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Review

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Advances in Synbiotic Therapy in the Management of Gastrointestinal Diseases (Enteric Diseases) in Farm Animals

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ABSTRACT

Background: There are various emerging scientific evidences based on research trials and therapeutic practices that 'Synbiotics' (probiotics and prebiotics) play an important role in animal health and nutrition. There has been a significant increase in the characterization and verification of potential health benefits associated with the use of probiotics and prebiotics.
Objective: The primary clinical effects for the application of probiotics have been reported as the ability to modulate the balance and activities of the gastrointestinal (GI) microbiota, treatment of infectious diseases including viral, bacterial and antibiotic associated diarrhea, cellular immune-modulation, lowering of serum cholesterol, improvement in lactose digestion, alleviation of allergy related disorders, reducing the risk of colon cancer and imparting the colonization resistance effect on intestinal microbiota.
Results: The probiotic therapy also known as the microbial interference therapy (MIT) has in particular drawn the interest of animal clinicians, in the treatment of enteric infections of neonatal farm and food animals eliminating the entero-pathogens selectively while building up the normal intestinal flora to flourish. This cannot be achieved by the use of gut-active antibiotics, which lack the ability to discriminate between its friends and foes. The probiotic therapy in food animals has embarked upon establishing a new non-antibiotic arena in the treatment of their several infections, which ultimately not only eliminates the possibility of development of drug resistance but also render the food animals and their produce free from xenobiotic residual effects, which enter the human food chain.
Conclusion: In this review, the current knowledge on the contribution of the gut microbiota to the host well-being has been discussed. Moreover, the available information on probiotics and prebiotics and their application in animal health, production and nutrition has been reviewed.

KEY WORDS: Synbiotics; Gastrointestinal (GI); Probiotics.

ABBREVIATIONS: GI: Gastrointestinal; MIT: Microbial Interference Therapy; NK: Natural Killer; MOS: Mannose Oligosaccharide; FOS: Fructose Oligosaccharide; SARA: Subacute ruminal acidosis; LAB: Lactic Acid Bacteria; GL: Galactosyl-lactose; CEOS: Cello-oligosaccharide; MSPB: Multispecies probiotic; CSPB: Calf specific probiotic; GL: Galactosyl-Lactose.

INTRODUCTION

Probiotics and prebiotics are potentially able to modulate the balance and biological activities of the gastrointestinal (GI) microflora and are considered beneficial to the host. The conjunctional therapeutic or auxiliary use of both is called Synbiotic. Synbiotic have been used as functional foods. However, their efficacy varies and is inconsistent because of the dynamics of the GI community. Environmental factors including diet composition, feeding practices, and farm management have been shown to strongly affect the composition and functions of the microbiota in livestock animals.[1] Probiotics have the ability to enhance intestinal health by stimulating the development of a healthy microbiota and thus stimulating the gut colonization resistance. It is important for these prebiotics and probiotics not to disturb the indigenous population,

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which has adapted to the environment of the GI tract of the host. Most of the bacterial community of GI tract of mammals is occupied by two phyla, *Bacteroidetes* and *Firmicutes*.[2,3] The probiotics have beneficial effects like maintenance of intestinal homeostasis, competitive elimination of pathogens, production of antimicrobial compounds like bacteriocins, promotion of gut barrier function and immune modulation through build up of macrophages, natural killer (NK) cells, antigen-specific cytotoxic T-lymphocytes and the release of various cytokines in a strain-specific and dose-dependent manner.[4] Prebiotics are non-digestible food ingredients which when consumed in sufficient amounts; selectively stimulate the growth and activity of one or a limited number of microbes in the gut, including the probiota. The mannose oligosaccharide (MOS) and fructose oligosaccharide (FOS) are the best two examples.

GASTROINTESTINAL MICROBES IN CATTLE

Neonatal ruminants, including calves, kids and lambs are unique because they are physically and functionally two different types of animals with respect to their GI system at birth and after birth.[5] The intestine of a newly born calf is sterile and immediately after birth colonization of the GI tract begins, and complex and dynamic microbial ecosystem is established in large intestines with high densities of living bacteria as the animal matures. Changes are observed in the GI microbiota of young calves with respect to the metabolic and physiological development of the GI tract. The immature and fluctuating gut microbiota and abrupt changes in diet, may lead to an increase in the susceptibility of young animals to pathogen colonization, and subsequent diarrhea and respiratory diseases. GI microbial communities are involved in the digestion and fermentation of plant polymers, which is of particular importance in mature herbivorous animals.[6] Different microorganisms interact with one another and participate in the systematic digestion of fibrous plant material which they anaerobically ferment into end products that are in turn used as energy sources by the host.[7] Numerous factors such as dietary and management factors can strongly affect the structure and activities of these microbial communities, sometimes leading to impaired health and performance in livestock animals.[8] Sub-acute ruminal acidosis (SARA) is a good example of digestive dysfunction that is increasingly becoming a health problem in the livestock where there is an alteration of the microbial flora.

THERAPEUTIC APPLICATION OF PROBIOTICS IN CALVES

Probiotics such as *Lactobacillus*, *Saccharomyces* or *Bacillus* species generally target the lower intestine and bring about stabilization of the gut microbiota, and decrease the risk of pathogen colonization in young pre-ruminants. The well-known probiotic supplements for young calves are the Lactic Acid Bacteria (LAB) that finds application in regular feeding practices. Such probiotics have beneficial effects in that they balance the gastrointestinal tract microbiota and thus, promote animal nutrition and health. The chief health problem in neonatal calves is neonatal enteritis, manifested by diarrhea, which is treated using antibiotics that are generally used to prevent calves from scouring. However, probiotics/prebiotics have been developed as alternatives to improve animal health and productivity because of the increasing safety concerns regarding the risks of antibiotic resistance and persistence of xenobiotic residues in animal products.[9,10] In calves, fed fermented milk with either mixed Lactic acid bacteria or *L. acidophilus* or *Saccharomyces cerevisiae*, reduction in the incidence of diarrhea is reported.[11-13] Oral treatment with Neomycin and *L. sporogenes* in two groups of undifferentiated diarrhoeic calves had the same therapeutic effects, showing that antibiotic treatment of scouring calves can be replaced with the use of probiotics.[14] In a treatment trial, the therapeutic efficacy of Norfloxacin + Metronidazole was not higher than the efficacy of *L. sporogenes* + *L. acidophilus* in a group of diarrhoeic calves.[15] The adherence of pathogens to the intestinal niches decrease with early colonization by *Lactic acid bacilli* in the intestinal ecosystem. Weight gain and immunocompetence in young calves has been shown to improve with a stable microbial load of *Lactobacillus species.*[16] The oligosaccharides are harnessed with specific functions in calves. The MOS are believed to block colonization of pathogens in the digestive tract. Likewise, feeding FOS in combination with spray-dried bovine serum to calves, reduced the incidence and severity of enteric diseases. FOS also prevents the adhesion of Enterobacteriaceae, most notably *Escherichia coli* and *Salmonella,* to the intestinal epithelium.[17,18] Another sugar like Galactosyl-lactose (GL) that is a trisaccharide (galactose plus lactose) produced by the enzymatic treatment of whey with beta-galactosidase has also been suggested to have important functions in calves. Supplementation with MOS, FOS and GL may improve the growth performance of calves in both pre-weaning and post-weaning stages.[19] Cello-oligosaccharide (CEOS) also used as a probiotic in calves, was utilized by specific microbes inhabiting the calf intestines. It has been observed that CEOS feeding increases the number of butyric acid-producing bacteria belonging to *C. coccoides* and *E. rectale.*[20] It is a valuable source of energy, and is also involved in the growth and differentiation of intestinal cells in the large intestines, thus improving its epithelial structure[21] enhancing digestion and absorption efficiencies. An *in vivo* CEOS feeding improved daily weight gain and feed efficiency in calves during the post-weaning period which was attributed to the enhancement in ruminal fermentation. CEOS also acts as a source of nutrition for various types of microbes. The various types of probiotics used in calves also include yeast culture, Multispecies probiotic (MSPB) or Calf specific probiotic (CSPB), *Lactobacillus casei* with the effects on the increase in body weight and feed efficiency.

AUXILIARY EFFECT OF PROBIOTICS/PREBIOTICS ON THE PERFORMANCE OF HEIFERS, LACTATING COWS, AND BEEF CATTLE

Probiotics and prebiotics (synbiotics) for adult ruminants are mainly responsible for selective and efficient fibre digestion by

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rumen microorganisms and to ameliorate gastrointestinal disease symptoms. It has been observed in a recent study that yeast supplementation in ruminants increased dry matter intake, milk yield, rumen pH, rumen volatile fatty acid concentration, and organic matter digestibility.[22] The different types of probiotics have positive effects on various digestive processes in ruminants which include cellulolytic functions, synthesis of microbial proteins, and protection of animals from gastrointestinal diseases.

Different strains of yeast mostly *Saccharomyces cerevisiae* are the primary forms of probiotics commonly used in dairy cows. Lactate-producing bacteria such as *Enterococcus* and *Lactobacillus*, which sustain lactic acids are less commonly used than *Streptococcus bovis*, which may represent a possible means of limiting acidosis in high-concentrate-fed animals especially feedlot cattle.[23] In order to avoid the accumulation of ruminal lactate in ruminants, administration of combinations containing *Megasphera elsdenii* or *Propionibacterium* species that utilize lactate have also been administered as direct fed microbials.[24,25] The most consistent effects following the addition of yeast cultures to the diet include improved productivity in both lactating and growing animals. The mode of action of yeast-products has not yet been elucidated in detail, but is generally considered to involve changes in rumen fermentation rates and patterns. Certain strains of active dry yeast are particularly effective at raising and stabilising ruminal pH by stimulating certain populations of ciliate protozoa, which rapidly engulf starch and, thus, effectively compete with amylolytic lactate producing bacteria.[26,27] Yeast has the potential to alter the fermentation process in the rumen in a manner that reduces the formation of rumen gas. The cells of *S. cerevisiae* provide growth factors for rumen microbes, including organic acids and oligosaccharides, B vitamins and amino acids which stimulate microbial growth in the rumen, thereby indirectly stabilizing ruminal pH.[28] Another function of yeast in the rumen is scavenging of oxygen which creates the more anaerobic environment required by rumen microorganisms.[29] Thus, yeast acts not only as probiotic but also helps other rumen community members to grow, and thus acts as a prebiotic. Yeast supplementation also increased the abundance of Lactate-utilizing bacteria such as *Megasphaera* and *Selenomonas* as well as fibrolytic groups such as *Fibrobactor* and *Ruminococcus,* thus improving cellulolytic activity as a supposed mode of action of yeast. In a large scale trial, steers fed a standard steam-flanked corn-based finishing diet containing *L. acidophilus* which showed a reduction of *E. coli* O157 fecal shedding by 57%[30] and by 35% in beef cattle.[31] In dairy ruminants, live yeasts have been shown to improve performance by increasing dry matter intake and milk yield.[32]

The use of prebiotics in cattle has some disadvantages due to the ability of ruminants to degrade most of the prebiotics; however, enhancements in rumen protective technologies such as lipid encapsulation, polymer protection, etc., may allow these compounds to be used in feedlot and dairy cattle.[33] Supplementation of Sorbitol, L-arabinose, trehalose and rhamnose in cattle rumen medium displaced *E. coli* O157:H7 within 72 hours,[34] thus reducing the GI tract infections.

APPLICATIONS OF PROBIOTICS/PREBIOTICS IN PIGS

Probiotics have been used in pigs to decrease the pathogen load and ameliorate gastrointestinal disease symptoms. In neonatal pigs, it has been observed that porcine-derived CE culture of known bacterial composition reduced the mortality and shedding of enterotoxigenic *E. coli* and *Salmonella enteric* serovar *choleraesius.*[35] The frequency of diarrhoea was reduced with improved performance as indicated by weight gain, by daily supplementation of *Enterococcus faecium* orally to piglets from birth to weaning[36] and it was observed that *Enterococcus faecium* reduced the population of *Enterococcus faecalis* and other enteropathogenic bacteria responsible for the onset of post-weaning diarrhoea in piglets.[37] The mode of action of probiotics in swine showed a correlation between their administration and the decline of virulence gene expression of the resident *E. coli* microbiota of the host. In neonatal weaned pigs, supplementation of the diet with a strain of *Lactobacillus plantarum* resulted in an increase in the total gut population of Lactobacilli. A synbiotic product containing *L. plantarum*, fructo-oligosaccharide and maltodextrin reduced *E. coli* 08:K88 counts in the jejunum and colon of piglets was observed due to increased acetate concentrations in the ileum and colon.[38] The *L. sorbitus* significantly improved daily weight gain and reduced the levels of Enterotoxigenic *E. coli* (ETEC) in the ileum when fed directly to piglets after weaning.[39] Diarrhoea induced by *E. coli* K 88 in post weaning piglets was cured by supplementation of probiotic containing *L. rhamnosus*, possibly *via* modulation of intestinal microflora, regulation of production of systemic inflammatory cytokines and enhancement of intestinal antibody defences.[40]

Administration of *Lactobacilli* and *Bifidobacteria* in pigs immediately after birth reduced the incidence and severity of necrotizing enterocolitis and colonization density of the highly pathogenic *Clostridium perfringens*.[41] *Bifidobacterium lactis* and *Lactobacillus rhamnosus* in addition individually reduced adherence of each other and that of *Salmonella, E. coli, Clostridium* species to the intestinal mucosa in swine, thus reducing the severity of clinical diseases.[42] It was observed that *Bifidobacterium lactis* HN019 reduced *E. coli* infections and post-weaning diarrhoea associated with rota virus in pigs.[43] The administration of *Bifidobacterium animalis* subsp. *lactis* showed increased growth rate and ratio of *Bifidobacteria* to *E. coli* in the gut in weaning piglets.[44] It has been reported that feeding of probiotic combinations containing *Lactobacillus, Saccharomyces* and *Pediococcus,* resulted in an increased potential to modulate IgA secretion in the gut, reduced bacterial translocation to mesenteric lymph nodes, and activated the lymphocyte population following the enterotoxigenic *E. coli* infection in swine. It was reported that feeding of probiotics containing *Bacillus* species such as *Bacillus subtilis*, and *Bacillus lichiniformis* in pigs caused a reduction in scours, morbidity and mortality.[45] Different types of probiotics/prebiotics were added to the diet of pigs to test their influence on gastrointestinal microbiota or on health status improvement when challenged with pathogens such as Transgalacto-oligosaccharides (TOS) included at 35 g/kg in growing pigs which resulted in a significant increase in

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Table1: Recent Probiotic/Prebiotic Trials Applied for Young Cattle.

Targets and materials applied	Positive effects
Yeast culture	Increased feed efficiency by enhancing rumen fermentation rates, stabilising ruminal pH
Lactobacillus casei	Increased weight gain by balancing the GI tract microbiota
L. acidophilus	Prevent rotavirus and antibiotic associated diarrhea
L. sorbitus	Increased weight gain, immunocompetence
Bifidobacterium	Good health status by maintaining a balance of microbiota in GIT
Fructooligosaccharide (FOS)	Increased feed efficiency, reduced severity and incidence of enteric diseases by blocking colonization of pathogens
Mannoseoligosaccharide (MOS)	Increased health and performance by blocking colonization of pathogens
Cellooligosaccharide	Increased weight gain by modulating the intestinal bacterial community, enhancement of ruminal fermentation

the fecal *Bifidobacteria, Lactobacilli* and enhanced saccharolytic activities in the porcine colon. Similarly, Galacto-oligosaccharide (GOS) mixture supplied at 40 g/kg of diet potentially inhibited the attachment of enterotoxigenic *E. coli*, *Salmonella* to HT29 cells, showed an increase in the density of *Bifidobacterium* and acetate concentration, and resulted in the decrease of pH compared with control diet (Table 1).[46,47]

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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