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A. NAWAB, W. LIU, G. LI, F. IBTISHAM, D P. FOX, Y. ZHAO, J. WO, M. XIAO, Y. NAWAB, L. AN

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Review article
Ανασκόπηση

The Potential Role of Probiotics (nutraceuticals) in Gut Health of Domestic Animals; an Alternative to Antibiotic Growth Promoters

A. Nawab[1], W. Liu[1], G. Li[1], F. Ibtisham[1], D. P. Fox[2], Y. Zhao[1], J. Wu[1], M. Xiao[1], Y. Nawab[3], L. An[1*]

1 Department of Livestock Production and Management, Faculty of Animal Sciences, College of Agricultural Sciences, Guangdong Ocean University, Zhanjiang 524088, Guangdong, China*

2 Department of Foreign Language, Guangdong Ocean University, Zhanjiang 524088, Guangdong, China

3 Faculty of Veterinary Medicine, PMAS-Arid Agriculture University Rawalpindi, Pakistan

ABSTRACT. The term gut health is currently becoming more important for domestic animals including poultry. Gut health refers to the fundamental organ system which covers multiple positive functions like effective digestion, stabilizing intestinal microbiota, gut pH and modulation of effective immune response. Gut health depends on proper balance of microbial population. A wide range of feed and pathogen associated factors influence this balance, and adversely affect the animal health status and production performance. Antibiotic stimulators have been used in farm animals to achieve maximum production. But drug resistance and residual effects of antibiotics in animal products (milk, meat and egg etc.) have raised serious issues in human life. Therefore, The European Union (EU) has strictly banned the application of antibiotic stimulators in livestock nutrition in several others countries including China. As a result, an alternative to antibiotic growth promoters are required to support the profitable and sustainable animal production system. Probiotics as nutraceuticals has been categorized as an alternative natural feed supplement for commercial utilization. Such products have been recognized as safe feed additives in animal industry. Very few studies have comparatively described the effect of probiotics on gut health of domestic animals. Therefore, the aim of this review is not only to explore the beneficial effects of probiotics in improving gut health of domestic animals as an alternative to antibiotic growth promoters, but also to evaluate the probiotics associated health and risk factors, and to provide comprehensive scientific information for researchers, scientists and commercial producers.

Keywords: Animal production, Antibiotic growth promoters, Domestic animals, Gut health, Immune response, Probiotics

Corresponding Author:
Lilong An
Haida Road, Mazhang District, Zhanjiang 524088, Guangdong, China
Email; anlilong@126.com

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INTRODUCTION

Optimum production level and best feed efficiency ratio are two main objectives in animal production system, which can be achieved by using of probiotics. A number of factors affect the production of animals including genetic potential, quality of feed, environmental stress and disease incidence. Excluding these factors, intestinal health has become the topic of great interest in animal production (Rinttila and Apajalahti, 2013). However, the term is specified to the gastrointestinal tract only and does not comprise other organs (Lalles et al., 2007). Gut mucosa acts as selectively permeable barrier between the lumen environment and the internal body tissues (Yegani and Korver, 2008; Markowiak and Śliżewska, 2018).

The gut is the major site for different processes such as digestion and fermentation of feed, nutrient absorption and metabolism, along with intestinal integrity and immune system development (Sommer and Kiel, 2013; Roselli et al., 2017). An animals' gut mucosa acts as an effective barrier between the tissues of the animal and its luminal content (Yegani and Korver, 2008). The gut is also a main site of extensive exposure to environmental benefits as well as harmful pathogens (Servin, 2006). Therefore, intestinal mucosa is a good determinant of gut health and optimal performances of the animals (Markowiak and Śliżewska, 2018). A lot of factors including feed, environment and infectious agents appear to affect the gut health and function which may consequently affect the animals health and production performance (Yegani and Korver, 2008).

Overuse and misuse of antibiotics cause antibiotic resistance in farm animals (Kabir, 2009) resulting in high residual effects in animal products such as meat, milk and egg which can develop drug-resistant microorganisms in human life and exerting deleterious effects on the environment (Olatoye and Ehinwomo, 2010; Markowiak and Śliżewska, 2018). Hence, in 2006, the European Union (EU) banned the usage of AGPs, which has now been followed by many other countries including China (Markowiak and Śliżewska, 2018). Therefore, in China, the poultry and livestock industry is now struggling to maintain animal production due to high feed costs and the restriction of AGPs in animal feeds. On the other hand, both consumers and manufacturers are now seeking alternatives to AGPs to confirm the safety of animal products (Smith et al. 2002). Experts have continuously worked to formulate natural, safe and effective growth promoters referred to as probiotics which might play a significant role for improving gut microbiota and gut health of domestic animals (Azzaz et al., 2012). Biotechnology has significant impact on animal nutrition and has given permission to produce large amounts of large amounts of probiotic supplements and their metabolites (Chauhan and Ak, 2014). Probiotics enhance feed intake, milk production, immune system and gut health (El-din, 2015; Roselli et al., 2017; Markowiak and Śliżewska, 2018) but it has reported that probiotic have different consequences on gut health of domestic animals (cattle, buffalo, pig and poultry) depending upon its composition, animals age and utilization in animal feeding (Markowiak and Śliżewska, 2018). Very few studies have thoroughly explored the effect of probiotic as nutraceuticals on gut health in domestic animals. Therefore, this review aims is to evaluate the potential role of probiotics (nutraceuticals) on intestinal health of domestic animals and their possible outcomes on animal physiology. The safety and hazards associated with probiotics have also been briefly summarized.

PROBIOTIC AS NUTRACEUTICALS: WHAT ARE THEY?

The term "nutraceutical" can be defined as any food or food particles that play an essential role in maintaining normal body function that provides health benefits, including the prevention and treatment of a disease (Das et al., 2012). Nutraceuticals are obtained from dietary supplements (probiotics, prebiotics, synbiotics, organic acids, clay minerals, exogenous enzymes, recombinant enzymes, nucleotides and polyunsaturated fatty acids), isolated nutrients (vitamin, mineral, amino acids, fatty acids) and herbal products (herbs or botanical products) (Das et al., 2012). Very specifically, they have been tested for their potential to replace AGPs in livestock and poultry nutrition (Khan et al., 2012; Sethiya, 2016). Probiotics as nutraceuticals are primarily used to improve animal health towards different infectious agents rather than normal nutrition. The potentials of these probiotics in improving gut morphology, gut health and nutrient absorption may also encourage animal owners to utilize this feed supplementation to support intestinal health and production performance of farm animals.

SELECTION CRITERIA OF PROBIOTICS

Whereas selecting the probiotics, certain points must be taken into consideration: production, administration, application, colonial survival in the host and their physiological benefits. Probiotics should have the following properties in order to be effective: they must be able to produce antimicrobial property towards pathogens (Kullen and Klaenhammer 2000), they must have ability to adhere with intestinal epithelium and colonize the lumen of the gastrointestinal tract, they must have a positive effect on animals (non-pathogenic, non-reactive and non-toxic) (Roselli et al., 2017), they must be able to withstand the gastric acidity, bile salts and digestive enzymes (Parvez et al., 2006), they must have ability to reduce the incidence and severity of pathogen adhesion, they must have ability to stabilize normal gut microflora and be associated with health benefits (Markowiak and Śliżewska, 2018).

MODE OF ACTION OF PROBIOTICS

The significant property of probiotics is the ability to reduce incidence and severity of diseases due to development of colonization resistance or inhibitory effects towards pathogens. However Probiotics hinder pathogenic bacteria both in vitro and in vivo by different mechanisms of action, the exact method in which they exert their positive effects has not been fully determined (Kechagia et al., 2013). However, Seo et al. (2010) enlisted several possible modes of action of probiotics in domestic animals (ruminant, pig and poultry) (Table 1) such as: maintain the normal gut microbial growth by competitive exclusion and antagonism (Oliveira et al., 2000; Kabir 2009; Binek, 2016), alter the pattern of ruminal fermentation, improve feed intake and nutrient digestibility (Ghareeb and Zentek, 2006), and the supply of nutrients to the small intestine, higher nutrient retention rate and decreased stress by immunostimulation. Other mechanisms have been suggested specifically by several authors to illuminate positive effects of probiotics (Markowiak and Śliżewska, 2018) which can be explained as following; production of antimicrobial substances (acids, bacteriocins, antibiotics) (Vandenbergh, 1993), competition with detrimental organisms for adhesion sites (Retta, 2016), modulate immune response through increasing phagocytic activity of macrophages and natural killer cells (Erika et al., 2001), reduction of bacterial toxin metabolism metabolism (Markowiak and Śliżewska, 2018) and variation of enzymes secretion (Azzaz et al., 2015). These mechanisms may benefits ruminant by increasing nutrient absorption through reducing the

Table 1. Mode of action of probiotics

Item	Description
Competitive exclusion	Compete for nutrients in the gastro-intestinal Exclusion property towards pathogens
Antimicrobial effects	Produce antimicrobial substances which have bacteriostatic or bactericidal properties Reduce luminal pH and Inhibits the growth of bacteria (G-negative) by producing hydrogen peroxide
Immune booster	Stabilize intestinal integrity and improve the gut innate immune response Improve gut innate immune response through chloride secretion or increasing mucus production
Antitoxin effects	Inhibits toxin expression in pathogenic bacteria Neutralize pathogens by producing enterotoxins
Effect on nutrient digestibility	Increase digestive enzyme activity in the gastrointestinal tract Increase the digestion and absorption of nutrients
Ant-oxidative activity	Stress mitigation ability

thickness of an inflamed intestinal epithelium. If the thickness of the intestinal wall is decreased, bacterial feed supplementation could improve the efficiency of energy utilization by reducing the energy used for tissue turnover in the gastrointestinal tract (Peterson et al., 2007).

COMPETITIVE EXCLUSION

Competitive exclusion (CE) can be defined as the response of healthy gut microbiota to protect the intestine towards the establishment of pathogens and to reduce infection of the gastrointestinal tract in animals (Markowiak and Śliżewska, 2018). Probiotics have exclusion property towards pathogens both in case of preventive and therapeutic management. Gut epithelia have receptors for microorganism adhesion; both beneficial and pathogenic microorganisms for the same intestinal sites. Probiotic adhesion quality blocks the association between gut epithelia and infectious agents (Yang et al., 2015). Thus, probiotics based bacteria eliminate microorganism and prevent the gut infection of farm animal including cattle, buffalo, sheep, goat, pig and poultry (Liao and Nyachoti, 2017).

The mechanism of CE also specifies that probiotics and pathogenic bacteria compete for nutrient absorption (Yang et al., 2015). This competition between good and harmful bacteria can cause a reduction in pathogens. In addition, energy utilization may decrease bacterial growth and prevent pathogens from resisting the effects of gut peristalsis (Cho et al., 2011; Yirga, 2015). Hence, probiotics have been widely used in animal and poultry farming due to their ability to inhibit the harmful effects of pathogens like *Clostridium perferinges, Salmonella, Campylobacter jejuni and Escherichia coli* (Bermudez-Brito et al., 2012; Goudarzi et al., 2014; Syngai et al., 2016). Another study reported that with the administration of *L. rhamnosus* GG in rats, the first day pups reduce the adhesion and colonization of enteroinvasive *E. coli* (Sherman and Bennett, 2004). It has been observed that probiotic strains (*L. johnsonii* NCC 533, *L. casei* Shirota and *L. acidophilus* LB) control the infection of *H. pylori* and gastritis in mice models (Sgouras et al., 2005; Isobe et al., 2012).

ANTIMICROBIAL SUBSTANCES

Probiotic containing beneficial bacteria, once established in the intestine, may produce antimicrobial substances that may hinder the growth of pathogens in the gut of cattle, pig and poultry (Yirga, 2015; Bajagai et al., 2016). Many probiotic bacteria, comprising lactic acid bacteria (LAB) (Flynn et al., 2002), *bacillus* (Hyronimus et al., 2000) and *bifidobacteria* (Cheikhyoussef et al., 2008), can produce various types of heat resistant bacteriocins (Cotter et al., 2005) which have antimicrobial property towards pathogenic microorganism of animals including *Staphylococcus*, *Bacillus, Listeria, Enterococcus*, and *Salmonella* species (Flynn et al., 2002; Corr et al., 2007).

Probiotics such as *Lactobacillus* ferment lactose to lactic acid, reducing the pH of gut to a level that pathogenic bacteria cannot tolerate (Bajagai et al., 2016). Some strains also produce hydrogen peroxide, which hinders the growth of gram-negative bacteria (Yirga, 2015; Bajagai et al., 2016). These substances have detrimental effects on pathogens, which is mainly due to reducing pH of gut. A decline in pH may partially unbalance the secretion of hydrochloric acid in the stomach of young piglets. It can reduce the stomach ability to digest and absorb feed and kill off pathogens (Kenny et al., 2011). Furthermore, yeasts have also been reported to stabilize the ruminal pH and reduce the risk of acidosis by competing with lactic acid producing bacteria (Yirga, 2015). The digestion and feed intake can be improved by modifications of ruminal microbiota. Probiotics produce antioxidants, organic acids, reuterin, microcin and bacteriocins (Yirga, 2015). These substances may decrease not only the number of potential pathogens but may also hinder bacterial metabolism and toxin production (Eswara et al., 2010; Hou et al., 2015). LAB produce bacteriocins to deactivate the gram negative bacteria in combination with other environmental elements such as organic acids, low temperatures, and detergents (Alakomi et al., 2003). Furthermore, they can inhibit amine synthesis. Coliform bacteria decarboxylate amino acids to produce amines (toxic to epithelium) which can affect gut mucosa and cause diarrhea in young calf. If coliforms bacterial growth can be prevented, then amine production can also be hindered (Yirga, 2015), which may be advantageous in preventing neonatal diarrhea and calf mortality.

EXCLUSION OF NUTRIENTS

Probiotics have been designated to enhance the digestion and absorption of nutrients. The improved production of animals due to probiotics can be associated with an increase in digestion and absorption of nutrients (Markowiak and Śliżewska, 2018). The response of L. bulgaricus in broiler chickens diets was different depend on supplementation of various level of probiotic. There was no significant effect on digestibility of crude protein (CP) or fat at a rate of 2 ×106 cfu/g, but there was an increase in CP, fat and weight gain (WG) 7 to 11%, 6.5 to 13.4%, 7.9 to 11.7% respectively, at a rate of 6 ×106 cfu/g and 8 ×106 cfu/g (Apata, 2008). Another study observed that probiotic (AgiPro A100) offered to broiler chickens had increased dry matter (DM) digestibility by 12.4% at 42 day trial (Li et al., 2008) and no effects were reported on weight gain (WG), average daily gain (ADG), feed intake (FI) and feed conversion ratio (FCR). A similar study revealed that probiotics improved the ileal digestibility of essential amino acids (EAA), increased 5% WG (Zhang and Kim, 2014) and enhanced the bioavailability of calcium in broiler chickens (Chawla et al., 2013).

Probiotics increase the absorption of nutrients in the diet which may be due to the increase enzyme activity in the gastrointestinal tract. Probiotics containing *Lactobacillus* altered the enzyme activity in the gastrointestinal tract of domestic animals. L. acidophilus given at a rate of 2 $\times 10^6$ cfu/g of feed had increased the amylase activity in the small intestines of chickens (Jin et al., 2000). But, there was no change in proteolytic and lipolytic activity. The result indicated that a 4.6% increase in WG and a 5% increase in feed efficiency were due to the enhanced activity of amylase in the small intestine. A similar study has been reported that commercial probiotics (Probios) containing L. acidophilus, L. plantarum, L. casei and E. faecium increased the sucrose, lactase and amylase activity but no effects were observed on peptidase activity in the small intestine of young piglets (Collington et al., 1990). Bacillus amyloliquefaciens (spore forming bacteria) produce extracellular enzymes including α-amylase, cellulase, proteases and metalloproteases (Gangadharan et al., 2008) which may increase nutrient digestion. Probiotics improved the gut enzyme activity due to modification in the gut micro ecosystem and reduced the incidence of ruminal acidosis by stablizing the ruminal volatile fatty acids (VFAs) (Arcos-Garcıia et al., 2000).

Feed containing probiotics yeast culture (YC) exposed to lambs at concentration 0, 3, and 6 g/day, increased digestibility of dry matter (DM), organic matter (OM), crude protein (CP) at a concentration 3 g/day compared to the control group (Haddad and Goussous, 2005). Mukhtar et al (Mukhtar et al., 2010) reported that lambs given a concentrated probiotic diet had higher DM and CP digestibility than lambs without probiotics. In addition, it was reported that probiotics fed to growing lambs had enhanced digestibility of DM, OM, CP, CF, ether extract (EE), and nitrogen free extract (NFE) compared to the control group. No significant differences were observed in nutrients digestibility except for CP (Hillal et al., 2011). In contrast, another study indicated that probiotic mixed feed of weaned goats (Whitley et al., 2009) or lambs (Ding et al., 2008) did not affect the DM, OM, and CP digestibility compared to control group. Inconsistencies in the results of these studies may be due to variations in the animal models, environment, administration, composition and quality of probiotic, or supplementation times duration (Whitley et al., 2009). Probiotics improved the intestinal villi and villus height: crypt ratio in poultry (Biloni et al., 2013; Jayaraman et al., 2013; Afsharmanesh and Sadaghi, 2014), by increasing the surface area for nutrient absorption. Yeast also has the potential to change the metabolic process and to reduces the methane gas production in rumen (Chung et al., 2011). Hence, nutritionists have determined that probiotics have significant effects on nutrient digestibility.

REDUCING AMMONIA PRODUCTION

In poultry housing, ammonia is excreted due to rich protein diets. Ammonia has detrimental effects on the eyes and nasal cavity of affected chickens due to the gas alkalinity and corrosiveness. NH3 in respiratory tract reacts with the moisture and forms a corrosive alkaline solution (ammonium solution). The ammonium solution paralyze the respiratory cilia and reduce immunity in the respiratory system which increase the disease susceptibility especially E.coli (Maliselo and Nkonde, 2015). Ammonia emission causes keratoconjunctivitis in poultry birds including photophobia, excessive lacrimation, respiratory distress, and/or closure of the eyelids. Regarding this concern, probiotics acts as antagonists of ammonifying bacteria that harbors the gut of poultry and prevents keratoconjunctivitis from developing (Patterson and Burkholder, 2003; Sarangi et al., 2016). They reduce nutrient deterioration and reduce ammonia production in the gut lumen. Probiotics *(Lactobacillus casei*) reduces the activity of urease in the gut of chickens and ultimately decrease uric acid, ammonia, urea and non-protein nitrogen sources (Fuller, 2001; Patterson and Burkholder, 2003). A diet con-

Table 2. Probiotics commonly used in animal nutrition

Genus	Species	Genus	Species
Lactobacillus	*L. acidophilus* *L. lactis* *L. amylovorus* *L. cellobiosus* *L. casei* *L. brevis* *L. plantarum* *L. fermentum* *L. crispatus* *L. curvatus* *L. farmicinis* *L. gasseri* *L. johnsonii* *L. paracasei* *L. reuteri* *L. rhamnosus* *L. sobrius* *L. bulgaricus* *L. delbrueckii subsp. bulgaricus* *L. salivarius*	*Enterococcus*	*E. faecium* *E. faecalis*
		Pediococcus	*P. acidilactici* *P. parvulus* *P. pentosaceus subsp. Pentosaceous*
		Lactococcus	*L. lactis*
		Streptococcus	*S. bovis* *S. diacetylactis* *S. thermophilus* *S. gallolyticus* *S. salivarius* *S. faecalis* *S. infantarius* *S. faecium* *S. cremoris* *S. intermedius;*
Bifidobacterium	*B. lactis* *B. bifidum* *B. bifidus* *B. longum* *B. thermophilum* *B. breve* *B. pseudolongum* *B. adolescentis* *B. animalis* *B. infantis*	*Aspergyllus*	*A. oriza* *A. niger*
		Escherichia	*E. coli strain nissle*
		Propionibacterium	*P. jensenii* *P. freudenreichii* *P. acidipropionici* *P. shermanii*
Bacillus	*B. cereus* *B. coagulans* *B. megaterium* *B. subtilis* *B. mesentricus* *B. amyloliquefaciens* *B. licheniformi* *B. polymyxa* *B. toyonensis*	*Saccharomyces*	*S. boulardii* *S. cerevisiae* *S. carlsbergensis* *S. pastorianus* *S. servisia*
		Prevotella	*P. bryantii*
		Clostridium	*C. butyricum*
Leuconosto	*L. mesenteroides* *L. citreum* *L. lactis*	*Candida*	*C. utilis* *C. pintolepesii;*
		Brevibacillus	*B. laterosporus*
		Megasphaera	*M. elsdenii*

References: (Pollmann et al., 1980; Azizpour et al., 2009; Le Bon et al., 2010; Meng et al., 2010; Daudelin et al., 2011different litters of pigs were randomly assigned to one of the following treatments: 1; Pan et al., 2011; Rastogi et al., 2011; Ibrahim et al., 2012; Kechagia et al., 2013; Yirga, 2015; Lv et al., 2015; Bajagai et al., 2016) taining probiotics such as *Streptococcus faecium* and *Bacillus subtilis* also decreases the ammonia concentration in the excreta of poultry birds.

PROBIOTICS AND ITS SIGNIFICANCE

According to FAO/WHO, Probiotics are referred as "living microorganism which, when administrated in excessive amounts confer a healthy benefits to the host" via improving the host gut microbial population, improving the colonization resistance towards pathogens and stimulating the immune responses (Das et al., 2012; Bajagai et al., 2016; Jaiswal et al., 2017). Various microorganism strains are being used in probiotic preparations are vary in composition, such as LAB (*Lactobacillus bulgaricus, Lactobacillus acidophilus, Lactobacillus lactis, Lactobacillus casei, Lactobacillus plantarum, Lactobacillus salivarius, Streptococcus thermophilus, Enterococcus faecium, Enterococcus faecalis and Bifidobacterium spp*) are the most common type of probiotic bacteria (Kabir, 2009; Markowiak and Śliżewska, 2018) (Table 2).

EFFECTS OF PROBIOTICS ON ANIMAL PRODUCTION

The significant effects of probiotics in human and domestic animal health have been well documented. Probiotics have favorable effects on FCR, WG, milk yield, gastrointestinal microbiota, pH and intestinal immunity as well as animal health status (Table 3) (Kritas et al. 2006; Bhandari et al., 2010; Kenny et al., 2011; Upadhaya et al., 2015; Markowiak and Śliżewska, 2018). A study reported that probiotics given to sheep had increased feed intake and growth performance (Khalid et al., 2011). A small ruminant study determined that increased number of cellulolytic bacteria may improve growth rate, nutrient digestibility and fermentation process (Soren et al., 2013). Probiotics containing S. cerevisiae and E. faecium fed to cattle had increased milk fat concentration due to increased production of volatile fatty acids (VFAs) (Oetzel et al., 2007).

Effects of Probiotics on Cattle

LAB is a well-practiced probiotic strain in ruminant nutrition. Diarrhea is the main cause of death in young calves leading to major economic losses (Cowles et al., 2006; Markowiak and Śliżewska, 2018); thus, its prevention is important to economically support the calf producers (Servin, 2004; Timmerman et al., 2005). Numerous published data shows that probiotics can improve the balance of gut microbiota (Aattour et al., 2002), reduce the gut pH and infectious agents by enhancing immunological response (Musa et al., 2009; Sanchez et al., 2017).

For several years, AGPs have been used to prevent the economic losses in the animal industry. But antibiotic resistance in food animal and antibiotic residues in animal products has generated public health concerns (Martinez-Vaz et al., 2014) .In this circumstance, probiotics have been categorized as one of the alternatives in animal feed (Gyles, 2007), preventing the production of E. coliin in the intestine, and to reduce the incidence of diarrhoea in ruminants (Reid and Friendship, 2002; Bahari, 2017; Markowiak and Śliżewska, 2018). However, the phenomenon of probiotics in gut microbiota currently remains unclear. The most common probiotics species, *lactobacillus*, *bifidobacterium* and yeast strains have been well documented in rumen development and gestrointestinal health status (Uyeno et al., 2010; Bahari, 2017). LAB strains modulate rumen microbiota (Weinberg et al., 2004; Han et al., 2014; Goto et al., 2016), increased the DMI, WG and improved animal health. Published data has reported that probiotics containing *Lactobacillus* or *Enterococcus* strains have reduced the incidence of acidosis in lactating cattle (Goto et al., 2016). The principle concept is that probiotics may reduce pH by decreasing lactic acid formation and enhancing the consumption of lactic acid by ruminal bacteria (Goto et al., 2016; Roselli et al., 2017).

Moreover, LAB strains may inhibit the adhesion of pathogens to gut mucosa during the initial days of colonization (Isolauri et al., 2001; Bahari, 2017). It has been investigated that feed containing *Lactobacillus* species had increased WG and immunocompetence in young calves (Al-Saiady, 2012). In contrast, previous findings related to probiotics have remained ambiguous in calf studies. The efficiency of probiotics may be different depending on the health conditions of calves, because in previous findings, the consequences of probiotics were signif-

Table 3. Effect of probiotics on animal production

Probiotic strains	Species	Consequences	References
Bacillus licheniformis *Bacillus subtilis*	Holstein calves	Higher ADG and live weight.	(Kowalski et al., 2009)
Bacillus licheniformis *Bacillus subtilis*	Holstein cows	Increases milk production, protein, ruminal digestibility and total VFA contents.	(Qiao et al., 2010)
Enterococcus faecium *Saccharomyces cerevisiae*	Cow	Improves milk fat % in first lactating cow	(Oetzel et al., 2007)
Propionibacterium strain P169	Cow	Improves energetic efficiency, propionate concentration, lower acetate contents	(Weiss et al., 2008)
Prevotella bryantii	Cow	Increases milk fat %, acetate and butyrate concentration, and decrease lactate concentration	(Chiquette et al., 2008)
Propionibacterium strain P169 *Yeast culture*	Cow	Increases propionate concentration, ruminal digestibility, microbial N synthesis, or passage rates did not report any difference	(Lehloenya et al., 2008)
Multi-species probiotic	Young cattle	Improves WG	(Bayatkouhsar et al., 2013)
S. cerevisiae	Lactating cattle	Increases milk fat production	(Alugongo et al., 2017)
S. cerevisiae	Camel	Improved weight gain and feed intake	(Mohamed et al., 2009)
S. cerevisiae	Buffalo calf	Improves cellulose digestibility	(Kumar et al., 1994)Saccharomyces cerevisiae plus growth medium
L. plantarum	Pig	Improved growth and pork quality	(Yang et al., 2015)
Enterococcus faecium	Weaned piglets	Improves FCR and growth rate	(Wang et al., 2016)the third and the fifth day after birth, while the control group received 2 ml of 10% sterilised skimmed milk without probiotics at the same time. Results showed that oral administration of E. faecium EF1 was associated with a remarkable increase on the body weight of piglets for both suckling and weaning periods, by 30.73% (P<0.01
E. faecium, *L. acidophilus, Pediococcus pentosaceus,* *L plantarum*	Weaned piglets	Improves FCR, feed intake and WG	(Giang et al., 2010)
Pediococcus acidilactici, *Lactococcus lactis,* *L. casei,* *Enterococcus faecium*	Weaned piglets	Improves growth rate, decreases coliform counts by facilitating antimicrobial substances	(Guerra et al., 2017)
Bacillus licheneformis	Broiler chicken	Improves FCR and growth performance	(Liu et al., 2012)
Lactococcus lactis CECT 539, *Lactobacillus casei* CECT 4043	Broiler chicken	Improves health and growth performance	(Fajardo et al., 2012)

icant in less healthy control calves (Timmerman et al., 2005; Bayatkouhsar et al., 2013). Under stressed conditions, probiotic bacteria can be used to decrease the severity of scours caused by imbalance of intestinal microbiota (Markowiak and Śliżewska, 2018). Amazingly, the particular lactobacilli and bifdobacteria strains reduce the pathogenicity by decreasing the effects of pathogens, while modulating the immune system to infections is still unclear (Servin, 2004; Al-Saiady 2012).

Effects of Probiotics on Pigs

Probiotics given to humans and livestock have improved gut microbiota, gut immunity, and shown good resistance to pathogens. It has also decreased harmful infectious agents and improved overall animal health (Bhandari et al., 2010; Kenny et al., 2011; Yirga, 2015; Roselli et al., 2017). The pathogenic bacteria like Salmonella enterica and Streptococcus suis caused diarrhea and a reduction in growth in young pigs (Kenny et al., 2011), during the first days of life. Probiotics utilization protects the neonatal piglets from intestinal infections during their initial age (Roselli et al., 2017). Post weaning, the piglets are highly exposed to enteric diseases due to the imbalance of beneficial and pathogenic gut bacteria. It has been reported that probiotics decreased 21% post weaning diarrhea out of 38% and 16.2% pre-weaning mortality out of 22.3%. (Taras et al., 2006; Lalles et al., 2007; Liao and Nyachoti, 2017). Supplementation of LAB species (L. acidophilus C3, E. faecium 6H2, L. fermentum NC1 and Pediococcuspentosaceus D7), B. subtilis H4 or cumulative with S.boulardii had found positive consequences in diarrhea reduction (Giang et al., 2012).

A study of piglets by Liu et al. (2014) stated that L. reuteri I5007 plays a beneficial role in the gut health of young pigs by modulating microbial population and intestinal development. Denaturing gradient gel electrophoresis (DGGE) examined that L. reuteri I5007 reduced the numbers of Clostridium spp by affecting the colonic microbial environment on day 14. Application of L. reuteri BSA131 reduced the population of enterobacteria in feces of weaning pigs (Chang et al., 2001). Significantly, *Lactobacillus* species comprising L. gasseri, L. reuteri, L. acidophilus and L. fermentum reduced *E. coli* and aerobic counts, and increased Lactobacilli and anaerobic counts in the digesta compared with a control group (Huang et al., 2004). Furthermore, a report suggested that LAB strains especially L. reuteri I5007 given through oral administration not only enhanced the butyrate and branched chain fatty acids concentration but also reduced the Clostridium spp by decreasing luminal pH to a level where pathogen bacteria cannot cause infection (Liu et al., 2014; Bajagai et al., 2016). It is compulsory to mention that different factors such as differences in doses, microbial strains, age, health status and pig husbandry management may help to explain the different consequences of same probiotic application in domestic animal trials (Bajagai et al., 2016). In addition, probiotic strains may not only decrease the pathogens but also reduce their metabolism and toxin production (Ng et al., 2009; Hou et al., 2015; Roselli et al., 2017). The probiotic strain E.coli produced microcin which may reduce intestinal pathogen, commensal E. coli, adhesion of *E. coli*, and Salmonella enterica associated pathogen (Setia et al., 2009; Bhandari et al., 2010; Krause et al., 2010; Sassone-Corsi et al., 2016). Therefore, available evidence has suggested that *E. coli* and L. reuteri strains have an essential role to improve gut health and immunity (Roselli et al., 2017).

Effects of Probiotics on Poultry

The probiotics application has become popular due to its favorable effects on gut health and production performance of farm animals including chickens (Khaksefidi and Ghoorchi, 2006; Zulkifli et al., 2000; Mookiah et al., 2014; Sarangi et al., 2016). Currently, antibiotic resistance in poultry products has forced scientific authorities to ban the application of AGPs (Park et al., 2016; Wang et al., 2017). Probiotic based bacterial diet given to day old chicks have ability to establish in the gut ecosystem (Jaiswal et al., 2017), hence they are well recognized as normal intestinal microbiota of chicken (Kizerwetter-Swida and Binek, 2005; Qin et al., 2018).

LAB, especially *Lactobacillus* strains, is commonly used as probiotics. Probiotics bacterial strains should be isolated from the natural gastrointestinal microbiota of the same animals in order to get more specific results (Kizerwetter-Swida and Binek, 2005). However, potential probiotic strains may improve the gastrointestinal health and microbiota by affecting the gut microbiota ecosystem (Khaksefidi and Ghoorchi, 2006; Nayebpor et al., 2007; Sugiharto, 2016; Markowiak and Śliżewska, 2018) Specifically, the literature findings indicated that the *Lactobacillus* strain has inhibitory action towards enteric pathogens like Salmonella, *E. coli* and Clostridium perfringens (Kizerwetter-Swida and Binek, 2005, Cao et al., 2013; Wang et al., 2017). This phenomenon is due to production of antimicrobial substances by probiotics as well as nutrient competition between beneficial and pathogenic bacteria for adherence sites on the intestinal epithelium (Hayek et al., 2013; Song et al., 2012).

EFFECTS OF PROBIOTICS ON NUTRIENT DIGESTIBILITY

Probiotics products in market have an excellent ability to avoid digestive disorder (Nagaraja and Titgemeyer, 2007; Sanchez et al., 2017). Acidosis is common digestive disorder that not only affects the rumen ecosystem, but also decreases the production of animals (Enemark, 2008). In vitro scientific studies have found that yeasts (Saccharomyces cerevisiae) might affect the stability of lactate forming bacteria by reducing lactate production (Streptococcus bovis) and enhance lactate consumption by Selenomonas ruminantium or Megasphaera elsdenii (Rossi et al., 2004).

Significantly, it has reported that S. cerevisiae (yeast strain) plays a vital role in improving the cellulolytic bacterial activity (Arcos-Garcıia et al., 2000; Mosoni et al., 2007; Chung et al., 2011), which cause starch degradation and effectively competed with amylolytic lactate forming bacteria (Yutaka et al., 2015; Thrune et al., 2009). A trial in male goat (buck) has investigated that S. cerevisiae supplemented diet had improved nutrient digestibility then roughage feeding (El-Ghani, 2004). The potential effect of S. cerevisiae supplementation is generally considered a result of variations in the rumen fermentation process, which may improve nutrient digestibility and decrease the methane gas emission (Chung et al., 2011).

EFFECTS OF PROBIOTICS ON GUT MICROBIOTA

The gut of animals is inhabited by a complex and dense community of bacteria, archaea, fungi, protozoa and viruses (Markowiak and Śliżewska, 2018). In farm animals, the total number of gut microbial cells exceeds the host cells by at least one order of magnitude (Kim and Isaacson, 2015). The gut microbiota shows an increase in numbers, concentration and diversity from the proximal to the distal gastrointestinal tract. For example, in pigs, the stomach and proximal small intestine comprise moderately small numbers of bacteria (103–105 bacteria/g or ml of contents); but with increased *Lactobacillus* spp. and Streptococcus spp. (Roca et al., 2014). In contrast, the distal small intestine inhabits a greater number of bacteria (108 bacteria/g or ml of contents) (Gaskins, 2000). Numerous studies have found that the microbes are radially distributed within the gut tract (Gaskins, 2000; Wang et al., 2017). The gut micro ecosystem comprises of four points: i) the intestinal lumen, ii) the unruffled mucus layer (cover mucosa), iii) the deep mucus layer establish in the crypts, iv) surface of the intestinal epithelial cells. The variety of microbial populations within gut micro ecosystems is influenced by certain factors such as gut peristalsis, pH, anoxic conditions, dietary composition, inhibitory agents (bacteriocins), SCFA, and competitive exclusion (Gaskins, 2000; Pluske et al., 2003; Wang et al., 2017). Taking these factors into consideration, researchers have concluded that probiotics and their related health effects may perform a significant role in stabilizing the gut microflora and definitely gut health.

EFFECTS OF PROBIOTICS ON GUT HEALTH

In literature, the term ‘gut health’ lacks clear definition, however, it has been used constantly in human medicine (Tuohy et al., 2003; Jacobs et al., 2009) as well as in animal health (Lalles et al., 2007; Choct,

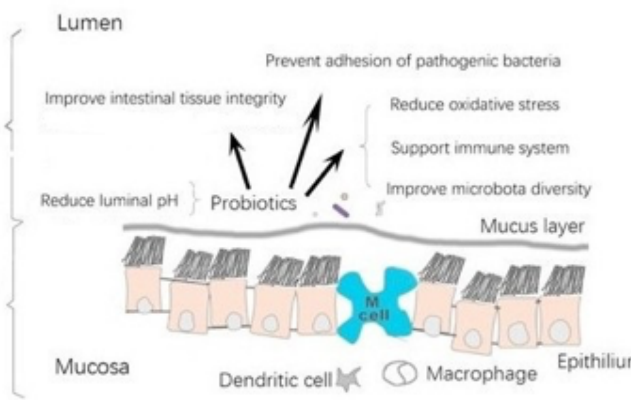

Fig 1. Effects of probiotics on gut health of domestic animals

Table 4. Effect of probiotics on gut health of domestic animals

Probiotic strains	Species	Consequences	References
Bacillus species or LAB species	Young calf	Balance the gut microbial ecosystem and reduce the adhesion of pathogen	(Yutaka et al., 2015)
LAB species (*Lactobacilli* and *Enterococci*)	Cattle	stabilize the rumen pH	(Jeyanathan et al., 2014)
M. elsdenii and *Selenomonas ruminantium* sub spp	Cattle	Stabilize the rumen pH, rumen microbiota, improve the immune action and enhance plant cell walls degradation in the rumen	(Johanne, 2009; El-Tawab et al., 2016)
Saccharomyces cerevisiae	Young calf	Improve the intestinal health, rumen microbiota and reduce the adhesion of pathogen	(Chaucheyras-Durand and Durand, 2010)
Bacillus cereus var. Toyoi Saccharomyces boulardii	Sheep	Improves humoral immunity	(Retta, 2016)
Enterococcus faecium	Pig	Reduce the intestinal *E. coli*, *Clostridium,* and *Enterobacterium* species	(Bajagai et al., 2016)
Lactobacillus species	Pig	Immunomodulators, improve antibody status, killer cells, macrophage response, and interferon production	(Cho et al., 2011)
Saccharomyces cerevisiae	Pig	Reduce risk of pathogens and diarrhea	(Liao and Nyachoti, 2017)
Bacillus subtilis	Chicken	Reduce 58% of the number *of S. heidelberg* colonization	(Knap et al., 2011)
L. acidophilus *L. salivarius*	Chicken	Improves T helper cells (Th), anti-inflammatory cytokines (IL-10) and transforming growth factor (TGFβ) in caecal tonsil cells	(Brisbin et al., 2010; Sugiharto, 2016)
Bacillus mesentericus, *E. faecalis* and *Clostridium butyricum*	Chicken	Reduce the diarrhea incidence	(Rodriguez-Fragoso et al., 2012)
Aspergillus, *Bacillus, Bifidobacterium,* *Candida Enterococcus, Lactobacillus, Saccharomyces Streptococcus,*	Chicken	Reduce risk of *E. coli*, *Clostridium perfringens or Salmonella*	(Kral et al., 2012; Syngai et al., 2016)
L. reuteri C1, C10*,* C16; *L. gallinarum* I16, I26; *L. brevis* I12, I23, I25, I218, I211, *L. salivarius* I24	Chicken	Increases the *lactobacilli, bifidobacteria* and decreases the *E.coli* caecal populations	(Mookiah et al., 2014)

2009). Gut health refers to the health status of the upper and lower gastrointestinal tract; with possibly more emphasis on the lower GI tract. The main function of gut is to stabilize nutrients, water and electrolyte proportions, mucus secretion, cytokine expression and immune system development (Corthesy et al., 2007; Niba et al., 2009; Yitbarek et al., 2015; Wang et al., 2017),

In addition, it acts as a barrier to eliminate toxins and infectious agents (Fig. 1) (Roselli et al., 2017). Even with these functions, certain types of bacterial pathogens inhabit the gut and disturb the gut ecosystem (Markowiak and Śliżewska, 2018). For example, the numbers of pathogenic bacteria i.e. E.coli proliferates and exceeds other bacteria in post-weaning pigs, causing gastrointestinal disease (Fairbrother et al., 2005). The gut microbiota ecosystem is influenced by many factors such as feed composition (carbohydrates: protein), feed additives (probiotic, prebiotic, organic acids, feed enzyme), feeding practices, antibiotics agents, disease status, weaning age, seasonal stress, genetics and animal housing environment (Gaskins, 2000; Pluske et al., 2003; Zoetendal et al., 2004; Torok et al., 2011; Wang et al., 2017). These factors all have potential role in the health of gut microbiota.

The term 'optimal' and 'normal' gut microbiota has created confusion among nutritionist. Metzler et al. (2005) suggested that the term 'optimal' gut microbiota should be used rather than 'normal' microbiota, because it is very difficult to define what is 'normal' concerning the condition of growing pigs and chickens. Animal producers are trying to keep animals healthy and free of pathogens to achieve maximum healthy production (Roselli et al., 2017). Sometimes clinical illness and rarely death cause economic losses to the pig and poultry industry due to variation of gut microbiota (Lange et al., 2010). Therefore, probiotics have significant effects to improve the gut stability of domestic animals (Table 4). For example the outbreak of necrotic enteritis is a key problem in poultry caused by the intake of a concentrated diet (viscous grain) (Jia et al., 2009; Palliyeguru et al., 2010). The decrease in gut motility has been linked with high digesta viscosity which provides a favorable environment to Clostridium perfringens in the upper gestrointestinal tract (Timbermont et al., 2011). Swine dysentery and collibacillosis have been associated with consumption of a viscous fibrous diet (McDonald et al., 2001; Hopwood et al., 2004; Montagne et al., 2004; Wilberts et al., 2014). This has been related to an increase in digesta viscosity with a reduction in endogenous secretion and nutrient digestibility in the gastrointestinal tract. Therefore, probiotics have been given full consideration as alternatives to feed additives to stabilize the gut microbiota of domestic animals.

EFFECT OF PROBIOTICS ON GUT ASSOCIATED IMMUNE RESPONSES

The basic purposes of immunomodulation in domestic animals include: to initiate powerful and persistent immune system responses towards infectious agents, to modulate the maturation of acquired and innate immunity during the neonatal period and in young disease sensitive animals. Also to augment local defensive immune responses at susceptible sites such as in dairy cattle (mammary gland) or in young animals (gut), to overcome the immunosuppressive effects of stress and environmental pollution (Roselli et al., 2017).

Probiotics play a fundamental role in the development of immune system neonates (Balevi et al., 2001). Recently, it has become the topic of interest for researchers to explore the beneficial effects of probiotics in the gut and those associated with maintaining a healthy immune system in domestic animals. Regular utilization of probiotics stimulate both humoral and cell mediated immunity through increased production of natural cytokines, macrophage, lymphocyte, killer cell and immunoglobulin (IgG, IgM and IgA) (Balevi et al. 2001; Koenen et al. 2004; Yurong et al. 2005; Farnell et al., 2006; Cho et al., 2011; Roselli et al., 2017).

Several authors have revealed that microbial populations can support the animals defense mechanism towards pathogens by stimulating the gut immune response (Markowiak and Śliżewska, 2018). This may strengthen the immune systems reaction by enhancing phagocytic activity and the production of antibodies (Yirga, 2015). Probiotic bacteria are important to the immune system because when pathogens are recognized by antigen presenting cells (APC), they are eliminated by leukocytes (Butaye et al., 2003). Some strains of probiotics such as *Lactobacillus* have the capability to modulate the immune system. Yirga has explained two reasons of immunomodulation: i) They can either move through the intestinal wall as viable cells or multiply ii) the antigens released by the dead organisms definitely stimulate the immune system. Therefore, this factor induces the immune response (Yirga 2015).

Probiotics based L. reuteri may augment or reduce the innate immune action through stimulation of pro-inflammatory cytokines in pigs. L. reuteri strains can be divided into two subgroups, immunosuppressive (ATCC PTA 6475 and ATCC PTA 5289) and immunostimulatory strains (ATCC 55730 and CF48-3A), and each subgroup has potential therapeutic value (Jones and Versalovic, 2009). Oral consumption of L. reuteri I5007 could improve T-cell differentiation and induce ileal cytokine expression, which proposes that this probiotic strain might modulate immune function in young piglets (Wang et al., 2009). Another study by Yu et al. (2008) reported that L. reuteri I5007 diets fed to young piglets had increased serum specific anti-OVA IgG level. In a recent study on neonatal piglets, it has been reported that L. reuteri decreases the mRNA expression of IL-1β in the ileum (Dowarah et al., 2017). A similar study reported that L. reuteri with L. acidophilus might help to maintain immunological homeostasis in young gnotobiotic pigs infected with rotavirus by regulating TGF-β production (Azevedo et al., 2012).

However, it is still unclear how a host body recognizes the pathogens and beneficial bacteria that ultimately cause immune activation or deactivation (Vinderola et al., 2005; Hardy et al., 2013), literature findings have revealed that Pathogen-associated molecular patterns (PAMP) or recent correct term microbe-associated molecular patterns (MAMPs) are pathogen associated molecules, that stimulate the innate immune system. They are recognized by

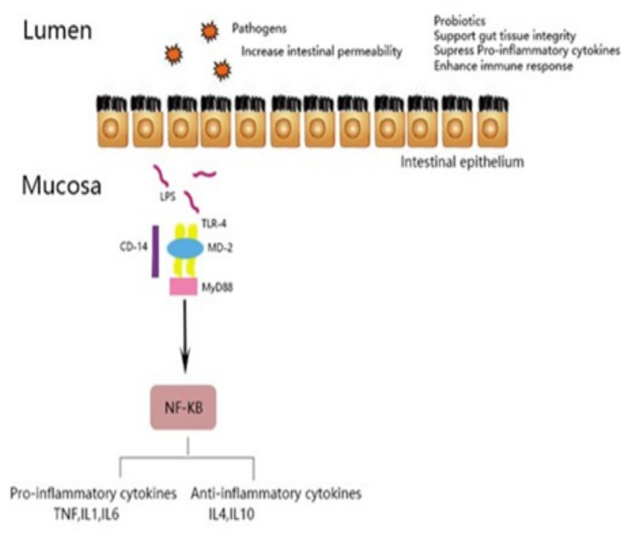

Fig 2. Effect of probiotics on immune responses

pattern recognition receptors (PRRs) of the gastrointestinal mucosa (Lebeer et al., 2010). The gut epithelia and dendritic cells (DC) initially recognize the MAMPs (LPS and bacterial DNA etc.) and then interact with PRRs to stimulate innate as well as adaptive immunity (Rachmilewitz et al., 2004; Lebeer et al., 2010).

Toll-like receptors 4 (TLR4) is a trans-membrane proteins, an important member of the toll-like receptors family, which detect the PRRs and activate the NF-κB (intracellular signaling pathway), which ultimately activate immune response by producing pro-inflammatory cytokines (Fig. 2) (Lebeer et al., 2010; Gu et al., 2016). Some studies exposed that IgA is the dominant immunoglobulin in the intestine and plays a key role in immunity (Mahfuz et al., 2017). IgA-producing B cells increased the gut IgA without increasing the production of CD4+ T-cells (Vitini et al., 2000; Vinderola et al., 2005). The probiotics increased the production of IL-6 by the gut epithelia which caused in variation of B-cells for producing IgA and IgM (Vinderola et al., 2005). Therefore, this phenomenon of IgA plays a key role in the eradication of harmful bacteria via combined with the gut-mucins. On the other hand, it is difficult to completely conclude that probiotics contribute significantly to the immune system of the host as they are not intended to eradicate invasive pathogens in the gastrointestinal tract. Therefore, such positive effects are always compromised due to the animals immunological status (Patil et al., 2015). The available data and previous findings reported that some combination of probiotic strains have generated positive results in the various animal studies (Yirga, 2015).

SAFETY AND RISK ASSOCIATED WITH PROBIOTICS APPLICATION

Safety Factors related to Probiotics

Probiotics have excellent effects throughout the gastrointestinal tract. All these microbes are of natural origin; thus any deleterious effect is highly questionable. But probiotic registration plays a significant role in environmental safety and it has better safety records than antibiotics feed additives. Several studies have been conducted with no adverse effects being reported on animal health. Concisely, they are not transmitted from the gut to the body of animal. They are safe, have no food transmission from animal origin to human, and do not cause residual effects (Kubiszewska et al., 2014; Bajagai et al., 2016). Most of the scientific data is available on the safety of probiotics based *Lactobacillus* and *Bifidobacterium* (Hempel et al. 2011; Shanahan 2012). Thus more exploration is needed for safe application of probiotics. Specifically, Bajagai et al. (2016) have reported that probiotics formulator should emphasize 4 factors to avoid the recent allegation made on probiotic safety (Bajagai et al. 2016).

i. Probiotic strains cannot be considered as 100% safe or with zero risk, like in case of drugs.
ii. The risk of probiotics application depends on immunity and health status of animal. Therefore, probiotics may be safe in one animal (healthy) but may not be safe in another (immune deficient).
iii. Each specific probiotic species cannot be evaluated based on other probiotics, as each product has their own safety and risk evaluation plan based on each case study.
iv. Lack of public awareness to hazardous effects of probiotics, so there is need to inform the consequences of probiotic risk to general public.

Risk Factors related to Probiotics

However probiotics based microorganisms are generally safe in animal feed, but preventive measurement should be taken to prevent humans, animals, and the environment from unsafe microorganisms. Specifically, probiotics associated risks in animal diets should be assessed as follows (Marteau, 2001; FAO/WHO, 2002; Doron and Snydman, 2015; Bajagai et al., 2016):

i. Infection (gut or systemic) of the animal fed probiotics.
ii. Transmission of antibiotic resistance from probiotics to pathogenic microbes.
iii. Transfer of infectious agents to the environment from the animal production system.
iv. Infection (gut or systemic) of the handlers of animal/feed.
v. Toxic effects on the host due to transfer of toxins (entero and emetic toxins) from probiotics microbes.
vi. Hyper-activation of the immune response of animals.
vii. Infection (gut or systemic) of the humans ingesting animal products produced from probiotics given to animals.
viii. Sensitization (skin, eye or mucus membrane) of the probiotics handlers.

CONCLUSION AND RECOMMENDATION

Probiotics plays a beneficial role in domestic animals via stabilizing the gut morphology, gut function and gut pH as well as modulation of immune response. It may also reduce the incidence of calf diarrhea; calf morbidity/mortality thereby supporting the animal industry to the threat of economic losses. Recently, the effect of probiotics as nutraceuticals on the gut health of domestic animals was explored showing amazing results. In this circumstance, good management of probiotic supplementation ideally maintains the gut ecosystem of domestic animals and protects them from enteric pathogens. Furthermore, these probiotic products have been documented as relatively safe compared to antibiotic growth promoters. But personal precautions should be taken before using it in animal nutrition to avoid hazardous effects of human health associated with it. Probiotics influence the intestinal microbiota and augments the humoral and cellular immunity, which could successfully develop natural antibodies. On the other side, researchers have allowed genetic manipulations of probiotics strains to improve the development of new advantageous microbes. The available findings have provided us with adequate data on probiotics containing *Lactobacillus* and *Bifidobacterium* strains but lacking data on other probiotic microorganisms. Therefore, there is need to explore each microorganism on the strain level to confirm their potential effects on animal health. In addition, probiotic bacteria should not have the ability to produce antibiotic resistance genes; otherwise these will not be suitable for animal industry.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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Abbreviations

WHO: world health organization; VFAs: Volatile fatty acids; EE: Ether extract; NFE: Nitrogen free extract; IgG: ImmunoglobulinG; IgM: ImmunoglobulinM; IgA: ImmunoglobulinA; APC: Antigen presenting cells; IL-1β: Interleukin-1 beta; TGF-β: Transforming growth factor beta; Anti-OVA: Anti-ovalbumin; CE: Competitive exclusion; ETEC: Enterotoxigenic Escherichia coli (ETEC) IPEC-J2: Intestinal porcine epithelial cell- jejunum; LAB: Lactic acid bacteria; YC: Yeast culture; PAMP: Pathogen-associated molecular patterns; MAMPs: Microbe-associated molecular patterns; PRRs: Pattern recognition receptors; DC: Dendritic cells; LPS: Lipopolysaccharide; DNA: Deoxyribonucleic acid; mRNA: Messenger ribonucleic acid; TLR4: Toll-like receptors 4; DM: Dry matter; WG: Weight gain; ADG: Average daily gain; DMI: Dry matter intake; FI: Feed intake; FCR: Feed conversion ratio; FEE: Feed efficiency ratio; EAA: Essential amino acids; AGPs: Antibiotic growth promoters; DGGE: Denaturing gradient gel electrophoresis; PUFA: Polyunsaturated fatty acids; IL-2: Interleukin-2; IFN: Interferon; C-C: Carbon-Carbon; EU: European union; FAO: Food and Agriculture Organization; FOS: Fructo-oligosaccharides; GOS: Galacto oligosaccharides; MOS: Mannanoligosaccharides; XOS: XOS: Xylo-oligosaccharides; IMO: Isomaltooligosaccharides; SCFA: Small chain fatty acids;

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