

Literature Review – Probiotics

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INTRODUCTION

Probiotics, as defined by the Food and Agriculture Organization of the United Nations (FAO) and World Health Organization (WHO) in 2006,¹ comprise live microorganisms which, when administered in adequate amounts, confer a health benefit on the host. In human medicine, much research has been performed, and the list of documented health benefits is growing, ranging from amelioration of irritable bowel symptoms in children to improvement of oral health or prevention of recurrent urinary tract infections in adults.² It is not a large leap, therefore, to hypothesize that supplementation of a pet's diet with probiotics could help prevent or treat certain diseases. This thinking has sparked development of a myriad of products marketed for use in companion animals, including specially formulated supplements and diets. Such products have now found their way into veterinary practice.³

Most commercially available probiotic products sold for use in companion animals contain *Lactobacillus* spp. or *Bifidobacterium* spp.⁴⁻⁷ Certain species of enterococci are also commonly used. Each product may be advertised as containing one to several bacterial species. When selecting probiotics for potential use, it is important to consider that not all bacteria with probiotic potential behave the same. Different species of the same bacterial genus may act similarly in laboratory conditions; however, their *in vivo* effects may be dissimilar. For example, *Lactobacillus johnsonii* and *Lactobacillus paracasei*

CLINICAL BOTTOM LINE

- Probiotics are believed to aid in the treatment or prevention of disease by modifying the balance of gastrointestinal (GI) microflora or modulating the host's immune response.
- Although clinical beneficial effects of probiotics have been well-documented in human medicine, they have not yet been convincingly demonstrated in dogs and cats.
- Few studies have examined the effects of probiotics in cats. In dogs, particular strains of *Bifidobacterium animalis* and *Lactobacillus acidophilus* show promise in the treatment of specific GI ailments. Future research into these and other probiotics may yield more robust evidence of health benefits.
- Manufacturing standards and minimum effective dosages have not yet been established for veterinary probiotics and are needed before they can be recommended for pets.
- Diets should not be selected on the basis of probiotic claims; poor control of microbial content and lack of established clinical effects render such diets of questionable benefit.
- In some situations, probiotics may be harmful to both pets and their owners.
- Veterinarians should approach probiotic use the same as they would any new drug use.

have certain similar growth, acid-resistance and cell adhesion properties when evaluated *in vitro*. On the other hand, after oral administration in mice, there are clear differences between the two species in efficiency of intestinal mucosa colonization and on antibody production by the mucosal cells.⁸ Further, probiotics that have beneficial effects in certain animal species do not necessarily have the same effects in others. An example of this is *Enterococcus faecium* strain SF68, the oral administration of which decreases fecal shedding of cysts and improves the immune response to giardiasis in rats,⁹ but not in dogs.¹⁰

Several mechanisms of action have been proposed to explain how probiotic organisms may act within a host to yield beneficial effects. These can be grouped into two categories: suppression of certain gastrointestinal (GI) microflora, and immunomodulation of the host. Possible mechanisms of floral suppression include release of antimicrobial compounds, competition for nutrients, or competition for adhesion sites in the intestines.¹¹⁻¹³ Suggested mechanisms of immunomodulation include an increase in antibody¹⁴ or cytokine¹⁵ production, modulation of phagocytosis and stimulation of nonspecific immunity.

In human applications, probiotics may be regulated by the U.S. Food and Drug Administration (FDA) as dietary supplements, foods or drugs, depending on the product's intended use.¹⁶ In veterinary applications, the category or categories into which probiotic products fall is less clear, and regulations appear less stringent than those for drugs. Certain guidelines do exist, however, for the evaluation of probiotics for food use in humans,¹ and these guidelines may be adapted to evaluation of probiotics for general use in companion animals (*Figure 1*, page 3).

The purpose of this report is to perform such an evaluation by reviewing the available literature on bacteria used for probiotic purposes to determine

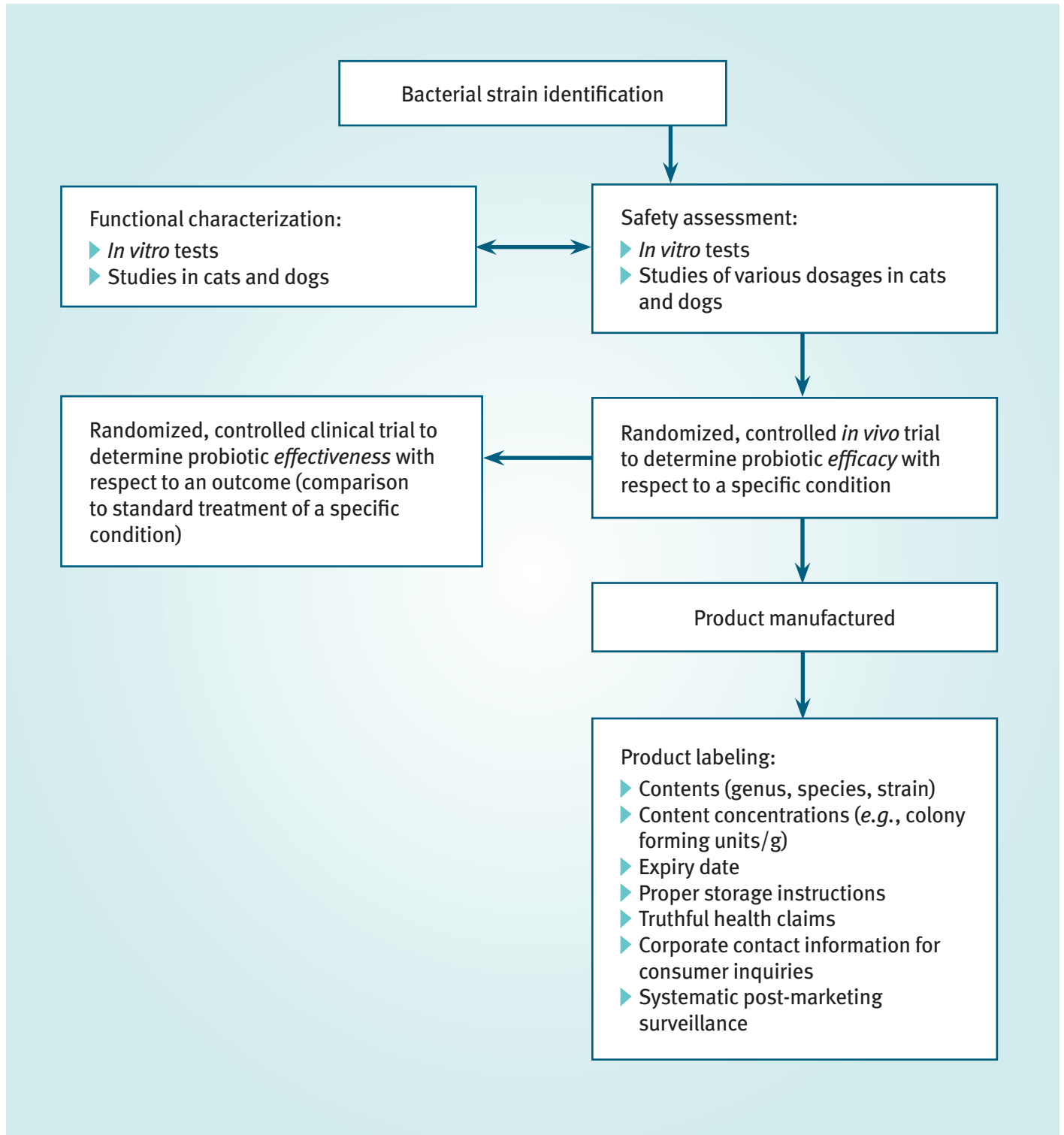
whether sufficient evidence exists as to the effectiveness and safety of these products for use in dogs and cats.

PRODUCT VIABILITY

An essential element of the FAO/WHO definition of probiotics is viability: organisms must be alive in order to exert their effects. The first point at which viability is challenged is at the manufacturing stage. In the United States, commercially available probiotics are produced in various forms including powders, granules, pastes, liquids, capsules and tablets, and the organisms must survive formula preparation. For probiotics incorporated into pet food, the challenge for survival is even greater because of the manufacturing processes. During production, wet pet food is heated once canned, destroying microbes; therefore, most commercial food sold as containing probiotics is of the dry, kibble variety, in which organisms can be added after the heating process.

The first study¹⁷ conducted to assess the feasibility of including probiotics in a commercial dry dog food involved the probiotic *Bacillus* CIP 5832. In that study, the bacterium was incorporated into dog food prior to the expansion-extrusion stage of production that involves heat, with the ultimate goal of assessing whether the probiotic would survive and thus be available to dogs.¹⁷ Researchers found that > 99 percent of viable bacterial spores were lost during manufacturing of kibble containing the organism. When the organisms were applied as a kibble coating, only 60 percent or less of the expected levels of viable spores remained afterward. However, up to 25 percent of the remaining spores survived on the food for a full year. A later study¹⁸ revealed that *L. acidophilus* could be successfully incorporated into dry food during production through a post-extrusion coating process. Storage of the product during the study period (four weeks) did not appear to significantly affect viability.

Figure 1. Suggested Steps for Evaluating Probiotics Intended for Use in Dogs and Cats
(Adapted from FAO/WHO 2006)



Interestingly, canine feeds not marketed as containing probiotic agents have also been found to contain low volumes of potential probiotic enterococci.¹⁹ These bacteria likely originated from fecal contamination of the feed ingredients themselves.

The second point at which viability is challenged is during passage through the GI tract. The microbial population in the healthy mammalian GI tract is believed to provide an important barrier to adhesion, colonization and infection by exogenous pathogens.²⁰ For a probiotic to be successful, it must not only survive exposure to gastric acid and bile after ingestion but must also be capable of colonizing the GI tract in the presence of the pre-existing microflora.²¹⁻²³

Some evidence exists that certain probiotics do survive GI transit in dogs. In an experiment involving healthy adult Beagles,²⁴ groups of dogs received a range of doses of *Lactobacillus rhamnosus* strain GG (LGG), a bacterium isolated from humans and shown in several studies to be effective in preventing or treating diarrhea of various origins in humans.²⁵ A freeze-dried, commercially available form of LGG was mixed in with canned dog food, which was then fed to the dogs once a day for five days. For up to 11 days after treatment began, fecal samples were collected for isolation of LGG to indicate whether the LGG had survived and possibly colonized the GI tract. Results suggested the LGG was indeed capable of surviving passage, with the highest LGG dose (5×10^{10} colony forming units/day) detected in the feces of all four dogs that received the high dose 24 hours after treatment ceased. Three dogs continued to shed LGG in their feces for 48 hours after treatment ceased, and one dog was still shedding the organism 72 hours after treatment ceased. The authors commented, however, that to achieve a dose this great, one would need to administer 50 capsules of the product used/day, suggesting that other organisms, perhaps of canine origin, would be a superior choice because canine

strains are better adapted to colonizing the canine gut than human strains of bacteria (*i.e.*, strains can be biologically very species-specific).

Another study¹⁷ showed that healthy research dogs consuming *Bacillus* CIP 5832, in supplement form for two weeks and mixed in with kibble for another week, had both the spore and vegetative form of the organism in their feces 24 hours after kibble feeding began and for up to three days after that feeding ceased. Thus, the bacterium appeared to have been able to grow in the GI tract. In a similar study,¹⁸ healthy research dogs fed a dry food manufactured with an *L. acidophilus* coating (applied after heating) for four weeks, had the organism in their feces while the food was being fed but not two weeks afterward. All studies showed that colonization, if achieved, was temporary and depended on continued probiotic consumption. It follows that to maintain colonization, sustained consumption would be necessary. However, no studies have involved evaluation of the effects of long-term probiotic consumption on companion animals. Findings indicative of transient colonization and/or changes in microfloral diversity in healthy dogs have also been reported for *Lactobacillus animalis* LA4,²⁶ *Lactobacillus fermentum* LAB8, *Lactobacillus salivarius* LAB9, *Weissella confuse* LAB10, *L. rhamnosus* LAB11 and *Lactobacillus mucosae* LAB12,²⁷ *Bifidobacterium animalis* AHC7²⁸ and *E. faecium* SF68.¹⁴

Only two feline studies have yielded evidence of probiotic survival in the feline GI system. The first involved *L. acidophilus* DSM13241, which was incorporated into a dry food fed to healthy cats for 4.5 weeks.²⁹ The second involved *E. faecium* SF68, which was fed to specific-pathogen-free kittens in a palatability enhancer (chicken digest) for 27 weeks.³⁰

HEALTH BENEFITS

In the literature on the health benefits of probiotics for cats and dogs, the predominant type of study

involves tightly controlled experimental conditions. This type of study design is optimal for controlling factors such as differences in breeds, ages or management practices that may have an effect on whether a particular probiotic will work as intended; in this setting, effects observed can be attributed to the probiotic more confidently than when a more heterogeneous animal group is evaluated in a clinical trial involving less controllable, real-life conditions. However, the benefit of real-life versus experimental study designs is that investigators can evaluate a probiotic in the animals and circumstances for which the product is intended to be used.

In a 10-month experimental study,¹⁴ 8-week-old puppies of various breeds, raised in a research setting, were fed one of two kibble diets, only one of which was supplemented with a particular commercially available strain of *E. faecium* SF68. All puppies were vaccinated at 9 and 12 weeks of age against canine distemper virus (CDV). Serial testing revealed higher plasma concentrations of CDV-specific IgA and IgG in puppies that received the probiotic than in those that did not, starting 18 weeks after feeding began, suggesting that canine distemper would be more effectively prevented in the probiotic-treated puppies. However, the technique used to determine whether SF68 bacteria were present in the feces of treated dogs was pulsed-field gel electrophoresis, which can only reveal whether the organisms were present and not whether they had survived GI passage, and organisms must be viable to qualify as probiotics. A similar study³⁰ was conducted in pathogen-free 6-week-old kittens that received multivalent vaccines at the same time points as the puppies. Although antibody responses to the vaccines were measured, the only significant ($P = 0.02$) difference between kittens that received the probiotic and those that did not was an increased number of CD4+ lymphocytes at 27 weeks of age, which the investigators presumed was a nonspecific immune response.

The effectiveness of three strains of *Lactobacillus* (*L. acidophilus* NCC2628 and NCC2766 and *L. johnsonii* NCC 2767), referred to as a probiotic cocktail, in modulating cytokine production in dogs with chronic enteropathies was evaluated *ex vivo* by culturing duodenal specimens from affected and control dogs with the organisms.¹⁵ The probiotics induced a decrease in the ratio of pro-inflammatory cytokine expression (TNF- α , IFN- γ and IL-12p40) to regulatory cytokine expression (IL-10) in affected dogs, suggesting this bacterial combination may have promise for treatment of dogs with chronic enteropathies. However, the research group failed to find a similar immunomodulation effect in a subsequent clinical trial involving dogs with food-responsive diarrhea fed an elimination diet and the same probiotic cocktail as before, or a placebo daily for four weeks.³¹ This discrepancy illustrates the importance of following up *in vitro* studies with *in vivo* trials before conclusions are drawn.

Another study¹⁸ found that healthy dogs fed kibble coated with *L. acidophilus* had increased volumes of lactobacilli (considered healthy bacteria) and decreased volumes of clostridia (potentially pathogenic bacteria) in their feces. In addition, the dogs had increases in several hematologic parameters including neutrophil, monocyte and red blood cell (RBC) counts and a decrease in RBC fragility. The clinical importance of these findings was not evaluated, however.

The effects of *L. acidophilus* ingestion have also been evaluated in healthy cats.²⁹ Cats receiving a diet supplemented with strain DSM13241 for a 4.5-week period had a decrease in fecal amounts of *Clostridium* spp. and *E. faecalis* (potential opportunistic pathogens) and an increase in beneficial lactobacilli. Purported immunological effects included a decrease in plasma endotoxin concentrations, increase in peripheral phagocyte activity, decrease in circulating

lymphocyte concentrations and increase in circulating eosinophil concentrations.

One limitation to the aforementioned studies is that although significant effects were demonstrated, the clinical importance of these effects is debatable. For example, it is unknown whether the changes in immune function would lead to increased protection against infectious agents or resolution of clinical signs in diseased animals. Such questions need to be answered before recommendations can be made regarding the probiotics' usefulness in treating or preventing disease.

Clinical trials of probiotic effectiveness in treating existing illness in dogs are few and limited in scope; in cats, they are nonexistent. In a randomized, controlled clinical trial,³² the duration of abnormal fecal production in 36 client-owned dogs with acute gastroenteritis was found to be significantly ($P = 0.04$) shorter in dogs that received a probiotic cocktail containing five species of bacteria (1.3 days; $n = 15$) than in dogs that received a placebo (2.2 days; $n = 21$). However, the duration of vomiting did not differ between groups.

A reduction in the time to resolution of abnormal fecal production was also detected in a study³³ of *B. animalis* AHC7 in dogs with acute idiopathic diarrhea. Diarrhea resolved in 6.6 ± 2.7 days (least squares mean \pm SE) for 18 dogs fed a placebo, versus 3.9 ± 2.3 days for 13 dogs fed the probiotic ($P < 0.01$). In addition, metronidazole treatment was only required in five (38 percent) treated dogs versus nine (50 percent) control dogs. This suggests that this particular probiotic strain may be useful in treating idiopathic diarrhea in dogs.

A small laboratory-based study³⁴ of six German Shorthair Pointers with non-specific dietary sensitivity showed that feeding of a diet coated with *L. acidophilus* DSM13241 improved fecal

quality and defecation frequency; however, there appeared to be no significant effect on concentrations of fecal microflora, including *Clostridium perfringens*, *Escherichia* spp., *Lactobacillus* spp. and *Bifidobacterium* spp.

Another laboratory study³⁵ was conducted to evaluate the effect of *L. rhamnosus* GG on 16 Beagle puppies with induced atopic dermatitis attributable to cutaneous *Dermatophagoidea farinae* (dust mite) sensitization. Puppies that received the probiotic from 3 to 6 weeks of age ($n = 9$) had a significantly ($P < 0.001$) lower serum titer of allergen-specific IgE at 24 weeks of age than those that did not ($n = 7$). It should be noted that probiotic treatment involved five capsules/day, and the investigator remarked that a suitable dose for an adult dog would be three to 25 capsules/day. In addition, although an immunologic effect was detected, there was no difference between treatment groups with respect to clinical signs of dermatitis.

In cats, evidence regarding probiotic efficacy is severely lacking. The one study³⁶ that does exist examined the effects of probiotics on viral respiratory illness and was preliminary in nature. In that study, *E. faecium* SF68 supplementation in 12 cats with latent feline herpesvirus-1 that received no other treatment resulted in a greater diversity of fecal microflora in treated versus untreated cats, and investigators interpreted this as suggesting a more stable microbiome in those treated cats. In addition, improvement in conjunctivitis was noticed in some treated cats.

All of the aforementioned trials involved small sample sizes, and some involved specific animal breeds. Therefore, although the information provided is valuable in elucidating the clinical effects of the probiotics evaluated, the generalizability of these findings to other dogs and cats is limited.

SAFETY

The bulk of the available literature, albeit limited, suggests that many commercially available probiotic organisms are safe for administration to healthy cats and dogs (Table 1, pages 8). In studies in which probiotic effects in diseased animals were determined, safety was either not evaluated or not reported. Despite the lack of reports of adverse probiotic clinical effects, there is evidence that certain bacteria used as probiotics are potentially harmful. In an *in vitro* study,³⁷ investigators sought to determine the ability of specific lactobacilli and enterococci to inhibit pathogen colonization of the mucosa of the canine jejunum. They found that two strains of *E. faecium* (M74 and SF273) actually increased mucosal adhesion of *Campylobacter jejuni* relative to adhesion in untreated control mucosa. This finding has implications not only for canine health but also for human health, as *C. jejuni* is zoonotic.

Antimicrobial resistance in probiotic organisms is another factor that should be considered when evaluating safety. Resistance is of concern not only because pets may acquire resistant organisms but also because of the potential for resistance determinants to be spread from harmless bacteria to opportunistic pathogens already within the host. The FAO/WHO¹ recommends antimicrobial resistance patterns be assessed for all products, yet studies of antimicrobial resistance in currently available products for dogs and cats have not been reported to date.

CHALLENGES

Dosage determination. An important aspect of the definition of probiotics is that they should exert beneficial effects in the host when administered in adequate amounts. However, there appears to be only one study²⁴ in which the effect of various dosages of an organism (LGG) was evaluated, and that study was limited to dogs. It revealed that a dose of 5×10^{11} CFU of LGG/day resulted in significantly greater fecal

colonization with LGG than smaller doses; however, whether this dose would be clinically effective was not evaluated. The fact that the same dose of the same probiotic led to a reduction in immunologic indicators of atopic dermatitis in Beagle puppies but no corresponding decrease in clinical signs³⁵ suggests either this dose is not sufficient or the organism provides no clinical benefit in this setting.

Other reported studies of the efficacy and effectiveness of specific probiotic organisms in dogs and cats have involved evaluation of differing dosages (Table 1, pages 8-9), making interpretation of the results difficult, for it is unknown whether these dosages were sufficient to exert their intended effects.

Quality control. Although quality control in probiotic production has been in question for at least 10 years, it remains an issue. Misrepresentation of bacterial species contained in commercially available, veterinary probiotic supplements is common.^{6,7} In some circumstances, information on the organisms contained is lacking altogether, as is an expiration date. Attempts to culture the products in the laboratory yield variable results, ranging from no growth, to growth of unexpected organisms.

Microbial content in canine and feline diets purported to contain probiotics is also poorly controlled. A study of 19 unidentified commercial pet foods (13 canine and six feline) reported to contain probiotics revealed that none contained all of the organisms claimed on the labels.⁶ Additionally, five diets yielded no relevant bacterial growth. The researchers indicated that for even those diets that did yield growth, it was unclear whether the degree of supplementation provided by the diets would be clinically relevant and, as such, the diets were all likely poor sources of probiotics.

Nonviable organisms. Interestingly, despite the word “live” being integral to the definition of “probiotic,”

Table 1. Summary of Evidence Regarding the Use of Various Individual Microorganisms as Probiotics in Cats and Dogs

Organism	Dose Used	Survives Manufacture and Storage?	Non-pathogenic/Nontoxic?	Colonizes the Gastro-intestinal Tract?	Significant ($P < 0.05$) Effect?	Reference
<i>Bacillus</i> CIP 5832	1.5 X 10 ⁶ CFU/g of diet for one week	YES	NE*	YES	NE	Biourge V, Vallet C, Levesque A et al. 1998
<i>Bifidobacterium animalis</i> AHC7	5 X 10 ¹⁰ CFU/day for at least 12 weeks	NE	YES	YES	Reduction in time to resolution and need for metronidazole in dogs with acute idiopathic diarrhea	Kelley RL, Soon Park J, O'Mahony L et al. 2010
	1.5 X 10 ⁹ CFU/day for six weeks	NE	YES (dogs)	Not mentioned	Reduction in <i>Clostridium difficile</i> carriage in healthy adult dogs	O'Mahony D, Murphy KB, MacSharry J et al. 2009
<i>Enterococcus faecium</i> SF68	5 X 10 ⁸ CFU/day for 44 weeks	NE	YES (dogs)	MAYBE	Increased antibody production in healthy vaccinated puppies	Benyacoub J, Czarnecki-Maulden GL, Cavadini C et al. 2003
	5 X 10 ⁹ CFU/day for 27 weeks	NE	YES (cats)	MAYBE	Increased CD4+ lymphocytes in healthy kittens; no significant increase in antibody production	Veir J, Knorr R, Cavadini C et al. 2007
	5 X 10 ⁸ CFU/day for 140 days	NE	Not reported	NE	Cats with chronic latent herpesvirus: 1 infection fed probiotic had more microbially diverse feces than control cats	Lappin MR, Veir JK, Satyaraj E et al. 2009
	5 X 10 ⁸ CFU/day for six weeks	NE	Not reported	NE	Fails to influence cyst shedding or immune responses in dogs with giardiasis	Simpson KW, Rishniw M, Bellosa M et al. 2009

* Not evaluated

Organism	Dose Used	Survives Manufacture and Storage?	Non-pathogenic/ Nontoxic?	Colonizes the Gastro-intestinal Tract?	Significant ($P < 0.05$) Effect?	Reference
<i>Lactobacillus acidophilus</i> DSM13241	> 10^9 CFU/day for two weeks	YES	YES (dogs)	YES	Decreased levels of <i>Clostridium</i> spp. in feces of healthy adult dogs, reduction in RBC fragility; immunomodulation	Baillon ML, Marshall-Jones ZV, Butterwick RF et al. 2004
	6 X 10^6 CFU/g of dry dog food consumed/day for 12 weeks	NE	YES (dogs)	YES	Improved fecal quality and defecation frequency in dogs with non-specific dietary insufficiency	Pascher M, Hellweg P, Kohl-Parisini A et al. 2008
	2 X 10^8 CFU/day for 4.5 weeks	NE	YES (dogs)	YES	Decreased amounts of <i>Clostridium</i> spp and <i>Enterococcus faecalis</i> in feces; immunomodulation	Marshall-Jones ZV, Baillon ML, Croft JM et al. 2006
<i>Lactobacillus animalis</i> LA4	0.5 g/day for 10 days	NE	YES (dogs)	YES	NE	Biagi G, Cipollini I, Pompei A, et al. 2007
<i>Lactobacillus rhamnosus</i> strain GG	From 1×10^9 to 5×10^{11} CFU/day for five days	NE	YES (dogs)	YES	NE	Weese JS, Anderson ME 2002
	Approximately 10×10^{10} CFU/day for 21 weeks	NE	Not reported	NE	Decrease in allergen-specific IgE titer in puppies with induced atopic dermatitis	Marsella R 2009

* Not evaluated

evidence is mounting that certain proposed probiotic agents have effects even when nonviable.¹³ Therefore, although dead organisms do not meet the definition of probiotics, the lack of viable organisms in certain products may not necessarily predict lack of therapeutic benefits. Conclusions should be reserved until this hypothesis has been investigated further.

CONCLUSION

Probiotics are being used in veterinary practice, despite the paucity of evidence supporting their clinical impact. In some situations, probiotic administration may be harmful; the lack of reports on harmful effects should be considered cautiously in light of the general dearth of studies into probiotic safety and minimum effective dosage in cats and dogs. Evidence that a probiotic has immunomodulatory effects is not enough to support its use, particularly when the clinical nature of those effects is largely unknown. The same is true when probiotics are used to establish and maintain a healthy microfloral population in the gut. To date, there has been insufficient research into how combinations of various probiotic organisms behave in a host. None of the studies discussed in this review evaluated safety over prolonged periods of administration.

Despite these limitations, the potential therapeutic effects of probiotics should not be dismissed, particularly given the positive effects documented for prevention and treatment of a wide range of human diseases. Certain organisms in a standardized form and dosage may indeed be effective in improving

and maintaining the health of cats and dogs. In dogs, particular strains of *B. animalis* and *L. acidophilus* show promise for the treatment of specific GI ailments such as idiopathic diarrhea, but additional research is needed before definitive conclusions can be drawn. More experiments and clinical trials are needed to identify specific probiotic bacterial species, minimum effective dosages, potentially adverse effects and their impact on pet well-being. More control and regulation is needed at the manufacturing stage. In the absence of such evidence and regulation, veterinarians are cautioned to approach probiotics as they would a new drug, taking both their experience and the available published evidence into account. Label claims for probiotic supplements and pet food should be scrutinized and vendors encouraged to provide evidence supporting those claims.

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