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Probiotics as Feed Additives in Pigs with Special Reference to Swine Health and Production

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Abstract

The importance of probiotics as alternatives to antibiotics in animals, especially in swine health and production is globally accepted and gaining more and more interest recently. Probiotics can provide a wide variety of health benefits to the host when administrated in adequate amounts. The most frequently used as probiotic agents are lactic acid bacteria (LAB). Former studies demonstrated that dietary supplementation of probiotics had growth promoting effects on pigs. In this review, we will give an overview on the current use of probiotics in swine industry.

Keywords: immune response, meat quality, growth response

Introduction

In early 20th century the Nobel laureate Elie Metchnikoff first introduced the concept of probiotics. He proposed that ingestion of beneficial live microorganisms have positive effect on the health of a being, by manipulating the gut environment. Several studies were carried out depending upon his doctrine both in humans as well as in animals. Probiotics can promote intestinal health along with its mucosal immune response by enhancing colonization of beneficial microbiota by limiting of colonization of pathogenic bacteria (W. C. Liu et al., 2018). A sound pig gastrointestinal tract is usually inhabited by wide variety of commensal microbiota. 1gm gut content of healthy pig colon has at around 1×10^{10} - 1×10^{11} bacteria (Fuller, 1989).

German scientist Werner Kollath in 1953 first use the term "probiotic" derived from the Latin 'pro' and the Greek 'bios' together meaning "for life", has a contrast with the term antibiotic which means "against life". Several definitions have been proposed to explain the term "probiotic" over the years (Sperti, 1971; Azizpour et al., 2009;) . FAO/WHO define probiotic as "live microorganisms which, when administered in adequate amounts, confer a good health benefit on the host" (FAO/WHO, 2002). A wide range of commensal microorganisms strains are being commercially promoted and marketed for animals as probiotics (Agazzi, 2015). Some of them can produce certain beneficial effect in the host while some of them not effective (Weichselbaum, 2009). However commercially selected stains are generally resistant to gastric acid as well as bile acid and they can potentially colonize in the intestine of host or can resist pathogenic microorganisms(Cho et al., 2011; Azizpour et al., 2009; Fuller,2009). A variety of LAB or lactic acid bacteria are commonly used as probiotics. This LAB group are generally gram-positive, acid-tolerant, mostly non-sporulating, non-respiring rod (bacillus) or spherical (coccus) shaped. LAB include variety of bacterial genera like, Lactobacillus, Bifidobacterium, Lactococcus, Lactosphaera, Leuconostoc, Melissococcus, Oenococcus, Pediococcus, Streptococcus, and Enterococcus (Yang et al., 2015). In this review we focus on the developments in probiotics and its health benefits to the host when administrated in adequate amounts.

Microbial succession in early life

The gut of new born piglet has long been thought to remain sterile prior birth and this germ free-state rapidly modified to highly dense microbial population shortly after birth, popularly known as microbial succession (Isaacson & Kim, 2012). Recent studies in mice and human brings out presence of some microbes into the meconium of newborns and amoniotic fluid of pregnant mice, which indicating in utero microbial colonization

(Ardissone et al., 2014) . In pig it is not proved yet. However, a fully grown microbial population is established in pig almost within a week following birth (Bauer et al., 2006; H. B. Kim & Isaacson, 2015; Tortuero et al., 1995). This population has a great diversity which forms a complex micro-ecosystem and makes a symbiotic relationship with the host (Fouhse et al., 2016).The diversity of microbial population is greatly affected by multiple factors like parturition time, mode of delivery, environment(Macpherson & Harris, 2004; Schmidt et al., 2011). Last few years ample of studies illustrated that kids born per-vaginally have microbial colonization resembles to the vaginal micobiota of mother. Likewise kids delivered by caesarean section (C-section) have identical microbial population of mother's skin (Bäckhed et al., 2015; Dominguez-Bello et al., 2010; Groer et al., 2014). Although till now C-section is not a usual way of action in swine industry. In future if C-section is follows in swine industry this query will be a important fact in health criteria of neonates (Hayashi et al., 2007).

Gut Microbial Diversity

A healthy swine gut is normally inhabited by dynamic microbial organism viz. bacteria, virus, fungi etc. Most of them are bacteria. Around 10^{12}-10^{14} bacteria resides in pig intestine which is 10 times more than their cells of body (Luckey, 1972). Bacteriodetes and Firmicutes are the two major phyla mostly occupying 90% of total bacterial population. Remaining part of the population covered by certain other phyla viz. Spirochaetes, Proteobacteria and Tenericutes (Pajarillo et al., 2014). Plenty of studies proved that gut microbial population modulates in different stage of life in response to changes in the feeding behavior, stress and illness (Konstantinov et al., 2006; Lallès et al., 2007). Before weaning Farmicutes are dominate in the gut which gradually subside after weaning and relative abundance of Bacteriodetes is increased by the time (Pajarillo et al., 2014). This is mainly because of their feeding pattern. Before weaning neonates take milk rich in lactose which can be utilized by Firmicutes. Likewise after weaning pigs mostly consume cellulose containing feed that is metabolized by Bacteriodetes (Hayashi et al., 2007; Lamendella et al., 2011). So probiotics should be selected according to the phase of life as microbial population of swine gut modulates in every phase.

Symbiosis and Dysbiosis

Trillions of bacteria take shelter, grow and colonized in the intestine. They set up a potent mutual relationship with the host where everyone gets benefit. This mutual relation is designated as symbiosis (Fouhse et al., 2016). Any changes in the resident bacterial colonization break that relationship with the host called dysbiosis (Petersen & Round, 2014). The consequences of dysbiosis are (1) qualitative and quantitative changes in the microbial population, (2) diminish the metabolic activities of commensal gut microbiota, (3) variation in the floral distribution and (4) expansion of pathogenic microbiota which leads to manifestation of several harmful events such as gas bloating, diarrhea, constipation and ulcer (Cho et al., 2011; Peterson et al., 2015).

Influence of Probiotics in swine production

Modification and maintenance of gut microbiota

Suitable probiotic supplementation facilitates colonization of beneficial microorganism and check the growth of pathogens that ultimately results better health and performance of pigs, as this beneficial microorganism aids in the digestion, metabolism and better nutrient utilization of host (Kenny et al., 2011; Lescheid, 2014; Veizaj-Delia & Pirushi, 2012; Yirga, 2015). Several studies were done in past few years which appreciate the impact of probiotics on microbial population especially on weaned piglets (Table 1). Weaning is a very stressful condition for pigs, leading to remarkable changes in the gut microbiota. During this time piglets are heavily infected by pathogens such as enterotoxigenic strains of E. coli (Konstantinov et al., 2006).

Table 1: Effect of probiotics on population of pathogens

Reference	Bacterial stain used as Probiotic	Effect
(Le Bon et al., 2010)	Saccharomyces cerevisiae ssp. boulardii (CNCM I-1079) and Pediococcus acidilactici (CNCM MA 18/5 M)	Antagonized the growth of E. coli in weaned piglets
(Pospíšková et al., 2013)	Monoculture of E. faecium	Inhibit E. coli and C. perfringens in weaned piglets
(Bajagai et al., 2016)	Combined probiotic	Enhances the colonisation of LAB and limits Clostridium, E. coli, and Enterobacterium spp. in weanling pigs

Probiotics can modulates the gut microbiota mainly via two ways, they are,

Competition with the pathogenic microorganism

Once probiotic microorganism established and colonized in the gut, they started to compete with the harmful microbiota both for adhesion site and nutrition that reduces chances of infection (Cho et al., 2011). It is formulated pathogenic bacteria need to attached with the gut epithelium to express their harmful effect (Bajagai et al., 2016; Yirga, 2015). Probiotics inhibit adherence of pathogenic organism by blocking the receptor cites (Table 2). Certain species of probiotics can block the nutrient absorption sites of pathogens which results death of pathogenic bacteria (F. Yang et al., 2015).

Table 2: Studies related to the strategy of probiotics to inhibit harmful microbes via competition

Reference	Bacterial stain used as Probiotic	Effect
(Bhandari et al., 2010)	non-pathogenic Escherichia coli	Inhibit the attachment of E. coli K88 to the intestine of piglets
(Daudelin et al., 2011)	Pediococcus acidilactici and Saccharomyces cerevisiae boulardii	Limit the adherence of O149 enterotoxigenic Escherichia coli
(Daudelin et al., 2011; Konstantinov et al.,	lactic acid bacteria including Pediococcus acidilactici	Stop enterotoxigenic E. coli to assemble with the intestinal mucosa
	Saccharomyces cerevisiae fermentation products (YFP)	Spare the engagement of Escherichia coli K88+(ETEC) in the gut

Production of antimicrobial substances

Pollmann et al., (1980) reported that probiotics can generate antimicrobial substances which can suppress the growth of pathogenic bacteria. Cho et al., (2011) and Bajagai et al., (2016) proves those antimicrobial substances have broad spectrum antimicrobial property and they can sustain the gut microbial equilibrium. Certain probiotic bacteria such as LAB, E. coli generate some antimicrobial substances and creates acidic environment in small intestine which check the growth of pathogenic bacteria mentioned below in Table 3.

Table 3: Antimicrobial property of probiotics

Probictic strain	Antimicrobial substances	Effect	Reference
LAB	Short chain fatty acids like lactic acid, acetic acid, butyric acid	Decreases the luminal ph which is not suitable for the growth of pathogens	(Bajagai et al., 2016; Pollmann et al., 1980)
Probiotic E. coli	Microcin	Limit the growth of adherent-invasive E. coli and Salmonella	(Bhandari et al., 2010; Krause et al., 2010; Setia et al., 2009)(Lamendella et al., 2011)
LAB	Lactic acid	Destroy outer membrane of E. coli ATCC 35150 (O157:H7), Pseudomonas aeruginosa ATCC9027, and Salmonella enterica serovar Typhimurium SL696 (34)	(Alakomi et al., 2005)

LAB = Lactic acid bacteria

In addition probiotic bacteria also produce a variety of substances including antimicrobial peptides (defensins), bacteriocin, reuterins, microcin, hydrogen peroxide and antioxidants. These substances inhibit colonization, metabolism and toxin production of detrimental bacteria (Bajagai et al., 2016; Hou, Zeng, et al., 2015; Yirga, 2015).

Advancement of nutrient digestibility

Numerous previous studies on pigs documented that probiotics can enhance the apparent digestion and absorption of dry matter, crude protein, crude fiber, organic matter, energy and phosphorus (Ahmed et al., 2014; Cai et al., 2015; Giang et al., 2011). For example Meng et al. (2010) demonstrated that probiotic supplementation in weaned pigs can raise the apparent digestibility of crude protein and energy. The study related to the nutrient digestibility shortly narrated in Table 4.

Table 4: Study increases digestibility in pigs

Strain of probiotics	Dosage (CFU/gm)	Effect	Reference
Complex lactobacilli preparation	2.4×10^5	Enhance apparent digestibility of crude protein and phosphorus in weaned pigs	(Huang et al., 2004)
Lactobacillus fermentum	5.8×10^7	Maximized crude protein digestibility	(Yu et al., 2008)
L. reuteri and L. plantarum complex	1×10^6	Increases apparent total tract digestibility of nitrogen and energy	(Zhao & Kim, 2015)

Three different LAB complex		Apparent total tract digestibility of crude protein and crude fiber increased in during the first 2 weeks	(Giang et al., 2010)
Complex 1(Enterococcus faecium, acidophilus, Pediococcus pentosaceus)	(3×10^8, 4×10^6, 3×10^6)		
Complex 2(Lactobacillus acidophilus, plantarum, Enterococcus faecium)	(3×10^8, 4×10^6, 2×10^6)		
Complex 3(L. acidophilus L. plantarum 1K8, L. plantarum 3K2)	(4×10^6, 2×10^6, 7×10^6)		

In general, digestibility of nutrients proportionate with the enzymatic action of GI tract. Subsequent colonization some probiotic stain like lactobacilli potentiate the activity of useful enzymes such as β-galactosidase which could improves nutrient digestibility. A study was performed by Kim et al. (2007) to determine the effects of Lactobacillus sp. PSC101 on nutrient digestibility. The study disclosed that lactobacillus can produce active dietary enzymes, such as amylase, lipase, phytase, and protease in weaned pigs. In addition H.F. et al., (2008) also reported that lactobacilli yields lactic acid and proteolytic enzymes that can maximized the nutrient digestibility. Patarapreecha et al., 2018 conduct an experiment on pigs using Bacillus subtilis as a probiotics and appears that it favor better nutrient digestibility. Another study on Bacillus amyloliquefaciens claimed that they can generate several types of extracellular enzymes such as α-amylase, cellulase, proteases and metalloproteases, which elucidate probiotic supplementation can improve the nutrient digestibility (Bajagai et al., 2016).

Influence on growth performance

Growth is an important component of animal industry, as it determined the profit. Generally it is measured by following parameter such as average daily gain (ADG), average daily feed intake (ADFI), and feed con- version ratio (FCR). Several studies were done in past few decades to determine the effect of probitic supplementation on growth performance of pigs. Some of them proved effective some were not. In this review literature we summarized few representative studies which have significant impact on growth of pigs are shown in table 5.

Table 5: Positive effect of probitics on growth performance in pigs

List of studies performed on weaned pigs					
Strains of probiotics	**ADG**	**ADFI**	**FCR**	**Study period after weaning(days)**	**Reference**
Enterococcus faecium, Lactobacillus acidophilus, Lactobacillus plantarum	+	+	-	14	(Giang et al., 2010)
Saccharomyces cerevisiae subsp. boulardii	ns	ns	-	28	(Le Bon et al., 2010)
Bacillus subtilis, Bacillus licheniformis	+	+	-	28	(Ahmed et al., 2014)
Lactobacillus plantarum GF103, Bacillus subtilis B27	+	-	-	35	(Dong et al., 2014)

Lactobacillus reuteri, Lactobacillus plantarum	+	-	-	28	(Zhao & Kim, 2015)
Bacillus subtilis, Bacillus amyloliquefaciens	+	+	-	42	(Cai et al., 2015)
Lactobacillus acidophilus, Bacillus subtilis, Saccharomyces cerevisiae	+	+	-	28	(Choi et al., 2016)
Lactobacillus acidophilus, Bacillus subtilis, Saccharomyces cerevisiae	+	+	-	35	(Kim et al., 2017)
List of studies performed in growing and finishing pigs					
Lactobacillus acidophilus, Saccharomyces cerevisae, Bacillus subtilis	+	ns	ns	42	
Bacillus subtilis, Bacillus coagulans, Lactobacillus acidophilus	+	ns	ns		
Bacillus subtilis, Clostridium butyricum	+	ns	-	60	(Meng et al., 2010)
Bacillus licheniformis, Bacillus subtilis	+	ns	-	50	(Jørgensen et al., 2016)
Bacillus coagulance, Bacillus licheniformis, Bacillus subtilis	+	ns	-	112	(Balasubramanian et al., 2016)

ADG = average daily gain; FCR = feed conversion ratio; ADFI = average daily feed intake; + = significantly increase; - = significantly decrease; ns = no significant change

Whereas some study provided inconsistent result those are put together below (Table 6).

Table 6: List of inconsistent studies performed on pigs

Studies performed on weaned pigs					
Strains of probiotics	**ADG**	**ADFI**	**FCR**	**Period after weaning(days)**	**Reference**
Lactobacillus gasseri, Lactobacillus fermentum, Lactobacillus reuteri Lactobacillus acidophilus	ns	ns	ns	21	(Huang et al., 2004)
Enterococcus faecium, Lactobacillus salivarius, Lactobacillus reuteri, Bifidobacterium thermophilum	ns	ns	ns	28	(Mair et al., 2010)
Lactobacillus amylovorus, Lactobacillus mucosae, Lactobacillus salivarius, Lactobacillus reuteri, Lactobacillus johnsonii	ns	ns	ns	21	(Lähteinen et al., 2015)

Studies performed on grower and finisher pigs					
Bacillus subtilis, Bacillus licheniformis	Ns	+	ns		
Bacillus subtilis, Bacillus licheniformis	Ns	+	ns		(Y. Wang et al., 2009)
Bacillus subtilis, Saccharomyces cerevisiae	Ns	ns	ns	75	(Giang et al., 2011)

ADG = average daily gain; FCR = feed conversion ratio; ADFI = average daily feed intake; + = significantly increase; - = significantly decrease; ns = no significant change

From the previous findings it is very much clear that probiotic supplementation not always encourage the growth performance of pigs. Outcome of those studies altered may be due to the stains and doses of used probiotics, age of the animal, surrounding environment, strategies of probiotic supplementation (Giang et al., 2010; Jørgensen et al., 2016). However, according to the previous studies it appears that the beneficial effect of probiotics is more prominent in weaned piglets.

Impact on meat quality and texture

Pork is the most frequently consumed meat in the world and its demand increasing day by day (Murphy et al., 2014). Probiotic supplementation may significantly improves the pork quality, produces more vivid color, enhances the water holding capacity and reduces drip loss and thiobarbituric acid reactive substances (TBARS) values of meat from finishing pigs (Giang et al., 2011; Jukna et al., 2005). Redness of meat mainly depends on the myoglobin concentration which alters with the oxidation of myoglobin (Livingston & Brown, 1981). Meat color is the most significant sensory trait of red meat which affecting consumer purchasing decisions as it indicates the freshness of meat (Morrissey et al., 1994). Drip loss and muscle WHC (water holding capacity) are the important qualitative character of meat. Lower drip loss and higher WHC indicates better quality meat. WHC not only affects the meat juiciness also concerned with other eating-related qualities, such as taste and aroma (Chen et al., 2009). TBARS value measure the lipid oxidation of meat. Low TBRAS value indicates less oxidation take place (Yang et al., 2006). In this regard Ko & Yang (2008) performed a study on finishing pigs and proved that green tea probiotics containing L. acidophilus 3.2×10^8 cfu/g, L. plantarum 2.2×10^8 cfu/g, B. subtilis 4.5×10^9 cfu/g and S. cerevisiae 5.2×10^8 cfu/g significantly reduced the TBARS value of loin meat. Beside this Kim et al. (2008) reported that 0.1% complex probiotics (S. cerevisiae 1.0×10^8 cfu/g, Phaffia rhodozyma 1.0×10^8 cfu/g L. crispatus 1.0×10^8 cfu/g, L. plantarum 1.0×10^8 cfu/g, Enterococcus faecium 1.0×10^8 cfu/g) supplementation in finishing pigs diets can minimize drip loss and enhance meat redness. Meng et al. (2010) also suggested that 0.2% complex probiotics (Clostridium butyricum 1.0×10^9 cfu/g and B. subtilis, 1.0×10^{10} cfu/g) supplementation increased the sensory color of pork. Another study was done by Balasubramanian et al., (2016) on growing-finishing pig using Bacillus-based probiotic mixture (B. coagulance 1×10^8 cfu/g, B. licheniformis 5×10^8 cfu/g, and B. subtilis 1×10^9 cfu/g). He observed that feeding Bacillus-based probiotic mixture could enhance the sensory color of pork and it can reduce the drip loss of right loin muscle. Few studies claim that the beneficial effects of complex probiotics on meat quality seen possibly due to the antioxidant properties of probiotics. Further studies required to establish the main reason behind this (W. C. Liu et al., 2018).

Impact on host immune response

Germ free animal can develop and rear in absence of any microbial colonization. But those animals have some major shortcoming in their certain bodily system, for instance the mucosal and systemic immune system, development of the gut associated lymphoid tissue (GALT) and susceptibility as well as immune response towards the pathogenic microorganisms (Lee & Mazmanian, 2010; Roselli et al., 2017). Intestinal epithelial cells

(IECs) act as a physical barrier between luminal contents and the immune system. IECs have some pathogen sensing and antigen presenting cells and molecules such as intraepithelial lymphocytes (IELs), Toll-like receptors (TLRs) and class II major histocompatibility complex (MHC II). It is observed that germ free mice have lower expression of TLRs and MHC II molecules (Lundin et al., 2008; Matsumoto et al., 1992). IELs also low in number in that animal (Imaoka et al., 1996). This gives an idea about the contribution of commensal gut micobiota to the development and function of host immune system.

Probiotic bacteria not only help in the colonization of commesal microorganism, also can modulate the immune system through adjusting the immune response directly or indirectly. They can directly enhance the production of pro-inflammatory as well as the anti-inflammatory substances, increase the production of immunoglobins, encourage the activity of macrophage or natural killer cells which modulates the host defense system. In addition they can enhance gut epithelial barrier through up-regulation of tight junctions (TJs) and alter the mucous secretion which comes under indirect pathway (La Fata et al., 2017). TJs ate the multi-protein complex consisting of trans-membrane and membrane-associated proteins which maintain the integrity of gut epithelium (Wang, 2019). It is proved that Immunoglobulins A (IgA) and G (IgG) are the most two immunoglobins whose production and circulation can be stimulated by probiotic supplementation (Bajaj et al., 2015; Vondruskova et al., 2010). Nevertheless it is clear that directly or indirectly probiotics can modulate both the innate and adaptive immune response of host (Oelschlaeger, 2010).

Role in the production of immunoglobulins

Serum immunoglobin (IgA, IgG and IgM) level determine the effectiveness of probiotic supplementation on humoral immunity, where influence on gut immunity measure by the secretory IgA content in luminal samples (T. Wang et al., 2019).

Effect on serum immunoglobulins

Numerous studies proved that probiotic bacteria are able to change in the immunoglobulin level of serum .For example, Dong et al., (2014) demonstrated that the serum IgA level improved after 2 weeks probiotic (L. plantarum and B. subtilis) supplementation. Ahmed et al., (2014) exert that serum IgG level was elevated by 0.04% Bacilli-based probiotic treatment in piglets challenged with Salmonella enterica serovar Typhimurium KCTC 2515 and Escherichia coli KCTC 2571. Naqid et al., (2015) claims that inclusion of Lactobacillus plantarum B2984 in the diet of piglets (~1×10^{10} cfu/animal/day) enhanced serum IgM, IgG and IgA. Likewise Ayala et al., (2015) reported that there was an increase in the concentration of serum G immunoglobulins in the Bacillus subtilis C-34 treated sows. Lactobacillus based probiotic (Lactobacillus reuteri ZJ625, Lactobacillus reuteri VB4, Lactobacillus salivarius ZJ614, and Streptococcus salivarius NBRC13956) treatment on weaned piglet also show the same result on serum IgG (Dlamini et al., 2017). In addition Zhu et al., (2017) observed that piglets fed soybean meal fermented by L. plantarum, B. subtilis and S. cerevisieae had significantly higher serum IgA, IgG and IgM level. Moreover Shin et al., (2019) proved immunomodulatory effect of L. plantarum JDFM LP11 which elevated serum IgM level in weaned piglets.

Effect on mucosal immunoglobulins

It is well established that intestinal immunoglobulins play an important role in the clearance of pathogenic microorganism (Takahashi et al., 1998). Gut microbiota also take part in the production of mucosal immunoglobins. Gut microbiota and the secretory IgA together act as the first line of defense against pathogenic microorganism (MacDonald & Monteleone, 2005). Mach et al., (2015) find out secretory mucosal IgA concentrations are positively correlated with *Prevotella* abundance. It was reported that *B. cereus* var. toyoi feed supplementation led to an increased intestinal IgA secretion both in sows and piglets (Scharek et al., 2007). Zhang et al., (2008) indicated that LAB (Lactobacillus acidophilus and L. reuteri) supplementation in gnotobiotic (Gn) pig potentiate intestinal immunity by increasing IgM and IgG titer and total intestinal IgA secreting cell responses. Similarly number of IgA producing cell were significantly increased in the duodenum and ileum by dietary administration of the L. salivarius B1 or B. subtilis RJGP16, or co-administration of the two probiotic in newborn piglets (Deng et al., 2013). Another study formulated by Kandasamy et al., (2015) using Lactobacillus rhamnosus strain GG and Bifidobacterium animalis lactis Bb12 against human rotavirus (HRV) infection in pig model. The study shows that LGG+Bb12 probiotics significantly enhanced small intestinal HRV IgA antibody and total IgA responses in post-challenge vaccinated piglets. It is assumed that this immunomodulatory effect of probiotics is observed may be due to the induction of dendritic cells and pattern recognition receptors of gut mucosa which significantly increases IgA responses and production.

In the mean time some studies claims that probiotic supplementation may reduce mucosal sIgA concentration due to improved barrier protection and reduced bacterial translocation. For example, Lessard et al., (2009) reported that Pediococcus acidilactici (PA) or PA+ Saccharomyces cerevisiae ssp. boulardii (SCB) supplementation reduce the sIgA concentration in ileal flushes. Beside this, Tejada-Simon et al., (1999) shows that mice treated with Lactobacillus bulgaricus and Streptococcus thermophilus decreased fecal sIgA titers against cholera toxin, while sIgA titers increased in those treated with Lactobacillus acidophilus and Bifidobacterium spp. This study indicates production of natural and specific sIgA in the gut are highly strain specific. Some induces sigA production whereas some reduces. Bos et al., (2001) also reported the same.

Beside this, time depended effect also reported. For instance, Perdigon et al., (1995) observed a significant increase in the sIgA-producing plasma cell number in mice treated with L. acidophilus in day 2 and 5, but decreased in day 7. Therefore, effect of probiotics on mucosal IgA production remains enigmatic and further study is needed.

Effect on cytokines production

Cytokines are important biological biomarkers which regulate the innate and adaptive immune response of body. Probiotics have been known to take part in the release of different biological biomarkers including interleukins (ILs), interferons (IFNs), tumor necrosis factors (TNFs), transforming growth factor (TGF), and chemokines (Foligné et al., 2010; Savan & Sakai, 2006). Cytokines are well characterized as pro-inflammatory and anti-inflammatory cytokines based on their influence on inflammation. Interleukin-1β (IL-1β), IL-6, IL-8, IL-12, IL-18, tumor necrosis factor (TNF), gamma-interferon (IFN-γ) are classified as pro-inflammatory cytokines whereas IL-4, IL-5, IL-10, IL-13, IFN-α and transforming growth factor-β (TGF-β) are marked as anti-inflammatory cytokines (Azad et al., 2018; Cavaillon, 2014)

Effect on intestinal cytokine expression

A number of studies proved the significant role of probiotic bacteria in production of pro- and anti-Inflammatory cytokines. For an example, mice treated with Lactobacillus rhamnosus was shown to reduce IL-6, TNF-α, IFN-γ gene expression of intestinal epithelial cell (Yan et al., 2011). Finamore et al., (2012) observed that orally Lactobacillus rhamnosus GG (LGG) or Bifidobacterium animalis supplementation in immunized rats increased IL-10 and TGF-β expression in mesenteric lymph nodes. Herfel et al., (2013) reported that ileal TNF and IL-10 expression tended to increase with Bifidobacterium longum supplementation in newborn piglets. In neonatal piglets, L. reuteri has been found to decrease the mRNA expression of IL-1β (pro-inflammatory) and IL-10 (anti-inflammatory) in the ileum after 14 days of treatment (H. Liu et al., 2014). In addition, Lähteinen et al., (2015) reported an up-regulation of IL-4 and IFN-α (anti-inflammatory) in the cecum, with down-regulation of IL-8 and TNF (pro-inflammatory) in the colon in the piglets fed with multispecies lactobacillus. The mRNA expression of TGF-β1 also diminished in the jejunum, ileum and colon of the treated animals. Moreover Hou et al., (2015) published that relative abundance of mRNA expression of TGF-β was increased while IFN-γ was decreased in the mesenteric lymph nodes of piglets treated with *L. reuteri*.

Effect on serum cytokine profile

Probiotic bacteria also have the capability to modulate the serum cytokine profile which can be proved by several studies. For instance, administration of Lactobacillus rhamnosus GG (LGG) before E. coli k88 infection attenuated the elevation of serum IL-6 (associated with piglet diarrhea) induced by E. coli. Serum TNF-α (anti-inflammatory) was also increased in the treated piglets. This study showed that LGG was effective as preventive therapy for post-weaning diarrhea induced by E. coli k88 (Zhang et al., 2010). Previous study shows that probiotic Bifidobacterium can increase serum TGF-β levels (Ouwehand et al., 2008). Czyzewska-Dors et al., (2018) reported a higher concentration of IFN-α, IFN-γ, IL-12, and IL-10 were observed in pigs supplemented with probiotic bacteria. Another recent study found that L. plantarum PFM105 supplementation increase serum levels IL-10 and TGF-β in weaned piglets (Wang et al., 2019). Moreover, Laskowska et al., (2019) claims that use of multi-microbial probiotic formulation in sows during pregnancy was followed by an increase in the concentration of serum pro-inflammatory cytokines, i.e., IL-2, TNF-α, and IFN-γ, and anti-inflammatory, i.e., IL-4, IL-10 and TGF-β.

At the same time, some study shown that probiotic supplementation does not reflect the serum cytokine level. Baken et al., (2006) reported that Wistar WU rats orally administered with L. casei Shirota which did not alter serum cytokine level. Wang et al., (2009) demonstrated that L. fermentum I5007 supplementation in weaned piglets had no effect on serum cytokines level. This discrepancy may be attributed to the probiotic strain and the health status of introduced animals.

Effect on maturation and development of important immune cells and receptors

Beneficial effect on development and maturation of different regulatory T cells, including Th3, Tr1, CD4+CD25+ regulatory, CD8+ suppressor cells are established by several studies. These immune cells and their receptors sustain intestinal homeostasis and the equilibrium between tolerance and reactivity to ingested food antigens as well as to commensal microbiota (Thomas & Versalovic, 2010). Schierack et al., (2007) and demonstrated that intraepithelial CD8+ and CD25+ T cell population was enhanced in the piglets treated with Bacillus cereus var. toyoi. Likewise, Walsh et al., (2008) observed that Lactobacillus salivarius treated piglets have decreased CD25 induction on T cells and decreased CTLA-4 induction on CD4 T cells. Treated group also have increased CD4+ CD8+ T cells proportion within the peripheral T-cell population. CD25 and CTLA-4 are important T cell receptor which plays a key role in regulation of T cell activation (Inobe & Schwartz, 2004; Piriou et al., 2003). Decrease in the induction of these cell receptor proved the immunomodulatory effect of probiotics. Beside this, CD4+CD25+Foxp3+ T cell expansion in mesenteric lymph node was observed in Lactobacillus rhamnosus GG (LGG) fed rats (Finamore et al., 2012). Moreover, Laskowska et al., (2019) also proved that probiotic supplementation may increased regulatory T cell expression and polarized the immune response from Th1 to Th2.

However, some studies fail to show any beneficial effect on the immune cells (Galdeano & Perdigo, 2014; Gill et al., 2000; Wang et al., 2009)

Intestinal development

Villus height and crypt depth are the most two important measure which indicates the maturity and functional capability of enterocytes. Intensity of intestinal absorption is increases with the villi height as it provide more area for absorption (Hampson, 1986). Weaning is a very stressful condition which leads to villous atrophy and crypt hyperplasia with a consequent impairment of nutrient digestion and absorption (Boudry et al., 2004; Hampson, 1986). Probiotics have been proved to enhancing the gut health and development by minimize the weaning stress. Bontempo et al., (2006) reported that dietary supplementation of S. cerevisiae ssp. Boulardii increases villus height and crypt depth of weanling piglets. Gebert et al., (2011) observed that the ratio of villous height: crypt depth was greater in the ileum and duodenum of pigs fed with L. brevis 1E1 compared to control one. Application of B. subtilis-based multi-strain probiotics showed an increase villi length of duodenum and jejunum in weaning pigs (Cai et al., 2015). Similarly, Choi et al., (2016) found that L. acidophilus, B. subtilis and S. cerevisiae complex probiotic supplementation improved the villi length of duodenum, jejunum and ileum. Moreover, Zhu et al., (2017) observed that villus height in the duodenum, jejunum, and ileum was significantly higher and the crypt depth was significantly lower in piglets fed soybean meal fermented by L. plantarum, B. subtilis and S. cerevisieae. Wang et al., (2019) concluded that L. plantarum PFM105 significantly increased the villus height in the jejunum and ileum of weaned piglets, which may be the main reason of improved growth performance. Shin et al., (2019) use another strain (JDFM LP11) of L. plantarum and found an increased villus height in segments of duodenum, jejunum, and ileum.

However, some study fails to show any positive effect on intestinal development. Walsh et al., (2008) and Choi et al., (2011) did not find any influence of complex probiotic on intestinal health and morphology. So, further studies needed to explore the underlying mechanism.

Antioxidant property and probiotics

Piglets are subjected to many stressors such as nutritional, psychological and environmental stressors during the post-weaning period which can increase diarrheal incidence, reduce growth performance, change gut microbial diversity, increase susceptibility to pathogenic microorganisms and even cause death in serious condition (Hampson, 1986). Not only in piglets, stress can hamper the growth and immune response of adult animal also (Duthie et al., 1989; Lauridsen et al., 1999). Stress induces the production of reactive oxygen (ROS) and nitrogen species (RNS) including superoxide anion, hydroxyl radical, hydrogen peroxide, singlet oxygen, nitric oxide and nitrogen dioxide (Devasagayam et al., 2004). A certain concentration of ROS is required for normal cellular function like energy production, phagocytosis and intercellular signaling regulation (Nordberg & Arnér, 2001; Poli et al., 2012). But when the concentration exceeds from normal cellular level, ROS can damage of its own cellular DNA, protein and lipid (Schieber & Chandel, 2014). This harmful effect of ROS neutralized by several anti-oxidant defense mechanisms, which including antioxidant enzymes such as superoxide dismutase (SOD), catalase, glutathione-peroxidase (GSH-Px) as well as non-enzymatic substances like glutathione (GSH), heat shock protein (HSP) and ascorbic acid (Birben et al., 2012; Shalini et al., 2015; Zininga et al., 2018). ROS produces their detrimental effect by stealing electrons from adjacent bimolecule. SOD is the first step cells use to stop this process. SOD converts superoxide radicals to the less toxic hydrogen peroxide which converted to non-toxic water by either catalase or GPx. Therefore, measurement of these enzymes can be used to assess the antioxidant status of an individual.

One of the major targets of ROS is the cell membrane where they induce lipid peroxidation resulting in the production of MDA which can react with biomolecules and exert cytotoxic and genotoxic effect (Ardestani & Yazdanparast, 2007). So, MDA is an important indicator of oxidative stress in an organism.

Hormones like cortisol and thyroid stimulation hormone (TSH) also related to the host stress response (Helmreich & Tylee, 2011; Stephens et al., 2014). Duthie et al., (1989) proved that stress-susceptible pigs have defective antioxidant defense mechanisms. Studies over the last few decades proved that consumption of probiotics alone or with food can improve antioxidant activity and reduce damage by ROS. For instance, Wang et al., (2009) suggested that the application of Lactobacillus fermentum in growing and finishing pigs improved the antioxidant status of pigs as exhibited by increased levels of antioxidant enzymes such as SOD and GSH-Px. Serum and muscle malondialdehyde (MDA) levels also decrease in the treated group. Additionally, Cai et al., (2014) observed that oral administration of L. fermentum I5007 to piglets early in life significantly increases glutathione concentration, the activity of GSH-Px, and the total antioxidant capacity in plasma of piglets. Likewise, Supplementation of *Lactobacilli sp.* increased serum concentration of SOD, GSH-Px and catalase, while decreased the concentration of MDA in mice (Tang et al., 2016) and weaning piglets (Wang et al., 2012). Beside this, Wang et al., (2017) reported that the serum total antioxidant capacity (T-AOC) and SOD activities and GSH levels were significantly enhanced in Bacillus amyloliquefaciens treated piglets.

Effects of Probiotics on Lipid Profiles

Cholesterol (CT) is a lipophilic molecule and an essential component of mammalian cell membranes.

Nearly 65-80% of total cellular cholesterol resides in the cell membrane (Soccio & Breslow, 2004). Cholesterol is essential both for humans and animals as it play important role in synthesis of cell membrane, steroid hormones, bile acids and in the process of bidirectional transference of adipose fat and blood glucose with the liver (Olson, 1998; White & Venkatesh, 2011). But higher level of cholesterol or hypercholesterolemia associated with serious diseases like atherosclerotic vascular disease both in humans and animals (Soccio & Breslow, 2004). Pathogenesis of atherosclerotic lesions is common in humans and pigs due to high anatomic and physiological similarities. Higher concentration of low density lipoprotein (LDL) cholesterol and triglycerides (TG) and lower concentration of functional high density lipoprotein (HDL) are strongly related with the atherosclerotic cardiovascular disease. Previous studies on human and pigs have documented the hypocholesterolemic effect of probiotics. For example Yu et al., (2004) reported that inclusion of probiotics (Lactobacillus acidophilus, Lactobacillus pentose and Bacillus subtilis) in piglets diet decreased serum concentration of TC and LDL, while increased HDL concentration. Likewise, Hung et al., (2008) demonstrated that feeding soybean meal fermented by probiotic bacteria decrease the serum concentration of TC, LDL and TG.

Conclusions

From the previous studies it is clear that the use of probiotics could improve the growth performance in weaning, growing and finishing pigs. However, the effect of probiotics application is not always consistent. The effects of probiotic could be affected by strain of probiotics, dosage of selected probiotics, feed form and their interaction with used probiotics, age of animals and surrounding environment of the animal. Therefore, more studies are required to standardize the supplementation protocol including dosages, treatment duration, and to evaluate the bioactivity of probiotics during feed processing. Different coating technique such as microencapsulation should be developed to maintain bacterial stability in the gut which will increase the beneficial effect of probiotics.

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