Strategic use of feed ingredients and feed additives to stimulate gut health and development in young pigs

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ABSTRACT

There is a wide interest in developing management and feeding strategies to stimulate gut development and health in newly-weaned pigs, in order to improve growth performance while minimizing the use of antibiotics and rather expensive feed ingredients, such as milk products. A better understanding of the mechanisms whereby antibiotics influence animal physiology, as well as appropriate use of disease models and in vitro techniques, will lead to the development of alternatives to in-feed antibiotic. Given the considerable advances made in the understanding of intestinal nutrient utilization and metabolism, a complimentary goal in nutrition might be to formulate young pig diets with the specific task of optimizing the growth, function and health of the gut. Important aspects of gut health-promoting pig diets are: reduced content of protein that is fermented in the pigs’ gut, minimal buffering capacity, minimal content of anti-nutritional factors, and supply of beneficial compounds such as immunoglobulins. The optimum dietary level and type of fibre will vary with the nature of enteric disease challenges and production objectives. These diet characteristics are influenced by feed ingredient composition and feed processing, including feed fermentation and application of enzymes. A large number of feed additives have been evaluated that are aimed at (1) enhancing the pig’s immune response (e.g. immunoglobulin; ω-3 fatty acids, yeast derived β-glucans), (2) reducing pathogen load in the pig’s gut (e.g. organic and inorganic acids, high levels of zinc oxide, essential oils, herbs and spices, some types of prebiotics, bacteriophages, and anti-microbial peptides), (3) stimulate establishment of beneficial gut microbes (probiotics and some types of prebiotics), and (4) stimulate digestive function (e.g. butyric acid, gluconic acid, lactic acid, glutamine, threonine, cysteine, and nucleotides). When manipulating gut microbiota the positive effects of gut health-promoting microbes should be weighed against the increased energy and nutrient costs to support these microbes. In some instances feed additives have been proven effective in vitro but not effective in vivo. The latter applies in particular to essential oils that have strong anti-microbial activity but appear not to be effective in controlling bacterial pathogens when fed to pigs. A combination of different approaches may provide the most effective alternative to in-feed antibiotics.

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1. Introduction

There is a wide interest in developing management and feeding strategies to stimulate gut development and health in young pigs. The ultimate aim of these strategies is to improve productivity of pigs around the time of weaning, while
minimizing the use of antibiotics and rather expensive feed ingredients, such as milk products. Indeed, under practical conditions and both shortly before and after weaning pigs probably achieve less than 50% of their growth performance potential (Harrell et al., 1993).

Large amounts of research have been conducted evaluating the impact of a wide range of feed ingredients and feed additives on various aspects of gut health and development in pigs. Moreover, extensive reviews have been written on this topic (e.g. Simon et al., 2003; Mroz et al., 2006; Lallis et al., 2007; Halas et al., 2007). It is beyond this contribution to summarize the vast amount of information that has been generated in this area of research. The focus of this paper is to highlight key underlying concepts that allow a better understanding of the value of selected nutrients, feed ingredients and additives to stimulate gut health and development. The emphasis is on a newly-weaned pig, but concepts may be relevant to older pigs as well.

2. Experimental approaches to explore gut health and development

The gastrointestinal tract (GIT) of a pig is a complex environment. In particular in newborns and around the time of weaning, the pigs’ gut rapidly changes in size, has high protein turnover rates, undergoes rapid changes in microbiota, and quickly alters its digestive and immune functions (Pluske et al., 1997; Vente-Spreeuwenberg and Beynen, 2003; Burrin and Stoll, 2003; Lallis et al., 2004). These changes are influenced by the pigs’ environment, feeding strategies, age at weaning, and pig genotype and are mediated by psychological and behavioural stress. Burrin and Stoll (2003) have divided these changes into the acute phase, observed within the first five to seven days after weaning, and the adaptive phase, which occurs subsequently (Fig. 1). Burrin and Stoll (2003) make the distinction between acute and adaptive phases based primarily on the changes in feed intake, since it takes about seven days for weaned pigs to learn how to eat and resume a level of dry matter intake (at least) that is comparable to that during the pre-weaning period (Pluske et al., 1997).

Given these complexities and rapid changes after weaning it is naive to suggest that a limited number of feed additives can be effective in stimulating gut development and health in different groups of pigs that are managed under wide ranging environmental conditions. This also supports the need to explore underlying mechanisms when evaluating the functional properties of feed ingredients and feed additives, so that we may better understand under what conditions we can achieve the optimal response to dietary interventions. Key aspects of gut functionality that should be considered include digestive capacity (activity of pancreatic and brush-border enzymes), absorptive capacity, chemical and physical barrier, microbiota load and diversity, and immune function. Within this context it is remarkable how limited our understanding is of how antibiotics interact with gut tissue, either directly or indirectly via microbiota and fermentation products (e.g. Niewold 2007). Such understanding is critical for finding effective alternatives to antibiotics.

Ultimately, we wish to improve productivity of pigs managed under commercial conditions. However, it is generally a challenge for researchers to obtain reliable experimental data from commercial pig units that will allow us to explore underlying mechanisms or to evaluate a wide range of feed additives. On the other hand, it can be a challenge to properly represent commercial conditions in research units. Here the use of in vitro techniques and infectious disease models may be considered as well. For example, using chambers may be used to evaluate various aspects of mucosal functionality—such as permeability, absorptive capacity and secretary function—allowing a rapid screening of feed additives and feed ingredients (Boudry et al., 2004; Montagne et al., 2007). Alternatively, the antimicrobial properties of a wide range of feed additives may be explored in a very simple in vitro system (Si et al., 2006a,b). But care should be taken with the interpretation of in vitro findings. For example, the in vitro determined anti-microbial properties of various essential oils are diminished substantially when these are determined with the presence of feed in the in vitro system (Si et al., 2006b), probably because essential oils are adsorbed quickly to feed particles. Observations made in vitro need to be confirmed with key measurements made in vivo.

One approach to evaluating substitute products for antibiotics in vivo is to use an appropriate disease model. In the post-weaning period where obviously most interest lies with the use of alternative/replacement products for antimicrobials, numerous research groups have used a challenge model per os of post-weaning diarrhoea (PWD) using specific pathogenic strains of enterotoxigenic Escherichia coli (ETEC) (e.g. Madec et al., 2000; Owusu-Asiedu et al., 2002, 2003a,b; Montagne et al., 2004; Bhandari et al., 2008). Such models have been used, amongst other things, to examine whether a particular feed additive or dietary strategy is effective in controlling PWD. Other authors (e.g. Bhandari et al., 2008) used a disease challenge model to examine effects of feeding different diets on microbial diversity and inflammatory responses after weaning. A major advantage of using such an in vivo model is that the impacts of the particular product/diet can be assessed within the context of an infectious pathogenic agent being part of the ecosystem of the gastrointestinal tract. However some key concerns still exist regarding effects of a challenge model on between-animal variabilities, both in pathogen load and in the animal's

![Fig. 1. Acute and adaptive phases in development of early-weaned pigs (adapted from Burrin and Stoll, 2003).](image-url)
response to the pathogen, changes in the pig’s responses to different pathogens. A criticism often directed at disease challenge models to induce diarrhoea after weaning is that the incidence and severity of the diarrhoea observed is often less than that experienced in commercial herds where dietary anti-microbial compounds are not included (Callesen and Hansen, personal communication; Denmark). Indeed, there is often a fine line in using an E. coli-challenge model between causing a mild level of diarrhoea and (unintentionally) causing enterotoxaemia and the death of some pigs.

In the absence of an in vitro system that effectively simulates the dynamic nature of the gastrointestinal tract, interesting findings have arisen from using disease models. For example, a recent study by Halas et al. (2009) tested the hypothesis that feeding diets supplemented with inulin (8% of the diet) and benzoic acid (0.5% of the diet) will reduce faecal ETEC shedding and the incidence of PWD, following oral dosing of pigs after weaning with 3 ml of broth containing 3 x 10^7, 2 x 10^9, 1 x 10^10 and 5 x 10^10 colony-forming units (CFU) of a freshly grown strain of ETEC serotype O149:K91:K88 (toxins LT, STa, and STb). Dietary supplementation with inulin, either alone or in combination with benzoic acid, reduced the number of days of diarrhoea in pigs weaned at 21 days of age without significantly affecting average ETEC shedding (Table 1). Benzoic acid, on the other hand, did not affect the incidence of PWD and did not reduce average ETEC shedding when supplemented without inulin. Some previous studies have found no relationship between clinical signs of diarrhoea and ETEC shedding (Madec et al., 2000; Callasen et al., 2007; Kim et al., 2008). In the Halas et al. (2009) study, however, a higher faecal consistency score (more wet faeces) was associated with increased faecal ETEC shedding (R^2 = 0.394, P = 0.001). This may be a reflection of inulin, either by itself or in combination with benzoic acid, reducing the number of faecal ETEC shedding days (P = 0.041).

For an extensive assessment of indicators of gut functionality in young pigs the reader is referred to Montagne et al. (2007). In this review indicators are suggested to assess gut functionality during the acute post-weaning phase, in response to feed intake, and to characterize gut maturation. The rapid development of molecular techniques will allow us to study mechanisms at a more fundamental level based on gene expression profiles, genetic markers, proteomics and metabolomics.

### 3. Feeding the gut

A major consequence of the events that occur in the post-weaning period is essentially a remodelling of the entire GIT, and in this are changes in the way that the GIT functions from a biochemical, physiological and immunological perspective. In the past, diets for newly-weaned pigs have largely been formulated on the basis of overcoming the limitations or immaturity in digestive tract function (e.g., pancreatic and brush-border enzymes) in order to maximize growth of the whole animal, with due recognition to the cost of raw materials and processing. Research summarised in the excellent review by Burrin and Stoll (2003), and more recently with reference to the amino acid arginine (e.g. Wu et al., 2007), suggests that given the considerable advances made in the understanding of intestinal nutrient utilization and metabolism, an alternate or even complimentary goal in nutrition might be to formulate young pig diets with the specific task of optimizing the growth, function and health of the gut. Burrin and Stoll (2003) extensively summarised the major nutrients involved in GIT metabolism in the young pig, and from this discussion of intestinal nutrient utilization, suggested the most promising candidates to be glutamine, glutamate and threonine for the formulation of a ‘gut friendly’ diet. In this regard, several essential and non-essential amino acids are thought to play a role with regard to their metabolic, physiological, immunological and therapeutic effects on the GIT and on the whole organism (review by Kim et al., 2007). Apart from their role as building blocks for peptides and proteins, amino acids can have bioactive properties. Particularly in certain disease conditions, specific amino acids can promote health by improving (gut) tissue anabolism, by reducing stress and by modulating immunology. These amino acids can be supplemented to the diet in case of a relative deficiency during disease. Indeed, experimental results suggest that the profile of amino acids required for the immune system differs substantially from that for growth (Reeds et al., 1994). On top of that, surplus administration of certain dietary amino acids has been shown to be necessary for inducing significant bioactivity for therapeutic purposes (Massey et al., 1998).

### 4. Dietary fibre in post-weaning diets

The roles of ‘dietary fibre’ in post-weaning diets for pigs and its relationship to post-weaning disturbances such as diarrhoea have been of interest to nutritionists and veterinarians for many years, and continues to be so. Curiously, and unlike nutrients and dietary components (e.g. energy) where there are firm dietary recommendations, there are no such recommendations for ‘dietary fibre’, with the dietary level used being a consequence of the ingredients used to make the diet at least-cost. Partly because of this, there has been

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Table 1: Effects of benzoic acid (BA) and inulin (IN) supplementation on the incidence of diarrhoea, faecal consistency (FC) and ETEC shedding in ETEC-challenged weaner pigs.

<table>
<thead>
<tr>
<th>Dietary treatment</th>
<th>Benzoic acid, %</th>
<th>0</th>
<th>0.5</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inulin, %</td>
<td></td>
<td>8</td>
<td>8</td>
<td>0.28</td>
</tr>
<tr>
<td>Days with diarrhoea</td>
<td></td>
<td>2.6</td>
<td>1.2</td>
<td>2.9</td>
</tr>
<tr>
<td>Average FC</td>
<td></td>
<td>3.2</td>
<td>2.9</td>
<td>3.1</td>
</tr>
<tr>
<td>Days with ETEC shedding</td>
<td></td>
<td>1.3</td>
<td>0.7</td>
<td>1.2</td>
</tr>
</tbody>
</table>

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a Adapted from Halas et al. (2009). Values represent means and pooled standard errors.

b Diarrhoea represents number of days with FC ≥ 4. Diarrhoeal days ranged from day 4 to day 9 post-weaning.

c Least-square means and pooled standard errors from observations on days 4, 5, 6, 7, 8 and 9 (individual observation for each pig; FC ranges from 1 to 5).

d Mean values and pooled standard errors; ETEC shedding represents number of days between days 4 and 7 post-weaning with ETEC ≥ 1.
considerable interest in the use of ‘dietary fibre’ in ameliorating post-weaning GIT disturbances.

Reports dating back to the 1960s and 1970s showed that the addition of insoluble fibre sources such as the husks from cereals, e.g., barley, could reduce the excretion of haemolytic E. coli and the incidence of diarrhoea after weaning. For example, Smith and Halls (1968) found that barley hulls fed *ad libitum*, but not pearl barley meal, prevented disease in weaner pigs inoculated with *E. coli*. Those fed barley meal remained susceptible to PWC. The barley fibre used was the outer hull of barley, collected in the making of pearled barley. barley hulls contain a considerable amount of insoluble non-starch polysaccharides (NSP) and lower levels of soluble NSP. barley meal, on the other hand, would have a higher proportion of soluble NSP. Diets used in trials by Bertschinger et al. (1978,1979) that were associated with reduced *E. coli* proliferation and diarrhoea were high in crude fibre (10–17%) and low in nutrients, particularly crude protein. Moreover, Bolduan et al. (1988) and Aumaitre et al. (1995) commented that the ‘appropriate addition’ of insoluble fibre sources might ameliorate PWD. Bolduan et al. (1988), for example, presented evidence showing that the production of diaminos in the colon, which are implicated in PWD, reduced linearly with an increase in the crude fibre content of a weaner feed.

Nevertheless and as evidenced by research in Australia and Spain using cooked/uncooked rice fed to newly-weaned pigs (e.g. Hopwood et al., 2005; Vicente et al., 2008), feeding diets lower in dietary fibre paradoxically may also have benefits in terms of reducing PWD and (or) enhancing growth in the post-weaning period. Using an *E. coli*-challenge model, McDonald et al. (2001a,b) demonstrated that feeding a diet based on cooked white rice and animal protein sources reduced the number of ETEC in the small intestine and colon commensurate with better post-weaning performance, relative to pigs fed pearl barley (Table 2). These data suggest that the question of the correct amount of dietary fibre to include in a weaner diet is complex, as it most likely depends on what the nutritionist/producer is trying to achieve, and may be better answered by investigating dietary ingredients that deliver an appropriate combination of carbohydrates (e.g. differing in digestibility and fermentability), as well as proteins, to the GIT to address the issue. For example, the dietary mix of carbohydrates might well be different to ameliorate PWD than to maximize lean tissue gain.

### 5. Dietary crude protein in post-weaning diets

Another purported strategy to ameliorate PWD that is perhaps more unambiguous is the alteration of the protein quantity and (or) quality to manipulate gastrointestinal structure and function, including that of the microbiota. An imbalance between fermentable carbohydrates and potentially fermentable protein (i.e. undigested nitrogen entering the large intestine) has been proposed as a mitigating factor in the aetiology of PWD of newly-weaned pigs (Bikker et al., 2006; Piva et al., 2006; Kim et al., 2008). Metabolism of proteinaceous materials by the microbiota in the large intestine may increase levels of potentially toxic substances such as ammonia, amines, indoles, phenols and branched-chain fatty acids (BCFA), which have been implicated in the pathogenesis of PWD (Anderson et al., 2000; Gaskins, 2001; Pluske et al., 2002; Houdijk et al., 2007). Indeed, feeding weaned pigs a lower level of crude protein caused lower ammonia concentrations in the small intestine (Bikker et al., 2006) and decreased plasma urea nitrogen, ammonia nitrogen and volatile fatty acids in the ileal digesta (Nyachoti et al., 2006). These data are indicative of reduced protein fermentation by the microbiota, and indicate that feeding lower protein diets could be used to reduce PWD in piglets fed antibiotic-free diets. A potential disadvantage of feeding a low protein diet is compromised growth following weaning caused by a reduced supply of essential AA, such as isoleucine and valine (Nyachoti et al., 2006), however this can be overcome by adding these amino acids in crystalline form. Alternatively, the provision of additional fermentable carbohydrates in the diet of newly-weaned pigs can reduce the extent or negative impact of protein fermentation, as has been shown by Jeaunord et al. (2008).

A study by Heo et al. (2008) was conducted to test the hypotheses that feeding a diet low in protein but supplemented with essential crystalline amino acids to maintain an ‘ideal pattern’ in the diet would first, reduce indices of protein fermentation in the GIT and reduce the incidence of PWD, and second, not compromise growth to approximately 15 weeks of age. In this study the dietary protein level was reduced from 243 g/kg to 173 g/kg while maintaining diet digestible energy content, largely by replacing soybean meal with wheat oat groats and barley. Reducing the dietary protein decreased the levels of faecal ammonia nitrogen and PUN indicative of decreased protein fermentation, which is comparable to work published elsewhere (Nyachoti et al., 2006). Commensurately, this strategy decreased the number of antibiotic treatments, improved faecal consistency with an

<table>
<thead>
<tr>
<th>Carcass gain, g/day</th>
<th>Non-infected pigs</th>
<th>Infected pigs</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rice b Barley c</td>
<td>74</td>
<td>26</td>
<td>28 − 56</td>
</tr>
<tr>
<td>Large intestine, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LW d</td>
<td>2.7</td>
<td>3.8</td>
<td>2.6</td>
</tr>
<tr>
<td>VFA (mM), distal colon</td>
<td>84</td>
<td>114</td>
<td>60</td>
</tr>
<tr>
<td>pH, distal colon</td>
<td>6.8</td>
<td>6.1</td>
<td>6.8</td>
</tr>
<tr>
<td>E. coli in jejunum e</td>
<td>0</td>
<td>0</td>
<td>0.9</td>
</tr>
<tr>
<td>E. coli in colon e</td>
<td>0</td>
<td>0</td>
<td>3.2</td>
</tr>
<tr>
<td>Viscosity in ileum, cP</td>
<td>2.1</td>
<td>2.8</td>
<td>1.6</td>
</tr>
</tbody>
</table>

* P<0.05, ** P<0.01, *** P<0.001, NS: not significant.

Adapted from McDonald et al. (2001a,b). Values represent treatment means and standard error of means.

Rice: cooked white rice (702 g/kg, 4 g/kg dietary soluble NSP content) plus animal protein sources (197 g/kg).

Barley: pearl barley (500 g/kg; 25 g/kg dietary soluble NSP content) plus rice (275 g/kg) and animal protein sources (200 g/kg).


Expressed as log10 CFU (colony-forming units) of haemolytic *E. coli* per gram of mucosal scraping.
accompanying increase in the faecal DM content and did not impact growth performance.

6. Plasma proteins and its alternatives

The addition of (spray-dried) plasma products to diets has revolutionized the feeding of newly-weaned pigs, and especially of pigs weaned before 18 days of age, in the last 15 years. Products such as spray-dried porcine plasma (SDPP), where used, generally enhance performance through increased feed intake and feed efficiency in the immediate post-weaning period. Mechanisms for such effects have been studied (see review by Lallès et al., 2004), including immunoglobulin-independent, glycoprotein-enhanced protection against E. coli and the specific protection brought about by plasma immunoglobulins (van Dijk et al., 2001). Nevertheless, alternative products to SDPP have been studied and in recent times, numerous experiments have examined feeding bovine colostrum products to weanling pigs. This is because bovine colostrum contains high levels of immunoglobulins and growth factors such as IGF-1, and may be viewed as a “safer” product to feed than animal plasma. Dunshea et al. (2002) compared diets containing preparations of freeze-dried porcine plasma and freeze-dried bovine colostrum after weaning at 14 days of age. These diets were compared with a diet consisting of soybean meal and a diet with animal protein sources. There were no effects of diet on performance in the first 4 days after weaning. However, between 18 and 21 days of age, pigs fed the soybean-meal-containing diet ate less and grew slower than pigs fed the other diets. By 35 days of age, pigs fed diets containing colostrum and plasma were, on average, 6% heavier than pigs fed the other diets. Under these experimental conditions the use of bovine colostrum and a combination of animal protein sources was comparable with using freeze-dried porcine plasma in diets for early-weaned pigs. Inclusion of soybean meal in diets, however, resulted in inferior performance. King et al. (2007) and Boudry et al. (2008) noted improvements in pig performance in the first 14 days after weaning at 21 days of age with the inclusion of a bovine colostrum product in the diet. King et al. (2007) also observed that villous height and crypt depth were increased and decreased, respectively, in the proximal jejunum, mid jejunum and distal ileum of pigs consuming dietary bovine colostrum. Furthermore, midjejunal lamina propria CD4(+) and CD8(+) T-lymphocyte density was increased by 28 and 37%, respectively, in piglets consuming dietary bovine colostrum. In another study, King et al. (2008) evaluated the effects of dietary spray-dried bovine and porcine plasma and spray-dried bovine colostrum on growth performance and intestinal histology in weaner pigs. No differences in average daily feed intake and growth rate were observed among dietary treatment groups.

7. Selected feed additives

A large number of feed additives have been evaluated that are aimed at either (1) enhancing the pigs’ immune response (e.g. immunoglobulin; ω-3 fatty acids, yeast derived β-glucans), (2) reducing pathogen load in the pig’s gut (e.g. organic and inorganic acids, high levels of zinc oxide, essential oils, herbs and spices, some types of prebiotics, bacterio-

7.1. Organic and inorganic acids

Various extensive reviews have been written about the use of organic and inorganic acids in pig diets (e.g. Partanen, 2001; Decuyper and Dierick, 2003; Mroz et al., 2006). The positive effects of feeding acids to pigs on gut health and development, and indirectly on pig health and productivity, may be attributed to various factors, including: (1) antimicrobial activity of non-dissociated organic acids; (2) lowering digesta pH, in particular in the stomach, aiding protein digestion; (3) lowering stomach emptying rate; (4) stimulating (pancreatic) enzyme production and activity in the small intestine; and (5) providing nutrients that are preferred by intestinal tissue thereby enhancing mucosal integrity and function. Because of these beneficial and synergistic effects, different combinations of organic and inorganic acids are used widely in diets for newly-weaned pigs, and used increasingly in diets for growing-finishing pigs and sows. The effectiveness of feeding acids to pigs will vary with the types and combinations of acid, the animal’s state and feed characteristics, in particular the diet’s buffering capacity (Blank et al., 1999; Mroz et al., 2006).

A relatively recent development is the encapsulation of acids for targeted delivery to different gut segments. Studies, such as those conducted by Piva et al. (2007) have shown that relatively simple encapsulation is effective in delaying absorption of dietary acids and allowing more effective delivery of acids to the distal ileum, caecum and colon of piglets. The latter may also be achieved by feeding acids in the form of specific salts. For example, Canibe et al. (2001) showed that feeding potassium-diformate is effective in raising formic acid levels at the distal ileum of pigs at 28 days after weaning. The latter likely contributes to the observed larger positive effects of feeding potassium-diformate on growth performance of pigs, as compared to other forms of formate (Overland et al., 2000). Decuyper and Dierick (2003) stressed the strong anti-microbial properties of medium-chain fatty acids. The combined feeding of triacylglycerols containing medium-chain fatty acids and exogenous lipolytic enzymes appears promising and requires further exploring.

Among organic acids and in terms of impact on the animal’s physiology, lactic and butyric acid are of special interest (e.g. Mroz et al., 2006). The beneficial effects of lactic acid on pig growth performance have been documented and may be attributed largely to its anti-microbial properties and stimulation of endogenous enzyme production (see review Mroz et al., 2006). Butyric acid is a preferred energy source for enterocytes and has been shown to be effective in enhancing intestinal cell proliferation (e.g. Sakata, 1987; Kien et al., 2007). However, the beneficial effects of feeding butyric acid, or relatively odorless sodium butyrate, on growth performance of newly-weaned piglets have been small or could not
be detected (Biagi et al., 2006; Weber and Kerr, 2008). This lack of response may be attributed to endogenous fermentative butyric acid production (Sakata, 1987), which may be stimulated by feeding easily fermentable fibre from sources such as inulin or beet pulp to young pigs (Jeaurond et al., 2008). Indeed, butyric acid-producing bacteria have been identified in the mucosa-associated microbiota (Richards et al., 2005). It is of interest to note that microbes can use gluconic acid as substrate for butyric acid production. Therefore, gluconic acid may be explored further as a rather inexpensive source of butyric acid for use in animal nutrition (Biagi et al., 2006).

A potential concern is the development of microbial resistance to acids, which has been defined as the ability to withstand an acid challenge of pH 2.5 or less (e.g. Castanie-Cornet et al., 1999). Inducible and acid resistance proteins have been observed in E. coli (Sato et al., 2000) and Salmonella typhimurium (Bang et al., 2000). However, to our knowledge no information is available about changes in the distribution of genes involved in production of acid resistance proteins across microbial populations in animals, in particular in response to feeding organic acids.

7.2. Feed enzymes

The main goal for using exogenous feed enzymes in swine diets has been to improve the nutritive value of feedstuffs. This is achieved through several mechanisms including the breakdown of anti-nutritional factors present in feed ingredients, elimination of nutrient encapsulation effect thus increasing availability, breakdown of specific chemical bonds in raw materials that are otherwise not cleaved by endogenous enzymes, thus releasing more nutrients, and complementation of the enzymes produced by young animals (Simon, 1998; Bedford and Schulze, 1998). Majority of the vegetable feedstuffs used in swine diets contain a considerable amount of non-starch polysaccharides (NSP) whose anti-nutritional effects are well-established and has been a subject of intense research (de Lange et al., 2000). Thus, the use of carbohyd rase enzymes in swine diets has mainly focused on eliminating the anti-nutritional activities associated with the NSP components of feed. Indeed, several studies have shown that with appropriate enzyme preparations, these anti-nutritional effects can be minimized with a potential improvement in the nutritional value of feedstuffs for young pigs (Simons et al., 1990; Li et al., 1996; Omogbenigun et al., 2004) and that a combination of different enzyme activities is required for degradation of complex NSP to improve nutrient utilization (Meng et al., 2005).

In addition to improved nutrient utilization, enzymes may improve performance of young pigs through the production of a variety of polysaccharide hydrolysis products that have a direct effect on intestinal health by manipulating the growth of gastrointestinal microorganisms (Vahjen et al., 1998; Bedford, 2000; Williams et al., 2001; Pluske et al., 2002). Indeed, studies with nursery pigs (Kim et al., 2003) and broilers (Mathlouthi et al., 2002) suggest that the use of feed enzymes may have a positive impact on intestinal health. In a study with piglets, Inborr and Ogle (1988) reported that supplementing moistened barley with a mixture of carbohydrate degrading enzymes was effective in reducing both the incidence and severity of diarrhoea. In recent studies utilizing an in-situ model of secretory diarrhoea in piglets, Kiarie et al. (2008) reported that NSP hydrolysis products generated by incubating soybean meal and canola meal with a multi-carbohydrase enzyme blend were beneficial in maintaining intestinal barrier function during enterotoxigenic E. coli infection. Similar observations were obtained with NSP hydrolysis products from wheat and flaxseed. These observations could be explained by various mechanisms, including the possibility that hydrolysis products interfere with the attachment of pathogens to the intestinal mucosa, which is an important first step in infection. These products may also act as probiotics (Cummings and MacFarlane, 2002), favouring the proliferation of lactic acid-producing bacteria as has been shown by Högberg and Lindberg (2004) and Kiarie et al. (2007) and which in turn may indirectly prohibit the growth of certain pathogenic species (Choi et al., 1994).

Feed enzymes may also improve gut health by reducing the intestinal viscosity due to soluble NSP, which might reduce rate of digesta passage, diffusion of digestive enzymes, and increase endogenous gut protein secretions. This will in turn increase substrate availability in the lower gut for microbial proliferation (Verstegen and Williams, 2002; Omogbenigun et al., 2004), as discussed in Section 6. Among other effects, increased viscosity of intestinal digesta in weaned pigs enhances proliferation of pathogenic bacteria like enterotoxigenic E. coli and Brachyspira pilosicoli (McDonald et al., 2001a,b; Hopwood et al., 2002, 2004). Thus, it has been hypothesized that supplementing swine diets with enzymes to digest soluble NSP will minimize intestinal microbial load which in turn will increase nutrient availability to the host and minimize proliferation of pathogenic bacteria.

7.3. Pre and probiotics

A probiotic is defined as a live microorganism which when administered in adequate amounts confers a health benefit on the host (FAO/WHO 2002). For young piglets, a probiotic is expected to deliver at least one of the following functions to the GIT: (1) stimulating the development of a healthy microbiota—predominated by beneficial bacteria, (2) preventing enteric pathogens from colonization, (3) increasing digestive capacity and lowering the pH, (4) improving mucosal immunity, or (5) enhancing gut tissue maturation and integrity. In practice, probiotic cultures need to have the following characteristics in order to exert a positive effect on pig performance: (1) the ability to colonize the GIT, (2) high growth rate and a low requirement for nutrients, (3) suppress enteric pathogens, either its cells or metabolites, (4) grown easily on a large scale under commercial conditions; and (5) survive in in-feed and from the manufacturing process with a stable activity.

Lactic acid bacteria (LAB) (including Lactobacillus, Bifidobacterium, and Enterococcus) and bacilli have largely been used as probiotic bacteria for food animal production in the past. Lactobacillus, Bifidobacterium, and Enterococcus are normal residents in the gut. Lactobacillus, in particular, is dominant at the early stage of development of pig gut microbiota (Richards et al., 2005), including the period immediately post-weaning (Li et al., 2003). This group of bacteria thus has an advantage over others in ecology for
colonizing the gut. LAB are acid producers through fermentation, which can lower the pH of gut contents and benefit intestinal functions. In addition, they can inhibit enteric pathogens (Vandenbergh, 1993) and improve the host immunity (Niers et al., 2005). Nonetheless, LAB are not spore-forming bacteria and some of them are less tolerant to oxygen. Survival during manufacturing and storage of feed, as well as the delivery to the animal’s GIT, could be a concern, unless they are protected. In contrast to LAB, bacilli are Gram-positive spore-forming bacteria; spores are relatively stable during feed manufacturing and delivery. In general, Bacillus species have a well-developed enzyme system. Some members have been used for commercial production of enzymes, such as amylases and proteases (Schallmey et al., 2004), which may complement the pig’s endogenous digestive enzymes. In general, probiotic effects are associated with specific bacterial isolates. How to select and maintain the property of a probiotic, therefore, remains critical and challenging in the successful development and application of probiotics.

There have been a large number of in vivo studies to assess the effect of probiotics on the performance of newly-weaned piglets. Recently, it was reported that in 30 out of 31 performance studies, piglets demonstrated a positive growth response to the supplementation of a combination of Bacillus licheniformis and Bacillus subtilis in diets (Kremer, 2006). Different LAB isolates, mainly from Lactobacillus and Bifidobacterium species, have also been reported to have positive effects on the performance of newly-weaned piglets (reviewed by Stein and Kil, 2006). In particular, Lactobacillus sobrius 001T with an inhibitory effect towards enterotoxigenic E. coli (ETEC) K88 was recently demonstrated to have a probiotic effect by reducing ideal ETEC abundance and promoting the growth of piglets orally challenged with ETEC K88 (Konstantinov, 2005). However, there are also reports of in vivo studies showing no responses of piglets to tested probiotic bacteria (Jost and Bracher, 1999). Furthermore, an adverse effect of the supplement with Lactobacillus rhamnosus GG (originally used for human subjects) has even been described, in which the supplement enhanced ETEC abundance and did not reduce the growth of weaning piglets orally challenged with an ETEC (reviewed by Lallès et al., 2007).

The inconsistency in the reports of probiotic effects indicates the high degree of complexity in the development and application of probiotics. It highlights the need for scientific research to better understand the mode of action and molecular mechanisms underlying the probiotic effects. Also, scientific evaluation of newly-developed probiotic products and good quality control practices at every step throughout the manufacturing, maintenance, handling and application are critical to ensure the achievement of expected probiotic effects. Clearly, easy measurement(s) of the characteristics relating to probiotic effects would assist such quality control, and this is often lacking. Probiotic bacteria are live organisms with dynamic changes in their metabolism. Phenotypes of a particular probiotic are subject to the influence by many internal and external factors, which will affect the efficacy of probiotics. Identification of relationships among these factors is thus required for effective use and development of novel probiotics.

A prebiotic is a non-digestible food ingredient that alters the composition, or metabolism, of the gut microbiota in a beneficial manner. It is, therefore, expected that prebiotics benefit the host in a manner similar to probiotics. In practice, bifidobacteria and lactobacilli have been almost exclusively the targets of prebiotics (Bouhnik et al., 2004). For newly-weaned piglets, the dietary supplement of fermentable carbohydrates is generally regarded as a comparatively straightforward approach to improve microbiota composition and functionality of both the small and large intestine (Williams et al., 2001; Bauer et al., 2006). Recent studies demonstrated that the addition of sugar beet pulp, inulin, lactulose and wheat starch to the diet, designed to stimulate the fermentation along the entire gut, altered the composition of bacterial microbiota in the gut of newly-weaned piglets (Konstantinov et al., 2003, 2004). The supplement of inulin to different basal diets also affected the proportion of piglets with detectable levels of bifidobacteria, but not lactobacilli (Loh et al., 2006). Inulin has also been shown to be able to improve small intestinal architecture when dietary lactose levels were low (Pierce et al., 2006). Thus increased intake of prebiotics can contribute to the gut health. Prebiotics are generally cheaper, lower risk, and easier to handle and to incorporate into diets than probiotics. Combining prebiotics with probiotics (symbiotics) may increase the efficacy of probiotic effects on gut health and development in newly-weaned piglets.

7.4. Essential oils

Essential oils are volatile components of plants that have been used in food preparation since antiquity. These oils are generally recognized as safe (GRAS) by the Food and Drug Administration (FDA) of the United States and have been used as artificial flavourings and preservatives, in the manufacture of perfume, and in over-the-counter formulations of medicines. Some essential oils have strong antimicrobial activity (Kalemba and Kunicka, 2003), particularly those containing phenolic structures (Dorman and Deans, 2000). The strong anti-microbial activity of phenolic essential oils, such as carvacrol and thymol, is attributed to their delocalized electrons and the presence of a hydroxyl group on the phenolic ring (Ultee et al., 2002). The oils initiate damage to the bacterial cell membrane, which compromises pH homeostasis and equilibrium of inorganic ions across the bacterial cell membrane (Lambert et al., 2001). This leads to the collapse of the proton motive force and depletion of the ATP pool in the microbe (Ultee et al., 2002). Essential oils have also been shown to have a certain degree of selectivity. Lin et al. (2000) reported more inhibition towards Gram-negative Salmonella and E. coli than to Gram-positive Listeria monocytogenes. In our in vitro studies, we also observed that essential oils exhibited a high efficacy against pure cultures of S. Typhimurium DT104, E. coli O157:H7, and E. coli K88 with little inhibition towards Lactobacillus and Bifidobacterium in mediums that contained pig cecal digesta (Si et al., 2006a). Essential oils usually have the characteristic odour or flavour of the plant from which it is extracted. Therefore, they may improve performance of animals not only by controlling enteric pathogens but also by increasing palatability of diets.
Essential oils have been extensively studied and used in a wide range of food systems to increase the safety and shelf life of foods (Burt, 2004). However, their impacts on growth performance of newly-weaned pigs have been inconsistent, although changes in gut microbiota composition were observed (Manzanilla et al., 2004; Gong et al., 2008). The anti-microbial activity of essential oils tends to be diminished when they are tested in vivo (Gößling, 2001). Essential oils are generally hydrophobic. They can be absorbed quickly after oral, pulmonary or dermal administration (Kohlert et al., 2000). In piglets, essential oils were found to be absorbed nearly completely in the stomach and the proximal small intestine within 2 h after oral administration (Michiels et al., 2008). We also found that feed contributes to the loss of anti-microbial activity of essential oils in pig performance studies (Si et al., 2006b); oils were mostly absorbed to feed articles as revealed by gas chromatography (unpublished data). Together, these observations suggest that essential oils need protection for delivery to the target site within the pig’s GIT to exert their anti-microbial activity. As mentioned earlier in the section about organic and inorganic acids, microencapsulation may be a means to achieve this. In fact, human clinical studies have shown that enteric-coated essential oil (peppermint) capsules exhibited a better performance in treatment of irritable bowel syndrome compared to the uncoated formulation (Liu et al., 1997; Logan and Beaulne, 2002). The improvements have presumably been attributed to the delayed absorption of the coated peppermint oils and the prolonged contact between peppermint oil and bacterial cells. In our recent effort, carvacrol was used as a model essential oil and successfully encapsulated in microcapsules made from Cal alginate hydrogel using an emulsion-extrusion technology with high encapsulation efficiency. Encapsulated carvacrol retained its high anti-microbial activity towards \textit{E. coli} K88 in a culture medium, as well as in a simulated gastrointestinal model (Wang et al., 2009). It remains to be determined if the encapsulated essential oil will reduce the burden of enteric pathogens in the gut of weaning piglets and improve pig performance.

**8. Conclusions**

Large amounts of research have been conducted evaluating the impact of a wide range of feed ingredients and feed additives on various aspects of gut health and development in pigs, in order to improve growth performance around the time of weaning while minimizing the use of antibiotics and rather expensive feed ingredients, such as milk products. A better understanding of the mechanisms whereby nutrients, feed ingredients and feed additives influence animal physiology will lead to the development of alternatives to in-feed antibiotics. Given the considerable advances made in the understanding of intestinal nutrient utilization and metabolism, a complimentary goal in nutrition might be to formulate young pig diets with the specific task of optimizing the growth, function and health of the gut. A large number of feed additives have been evaluated that are aimed at (1) enhancing the pig’s immune response, (2) reducing pathogen load in the pig’s gut, (3) stimulate establishment of beneficial gut microbes, and (4) stimulate digestive function. In this review, a select number of feed additives (organic and inorganic acids, feed enzymes, pre- and probiotics, essential oils) are discussed. These additives all have the potential to improve pig productivity. However, more research is required to optimize the pigs’ response to these feed additives under varying conditions. A key concern with several of these additives is their effective delivery to the targeted location in the pig’s gastrointestinal tract. A combination of different approaches may provide the most effective alternative to in-feed antibiotics.

**Conflict of interest**

All authors acknowledge that there are no conflicts of interest concerning the information that is provided in the paper.

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