Are probiotics an effective treatment in acute enteropathies in dogs? A literature review

[1]Maria C. Matei, [1]Hugo Haab, [1]Victoria Buza, [2]Călin Lațiu, [3]Andrei R. Szakacs, [1]Laura C. Ștefănuț

[1] Department of Animal Physiology, Faculty of Veterinary Medicine, University of Agricultural Sciences and Veterinary Medicine Cluj-Napoca, Cluj, Romania; [2] Department of Animal Sciences, Faculty of Animal Sciences, University of Agricultural Sciences and Veterinary Medicine Cluj-Napoca, Cluj, Romania; [3] Department of Animal Nutrition, Faculty of Veterinary Medicine, University of Agricultural Sciences and Veterinary Medicine Cluj-Napoca, Cluj, Romania. Corresponding author: V. Buza, victoria.buza@usamvcluj.ro

Abstract. Recently, the interest in probiotics has increased and this type of treatment has started to be used as an additional or even alternative therapy in dogs with diarrheal syndrome linked with different types of enteropathies. Probiotics are live formulas that, if administered in an adequate amount, are able to produce a benefic effect for the host. It is believed that their effect can potentiate the effect of the classical treatment and decrease the severity of the symptoms associated with enteropathies. This review includes studies focused on dogs with acute enteropathy diagnostics that were treated with probiotics. Other animal species (experimental studies on laboratory animals, large animals or cats) were excluded during the selection process. The triage of the studies was conducted based on title and abstract. Currently, the hypothesis that probiotics are definitively effective in dogs with acute enteropathies may need more explorations and stronger evidence to support it. However, it can be considered that probiotics most likely improve the condition of animals with gastro-intestinal problems.
Key Words: canine, diarrhea, effectiveness, probiotics.

Introduction. Acute enteropathies in dogs are a common condition that leads to gastrointestinal manifestation and are strongly connected with potential intestinal dysbiosis. This state is defined as a modification of the intestinal microbiome with an impact on the resident microbial number or proportion, with gastrointestinal manifestations as a result (Honneffer et al 2014; Barko et al 2018). It is not completely known if those symptoms are an effect of dysbiosis or the cause, because intestinal inflammation can lead to dysbiosis, and dysbiosis is able to aggravate the inflammation (Suchodolski 2016). Moreover, changes in the gastro-intestinal microbiome are strongly correlated with different pathologies, like inflammatory bowel disease, asthma, metabolic syndromes, obesity, cardiovascular diseases or immune-mediated diseases (Barko et al 2018). However, the most visible results of dismicrobism are gastro-intestinal manifestations, such as diarrhea.

A common approach that affects intestinal microbiome, regardless of the species, is represented by antibiotic treatments. For example, it is proved that fecal microbiome is strongly affected by ciprofloxacin treatment, which is able to reduce the taxonomic diversity of the bacteria and their abundance (Dethlefsen et al 2008; Dethlefsen & Relman 2011). However, the antibiotic therapy is not the only treatment that affects the gastro-intestinal (GI) microbiome. In dogs, omeprazole treatment can lead to an increase in the number of bacteria from *Firmicutes* and *Fusobacterium* genera (Garcia-Mazcorro et al 2012).

In order to protect the GI microbiome and also to treat or prevent different GI pathologies, scientists have tried different approaches. One of them is represented by bacteriotherapy that includes the usage of three product categories: prebiotics,

probiotics and sinbiotics (Patel et al 2015). The term probiotic was first used in 1965 by Lilly and Stillwell in to describe a substance secreted by a microorganism, with an effect on the growth of another microorganism (Lilly & Stillwell 1965; Hawrelak 2013; Khalighi et al 2016). In 1974, Parker modified the definition, and the term probiotic was characterized as microorganisms or substances that contribute to the intestinal microbial equilibrium (Parker 1974; Hawrelak 2013; Khalighi et al 2016). Nowadays, probiotics are considered live formulas that, if administered in a correct amount, are able to produce benefic effects to the host (FAO/WHO 2002).

Regarding the therapeutic effect of probiotics, the first proof can be found at the start of the 20th century. Warden (1909) reported that *Streptococcus lacticus* and *Bacillus bulgaricus* used in the treatment of autoimmune arthritis produced an improvement in the general health status (Warden 1909; Barko 2018).

Nowadays, probiotics are largely used in different conditions. In veterinary medicine, especially for dogs, probiotics are used as an alternative therapy for different pathologies, including acute enteropathies with diarrheal manifestations, with an infectious or non-infectious cause (Schmitz & Suchodolski 2016). However, the efficacy of probiotics is variable in different conditions, like stress induced diarrhea, antibiotic induced diarrhea or even idiopathic diarrhea, depending on the type of probiotic used (Schmitz & Suchodolski 2016). Acute enteropathies in dogs are common and probiotics are considered a valuable solution for improving the health status of dogs. The aim of the present review is to compare the results of various studies in order to establish the probiotics potential benefits in the treatments of acute enteropathies in dogs.

Material and Method

Search strategy and study selection. The electronic databases PubMed, Google Scholar and Embase were used. Literature search was conducted based on the following key words: dogs, probiotics, enteropathies, diarrhea. 2357 studies were identified. After a thorough refinement, only studies that assess probiotic efficacy in the treatment of acute enteropathies in dogs were selected. Out of 2357 studies, 6 met our criteria.

Inclusion and exclusion criteria. Randomized double-blinded placebo-controlled clinical trials published in peer-review journals were selected. They have to assess probiotic efficacy in the treatment of acute enteropathies in dogs. Only studies that examined the effect of at least 7 days of treatment of probiotics were included. No specifications of breed or age were applied. The dogs may come from a kennel or belong to a private owner. The trial has to compare, *in vivo*, clinical effects of an intervention with probiotics to one using placebo. All species and strains of probiotics were included. The mode of administration was not a discriminative criterion. The primary outcomes were effects of probiotics on signs of acute enteropathies. These signs were evaluated using the following variables: activity, appetite, vomiting frequency, defecation frequency, weight change, feces consistency and hospitalization duration.

Data abstraction. Information was extracted from trials and arranged in tables summarizing different features of the studies: characteristics of the studies, characteristics of the dog population, the type of intervention and the tests carried out by the authors.

Results and Discussion. According to the inclusion criteria, 6 studies were selected. A total number of 192 dogs were included in those studies. In all studies, the dogs were divided in two groups: placebo (n=98 dogs, 51.04%) and active arm that received different probiotics formulas (n=94 dogs, 48.96%). Each group had clinical signs of diarrhea, with different possible causes. The symptoms were reported differently in each study, the responsible person being represented either by the clinicians or by the owner (Aktaş et al 2007; Kelley et al 2009; Herstad et al 2009; Gómez-Gallego et al 2016; Ziese et al 2018; Shmalberg et al 2019). Moreover, each study reported a follow-up period that varies from study to study (Table 1).

Table 1

Characteristics of the studies

Reference	*N (Pl/Pr)*	*Reporter of signs*	*Follow-up period*	*Possible cause of diarrhea*
Aktaş et al 2007	16 (8/8)	Clinicians	10 day study	Lincomycin-induced diarrhea
Kelley et al 2009	31 (18/13)	Stool score was recorded daily by trained personnel	Study lasting 2 weeks	Acute diarrhea of various causes
Herstad et al 2009	36 (21/15)	Owners at home	All dogs recovered in 8 days	Acute uncomplicated diarrhea
Gómez-Gallego et al 2016	44 (19/25)	Owners by a questionnaire	6 months	Acute self-limiting diarrhea (variable causes)
Ziese et al 2018	25 (12/13)	The owners at home or the clinician	Study lasting 21 days	Acute Hemorrhagic Diarrhea Syndrome (exclusion diagnosis)
Shmalberg et al 2019	40 (20/20)	Owners filled a survey (not daily)	Survey sent 6 months after end of treatment for follow-up	Acute diarrhea (but not AHDS)
Total	192(98/94)			

Note: N - number of participants; Pl - placebo group; Pr - probiotic group.

The heterogeneity of the groups is variable in all those studies. In three from six studies (Kelley et al 2009; Herstad et al 2009; Shmalberg et al 2019), the mean age of the dogs is reported, while in the other three it is not reported (Aktaş et al 2007; Gómez-Gallego et al 2016; Ziese et al 2018). Moreover, the mean age of the active arm groups (probiotic groups) is more or less similar with the mean age of the placebo groups. Regarding the gender of the dogs included in all the studies, one study reported 14 males and 10 females (Aktaş et al 2007), while the other six did not mentioned the gender distribution among the groups. The same observation is available in the case of the breed of dogs: one study reported the breeds of the dogs included in the study. The mean body weight was mentioned in two from six studies. Taking into consideration all these aspects, the heterogeneity of the groups may be considered (Table 2).

Table 2

Characteristics of participants

Authors	*Mean age (in years)*	*Age Pr*	*Age Pl*	*Gender*	*Breed*	*Mean body weight (kg)*
Aktaş et al 2007	Not mentioned	Not mentioned	Not mentioned	14 males and 10 females used in the study	Not mentioned	Not mentioned
Kelley et al 2009	1.58 (+/- 0.18)	1.58 (+/- 0.18)	1.58 (+/- 0.18)	Not mentioned	From a large guide dog organization: 10 German shepherds 2 Golden retrievers 11 Labrador retrievers 8 Labrador-Golden crosses	Similar between the two groups (figure not mentioned)
Herstad et al 2009	4.1 (+/- 3.3)	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned
Gómez-Gallego et al 2016	6 months or older	Not mentioned	Not mentioned	Not mentioned	Not mentioned	23.7 (+/- 14.2)
Ziese et al 2018	Not mentioned	6 (3.9)	5.5 (3.9)	"No significant differences" (p=0.561)	"No significant differences" (p=0.39)	"No significant differences" (p=0.397)
Shmalberg et al 2019	5.6 +/- 3.6	5.3 +/- 3.2	5.7 +/- 3.9	Not mentioned	Not mentioned	21.2 +/- 11.8

Note: Age Pr - Age of Probiotic group; Age Pl - Age of Placebo group.

The distribution among the studies groups was based on several criteria, specific for each study. 5 of 6 studies (Aktaş et al 2007; Herstad et al 2010; Gómez-Gallego et al 2016; Ziese et al 2018; Shmalberg et al 2019) performed a clinical examination for all the dogs included in their groups, while for one study this aspect in not mentioned (Kelley et al 2009). However, for all the 192 dogs, an initial evaluation of the severity of the diarrhea was performed. Regarding the paraclinical examinations, the blood analyses were performed for 125 dogs (Table 3).

All but 44 patients received additional therapies to treat their gastro-intestinal symptoms or with a supportive role. However, it is not clear in the case of the fourth study (Gómez-Gallego et al 2016) if the additional therapy was absent or not clearly mentioned in the protocol. The choice of the probiotic was different in each study group. The diet of the dogs during the study periods was different from study to study. 92 dogs did not receive a standardized diet, while in the case of the other 100 dogs the diet was almost standardized (Table 4). Dogs mostly presented an acute self-limiting idiopathic diarrhea. Nearly all authors mentioned in their introductions that the usual cause of this type of diarrhea is dietary sensitivity or pathogens such as *Giardia*, *Isospora*, *Cryptosporidium*, *Escherichia coli*, enterotoxigenic *Clostridium perfringens* and toxigenic *Clostridium difficile*. Two studies chose a particular type of diarrhea: lyncomicin-induced diarrhea (Aktaş et al 2007) and Acute Hemorrhagic Diarrhea Syndrome (Ziese et al 2018). In all studies, the authors excluded dogs with an underlying serious disease. However, this process of exclusion was mostly realized based on clinical signs, except for one study where a complete diagnostic workup was done (hematological exam, biochemistry, abdominal ultrasound if necessary, screening for parvovirosis, pancreatitis, Addison disease, giardiasis and parasites) (Ziese et al 2018).

The term probiotic is defined as a mixture of living microorganisms, which, if consumed in adequate amounts, provide the host with a health benefit (FAO/WHO 2002; Schmitz & Suchodolski 2016). Some researchers consider this term to be one that would rather describe products with an active pharmaceutical effect of live microorganisms, administered to animals or humans to improve their health. In general, probiotics contain bacteria and fungi of an exogenous and endogenous nature, which interact with host systems through various mechanisms (Schmitz & Suchodolski 2016). In the context of the spread of therapy with various antimicrobial substances that have recently lost their effectiveness, probiotics have begun to be used more widely, in human medicine, in various pathologies, having a proven effectiveness. This has also been extrapolated to veterinary medicine, with promising results. The importance of probiotics for the medical world, both human and veterinary, is given by their ability to provide an alternative treatment or prevention for various pathologies. This alternative is also supported by the low risk that probiotics pose to the patient's health. This is validated by studies, which do not report statistically significant increased values compared to control groups that did not consume probiotics (Surawicz & Brandt 2016, Khalighi et al 2016). However, in the case of individuals with impaired immune status, the administration of this type of treatment is controversial (Surawicz & Brandt 2016, Khalighi et al 2016).

Although probiotics have come into frequent use by veterinarians, studies are still ongoing and the number of bacterial strains with a probiotic role already in use is still small. Currently, at European level, only 4 strains with potential probiotic effect, registered and used as medicines, have been examined and approved by EFSA (European Food Safety Authority). Of these, 2 strains belong to the genus *Enterococcus* (*Enterococcus faecium* NCIMB 10415 E1705 and *E. faecium* NCIMB 10415 E1707), one strain to the genus *Lactobacillus* (*Lactobacillus acidophilus* DSM 13241) and a strain of the genus *Bifidobacterium* (BifidoB). Of these, strains of the genus *Enterococcus* have been approved and used in advance in farm animals. For this reason, EFSA concluded that it does not pose a potential danger, if used in small animals. As for the *Lactobacillus* strain, no risk has been reported as it is antibiotic-sensitive, so the potential danger can be combated if necessary. *B. animalis* was the last strain analyzed and approved. Although its resistance to antibiotics could not be explained by genetic notions, EFSA approved its use, with reservations about the efficacy of the product (Schmitz & Suchodolski 2016).

Table 3

Assessments conducted in the studies

References	*Scoring method*	*CBC/b*	*F.E.*	*C.E.*	*I.E.*	*Other diseases*
Aktaş et al 2007	Diarrhea or not (no scoring).	Blood count done, but no mention of results and/or exclusion of positive patients.	Sample collection, but no mention of results and/or exclusion of positive patients. Feces cultures.	Yes	Yes (visually)	Dog with abnormalities were excluded from placebo and probiotic group, but "data are not shown".
Kelley et al 2009	Stool score: 1=firm; 2=soft; 3=viscous; 4=watery	Not done.	Fecal samples just mentioned.	Not mentioned	Implied (only visually)	All dogs presenting serious clinical signs were excluded from the study.
Herstad et al 2009	"Normal" or "abnormal" stools	Not done.	Fecal analysis done, but no mentioning of results and/or exclusion of positive patients. Negative cultures.	Yes	Yes, by different veterinarians (visually); stool frequency and other signs were detailed	Excluded in case of chronic diseases.
Gómez-Gallego et al 2016	"DOGRISK" questionnaire; Waltham Fecal Scoring System	Blood analysis done, but no mention of results and/or exclusion of positive patients.	Flotation and PCR, but no mention of results.	Yes	Yes (visually)	Patients excluded if so.
Ziese et al 2018	Canine hemorrhagic Diarrhea Severity Index; fecal consistency: 0=normal; 1=soft; 2=very soft; 3=watery	CBC and biochemistry done, but no mention of results and/or exclusion of positive patients.	Fecal sample for analysis of microbiota + PCR.	Yes	Evaluation with the dysbiosis index at the beginning and during the study (visually)	Ultrasound and Urine specific gravity done in case of azotemia to exclude these patients.
Shmalberg et al 2019	Score of 3 or less represents feces that has form.	CBC and biochemistry done. Exclusion if abnormal findings.	Flotation done. Exclusion if abnormal finding, but low number of parasite ova tolerated.	Yes	Yes	Dogs with evidence of serious diseases were excluded from the study, based on clinical signs.

Note: CBC/b - Complete blood count/biochemistry; F.E. - fecal examination; C.E. - clinical examination; I.E. - initial evaluation of severity of diarrhea.

Table 4

Types of interventions

Authors	*Pr*	*Pr conservation*	*A.T.*	*Diet*
Aktaş et al 2007	*Saccharomyces boulardii*	Not mentioned	Vaccination and anti-parasite drug administration were applied to all dogs.	Commercial dog feed, not standardized
Kelley et al 2009	*Bifidobacterium animalis* strain AHC7 (effectiveness in treating antibiotic-associated diarrhea in humans)	Survived freeze-drying and storage at room temperature	Metronidazole blinded administration based at the clinician's discretion. Routinely treated with ivermectin and pyrantel. Not standardized.	Daily ration of Eukanuba or Iams maintenance diets. Almost standardized.
Herstad et al 2009	"ZooLac Propaste"*(Lactobacillus farciminis, Pediococcus acidilactici* and others)	Viability not monitored regularly at established intervals. Diminution of potency of probiotics reported.	Two patients in each group were treated with trimethoprim sulfadiazine without a well-considered medical indication. Not standardized (possible confounding variables).	Not standardized
Gómez-Gallego et al 2016	Sour-milk product (*Lactobacillus* spp.)	"remained viable for the recommended usage time [...]"	Not mentioned	Almost standardized. Rice and a low-fat protein source.
Ziese et al 2018	Vivomixx ("high potency" *Streptococcus thermophilus* DSM24731, *Lactobacillus acidophilus* DSM24735®, *Lactobacillus plantarum* DSM24730®, *Lactobacillus paracasei* DSM24733®, *Lactobacillus delbrueckii* subsp. *bulgaricus* DSM24734, *Bifidobacterium breve* DSM24732®, *Bifidobacterium longum* DSM24736®, *Bifidobacterium infantis* DSM24737®), chose because of clinical response in dog with IBD	Stored under refrigerated conditions to ensure maximum potency.	Standardized (fluid therapy, maropitant, analgesics)	Gastrointestinal diet (Royal Canin)
Shmalberg et al 2019	*Bifidobacterium* spp. and *Lactobacillus* spp.	Probiotic potency was tested by the manufacturer at 8 and 18 months.	Clinicians were permitted to administer fluid therapy, fenbendazole, and/or maropitant at their discretions.	Diet was uncontrolled in the treatment period.

Note: Pr - probiotic type and strains; Pr conservation - Conservation requirements for probiotics; A.T. - additional therapy; IBD- inflammatory bowel disease.

The use of probiotics as an alternative therapy in dogs, in various disease conditions, has gained more and more ground. Thus, in the case of acute diarrhea, either infectious or non-infectious, the treatment associated with probiotics has a beneficial effect. In a comparative study between probiotic-treated parvovirus dogs and parvovirus dogs in whose treatment regimen no probiotic was introduced, it was concluded that the survival rate of the first group was significantly increased compared to the second group (Arslan et al 2012; Schmitz & Suchodolski 2016). In the specialized literature situations are reported where the use of probiotics has led to a decrease in the number of *Ancylostoma* eggs (Coelhoet al 2013; Schmitz & Suchodolski 2016). In other cases where diarrhea was not associated with an infectious cause, such as stress diarrhea (or kennel stress), antibiotic-induced diarrhea, or idiopathic diarrhea, the results of probiotic use vary, depending on the type of probiotic used (Schmitz & Suchodolski 2016). Improved fecal scores have been observed in dogs with stress-induced diarrhea who have been treated with *Bifidobacterium animalis* AHC7 (Kelley et al 2009; Schmitz & Suchodolski 2016). The same strain had beneficial effects in dogs with idiopathic diarrhea treated with metronidazole (Schmitz & Suchodolski 2016).

The inclusion of probiotics in treatment regimens for chronic diarrhea has also become a commonly used practice. In the human population, an exaggerated response of the immune system on the microbiome adhering to the intestinal wall or present in the lumen is involved in the pathogenesis of chronic inflammatory diseases of the gastrointestinal tract, and this mechanism of action can be extrapolated to the dog (Schmitz & Suchodolski 2016). The combination of a probiotic leads to the modulation of normal bowel function and the restoration of the microbiome (Schmitz & Suchodolski 2016). In five from the six studies (Aktaş et al 2007; Kelley et al 2009; Herstad et al 2010; Ziese et al 2018; Shmalberg et al 2019) included in our review, the probiotic treatment was combined with additional treatments. In the fourth study (Gómez-Gallego et al 2016), there was no mention of additional therapy used. The probiotics strains used in the six studies were represented by *Sacharomices bouladii*, *Bifidobacterium animalis* strain AHC7, *Lactobacillus* spp., *Pediococcus acidilactici* and *Bifidobacterium* spp. In two out of four studies, clinicians were permitted to administer, at their discretion, additional therapies (fluid therapy, maropitant, fenbendazole) (Shmalberg et al 2019) and trimethoprim-sulfadiazine (Table 3) (Herstad et al 2010). These therapies could have diminished the duration of diarrhea. In one experiment, dogs were excluded if the clinicians identified the need of additional therapies (Herstad et al 2010).

As imbalances in the intestinal microbiome affect the whole body, therapies have been developed to manipulate it. They are designed to change the microbial populations associated with dysbiosis with those related to health. Many studies have shown improved health after the administration of bacterial components. Interpretation of these data is difficult, given that a change in the composition of the microbiome does not necessarily mean an improvement in the clinical condition. Moreover, these improvements in clinical status can occur without a detectable change in the microbiome, or, following changes in bacterial populations, it is not mandatory to be reflected in a change in clinical status (Barko et al 2018).

However, the presence of diarrhea as a symptom may be influenced by several external and internal factors. An external factor is represented by the diet of the animals. Notable etiologies of acute diarrhea include dietary indiscretion or sudden change. The diet composition may be considered a confounding factor in this type of studies. In the six studies selected, none of them used a standardized diet to avoid this confounding factor. In the second study (Kelley et al 2009), authors tried to standardize the food. Dogs were given daily a fixed ration of two products, but they were different in composition. Internal confounding factors may be represented by the age, breed and the body weight of the patients. The dogs enrolled in the studies were poorly characterized, so a difference of age, breed or body weight may have interfered with the results. In the second study (Kelley et al 2009), a significant resolution of diarrhea was observed in the probiotic group compared to the placebo one; although, as indicated in the Table 2, the participants were younger than in other studies. In this trial, 1.58 (+/- 0.18) years was the mean age (Kelley et al 2009). It cannot be concluded that probiotics are more

efficient in younger dogs, taking into consideration only this. Further research should include subgroups based on age. All the studies may also be underpowered by the small size of the study group. None of the six studies included reported adverse effects, and two of them claimed the absence of any (Herstad et al 2010; Shmalberg et al 2019).

Not all strains of bacteria considered as probiotics give equal benefit. As indicated earlier, some strains act on some inflammatory pathways. For example, *Faecalibacterium* may have anti-inflammatory properties (Ziese et al 2018), while others act in reducing the number of pathogenic bacteria in the gut, whereas some can enhance immune functions. So, if the mechanism of action of a probiotic is known, we can administer it safely in certain circumstances. However, sometimes, the problem is more complex when addressed to the probiotic mechanism of action, more exactly, the way in which it is able to colonize the GI tract. For example, *Clostridium perfringens* is a commensal of the intestinal tract and can be found up to 76% in the feces of healthy non-diarrheic dogs (Ziese et al 2018), but studies also showed an increase of *C. perfringens* in dogs with diarrhea. In this case, the colonization of the microbiota by a probiotic should only be partial, since *C. perfringens* is also present in the digestive tract of healthy animals.

Conclusions. Probiotics are used nowadays as an additional therapy in treating diarrhea caused by acute enteropathies in dogs. However, at the present moment, the evidence is not sufficiently powerful to claim neither effectiveness, nor inefficacy of probiotics in reducing the duration of this symptom in dogs. Clinicians should deliver particular strains of bacteria when the effectiveness is supported by strong documented evidence. Still, in the actual context of rising the antimicrobial resistance, the potential benefit of probiotics should not be neglected when choosing a therapy scheme in acute gastrointestinal problems in dogs.

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Authors:
Maria-Cătălina Matei, Department of Animal Physiology, Faculty of Veterinary Medicine, University of Agricultural Sciences and Veterinary Medicine Cluj-Napoca, Calea Manastur no. 3-5, 400372 Cluj, Romania, e-mail: catalina.matei@usamvcluj.ro
Hugo Haab, Department of Animal Physiology, Faculty of Veterinary Medicine, University of Agricultural Sciences and Veterinary Medicine Cluj-Napoca, Calea Manastur no. 3-5, 400372 Cluj, Romania, e-mail: hugo.haab55@gmail.com
Victoria Buza, Department of Animal Physiology, Faculty of Veterinary Medicine, University of Agricultural Sciences and Veterinary Medicine Cluj-Napoca, Calea Manastur no. 3-5, 400372 Cluj, Romania, e-mail: victoria.buza@usamvcluj.ro
Călin Lațiu, Department of Animal Sciences, Faculty of Animal Sciences, University of Agricultural Sciences and Veterinary Medicine Cluj-Napoca, Calea Manastur no. 3-5, 400372 Cluj, Romania, e-mail: calin.latiu@usamvcluj.ro
Andrei Radu Szakacs, Department of Animal Nutrition, Faculty of Veterinary Medicine, University of Agricultural Sciences and Veterinary Medicine Cluj-Napoca, Calea Manastur no. 3-5, 400372 Cluj, Romania, e-mail: andrei.szakacs@usamvcluj.ro
Laura-Cristina Ștefănuț, Department of Animal Physiology, Faculty of Veterinary Medicine, University of Agricultural Sciences and Veterinary Medicine Cluj-Napoca, Calea Manastur no. 3-5, 400372 Cluj, Romania, e-mail: cristina.stefanut@usamvcluj.ro

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