



# Open-label trial of a multi-strain synbiotic in cats with chronic diarrhea

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## Abstract

This study was designed to test the hypothesis that in cats with chronic diarrhea the daily administration of a proprietary synbiotic (Proviale-DC) would result in an improvement in stool character, as assessed by the owner. Adult cats with chronic diarrhea were recruited for the study and screened for systemic diseases. Fecal flotation, wet mount, immunofluorescence assay (IFA) for *Giardia* and *Cryptosporidium* species, and *Tritrichomonas* species polymerase chain reactions (PCRs) were used to screen for intestinal parasitism. The synbiotic was administered for 21 days; otherwise, no changes were made to ongoing treatment(s) or diet. The severity of the diarrhea was assessed using a standardized fecal scoring system and the owner's subjective perception before, and after, supplementation. 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 following a 21-day course of synbiotic supplementation.

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## Introduction

Chronic diarrhea is a common presenting complaint in cats of all ages. Frequently, the history, physical examination and minimum database fail to reveal an underlying cause for the diarrhea. Also, in a number of cases, the fecal examination shows no evidence of parasitism and trial treatment with an anthelmintic agent does not lead to resolution of the diarrhea. Further diagnostic testing can be expensive (eg, endoscopy, abdominal ultrasound), invasive (eg, endoscopy), non-specific (eg, serum folate and cobalamin concentrations) and may often be declined by the owners, and some form of symptomatic therapy is often recommended.<sup>1,2</sup> The use of dietary intervention in cases of chronic feline diarrhea has been shown to be beneficial in a significant number of cats.<sup>3</sup> A positive response to a limited antigen or hydrolyzed protein diet may suggest dietary antigens as a potential cause of gastrointestinal dysfunction and clinical diarrhea. Another potential therapeutic target for cats with chronic diarrhea is the gastrointestinal microbiota. The quantitative and qualitative composition of the bacterial microbiota within the gastrointestinal tract can influence components of both the immunologic and inflammatory response

systems, and presumably, have an effect on clinical signs.<sup>4</sup> Probiotics are defined as live organisms of the physiologic bacterial ecosystem that provide a benefit to the host when provided in adequate quantities.<sup>5</sup> Although the mechanism of action of probiotics is not completely understood, they are likely to exert an effect on the resident intestinal microbiota of cats and may also affect the intestinal and systemic immune system.<sup>6</sup> Probiotics have been shown to help in the prevention of diarrhea, as well as reduce the duration and frequency of diarrhea in humans, although results are variable and both the specific cause of the diarrhea and the specific strain(s) and number of probiotic organisms are important factors to consider.<sup>7</sup> To date, very few studies

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have addressed the efficacy of probiotics in dogs or cats with chronic diarrhea. One prospective double-blinded, randomized, placebo-controlled trial compared supplementation with a multi-strain probiotic formulation to a placebo in dogs with food-responsive diarrhea.<sup>8</sup> This study failed to identify a significant difference in the clinical score between groups either before or following supplementation, but all dogs in both groups had been switched to an elimination diet at the beginning of the trial. This dietary intervention likely resulted in the significant improvement seen in the clinical scores for both groups, and potentially masked any effect the probiotic may have had.<sup>8</sup> Pascher et al looked at the effect of a single-strain probiotic formulation (*Lactobacillus acidophilus* DSM 13241 at  $6 \times 10^6$  cfu/g) in dogs with non-specific dietary hypersensitivity.<sup>9</sup> Probiotic supplementation significantly improved fecal consistency and reduced defecation frequency.<sup>9</sup> A randomized, double-blind study compared a multi-strain probiotic to placebo administration in cases of acute gastrointestinal disease in dogs.<sup>10</sup> Use of the probiotic significantly shortened the duration of diarrhea in these dogs.<sup>10</sup> A species-specific probiotic formulation containing *Lactobacillus* species and *Enterococcus faecium* was administered to juvenile captive cheetahs, who frequently present with diarrhea presumed to be secondary to infection with enteric bacterial pathogens. Compared with a control group, there was a significant increase in body weight after 28-days of probiotic supplementation.<sup>11</sup> There was also a significant improvement in fecal quality, and an absence of fecal mucus and blood during probiotic supplementation.<sup>11</sup> In a double-blinded, placebo-controlled trial, a single-species probiotic formulation containing *E faecium* SF68 (Fortiflora; Nestle Purina, Vevey, Switzerland,  $1 \times 10^8$  cfu/g) was fed to shelter cats for 4 weeks. The percentage of cats with diarrhea for more than 2 days was significantly lower in the group of cats treated with the probiotic when compared with the placebo group.<sup>12</sup>

The current study was designed to test the hypothesis that, in client-owned cats with chronic diarrhea, daily administration of a proprietary synbiotic (multi-species probiotic plus prebiotics: Provable-DC; Nutramax Laboratories, Edgewood, MD, USA) would result in an improvement in stool character as assessed by the owner. The study design was chosen to confirm or refute pervasive, but largely anecdotal, reports by owners of cats with chronic diarrhea, that probiotic-containing products are beneficial and safe. To the authors' knowledge, this is the first study that examines the effect of a synbiotic formulation in domestic cats with naturally-occurring chronic diarrhea.

## Materials and methods

Inclusion criteria for study entry were age ( $\geq 1$  year) and chronicity of diarrhea ( $\geq 3$  weeks with no perceived

improvement). History, physical examination, serum biochemical profile, complete blood count and urinalysis were performed, and any evidence of systemic disease served as an exclusion criterion for the cat from participation. In cats that were identified as having signs consistent with hyperthyroidism, a total thyroid hormone concentration (total  $T_4$ ) was measured and an increased serum total  $T_4$  concentration led to exclusion of the cat from study participation. Prior to entry, fecal samples from all cats were evaluated by fecal flotation, fecal wet mount and *Giardia* and *Cryptosporidium* species immunofluorescence assay (IFA) (Merifluor IFA kit; Meridian Bioscience, Cincinnati, OH, USA). Although none of the cats was less than 1 year of age, a polymerase chain reaction (PCR) for *Tritrichomonas foetus* was performed as part of the fecal screen (nested PCR).<sup>13</sup> Identification of parasitism by fecal examination excluded cats from participation in the study.

A client questionnaire was used to determine if any medications, treatments, supplements or dietary changes had been initiated within the 3 weeks prior to entry into the study. If so, the cat was excluded from participation. If the cat had received a probiotic within the 3 weeks preceding entry, the cat was also excluded from the study. If any ongoing intervention had been initiated greater than 3 weeks prior to study entry, it was confirmed that the diarrhea had not improved in the 3 weeks leading up to the study and the treatment was continued as prescribed throughout the duration of the synbiotic supplementation.

All cats meeting the inclusion criteria and not excluded for any of the stated reasons were prescribed a 21-day course of a proprietary synbiotic supplementation. The prescribed synbiotic is a commercially-available product for use in dogs and cats (Provable-DC; Nutramax Laboratories). Each capsule contains a minimum of 5 billion colony forming units (cfu) of bacteria (guaranteed analysis). The seven bacterial strains that are present in the formulation include *E faecium*, *Streptococcus (Enterococcus) thermophilus*, *Lactobacillus acidophilus*, *L bulgaricus*, *L casei*, *Bifidobacterium bifidum*, and *L plantarum* (Table 1). Additional ingredients of note are two prebiotics. The exact composition of the bacterial strains and prebiotics are proprietary. The combination of a probiotic and prebiotic are what defines this particular product as a synbiotic. Owners were instructed to open the capsule and mix the entire contents of the capsule into the cat's food once a day. Owners were also asked to monitor the cat for subsequent refusal to eat the entire meal or any other significant changes associated with consumption of the meal with the added supplement, such as ptyalism, nausea, vomiting or regurgitation. Refusal to consume the food with the added supplement or report of any of these side-effects constituted a criterion for exclusion

**Table 1** Probiotic bacterial strains in Provable-DC

Bacterium	Strain
<i>Enterococcus faecium</i>	NCIMB 30183
<i>Streptococcus salivarius</i> subspecies <i>thermophilus</i>	NCIMB 30189
<i>Bifidobacterium bifidum</i>	NCIMB 30179
<i>Lactobacillus acidophilus</i>	NCIMB 30184
<i>Lactobacillus casei</i> subspecies <i>rhamnosus</i>	NCIMB 30188
<i>Lactobacillus plantarum</i>	NCIMB 30187
<i>Lactobacillus delbrueckii</i> subspecies <i>bulgaricus</i>	NCIMB 30186

The exact proportions of each probiotic strain are proprietary

from the study and discontinuation of attempted supplementation.

The same questionnaire was used to quantify the duration, frequency and severity of the diarrhea for the month prior to entry into the study. A standardized fecal scoring system was used by the owners to score their cats' bowel movements. This scoring system was based on the Purina fecal scoring system where a specific description of the stool is associated with a particular number ([www.foothillpethospital.com/fecalscoring.html](http://www.foothillpethospital.com/fecalscoring.html)). As shown on the chart, the scores ranged from 1 to 7, with 1 being described as 'very hard' and 7 being described as 'watery'. A follow-up questionnaire containing the same fecal scoring system was completed by owners, assessing the first observed stool on the last day of synbiotic supplementation or as shortly thereafter as possible. The follow-up questionnaire also asked owners to give a subjective evaluation of their cat's stool character over the course of supplementation that combined assessment of both character and frequency in terms of 'got worse', 'no change' or 'improved'.

The D'Agostino and Pearson omnibus test was used to test each data set for normality. For evaluation of pre- and post-supplementation fecal scores the non-parametric Wilcoxon matched pairs (two-tailed) test was used. A two-tailed Student's *t*-test for unpaired samples assuming unequal variance was used to compare age and body weight between cats whose owners reported that stool character 'improved' versus those of cats whose owners reported either 'no change' or 'got worse'. Values are reported as means  $\pm$  standard deviation, and significance was defined as  $P < 0.05$ . All aspects of this study were carried out in accordance with the Colorado State University Animal Care and Use Guidelines (IACUC Protocol 09-097A-01).

## Results

Sixty-three cats were entered into the study. One cat was excluded because of refusal to eat a meal containing the synbiotic. No other adverse effects were reported by the

owners of the cats in relation to ingestion of the supplement. Nine cats were excluded following identification of parasites on fecal examination, including *Giardia* species (four), *Tritrichomonas* species (three), and *Cryptosporidium* species (two). Therefore, 53 cats met the inclusion criteria, completed the study and were included for analysis. None of the cats was reported to have evidence of a chronic disease beyond gastrointestinal signs historically. Also, none of the cats was found to have any remarkable abnormality on physical examination, or evidence of renal disease, diabetes mellitus, hyperthyroidism, or liver disease based on the serum biochemical profile, significant inflammation or anemia based on a complete blood count, or urinary tract infection or proteinuria based on urinalysis.

The mean fecal score for the 53 cats completing the study decreased from  $6.0 \pm 1.0$  to  $4.4 \pm 1.6$ , representing a significantly ( $P < 0.001$ ) firmer stool than before the start of the study.

Thirty-eight owners (72%) reported that their cat's diarrhea 'improved' with supplementation, while 13 (24%) owners reported 'no change' and two owners (4%) reported that their cat's diarrhea 'got worse'. The fecal score reported by owners of cats in the 'improved' group decreased significantly following supplementation, from  $6.0 \pm 1.0$  to  $3.7 \pm 1.4$  ( $P < 0.0001$ ). The fecal score reported by owners of cats in the 'no change' or 'got worse' group did not change significantly following supplementation, from  $6.0 \pm 0.9$  to  $5.9 \pm 1.0$  ( $P = 0.75$ ). There were no significant differences between cats whose owners reported that stool characteristics 'improved' compared with cats whose owners reported either 'no change' or 'got worse' for age ( $7.6 \pm 5.2$  years vs  $6.9 \pm 4.7$  years;  $P = 0.80$ ) or body weight ( $4.2 \pm 1.6$  kg vs  $4.5 \pm 6.1$  kg;  $P = 0.77$ ). Thirty-nine percent ( $n = 15$ ) of the cats in the 'improved' group and 54% ( $n = 7$ ) of the cats in the 'no change' group received medications or supplements beginning more than 3 weeks prior to study entry; one of the 'got worse' cats received medication during this time. Of those cats that were receiving medication(s) prior to entry into the study, and therefore continued that medication through the course of supplementation, the most common medications given to cats in the 'improved' group were metronidazole (19%), another antibiotic (marbofloxacin, clavimox or amoxicillin, 14%) or prednisolone (14%). The most common medications given to cats in the 'no change' group were metronidazole (13%) and prednisolone (13%), while one cat in the 'got worse' group was on prednisolone. A large variety of diets were being fed to cats in all three groups. A hypoallergenic or hydrolyzed diet was being fed to 13% ( $n = 5$ ) of the cats in the 'improved' group and 38% ( $n = 5$ ) of the cats in the 'no change' group. A low-residue diet specifically marketed for gastrointestinal disease was being fed to 13% ( $n = 5$ ) of the cats in the 'improved' group and 15% ( $n = 2$ )

**Table 2** Duration of the diarrhea prior to entry into the study

Diarrhea	Group		
	Improved (n = 38 total)	No change (n = 13 total)	Got worse (n = 2 total)
3 weeks	3% (1)	8% (1)	0% (0)
3 months	36% (14)	15% (2)	0% (0)
6 months	16% (6)	23% (3)	50% (1)
>6 months	45% (17)	54% (7)	50% (1)

**Table 3** Frequency of the diarrhea prior to entry into the study

Diarrhea	Group		
	Improved (n = 38 total)	No change (n = 13 total)	Got worse (n = 2 total)
<1×/week	3% (1)	0% (0)	0% (0)
1×/week	8% (3)	8% (1)	0% (0)
1×/day	60% (23)	15% (2)	50% (1)
>1×/day	29% (11)	77% (10)	50% (1)

of the cats in the 'no change' group. Neither of the cats in the 'got worse' group was being fed a diet specific for gastrointestinal disease. A comparison of the duration and frequency of the diarrhea for these three groups is shown in Table 2 and Table 3.

## Discussion

Although adult cats were screened for systemic diseases and fecal parasitism, the inclusion criteria for this open-label study were purposefully broad in an attempt to mimic the clinical scenario in which probiotics, prebiotics and synbiotics are frequently used.

The mean fecal score, as judged by the owner, for the 53 cats completing the study decreased from 6.0 to 4.4, representing a significantly ( $P < 0.001$ ) firmer stool character after supplementation. This was an open-label trial with no placebo control group, hence, it is impossible to quantify the degree of improvement that might be attributable to the 'placebo effect'. A number of steps were taken in the study design to ensure that there were no changes to the cat's treatment(s) or diet beyond the addition of the synbiotic supplementation. Greater than half of the cats were not taking any medication and one of the inclusion criteria was that for those that were being medicated, the owners had not perceived a change in the diarrhea for 3 weeks prior to initiating supplementation. Somewhat surprisingly, a relatively small percentage of the cats were on a diet designed for cats with gastrointestinal signs. Therefore, standardizing the diet for this study would have meant that the majority of cats would

have needed to undergo a change in diet and be switched to a diet intended for patients with gastrointestinal disease, which would have potentially made it more difficult to attribute the perceived change in clinical signs to synbiotic supplementation. The 'placebo-effect' is clearly a potentially important confounding factor, although 28% of owners reported seeing no change or a worsening of the diarrhea during supplementation. This finding highlights the fact that synbiotic supplementation is not likely to be beneficial in all patients with chronic diarrhea. The optimal duration of probiotic treatment remains to be determined and the cases in this study may have demonstrated further benefit if therapy had been continued beyond the 3-week course. It has been shown that changes in bacterial groups are seen following a 3-week administration of the same probiotic product in cats, but without concurrent changes in gastrointestinal functions test or other biochemical parameters.<sup>14</sup> As with the use of probiotics in humans with gastrointestinal diseases, the effectiveness of supplementation in veterinary patients is likely to hinge on the combination of appropriate cases with specific probiotic strains.<sup>5</sup>

The objective measure (fecal score) appeared to match the subjective measure (owner's stated observation of improved, no change, or got worse) of stool character.

Seventy-two percent of owners perceived an improvement in their cat's chronic diarrhea following a 21-day course of synbiotic supplementation. This appears to confirm the impression from anecdotal reports that owners perceive an improvement in their cats' diarrhea with administration of a probiotic supplement.<sup>15</sup> This is also



consistent with the clinical impression that owners of cats with chronic diarrhea are motivated to use supplements such as probiotics, prebiotics or synbiotic combinations. This makes our finding of no adverse effects particularly important. The synbiotic used in this study contains a minimum of 5 billion cfu per dose and appears to be safe when administered to cats with chronic diarrhea at the recommended dose — at least for the 21-day timeframe covered by this trial. Because both the safety and effect of probiotic formulations are strain-specific, this statement cannot be extrapolated to the use of other probiotics in cats. This is consistent with the use of probiotics in people where adverse effects are rare unless the patient is significantly immunocompromised.<sup>16</sup> This study would also suggest that the majority of owners who present cats for non-specific chronic diarrhea will perceive an improvement in their cats' stool character during such supplementation, further motivating them to pursue and comply with this specific treatment or similar recommendations for therapy.

It would be potentially useful to identify clinical criteria that would predict perceived therapeutic success, or failure, prior to initiation of supplementation. Unfortunately, no such discerning characteristics were clearly revealed by this study. The results illustrated by Table 2 and Table 3 might suggest that the duration and frequency of diarrhea was somewhat more severe in the 'no change' and 'got worse' groups compared to the 'improved' group, but it would be premature to draw a general conclusion from these findings. Although an effort was made to rule out a number of systemic diseases that might have contributed to the clinical presentation, it is certainly possible that some of the cats in the study had occult disease.

The interactions between probiotics and antibiotics are still being elucidated. Probiotics such as *E faecium* have the potential to modulate the virulence factors and antibiotic susceptibility of certain pathogenic bacteria, and probiotics have been used to treat antibiotic associated diarrhea and hospital-acquired *Clostridium difficile* diarrhea.<sup>17,18</sup> *Lactobacillus* species isolates have demonstrated resistance to macrolides, penicillins and tetracycline antibiotics, and the ability to acquire antibiotic resistance or transfer resistance to pathogenic bacteria is an obvious area of concern requiring further research.<sup>19</sup>

The main limiting factor of this study was the lack of a control group that received a placebo instead of the symbiotic supplement. However, the potential of receiving a placebo may have led many owners to refuse participation in the trial and may have severely limited enrollment and was thus not attempted. Also, it should be pointed out that, while chronic diarrhea in cats can be waxing and waning, spontaneous improvement of stool quality in 72% of all cats with chronic diarrhea would be highly surprising. Nonetheless, this limitation would

suggest that in the future such a double-blinded, placebo-control study should be conducted to confirm our results.

This study showed that a majority of owners of cats with chronic diarrhea perceive an improvement in stool character following supplementation with a synbiotic product featuring multi-species probiotics. A significant decrease in the objective measure of stool character is consistent with an actual improvement in the diarrhea, although the 'placebo effect' must be taken into consideration. Administration of this particular synbiotic product appeared to be well tolerated, safe and not associated with adverse effects. In 28% of the cats receiving supplementation, the owners did not perceive any change or reported that stool character got worse. The variable response to supplementation may have a number of explanations and emphasizes the importance of future studies utilizing a placebo-control group, cats with a definitive diagnosis, and testing a variety of different probiotic species as part of the synbiotic therapy.

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**Conflict of interest** Nutramax Laboratories supplied the synbiotic used in this study (Provable-DC) but otherwise did not provide any financial support and had no role in study design, data collection, analysis, interpretation or preparation of the manuscript. The Morris Animal Foundation had no role in study design, data collection, analysis, interpretation or preparation of this manuscript.

## References

- 1 Cave NJ, Marks SL, Kass PH, Melli AC and Brophy MA. **Evaluation of a routine diagnostic fecal panel for dogs with diarrhea.** *J Am Vet Med Assoc* 2002; 221: 52–9.
- 2 Suchodolski JS. **Alteration in the small intestinal microflora (small intestinal bacterial overgrowth).** In: JM Steiner (ed), *Small animal gastroenterology*. Hannover: Schlütersche Verlagsgesellschaft mbH, 2008, pp 202–7.
- 3 Guilford WG, Jones BR, Markwell PJ, Arthur DG, Collett MG and Harte JG. **Food sensitivity in cats with chronic idiopathic gastrointestinal problems.** *J Vet Intern Med* 2001; 15: 7–13.
- 4 Suchodolski JS. **Companion animals symposium: microbes and gastrointestinal health of dogs and cats.** *J Anim Sci* 2011; 89: 1520–30.
- 5 Gareau MG, Sherman PM and Walker WA. **Probiotics and the gut microbiota in intestinal health and disease.** *Nat Rev Gastroenterol Hepatol* 2010; 7: 503–14.
- 6 Marshall-Jones ZV, Baillon ML, Croft JM and Butterwick RF. **Effects of *Lactobacillus acidophilus* DSM13241 as a probiotic in healthy adult cats.** *Am J Vet Res* 2006; 67: 1005–12.
- 7 Preidis GA, Hill C, Guerrant RL, Ramakrishna BS, Tannock GW, et al. **Probiotics, enteric and diarrheal diseases, and global health.** *Gastroenterology* 2011; 140: 8–14.
- 8 Sauter SN, Benyacoub J, Allenspach K, Gaschen F, Ontsouka E, Reuteler G, et al. **Effects of probiotic bacteria in dogs**

- with food responsive diarrhoea treated with an elimination diet.** *J Anim Physiol Anim Nutr* 2006; 90: 269–77.
- 9 Pascher M, Hellweg P, Khol-Parisini A and Zentek J. **Effects of a probiotic *Lactobacillus acidophilus* strain on feed tolerance in dogs with non-specific dietary sensitivity.** *Arch Anim Nutr* 2008; 62: 107–16.
  - 10 Herstad HK, Nesheim BB, L'Abée-Lund T, Larsen S and Skancke E. **Effects of a probiotic intervention in acute canine gastroenteritis – a controlled clinical trial.** *J Sm Anim Pract* 2010; 51: 34–8.
  - 11 Koeppel KN, Bertschinger H, van Vuuren M, Picard J, Steiner J, Williams D, et al. **The use of a probiotic in captive cheetahs (*Acinonyx jubatus*).** *J S Afr Vet Assoc* 2006; 77: 127–30.
  - 12 Bybee SN, Scorza AV and Lappin MR. **Effect of the probiotic, *Enterococcus faecium* SF68, on presence of diarrhea in cats and dogs housed in an animal shelter.** *J Vet Intern Med* 2011; 25: 856–60.
  - 13 Gookin JL, Birkenheuer AJ, Breitschwerdt EB and Levy MG. **Single-tube nested PCR for detection of *Tritrichomonas foetus* in feline feces.** *J Clin Microbiol* 2002; 40: 4126–30.
  - 14 Garcia-Mazcorro JF, Laneri D, Dowd SE, Paddock, CG, Gruetzner N, Steiner JM, et al. **Effect of a multi-species synbiotic formulation on fecal bacterial microbiota of healthy cats and dogs as evaluated by pyrosequencing.** *FEMS Microbiol Ecol* 2011; 78: 542–554.
  - 15 [http://www.amazon.com/Purina-Veterinary-Diets-Fortiflora-Sachets/product-reviews/B001650NNW/ref=sr\\_1\\_1\\_cm\\_cr\\_acr\\_txt?ie=UTF8&showViewpoints=1](http://www.amazon.com/Purina-Veterinary-Diets-Fortiflora-Sachets/product-reviews/B001650NNW/ref=sr_1_1_cm_cr_acr_txt?ie=UTF8&showViewpoints=1) (accessed 14 December 2011)
  - 16 Liang MT. **Safety of probiotics: translocation and infection.** *Nutr Rev* 2008; 66: 192–202.
  - 17 Ditu LM, Chifiriuc MC, Bezirtzoglou E, Voltsi C, Bleotu C, Pelinescu D, et al. **Modulation of virulence and antibiotic susceptibility of enteropathogenic *Escherichia coli* strains by *Enterococcus faecium* probiotic strain culture fractions.** *Anaerobe* 2011; Jun 23 [Epub ahead of print].
  - 18 Hickson M. **Probiotics in the prevention of antibiotic-associated diarrhoea and *Clostridium difficile* infection.** *Therap Adv Gastroenterol* 2011; 4: 185–97.
  - 19 Drago L, Mattina R, Nicola L, Rodighiero V and De Vecchi E. **Macrolide resistance and in vitro selection of resistance to antibiotics in *Lactobacillus* isolates.** *J Microbiol* 2011; 49: 651–6.