Animal Feed Science and Technology 245 (2018) 117–125

Contents lists available at ScienceDirect

Animal Feed Science and Technology

journal homepage: www.elsevier.com/locate/anifeedsci

Low dose of coated zinc oxide is as effective as pharmacological zinc oxide in promoting growth performance, reducing fecal scores, and improving nutrient digestibility and intestinal morphology in weaned pigs

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ARTICLE INFO

Keywords:
Coated zinc oxide
Fecal scores
Growth performance
Intestinal morphology nutrient digestibility
Weaned pigs

ABSTRACT

This study was conducted to evaluate the effects of coated zinc oxide on growth performance, nutrient digestibility, fecal scores, minerals concentrations in serum, fecal zinc, intestinal morphology, and selected microbial population in weaned pigs. A total of 192 crossbred [(Yorkshire × Landrace) × Duroc] weaned pigs (7.42 ± 0.97 kg) were randomly assigned into one of the following dietary treatments: (1) negative control (NC): basal diet; (2) positive control (PC): NC + 2500 mg/kg conventional zinc oxide; (3) CZO300: NC + 300 mg/kg coated zinc oxide; (4) CZO500: NC + 500 mg/kg coated zinc oxide; (5) CZO1000: NC + 1000 mg/kg coated zinc oxide; (6) CZO2000: NC + 2000 mg/kg coated zinc oxide. Each treatment had 8 replicate pens, with 4 pigs per pen. Pigs fed PC, CZO500, CZO1000, and CZO2000 diets had higher ($P < 0.01$) average daily gain (ADG) than those fed NC diet during days 0–21. During days 0–42, supplementation of coated zinc oxide at levels of 500, 1000, and 2000 mg/kg increased ADG compared with NC treatment ($P < 0.05$). Pigs fed PC, CZO300, CZO500, CZO1000, and CZO2000 diets had lower ($P < 0.01$) fecal scores compared with those fed NC diet during weeks 1, 2, and 3, but no significant difference was observed among coated zinc oxide-supplemented diets. Pigs fed the PC, CZO1000, or CZO2000 diet had greater ($P < 0.05$) coefficient of total tract apparent digestibility of dry matter than pigs fed NC diet. Compared with pigs fed NC diets, pigs fed the PC diet or coated zinc oxide-supplemented diets had increased ($P < 0.01$) serum and fecal zinc concentrations. Duodenal villus height and ratio of villus height to crypt depth of pigs fed PC, CZO1000, and CZO2000 diets were higher ($P < 0.05$) than those of pigs fed NC diet, whereas no significant differences were observed between pigs fed the PC, CZO1000, and CZO2000 diets. In conclusion, supplementing low doses (500–1000 mg/kg) of coated zinc oxide were as effective in stimulating growth, alleviating post-weaning diarrhea, and improving small intestinal morphology and nutrient digestibility as when a pharmacological level of zinc oxide (2500 mg/kg) was included. Additionally, low doses of coated zinc oxide reduced the amount of zinc excreted into the feces compared with 2500 mg/kg conventional zinc oxide.

Abbreviations: ADFI, average daily feed intake; ADG, average daily gain; CTTAD, coefficient of total tract apparent digestibility, apparent total tract digestibility; CFU, colony forming units; DM, dry matter; G:F, gain to feed ratio; N, nitrogen

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https://doi.org/10.1016/j.anifeedsci.2018.06.011
Received 4 October 2017; Received in revised form 5 May 2018; Accepted 25 June 2018

1. Introduction

Due to the changes in diet, separation from the sows, and environmental and social adaptations, weaned pigs are associated with growth retardation and post-weaning diarrhea (Kim et al., 2012; Lei et al., 2017). In practice, pharmacological level of zinc in the form of zinc oxide is often fed to weaned piglets to alleviate post-weaning diarrhea and improve gut health and growth performance (Carlson et al., 1999; Grilli et al., 2015; Milani et al., 2017). Previous studies have showed that pharmacological levels of zinc oxide, above 2000 mg/kg, improved small intestinal morphology (Li et al., 2001), intestinal microbial balance (Katouli et al., 1999), activity of digestive enzymes in the pancreatic tissue (Hedemann et al., 2006), and growth performance (Zhang and Guo, 2007, 2009; Hu et al., 2013aa; Long et al., 2017) in weaned pigs.

However, zinc oxide supplementation at a pharmacological level is criticized due to the potential environmental pollution related to the high amount of zinc excreted in the feces (Case and Carlson, 2002; Broom et al., 2006). As an amphoteric molecule, zinc oxide is almost insoluble in water, but has a high solubility at acidic pH. In the low pH gastric environment, most soluble zinc oxide is absorbed, thus just a small amount of zinc oxide is remained un-absorbed and can work in the intestine where is the main action site of zinc oxide (Shen et al., 2014; Starke et al., 2014). It is noted that controlling the release of zinc oxide in the gastrointestinal tract may improve efficacy of zinc oxide, thereby reducing feces excretion (Kim et al., 2012; Hu et al., 2013b; Grilli et al., 2015). Piva et al. (2007) reported that lipid coating allows the slow-release of the active ingredients along the intestine. We hypothesized that with coated zinc oxide, similar effects in promoting growth performance and reducing diarrhea could be reached with a lower dose as compared to conventional (uncoated) zinc oxide, thereby reducing zinc excretion in feces. Therefore, the objective of this study was to determine effects of coated zinc oxide on growth performance, nutrient digestibility, fecal scores, minerals concentrations in serum, fecal zinc, intestinal morphology, and selected microbial population in weaned pigs.

2. Materials and methods

The experimental protocols describing the management and care of animals were reviewed and approved by the Animal Care and Use Committee of Dankook University.

2.1. Source of coated zinc oxide

The coated zinc oxide used in this study was provided by a commercial company (Morningbio Co., Ltd., Cheonan, Korea). This product was protected using lipid matrix coating and contained 40% zinc oxide and 60% hydrogenated palm oil.

2.2. Animals and experimental design

A total of 192 crossbred piglets [(Yorkshire × Landrace) × Duroc] weaned at 28 days of age (7.42 ± 0.97 kg) were used in a 42-day feeding trial. Pigs were allotted into 6 dietary treatments according to initial body weight and sex in a randomized block design experiment. Each treatment comprised 8 pens, with 4 pigs (2 barrows and 2 gilts) each. The dietary treatments included: (1) negative control (NC): basal diet; (2) positive control (PC): NC + 2500 mg/kg conventional zinc oxide; (3) CZO300: NC + 300 mg/kg coated zinc oxide; (4) CZO500: NC + 500 mg/kg coated zinc oxide; (5) CZO1000: NC + 1000 mg/kg coated zinc oxide; (6) CZO2000: NC + 2000 mg/kg coated zinc oxide. These pigs were subjected to a feeding program consisting of two phases: phase 1 (days 0–21) and phase 2 (days 21–42). All experimental diets were formulated to meet nutrient requirements suggested by the NRC (2012; Table 1). The analyzed zinc concentrations of experimental diets are presented in Table 2. The form of the experimental feed was mash. All pigs had *ad libitum* access to feed and water throughout the 42-day experimental period. Pigs were kept on slatted plastic floors in an environmentally-controlled room. At the beginning of the experiment, room temperature was maintained at 30 °C, and gradually reduced by 1.5 °C/wk. Each pen was equipped with a one-side feeder and a nipple waterer.

2.3. Sampling and measurements

Individual pig weight and feed consumption by pen were recorded on days 0, 21, and 42. Average daily gain (ADG), average daily feed intake (ADFI), and gain to feed ratio (G:F) were calculated accordingly.

To estimate the coefficient of total tract apparent digestibility (CTTAD) of dry matter (DM) and nitrogen (N), pigs were offered diets supplemented with chromic oxide (2 g/kg) as an indigestible marker from days 36–42. After mixing with chromic oxide, feed samples from each treatment were collected and stored at −20 °C until subsequent analysis were conducted. On day 42, fecal samples were collected from all pens (1 barrow and 1 gilt per pen) via rectal massage. Fecal samples from the same pen were pooled and mixed immediately, after which samples were stored at −20 °C until subsequent analysis were conducted. For chemical analysis, fecal samples were oven-dried at 60 °C for 72 h, after which feed and fecal samples were ground to pass through a 1.0-mm screen for analysis of DM (method 930.15) and N (method 984.13) using the AOAC (2007) procedures. Dietary and fecal zinc concentration was analyzed with flame atomic absorption spectrophotometry (AA-6300, Shimadzu Corp., Tokyo, Japan). Chromium was analyzed via UV absorption spectrophotometry (UV-1201, Shimadzu Corp., Kyoto, Japan), according to the method described by Williams et al. (1962). The CTTAD was then calculated using the following formula:

$$CTTAD = 1\text{-}(Nf \times Cd)/(Nd \times Cf),$$

Table 1
Composition of the experimental diets, as-fed basis.

Items	Phase 1 (days 0– 21)	Phase 2 (days 21– 42)
Ingredients, g/kg		
Extruded corn	356.3	447.0
Soybean meal	195.9	305.0
Biscuit meal	50.0	90.0
Fish meal	43.0	26.5
Fermented soybean meal	84.0	–
Soy oil	50.0	30.0
Milk product	20.0	20.0
Whey powder	100.0	62.5
Sugar	20.0	–
Monocalcium phosphate	10.0	6.0
L-Lysine·HCl	2.5	1.6
DL-Methionine	1.5	1.4
L-Threonine	0.8	–
Lactose	58.0	–
Vitamin premix[a]	1.0	1.0
Trace mineral premix[b]	2.0	2.0
Limestone	2.0	3.0
Salt	2.0	3.0
Choline chloride	1.0	1.0
Calculated composition, MJ/kg		
Metabolizable energy	14.65	14.44
Analyzed composition, g/kg		
Crude protein	212.1	203.5
Lysine	15.2	14.4
Methionine	5.1	4.9
Calcium,	8.0	7.7
Total phosphorus	7.6	7.3

[a] Provided per kilogram of complete diet: 11,025 IU vitamin A, 1103 IU vitamin D_3, 44 IU vitamin E, 4.4 mg K, 8.3 mg riboflavin, 50 mg niacin, 4 mg thiamine, 29 mg D-pantothenic acid, 166 mg choline, 33 μg vitamin B_{12}.
[b] Provided per kilogram of complete diet: 80 mg Fe (as $FeSO_4 \cdot H_2O$); 12 mg Cu (as $CuSO_4 \cdot 5H_2O$); 85 mg Zn (as $ZnSO_4$); 8 mg Mn (as MnO_2); 0.28 mg I (as KI); 0.15 mg Se (as $Na_2SeO_3 \cdot 5H_2O$).

Table 2
Analyzed zinc concentrations of experimental diets[a].

Items, g/kg	Phase 1 (days 0 to 21)	Phase 2 (days 21 to 42)
NC	0.125	0.133
PC	2.166	2.159
CZO300	0.236	0.240
CZO500	0.293	0.301
CZO1000	0.461	0.459
CZO2000	0.788	0.781

[a] Dietary treatments were as follow: (1) negative control (NC): basal diet; (2) positive control (PC): NC + 2500 mg/kg conventional zinc oxide; (3) CZO300: NC + 300 mg/kg coated zinc oxide; (4) CZO500: NC + 500 mg/kg coated zinc oxide; (5) CZO1000: NC + 1000 mg/kg coated zinc oxide; (6) CZO2000: NC + 2000 mg/kg coated zinc oxide.

where Nf = nutrient concentration in feces (g/kg), Nd = nutrient concentration in diet (g/kg), Cd = chromium concentration in diet (g/kg), and Cf = chromium concentration in feces (g/kg).

Subjective fecal scores were recorded for clinical signs of diarrhea at 0800 h each morning throughout the experiment by a single blinded observer, using the 5-grade scoring system described by O'Shea et al. (2014). Briefly, 1 = well-firmed feces; 2 = slightly soft feces; 3 = soft and partially formed feces; 4 = loose and semi-liquid feces; 5 = watery and mucus-like feces.

At the end of the experiment, after body weight measurement, 8 pigs (1 pig per pen) were randomly selected from each treatment and blood samples were harvested via anterior vena cava puncture using a sterile syringe into non-heparinized tubes (10 mL). Blood samples were allowed to rest at room temperature for a few minutes and centrifuged at 1500 × *g* at 4 °C for 20 min to get serum and then frozen at −20 °C until analysis. Contents of iron, copper, zinc, and phosphorus were analyzed with flame atomic absorption spectrophotometry (AA-6300, Shimadzu Corp., Tokyo, Japan).

All pigs supplying blood samples were sacrificed by electrical stunning and exsanguination to collect small intestinal tissue (for histomorphology determination) and digesta (for lactic acid bacteria and coliform bacteria counts). The digesta from duodenum, jejunum, ileum, and cecum were separately obtained and placed on ice and immediately transported to the laboratory for microbial analysis. The samples of intestinal segments from the region of the duodenum, jejunum, and ileum after removal of its contents were

flushed with physiological saline and fixed by immersion in 10% (vol/vol) buffered formalin for the histological study.

For digesta microbial analysis, digesta sample (1 g) from duodenum, jejunum, ileum, and cecum was diluted with 9 mL of 10 g/kg peptone broth (Becton, Dickinson and Co., Franklin Lakes, NJ, USA) and homogenized. Then, 10-fold dilutions of fecal samples were performed (ranging from 10^{-1} to 10^{-8}) and then cultivated onto MacConkey agar plates (Difco Laboratories, Detroit, MI) for the enumeration of coliform bacteria and lactobacilli medium III agar plates (Medium 638; DSMZ, Braunschweig, Germany) for the enumeration of lactic acid bacteria. The lactobacilli medium III agar plates were then incubated for 48 h at 39 °C under anaerobic conditions, while the MacConkey agar plates were incubated for 24 h at 37 °C. The coliform bacteria and lactic acid bacteria colonies were counted immediately after removal from the incubator. Values were reported as $\log_{10}$ colony-forming units per gram.

Three cross-sections of 4 μm for each intestinal sample were prepared after staining with hematoxylin and eosin using standard paraffin embedding procedures. Morphometric measurements were performed with a light microscope fitted with an image analyzer (Image Pro Plus; Media Cybernetics, Bethesda, MD, USA). A total of 10 intact, well-oriented crypt-villus units were selected for each intestinal cross-section. Villus height was measured from the tip of the villi to the villus crypt junction. Crypt depth was defined as the depth of the invagination between adjacent villi.

2.4. Statistical analysis

All data were analyzed as a completely randomized block design using the GLM procedure of SAS (version 9.2; SAS Institute, Cary, NC). When significant differences were identified among treatment means, they were separated using Tukey's range test. Each pen or individual pig was considered as the experimental unit. Probability values less than 0.05 were considered statistically significant.

3. Results

3.1. Growth performance

Effects of coated zinc oxide supplementation on growth performance are shown in Table 3. Pigs offered the PC, CZO500, CZO1000, and CZO2000 diets exhibited higher ($P < 0.01$) ADG than those fed NC diet during days 0–21. During days 0–42, supplementation of coated zinc oxide at levels of 500, 1000, and 2000 mg/kg increased ADG compared with NC treatment ($P < 0.05$). However, ADFI and G:F were not affected by dietary treatments throughout the experiment ($P > 0.05$).

3.2. Fecal scores

Pigs fed the PC, CZO300, CZO500, CZO1000, and CZO2000 diets had lower ($P < 0.01$) fecal scores compared with those fed the NC diet during first 3 weeks, but no significant difference was observed among coated zinc oxide-supplemented diets (Table 4). Dietary treatments did not affect fecal scores during week 4, 5, or 6 ($P > 0.05$).

3.3. Coefficient of total tract apparent digestibility

The CTTAD of DM was greater ($P < 0.05$) for the PC, CZO1000, or CZO2000 diets than that for the NC diet (Table 5). The CZO1000 diet had greater ($P < 0.05$) CTTAD of DM compared with CZO500 diet. The CTTAD of N was greater ($P < 0.05$) for the PC

Table 3
Effects of coated zinc oxide supplementation on growth performance in weaned pigs.

Items	Dietary treatment[1]						SEM[2]	*P*-value
	NC	PC	CZO300	CZO500	CZO1000	CZO2000		
Days 0-21								
ADG, g/d	340[c]	360[ab]	345[bc]	363[a]	370[a]	366[a]	5.51	0.005
ADFI, g/d	515	540	510	533	537	545	10.61	0.166
G:F	0.659	0.668	0.677	0.680	0.690	0.671	0.018	0.900
Days 21-42								
ADG, g/d	493	513	518	521	530	527	15.10	0.597
ADFI, g/d	804	847	830	831	847	824	14.28	0.320
G:F	0.614	0.606	0.624	0.627	0.625	0.640	0.023	0.931
Overall (days 0-42)								
ADG, g/d	416[b]	437[ab]	432[ab]	442[a]	450[a]	446[a]	7.23	0.047
ADFI, g/d	660	693	670	682	692	684	9.24	0.129
G:F	0.631	0.630	0.644	0.648	0.650	0.652	0.015	0.799

[a,b]Means in the same row with different superscripts differ ($P < 0.05$).

[1] Dietary treatments were as follow: (1) negative control (NC): basal diet; (2) positive control (PC): NC + 2500 mg/kg conventional zinc oxide; (3) CZO300: NC + 300 mg/kg coated zinc oxide; (4) CZO500: NC + 500 mg/kg coated zinc oxide; (5) CZO1000: NC + 1000 mg/kg coated zinc oxide; (6) CZO2000: NC + 2000 mg/kg coated zinc oxide.

[2] pooled standard error of the mean.

Table 4
Effects of dietary coated zinc oxide supplementation on fecal scores in weaned pigs.[1].

Items	Dietary treatment[2]						SEM[3]	*P*-value
	NC	PC	CZO300	CZO500	CZO1000	CZO2000		
Week 1	4.18[a]	3.25[b]	3.27[b]	3.18[b]	3.20[b]	3.21[b]	0.073	< 0.001
Week 2	3.66[a]	3.16[b]	3.11[b]	3.16[b]	3.16[b]	3.11[b]	0.043	< 0.001
Week 3	3.45[a]	3.14[b]	3.16[b]	3.09[b]	3.09[b]	3.11[b]	0.046	< 0.001
Week 4	3.20	3.07	3.11	3.14	3.09	3.13	0.029	0.079
Week 5	3.14	3.07	3.13	3.11	3.14	3.11	0.048	0.889
Week 6	3.16	3.07	3.09	3.09	3.09	3.14	0.049	0.663

[a,b]Means in the same row with different superscripts differ (P < 0.05).
[1] Fecal score: 1 = well-firmed feces; 2 = slightly soft feces; 3 = soft and partially formed feces; 4 = loose and semi-liquid feces; 5 = watery and mucus-like feces.
[2] Dietary treatments were as follow: (1) negative control (NC): basal diet; (2) positive control (PC): NC + 2500 mg/kg conventional zinc oxide; (3) CZO300: NC + 300 mg/kg coated zinc oxide; (4) CZO500: NC + 500 mg/kg coated zinc oxide; (5) CZO1000: NC + 1000 mg/kg coated zinc oxide; (6) CZO2000: NC + 2000 mg/kg coated zinc oxide.
[3] Pooled standard error of the mean.

Table 5
Effects of dietary coated zinc oxide supplementation on apparent total tract digestibility in weaned pigs.

Items	Dietary treatment[1]						SEM[2]	*P*-value
	NC	PC	CZO300	CZO500	CZO1000	CZO2000		
Dry matter	0.800[c]	0.815[ab]	0.807[abc]	0.805[bc]	0.817[a]	0.814[ab]	0.004	0.013
Nitrogen	0.793[b]	0.821[a]	0.808[ab]	0.817[ab]	0.816[ab]	0.824[a]	0.009	0.041

[a,b]Means in the same row with different superscripts differ (*P* < 0.05).
[1] Dietary treatments were as follow: (1) negative control (NC): basal diet; (2) positive control (PC): NC + 2500 mg/kg conventional zinc oxide; (3) CZO300: NC + 300 mg/kg coated zinc oxide; (4) CZO500: NC + 500 mg/kg coated zinc oxide; (5) CZO1000: NC + 1000 mg/kg coated zinc oxide; (6) CZO2000: NC + 2000 mg/kg coated zinc oxide.
[2] Pooled standard error of the mean.

and CZO2000 diets compared with the NC diet.

3.4. Plasma mineral status and fecal zinc

Serum copper, iron, and phosphorus concentrations were not affected by dietary treatments (Table 6). Compared with pigs fed the NC diet, pigs receiving the PC diet or coated zinc oxide-supplemented diets had increased (*P* < 0.01) serum and fecal zinc concentrations. Moreover, all the coated zinc oxide-supplemented groups had reduced (*P* < 0.01) serum and fecal zinc concentrations compared with the PC treatment.

Table 6
Effects of dietary coated zinc oxide supplementation on blood mineral concentrations and fecal zinc contents in weaned pigs.

Items	Dietary treatment[1]						SEM[2]	*P*-value
	NC	PC	CZO300	CZO500	CZO1000	CZO2000		
Serum								
Zinc, ug/dL	54.3[c]	177.5[a]	74.8[b]	79.5[b]	80.3[b]	87.0[b]	6.73	< 0.001
Phosphorus, mg/dL	3.35	2.52	2.54	2.97	2.55	3.2	0.49	0.754
Copper, ug/dL	231.1	180.5	201.0	210.0	183.3	208.6	18.37	0.422
Iron, ug/dL	112.5	99.8	98.5	101.0	99.3	101.0	15.44	0.987
Feces								
Zinc, g/kg	0.79[f]	12.13[a]	1.79[e]	2.47[d]	3.65[c]	5.55[b]	0.19	< 0.001

[a,b]Means in the same row with different superscripts differ (*P* < 0.05).
[1] Dietary treatments were as follow: (1) negative control (NC): basal diet; (2) positive control (PC): NC + 2500 mg/kg conventional zinc oxide; (3) CZO300: NC + 300 mg/kg coated zinc oxide; (4) CZO500: NC + 500 mg/kg coated zinc oxide; (5) CZO1000: NC + 1000 mg/kg coated zinc oxide; (6) CZO2000: NC + 2000 mg/kg coated zinc oxide.
[2] Pooled standard error of the mean.

Table 7
Effects of dietary coated zinc oxide supplementation on intestinal morphology in weaned pigs.

Items,	Dietary treatment[1]						SEM[2]	*P*-value
	NC	PC	CZO300	CZO500	CZO1000	CZO2000		
Villus height, μm								
Duodenum	270.90^{c}	338.55^{a}	294.23^{bc}	298.73^{bc}	334.90^{a}	322.15^{ab}	11.61	0.004
Jejunum	270.18	322.65	280.33	285.65	296.13	301.38	20.21	0.555
Ileum	280.05^{b}	336.33^{a}	290.48^{b}	288.13^{b}	304.15^{ab}	310.55^{ab}	10.56	0.018
Crypt depth, μm								
Duodenum	197.93	192.78	198.83	194.48	199.58	192.10	8.24	0.982
Jejunum	184.30	196.55	193.63	201.30	191.03	196.93	9.36	0.850
Ileum	191.15	198.45	198.33	196.60	195.08	200.60	9.13	0.982
Villus height to crypt depth ratio								
Duodenum	1.37^{b}	1.76^{a}	1.48^{ab}	1.53^{ab}	1.69^{a}	1.67^{a}	0.12	0.045
Jejunum	1.47	1.63	1.45	1.42	1.55	1.53	0.11	0.851
Ileum	1.46	1.69	1.47	1.48	1.56	1.55	0.14	0.484

[a,b]Means in the same row with different superscripts differ ($P < 0.05$).
[1] Dietary treatments were as follow: (1) negative control (NC): basal diet; (2) positive control (PC): NC + 2500 mg/kg conventional zinc oxide; (3) CZO300: NC + 300 mg/kg coated zinc oxide; (4) CZO500: NC + 500 mg/kg coated zinc oxide; (5) CZO1000: NC + 1000 mg/kg coated zinc oxide; (6) CZO2000: NC + 2000 mg/kg coated zinc oxide.
[2] Pooled standard error of the mean.

3.5. Intestinal morphology

Duodenal villus height and villus height to crypt depth ratio of pigs on the PC, CZO1000, and CZO2000 diets were higher ($P < 0.05$) than those of pigs offered the NC diet, whereas no significant differences were observed between pigs fed the PC, CZO1000, and CZO2000 diets (Table 7). Pigs receiving the PC diet had greater ($P < 0.05$) ileal villus height than those offered the NC, CZO300, and CZO500 diets. There were no significant differences in crypt depth for any of the intestinal segments among dietary treatments ($P > 0.10$).

3.6. Intestinal shedding of lactic acid bacteria and coliform bacteria

Lactic acid bacteria or coliform bacteria counts in duodenum, jejunum, ileum or cecum were not affected by coated or conventional zinc oxide inclusion ($P > 0.10$; Table 8).

4. Discussion

Due to the antimicrobial effect, zinc oxide, at pharmacological level, has been supplemented in weaned pig diets to prevent post-weaning diarrhea and promote growth performance, especially for the first 2–3 weeks post-weaning (Roselli et al., 2003; Heo et al., 2013; Hu et al., 2013aa; Grilli et al., 2015; Walk et al., 2015; Song et al., 2015; Milani et al., 2017). In the present study, in agreement

Table 8
Effects of dietary coated zinc oxide supplementation on intestinal counts of lactic acid bacteria and coliform bacteria in weaned pigs.

Items, log_{10} CFU/g	Dietary treatment[1]						SEM[2]	*P*-value
	NC	PC	CZO300	CZO500	CZO1000	CZO2000		
Duodenum								
Coliform bacteria	3.56	3.64	3.62	3.58	3.58	3.60	0.16	0.979
Lactic acid bacteria	7.22	7.11	7.17	7.20	7.21	7.23	0.13	0.989
Jejunum								
Coliform bacteria	3.85	3.91	3.85	3.80	3.85	3.84	0.17	0.924
Lactic acid bacteria	7.27	7.25	7.24	7.19	7.28	7.19	0.11	0.958
Ileum								
Coliform bacteria	4.41	4.43	4.47	4.38	4.38	4.31	0.07	0.815
Lactic acid bacteria	6.29	6.39	6.35	6.37	6.34	6.39	0.19	0.909
Cecum								
Coliform bacteria	4.55	4.56	4.54	4.60	4.67	4.68	0.09	0.972
Lactic acid bacteria	7.48	7.39	7.42	7.32	7.41	7.33	0.12	0.945

[1] Dietary treatments were as follow: (1) negative control (NC): basal diet; (2) positive control (PC): NC + 2500 mg/kg conventional zinc oxide; (3) CZO300: NC + 300 mg/kg coated zinc oxide; (4) CZO500: NC + 500 mg/kg coated zinc oxide; (5) CZO1000: NC + 1000 mg/kg coated zinc oxide; (6) CZO2000: NC + 2000 mg/kg coated zinc oxide.
[2] Pooled standard error of the mean.

with these findings, pigs offered the PC diet (days 0–21) had higher ADG compared with pigs receiving the NC diet. The improvement in growth performance is probably the consequence of increased nutrient digestibility and improved intestinal morphology. In addition, although antioxidant status and immune function were specifically determined in this study, it has been proposed that the pharmacological dose of zinc oxide may regulate intestinal immune-associated gene expression and modulate the antioxidant capacity, thereby improving growth performance (Zhu et al., 2017). However, variable results have been reported on the effects of pharmacological levels of zinc oxide on growth performance of weaned pigs. Shen et al. (2014) and Jang et al. (2014) reported that no improvements in ADG, ADFI, and G:F were observed in weaned pigs receiving diets supplemented with pharmacological levels (2250 or 2500 mg/kg) zinc in the form of conventional zinc oxide. Moreover, supplementation with conventional zinc oxide at a pharmacological dose may pose a threat from an environmental perspective, because the major part of ingested zinc oxide is excreted with the feces (Meyer et al., 2002; Jondreville et al., 2003; Miller et al., 2009). Zinc oxide is almost insoluble in water, but in the low pH gastric environment, most zinc oxide is solubilized, thus just a small amount of zinc oxide is remained un-absorbed and can work in the intestine. To overcome this limitation, it was assumed that a controlled release of zinc oxide along the intestine through the use of slow-release techniques might improve its efficacy. Lipid coating ensures that zinc oxide reaches the small intestine whereby the lipid coating is gradually removed by pancreatic lipases (Claus et al., 2007). In this study, we evaluated the hypothesis that similar effects in promoting growth performance could be reached with a lower dose coated zinc oxide as compared to pharmacological level conventional zinc oxide. The results from the present experiment indicated that low doses (500, 1000, and 2000 mg/kg) of coated zinc oxide had equaled growth-promoting effects as the pharmacological dose of conventional zinc oxide. Additionally, in the present study, the ADG reached a plateau after the concentration of 500 mg/kg and further increase in the concentration of coated zinc oxide did not impact the growth performance, suggesting that the maximum effect of coated zinc oxide has been reached between 500 and 1000 mg/kg.

Due to nutritional, psychological, and environmental stressors, weaning is often associated with post-weaning diarrhea (Kim et al., 2012). The results from the present study support the findings of Cho et al. (2015); Song et al. (2015), and Milani et al. (2017) showing that feeding pharmacological level of zinc oxide alleviates post-weaning diarrhea indicated as reduced fecal scores. In addition, as expected in the present study, low dose (300 mg/kg) of coated zinc oxide was enough to have similar effects in reducing fecal scores as the high dose of conventional zinc oxide during the first 3 weeks post weaning. Similarly, the results of Shen et al. (2014) demonstrated that supplementation of coated zinc oxide at levels of 380 and 570 mg/kg and 2250 mg/kg conventional zinc oxide had comparable effects in reducing diarrhea index in weaned pigs. In a study with enterotoxigenic *Escherichia coli* K88 challenged weaned pigs, Kim et al. (2015) also reported that both 100 mg/kg of lipid-coated zinc oxide and 2400 mg/kg conventional zinc oxide were effective in reducing fecal scores. It is well documented that the occurrence of diarrhea is closed related to the increase in intestinal permeability (Huang et al., 2015; Fan et al., 2017). Zhang and Guo (2009) reported that supplemental pharmacological level of zinc oxide reduced intestinal permeability by enhancing the expression and production of tight junction proteins (occludin and zonula occludens protein-1). Therefore, the alleviated post-weaning diarrhea by conventional or coated zinc oxide can be attributed to the decrease in intestinal permeability.

In the present study, pigs offered the PC diet or diets supplemented with 1000 or 2000 mg/kg coated zinc oxide had higher CTTAD of DM and N compared with those receiving the NC diet. The increased DM and N digestibility partially explain the improvement of growth performance of pigs fed diets supplemented with coated and conventional zinc oxide. Zinc oxide may improve digestive enzymes activities in pancreatic tissue and small intestine thereby improving nutrient digestibility (Hu et al., 2012b). The improved nutrient digestibility could be also attributed to the improved small intestinal morphology which enhances nutrient absorption (Furbeyre et al., 2017). The improvement in nutrient digestibility is in agreement with O'Shea et al. (2014); Lee et al. (2016), and Hosseindoust et al. (2017), where weaned pigs offered diets containing pharmacological levels of zinc oxide had higher CTTAD of DM and N compared with those fed the basal diet. In contrast to the present results, Heim et al. (2014) indicated that addition of pharmacological levels of zinc oxide (3100 mg/kg during days 1–14 and 2600 mg/kg during days 15–32 post weaning) reduced CTTAD of DM and N. Han and Thacker (2010) observed that supplementation of zinc oxide at levels of 1500 or 2500 mg/kg reduced CTTAD of DM but had no effect on CTTAD of N in weaned pigs.

Serum concentrations of minerals can be used as an indicator of mineral status of the animal (Walk et al., 2013). Consistent with previous studies (Rincker et al., 2005; Han and Thacker, 2010; Davin et al., 2013), serum iron, phosphorus, and copper in the present study were not affected by dietary treatments. Serum zinc concentrations were lower in pigs offered the NC diet than that in those receiving the PC diet or diets supplemented with coated zinc oxide. Similarly, as expected, serum zinc levels in pigs fed diets supplemented with coated zinc oxide were lower compared with those of pigs offered the PC diet. The difference should be the portion of blood zinc in pigs fed diets supplemented with coated zinc dietary treatments was lower than those fed conventional zinc oxide diet. It is also possible that the coated zinc oxide is less available for immediate uptake. Similar to the results of our experiment, Shen et al. (2014) found that supplementation with 2250 mg/kg zinc from zinc oxide increased serum zinc concentration compared with 250 mg/kg zinc from zinc oxide, but coated zinc oxide did not affect serum zinc levels. The use of pharmacological levels of zinc oxide may cause environmental pollution because a significant portion of ingested zinc oxide is un-absorbed and instead excreted in the feces (Buff et al., 2005; Milani et al., 2017). In the present study, fecal zinc excretion was lower in pigs offered the NC diet and diets containing coated zinc oxide compared with those fed the PC diet. Thus, results of this experiment suggest that coated zinc oxide was effective in reducing fecal zinc excretion.

The structure and integrity of small intestinal epithelium are important factors contributing to intestinal immune function and digestive capacity. The improved gut morphology implies increased intestinal capacity for nutrients absorptions, which is necessary for growth and intestinal health of weaned piglets (Giannenas et al., 2016; Long et al., 2018). It has been reported that addition of pharmacological zinc oxide improve intestinal morphology in weaned pigs (Li et al., 2001, 2006; Song et al., 2015; Wang et al.,

2017). In addition, inclusion of 2250 mg/kg zinc from conventional zinc oxide or low doses (380 and 570 mg/kg) of zinc from coated zinc oxide had the similar effects to improve small intestinal morphology in weaned pigs (Shen et al., 2014). In agreement with these findings, results of the present study demonstrated that supplementation with 2500 mg/kg conventional zinc oxide and coated zinc oxide at the levels of 1000 or 2000 mg/kg improved villus height and the ratio of villus height to crypt depth in the duodenum, which may be indicative of an improved absorptive capacity. The intestinal development is related to enterocyte proliferation and differentiation (Aito-Inoue et al., 2007). The insulin-like growth factor I (IGF- I) is a good regulator of the proliferation and differentiation of enterocyte. Burrin et al. (1996) found that orally administered IGF-I increased intestinal (jejunum and ileum) villous height in neonatal piglets. Li et al. (2006) reported that dietary supplementation with 3000 mg/kg zinc in the form of conventional zinc oxide enhanced small intestinal villous height accompanied by increased expression of IGF-I and IGF-I receptor (IGF-IR) genes at both the mRNA and protein level in the small intestinal mucosa in weaned pigs. Shen et al. (2014) also observed that both high dose (2250 mg/kg) zinc from conventional zinc oxide and low doses (250, 380, and 570 mg/kg) zinc from coated zinc oxide enhanced the mRNA expression of IGF-I. Therefore, the possible reason for the improved intestinal morphology by supplementation conventional (2500 mg/kg) or coated (1000 or 2000 mg/kg) zinc oxide may be the enhancement of expression of IGF-I and IGF-IR expression in the gastrointestinal tract.

Although it has been reported extensively that dietary supplementation with pharmacological doses of zinc oxide modifies intestinal microbial composition or their activities in weaned pigs (Vahjen et al., 2011; Pieper et al., 2012; Starke et al., 2014; Yu et al., 2017), others have not made similar results. For instance, Li et al. (2001) demonstrated that zinc oxide had no effect on *Enterobacteriaceae*, *Lactobacilli*, and *Clostridia* in ileal digesta and feces in piglets, which is consistent with the findings of the present study showing that coliform bacteria and lactic acid bacteria counts in small intestine or cecum were not affected by supplementation with coated or conventional zinc oxide. In a study by Hu et al. (2012a), dietary addition of 2000 mg/kg zinc as zinc oxide had no effect on *Clostridium* counts in small intestine and *Escherichia coli* counts in the small intestine and colon. Similarly, Molist et al. (2011) observed that 3000 mg/kg conventional zinc oxide had no effects on fecal *Enterococci*, *Escherichia coli,* and coliforms counts in weaned pigs. The inconsistent effects of dietary zinc oxide on intestinal bacterial compositions are possibly caused by (1) the doses, forms, and duration of zinc oxide supplemented to the diets, (2) the different samples from various locations of gastrointestinal tracts, (3) the different methods used for analyzing changes in the microbial community, and (4) the dynamic microbial community in the gastrointestinal tracts (Vahjen et al., 2011; Pieper et al., 2012; Sales, 2013; Starke et al., 2014).

5. Conclusion

In summary, supplementing low doses (500–1000 mg/kg) of coated zinc oxide were as effective in stimulating growth and alleviating post-weaning diarrhea, improving small intestinal morphology and nutrient digestibility as when a pharmacological level of zinc oxide (2500 mg/kg) was included. Additionally, coated zinc oxide reduced the amount of zinc excreted into the feces compared with 2500 mg/kg conventional zinc oxide.

Conflict of interests

The authors declare no conflict of interest.

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