINDICATIONS

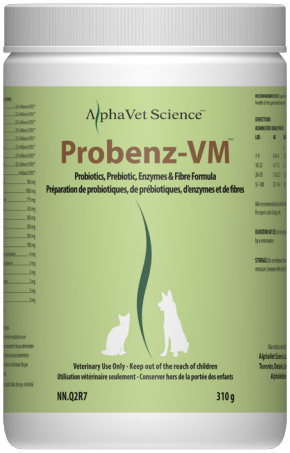
- Contraindicated in pregnant and nursing dogs and cats.
- Contraindicated in dogs and cats undergoing diagnostic test for acute pancreatitis and acute attacks of chronic pancreatitis as Probenz-VM™ contains protease, amylase, and lipase which can alter test results.
- Contraindicated in dogs and cats with known yeast allergy.

DURATION OF USE

- Not for long term use, unless directed by a veterinarian.

AlphaVet Science™

Probenz-VM™



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