Animal Nutrition 17 (2024) 297–311

Contents lists available at ScienceDirect

Animal Nutrition

journal homepage: http://www.keaipublishing.com/en/journals/aninu/

Review Article

# Nutrition strategies to control post-weaning diarrhea of piglets: From the perspective of feeds

Qingsong Tang [a], Tianyi Lan [a], Chengyu Zhou [a], Jingchun Gao [a], Liuting Wu [a], Haiyang Wei [a], Wenxue Li [a], Zhiru Tang [a], Wenjie Tang [b], Hui Diao [b], Yetong Xu [a], Xie Peng [a], Jiaman Pang [a], Xuan Zhao [a], Zhihong Sun [a, c, *]

[a] Laboratory for Bio-Feed and Molecular Nutrition, College of Animal Science and Technology, Southwest University, Chongqing 400715, China
[b] Animal Breeding and Genetics Key Laboratory of Sichuan Province, Sichuan Animal Science Academy, Chengdu 610066, China
[c] Yibin Academy of Southwest University, Yibin 644005, China

ARTICLE INFO

*Article history:*
Received 9 September 2023
Received in revised form
26 January 2024
Accepted 21 March 2024
Available online 26 March 2024

*Keywords:*
Post-weaning diarrhea
Fluid secretion
Feed
Nutritional regulation strategies
Piglet

ABSTRACT

Post-weaning diarrhea (PWD) is a globally significant threat to the swine industry. Historically, antibiotics as well as high doses of zinc oxide and copper sulfate have been commonly used to control PWD. However, the development of bacterial resistance and environmental pollution have created an interest in alternative strategies. In recent years, the research surrounding these alternative strategies and the mechanisms of piglet diarrhea has been continually updated. Mechanically, diarrhea in piglets is a result of an imbalance in intestinal fluid and electrolyte absorption and secretion. In general, enterotoxigenic *Escherichia coli* (ETEC) and diarrheal viruses are known to cause an imbalance in the absorption and secretion of intestinal fluids and electrolytes in piglets, resulting in diarrhea when $Cl^-$ secretion-driven fluid secretion surpasses absorptive capacity. From a perspective of feedstuffs, factors that contribute to imbalances in fluid absorption and secretion in the intestines of weaned piglets include high levels of crude protein (CP), stimulation by certain antigenic proteins, high acid-binding capacity (ABC), and contamination with deoxynivalenol (DON) in the diet. In response, efforts to reduce CP levels in diets, select feedstuffs with lower ABC values, and process feedstuffs using physical, chemical, and biological approaches are important strategies for alleviating PWD in piglets. Additionally, the diet supplementation with additives such as vitamins and natural products can also play a role in reducing the diarrhea incidence in weaned piglets. Here, we examine the mechanisms of absorption and secretion of intestinal fluids and electrolytes in piglets, summarize nutritional strategies to control PWD in piglets from the perspective of feeds, and provide new insights towards future research directions.


## 1. Introduction

Post-weaning diarrhea (PWD) is one of the largest sources of economic loss in swine production worldwide. Early weaning of piglets frequently disturbs intestinal morphology and undermines the intestinal barrier function, resulting in diarrhea, dehydration, retarded growth, and increased mortality rates (Cao et al., 2022). Post-weaning diarrhea in piglets is closely associated with changes in the nutrient composition and levels of diets, and is accompanied by environmental, psychological and microbiological changes (Rist et al., 2013). These changes usually disrupt the digestive and intestinal functions of the piglets (Souza et al., 2011). At the same time, early weaning of piglets cannot digest solid feed well due to insufficient secretion of digestive enzymes in the incomplete function of the gastrointestinal tract, which is very likely to lead to the damage of intestinal barrier function, including disruption of tight junction proteins, increase in intestinal permeability, and

* Corresponding author.
*E-mail address:* s765210@swu.edu.cn (Z. Sun).
Peer review under responsibility of Chinese Association of Animal Science and Veterinary Medicine.

Production and Hosting by Elsevier on behalf of KeAi

https://doi.org/10.1016/j.aninu.2024.03.006

electrolyte imbalance (Ma et al., 2021a,b; Wang et al., 2016). In addition, weaning stress often causes low immune function in piglets, and makes the intestine susceptible to be attacked by pathogens such as enterotoxigenic *Escherichia coli* (ETEC) and diarrhea virus, which can easily cause intestinal inflammation and PWD (Lodemann et al., 2017). It is difficult for the piglet to dynamically process large amounts of fluid in the intestinal lumen in an organized manner when it is challenged by multiple stresses. In some large-scale pig farms, the diarrhea incidence of piglets is as high as 50%, and the mortality rate is 15% to 20%. In the past decades, antibiotic growth promoters and high dose of zinc oxide and copper sulfate have been widely used in piglet diets to control the diarrhea incidence during the weaning transition. However, the addition of antibiotics, high doses of zinc oxide and copper sulfate to diets of weaned piglets has been challenged by problems of bacterial resistance and has faced restricted use worldwide (Jensen et al., 2016; Pilote et al., 2019). So far, we still do not have a single "magic bullet" to replace antibiotics and high copper and zinc in the diets of weaned piglets.

Finding alternative ways to reduce PWD in piglets has become a priority for sustainable pig production due to the environmental, health and safety concerns. An important change during the weaning period of piglets is the change in diet, including changes in nutrient composition and levels, and the pathogens, antigenic proteins and mycotoxins are important factors to be considered that can cause or exacerbate PWD in piglets. In the last few years, significant progress has been made in the studies towards the mechanism of PWD in piglets as well as the effects of the composition and nutritional properties of dietary ingredients. The modification of dietary composition is one of the important directions to reduce the risk of PWD. The goal of this review, therefore, is to describe the mechanisms of absorption and secretion of intestinal fluids and electrolytes in diarrheic piglets, as well as the pathogenesis of ETEC and diarrheal viruses. Building on this knowledge, we review the effects and propose mechanisms of CP levels, antigenic proteins, acid-binding capacity (ABC) and deoxynivalenol (DON) in diets on diarrhea in weaned piglets. Finally, we discuss recent strategies for nutritional regulation from perspective of diets, and examine the main challenges in the development of therapeutic treatments for diarrhea in weaned piglets.

## 2. Mechanisms of diarrhea in piglets

### 2.1. Mechanisms of fluid secretion and absorption

The fluid load primarily comes from drinking water, salivary glands, digestive secretions from the stomach, pancreas, and gallbladder, as well as the intestinal secretions used to maintain chyme fluidity. The intestinal epithelium is the primary site of fluid absorption and secretion in animals, and both the small and large intestines have a high capacity for fluid absorption and storage. In the intestine, fluid absorption and secretion are mediated by paracellular and partially transcellular pathways (Nagaraju et al., 2016). Fluid absorption and secretion by the paracellular pathway is linked to intestinal permeability, which is controlled by intercellular tight junction proteins, and the transcellular pathway is controlled by aquaporins (AQPs) in the cell membrane (Hu et al., 2015; Ikarashi et al., 2016; Krug et al., 2014). The major AQPs in the intestine of pig are AQP1, AQP2, AQP3, AQP4, AQP5, AQP8 and AQP9, which are mainly distributed in the basolateral membrane of the villus-tip epithelial cells and the basolateral membrane of crypt cells (Matsuzaki et al., 2004; Ren et al., 2023). Abnormal expression of AQPs leads to disturbed fluid and electrolyte transport in the intestinal lumen, and the altered conformation and distribution of AQPs also contribute to the occurrence of diarrhea (Zhu et al., 2017). In addition, differences in osmotic pressure gradients induced by the absorption and secretion of fluid solutes (glucose, amino acids, and fatty acids) and electrolytes are important drivers of fluid absorption and transport in the intestine (Keely and Barrett, 2022). In the intestine, cells on the surface of the finger villi carry out most of the $Na^+$ and fluid uptake processes, the crypt is the main site of $Cl^-$ and fluid secretion (Foulke-Abel et al., 2016). Under normal conditions, the processes of intestinal fluid and electrolyte absorption and secretion are tightly regulated, with fluid and $Na^+$ absorption predominating, thus permitting the large amount of fluid that passes through the intestine each day to be reabsorbed into the bloodstream (Keely and Barrett, 2022). However, in piglets with secretory diarrhea, there is a dynamic imbalance between intestinal fluid absorption and secretion, which is usually accompanied by excessive fluid secretion and reduced electrolyte absorption (Thiagarajah et al., 2015). Most of the intestinal luminal fluid is absorbed and secreted in a passive transport mode, which is co-regulated by active transport osmosis of ions (mainly $Na^+$, $Cl^-$, $HCO_3^-$ and $K^+$) and solutes (Thiagarajah et al., 2015). The diarrhea process is mainly driven by the synergistic activity of AQPs, $Na^+/K^+$-ATPase, $Na^+—K^+—2Cl^-$ cotransporter 1 (NKCC1), $K^+$ channels and $Cl^-$ channels. The mechanisms of fluid and electrolyte absorption and secretion in the intestine are shown in Fig. 1.

Intestinal luminal fluid absorption is mainly driven by the basolateral $Na^+/K^+$-ATPase, with $Na^+$, $Cl^-$ and glucose entering the circulation by active transport to the submucosa along with fluid absorption (Cummings, 1984). In the small intestine, they are mainly transported via $Na^+/H^+$ exchanger 3 (NHE3), sodium glucose cotransporter 1 (solute carrier family 5 member 1 [SLC5A1]), $Cl^-/HCO_3^-$ exchanger (solute carrier family 26 member 3 [SLC26A3] and solute carrier family 26 member 6 [SLC26A6]) to facilitate liquid absorption (Lin et al., 2011; Walker et al., 2009). Electroneutral fluid absorption occurs through the synergistic action of NHE3 and $Cl^-/HCO_3^-$, with SLC26A6 for $HCO_3^-$ absorption and SLC26A3 for $Cl^-$ absorption in the jejunum and colon (Seidler, 2013; Xia et al., 2014). In addition, short-chain fatty acid transporter in colonic fluid usually also promotes the absorption of electrically neutral fluid (Canessa et al., 1993; Krishnan et al., 1999). $Ca^{2+}$ and cyclic nucleotides including cyclic adenosine 3′—5′-monophosphate (cAMP) and cyclic guanosine 3′—5′-monophosphate (cGMP) in epithelial cells inhibit the absorption of $Na^+$, $Cl^-$, and fluid in the intestinal cavity by inhibiting the activity of $Na^+$ transporters on the cell membrane (Hoque et al., 2010; Namkung et al., 2010a,b).

Fluid secretion is driven by an osmotic gradient established by active transmembrane electrolyte transport, and the $Na^+/K^+$-ATPase provides a large amount of energy to maintain this gradient (Keely and Barrett, 2022). The major transporters involved in secretion are the intestinal epithelial parietal $Cl^-$ channel and the basolateral NKCC1 and $K^+$ channels (Rao, 2019). The $Na^+/K^+$-ATPase pumps two $K^+$ into the cell and expels three $Na^+$ to maintain lower intracellular $Na^+$ levels. At the same time, $K^+$ is pumped through $K^+$ channels such as potassium voltage-gated channel subfamily Q member 1 (KCNQ1) and potassium calcium-activated channel subfamily N member 4 (KCNN4) in the basal lamina of the cell, providing the chemical driving force for $Cl^-$ to pass through chloride channels (Abbott, 2016; Matos et al., 2007). The cations that NKCC1 cotransports $Na^+$ and $Cl^-$ into the epithelial cell must subsequently be extruded to maintain the driving force for $Cl^-$ efflux across the apical membrane (Keely and Barrett, 2022). $Na^+$ is excreted via the $Na^+/K^+$-ATPase pump, whereas $K^+$, which enters the cell via either NKCC1 or $Na^+/K^+$-ATPase, is excreted via $K^+$ channels in the basolateral membrane. The synergistic action of $Na^+/K^+$-ATPase, NKCC1, and $K^+$ channels on the basolateral side of the intestinal epithelial cell leads to intracellular $Cl^-$ accumulation,

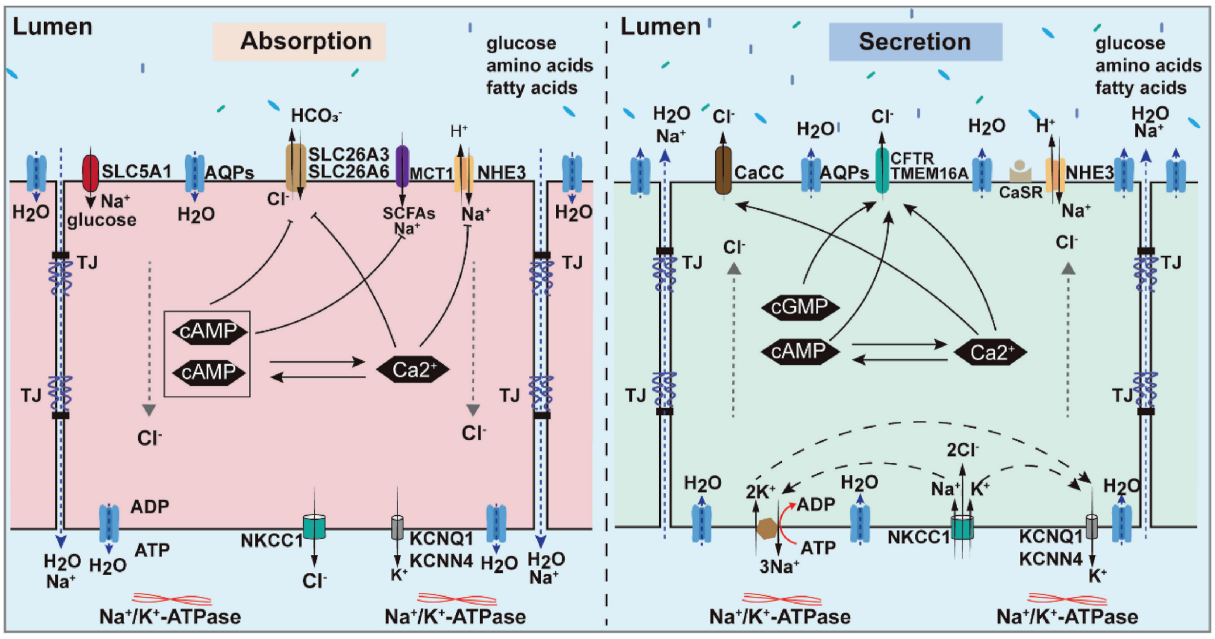


**Fig. 1.** Mechanisms of diarrhea in weaned piglets. The electrolyte gradient is a major driver of fluid absorption and secretion, and $Na^+/K^+$-ATPase provides a large amount of energy to maintain the electrolyte gradient. Fluid absorption is driven by the active transport of $Na^+$ between epithelial cells and the uptake of $Cl^-$, a process that is largely dependent on NHE3, SLC5A1, SLC26A3, SLC26A6, and MCT1. Fluid secretion is driven by $Cl^-$ secretion. $Na^+/K^+$-ATPase provides energy for $Na^+$ pumping out of the cell, and $K^+$ channels (KCNQ1 and KCNN4) and NKCC1 work together to form an electrochemical gradient that drives $Cl^-$ into the cell. $Cl^-$ enters the intestinal lumen from the $Cl^-$ channels (CFTR, TMEM16A, and CaCC) to form an osmotic gradient that drives fluid secretion. SLC5A1 = solute carrier family 5 member 1; AQPs = aquaporins; SLC26A3 = solute carrier family 26 member 3; SLC26A6 = solute carrier family 26 member 6; MCT1 = monocarboxylate transporter 1; NHE3 = $Na^+/H^+$ exchanger 3; TJ = tight junction; SCFAs = short chain fatty acids; cAMP = cyclic adenosine 3′–5′-monophosphate; cGMP = cyclic guanosine 3′–5′-monophosphate; NKCC1 = $Na^+$–$K^+$–$2Cl^-$ cotransporter 1; KCNQ1 = potassium voltage-gated channel subfamily Q member 1; KCNN4 = potassium calcium-activated channel subfamily N member 4; CaCC = calcium-activated chloride channels; CFTR = cystic fibrosis transmembrane conductance regulator; TMEM16A = transmembrane protein 16A; CaSR = calcium-sensing receptors.

creating an intracellular-extracellular electrochemical gradient. Subsequently, $Cl^-$ is released from the cell into the intestinal lumen when $Cl^-$ channels including cystic fibrosis transmembrane conductance regulator (CFTR), calcium-activated chloride channels (CaCC), and transmembrane protein 16A (TMEM16A) open (Thiagarajah et al., 2015). In the intestinal lumen, $Na^+$ from passive transport through the paracellular pathway accumulates with $Cl^-$ from the intracellular pathway to form an osmotic gradient that drives fluid secretion and causes diarrhea. The activation of intracellular messengers, including $Ca^{2+}$ signaling and cyclic nucleotide (cAMP and cGMP), increases the conductance of $Cl^-$ channels at the enterocyte luminal membrane. This acts primarily on CFTR and CaCC of intestinal epithelial cells (Thiagarajah and Verkman, 2013). Throughout $Cl^-$ secretion, the binding of ATP to the nucleotide binding domains and phosphorylation of the R structural domain are required for $Cl^-$ channel opening, and cAMP-dependent protein kinase A, cGMP-dependent protein kinase G, protein kinase C, and phosphatases are the major regulators of phosphorylation of proteins such as CFTR (Callebaut et al., 2018; Poroca et al., 2020; Tien et al., 1994). In addition, cAMP-activated anion secretion in intestinal epithelial depends on the KCNQ1-KCNE3 $K^+$ channel (and is also dependent on cAMP), with KCNQ1-KCNE3 and TWIK-related acid-sensitive $K^+$ channels 2 playing important roles in intestinal anion and fluid secretion (Julio-Kalajzić et al., 2018). Intracellular calcium-sensing receptors (CaSR) in intestinal epithelial cells are thought to regulate intracellular signaling pathways and electrolyte absorption and secretion (Cooke et al., 1983; Geibel et al., 2006). Weaning stress in piglets also usually results in reduced digestion and absorption of nutrients in the piglet intestine, and excess solutes (usually nutrients, not electrolytes) that are retained in the intestinal lumen increase the osmotic pressure of fluids in the lumen and reduce fluid absorption.

### 2.2. Bacterial and viral diarrhea

ETEC infection is one of the most common factors for PWD and mortality in piglets. Most of the ETEC causing diarrhea in weaned piglets carried F4 (K88) or F18 trichomes, and ETEC with both types of trichomes accounted for 92.7% of the induced PWD (Frydendahl, 2002). After entering the animal's gastrointestinal tract, ETEC colonizes the small intestine (F4 tends to colonize the jejunum and ileum) by binding to the epithelial cell receptors via adhesins or by coating the epithelial mucus and rapidly multiplying while secreting large amounts of enterotoxin (Rhouma et al., 2017). ETEC adhere to the intestinal epithelium via colonization factors and secrete heat-stabilizing toxins and/or heat-apoptotic toxins (Smith et al., 2022). The enterotoxins, including stabilizing toxins and heat-apoptotic toxins, increase intracellular cyclic nucleotide levels, thereby activating CFTR and increasing $Cl^-$ secretion, leading to dysregulation of cellular ion transport and fluid secretion (Rao et al., 1980). In addition, binding of enterotoxin to enterocyte surface receptors induces activation of $Cl^-$ channels and basolateral NKCC1, leading to an increase in $Cl^-$ secretion and a decrease in $Na^+$ absorption, which accompanies a large amount of fluid entering the intestinal lumen (De Haan and Hirst, 2004; Thiagarajah and Verkman, 2003). Transport of bacterial toxin factors into the intracellular endoplasmic reticulum subsequently induce A subunit-mediated ADP-ribosylation of adenylyl cyclase, irreversibly activating the protein and triggering a dramatic increase in cAMP (Muanprasat and Chatsudthipong, 2013). At the same time, enterotoxin-mediated diarrhea is accompanied by increased secretion of large amounts of pro-inflammatory cytokines and decreased expression of intestinal intercellular tight junction proteins, which induces intestinal inflammation and increases permeability, accelerating fluid loss (Dreyfus et al., 1993;

Ngendahayo Mukiza and Dubreuil, 2013). ETEC K88 also reduced the expression levels of AQPs (AQP1, AQP3, AQP7, AQP9, AQP11) and NHE3, as well as cAMP response element binding protein (CREB) and protein kinase A in intestinal porcine epithelial cells (IPEC-J2) (Liu et al., 2022a; Zhu et al., 2017). Pathogenic bacterial infection increases intestinal permeability and decreases the apical abundance of NHE3, SLC5A1, and SLC26A3, leading to dysfunctional absorption of fluid and solutes in the intestine, causing diarrhea (Peritore-Galve et al., 2023). Bacteria can also activate $Cl^-$ secretion and inhibit $Na^+$ absorption by increasing several neurotransmitters and the activity of certain receptors (Wapnir and Teichberg, 2002).

Typically, viral infections cause outbreaks of diarrhea in piglets. In particular, porcine epidemic diarrhea virus (PEDV), porcine deltacoronavirus (PDCoV), and swine acute diarrhea syndrome-coronavirus (SADS-CoV) cause necrosis of intestinal epithelial cells in piglets, leading to villous atrophy and malabsorptive diarrhea (Wang et al., 2019a,b). Viral diarrhea is age-dependent and more pathogenic in piglets, leading to intestinal epithelium necrosis, villous atrophy, vomiting, diarrhea, and even death (Yan et al., 2022). Once in the animal intestine, the virus induces necrosis of intestinal epithelial cells and release of inflammatory factors, leading to changes in the structure or activity of water channel proteins and electrolyte transporter proteins, resulting in electrolyte imbalance and increased fluid secretion (Li et al., 2016). Viral infections cause diarrhea by decreasing NHE3 activity and blocking $Na^+$ transporters (Song et al., 2021a). Bacterial and viral infections predispose piglets to severe diarrhea at weaning. Since 2010, highly pathogenic PEDV, PDCoV and SADS-CoV have gradually swept through the global pig industry (Li et al., 2020). These viruses can usually infect pigs of different ages and breeds, causing severe watery diarrhea with a mortality rate of up to 30% to 40%, especially in neonatal piglets, which brings huge economic losses to the pig industry (Xu et al., 2018). It is universally acknowledged that ETEC K88 is one of the main causes of diarrhea in weaned pigs, and is strongly associated with retarded growth performance, intestinal barrier dysfunction, and microbiota disorders (Luise et al., 2019). Overall, pathogenic bacteria and viral infections are the main pathogenic factors causing diarrhea in early weaned piglets and have long threatened the healthy development of the pig industry.

## 3. Risk factors in feeds leading to diarrhea in piglets

The extent of intestinal fluid secretion in piglets depends on several factors, including dietary composition, pathogens, hormones, neurotransmitters, immune cell mediators, and intestinal microorganisms. The combined action of these extracellular factors on intracellular regulatory pathways regulates intestinal fluid secretion. For weaned piglets, dietary changes are a major challenge to normal intestinal absorption and secretion, and CP levels, antigenic proteins, ABC, DON and pathogens in the diets are major triggers of PWD in piglets.

### 3.1. Crude protein levels

Piglets require large amounts of protein after weaning to provide a source of amino acids, which are essential for growth and development and immune regulation (Rezaei et al., 2013). However, the incomplete digestive function of the gastrointestinal tract of piglets renders them incapable of secreting sufficient digestive enzymes to digest proteins, causing the excess proteins to enter the hindgut and be fermented by microorganisms. Fermentation of undigested proteins and amino acids by the intestinal microbiota is an important contributor to diarrhea. We summarized the effects of different levels of CP in diets on diarrhea incidence in weaned piglets (Table 1). Protein fermentation in the hindgut produces a number of metabolites, including short-chain fatty acids, sulfur-containing bacterial metabolites (methyl mercaptan, hydrogen sulphide), aromatic compounds (phenols, indole compounds), polyamines and ammonia (Wang et al., 2018). A large amount of ammonia leads to an increase in intestinal pH, creating a micro-ecological environment conducive to the growth and proliferation of pathogenic bacteria, which in turn may lead to bacterial infectious diarrhea in piglets (Bhandari et al., 2010). A research report that 22% and 24% CP diets reduced occludin expression levels, increased the number of pathogenic bacteria such as *E. coli* and *Clostridium difficile* in the intestine, and decreased the number of beneficial bacteria such as *Lactobacillus*, *Bifidobacterium*, and *Roseburia* (Ren et al., 2022). The increase in pathogenic bacteria such as *E. coli* and the damage to intestinal function caused by protein fermentation will further disturb the intestinal electrolyte metabolism, which in turn will cause piglet diarrhea (Argenzio, 1978; Yamamoto et al., 2007). In addition, a series of toxic substances such as cadaverine and putrescine produced by the fermentation of proteins can exacerbate diarrhea in piglets (Fairbrother et al., 2005; Nagy and Fekete, 2005). Ammonia, polyamines, indoles and phenols are also potentially toxic to the host, inducing intestinal inflammation and decreasing the reabsorption of intestinal luminal fluid by damaging the structure of the intestinal villi and increasing the permeability of the intestinal wall (Andriamihaja et al., 2010). Studies have shown that 23% CP diets increased the pH and ammonia-N concentrations in the colonic digesta and significantly increased the concentrations of the microbial metabolites such as putrescine, histamine and spermidine and, as a result, the diarrhea scores were significantly increased (Wen et al., 2018). High CP levels can also lead to imbalances in the expression of AQPs, resulting in imbalances in fluid absorption and secretion. It has been shown that feeding diets with high CP (30%) levels reduced the expression of AQP1, AQP3, AQP8, AQP10 and increased the diarrhea incidence of weaned piglets (Gao et al., 2020). A recent study showed that 22% and 24% CP diets resulted in abnormal expression of AQPs in the small intestine and colon, whereas 20% CP diets favored the normal expression of AQP4 in the small intestine and AQP2, AQP4, and AQP9 in the colon of weaned piglets, thus maintaining the balance of intestinal fluid absorption and secretion in piglets (Ren et al., 2023). Furthermore, in a study of 21-day-old weaned piglets, there was a gradual increase in $Cl^-$ concentration and CFTR expression levels in the colonic contents, as well as a gradual increase in diarrhea incidence (24.6% to 56.2%), with increasing dietary CP levels (17%, 19%, 23%) (Wu et al., 2015). Therefore, it can be concluded that high dietary CP levels lead to increased protein fermentation in the hindgut, which is detrimental to intestinal barrier function and electrolyte homeostasis.

### 3.2. Acid-binding capacity

The acidic environment of the nursing piglet stomach mainly depends on the fermentation of lactose in milk to produce lactic acid. The termination of the source of lactose after weaning leads to a decrease in lactic acid content and an increase in gastric pH (Zhao et al., 2021a,b). In addition, gastrointestinal pH is further reduced due to the decrease in gastric acid secretion capacity caused by weaning of piglets (Heo et al., 2013). Maintaining a low gastric fluid pH is critical to the intestinal health of weaned piglets as it positively affects nutrition, digestion, and suppression of pathogenic bacteria. Therefore, not only the nutritional composition (e.g., CP, energy, and amino acids) of the diet, but also the effect of the diets on the pH of the animal's gastrointestinal tract should be considered. Acid-binding capacity refers to the resistance of the diets to a low pH in the pig's stomach, is highly related to feedstuffs used in the diets. It can be calculated the milliequivalent (mEq) $H^+$ of

**Table 1**
Effect of different CP levels in the diets on diarrhea incidence of piglets.

| Weaning age | IBW, kg | Experimental period | CP levels | Diarrhea scores or incidence rates | References |
|---|---|---|---|---|---|
| 20-d-old | 5.53 | 1 to 14 d of age | 16%, 19%, 22% | Diarrhea score (1 to 7 d): 1.25 for 16% CP, 1.50 for 19% CP, 1.67 for 22% CP<br>Diarrhea score (8 to 14 d): 1.21 for 16% CP, 1.42 for 19% CP, 1.67 for 22% CP<br>(scores: 1 = normal feces, 2 = moist feces, 3 = mild diarrhea, 4 = severe diarrhea, 5 = watery diarrhea) | Limbach et al. (2021) |
| 21-d-old | 5.90 | 1 to 14 d of age | 17.5%, 25.6% | Not infected with *Escherichia coli*<br>Diarrhea incidence (1 to 7 d): 9.5% for 17.5% CP<br>Diarrhea incidence (1 to 14 d): 8.3% for 17.5% CP, 19.6% for 25.6% CP<br>Infected with *E. coli*<br>Diarrhea incidence (1 to 7 d): 21.4% for 17.5% CP<br>Diarrhea incidence (1 to 14 d): 31.5% for 17.5% CP, 44.6% for 25.6% CP | Heo et al. (2009) |
| 21-d-old | 5.99 | 1 to 14 d of age | 17%, 19%, 23% | Diarrhea incidence: 24.6% for 17% CP, 43.65% for 19% CP, 54.9% for 23% CP | Wu et al. (2015) |
| 28-d-old | 7.98 | 1 to 14 d of age | 17%, 30% | Diarrhea incidence: 13% for 17% CP, 96% for 30% CP | Gao et al. (2020) |
| NA | 8.25 | 1 to 21 d of age | 16%, 17%, 18%, 19%, 20%, 21% | Diarrhea score: 1.4 for 16% CP, 1.58 for 17% CP, 2.12 for 18% CP, 2.48 for 19% CP, 2.62 for 20% CP, 3.23 for 21% CP<br>(scores: 0 = normal feces, 1 = moist feces, 2 = mild diarrhea, 3 = severe and watery diarrhea) | Kim et al. (2023) |
| NA | 10.00 | 10 to 20 kg of BW | 12%, 14%, 16%, 18%, 20% | Diarrhea incidence:13.36% for 12% CP, 24.63% for 14% CP, 28.31% for 16% CP, 49.55% for 18% CP, 46.39% for 20% CP | Liu et al. (2022a) |

NA = not available in the publication; IBW = initial body weigh; CP = crude protein.

0.1 mol/L HCl or 0.1 mol/L NaOH required to reduce the pH of a sample (1 kg) to pH 4 (ABC-4) and pH 3 (ABC-3) by measuring 0.5 g of the sample (Lawlor et al., 1994). The ABC of feedstuffs or complete diets have a strong influence on pig gastrointestinal pH, nutrient digestibility and intestinal microbiology. Excessive ABC results in reduced digestibility of dietary CP, increased hindgut fermentation of CP, increased release of toxic substances such as ammonia and amines, increased piglet diarrhea and impaired growth performance (He et al., 2022). Furthermore, diets with excessive ABC will tend to raise the pH value of the gastrointestinal tract, leading to increased proliferation of diarrhea-causing bacteria, resulting in bacterial diarrhea. We summarized the initial pH, ABC-4 and ABC-3 in common feedstuffs of piglet, which can provide a reference for formulating diets of weaned piglets (Table 2).

### 3.3. Antigenic proteins

Soybean glycinin and β-conglycinin are the most abundant antigenic proteins in soybeans and are two major antinutritional factors that contributing to PWD in piglets. Soybean glycinin makes up 40% of total soybean protein and consists of six subunits (A1A2, A2B1a, AB, A5A4B3, A3B4, and A1bB2). Beta-conglycinin makes up 30% of total soybean protein and consists of three subunits, α′ (57 to 72 kDa), α (57 to 68 kDa), and β (45 to 52 kDa), which are all allergens (Krishnan et al., 2009). Due to insufficient enzyme secretion and the immature development of the digestive tract of weaned piglets, the digestion and absorption of antigenic proteins are very limited. Consequently, after entering the intestine, these proteins stimulate an immune response in the intestinal tissues, causing an allergic reaction (Wang et al., 2014, 2023). Undigested soybean glycinin and β-conglycinin may enter the intestinal tract which keeps the cells proliferating, destroys the cytoskeleton, causes apoptosis of small intestinal cells and trigger allergic reactions (Chen et al., 2014). Symptoms of allergic reactions in piglets mainly present as diarrhea, indigestion, growth retardation (Zheng et al., 2014). Additionally, soybean glycinin and β-conglycinin may induce intestinal injury and inflammation in piglets through the p38 mitogen-activated protein kinase (MAPK)/Jun N-terminal kinase/nuclear factor-κB (NF-κB) pathway, which leads to intestinal villus damage and increased intestinal mucosal permeability (Peng et al., 2018; Sun et al., 2008). Soy protein activates CaSR and intracellular $Ca^{2+}$ signaling, which may lead to an imbalance in electrolyte homeostasis, thereby inducing PWD in piglets (Wang et al., 2021d).

### 3.4. Deoxynivalenol

Deoxynivalenol, also known as vomitoxin, is one of the most common mycotoxins. It is a type B trichothecene and is a secondary metabolite of common field pathogens such as *Fusarium graminearum* and *Fusarium culmorum* (Mishra et al., 2020). Deoxynivalenol is one of the most prevalent mycotoxins in livestock feeds, contaminating many agricultural commodities, and is commonly detected in cereals, including maize, soybean, barley, wheat, oats, and their by-products (Sun et al., 2022; Wu et al., 2011). BIOMIN America, Inc. conducted an investigation in 2018, analyszing a total of 13,629 samples from 77 countries worldwide. The findings revealed that DON is one of the widespread toxins, with contamination rates (by continent) found as follows: 80% in Asia, 75% in Africa, 67% in North America, 67% in Central and South America, 65% in the Middle East, and 63% in Europe. In China, a study showed that DON was detected in up to 97% of feedstuffs and complete diets in pig farms in the Beijing area of China (Li et al., 2014). A recent study showed that 3507 feedstuffs samples from various provinces in China during 2018 to 2020 showed a DON detection rate of 96.4%, with average concentrations ranging from 458.0 to 1925.4 μg/kg, which is 0.1% and 0% to 8.9 % higher than the latest Chinese safety standard (GB 13078-2017) for feedstuffs and complete diets, respectively (Zhao et al., 2021a,b). Global warming and associated climatic changes are progressively increasing the susceptibility of crops to mycotoxin infection, further contributing to increased DON contamination in cereals.

DON is rapidly absorbed into circulation via the small intestinal epithelium and is absorbed at a much higher rate in pigs (82%) than in cattle (1%), sheep (5.9% to 9.9%) and chickens (19%) (Hou et al., 2023). Deoxynivalenol is rapidly and efficiently absorbed in the

**Table 2**
Acid-binding capacity of ingredients commonly used for weaned piglets.[1]

| Ingredients | Initial pH | ABC-4[2], mEq $H^+$/kg | ABC-3[2], mEq $H^+$/kg |
|---|---|---|---|
| Cereals | | | |
| Corn | 6.57 | 84 | 135 to 233 |
| Sorghum | 6.47 | 110 | NA |
| Wheat | 6.72 | 78 | 230 |
| Barley | 6.12 | 95 | 286 |
| Whole oats | 6.33 | 122 | NA |
| Oat groats | 6.44 | 107 | NA |
| DDGS | 4.85 | 147 | NA |
| Cereal blend | 6.08 | 107 | NA |
| Vegetable protein | | | |
| SBM (42% CP) | NA | NA | 980 to 1240 |
| SBM (48% CP) | NA | NA | 1025 to 1035 |
| Expelled SBM | 7.13 | 567 | NA |
| Full fat soya | 6.90 | 480 | 823 |
| Soy protein concentrate | 7.36 | 737 | NA |
| Fermented SBM | 4.69 | 207 | NA |
| Fermented soy isolate | 3.95 | −13 | NA |
| Enzymatically treated SBM | 6.29 | 753 | NA |
| Rapeseed meal | 6.30 | 498 | 945 |
| HPDDGs | 4.87 | 100 | NA |
| Animal proteins and milk | | | |
| Fish meal | 6.51 | 1059 | 1457 to 2100 |
| Spray-dried bovine plasma | 6.99 | 713 | NA |
| Meat and bone meal | 7.45 | 595 | 920 |
| Poultry meal | 6.74 | 1007 | NA |
| Spray-dried whey powder | 6.29 | 440 | NA |
| Whey permeate | 6.16 | 520 | NA |
| Crystalline lactose | 7.09 | 53 | NA |
| Microbial protein | | | |
| Yeast | 3.40 | 150 | 130 |
| Fat | 4.90 | 16 | 137 |
| Vitamins and minerals | | | |
| Ferrous sulfate | 3.20 | −655 | 93 |
| Calcium carbonate | 9.62 | 18,384 | 19,680 to 20,000 |
| Limestone flour | 9.30 | 12,932 | 15,044 |
| Copper sulfate | 5.10 | 92 | 269 |
| Zinc oxide | 8.93 | 19,092 | 17,908 |
| Monocalcium phosphate | 7.61 | 1587 | NA |
| Dicalcium phosphate | 6.81 | 1348 | 5666 to 10,105 |
| Calcium propionate | 9.11 | 9240 | NA |
| Sodium chloride | 6.75 | 49 | 162 |
| Vitamin premix | 6.99 | 10,767 | NA |
| Trace mineral premix | 5.37 | 7867 | NA |
| Vitamin trace mineral premix | 4.94 | 2542 | 5123 |
| Manganese | 8.22 | 2347 | NA |
| Sodium metabisulfite | 4.00 | 0 | NA |
| Choline chloride | 5.96 | 70.5 | 226 |
| Amino acids | | | |
| L-Lysine | 5.89 | 103 | 724 |
| DL-Methionine | 5.96 | 165 | 1219 |
| L-Threonine | 5.97 | 189 | 1386 |
| L-Tryptophan | 5.88 | 149.5 | 1272 |
| L-Valine | 5.53 | 193 | NA |
| L-Isoleucine | 5.76 | 200 | NA |
| Fiber source | | | |
| Beet pulp | 5.57 | 151 | NA |
| Acid | | | |
| Orthophosphoric acid | 1.60 | −8858 | −7957 |
| Fumaric acid | 2.30 | −10,862 | −4093 |
| Formic acid | 2.30 | −13,550 | −3473 |
| Citric acid | 2.20 | −5605 | −2349 |
| Ascorbic acid | 2.80 | −217 | −2249 |
| Malic acid | 2.20 | −7214 | −2550 |
| Lactic acid | 2.40 | −5079 | −1498 |
| Acetic acid | 2.90 | −2283 | −141 |
| Propionic acid | 3.00 | −1358 | −5 |
| Sorbic acid | 3.50 | −220 | 120 |

ABC-3 = acid-binding capacity to pH 3.0; ABC-4 = acid-binding capacity to pH 4.0; mEq = milliequivalent; NA = not available in the publication; SBM = soybean meal; DDGS = distillers dried grains with solubles; HPDDGs = high protein dried distillers' grains.

[1] Adapted from Batonon-Alavo et al. (2016), Hajati (2018), Lawlor et al. (2005), Mihok et al. (2022) and Stas et al. (2022).

[2] The ABC-4 and ABC-3 values of feedstuffs are calculated as the milliequivalent $H^+$ of 0.1 mol/L HCl or 0.1 mol/L NaOH required to reduce the pH of a 1-kg sample to pH 4 and pH 3 by measuring 0.5 g of the sample. The values of the column are averages.

upper part of the small intestine, which is the main target organ for DON damage (Waché et al., 2009). Weaned piglets consuming diets contaminated with low doses of DON for long periods may develop a variety of symptoms, including reduced feed intake and impaired intestinal function. High dose exposure to DON may result in more severe symptoms such as severe diarrhea, vomiting, gastroenteritis and gastrointestinal bleeding (Hooft and Bureau, 2021; Yao and Long, 2020). Deoxynivalenol binds to the eukaryotic 60S ribosomal subunit, blocking peptidyltransferase and inhibiting translation and at the same time inducing intestinal inflammation via MAPK through the ribotoxic stress response (Hooft and Bureau, 2021). Mitochondria are the primary organelles that control the distribution and concentration of $Ca^{2+}$ in the cell. Deoxynivalenol exposure increased intracellular ROS levels, induced mitochondrial damage and increased $Ca^{2+}$ flux, leading to oxidative stress and apoptosis in intestinal epithelial cells (Wang et al., 2021c; Zhou et al., 2017). In recent years, several studies have confirmed that the toxic effects of DON are closely linked to the damage of the intestinal structure, epithelial barrier and mucosal immunity in animals (Liu et al., 2020a; Wang et al., 2021b). These impairments can be a huge challenge for weaned piglets with immature immune systems. Studies have shown that feeding DON to weaned piglets reduced the number of intestinal goblet cells, and decreased the expression of zonula occludens-1 (ZO-1), claudin-1 and mucin-2, and inhibited the toll-like receptor 4 (TLR4)/nod-like receptor 3 (NLRP3) signaling pathway (Liu et al., 2022b). In addition, feeding DON-contaminated diets damages intestinal epithelial cells, and increased susceptibility to diarrhea-causing pathogens such as ETEC and diarrhea viruses (Ling et al., 2016; Liu et al., 2022c). Deoxynivalenol has been shown to exacerbate immunosuppression in weaned piglets under PEDV-infected conditions by inhibiting the TLR4/NLRP3 signaling pathway and promoting p38-mediated autophagy (Liu et al., 2020b, Liu et al., 2022c). In vivo and in vitro experiments shown that the combination of PEDV and DON reduced the expression of claudin-1 in the IPEC-J2 or intestine of weaned piglets, and enhanced the inflammatory response through the p38 and stimulator of interferon genes (STING) signaling pathways, and lead to an increase in the diarrhea incidence in piglets (Liu et al., 2020a; Zhang et al., 2020). A recent report showed that DON-supplemented diets resulted in increased expression of ferroptosis gene (divalent metal transporter 1 [DMT1]) and decreased expression of anti-ferroptosis genes such as ferroportin (FPN), ferroptosis suppressor protein 1 (FSP1) and CDGSH iron sulfur domain 1 (CISD1) in weaned piglets, and the induction of ferroptosis by DON was confirmed to be one of the causes of intestinal damage in piglets by using the RNAi technique and ferroptosis inhibitor treatment of IPEC-J2 (Liu et al., 2023). We summarized the cytotoxic effects of DON and the molecular mechanisms that cause diarrhea in piglets based on research in recent years (Fig. 2). These studies suggest that reducing mycotoxin contamination in feeds is an important part of controlling PWD.

## 4. Strategies for changing composition in diets to reduce diarrhea

### 4.1. Reducing CP levels in diets

Many studies have investigated the degree of reducing dietary CP required to effectively reduce PWD. Studies have shown that reducing dietary CP from 18.5% to 16.5% significantly reduces the diarrhea incidence in weaned piglets (Marchetti et al., 2023). Ammonia, amines, and hydrogen sulfide in the intestine linearly decreased when dietary CP levels were reduced (21%, 20%, 19%, 18%, 17%, and 16%), and diarrhea incidence was significantly reduced in weaned piglets (Kim et al., 2023). Under *E. coli* infection, weaned piglets fed diets containing 25.6% and 17.5% CP had diarrhea incidences of 44.6% and 31.5%, respectively, and in the absence of *E. coli* infection, the same piglets had diarrhea incidences of 19.6% and 8.3%, respectively (Heo et al., 2009). Feeding 19% CP levels (22% CP in the control group) reduced the diarrhea incidence in weaned piglets under different hygienic conditions (Lee et al., 2022). It is evident that reducing dietary CP levels is an effective strategy for controlling the incidence of diarrhea in weaned piglets, especially in environments with *E. coli* infection and poor sanitation. It is worth noting that the effect of dietary CP level on the growth performance of weaned piglets has been a matter of debate among researchers, and lowering it too much tends to limit the growth of piglets and reduce the economic efficiency of farming. The study showed that both average daily gain and gain/feed ratio were significantly reduced by diets with 19% and 16% CP levels (control 22% CP) (Limbach et al., 2021). However, it has also been shown that low-protein diets (as low as 16%) improve intestinal barrier function and reduce PWD in weaned piglets, but do not affect growth performance (Kim et al., 2023; Marchetti et al., 2023). One study showed that a strategy of using a low-protein diets of 17.3% CP for d 5, 7, 10, and 14 after weaning, followed by a switch to a 21.5% CP diets, resulted in a reduction in the piglet diarrhea incidence without affecting piglet growth performance (Heo et al., 2008). Similarly, feeding a low-protein diet (16.6% CP) at the 6 to 9 kg stage, followed by a switch to a standard CP level diet (19.1% CP) at 9 to 15 kg stage, also reduced the diarrhea incidence in piglets (Lynegaard et al., 2021). Adequate protein supply is critical because piglets have a high capacity for rapid growth and protein deposition, and protein intake is highly linearly correlated with ADG. Summarizing recent studies on dietary CP levels for weaned piglets, we can conclude that there exists a regression equation depicting the relationship between dietary CP levels and diarrhea incidence, represented as $Y = 3.532 \times X - 32.24$. Notably, for every 2% decrease in dietary CP levels, the diarrhea incidence is observed to decrease by 7.06% (Fig. 3). Therefore, a way to ensure dietary protein supply of weaned piglets, while avoiding excessive protein into the hindgut fermentation is a key issue in the technology of low-protein diets to reduce diarrhea. With the increasing research on technology of low-protein diets, studies have reported that a 3 to 4 percentage point reduction in CP levels accompanied by supplementation with crystalline lysine, threonine, tryptophan, methionine, and valine did not have a negative effect on animal performance and nitrogen deposition (Wang et al., 2018). It can be seen that reducing the CP level in piglet diets is an effective strategy to reduce PWD in piglets.

### 4.2. Reducing ABC in diets

Maintaining a well-structured diet that is low in ABC to support good intestinal barrier function and microbial homeostasis during the weaning period of piglets is essential to reduce piglet diarrhea incidence and improve growth performance. Therefore, the ABC of feedstuffs can be used as a nutritional constraint for dietary formulation, and reducing the ABC value of complete diets by selecting feedstuffs with lower ABC values and exogenously adding acids are good strategies for improving the intestinal barrier function and control diarrhea in weaned piglets (Huting et al., 2021). In general, cereals have low ABC values, ranging from 78 to 147 milliequivalent (mEq) $H^+$/kg for ABC-4 and 135 to 286 mEq $H^+$/kg for ABC-3, whereas protein feedstuffs have slightly higher ABC values, ranging from −13 to 1059 mEq $H^+$/kg for ABC-4 and 823 to 2100 mEq $H^+$/kg for ABC-3. Soybean meal (SBM) is known to be the most common source of protein in swine diets and is usually added at 15% to 30% in weaned piglets, but SBM has a high ABC-4 value (618 mEq $H^+$/kg) (Stein et al., 2008). Therefore, the use of

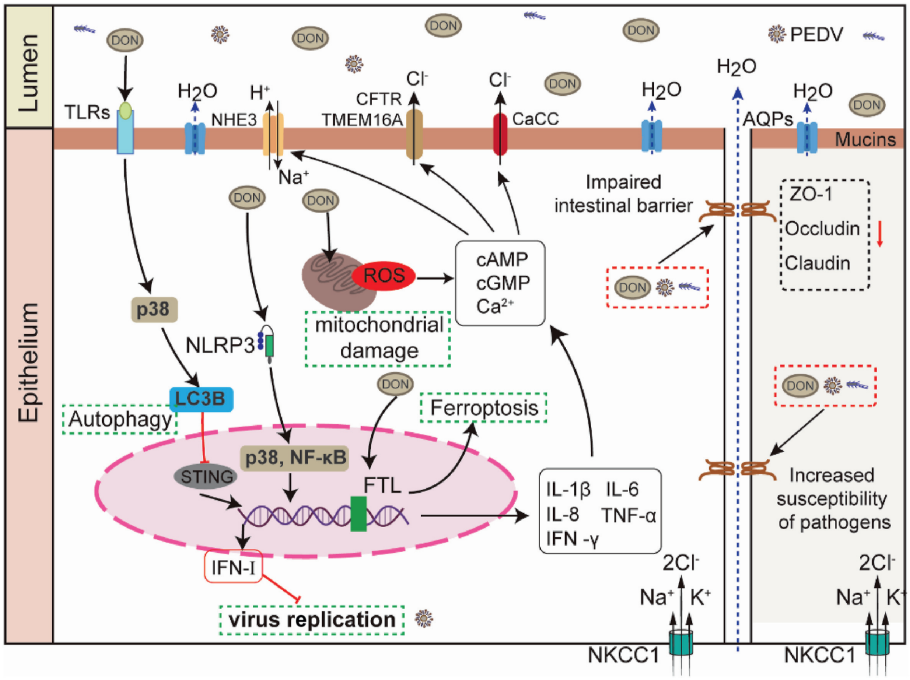


**Fig. 2.** Cytotoxic effects of deoxynivalenol (DON) and mechanisms of diarrhea induction. DON activates p38 signaling and triggers autophagy via LC3B and helps diarrhea virus evade natural immunity in the STING signaling pathway, leading to massive viral production. DON enhances the inflammatory response through the NLRP3 signaling pathway. DON induces production of ROS, leading to mitochondrial damage and activation of $Ca^{2+}$. DON induces ferroptosis through FTL. DON with diarrhea virus stimulates inflammatory cytokine production and induces $Cl^-$ secretion via cAMP, cGMP and $Ca^{2+}$ signaling. In addition, DON with pathogen infection decreased TJ protein expression and increased intestinal intercellular permeability. PEDV = porcine epidemic diarrhea virus; TLRs = toll-like receptors; NHE3 = $Na^+/H^+$ exchanger 3; CFTR = cystic fibrosis transmembrane conductance regulator; TMEM16A = transmembrane protein 16A; CaCC = calcium-activated chloride channels; AQPs = aquaporins; p38 = p38 mitogen-activated protein kinase; LC3B = light chain 3 β; STING = stimulator of interferon genes; NLRP3 = nod-like receptor 3; NF-κB = nuclear factor-κB; IFN-I = interferon-I; IL-1β = interleukin-1β; IL-6 = interleukin-6; IL-8 = interleukin-8; TNF-α = necrosis factor-α; IFN-γ = interferon-γ; NKCC1 = $Na^+$–$K^+$–$2Cl^-$ cotransporter 1; ZO-1 = zonula occludens-1; cAMP = cyclic adenosine 3′–5′-monophosphate; cGMP = cyclic guanosine 3′–5′-monophosphate; ROS = reactive oxygen species; FTL = ferritin light chain.

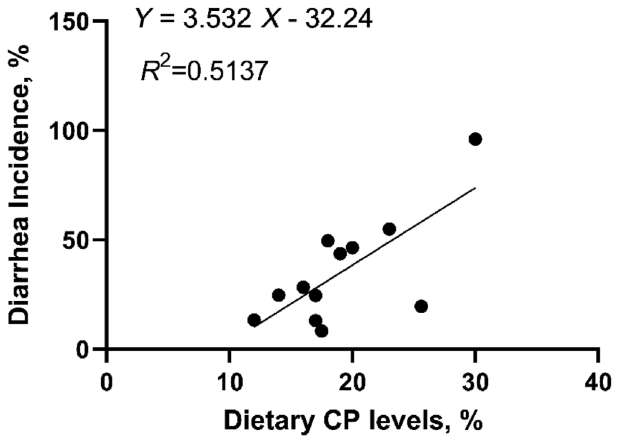


**Fig. 3.** Linear relationship between the dietary CP levels and diarrhea incidence for weaned piglets. The data of regression analyses were obtained from 4 published research papers evaluating the effect of diets with different levels of CP on diarrhea incidence in weaned piglets (Gao et al., 2020; Heo et al., 2009; Liu et al., 2022a; Wu et al., 2015). The initial weight of the piglets was 5.9 to 10 kg and the initial age was 21 or 28 d and Liu et al. (2022a) did not describe the initial age of piglets. CP = crude protein.

fermented SBM (ABC-4, 207 mEq $H^+$/kg) or fermented soy isolate (ABC-4, −13 mEq $H^+$/kg) to partially replace the amount of SBM used, as well as the application of low-protein forage techniques are good strategies to reduce the ABC of the diets. The mineral source was one of the key factors for the high ABC values of the feedstuffs, especially the ABC-4 of calcium carbonate, limestone flour, and zinc oxide were higher than 10,000 mEq $H^+$/kg. Calcium carbonate and limestone (as a Ca source) have an ABC-4 of 18,384 mEq $H^+$/kg and 12,932 mEq $H^+$/kg, respectively, and can therefore be partially replaced with monocalcium phosphate (ABC-4, 1587 mEq $H^+$/kg), dicalcium phosphate (ABC-4, 1348 mEq $H^+$/kg), or calcium propionate (ABC-4, 9240 mEq $H^+$/kg) as a Ca source. At the same time, the use of high doses of phytase reduces the amount of calcium carbonate and limestone flour used in the diets. For example, calcium and phosphorus levels should be reduced to 0.60% to 0.65% and 0.35% to 0.40%, respectively, in piglets during the first 2 weeks after weaning (He et al., 2022). High dosage of zinc oxide is widely used to reduce the diarrhea incidence of weaned piglets because of its strong bacteriostatic property. However, high dosage of zinc oxide leads to increase in ABC value of diets and bacterial resistance, and can also cause environmental pollution, so the use of zinc oxide in weaned piglets is also being gradually limited (Bonetti et al., 2021). Therefore, using low ABC feedstuffs to replace high ABC feedstuffs, as well as techniques such as low-protein diets and the addition of high doses of phytase can be some of the strategies to reduce dietary ABC.

Previous studies have reported that the addition of acidifiers can better reduce the ABC value of diets because organic acids have negative ABC values (ABC4 -13, 550 to −217 mEq $H^+$/kg) (Scholten et al., 2001). The main acidifiers used in weaned piglet diets are phosphoric acid, citric acid, sorbic acid, fumaric acid, malic acid, lactic acid, benzoic acid, and some fatty acids (formic acid, acetic acid, propionic acid, butyric acid, lauric acid, etc.). Acidifiers not only reduce the ABC in feedstuffs, but also penetrate pathogenic bacteria such as *E. coli*, *Salmonella*, and *Clostridium*, thus reducing pathogen infections in piglet (Grilli et al., 2015). Studies have

reported that the addition of 1% citric acid reduced gastric pH from 4.6 to 3.5 and the addition of 0.7% fumaric acid reduced gastric pH from 4.6 to 4.2 (Scipioni et al., 1979). It is important to note that excessive additions of acidifiers can reduce the palatability of diets and organic acids (formic, butyric, citric, and tartaric) have shown better palatability than inorganic acids (hydrochloric and phosphoric). Moreover, organic acids, as mostly biometabolic intermediates, can serve as a source of energy for the porcine intestine and improve the intestinal barrier function (Suiryanrayna and Ramana, 2015). Feeding 3000 mg/kg of complex organic acids (formic acid $\geq$23.9%, lactic acid $\geq$14.5% and citric acid $\geq$4.0%) has been shown to significantly reduce the diarrhea incidence and improve gut health and growth performance in weaned piglets (Li et al., 2023a). Organic acids have been shown to reduce PWD and improve the growth of weaned piglets by regulating redox homeostasis, intestinal barrier function and intestinal flora (Ma et al., 2021a,b; Xiang et al., 2021; Zeng et al., 2022).

### 4.3. Feed processing for reduced antigenic protein

Feedstuffs processing mainly includes physical methods (expansion, heating, mechanical processing), chemical methods (acid and alkali treatment, alcohol solution treatment, salt treatment), and biological methods (biofermentation, enzyme treatment, breeding). Most feedstuffs processing methods, including biofermentation, bulking, enzyme treatment, not only reduce or inactivate antigenic proteins and pathogens, but also physically alter the raw material through agglomeration or hydrolysis, thereby enhancing feed digestion and absorption (Cervantes-Pahm and Stein, 2010; Singh et al., 2007; Yuan et al., 2017). Consequently, the digestion and absorption of nutrients such as proteins and amino acids is improved, and the rate of hindgut fermentation and diarrhea of nutrients is reduced (Navarro et al., 2017). Fermented SBM is made by using SBM as the main ingredient and treating it with probiotics for fermentation pretreatment in order to reduce the presence of antinutritional factors such as soybean globulin, β-accompanied by soybean globulin, trypsin inhibitory factor, and soybean agglutinin. This process serves to improve the digestibility and absorption of small molecule peptides within SBM. Feed fermentation degrades proteins and carbohydrates into low molecular weight, water-soluble molecules, thus promoting of nutrient digestion and mitigating intestinal damage resulting from hindgut nutrient fermentation (Czech et al., 2021; Jiang et al., 2023; Yuan et al., 2017). In addition, the beneficial microorganisms in fermented feeds can inhibit the colonization of pathogenic bacteria such as *E. coli*, reducing the susceptibility to pathogens, especially in weaned piglets (Kiers et al., 2003; Pluske et al., 2002).

### 4.4. Biological approaches to detoxify DON

In the past, physical and chemical methods have been widely used to reduce mycotoxin levels in feeds. Physical detoxification includes sieving, stripping, grinding, washing, radiation treatment, thermal treatment and adsorption to feedstuff (Li et al., 2023b). Physical degradation has the problems of low degradation efficiency, high work intensity and expensive equipment. Chemical degradation methods typically use sodium selenite, sodium bisulphite and sodium metabisulfite, which primarily destroy the chemical structure of mycotoxins or to neutralize their active groups (He et al., 2022). Studies have shown that sodium metabisulfite at levels of 0.45% to 0.9% can destroy 70% to 100% of DON in processed grains or feeds in vitro at approximately pH 6.5, but not under acidic conditions (Dänicke et al., 2010a,b; Frobose et al., 2015). Chemical detoxification involves the use of oxidants, aldehydes, acids, bases, and several gases to detoxify DON-contaminated grains (Li et al., 2023c). Sulfite reducers, including sodium sulfite ($Na_2SO_3$), sodium bisulfite ($NaHSO_3$), and sodium metabisulfite (SMBS), have the ability to cleave disulfide cross-links (He et al., 2022). Several studies have shown that SMBS can destroy 70% to 100% of the DON in processed grains or feedstuffs in vitro (at concentrations ranging from 0.45% to 0.9%) at pH around 6.5 (Dänicke et al., 2009, 2010a,b; Frobose et al., 2015; Schwartz et al., 2013). Ozone degradation of DON (1 to 5 μg/mL) in solution has been shown to be as high as 93.6% to 98.3% (Li et al., 2015, 2019a,b; Ren et al., 2020). Studies have reported maize and wheat showed 63% to 90% ozone degradation rates (Kells et al., 2001; Young, 1986). However, traditional chemical methods for mycotoxin degradation often have limitations such as reduced nutritional value and palatability of feedstuffs, safety concerns, and expensive equipment (Ji et al., 2016).

In recent years, with the continuous development of biodegradation technology, biodegradation of mycotoxins has the advantages of environmental protection, safety and high efficiency, and has become an emerging and promising technology. The process of converting DON into low or non-toxic products using microorganisms and enzymes is the biological detoxification of DON. The main types of biological detoxification are isomerization, acetylation, glycosylation, oxidation, hydroxylation and hydrolysis (Guo et al., 2020). Bacteria, fungi and the enzymes that they produce are commonly used in these transformations, mainly soil bacteria, phytobacteria, animal rumen and intestinal microorganisms, and yeasts (Fig. 4). It has been shown that bacterial consortium LZ-N1 has stable and efficient DON conversion activity, and its two new strains (*Pseudomonas* sp. Y1 and *Lysobacter* sp. S1) can sustainably convert DON to 3-epi-DON and reduce DON toxicity (Zhai et al., 2019). *Agrobacterium*–*Rhizobium* strain E3-39 from soil oxidizes the 3-OH group of DON to form 3-keto-4-DON (3-keto-DON), resulting in a reduction of toxicity by over tenfold (Shima et al., 1997). Furthermore, soil-derived *Bacillus licheniformis* YB9, *Devosia insulae* A16, *desulfitobacterium* sp. PGC-3-9, and other bacteria had strong DON detoxification capacity, with degradation rates exceeding 82% during 24- to 48-h incubations (He et al., 2020; Wang et al., 2019a,b, 2020). The *Lactobacillus rhamnosus* can convert DON to 3-epi-DON in vitro and reduce the toxicity of DON in vivo (Qu et al., 2019). The BBSH 797 strain from the rumen can convert DON to deepoxy-deoxynivalenol (Fuchs et al., 2002). Strains of *Aspergillus oryzae* and *Rhizopus oryzae* were also found to adsorb and degrade DON. *A. oryzae* KKB4 and *R. oryzae* KP1R1 were inoculated into DON-contaminated corn and fermented for 10 days, resulting in DON reduction of 65.91% and 56.82%, respectively (Arifin et al., 2019). The study reported that the soil-derived fungus *Aspergillus tubingensis* NJA-1 had a significant ability to degrade DON, with a degradation rate of 94.4% (He et al., 2008). In addition, yeast can convert DON to DON-3-glucoside (Guo et al., 2020). In addition to the above microorganisms, proteins or enzymes produced by microorganisms can also convert DON or combine with DON to produce couplers that play an important role in detoxification. Certain enzymes produced by microorganisms can transform or bind mycotoxins. Some specific enzymes such as DePA, 3-acetyl DON oxidase, Fusarium trichothecene 3-O-acetyltransferases, 3-O-acetyltransferase, DdnA, DepB, UDP-glycosyltransferase are known to convert DON to low or non-toxic products (Fig. 4). UDP-glucosyltransferase was shown to glycosylate DON to DON-3-glucoside and reduced DON toxicity (He et al., 2018). In addition, several research have reported that peroxidase, b-xylanases and amylolytic enzymes can degrade DON (Feltrin et al., 2017; Gauterio et al., 2017). Because the enzymatic degradation is highly specific, efficient and environmentally friendly, studies are increasingly focusing on the identification, purification, and characterization of detoxification enzymes, as well as focusing on the

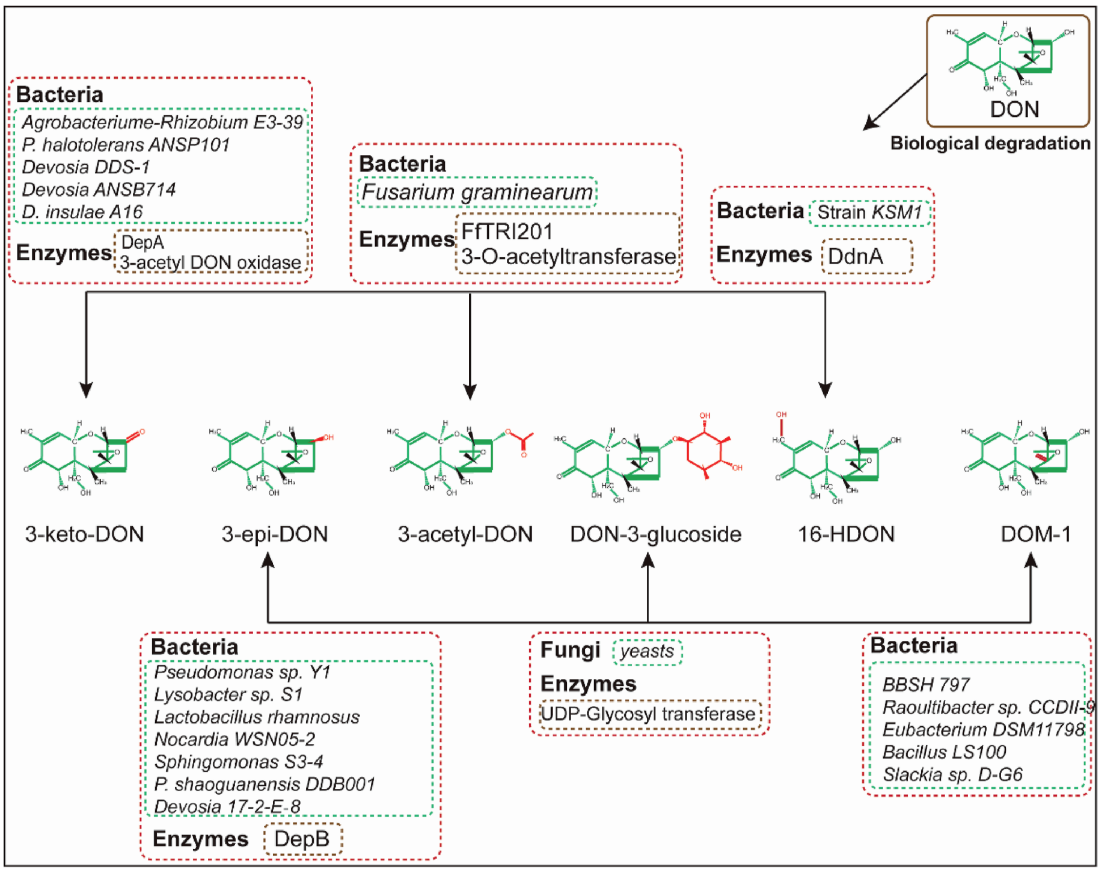


**Fig. 4.** Biological detoxification of deoxynivalenol (DON). Adapted from Hou et al. (2023), Li et al. (2023a) and Yao and Long (2020). The *Agrobacteriume–Rhizobium* strain E3-39, *D. insulae* A16, *Sphingomonas* S3-4, *Nocardia* WSN05-2, *P. shaoguanensis* DDB001, and *Devosia* sp. 17-2-E-8 were sourced from soil. The *Eubacterium* DSM11798 and BBSH 797 were sourced from the animal rumen. The *Raoultibacter* sp. DII-9, *Lactobacillus rhamnosus*, *Bacillus* LS100, and *Slackia* sp. D-G6 were sourced from the animal intestine. The strain KSM1 and *P. halotolerans* ANSP101 were sourced from water. The *Devosia* sp. DDS-1 were sourced from the plant. The yeasts, *Fusarium graminearum*, *Lactobacillus rhamnosus*, *Pseudomonas* sp. Y1, *Lysobacter* sp. S1, and *Devosia* sp. ANSB714 were sourced from others. DepA is a pyrroloquinoline quinone-dependent enzyme and DepB belongs to the aldehyde–ketone reductase family. Fusarium trichothecene 3-O-acetyltransferases (FfTRI201) are sourced yeast. 16-HDON = 16-hydroxy-DON; DOM-1 = deepoxy-deoxynivalenol; UDP = uridine diphosphate.

underlying catalytic mechanisms. In short, the use of biological approaches is a promising direction for treating and preventing harms caused by DON.

### 4.5. Dietary vitamin supplementation

In general, the vitamin content of the feed is low and does not meet the nutritional needs of the piglets, so additional vitamins must be used to supplement the diet. Deficiency in vitamins such as niacin (vitamin $B_3$), vitamin $B_6$, folic acid (vitamin $B_9$), vitamin A, and vitamin D damage the morphological structure of the small intestine and reduce the expression of functional genes involved in digestion and absorption (Chawla and Kvarnberg, 2014; Matsui et al., 2018). Niacin would improve intestinal morphology, tight junction protein expression and intestinal barrier function in weaned piglets (Feng et al., 2021; Liu et al., 2021; Yi et al., 2021). Dietary supplementation with 20.4 mg/kg niacin was able to increase the expression of intestinal ZO-1, AQP1 and AQP3, and decrease the diarrhea incidence of weaned piglets (Liu et al., 2022a). In an in vitro experiment, niacin attenuated the reduction of AQPs and ZO-1 expression caused by an infection of IPEC-J2 with ETEC K88 (Liu et al., 2022a). Niacin also attenuated the inflammatory response and diarrhea induced by PDCoV infection in weaned piglets by inhibiting the activation of the TLR2/TLR4-NF-κB signaling pathway in the intestine (Chen et al., 2022). Nicotinamide (amide compounds of niacin) activates the extracellular signaling-regulated kinase 1/2 (ERK1/2)/MAPK pathway to down-regulate transcription factor expression to inhibit PEDV and PDCoV replication (Li et al., 2023a). Dietary supplementation with 7 mg/kg vitamin $B_6$ significantly reduced diarrhea and improved intestinal morphology and immune status in weaned piglets fed a high-protein diets (Li et al., 2019a,b). Vitamin A (18,000 IU/kg) attenuates irinotecan-induced diarrhea in weaned piglets by modulating intestinal glial and immune cell infiltration and inflammatory response (Li et al., 2022). Studies have shown that folic acid supplementation at 9 mg/kg improved intestinal function and reduces the diarrhea incidence in weaned piglets, and supplementation to 18 mg/kg can down-regulate intestinal tumor necrosis factor-α (TNF-α) and reduce intestinal inflammation in weaned piglets (Wang et al., 2021a). Vitamins have important immunomodulatory functions, and adequate vitamin supplementation is an important way to alleviate diarrhea in piglets.

### 4.6. Novel treatment

Traditionally, antinutritional factors have been considered detrimental to pig production, but in recent years, some of them have been found to have good intestinal astringent properties and are particularly effective in alleviating diarrhea in piglet. Tannic acid has excellent intestinal astringent, antioxidant, anti-

inflammatory and antimicrobial properties, and improves intestinal function and diarrhea incidence in weaned piglets without negatively affecting growth performance (Caprarulo et al., 2020; Song et al., 2021b; Yu et al., 2020). It has been shown that dietary supplementation with 0.2% and 0.4% tannic acid reduced the number of *E. coli* in the colon of weaned piglets, increased the expression of intestinal ZO-1, ZO-2 and claudin-2, and reduced the diarrhea incidence (Song et al., 2021a). Dietary supplementation with 0.15% encapsulated tannic acid significantly increased the expression levels of ZO-1, claudin-1 and reduced PWD in piglets (Xu et al., 2022). Additionally, dietary tannic acid-chelated zinc could alleviate PEDV-induced damage and mitigated diarrhea of weaned piglets (Zhang et al., 2022). Mechanistically, tannic acid is an inhibitor of CFTR and CaCC, counteracting the control of CFTR and voltage-gated $K^+$ channels by pathogenic bacteria and inhibiting $Ca^{2+}$ activation, thereby reducing diarrhea caused by $Cl^-$ hypersecretion (Namkung et al., 2010a,b; Ramu et al., 2014; Thiagarajah et al., 2015). Dietary supplementation with tannic acid decreased intestinal CFTR and NHE3 expression and increased ZO-1 and occludin expression levels and reduced diarrhea incidence in weaned piglets challenged with ETEC K88 environment (Yi et al., 2023). In addition, by lectin conjugation, lectin increased the inhibitory potency of CFTR by up to 100-fold, blocking cholera toxin-induced intestinal fluid secretion (Sonawane et al., 2007). Plumbagin also inhibited the activity of intestinal epithelial CaCC and CFTR in colon of mouse, but had no effect on the activity of $Na^+$-$K^+$ ATPase or $K^+$ channels (Yu et al., 2019).

Insoluble fiber (e.g., wheat bran, oat hulls, barley hulls, and lignocellulose) reduced the residence time of digesta in the gastrointestinal tract, which reduced the proliferation of pathogens in the small intestine, thus contributing in particular to a lower risk of PWD disease (Molist et al., 2014; Tanghe et al., 2023). Accumulated evidence suggests that increasing dietary fiber levels and feeding different sources of fiber to early weaned piglets reduce the diarrhea incidence and improve growth performance (Adams et al., 2019; Liang et al., 2023a,b; Uddin et al., 2023). However, dietary fibers with low hydration properties exacerbate diarrhea and impair intestinal health and nutrient digestibility in weaned piglets (Huang et al., 2022). Therefore, intervening in the hydration properties of feedstuffs using specific dietary fiber can ameliorate diarrhea in weaned piglets and enhance intestinal health. Moderate levels of insoluble fiber sources are more beneficial in promoting intestinal health during the first two weeks after weaning of piglets, and the use of soluble fiber in early-weaned piglets in poor health is detrimental in mitigating PWD (Canibe et al., 2022). Thus, it can be seen that dietary fiber is one of the effective strategies for controlling diarrhea in early weaned piglets. Despite numerous studies supporting this conclusion, there is still a need to develop systematic feeding management strategies in the future.

In addition, non-starch polysaccharides are not detrimental to pig health, and increasing non-starch polysaccharides concentrations in diets that do not increase digestive viscosity may be beneficial in preventing post-weaning *E. coli* infections (Wellock et al., 2008). Recently it has been reported that decreased expression of microRNAs (miRNA) including ssc-miRNA-425-5p and ssc-miRNA-423-3p leads to an over-enrichment of microbial-produced succinic acid in the gut, increased fluid secretion from intestinal epithelial cells due to elevated $Cl^-$ secretion, and increased intestinal inflammatory response due to activation of the myeloid differentiation primary response 88 (MyD88)-dependent TLR4 signaling pathway, resulting in diarrhea (Zhou et al., 2022). MiR-let-7e and miR-27b derived from milk small extracellular vesicles inhibited PEDV infection (Liang et al., 2023a,b). However, miRNA-30d and miR-204 exacerbated *Clostridium perfringens* β2 toxin-induced inflammatory injury in IPEC-J2 cells by targeting proteasome activator subunit 3 or bcl-2 like protein 2 (Wang et al., 2021a; Xie et al., 2022). Thus, natural product and miRNA modulation strategies provide a new perspective on the prevention and treatment of piglet diarrhea at the molecular level.

## 5. Conclusion and perspective

A dynamic imbalance in the absorption and secretion of intestinal fluids is the underlying cause of diarrhea in piglets. The processes of intestinal luminal fluid absorption and secretion are driven by the active transport of electrolytes ($Na^+$, $Cl^-$, $HCO_3^-$, and $K^+$) and solutes (glucose, amino acids, fatty acids, etc.) and are closely linked to AQPs and intestinal permeability. Bacterial and viral infections usually cause imbalances in electrolyte absorption and secretion in the intestinal lumen of piglets, and the nutrient level and composition of feeds influence the pathogenicity of bacteria and viruses. Based on the literature report, excessive levels of CP in the diets, stimulation by antigenic proteins, and DON contamination are important factors contributing to the imbalance of intestinal fluid absorption and secretion. Although various dietary strategies (e.g. CP reduction, ABC reduction, processing, vitamin supplementation, vomitoxin detoxification) have been widely recognized as promising strategies to reduce PWD in piglets, an integrated approach should be taken to control PWD, including nutritional and management-related measures. Finally, it is necessary to consider the impact on the growth performance of weaned piglets and economic benefits of these strategies. For example, excessive reduction in CP levels can lead to piglet growth restriction, and excessive reduction in ABC can reduce the palatability of the feeds and increase costs related to feed processing.

## Author contributions

**Qingsong Tang:** Investigation, Original draft preparation. **Tianyi Lan**, **Chengyu Zhou**, **Jingchun Gao**, **Haiyang Wei**, **Liuting Wu**, **Wenxue Li**, **Wenjie Tang**, **Hui Diao:** Investigation, Revising and reviewing. **Yetong Xu**, **Xie Peng**, **Jiaman Pang**, **Xuan Zhao**, **Zhiru Tang:** Reviewing and editing. **Zhihong Sun:** Conceptualization and proofreading.

## Declaration of competing interest

We declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence our work, and there is no professional or other personal interest of any nature or kind in any product, service and/or company that could be construed as influencing the content of this paper.

## Acknowledgments

This study was funded by grants from the National Natural Science Foundation of China (32272889), the National Center of Technology Innovation for Pigs (NCTIP XD/B04), the Sichuan Science and Technology Program (2023ZHYZ0007), and the Southwest University Graduate Student Research and Innovation Program (SWUB23063).

## References

Abbott GW. Regulation of human cardiac potassium channels by full-length KCNE3 and KCNE4. Sci Rep 2016;6:38412.

Adams S, Xiangjie K, Hailong J, Guixin Q, Sossah FL, Dongsheng C. Prebiotic effects of alfalfa (*Medicago sativa*) fiber on cecal bacterial composition, short-chain fatty acids, and diarrhea incidence in weaning piglets. RSC Adv 2019;9(24): 13586–99.

Andriamihaja M, Davila A, Eklou-Lawson M, Petit N, Delpal S, Allek F, et al. Colon luminal content and epithelial cell morphology are markedly modified in rats fed with a high-protein diet. Am J Physiol Gastrointest Liver Physiol 2010;299(5):G1030–7.
Argenzio RA. Physiology of diarrhea – large intestine. J Am Vet Med Assoc 1978;173:667–72.
Arifin AA, Setyabudi FMCS, Sardjono. Local strains *Aspergillus oryzae* KKB4 and *Rhizopus oryzae* KP1R1 as a reducing and detoxifying agents for deoxynivalenol. Malays J Microbiol 2019;15(3):182–7.
Batonon-Alavo DI, Bouza B, Cholet JCG, Mercier Y. A method for determination of the acidifying value of organic acids used in pigs diets in the acid binding capacity at pH 4 (ABC-4) system. Anim Feed Sci Technol 2016;216:197–203.
Bhandari SK, Opapeju FO, Krause DO, Nyachoti CM. Dietary protein level and probiotic supplementation effects on piglet response to *Escherichia coli* K88 challenge: performance and gut microbial population. Livest Sci 2010;133(1–3):185–8.
Bonetti A, Tugnoli B, Piva A, Grilli E. Towards zero zinc oxide: feeding strategies to manage post-weaning diarrhea in piglets. Animals 2021;11(3):642.
Callebaut I, Chong PA, Forman-Kay JD. CFTR structure. J Cyst Fibros 2018;17(2S):S5–8.
Canessa CM, Horisberger JD, Rossier BC. Epithelial sodium channel related to proteins involved in neurodegeneration. Nature 1993;361(6411):467–70.
Canibe N, Højberg O, Kongsted H, Vodolazska D, Lauridsen C, Nielsen TS, et al. Review on preventive measures to reduce post-weaning diarrhoea in piglets. Animals 2022;12(19):2585.
Cao S, Hou L, Sun L, Gao J, Gao K, Yang X, et al. Intestinal morphology and immune profiles are altered in piglets by early-weaning. Int Immunopharmacol 2022;105:108520.
Caprarulo V, Hejna M, Giromini C, Liu Y, Dell'Anno M, Sotira S, et al. Evaluation of dietary administration of chestnut and quebracho tannins on growth, serum metabolites and fecal parameters of weaned piglets. Animals 2020;10(11):1945.
Cervantes-Pahm SK, Stein HH. Ileal digestibility of amino acids in conventional, fermented, and enzyme-treated soybean meal and in soy protein isolate, fish meal, and casein fed to weanling pigs. J Anim Sci 2010;88(8):2674–83.
Chawla J, Kvarnberg D. Hydrosoluble vitamins. Handb Clin Neurol 2014;120:891–914.
Chen J, Wang J, Song P, Ma X. Determination of glycinin in soybean and soybean products using a sandwich enzyme-linked immunosorbent assay. Food Chem 2014;162:27–33.
Chen Y, Li P, Zhen R, Wang L, Feng J, Xie Y, et al. Effects of niacin on intestinal epithelial barrier, intestinal immunity, and microbial community in weaned piglets challenged by PDCoV. Int Immunopharmacol 2022;111:109054.
China National Standard. Hygienical standard for feeds. GB 13078-2017. Beijing: Standards Press of China; 2017.
Cooke HJ, Shonnard K, Wood JD. Effects of neuronal stimulation on mucosal transport in Guinea pig ileum. Am J Physiol 1983;245(2):G290–6.
Cummings JH. Colonic absorption: the importance of short chain fatty acids in man. Scand J Gastroenterol Suppl 1984;93:89–99.
Czech A, Grela ER, Kiesz M. Dietary fermented rapeseed or/and soybean meal additives on performance and intestinal health of piglets. Sci Rep 2021;11(1):16952.
Dänicke S, Hegewald A, Kahlert S, Kluess J, Rothkötter H, Breves G, et al. Studies on the toxicity of deoxynivalenol (DON), sodium metabisulfite, DON-sulfonate (DONS) and de-epoxy-DON for porcine peripheral blood mononuclear cells and the intestinal porcine epithelial cell lines IPEC-1 and IPEC-J2, and on effects of DON and DONS on piglets. Food Chem Toxicol 2010a;48(8–9):2154–62.
Dänicke S, Pahlow G, Beyer M, Goyarts T, Breves G, Valenta H, et al. Investigations on the kinetics of the concentration of deoxynivalenol (DON) and on spoilage by moulds and yeasts of wheat grain preserved with sodium metabisulfite ($Na_2S_2O_5$, SBS) and propionic acid at various moisture contents. Arch Anim Nutr 2010b;64(3):190–203.
Dänicke S, Pahlow G, Goyarts T, Rohweder D, Wilkerling K, Breves G, et al. Effects of increasing concentrations of sodium metabisulphite ($Na_2S_2O_5$, SBS) on deoxynivalenol (DON) concentration and microbial spoilage of triticale kernels preserved without and with propionic acid at various moisture contents. Mycotoxin Res 2009;25(4):215–23.
De Haan L, Hirst TR. Cholera toxin: a paradigm for multi-functional engagement of cellular mechanisms (review). Mycotoxin Res 2004;21(2):77–92.
Dreyfus LA, Harville B, Howard DE, Shaban R, Beatty DM, Morris SJ. Calcium influx mediated by the Escherichia coli heat-stable enterotoxin B (STB). Proc Natl Acad Sci U S A 1993;90(8):3202–6.
Fairbrother JM, Nadeau E, Gyles CL. *Escherichia coli* in postweaning diarrhea in pigs: an update on bacterial types, pathogenesis, and prevention strategies. Anim Health Res Rev 2005;6(1):17–39.
Feltrin ACP, Garcia SDO, Caldas SS, Primel EG, Badiale-Furlong E, Garda-Buffon J. Characterization and application of the enzyme peroxidase to the degradation of the mycotoxin DON. J Environ Sci Health B 2017;52(10):777–83.
Feng J, Wang L, Chen Y, Xiong Y, Wu Q, Jiang Z, et al. Effects of niacin on intestinal immunity, microbial community and intestinal barrier in weaned piglets during starvation. Int Immunopharmacol 2021;95:107584.
Foulke-Abel J, In J, Yin J, Zachos NC, Kovbasnjuk O, Estes MK, et al. Human enteroids as a model of upper small intestinal ion transport physiology and pathophysiology. Gastroenterology 2016;150(3):638–49.
Frobose HL, Fruge ED, Tokach MD, Hansen EL, Derouchey JM, Dritz SS, et al. The influence of pelleting and supplementing sodium metabisulfite ($Na_2S_2O_5$) on nursery pigs fed diets contaminated with deoxynivalenol. Anim Feed Sci Technol 2015;210:152–64.
Frydendahl K. Prevalence of serogroups and virulence genes in *Escherichia coli* associated with postweaning diarrhoea and edema disease in pigs and a comparison of diagnostic approaches. Vet Microbiol 2002;85(2):169–82.
Fuchs E, Binder EM, Heidler D, Krska R. Structural characterization of metabolites after the microbial degradation of type A trichothecenes by the bacterial strain BBSH 797. Food Addit Contam 2002;19(4):379–86.
Gao J, Yin J, Xu K, Han H, Liu Z, Wang C, et al. Protein level and infantile diarrhea in a postweaning piglet model. Mediat Inflamm 2020;2020:1937387.
Gauterio Victoria G, Reginatto Lais, Feltrin P, Carla A, et al. Use of partially purified peroxidase of agricultural by-product rice bran in deoxynivalenol reduction. J Chem Technol Biotechnol 2017;92(8):1998–2008.
Geibel J, Sritharan K, Geibel R, Geibel P, Persing JS, Seeger A, et al. Calcium-sensing receptor abrogates secretagogue-induced increases in intestinal net fluid secretion by enhancing cyclic nucleotide destruction. Proc Natl Acad Sci U S A 2006;103(25):9390–7.
Grilli E, Bari R, Piva A, Edrington TS, Pitta DW, Pinchak WE, et al. Organic acid blend with pure botanical product treatment reduces *Escherichia coli* and Salmonella populations in pure culture and in in vitro mixed ruminal microorganism fermentations. Foodborne Pathog Dis 2015;12(1):56–61.
Guo H, Ji J, Wang J, Sun X. Deoxynivalenol: masked forms, fate during food processing, and potential biological remedies. Compr Rev Food Sci Food Saf 2020;19(2):895–926.
Hajati H. Application of organic acids in poultry nutrition. Int J Avian Wildlife Biol 2018;3(4):324–9.
He C, Fan Y, Liu G, Zhang H. Isolation and identification of a strain of aspergillus tubingensis with deoxynivalenol biotransformation capability. Int J Mol Sci 2008;9(12):2366.
He L, Zhao X, Li J, Yang C. Post-weaning diarrhea and use of feedstuffs in pigs. Anim Front 2022;12(6):41–52.
He W, Shi M, Yang P, Huang T, Yuan Q, Yi S, et al. Novel soil bacterium strain desulfitobacterium sp. PGC-3-9 detoxifies trichothecene mycotoxins in wheat via de-epoxidation under aerobic and anaerobic conditions. Toxins 2020;12(6):363.
He Y, Ahmad D, Zhang X, Zhang Y, Wu L, Jiang P, et al. Genome-wide analysis of family-1 UDP glycosyltransferases (UGT) and identification of UGT genes for FHB resistance in wheat (*Triticum aestivum* L.). BMC Plant Biol 2018;18(1):67.
Heo J, Kim J, Hansen CF, Mullan BP, Hampson DJ, Pluske JR. Effects of feeding low protein diets to piglets on plasma urea nitrogen, faecal ammonia nitrogen, the incidence of diarrhoea and performance after weaning. Arch Anim Nutr 2008;62(5):343–58.
Heo JM, Kim JC, Hansen CF, Mullan BP, Hampson DJ, Pluske JR. Feeding a diet with decreased protein content reduces indices of protein fermentation and the incidence of postweaning diarrhea in weaned pigs challenged with an enterotoxigenic strain of *Escherichia coli*. J Anim Sci 2009;87(9):2833–43.
Heo JM, Opapeju FO, Pluske JR, Kim JC, Hampson DJ, Nyachoti CM. Gastrointestinal health and function in weaned pigs: a review of feeding strategies to control post-weaning diarrhoea without using in-feed antimicrobial compounds. J Anim Physiol Anim Nutr 2013;97(2):207–37.
Hooft JM, Bureau DP. Deoxynivalenol: mechanisms of action and its effects on various terrestrial and aquatic species. Food Chem Toxicol 2021;157:112616.
Hoque KM, Woodward OM, van Rossum DB, Zachos NC, Chen L, Leung GPH, et al. Epac1 mediates protein kinase A-independent mechanism of forskolin-activated intestinal chloride secretion. J Gen Physiol 2010;135(1):43–58.
Hou S, Ma J, Cheng Y, Wang H, Sun J, Yan Y. The toxicity mechanisms of DON to humans and animals and potential biological treatment strategies. Crit Rev Food Sci Nutr 2023;63(6):790–812.
Hu CA, Hou Y, Yi D, Qiu Y, Wu G, Kong X, et al. Autophagy and tight junction proteins in the intestine and intestinal diseases. Anim Nutr 2015;1(3):123–7.
Huang S, Cui Z, Hao X, Cheng C, Chen J, Wu D, et al. Dietary fibers with low hydration properties exacerbate diarrhea and impair intestinal health and nutrient digestibility in weaned piglets. J Anim Sci Biotechnol 2022;13(1).
Huting AMS, Middelkoop A, Guan X, Molist F. Using nutritional strategies to shape the gastro-intestinal tracts of suckling and weaned piglets. Animals 2021;11(2):402.
Ikarashi N, Kon R, Sugiyama K. Aquaporins in the colon as a new therapeutic target in diarrhea and constipation. Int J Mol Sci 2016;17(7):1172.
Jensen J, Larsen MM, Bak J. National monitoring study in Denmark finds increased and critical levels of copper and zinc in arable soils fertilized with pig slurry. Environ Pollut 2016;214:334–40.
Ji C, Fan Y, Zhao L. Review on biological degradation of mycotoxins. Anim Nutr 2016;2(3):127–33.
Jiang D, Yang M, Xu J, Deng L, Hu C, Zhang L, et al. Three-stage fermentation of the feed and the application on weaned piglets. Front Vet Sci 2023;10:1123563.
Julio-Kalajzić F, Villanueva S, Burgos J, Ojeda M, Cid LP, Jentsch TJ, et al. $K_{2P}$ TASK-2 and KCNQ1-KCNE3 $K^+$ channels are major players contributing to intestinal anion and fluid secretion. J Physiol 2018;596(3):393–407.
Keely SJ, Barrett KE. Intestinal secretory mechanisms and diarrhea. Am J Physiol Gastrointest Liver Physiol 2022;322(4):G405–20.
Kells SA, Mason LJ, Maier DE, Woloshuk CP. Efficacy and fumigation characteristics of ozone in stored maize. J Stored Prod Res 2001;37(4):371–82.
Kiers JL, Meijer JC, Nout MJR, Rombouts FM, Nabuurs MJA, van der Meulen J. Effect of fermented soya beans on diarrhoea and feed efficiency in weaned piglets. J Appl Microbiol 2003;95(3):545–52.

Kim H, Shin H, Kim YY. Effects of different levels of dietary crude protein on growth performance, blood profiles, diarrhea incidence, nutrient digestibility, and odor emission in weaning pigs. Anim Biosci 2023;36(8):1228–40.
Krishnan HB, Kim W, Jang S, Kerley MS. All three subunits of soybean beta-conglycinin are potential food allergens. J Agric Food Chem 2009;57(3):938–43.
Krishnan S, Ramakrishna BS, Binder HJ. Stimulation of sodium chloride absorption from secreting rat colon by short-chain fatty acids. Dig Dis Sci 1999;44(9):1924–30.
Krug SM, Schulzke JD, Fromm M. Tight junction, selective permeability, and related diseases. Semin Cell Dev Biol 2014;36:166–76.
Lawlor PG, Lynch PB, Caffrey PJ, O'Reilly JJ, O'Connell MK. Measurements of the acid-binding capacity of ingredients used in pig diets. Ir Vet J 2005;58(8):447–52.
Lawlor PG, Lynchi PB, Caffrey PJ. Measurements of the acid binding capacity of ingredients used in diets for starter pigs. Proc Br Soc Anim Prod 1994;1994:161.
Lee J, González-Vega JC, Htoo JK, Yang C, Nyachoti CM. Effects of dietary protein content and crystalline amino acid supplementation patterns on growth performance, intestinal histomorphology, and immune response in weaned pigs raised under different sanitary conditions. J Anim Sci 2022;100(10):skac285.
Li M, Guan E, Bian K. Detoxification of deoxynivalenol by (60)Co γ-ray irradiation and toxicity analyses of radiolysis products. J AOAC Int 2019a;102(6):1749–55.
Li M, Guan E, Bian K. Structure elucidation and toxicity analysis of the degradation products of deoxynivalenol by gaseous ozone. Toxins 2019b;11(8):474.
Li M, Huang Y, Jin H, Yuan D, Huang K, Wang J, et al. Vitamin A ameliorated irinotecan-induced diarrhea in a piglet model involving enteric glia modulation and immune cells infiltration. Nutrients 2022;14(23):5120.
Li MM, Guan EQ, Bian K. Effect of ozone treatment on deoxynivalenol and quality evaluation of ozonised wheat. Food Addit Contam A Chem Anal Control Expo Risk Assess 2015;32(4):544–53.
Li M, Zhang L, Pan L, Zhou P, Yu R, Zhang Z, et al. Nicotinamide efficiently suppresses porcine epidemic diarrhea virus and porcine deltacoronavirus replication. Viruses 2023;15(7):1591.
Li X, Zhao L, Fan Y, Jia Y, Sun L, Ma S, et al. Occurrence of mycotoxins in feed ingredients and complete feeds obtained from the Beijing region of China. J Anim Sci Biotechnol 2014;5(1):37.
Li Y, Gao H, Wang R, Xu Q. Deoxynivalenol in food and feed: recent advances in decontamination strategies. Front Microbiol 2023;14:1141378.
Li Z, Li B, Zhang L, Chen L, Sun G, Zhang Q, et al. The proliferation impairment induced by AQP3 deficiency is the result of glycerol uptake and metabolism inhibition in gastric cancer cells. Tumour Biol 2016;37(7):9169–79.
Li Z, Liu S, Zhao Y, Wang J, Ma X. Compound organic acid could improve the growth performance, immunity and antioxidant properties, and intestinal health by altering the microbiota profile of weaned piglets. J Anim Sci 2023;101:skad196.
Li Z, Ma Z, Li Y, Gao S, Xiao S. Porcine epidemic diarrhea virus: molecular mechanisms of attenuation and vaccines. Microb Pathog 2020;149:104553.
Liang C, Fu R, Chen D, Tian G, He J, Zheng P, et al. Effects of mixed fibres and essential oils blend on growth performance and intestinal barrier function of piglets challenged with enterotoxigenic *Escherichia coli* K88. J Anim Physiol Anim Nutr 2023a;107(6):1356–67.
Liang JQ, Xie M, Hou L, Wang H, Luo J, Sun J, et al. miRNAs derived from milk small extracellular vesicles inhibit porcine epidemic diarrhea virus infection. Antiviral Res 2023b;212:105579.
Limbach JR, Espinosa CD, Perez-Calvo E, Stein HH. Effect of dietary crude protein level on growth performance, blood characteristics, and indicators of intestinal health in weanling pigs. J Anim Sci 2021;99(6):skab166.
Lin R, Murtazina R, Cha B, Chakraborty M, Sarker R, Chen T, et al. D-glucose acts via sodium/glucose cotransporter 1 to increase NHE3 in mouse jejunal brush border by a $Na^+/H^+$ exchange regulatory factor 2-dependent process. Gastroenterology 2011;140(2):560–71.
Ling K, Wan MLY, El-Nezami H, Wang M. Protective capacity of resveratrol, a natural polyphenolic compound, against deoxynivalenol-induced intestinal barrier dysfunction and bacterial translocation. Chem Res Toxicol 2016;29(5):823–33.
Liu D, Ge L, Wang Q, Su J, Chen X, Wang C, et al. Low-level contamination of deoxynivalenol: a threat from environmental toxins to porcine epidemic diarrhea virus infection. Environ Int 2020;143:105949.
Liu D, Wang Q, He W, Ge L, Huang K. Deoxynivalenol aggravates the immunosuppression in piglets and PAMs under the condition of PEDV infection through inhibiting TLR4/NLRP3 signaling pathway. Ecotoxicol Environ Saf 2022;231:113209.
Liu M, Zhang L, Chu X, Ma R, Wang Y, Liu Q, et al. Effects of deoxynivalenol on the porcine growth performance and intestinal microbiota and potential remediation by a modified HSCAS binder. Food Chem Toxicol 2020;141:111373.
Liu M, Zhang L, Mo Y, Li J, Yang J, Wang J, et al. Ferroptosis is involved in deoxynivalenol-induced intestinal damage in pigs. J Anim Sci Biotechnol 2023;14(1):29.
Liu S, Qiu Y, Gu F, Xu X, Wu S, Jin Z, et al. Niacin improves intestinal health through up-regulation of AQPs expression induced by GPR109A. Int J Mol Sci 2022;23(15):8332.
Liu S, Zhu X, Qiu Y, Wang L, Shang X, Gao K, et al. Effect of niacin on growth performance, intestinal morphology, mucosal immunity and microbiota composition in weaned piglets. Animals 2021;11(8):2186.
Liu Y, Azad MAK, Zhao X, Zhu Q, Kong X. Dietary crude protein levels alter diarrhea incidence, immunity, and intestinal barrier function of Huanjiang Mini-pigs during different growth stages. Front Immunol 2022;13:908753.
Lodemann U, Amasheh S, Radloff J, Kern M, Bethe A, Wieler LH, et al. Effects of Ex vivo infection with ETEC on jejunal barrier properties and cytokine expression in probiotic-supplemented pigs. Dig Dis Sci 2017;62(4):922–33.
Luise D, Lauridsen C, Bosi P, Trevisi P. Methodology and application of *Escherichia coli* F4 and F18 encoding infection models in post-weaning pigs. J Anim Sci Biotechnol 2019;10:53.
Lynegaard JC, Kjeldsen NJ, Bache JK, Weber NR, Hansen CF, Nielsen JP, et al. Low protein diets without medicinal zinc oxide for weaned pigs reduced diarrhea treatments and average daily gain. Animal 2021;15(1):100075.
Ma J, Piao X, Shang Q, Long S, Liu S, Mahfuz S. Mixed organic acids as an alternative to antibiotics improve serum biochemical parameters and intestinal health of weaned piglets. Anim Nutr 2021a;7(3):737–49.
Ma X, Zhang Y, Xu T, Qian M, Yang Z, Zhan X, et al. Early-life intervention using exogenous fecal microbiota alleviates gut injury and reduce inflammation caused by weaning stress in piglets. Front Microbiol 2021b;12:671683.
Marchetti R, Faeti V, Gallo M, Pindo M, Bochicchio D, Buttazzoni L, et al. Protein content in the diet influences growth and diarrhea in weaning piglets. Animals 2023;13(5):795.
Matos JE, Sausbier M, Beranek G, Sausbier U, Ruth P, Leipziger J. Role of cholinergic-activated $K_{Ca}1.1$ (BK), $K_{Ca}3.1$ (SK4) and $K_V7.1$ (KCNQ1) channels in mouse colonic $Cl^-$ secretion. Acta Physiol 2007;189(3):251–8.
Matsui T, Yamashita H, Saneyasu K, Tanaka H, Ito K, Inagaki N. Vitamin D deficiency exacerbates sensitization and allergic diarrhea in a murine food allergy model. Allergol Int 2018;67(2):289–91.
Matsuzaki T, Tajika Y, Ablimit A, Aoki T, Hagiwara H, Takata K. Aquaporins in the digestive system. Med Electron Microsc 2004;37(2):71–80.
Mihok T, Hreško Šamudovská A, Bujňák L, Timkovičová Lacková P. Determination of buffering capacity of the selected feeds used in swine nutrition. J Cent Eur Agric 2022;23(4):732–8.
Mishra S, Srivastava S, Dewangan J, Divakar A, Kumar RS. Global occurrence of deoxynivalenol in food commodities and exposure risk assessment in humans in the last decade: a survey. Crit Rev Food Sci Nutr 2020;60(8):1346–74.
Molist F, van Oostrum M, Pérez JF, Mateos GG, Nyachoti CM, van der Aar PJ. Relevance of functional properties of dietary fibre in diets for weanling pigs. Anim Feed Sci Technol 2014;189:1–10.
Muanprasat C, Chatsudthipong V. Cholera: pathophysiology and emerging therapeutic targets. Future Med Chem 2013;5(7):781–98.
Nagaraju GP, Basha R, Rajitha B, Alese OB, Alam A, Pattnaik S, et al. Aquaporins: their role in gastrointestinal malignancies. Cancer Lett 2016;373(1):12–8.
Nagy B, Fekete PZ. Enterotoxigenic *Escherichia coli* in veterinary medicine. Int J Med Microbiol 2005;295(6–7):443–54.
Namkung W, Finkbeiner WE, Verkman AS. CFTR-adenylyl cyclase I association responsible for UTP activation of CFTR in well-differentiated primary human bronchial cell cultures. Mol Biol Cell 2010a;21(15):2639–48.
Namkung W, Thiagarajah JR, Phuan P, Verkman AS. Inhibition of $Ca^{2+}$-activated $Cl^-$ channels by gallotannins as a possible molecular basis for health benefits of red wine and green tea. FASEB J 2010b;24(11):4178–86.
Navarro D, Liu Y, Bruun TS, Stein HH. Amino acid digestibility by weanling pigs of processed ingredients originating from soybeans, 00-rapeseeds, or a fermented mixture of plant ingredients. J Anim Sci 2017;95(6):2658–69.
Ngendahayo Mukiza C, Dubreuil JD. *Escherichia coli* heat-stable toxin b impairs intestinal epithelial barrier function by altering tight junction proteins. Infect Immun 2013;81(8):2819–27.
Peng C, Cao C, He M, Shu Y, Tang X, Wang Y, et al. Soybean glycinin- and β-conglycinin-induced intestinal damage in piglets via the p38/JNK/NF-κB signaling pathway. J Agric Food Chem 2018;66(36):9534–41.
Peritore-Galve FC, Kaji I, Smith A, Walker LM, Shupe JA, Washington MK, et al. Increased intestinal permeability and downregulation of absorptive ion transporters NHE3, DRA, and SGLT1 contribute to diarrhea during clostridioides difficile infection. Gut Microbes 2023;15(1):2225841.
Pilote J, Letourneau V, Girard M, Duchaine C. Quantification of airborne dust, endotoxins, human pathogens and antibiotic and metal resistance genes in Eastern Canadian swine confinement buildings. Aerobiologia 2019;35(2):283–96.
Pluske JR, Pethick DW, Hopwood DE, Hampson DJ. Nutritional influences on some major enteric bacterial diseases of pig. Nutr Res Rev 2002;15(2):333–71.
Poroca DR, Amer N, Li A, Hanrahan JW, Chappe VM. Changes in the R-region interactions depend on phosphorylation and contribute to PKA and PKC regulation of the cystic fibrosis transmembrane conductance regulator chloride channel. FASEB Bioadv 2020;2(1):33–48.
Qu R, Jiang C, Wu W, Pang B, Lei S, Lian Z, et al. Conversion of DON to 3-epi-DON in vitro and toxicity reduction of DON in vivo by *Lactobacillus rhamnosus*. Food Funct 2019;10(5):2785–96.
Ramu Y, Xu Y, Shin H, Lu Z. Counteracting suppression of CFTR and voltage-gated $K^+$ channels by a bacterial pathogenic factor with the natural product tannic acid. eLife 2014;3:e3683.
Rao MC. Physiology of electrolyte transport in the gut: implications for disease. Compr Physiol 2019;9(3):947–1023.
Rao MC, Guandalini S, Smith PL, Field M. Mode of action of heat-stable *Escherichia coli* enterotoxin. Tissue and subcellular specificities and role of cyclic GMP. Biochim Biophys Acta 1980;632(1):35–46.
Ren D, Diao E, Hou H, Dong H. Degradation and ozonolysis pathway elucidation of deoxynivalenol. Toxicon 2020;174:13–8.

Ren Z, Fan H, Deng H, Yao S, Jia G, Zuo Z, et al. Effects of dietary protein level on small intestinal morphology, occludin protein, and bacterial diversity in weaned piglets. Food Sci Nutr 2022;10(7):2168–201.
Ren Z, Zhang X, Fan H, Yu Y, Yao S, Wang Y, et al. Effects of different dietary protein levels on intestinal aquaporins in weaned piglets. J Anim Physiol Anim Nutr 2023;107(2):541–55.
Rezaei R, Wang W, Wu Z, Dai Z, Wang J, Wu G. Biochemical and physiological bases for utilization of dietary amino acids by young pigs. J Anim Sci Biotechnol 2013;4(1):7.
Rhouma M, Fairbrother JM, Beaudry F, Letellier A. Post weaning diarrhea in pigs: risk factors and non-colistin-based control strategies. Acta Vet Scand 2017;59(1):31.
Rist VTS, Weiss E, Eklund M, Mosenthin R. Impact of dietary protein on microbiota composition and activity in the gastrointestinal tract of piglets in relation to gut health: a review. Animal 2013;7(7):1067–78.
Scholten RH, Rijnen MM, Schrama JW, Boer H, van der Peet-Schwering CM, Den Hartog LA, et al. Fermentation of liquid coproducts and liquid compound diets: part 2. Effects on pH, acid-binding capacity, organic acids and ethanol during a 6-day storage period. J Anim Physiol Anim Nutr 2001;85(5–6):124–34.
Schwartz HE, Hametner C, Slavik V, Greitbauer O, Bichl G, Kunz-Vekiru E, et al. Characterization of three deoxynivalenol sulfonates formed by reaction of deoxynivalenol with sulfur reagents. J Agric Food Chem 2013;61(37):8941–8.
Scipioni R, Zaghini G, Biavati B. Research on the use of acidified diets for early weaning of piglets. Nutr in anim 1979;(4):201–18.
Seidler UE. Gastrointestinal $HCO_3^-$ transport and epithelial protection in the gut: new techniques, transport pathways and regulatory pathways. Curr Opin Pharmacol 2013;13(6):900–8.
Shima J, Takase S, Takahashi Y, Iwai Y, Fujimoto H, Yamazaki M, et al. Novel detoxification of the trichothecene mycotoxin deoxynivalenol by a soil bacterium isolated by enrichment culture. Appl Environ Microbiol 1997;63(10):3825–30.
Singh S, Gamlath S, Wakeling L. Nutritional aspects of food extrusion: a review. Int J Food Sci Technol 2007;42(8):916–29.
Smith EM, Grassel CL, Papadimas A, Foulke-Abel J, Barry EM. The role of CFA/I in adherence and toxin delivery by ETEC expressing multiple colonization factors in the human enteroid model. PLoS Negl Trop Dis 2022;16(7):e10638.
Sonawane ND, Zhao D, Zegarra-Moran O, Galietta LJV, Verkman AS. Lectin conjugates as potent, nonabsorbable CFTR inhibitors for reducing intestinal fluid secretion in cholera. Gastroenterology 2007;132(4):1234–44.
Song Y, Luo Y, Yu B, He J, Zheng P, Mao X, et al. Tannic acid extracted from gallnut prevents post-weaning diarrhea and improves intestinal health of weaned piglets. Anim Nutr 2021;7(4):1078–86.
Song Z, Yan T, Ran L, Niu Z, Zhang Y, Kan Z, et al. Reduced activity of intestinal surface $Na^+/H^+$ exchanger NHE3 is a key factor for induction of diarrhea after PEDV infection in neonatal piglets. Virology 2021;563:64–73.
Souza TCRD, Landín GM, García KE. Some physiological and nutritional factors affecting the incidence of post-weaning diarrhea in piglets. Vet Mexic 2011;41(4):275–88.
Stas EB, Tokach MD, DeRouchey JM, Goodband RD, Woodworth JC, Gebhardt JT. Evaluation of the acid-binding capacity of ingredients and complete diets commonly used for weanling pigs. Transl Anim Sci 2022;6(3):txac104.
Stein HH, Berger LL, Drackley JK, Fahey GF, Parsons CM. Nutritional properties and feeding values of soybeans and their coproducts. 1st ed. Urbana (IL): Academic Press and AOCS Press; 2008.
Suiryanrayna MV, Ramana JV. A review of the effects of dietary organic acids fed to swine. J Anim Sci Biotechnol 2015;6:45.
Sun P, Li D, Dong B, Qiao S, Ma X. Effects of soybean glycinin on performance and immune function in early weaned pigs. Arch Anim Nutr 2008;62(4):313–21.
Sun Y, Jiang J, Mu P, Lin R, Wen J, Deng Y. Toxicokinetics and metabolism of deoxynivalenol in animals and humans. Arch Toxicol 2022;96(10):2639–54.
Tanghe S, De Vos M, Degroote J, Lannoo K, Vande Ginste J, D'Inca R, et al. Araceae root and citrus fibers tend to decrease Escherichia coli adhesion and myeloperoxidase levels in weaned piglets. Front Vet Sci 2023;10:1111639.
Thiagarajah JR, Donowitz M, Verkman AS. Secretory diarrhoea: mechanisms and emerging therapies. Nat Rev Gastroenterol Hepatol 2015;12(8):446–57.
Thiagarajah JR, Verkman AS. CFTR pharmacology and its role in intestinal fluid secretion. Curr Opin Pharmacol 2003;3(6):594–9.
Thiagarajah JR, Verkman AS. Chloride channel-targeted therapy for secretory diarrheas. Curr Opin Pharmacol 2013;13(6):888–94.
Tien XY, Brasitus TA, Kaetzel MA, Dedman JR, Nelson DJ. Activation of the cystic fibrosis transmembrane conductance regulator by cGMP in the human colonic cancer cell line, Caco-2. J Biol Chem 1994;269(1):51–4.
Uddin MK, Mahmud MR, Hasan S, Peltoniemi O, Oliviero C. Dietary micro-fibrillated cellulose improves growth, reduces diarrhea, modulates gut microbiota, and increases butyrate production in post-weaning piglets. Sci Rep 2023;13(1):6194.
Waché YJ, Valat C, Postollec G, Bougeard S, Burel C, Oswald IP, et al. Impact of deoxynivalenol on the intestinal microflora of pigs. Int J Mol Sci 2009;10(1):1–17.
Walker NM, Simpson JE, Brazill JM, Gill RK, Dudeja PK, Schweinfest CW, et al. Role of down-regulated in adenoma anion exchanger in $HCO_3^-$ secretion across murine duodenum. Gastroenterology 2009;136(3):893–901.
Wang G, Wang Y, Ji F, Xu L, Yu M, Shi J, et al. Biodegradation of deoxynivalenol and its derivatives by devosia insulae A16. Food Chem 2019a;276:436–42.
Wang J, Zeng L, Tan B, Li G, Huang B, Xiong X, et al. Developmental changes in intercellular junctions and Kv channels in the intestine of piglets during the suckling and post-weaning periods. J Anim Sci Biotechnol 2016;7:4.
Wang L, Ding L, Zhu W, Hang S. Soybean protein hydrolysate stimulated cholecystokinin secretion and inhibited feed intake through calcium-sensing receptors and intracellular calcium signalling in pigs. Food Funct 2021;12(19):9286–99.
Wang L, Li W, Xin S, Wu S, Peng C, Ding H, et al. Soybean glycinin and β-conglycinin damage the intestinal barrier by triggering oxidative stress and inflammatory response in weaned piglets. Eur J Nutr 2023;62(7):2841–54.
Wang L, Tan X, Wang H, Wang Q, Huang P, Li Y, et al. Effects of varying dietary folic acid during weaning stress of piglets. Anim Nutr 2021;7(1):101–10.
Wang Q, Vlasova AN, Kenney SP, Saif LJ. Emerging and re-emerging coronaviruses in pigs. Curr Opin Virol 2019b;34:39–49.
Wang S, Hou Q, Guo Q, Zhang J, Sun Y, Wei H, et al. Isolation and characterization of a deoxynivalenol-degrading bacterium bacillus licheniformis YB9 with the capability of modulating intestinal microbial flora of mice. Toxins 2020;12(3):184.
Wang S, Wu K, Xue D, Zhang C, Rajput SA, Qi D. Mechanism of deoxynivalenol mediated gastrointestinal toxicity: insights from mitochondrial dysfunction. Food Chem Toxicol 2021;153:112214.
Wang T, Qin G, Sun Z, Zhao Y. Advances of research on glycinin and β-conglycinin: a review of two major soybean allergenic proteins. Crit Rev Food Sci Nutr 2014;54(7):850–62.
Wang W, Yang Q, Huang X, Luo R, Xie K, Gao X, et al. Effects of miR-204 on apoptosis and inflammatory response of *Clostridium perfringens* beta2 toxin induced IPEC-J2 cells via targeting BCL2L2. Microb Pathog 2021;156:104906.
Wang Y, Zhou J, Wang G, Cai S, Zeng X, Qiao S. Advances in low-protein diets for swine. J Anim Sci Biotechnol 2018;9(1):60.
Wapnir RA, Teichberg S. Regulation mechanisms of intestinal secretion: implications in nutrient absorption. J Nutr Biochem 2002;13(4):190–9.
Wellock IJ, Fortomaris PD, Houdijk JGM, Wiseman J, Kyriazakis I. The consequences of non-starch polysaccharide solubility and inclusion level on the health and performance of weaned pigs challenged with enterotoxigenic *Escherichia coli*. Br J Nutr 2008;99(3):520–30.
Wen X, Wang L, Zheng C, Yang X, Ma X, Wu Y, et al. Fecal scores and microbial metabolites in weaned piglets fed different protein sources and levels. Anim Nutr 2018;4(1):31–6.
Wu Q, Lohrey L, Cramer B, Yuan Z, Humpf H. Impact of physicochemical parameters on the decomposition of deoxynivalenol during extrusion cooking of wheat grits. J Agric Food Chem 2011;59(23):12480–5.
Wu Y, Jiang Z, Zheng C, Wang L, Zhu C, Yang X, et al. Effects of protein sources and levels in antibiotic-free diets on diarrhea, intestinal morphology, and expression of tight junctions in weaned piglets. Anim Nutr 2015;1(3):170–6.
Xia W, Yu Q, Riederer B, Singh AK, Engelhardt R, Yeruva S, et al. The distinct roles of anion transporters SlC26A3 (DRA) and SlC26A6 (PAT-1) in fluid and electrolyte absorption in the murine small intestine. Pflug Arch 2014;466(8):1541–56.
Xiang X, Deng Z, Wang Y, Sun H, Wang L, Han Y, et al. Organic acids improve growth performance with potential regulation of redox homeostasis, immunity, and microflora in intestines of weaned piglets. Antioxidants 2021;10(11):1665.
Xie K, Yang Q, Yan Z, Gao X, Huang X, Wang P, et al. miR-30d inhibition protects IPEC-J2 cells against *Clostridium perfringens* beta2 toxin-induced inflammatory injury. Front Vet Sci 2022;9:909500.
Xu T, Ma X, Zhou X, Qian M, Yang Z, Cao P, et al. Coated tannin supplementation improves growth performance, nutrients digestibility, and intestinal function in weaned piglets. J Anim Sci 2022;100(5):skac88.
Xu Z, Zhong H, Zhou Q, Du Y, Chen L, Zhang Y, et al. A highly pathogenic strain of porcine deltacoronavirus caused watery diarrhea in newborn piglets. Virol Sin 2018;33(2):131–41.
Yamamoto T, Kuramoto H, Kadowaki M. Downregulation in aquaporin 4 and aquaporin 8 expression of the colon associated with the induction of allergic diarrhea in a mouse model of food allergy. Life Sci 2007;81(2):115–20.
Yan Q, Liu X, Sun Y, Zeng W, Li Y, Zhao F, et al. Swine enteric coronavirus: diverse pathogen-host interactions. Int J Mol Sci 2022;23(7):3953.
Yao Y, Long M. The biological detoxification of deoxynivalenol: a review. Food Chem Toxicol 2020;145:111649.
Yi H, Wang Z, Yang B, Yang X, Gao K, Xiong Y, et al. Effects of zinc oxide and condensed tannins on the growth performance and intestinal health of weaned piglets in ETEC-challenged environment. Front Microbiol 2023;14:1181519.
Yi Z, Tan X, Wang Q, Huang P, Li Y, Ding X, et al. Dietary niacin affects intestinal morphology and functions via modulating cell proliferation in weaned piglets. Food Funct 2021;12(16):7402–14.
Young Christopher J. Reduction in levels of deoxynivalenol in contaminated corn by chemical and physical treatment. J Agric Food Chem 1986;34(3):465–7.
Yu B, Zhu X, Yang X, Jin L, Xu J, Ma T, et al. Plumbagin prevents secretory diarrhea by inhibiting CaCC and CFTR channel activities. Front Pharmacol 2019;10:1181.
Yu J, Song Y, Yu B, He J, Zheng P, Mao X, et al. Tannic acid prevents post-weaning diarrhea by improving intestinal barrier integrity and function in weaned piglets. J Anim Sci Biotechnol 2020;11:87.
Yuan L, Chang J, Yin Q, Lu M, Di Y, Wang P, et al. Fermented soybean meal improves the growth performance, nutrient digestibility, and microbial flora in piglets. Anim Nutr 2017;3(1):19–24.
Zeng X, Yang Y, Wang J, Wang Z, Li J, Yin Y, et al. Dietary butyrate, lauric acid and stearic acid improve gut morphology and epithelial cell turnover in weaned piglets. Anim Nutr 2022;11:276–82.

Zhai Y, Hu S, Zhong L, Lu Z, Bie X, Zhao H, et al. Characterization of deoxynivalenol detoxification by *Lactobacillus paracasei* LHZ-1 isolated from yogurt. J Food Prot 2019;82(8):1292–9.
Zhang H, Deng X, Zhou C, Wu W, Zhang H. Deoxynivalenol induces inflammation in IPEC-J2 cells by activating P38 MAPK and EEK1/2. Toxins 2020;12(3):180.
Zhang Z, Wang S, Zheng L, Hou Y, Guo S, Wang L, et al. Tannic acid-chelated zinc supplementation alleviates intestinal injury in piglets challenged by porcine epidemic diarrhea virus. Front Vet Sci 2022;9.
Zhao J, Zhang Z, Zhang S, Page G, Jaworski NW. The role of lactose in weanling pig nutrition: a literature and meta-analysis review. J Anim Sci Biotechnol 2021a;12(1):10.
Zhao L, Zhang L, Xu Z, Liu X, Chen L, Dai J, et al. Occurrence of Aflatoxin B1, deoxynivalenol and zearalenone in feeds in China during 2018–2020. J Anim Sci Biotechnol 2021b;12(1):74.
Zheng S, Qin G, Tian H, Sun Z. Role of soybean β-conglycinin subunits as potential dietary allergens in piglets. Vet J 2014;199(3):434–8.
Zhou H, George S, Hay C, Lee J, Qian H, Sun X. Individual and combined effects of aflatoxin B(1), deoxynivalenol and zearalenone on HepG2 and RAW 264.7 cell lines. Food Chem Toxicol 2017;103:18–27.
Zhou X, Liu Y, Xiong X, Chen J, Tang W, He L, et al. Intestinal accumulation of microbiota-produced succinate caused by loss of microRNAs leads to diarrhea in weanling piglets. Gut Microbes 2022;14(1):2091369.
Zhu C, Ye JL, Yang J, Yang KM, Chen Z, Liang R, et al. Differential expression of intestinal ion transporters and water channel aquaporins in young piglets challenged with enterotoxigenic *Escherichia coli* K88. J Anim Sci 2017;95(12):5240–52.