Probiotics
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Abbreviations

FOS	Fructooligosaccharides
GIT	Gastrointestinal tract
LAPB	Lactic acid-producing bacteria
SCFA	Short-chain fatty acid

The environment of the gastrointestinal tract (GIT) is composed of a diverse microbiome. Interaction among microorganisms, changes in population composition, and interaction of microorganisms and microbial products with the host determine the health status of the GIT.[1] The normal microbiome in dogs and cats is primarily composed of organisms from the phyla Actinobacteria, Bacteroides, Firumicutes, Fusobacteria, and Proteobacteria.[2-5] It is proposed that alterations in the normal microbiome composition contribute to acute and chronic enteropathies on both a local and systemic level.[2,6-8]

Probiotics are "live microorganisms that, when consumed, have the potential to confer a beneficial health effect."[9] Effects result from alterations in gastrointestinal microbiome composition, displacement of enteric pathogens, release of beneficial metabolic products, and interaction with the host immune system. Ideally, the chosen probiotic restores the microbiome to its stable, pre-diseased state. The investigation of microorganisms and application in health and disease is on-going in veterinary medicine. The aim of this review was to evaluate the current evidence behind clinical use of probiotics in cats and dogs.

General considerations

Regulation of veterinary and human probiotic products varies based on location and specific marketing use. Commercial products often do not contain the species or concentration of bacteria as labeled; some products contain organisms not listed on the label, which occasionally include pathogenic species.[9,10] One study of 19 veterinary products found that none contained all organisms as labeled, and 58% of products contained additional, unlisted organisms.[10-13]

Even when a probiotic contains the species and concentrations as labeled, the effect of a specific product cannot be extrapolated from a different product. Manufacturing processes effect the characteristics of bacteria and their tendency to express desirable traits. For example, the growth media and viability of various *Lactobacillus sp* impacted efficacy in pathogen exclusion, including *Enterococcus canis, Salmonella enterica typhimurium,* and *Clostridium perfringens.*[14] In addition, many probiotic products are marketed as synbiotics, or combination products of bacteria and compounds that augment microorganism proliferation (i.e. prebiotics). For this reason, this review references the commercial product name when possible.

Furthermore, the ability of enteric pathogens to cause clinical disease depends on their ability to penetrate the intestinal biofilm and adhere to intestinal mucosa.[15] Likewise, probiotic bacteria must have similar qualities to exert a positive effect. This effect extends to interaction with mucosal immune cells, as well as the ability to interfere with adherence and proliferation of pathogenic bacteria. . Table 1 summarizes veterinary studies evaluating probiotics in-vitro. As in-vitro studies have limited value to predict clinical efficacy, this review focuses primarily on evidence from in-vivo studies.

Evidence of efficacy in healthy dogs

Table 2 summarizes in-vivo studies on probiotics in healthy dogs.

Enterococcus faecium --- Successful passage of *Enterococcus faecium* through the GIT, as well as persistence up to 3 months after cessation of supplementation, was documented in healthy dogs following oral administration of several strains, including SF68 (Fortiflora®)[ab].[16,17] Administration of *E. faecium* (Enteroferm®[c]) resulted in decreased fecal counts of *Clostridia* but variable impact on *Salmonella* and *Campylobacter* fecal counts in individual dogs, with no overall change across the study population.[18] Decreased fecal *Pseudomonas-type* bacteria and increased fecal lactic acid-producing bacteria (LAPB) were documented in an uncontrolled study.[17]

Systemic impact of *E. faecium* includes non-specific immune responses (i.e. increased peripheral neutrophil phagocystosis and lymphocyte blast transformation).[19] Whether these responses represent "augmented host resistance" or compensation to pathogen invasion is unknown.[19-21]

Lactobacillus --- Multiple studies have demonstrated passage and colonization of the GIT by *Lactobacillus spp (L. rhamnosus, L. fermentum, L. animalis, L. acidophilus)*.[17,22-28] Fecal persistence following cessation of administration was documented between 3 days and 6 months depending on species and dose.[22,27,29,30] In contrast, several studies have documented effective transit but not persistence for the same species, as well as related *Lactobacilli*. [31-33] Effects of treatment may persist longer than fecal microorganism presence, as demonstrated by decreased fecal microbial diversity despite the inability to detect supplemented bacteria.[32]

Per os *Lactobacillus* administration increased fecal *Lactobacillus* and *Entercoccus* counts.[29] In combination with the prebiotic inulin, increased fecal LAPB were noted, with longer duration of impact with synbiotic supplementation than probiotic alone. [24,28] Decreased fecal *Clostridia* and *Staphylococci* were documented with *L. fermentum* and *L. acidophilus* supplementation.[23-25,31] Impact of *Lactobacillus* supplementation on fecal *E. coli* and *Pseudomonas* counts is less consistent. One study documented decreases in both populations, but another study noted no impact on *E. coli* and increased *Pseudomonas* counts.[24,25,29]

Biologic effects of *Lactobacillus spp* on fecal characteristics have been demonstrated in several studies, including decreased pH and ammonia (*L fermentum*)[23,25,28] and increased pH with decreased ammonia (synbiotic *L acidophilus* combination). [34] No impact on pH or ammonia was noted in other study settings, demonstrating variable individual response to the same probiotic species in different formulations (*L. fermentum* with 1% chlorophyllin; *L. acidophilus; L. animalis*).[23,26,31] Alterations in fecal short-chain fatty acid (SCFA) and total branched chain fatty acids (BCFA) concentrations during probiotic administration have been described, suggesting an effect on colonic health and systemic inflammation.[23,25,34-37]A trend toward lower fecal output and improved fecal scores was demonstrated with a synbiotic combination of *L acidophilus* and the prebiotic fructooligosaccharides (FOS) and higher digestibility with *L. acidophilus* alone.[31,34] Effects on the local immune system have been suggested based on increased fecal IgA (*L. murinus*), but in that study there was no effect on fecal consistency, body weight, or body condition score.[38]

Documented systemic effects of *Lactobacillus spp* include increased serum IgG, neutrophils, monocytes, and red blood cell counts, and reduction in erythrocyte fragility and serum nitric oxide (*L. acidophilus*), as well as increased peripheral blood leukocyte phagocytic activity, hemoglobin concentration, and eosinophils (*L. fermentum*).[23,31]

Bifidobacterium animalis --- Few studies have evaluated supplementation of *B. animalis* in healthy dogs. One study demonstrated transit through the GIT but lack of persistence one week following completion of supplementation.[39] Impact of *B. animalis* on the microbiome has not been clearly defined. Decreased fecal *Clostridium difficile* and *Clostridium* cluster XVIII counts were documented after several weeks of supplementation.[39,40] Changes in *Clostridium perfringens,* total *Clostridia,* or total anaerobe counts have not been demonstrated.[40,41] Fecal coliform count decreased with supplementation, with concurrent increase in LAPB.[40,41] *Erysipelotrichaceae* proportions decreased one week after cessation of supplementation. No significant impact on the principal microorganism populations has been documented.[39]

Demonstrated local and systemic metabolic effects of *B. animalis* supplementation include increased fecal SCFA concentrations and decreased serum triglyceride concentrations.[41]

Bacillus spp --- Passage of *Bacillus* (Paciflor®[d]) through the GIT was documented via fecal bacterial counts, with no persistence 3-6 days after probiotic withdrawal.[16,42] Fecal total protein, lipid, dry matter, and metabolizable energy were not affected during 21-39 days of supplementation.[16,42]

Combination Probiotics --- Administration of a commercial combination of *E. faecium* (piglet isolate) and *Bacillus amyloliquefaciens* (soil isolate) reduced fecal *Clostridia* counts. Dogs had lower variation in fecal *E. coli* and *Enterobacteria* counts during administration.[16] Increased serum γ-globulin and β-2 globulin, with significant increase in α-2 globulin, were observed with administration of a probiotic combination (*Lactobacillus, Bifidobacterium Enterococcus*).The authors suggested these findings as a mechanism to decrease systemic inflammation.[43]

Passage, but not persistence, of *B. bifidum* and *Lactobacilli* through the GIT was documented during administration of the synbiotic Proviable ®[e] (*E. Faecium, B. bifidum, E. thermophiles, L. bulgaricus, L. casei, L. plantarum,* with FOS and arabinogalactans).[44] During administration of Proviable® fecal counts of *Enterococcus* and *Streptococcus* spp and proportions of family Eubacteriaceae (Firmicutes) and phylum Fusobacterium increased.[44] No impact was noted on local or systemic parameters (cobalamin, folate, serum or fecal IgA, trypsin-like immunoreactivity (TLI), pancreatic lipase immunoreactivity (PLI), or alpha proteinase).[44]

A similar synbiotic combination (Florentero®[f]; *E. faecium, Bacillus coagulans, L acidophilus,* FOS, mannanoligosaccharides) decreased fecal *Eubacteriaceae, Clostridia,* and *Erysipelotrichaceae* counts, and increased fecal *Lactobacillus* and *Bifidobacteria*. Dogs treated with this synbiotic had decreased fecal microbiota biodiversity with no change in fecal SCFA composition but fecal scores improved and they experienced fewer days of exercise-induced diarrhea.[45]

Evidence of efficacy in healthy cats

Table 3 summarizes in-vivo studies on probiotics in healthy cats.

Lactobacillus --- *Lactobacillus spp* administration in healthy cats decreased fecal counts of *Clostridia* and *Bifidobacteria* during treatment. Fecal *Coliform* and *Enterococcus* counts continued to decrease two weeks after cessation of treatment.[46] Treatment was associated with decreased fecal pH and decreased plasma lipopolysaccharide, suggesting improved GIT barrier function or decreased intraluminal endotoxin.[46]

Bifidobacterium --- Synbiotic *B. pseudocatenulatum* (cat isolate) and galactooligosaccharides administration resulted in effective transit and potential colonization of

Bifidobacterium. No change in other fecal microbial populations (*C. perfringens, Coliforms, Enterococcus)* was observed, but fecal ammonia decreased and fecal acetic acid increased.[47]

Combination products --- Proviable® administration resulted in successful passage of at least one probiotic strain in 73% cats, but persistence was not documented.[44] Proviable® increased fecal *Enterococcus* and *Streptococcus* counts; both decreased below baseline concentration after cessation of treatment. Fecal microbiota diversity decreased during Proviable® treatment, but there was no impact on relative proportions of the major phyla. *Lactobacillus* (Firmicutes) was increased during treatment, and the genus Collinsella (Actinobacteria) was significantly decreased during and after treatment. No impact was noted on fecal or serum parameters (cobalamin, folate, IgA, Trypsin-like immunoreactivity, pancreatic lipase immunreactivty, or alpha proteinase).[44]

Evidence of efficacy in dogs and cats with gastrointestinal illness

Table 4 summarizes the studies on probiotics in dogs and cats with gastrointestinal illness.

Acute enteropathy --- Dogs with exercise-induced stress diarrhea had faster clinical improvement, fewer diarrhea episodes, and resolution of clinical signs by 5 days with Fortiflora® supplementation; diarrhea did not resolve in control dogs.[g] In a shelter setting, treatment with Fortiflora® resulted in a lower percentage of cats experiencing diarrhea longer than 2 days but no such difference was observed in dogs. [48] Shelter dogs with diarrhea treated with Fortiflora® in combination with metronidazole had a more rapid improvement in fecal scores compared to untreated controls (2.8 vs 4.4 days, respectively), but fecal score at study completion was not different.[h] Some studies on the efficacy of Fortiflora® have not been published in a peer-review format, precluding full evaluation.

Treatment with *B. animalis* (canine isolate AHC7) prior to and during kenneling resulted in a dose-dependent reduction of episodes of stress-induced diarrhea, improvement of fecal scores, and increase in fecal *Bifidobacteria*. Fecal *Clostridium perfringens* counts were unchanged. [49] Administration of the same *B. animalis* isolate but at a higher dose (Prostora®[i]) resulted in a shorter duration of clinical signs in dogs suffering from acute idiopathic diarrhea when compared to placebo-treated dogs (3.9 vs 6.6 days).[50]

ZooLac ProPaste®[j], a combination of *L farciminis* (porcine isolate), *Pediococcus acidiliactici, Bacillus subtilis* (soil isolate), *Bacillus licheniformis* (soil isolate), and *L. acidophilus* (human isolate), has been studied in dogs with acute diarrhea of various etiologies. Compared to placebo, ZooLac ProPaste® administration 3 times daily at double the recommended dose, resulted in a tendency toward shorter duration of acute diarrhea (1.3 vs 2.2 days) with no impact on vomiting duration or combined clinical signs.[51]

In an experimental model of antibiotic-induced diarrhea, treatment with the yeast *Saccharomyces boulardii* after diarrhea onset was associated with shorter duration of clinical signs (2.9 vs 6.5 days, in treated vs untreated dogs, respectively) and faster normalization of fecal SCFA concentrations. Dogs that received the probiotic concurrently with antibiotics never developed diarrhea and had no change in fecal SCFA concentrations.[52]

Chronic enteropathy --- Evidence for efficacy of probiotics in dogs with chronic *Giardia* infection is limited. Shelter dogs with *Giardia* that were treated with Fortiflora®, in combination with metronidazole, had normal fecal consistency by study completion in comparison to 43% *Giardia*-positive dogs treated with only metronidazole[h]. Severity of clinical signs related to *Giardia* infection versus comorbidities was unknown, and the number of dogs with *Giardia* was small. Another study noted lack of clinical response or improvement in fecal shedding or

immune indicators in dogs with chronic *Giardia* infection and *E. faecium* SF68 supplementation.[53]

In dogs diagnosed with food-responsive enteropathy, probiotic supplementation (*L.acidophilus*, *L. johnsonii* combination; [Synbiotic D-C®[k]] *E. faecium*, FOS, Gum Arabic) and placebo resulted in similar improvement in clinical signs.[54,55] In contrast, dogs with idiopathic inflammatory bowel disease had less severe clinical signs and earlier clinical remission when treated with a probiotic (VSL#3[l]; *Lactobacillus, Bifidobacteria, and Streptococcus*) compared to dogs treated with metronidazole and prednisone (4.8 vs 10.6 days). [56] Treatment of dogs with chronically poor fecal scores with *L. acidophilus* reduced frequency of defecation and improved fecal consistency during supplementation and 4 weeks after cessation of treatment. Fecal dry matter was only increased during treatment. [57]

Supplementation with a combination of *L. acidophilus* and *L. johnsonii* (canine-isolates) or with Synbiotic D-C® had no effect compared to placebo on systemic inflammatory markers or local immune response, measured by cytokine expression on histology samples, in dogs with FRE.[5458] In dogs with inflammatory bowel disease, treatment with the probiotic VSL#3 had comparable effect to combination therapy of metronidazole and prednisone in terms of increased TGF-β, decreased CD3+ lymphocytes, and decreased overall inflammatory scores in intestinal biopsies.[56]

In cats with undefined chronic diarrhea, stool firmness increased in 72% of cats treated with Proviable®. However, this was an uncontrolled study in which cats received other treatments and response to treatment was subjectively evaluated by owners. [59] In a controlled study, cats with undefined chronic diarrhea experienced decreased frequency of severe diarrhea when fed an *E. faecium* SF68 probiotic.[60]

Evidence of efficacy in puppies and kittens

Table 5 summarizes studies on probiotics in puppies and kittens.

The impact of probiotic administration on the gastrointestinal microbiota, health and immunity, as well as clinical signs, in puppies and kittens has been evaluated in a small number of studies. A non-peer reviewed study demonstrated increased fecal *Bifidobacteria* and *Lactobacillus spp*, typically considered beneficial GIT bacteria, in puppies fed Fortiflora®. However, there was no difference between treated and untreated puppies in fecal *E. coli*, *Campylobacter*, or *Salmonella*[m]. *E. faecium* was inconsistently detected in the feces of kittens while treated with Fortiflora®, and none was detected one week after cessation of treatment. There was no difference in fecal quality or detection of fecal *Clostridium* enterotoxin among the kittens treated with probiotics compared to untreated kittens. [61] Healthy puppies treated with *Bacillus subtilis* had improved fecal scores and higher dry matter content, as well as lower ammonia levels, compared to untreated puppies. No difference in fecal output was noted however, and fecal scores were ideal in both groups. [62] Fermactiv®[n] (*E. faecium*) had positive effects in healthy puppies treated from 2-5 days of age; it was associated with improved nutrient digestibility in large breed puppies and improved daily weight gain in small breed puppies.[63] In contrast, Fortiflora® had no effect on weight gain in kittens.[61] Puppies and kittens treated with Fortiflora® from 8 – 52 and 7- 27 weeks of age, respectively, demonstrated enhanced immune responses to vaccination.[61,64]

In puppies treated for parvovirus enteritis with standard supportive care, adjunctive treatment with the probiotic VSL#3 was associated with reduced clinical signs, increased lymphocyte counts, and improved survival when compared to controls. It is unclear, however, if

disease severity was comparable at baseline, and it is possible that the difference in outcome was the result of selection bias and not treatment.[65]

During an acute diarrhea outbreak in kittens, a smaller percentage of kittens treated with *E. faecium* SF68 required other medical interventions in comparison to untreated kittens (9.5 vs 60%, respectively). Kittens receiving the probiotic experienced faster resolution of clinical signs (18 vs 45 days), increased fecal *Bifidobacteria,* decreased fecal *C. perfringens,* and increased serum IgA.[66]

Evidence of efficacy in dogs and cats with non-gastrointestinal illness

Probiotics have been evaluated in several non-gastrointestinal illnesses because of their potential effects on the immune system and systemic inflammation.[67-77] Table 6 summarizes studies on probiotics in dogs and cats with non-gastrointestinal illness.

Atopic Dermatitis --- Dogs sensitized to *Dermatophagoides farinae* had reduced reaction to intradermal skin testing and lower IgE titers when treated with a commercial *L. rhamnosus* probiotic (Culturelle HS®[o]). Clinical signs following allergen exposure were unchanged and skin biopsy showed no difference in filaggrin expression (a protein decreased in atopic dermatitis). At 3-4 years of age, treated dogs had reduced clinical signs following allergen exposure. [78-80]

Genitourinary --- Oral administration of a commercial synbiotic (Y+ Powder[p]; *Lactobacillus, Bifidobacterium, Bacillus,* yeast, enzymes, prebiotics) did not increase vaginal populations of LAPB in dogs.[81]

In contrast to the manufacturer's claim, administration of the synbiotic Azodyl®[q] (*Streptococcus thermophiles, L. acidophilus, Bifidobacterium longum*) had no effect on azotemia in cats with stable chronic kidney disease (CKD), in a double-blinded, controlled, randomized clinical trial.[82] However, the probiotic was not administered as an enteric-coated capsule as labeled, but the capsules were opened and contents sprinkled on the food. In an earlier study, an improvement in azotemia was observed in cats with CKD treated with Azodyl®. However, that study had multiple methodological flaws; it was an uncontrolled, non-blinded study in which the diagnosis of CKD was based on palpation of small kidneys in cats with persistent azotemia, with no documentation of urine specific gravity and no control for hydration status.[83] Also, cats recruited to that study were treated with a variety of diets and other concurrent medications.

Respiratory disease ---Treatment with Fortiflora® in cats chronically infected with herpes virus (FHV) had no significant impact on FHV-1 expression or viral shedding. However, cats experienced fewer episodes of conjunctivitis when treated with the probiotic compared to placebo.[84]

Clinical Summary

A clear role for treatment of dogs and cats with probiotics is undetermined based on current literature. Evidence in healthy dogs and cats, as well as animals with gastrointestinal and non-gastrointestinal illness, suggests an impact of probiotics on the gastrointestinal microbial population, metabolic status, and immune system, as well as systemic effects. Evidence in dogs is stronger than cats, with few controlled studies in cats. While some studies showed no effect of probiotics, the number of individual animals in most studies was small, and it is possible that differences were undetected due to low statistical power. Direct comparison of standardized formulations and duration of effect within a micro-organism species is needed. Furthermore, most studies do not speciate micro-organisms, limiting conclusions about the impact on pathogenic versus non-pathogenic species (e.g. pathogenic vs. commensal *Clostridia*). Whether a

specific product has the same impact in patients with an unstable intestinal microbiome as it does in healthy individuals is unknown. Therefore, the ability to extrapolate from healthy animals to patients with gastrointestinal illness in uncontrolled environments is questionable. Probiotic supplementation may play a larger role in patients with acute gastrointestinal disease, including stress-induced diarrhea, especially in shortening the time period to resolution of clinical signs when compared to standard therapies. Studies in dogs suffering from chronic enteropathies are more difficult to interpret because they are typically confounded by concurrent therapies. Overall, no significant side-effects were noted following probiotic administration in either cats or dogs, suggesting relative safety over a short period of time within the microbial populations studied. Longer term outcomes and administration periods still require evaluation.

Footnotes

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i. lams Prostora, Procter & Gamble Pet Care, USA
j. ZooLac Propaste, Chem Vet A/S, Denmark
k. Synbiotic D-C, Protexin Ltd, Somerset,UK
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n. Fermactiv, C. Richter Gesmbh Co, KG, Austria
o. Culturelle HS, Amerifit Brands/Culturelle, Cromwell, CT
p. Y+ Powder, Rayne Clinical Nutrition, Kansas City, MO
q. Azodyl, Vetoquinol, USA

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Tables

Study reference	Bacteria spp.	Study population	Sample type	Effect
Kainulainen et al (2015)	*Lactobacillus acidophilus*	Research dogs	Canine mucus	Adherence to canine mucus and intestinal epithelial cells; decreased LPS-stimulated IL-8 production; increased transepithelial electric resistance
Grzeskowiak et al (2014)	*Lactobacillus fermentum, L. plantarum, L. rhamnosus*	Research dogs	Canine mucous	Inhibition, displacement, and exclusion of *Enterococcus canis, Salmonella enterica typhimurium, Clostridium perfringens*
Schmitz et al (2013)	*Enterococcus faecium*	Research dogs (N= 4)	Blood	Increased TNF-α; no difference between flagellin stimulated samples
Ogue-Bon et al (2010)	*Bifidobacterium bifidum*	N= 3	Fecal	Growth and products of probiotic impacted by synbiotic type; Increased SCFA; Increased lactic acid; Decreased *Clostridia spp*
Perelmuter et al (2008)	*Lactobacillus murinus*	N= 1	Bacterial culture; canine mucous	Decreased growth with bile salts; growth at pH 2.5; Inhibition of *Clostridia* growth; Adhesion to glass and canine mucous
Biagi et al (2007)	*Lactobacillus acidophilus*	Research dogs (N= 2)	Fecal	Increased LAPB counts; Decreased *Enterococcus, Clostridium perfringens;* Decreased ammonia; Increased lactic acid
Laukova et al (2004)	*Enterococcus spp*	Research dogs	Jejunal chyme (canine); Mucus (human; porcine)	Correlation of adhesion among species; no host effect
Rinkinen et al (2003)	*Lactobacillus rhamnosus, Bifidobacterium lactis, Lactobacillus pentosus, Enterococcus faecium*	Research dogs (N= 6)	Various spp. mucous	Inhibition of *Clostridium perfringens;* Enhancement of *Campylobacter jejuni* growth by *Enterococci*; coaggregation of *L. rhamnosus, B. lactis, C. jejuni*
Rinkinen et al (2003)	*Lactobacillus rhamnosus, L. johnsonii, L. casei, Bifidobacterium lactis, Enterococcus faecium, L. bulgaris, L. pentosus*	Research dogs (N= 6)	Jejunal chyme	*L. rhamnosus* adhered best to mucous of all species; no species specificity
Rinkinen et al (2000)	*Lactobacillus spp, Bifidobacterium lactis, Enterococcus faecium*	Research dogs (N= 6)	Jejunal chyme	*L. rhamnosus* displayed best adhesion; adhesion reduced in all following treatment with chyme

Table 1. Probiotic bacteria, sample type, study population, and effect in studies of healthy dogs (in vitro).

Study reference	Bacteria spp.	Study population	Duration fed	Sample type	Effect
Strompfova et al (2015)	*Lactobacillus fermentum*	Research dogs (N= 40)	14 days	Blood; Fecal	Decreased fecal pH; increased fecal LAPB; decreased fecal Clostridium-like spp, Staphylococci; increased fecal SCFA concentrations; increased blood total leukocyte phagocytic activity, hemoglobin, eosinophil count
Strompfova et al (2014)	*Bifidobacterium animalis*	Research dogs (N= 20)	14 days	Blood; Fecal	Increased fecal LAPB during feeding; lower gram negative (Coliform) counts; increased fecal SCFA concentrations; Decreased serum albumin, triglycerides, increased alanine aminotransferase, alkaline phosphatase at various time-points
Tang et al (2014)	*Lactobacillus acidophilus*	Privately owned (N= 5)	3 days	Fecal	LAPB detected in fecal samples during feeding
Torkan et al (2014)	*Lactobacillus, Bifidobacterium, Enterococcus*	Research Persian shepherds (N= 10)	19 days	Blood	Decreased serum α2-globulin; increased β2-globulin; increased γ-globulin
Delucchi et al (2014)	*Lactobacillus murinus*	Privately owned (N= 13)	14 days	Fecal	Increased IgA
Gagne et al (2013)	*Enterococcus faecium, Bacillus coagulans, Lactobacillus acidophilus* synbiotic	Privately owned sled dogs (N= 20)	6 weeks	Fecal	Fewer days of diarrhea; Increased *Lactobacillus* counts; Decreased *Clostridia*, *Erysipelotrichaceae*, *Eubacteria*; Decreased microbiota diversity; no change SCFA
Gonzalez-Ortiz et al (2013)	*Bacillus amyloliquefaciens ; Enterococcus faecium*	Research dogs (N= 16)	39 days	Fecal	*Bacillus* detected during feeding; *Entercoccus* counts increased during and after feeding; Decreased *Clostridia* counts
Tang et al (2013)	*Lactobacillus acidophilus*	Privately owned (N= 1)	5 days	Fecal	LAPB detected in fecal samples during feeding and after 6 weeks
Kelley et al (2012)	*Bifidobacterium animalis*	Privately owned (N= 121)	8 weeks	Fecal	Higher fecal scores; dose related increase in fecal *Bifidobacterium*; dose related decrease in number of unacceptable stools
Strompfova et al (2012)	*Lactobacillus fermentum*	Research dogs (N= 12)	14 days	Fecal	LAPB counts increased during and after feeding; Decreased *Clostridia, Aeromonas, E. coli, Pseudomonas*; Decreased fecal pH; Increased SCFA
Strompfova et al (2012)	*Lactobacillus fermentum*	Research dogs (N= 32)	14 days	Blood; Fecal	Blood glucose increased during feeding; Increased LAPB fecal counts; Decreased fecal *Clostridia* counts; decreased fecal pH
O-Mahony et al (2009)	*Bifidobacterium animalis*	Research dogs (N= 11)	6 weeks	Fecal	Decreased Clostridia counts at weeks 5 & 6; total anaerobes not affected
Biagi et al (2007)	*Lactobacillus animalis*	Privately owned (N= 16)	10 days	Fecal	Increased LAPB fecal count
Manninen et al (2006)	*Lactobacillus fermentum, L. salivarus, L. rhamnosus, L.*	Research dogs (N= 5)	7 days	Jejunal chyme	LAPB viable in jejunal chyme; persistence of all strains except *L. fermentum* & *L. mucosae*; decreased microbiota diversity during feeding

	mucosae, W. confuse				
Marcinakova et al (2006)	*Enterococcus faecium*	Research dogs (N= 11)	7 days	Blood; Fecal	Decreased serum lipids, total protein; normalization serum cholesterol; fecal LAPB increased during feeding; Decreased *Pseudomas-like* spp after 7 days
Strompfova et al (2006)	*Lactobacillus fermentum*	Research dogs (N= 15)	7 days	Blood; Fecal	Decreased blood glucose; increased serum total protein; LAPB detected in fecal samples during administration and after 6 months
Baillon et al (2004)	*Lactobacillus acidophilus*	Research dogs (N= 15)	4 weeks	Blood; Fecal	Increased peripheral red blood cell count, hematocrit, neutrophil count during feeding; Serum IgG increased at end of feeding; Decreased red blood cell fragility and serum nitric oxide; fecal LAPB detected during feeding but no persistence; decreased fecal Clostridia counts
Vahjen et al (2003)	*Enterococcus faecium*	Privately owned (N= 12)	18 days	Fecal	Variable impact on *Salmonella, Campylobacter, Clostridia* counts
Swanson et al (2002)	*Lactobacillus acidophilus*	Research dogs (N= 40)	28 days	Fecal	Changes in SCFA concentrations, fecal dry matter, digestibility, fecal microorganisms counts; lower fecal ammonia
Weese et al (2002)	*Lactobacillus rhamnosus*	Research dogs (N= 32)	5 days	Fecal	LAPB detected in feces at levels higher than administered
Biourge et al (1998)	*Bacillus spp*	Research dogs (N= 5)	7 days	Fecal	*Bacillus* detected in feces during feeding; increased digestibility
Kanasugi et al (1997)	*Enterococcus faecium*	Research dogs (N= 5 study; 10 control)	1 day	Blood	Increased neutrophil phagocytosis, lymphocyte blast transformation activity

Table 2. Probiotic bacteria, sample type, study population, and effect in studies of healthy dogs.

Study reference	**Bacteria spp.**	**Study population**	**Duration fed**	**Sample type**	**Effect**
Biagi et al (2013)	*Bifidobacterium pseudocatenulatum*	Privately owned (N= 10)	15 days	Fecal	Increased fecal *Bifidobacteria* counts; Increased fecal acetic acid; Decreased fecal ammonia; No impact on *Clostridium perfringens,* Coliforms, *Enterococci*
Garcia-Mazcorro et al (2011)	*Lactobacillus acidophilus, L. casei, L. plantarum, L. bulgaricus, Streptoccocus salivarus, Enterococcus faecium*	Privately owned (N= 12)	21 days	Blood; Fecal	Detection of probiotic spp in fecal samples; Decreased diversity index; No change in serum cobalamin, folate, IgA, trypsin-like immunoreactivity, pancreatic lipase immunoreactivity or fecal IgA, alpha-proteinase
Marshall-Jones et al (2006)	*Lactobacillus acidophilus*	Research cats (N= 15)	4.5 weeks	Blood; Fecal	Decreased fecal *Clostridia,* Coliforms, *Enterococcus, Bifidobacteria;* Decreased red blood cell hemolysis;

						Decreased plasma endotoxin during feeding

Table 3. Probiotic bacteria, sample type, study population, and effect in studies of healthy cats.

Study reference	Bacteria spp.	Study population	Diagnosis	Duration fed	Sample type	Effect
Schmitz et al (2015)	*Enterococcus faecium*	Privately owned dogs (N= 7)	Food responsive enteropathy	6 weeks	Biopsy (intestinal)	Decrease in clinical disease index with no difference from placebo; no difference in cytokine expression from placebo
Rossi et al (2014)	*Lactobacillus, Bifidobacteria, Streptococcus*	Privately owned dogs (N= 30)	Inflammatory bowel disease	60 days	Biopsy (intestinal)	Improved histopathology scores with no difference between steroid control; Improved clinical scores with longer time to improvement than steroid control; Increased TGF-β; Decreased CD3+ T-cells
Arslan et al (2012)	*Lactobacillus, Bifidobacteria, Streptococcus*	Privately owned dogs (N= 20)	Parvovirus	1-3 weeks	Blood	Increased lymphocytes; Improved mortality rate
Hart et al (2012)	*Lactobacillus acidophilus, L. casei, L. plantarum, L. bulgaricus, Streptoccocus salivarus, Enterococcus faecium*	Privately owned cats (N= 53)	Chronic diarrhea	21 days	Fecal	Improved fecal score; Owner perceived clinical improvement in 72%, no change in 24%, worsening in 4%
Bybee et al (2011)	*Enterococcus*	Shelter dogs (N= 182), cats (N= 217)	Undefined diarrhea	4 weeks total (variable per animal)	Fecal	Lower percentage of cats affected with diarrhea lasting > 2 days; No difference in dogs
Herstad et al (2010)	*Lactobacillus farciminis, L. acidophilus Pediococcus acidiliactici, Bacillus subtilis, B.licheniformis*	Privately owned dogs (N= 36)	Acute diarrhea and vomiting	Until stool normalization	Fecal	Shorter duration to fecal quality normalization; no difference in vomiting
Kelley et al (2009)	*Bifidobacterium*	Privately owned dogs (N= 31)	Acute diarrhea	Until resolution of clinical signs; maximum 2 weeks	Clinical signs	Reduction in number of days with diarrhea
Simpson et al (2009)	*Enterococcus faecium*	Research dogs (N= 20)	Chronic *Giardia*	7 weeks	Fecal	No difference in *Giardia* shedding, IgA upregulation, or leukocyte phagocytosis
Pascher et al (2008)	*Lactobacillus acidophilus*	Research German Shorthair	Chronic diarrhea	12 weeks	Fecal	Reduced occurrence of poor fecal consistency or increased defecation rate; Increased fecal dry matter during feeding

		Pointers (N= 6)				
Aktas et al (2007)	*Saccharomyces boulardii*	Research dogs (N= 25)	Antibiotic induced diarrhea	10 days	Fecal	No diarrhea in dogs concurrently administered probiotic; shorter duration diarrhea in treated dogs; Normalization of fecal SCFA concentrations
Sauter et al (2006)	*Lactobacillus acidophilus; L. johnsonii*	Privately owned dogs (N= 21)	Food responsive enteropathy	4 weeks	Biopsy; Fecal	Decreased clinical disease index and increased folate, no difference from control; Trend toward higher fecal LAPB counts; Decreased fecal *Enterobacteria* with no difference between groups
Strompfova et al (2004)	*Lactobacillus*	Privately owned dogs (N= 6)	Chronic enteritis (3), HGE (1), Allergic intestinal disease (1), coprophagia (1)	7 days	Blood	Normalization of serum cholesterol, alanine aminotransferase

Table 4. Probiotic bacteria, sample type, study population, diagnosis, and effect in studies of cats and dogs with gastrointestinal illness.

Study reference	**Bacteria spp.**	**Study population**	**Diagnosis**	**Duration fed**	**Sample type**	**Effect**
Czarnecki-Maulden et al (unpublished)	*Enterococcus faecium*	Research dogs (N= 40)	Healthy puppies	1 year	Fecal	Increased *Bifidobacteria, Lactobacillus;* No difference in *E.coli, Campylobacter, Salmonella*
Gabinaitis et al (2013)	*Enterococcus faecium*	Research dogs (N= 12)	Healthy puppies	3 days	Blood; Fecal	Decreased blood glucose, cholesterol; Increased daily weight gain in small breed dogs; increased nutrient digestibility large breed dogs
Arslan et al (2012)	*Lactobacillus acidophilus, L. casei, L. plantarum, L. bulgaricus, Streptoccocus thermophilus, Bifidobacterium breve, B. longum, B.infantis*	Privately owned (N= 20)	Parvovirus enteritis (puppies)	1- 3 weeks	Blood	Earlier improvement in clinical score; Increased white blood cell counts (neutrophils, lymphocytes); Improved survival rate
Felix et al (2010)	*Bacillus subtilis*	Research dogs (N= 12)	Healthy puppies	25 days	Fecal	Improved fecal score; increased dry matter; decreased ammonia; No difference fecal output
Czarnecki-Maulden et al (2007)	*Enterococcus faecium*	Research cats (N= 31)	Acute diarrhea (kittens)	1 year	Blood; Fecal	Decreased percentage of cats requiring medical treatment; Faster resolution clinical signs; Increased peripheral blood IgA;

						Increased fecal *Bifidobacteria*; decreased fecal *Clostridium perfringens*
Veir et al (2007)	*Enterococcus faecium*	Research cats (N= 18)	Healthy pathogen-free kittens	20 weeks	Blood; Fecal	Increased serum post-vaccinal IgA; increased peripheral blood CD4 lymphocytes; No difference in fecal score or body weight; No difference fecal *Clostridium* enterotoxin
Benyacoub et al (2003)	*Enterococcus faecium*	Research dogs (N= 14)	Healthy puppies	44 weeks	Blood; Fecal	Increased plasma post-vaccinal IgA, IgG; Increased peripheral mature B lymphocyte population; Trend toward increased fecal IgA

Table 5. Probiotic bacteria, sample type, study population, diagnosis, and effect in studies of puppies and kittens.

Study reference	**Bacteria spp.**	**Study population**	**Diagnosis**	**Duration fed**	**Sample type**	**Effect**
Hutchins et al (2013)	*Lactobacillus, Bifidobacterium, Bacillus*	Privately owned dogs (N= 35)	Healthy dogs	2-4 weeks	Vaginal	No change vaginal LAPB populations
Marsella et al (2013)	*Lactobacillus rhamnosus*	Research dogs (N= 18)	Atopic dermatitis	5 months; study 1-2 years after discontinuation	Skin	No difference clinical scores; no difference dermal filaggrin expression
Marsella et al (2012)	*Lactobacillus rhamnosus*	Research dogs (N= 16)	Atopic dermatitis	5 months; study 3 years after discontinuation	Blood; skin	Reduced clinical signs to allergen exposure; Decreased peripheral blood IL-10; No difference in IgE, TGF-beta
Rishniw et al (2011)	*Lactobacillus acidophilus, Bifidobacterium longum, Streptococcus thermophiles*	Privately owned cats (N= 10)	Chronic kidney disease	2 months	Blood	No difference in blood urea nitrogen or creatinine
Lappin et al (2009)	*Enterococcus faecium*	Research cats (N= 12)	Feline herpes virus-1	140 days	Blood; oral cavity; fecal	Fewer episodes of conjunctivitis; no difference in FHV-1 expression or viral shedding; stable fecal microbiome
Marsella et al (2009)	*Lactobacillus rhamnosus*	Research dogs (N= 16)	Atopic dermatitis	5 months	Blood; skin	No difference in severity of clinical signs; Lower serum IgE titer; milder intradermal skin reaction
Palmquist (2006)	*Lactobacillus acidophilus, Bifidobacterium longum, Streptococcus thermophiles*	Privately owned cats (N= 7)	Chronic kidney disease	3 months	Blood	Decreased blood urea nitrogen, creatinine

Table 6. Probiotic bacteria, sample type, study population, diagnosis, and effect in studies of non-gastrointestinal illness.