# Some Growth Promoters Already Tried to Replace Antimicrobial Growth Promoter in Weaned Pig, a Review

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**Abstract -** A number of feed additives are marketed to assist in boosting the pigs' immune system, regulate gut microbiota, and reduce negative impacts of weaning and other environmental challenges. Some minerals (zinc and cooper), dietary nucleotide, Direct-fed microbial (DFM) and yeast, some microorganisms (Lactobacillus) and plant extracts are, when administered in adequate amounts, confer good health benefits onto the host, are a category of feed additives that can be used to replenish the gut microbial population while recuperating the host immune system.

**Keywords**: pig, Lactobacillus, zinc, cooper, plant extracts

## 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 [1, 2]. Immature immune system, hypothermia and immature gastrointestinal system at the time of birth are three important challenges for newborn piglets [3, 4]. Weanling piglets are more at risk of retarded growth as well as an increase in both morbidity and mortality in pigs [1, 4]. 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 (NH3-N)[2, 5]. 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[2]. Many countries including European Union countries and South Korea have banned the use of antibiotic as growth promoters (AGPs) in feed due to the antibiotic residues in animal products and bacterial resistance[6-8],[7]. Due to this concern, Sweden firstly prohibited the use of some of the antibiotics in animal feeds in 1986 [9, 10], and European Union (EU) member nations banned all antibiotic growth promoters in 2006 according to European Parliament and Council Regulation EC No. 1831/2003. Probiotics, prebiotics, enzymes, acidifiers, herbs, and plant extracts are the most widely researched potential alternatives to antimicrobial growth promoters (AGPs) [8, 10, 11].

## Mineral

Minerals are inorganic elements needed by pigs for maintenance, growth, and reproduction. Minerals needed in quantities greater than 100 mg/kg of feed are called macro minerals whereas minerals required in smaller quantities are called micro minerals or trace minerals[12]. Examples of micro minerals are Cu and Zn, which are needed for normal bodily functions of pigs. However, unlike most other minerals, Cu and Zn have antimicrobial properties and they are therefore often added to diets in quantities greater than what is needed to fulfill the nutritional requirements[12].

Nursery pigs usually require 80 to 100 mg/kg of Zn [12-14]; and deficiency of Zn in weanling pig diets leads to growth retardation, loss of appetite, skeletal abnormalities, and hyper keratinization of the skin called parakeratosis [12, 15]. However, use of pharmacological levels (2,000 to 4,000 mg/kg) of inorganic Zn in the form of ZnO is a common recommendation to reduce post-weaning diarrhea and improve growth performance [12, 16-19].

Copper is involved in metabolic reactions, including cellular respiration, tissue pigmentation, hemoglobin formation, and connective tissue development [12, 20]. Neonatal pigs usually require 5 to 6 mg/kg of Cu for normal metabolism [14];[12] but as pigs get older, the requirement for Cu decreases. Pigs deprived of copper develop critical dysfunctions and hypocuprosis [12, 21]. Microcytic anemia is a sign of copper deficiency due to its role in hemoglobin formation and development [12, 22]. Pigs may also suffer from bone abnormalities and unusual leg condition with various degrees of crookedness due to a lack of copper in the diet[12, 23]. Addition of pharmacological levels of Cu in pig diets has been a common practice to improve growth

performance, and supplementing Cu to diets fed to weanling pigs at 100 to 250 mg/kg may reduce post-weaning scouring and improve average daily gain (ADG) and average daily feed intake (ADFI) [12, 16, 24, 25].

Dietary nucleotides

Nucleotides are composed of a nitrogenous base (purine or pyrimidine) linked to a pentose (2-deoxyribose in DNA and ribose for RNA) sugar to which one or more phosphate group are attached [26]. Nucleotides and their related metabolic products play key roles in many biological processes and become essential dietary components when endogenous supply is insufficient for normal function. Nucleotides as feed additives have shown positive effects on the health of young animal [27, 28]. They have been reported to improve the performance and intestinal morphology of weanling pigs[27]. Moore et al[29] demonstrated that the intestinal villus height was higher for pigs receiving nucleotides, suggesting a beneficial effect on the growth of intestinal cells. Superchi et al.[30] also reported reduced cortisol levels in weaned pigs fed with diets supplemented with nucleotides and suggested that they may improve growth by modulating the adaptive response to weaning [28].

Andrade et al[28] reported that from day 14 to 34 of the experiment, growth performance was not affected (P > 0.05) by the treatments. For the total experimental period (day 1 to 34), increasing concentrations of dietary nucleotides linearly improved the final body weight (P = 0.005) and average daily gain (P = 0.008), but did not affect (P > 0.05) the average feed intake and gain:feed. Supplementation of nucleotides of up to 1,000 ppm of weanling pig diets has shown beneficial effects on reducing diarrhea [28, 31]. In addition, dietary nucleotide supplementations of 31 mg/L in formula-fed human infants showed a reduction in the occurrence of diarrhea, which may positively affect gastrointestinal microbiota[28]. In previous studies, the villus height of the duodenum of weanling pigs slaughtered at d 28 [31], d [28], and d 42 [29] post weaning increased with dietary nucleotide additions of 500, 600, and 2,000 ppm, respectively [28]. For broilers, dietary supplementation of up to 2,000 ppm of a commercial product providing nucleotides increased intestinal histology of weaned pigs, however, are able to decrease the population of Salmonella spp. at small intestine. However, some studies have demonstrated that supplementing the diet of weanling pigs with nucleotides does not alter intestinal morphology [32], and the intestinal and fecal bacterial count [26, 28].These findings suggested that differences in these results were related with diet composition, level of dietary added nucleotides, and their production process, in addition to the nutrition and health conditions of the animals[28].

## Probiotics

Probiotics have been defined by the World Health Organization as "microorganisms which, administered live and in adequate amounts, confer a benefit to the health of the host." Probiotics are considered to be able to destroy pathogenic microorganisms by producing antimicrobial compounds such as bacteriocins and organic acids, improve gastrointestinal microbial environment by adherence to intestinal mucosa thereby preventing attachment of pathogens and competing with pathogens for nutrients, stimulate the intestinal immune responses and improve the digestion and absorption of nutrients[10]. The commonly used probiotics include Bacillus, Lactobacillus, Lactococcus, Streptococcus, Enterococcus, Pediococcus, Bifidobacterium, Bacteroides, Pseudomonas, yeast, Aspergillus, and Trichoderma, etc. Microbiological feed addi- tives used in EU mainly include Bacillus (B. cereus var. toyoi, B. licheniformis, B. subtilis), Enterococcus (E. faecium), Lactobacillus (L. acidophilus, L. casei, L. farciminis, L. plantarum, L. rhamnosus), Pediococcus (P. acidilactici), Streptococcus (S. infantarius), and some fungi such as Saccharomyces cerevisiae and kluyveromyces [10, 33]. Japan started using probi- otics in 1960s, and China began the application of probiotics in 1980s. US-FDA approved 42 probiotics till 1989 [34].

## Direct-fed microbials (DFM) and yest

Direct-fed microbials, which may be more commonly known as probiotics, are defined as, "live microorganisms which, when administered in adequate amounts, confer a health benefit on the host" [12, 35]. Yeast include a broad range of products that may be available in pig feed, therefore, a brief overview of yeast will be separately discussed in the current review. Bacillus-based DFM are spore-forming, which makes them thermostable and able to survive at low pH. Bacillus-based DFM have been identified as potent producers of extracellular fiber-degrading enzymes, which may aid nutrient digestion and utilization (Ferrari et al., 1993; Schreier, 1993). Lactic-acid producing bacteria are not spore-forming and survival during feed processing is of concern [12, 36].

## Prebiotics

Prebiotics are non-digestible (by the host) food ingredients that have a beneficial effect through their selective metabolism in the intestinal tract [37]. Prebiotics include oligosaccharides (such as fructooligosaccharide (FOS), mannanoligosaccharide

(MOS)), polysaccharides, natural plant extracts, protein hydrolysates, polyols, etc. Prebiotics can selectively proliferate intestinal bacteria, promote immune functions and show antiviral activity. Some of them are able to promote mineral absorption and regulate metabolism[12]. The applications of prebiotics as feed additives began in the late 1980s. China began to use them in the late 1990s. Currently, the most promising prebiotics aremultifunctional oligosaccharides and acidifiers. Prebiotics are stable compounds with no residue, no induced resistance, and wide variety of sources. However, nowadays in EU manyprebiotic products are not authorizedas feed additives under the commission regulation (EC) 1831/2003 (European Commission,2003)[12]. This is due to some draw backs of this kind of products. First, prebiotics themselves cannot inhibit and kill pathogens, thus they cannot prevent or treat bacterial infections as antibiotics do. Second, feeding with large quantity of prebiotics may cause bloating, diarrhea, and other adverse reactions due to the fermentation in the gastrointestinal tract [10, 38]. Third, a study suggests that the prebiotic role of mannose is related to its oligosaccharide structure [10, 39]. Both β-galactomannan and MOS from yeast Saccharomyces cerevisiae attenuates Salmonella-induced secretion of IL6 and CXCL8, but cells treated with monosaccharide D-mannose show similar levels of these proinflammatory factors compared with the control of infection. Since the relationship between structure and physiological function of prebiotics is not clear, the efficacy of prebiotics is always variable with different animal species, ages, and physical conditions. Sometimes, mutual antagonism occurs. In addition, the high cost of prebiotic production limits their application in the animal husbandry industry [10].

## Synbiotics

Synbiotics are the joint preparations of probiotics and prebiotics, and thus have the dual role of them [10, 40]. There are some reports on the effect of synbiotics on the physiological and biochemical indexes of piglets including the enhancement of immune function in piglets, the improvement of average daily gain and digestibility, the reduction of diarrhea morbidity and mortality, the ease of weaning stress response, and the significant promotion of piglet performance [34]. However, the reports of the beneficial effects of synbiotics on swine production are still limited [41]. The mixing proportions of probiotics/prebiotics for the majority of synbiotics are inadequate [42], thus resulting in a non-synergistic effect. So far, synergymechanism of probiotics and prebiotics has not been thoroughly understood, the extensive application of synbiotics has a long way to go[10].

## Microorganism

The genus Lactobacillus has been reported as one of the major bacterial groups found in GIT [2, 43]. 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 [44]. 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 [2, 45]. These three species of Enterococcus are commonly used probiotics in animal/livestock feeding[2].

## Plant extracts

Plant extracts are secondary plant metabolites, which are responsible for the odor and color of plants. Plant extracts are composed of more than a hundred individual components and in two different forms: liquid oil and solid powder. Most of the oil formed plant extracts arewater-insoluble and often called essential oils. Plant extracts may be extracted from plants through steam distillation, maceration, cold pressing, and solvent extraction or may be synthesized [12, 46]. Plant extracts are of potential interest due to their potential biological functions, such as antiviral, antimicrobial, antioxidant, and anti-inflammatory effects [2]. This may lead to the ability to use plant extracts to replace antibiotics in-feed to improve performance and health of animals [12, 47]. Considering the large number of different groups of chemical components present in plant extracts, it is not surprising that several modes of action are involved in their anti-microbial effects[12]. The anti-inflammatory effects of plant extracts have been well identified in in vitro cell culture models. Plant extracts (i.e. carva- crol, cinnamaldehyde, eugenol. etc.) inhibit the production of proinflammatory cytokines and chemokines from endotoxin stimulated immune cells and epithelial cells [12, 48]. The research on the potential mechanisms of anti-inflammatory effects of plant extracts are still limited[12].

## Conclusion

A variety of strategies are needed to successfully wean pigs without the use of antibiotic growth promoters. Several feed additives may be effective in regulating intestinal environments and improving pig growth performance if diets without

antibiotic growth promoters are fed. From the literature it can be seen that, depending on the products used and the animal husbandry practices applied, feeding probiotics to pigs can improve pig gut health, nutrient digestibility, and growth performance. Using probiotics is generally regarded as safe to pigs, humans, and the environment, and it does not run high risks of introducing foreign chemicals or hazardous substances into food products of animal origin.

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