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Review Article

The use of *Lactobacillus* as an alternative of antibiotic growth promoters in pigs: A review

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ABSTRACT

Antibiotics, often supplemented in feed, used as a growth promoter, may cause their residual effect in animal produce and also trigger antibiotic resistance in bacteria, which is of serious concern among swine farming entrepreneurs. As an alternative, supplementing probiotics gained interest in recent years. *Lactobacillus* being the most commonly used probiotic agent improves growth performance, feed conversion efficiency, nutrient utilization, intestinal microbiota, gut health and regulates immune system in pigs. The characteristics of *Lactobacillus* spp. and their probiotic effects in swine production are reviewed here under.

1. Introduction

Various stress factors including nutritional, environmental and weaning, etc., at different stages of life affect the animal productivity and health. Weaning stress in piglets is the major cause for economic loss to pig farmers (Wilson et al., 1989). As the weaned piglets have limited digestive capacity, which triggers fermentation of undigested protein by opportunistic pathogens (mainly *Escherichia coli*, *Salmonella*) normally existing in gastrointestinal tract (GIT) which leads to production of branch chain fatty acids (BCFA) and ammonia nitrogen (NH_3-N) (Garcia et al., 2014). The BCFA and NH_3−N are the toxic metabolites to intestinal mucosa, which damage intestinal mucosa thereby ultimately result in diarrhea (Fuller, 1989; Jensen, 1998). This may usually cause a reduction in villous height and digestive enzyme activity for the first few days after weaning (Pluske et al., 1995). The common practice of supplementing antibiotics in livestock for improved animal performance was condemned due to its adverse effects on animal as well as human, the ultimate consumer of the animal produce. Since then, it has been the greatest challenge to farmers to rear healthy piglets devoid of antibiotics supplementation. However, these stress factors in livestock sector need to be addressed for profitable livestock farming.

In this scenario, latest reports indicate probiotic supplementation in swine seems to be a better alternative for antibiotic use addressing the safe animal produce as well as to combat economic losses in pig farming. The term “Probiotics” is derived from a Greek word ‘biotikos’ meaning ‘for live’, which was first coined by Parker (1974) and defined as the live microorganisms, when they were administered in adequate amounts, confer a health benefits on the host (FAO/WHO, 2002). At present, probiotics are classified by the US Food and Drug Administration as generally recognized as safe (GRAS) ingredients. Among various probiotic bacteria, *Lactobacillus* is the most commonly used probiotic agent (McCony and Gilliland, 2007). *Lactobacilli* are gram-positive, non-motile, non-spore forming, acid-tolerant, non-respiring rod shaped (bacillus), or spherical (coccus) bacteria which produce lactic acids as the major metabolic end-product of carbohydrate fermentation (Cho et al., 2009). In farm animal they confer good intestinal health by stimulating the growth of a healthy microbiota (Walter et al., 2008), preventing intestinal colonization of enteric pathogens (Huang et al., 2004; Lee et al., 2012), reduced faecal noxious gas emission (Hong et al., 2002), production of antimicrobial substances, antibiotic resistance patterns, improving digestive ability and antibody mediated

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immune response, and demonstrable efficacy and safety (Wang et al., 2012; Hou et al., 2015). Probiotics are generally host-species specific (Dunne et al., 1999) and believed to be more effective in their natural habitat i.e., target species (Kailasapathy and Chin, 2000). However, selection of probiotic microbes is one of the most important criteria to get a positive response. The objective of this paper is to enlighten the efficacy of various *Lactobacillus* spp. as probiotic in swine production.

2. Microorganism commonly used as probiotics

The microorganisms commonly used as probiotics in livestock are presented in Table 1. The genus *Lactobacillus* has been reported as one of the major bacterial groups found in GIT (Dibner and Richards, 2005). Till now, no report was found on safety concerns related to *Lactobacilli* in animals. The genera *Bifidobacteria* is found to be inhabitant of GIT of both animals and humans, which helps in maintaining microbial balance in the GIT by reducing the harmful pathogenic microbes thereby, associated with good health status of the host (Huang et al., 2004). The genus *Enterococcus* belongs to the lactic acid bacteria (LAB) group and found naturally in food products, which are normal commensals of human and animal. *Enterococcus faecium* is the most common in the animal GIT, while in human *E. faecium* and *E. faecalis* are prevalent (Fisher and Phillip, 2009). These three species of *Enterococcus* are commonly used probiotics in animal/livestock feeding.

Bacillus are Gram-positive, spores-forming microorganisms, commonly associated with soil, water and air, and present in the intestinal tract due to involuntary ingestion of contaminated feed. Though some of the *Bacillus* species are used as a probiotic, speculation exists for their ability to produce toxins (Gaggia et al., 2010). The yeasts are also comprised as a residual microbial system of the intestinal microbiome where *Saccharomyces cerevisiae* is widely present in the nature and used in food and beverage industry for its fermentation properties. It is also used as a probiotic especially in ruminants and pig feeding (Kumar et al., 2012).

Table 1
Different groups of lactic acid bacteria commonly used as probiotics in swine production.[1]

Genus	Species
Lactobacillus	*L. acidophilus*
	L. casei
	L. delbrueckii sub sp. *bulgaricus*
	L. brevis
	L. cellobiosus
	L. curvatus
	L. fermentum
	L. plantarum
	L. reuteri
	L. salivarius sub sp. *thermophilus*
	L. gasseri
Lactococus	*L. cremoris*
	L. lactis
Pediococcus	*P. acidilactici*
	P. pentosaceus sub sp. *pentosaceous*
Bifidobacterium	*B. bifidum*
	B. adolescentis
	B. animalis
	B. infantis
	B. longum
	B. pseudolongum
	B. thermophilum
Enterococcus	*E. faecium*
Bacillus	*B. subtilis*
	B. coagulans
	B. cereus
	B. licheniformis
Yeast	*Saccharomyces cerevisiae*
	Aspergillus oryzae

[1] Source: Dunne et al., 2001; Sekhon and Jairath, 2010.

3. Mode of action of *Lactobacilli* as probiotic

Lactobacilli stimulate rapid growth of beneficial microbiota in the GIT which become abundant and induce competitive exclusion of pathogenic bacteria either by occupying binding sites on intestinal mucosa or competing for nutrients and absorption sites with pathogenic bacteria (Malago and Koninkx, 2011; Zhao and Kim, 2015); by rapid utilization of energy source which may reduce the log phase of bacterial growth. Most of the enteric pathogens adhere to the intestinal epithelium through colonization thereby develop diseases (Walker, 2000). Consequently, the probiotic *Lactobacilli* have the ability to adhere the gut epithelium and thus compete with pathogens for adhesion receptors i.e., glycolconjugates (Umesaki et al., 1997). Probiotic bacteria produce organic acids, hydrogen peroxide, lactoferrin and bacteriocin which may exhibit either bactericidal or bacteriostatic properties (Jin et al., 1997; Pringsulaka et al., 2015). *Lactobacillus* have proven to be capable of acting as immune-modulators by enhancing macrophage activity (Perdigon et al., 1986), increasing the local antibody levels (Yasui et al., 1989), inducing the production of interferon (De Simone et al., 1986) and activating killer cells (Kato et al., 1984). They prevent the proliferation of coliform bacteria thus amine production diminishes which produced due to decarboxylation of amino acids by coliform bacteria.

4. Selection of *Lactobacilli* for feeding as probiotics

The followings are the criteria that can be used for the selection of microbial strains as probiotics.

1) Resistance to *in vitro/in vivo* conditions: they should be resistant to acidic pH and bile salt. After administration, the microbes should not be killed by the defense mechanisms of the host and should be resistant to the specific conditions occurring in the body.
2) Origin of the strain: probiotics are generally host-species specific (Dunne et al., 1999). It is believed that probiotic organism is more effective if it is naturally occurring in the target species (Kailasapathy and Chin, 2000). The strains should be properly isolated and identified before use.
3) Biosafety: *Lactobacillus*, *Bifidobacteria* and *Enterococcus* are the microbes which fall in the category of generally recognized as safe (GRAS) and are most widely used microorganisms as probiotics.
4) Viability/survivability and resistance during processing (e.g., heat tolerance or storage): thermophilic/thermo-tolerant organisms have an advantage as they withstand higher temperature during processing and storage.

However, other criteria might also be considered for selection of mono or multi strains bacteria as probiotics like as probiotic-symbiotic interaction, stimulation of healthy microbiota and suppression of harmful bacteria. Adopting these predetermined criteria, it could be possible to select the best strains of probiotics which could be effective therapeutically and nutritionally.

5. Mode of feeding probiotics

Mode of feeding probiotic affects the response of animal to the probiotic feeding. Generally cultures are fed either in form of lyophilized powder or live cells. When a lyophilized culture fed to the animal, it has to rejuvenate before expressing its biological activity which takes some time and also the viability of the culture is not assured. Whereas, when live culture is fed, the probiotic starts its biological activity immediately and the viability of the culture is assured. Further, cells can lose their viability and metabolic activity during lyophilisation. Therefore, a probiotic product is effective only when it contains viable as well as metabolic active cells.

6. Use of probiotic *Lactobacilli* spp. for swine production

Lactobacillus spp. has been reported as one of the major bacterial groups found in porcine gastrointestinal tract (Dibner and Richards, 2005). But all the species and strains of *Lactobacillus* cannot be equally effective as probiotic. Different species and even strains of species of microbes behave differently (Newbold et al., 1995). Therefore, source of microbe to be used as probiotic is one of the important factors to yield good response. A microbe fed exogenously as probiotic when enters the GIT has to compete with existing microbiome ecosystem in GIT (Verdenelli et al., 2009). These unfavorable circumstances in the GIT may hamper the proliferation of the microbe used as probiotic. To combat this problem, it is suggested that the microbe isolated from the host animal when used as probiotic gives better response. Host specificity was observed among *Lactobacilli* isolated from human and animal sources (Morelli, 2000). Hence, evaluating new sources of probiotics from swine origin is utmost necessary to improve pig farming. *Lactobacillus acidophilus* 30SC isolated from swine showed excellent acid resistance and bile tolerance compared to commercial probiotics strains that are presently used in dairy products (Oh et al., 2011). The scenario of using LAB as probiotic for swine production is illustrated considering recent reports across the world (Fig. 1 & Table 2).

6.1. Improved performance

In swine, the use of probiotics improves intestinal well-being which leads to improve performance. Higher growth rate and improved feed efficiency ratio results in improve profitability due to greater output and reduction in overhead costs (Campbell, 1997). However, age and weight at weaning are closely related to post-weaning growth rate. The administration of probiotics, soon after birth could be effective as probiotic bacteria by enhancing intestinal barrier function which restrict colonization of pathogenic bacteria to intestinal mucosa. This is evident with better absorption of nutrients and immunoglobulins of the colostrum, enabling better sustainability of the piglet, and minor loss of piglets at its first days of life (Abrahao et al., 2004). Supplementation of lactobacilli has

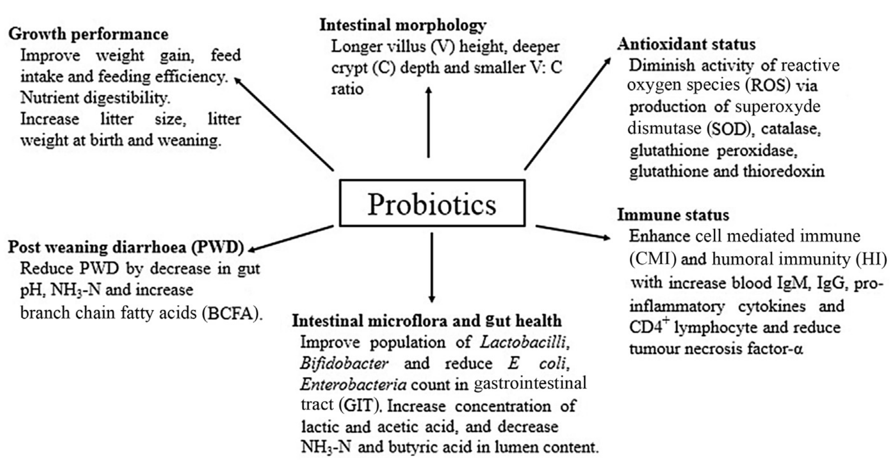

Fig. 1. Systemic diagram about the effects of *Lactobacillus* as probiotics in pigs.

Table 2
Application of different *Lactobacillus* sp. in various categories of pigs.

Used group	Strain	Effect of feeding	Reference
Suckling and nursery piglets	*B. pseudolongum* & *L. acidophilus*	Improved weight gain, feed conversion and fecal condition	Abe et al., 1995
	L. reuteri & *Bifidobacterium pseudolongum*	Better FCR with no differences in final weight, weight gain and feed intake	Afonso et al., 2013
	L. fermentum	Increased ADG reduced diarrhea incidence and numbers of *Clostridium* sp; reduced mRNA expression of *IL-1β* in the ileum	Liu et al., 2014
Weaned piglets	*L. gasseri*, *L. reuteri*, *L. acidophilus* & *L. fermentum*	Better growth performance, increased *Lactobacilli* with decreased *E. coli* counts and reduced post weaning diarrhea	Huang et al., 2004
	L. reuteri, *B. subtillis* & *B. licheniformis*	Increased nutrient digestibility, reduced faecal *Salmonella* and *E. coli* number, improved serum IgG level	Ahmed et al., 2014
Grower-finisher pigs	*L. gasseri*, *L. reuteri*, *L. acidophilus* and *L. fermentum*	Better ADG, ADFI and CP digestibility; improved serum specific anti-OVA IgG	Yu et al., 2008
	L. plantarum	Enhanced superoxide dismutase, glutathione peroxidase and	Wang et al., 2012
	L. fermentum	catalase	Wang et al., 2009a,b
	L. reuteri, *L. salivarius*, *L. plantarum* and Yeast complex	Improved ADG, ADFI and gain/feed, digestibility of DM and N	Shon et al., 2005
	E. faecium, *L. acidophilus*, *Pediococcus pentosaceus* and *L. fermentum*	Improved growth, FCR, digestibility of nutrients	Giang et al., 2011

resulted in improved growth and feed efficiency in nursery (Fialho et al., 1998) and weaning (Mishra et al., 2014) piglets.

A healthy intestinal tract has a dominance of LAB, however, this equilibrium within the intestinal tract is troubled when the animal is in stressful condition like castration, weaning, high temperature and humidity and change of feed (Jin et al., 1997). This could be improved by continuous feeding of lactobacilli, which encourages rapid growth of other beneficial bacteria and reduce the growth of pathogenic bacteria by competitive exclusion (Pan and Yu, 2014). Feeding of probiotics (*Lactobacillus* spp.) to weaning piglets resulted in an increased growth rate due to high feed intake and better feed conversion ratio. Supplementation of complex probiotics, including yeast (*S. cerevisiae*) and *Lactobacillus* spp. have been reported to improve growth performance of weaned piglets (Hong et al., 2002; Chen et al., 2005). Positive effects on growth, feed conversion efficiency and nutrient digestibility were also observed in grower-finisher pigs with supplementation of probiotic *Bacillus subtilis*, *Saccharomyces boulardi* and *L. acidophilus* C3 (Giang et al., 2011). Where, the effect of probiotic (*Lactobacillus reuteri*) in weaning piglets was comparable with antimicrobial growth promoter (Apramycin) in gain, feeding efficiency and nutrient digestibility (Ahmed et al., 2014). This might be due to increase activity of digestive enzymes like β-galactosidase by the supplementation of *Lactobacilli*, which stimulate gastrointestinal peristalsis and promote apparent nutrient digestibility (Wang et al., 2011; Zhao and Kim, 2015).

Effect of probiotic was also observed in sow with increased feed intake, number and growth of piglets at weaning (Pollmann et al., 2005) and also improve composition of milk (Alexopoulos et al., 2004). There is a lack of study conducted on sow to see the effect of *Lactobacilli* as probiotics, so it important to give emphasis on research in this aspect for better swine production. Supplementation of *L. johnsonii* XS4 (previously isolated from gastrointestinal tract of sow) from the 90th day of pregnancy up to weaning day (the 25th day of lactation) significantly increased litter weight at birth, litter weight after the 20th day of farrowing, the number of piglets at weaning and weaning weight of piglets (Wang et al., 2014).

6.2. Control of post-weaning diarrhea

At the time of weaning, entero-pathogens takes upper hand as weaning of the piglets reduce digestibility of high protein diet which results increase production of BCFA and NH_3–N leading to more incidence of diarrhea (Garcia et al., 2014). The BCFA and NH_3–N are the main toxic metabolites for intestinal mucosa and tagger of post weaning diarrhea in piglets (Williams et al., 2005). *E. coli* are the major enteropathogen of post-weaning diarrhea and causes 26% cases of neonatal diarrhea (Hoefling, 1989). Addition of *Lactobacilli* as a probiotic in the diet results beneficial fermentation resulting increased concentration of short chin fatty acids and lactic acid in GIT. These may reduce pH of the gut which in turn decrease growth of opportunistic entero-pathogens as they need alkaline medium to proper growth and multiplications.

6.3. Effect in intestinal microflora and gut health

Microflora in the digestive system plays a very important role in the defense mechanism of the body. The major intestinal microflora of pig are *Lactobacilli*, *Bifidobacteria*, *Streptococci*, *Bacteriodes*, *Clostridiums perfringes* and *E. coli* may vary with age. One of the important ability of stable microflora in gastrointestinal tract is colonization resistance. About 4–6 weeks is needed to establish a stable microflora in the GIT (Mul and Perry, 1994). However, supplementation of *Lactobacilli* in neonatal piglets helps in early development of stable gut microbflora, stimulation of immune system and prevents diarrhea. When piglets are weaned, the intestinal microflora of piglets is altered due to dietary and environmental change after weaning of piglets (Jensen, 1998). The entero-pathogenic *E. coli* are markedly increased in the anterior small intestine resulting post weaning diarrhea. Oral administration of *Lactobacillus fermentum* I5007 in formula-fed piglets improved intestinal health and reduced the number of potential entero-pathogens like *E. coli* and *Clostridia* in neonatal piglets (Liu et al., 2014). Addition of complex lactobacilli previously isolated from GIT of piglet (*Lactobacillus gasseri*, *L. reuteri*, *L. acidophilus*, *L. fermentum*, *L. johnsonii* and *Lactobacillus mucosae*) increased number of lactobacilli and bifidobacterium, also reduced *E. coli* and aerobic bacteria counts in jejunum, ileum, cecum and colon mucosa (Huang et al., 2004; Chiang et al., 2015). The effect was also persisted in grower-finisher pigs (Giang et al., 2011). Since, lactobacilli produced lactic acid, hydrogen peroxide and lactoferrin which may exhibit antagonistic activity against *E. coli* and *Enterobacteria* (Li et al., 2015). In addition, earlier report also revealed that dietary supplementation of complex of lactic acid bacteria increased concentrations of lactic acid and acetic acid in ileum and colon (Giang et al., 2010) of weaning piglets, whereas, faecal NH_3–N and butyric acid concentration was decreased in grower-finisher pigs (Chen et al., 2006). The increased concentration of lactic acid in supplemented group lowered the gut pH in treated groups as lactic acid act as an acidifying agent (Williams et al., 2005; Thu et al., 2011). This indicates that supplementation of various *Lactobacilli* sp. modulates gut microbial profile and thereby affected microbial metabolite production which results better gut health.

6.4. Improved immune status

The probiotics have the capacity to modulate the immune system of animal by enhancing the systematic antibody response to soluble antigens in the serum (Christensen et al., 2002). The immune-modulatory effects can even be achieved by dead probiotic bacteria or just probiotics derived components like peptidoglycan fragments or DNA. Dietary supplementation with probiotics enhanced humoral and cell mediated immune responses (Shu and Gill, 2002) with increased the serum concentration of IgM (Dong et al., 2013) and IgG (Ahmed et al., 2014) growing pigs. Probiotic supplementation in sow also increased IgG level in colostrum and plasma of piglets (Jang et al., 2013). Since, probiotics facilitate the suppression of lymphocyte proliferation and cytokine production by T cells which down regulating the expression of pro-inflammatory cytokines such as tumor necrosis factor-α (Isolauri et al., 2001). *L. fermentum* enhanced T-cell differentiation, induced cytokine expression in the ileum of *E. coli* challenged piglets with increased pro-inflammatory cytokines and percentage of $CD4^+$ lymphocyte subset in blood (Wang et al., 2009a,b). However, it is difficult to confirm that probiotics contribute significantly to the immune system of the host. The main reason behind this caveat is that probiotics differ from antibiotics in that they are not intended to eradicate invasive pathogens in the gastrointestinal tract. Therefore, such observed improvements or positive effects are always hindered due to the animal's immune status and the various applied situations.

6.5. Antioxidant status

An abnormality in the antioxidant defense system can increase the susceptibility of pigs to stress, resulting in decreased performance and reduced immune function. As a result of incomplete reduction of oxygen, the reactive oxygen are formed which includes superoxide anion, hydroxyl radical, hydrogen peroxide and singlet oxygen. A physiological concentration of reactive oxygen species

(ROS) is required for normal cell function, energy production, phagocytosis and intercellular signaling regulation. Early weaning of piglets cause oxidative stress by producing excessive quantities of ROS which not only damage proteins, lipids and DNA but also decline intestinal antioxidant enzyme activities under NF-κB, p65 and Nrf2/Keap1 signals (Yin et al., 2014, 2015). The probiotic cell have defenses mechanisms against the damaging effects of ROS by involving both in enzymatic (superoxide dismutase and catalase) and non-enzymatic components. The lactic acid bacteria diminish the activity of ROS through the production of superoxide dismutase (Stecchini et al., 2001) that converts superoxide radicals to oxygen and hydrogen peroxide. Some of the species of LAB may also produce catalase, which can destroy hydrogen peroxide at a very high rate that blocks formation of peroxyl radicals (Knauf et al., 1992) while some lactobacilli produced non-enzymatic antioxidants such as glutathione and thioredoxin to reduce reactive oxygen intermediates (De Vos, 1996). Supplementation of *Lactobacilli* sp. increased serum concentration of superoxide dismutase, glutathione peroxidase and catalase in suckling (Cai et al., 2014) and weaning piglets (Wang et al., 2012) whereas, total antioxidant capacity, hepatic catalase, muscle superoxide dismutase improved in grower-finisher pigs (Wang et al., 2009a,b).

6.6. *Effect on intestinal morphology*

The gastrointestinal tract is the main digestive and absorptive organ in animal. The GIT permits the uptake of dietary substances into systemic circulation and it also excludes pathogenic compounds simultaneously (Gaskins, 1997). There is a reduction in villous height (villous atrophy) and crypt depth at weaning (Pluske et al., 1996). As weaning leads to temporary starvation which resulted villous atrophy, reduces mucosal protein content and digestive enzymes activity (McCracken and Kelly, 1984). Hence, improve feed intake immediately after weaning reduced the histological changes of small intestinal morphology (Pluske et al., 1996). As feeding of probiotic increased daily feed intake thus it had positive effect on development of intestinal epithelium. However, the effects of probiotic on villus height may change depending upon species of microorganism. Longer villi (V) height, deeper crypt (C) depth and smaller V: C ratio was observed in pigs supplementation with *L. acidophilus* (Rodrigues et al., 2007), *Lactobacillus plantarum* (Suo et al., 2012) and *P. acidolactici* (Giancamillo et al., 2008). However, no change in the crypt depth was observed with *E. faecium* (Scharek et al., 2007).

7. Conclusion

In conclusion, the data available from various studies and application of *Lactobacilli* in swine husbandry clearly indicate that various *Lactobacilli* spp. have a great potential as an alternative of antibiotics. More attention should be paid for utilizing effects of different probiotic preparations and corresponding feeding strategy in pigs.

Conflict of interest

The authors declare that they have no completing of interests.

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