Effects of Sanguinarine on Growth Performance, Intestinal Morphology and Structure, and Small Intestinal Mucosal Immune Function in Weaned Piglets (Postprint)

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Abstract

This study aimed to investigate the effects of sanguinarine (SAN) on growth performance, intestinal morphology, and small intestinal mucosal immune function in weaned piglets. Thirty-six healthy "Duroc × Landrace × Yorkshire" three-way crossbred weaned piglets at 23 days of age with an average body weight of (6.55±0.18) kg were randomly assigned to three groups according to the principle of similar body weight and identical sex ratio. The groups were fed a basal diet (control group), basal diet + 75 mg/kg chlortetracycline (antibiotic group), or basal diet + 50 mg/kg SAN (SAN group), with 12 replicates per group and one pig per replicate, for a 21-day experimental period. The results showed: 1) Compared with the control group, the average daily gain and average daily feed intake in the SAN and antibiotic groups were significantly increased ($P<0.05$), while the feed-to-gain ratio and diarrhea rate were significantly decreased ($P<0.05$); however, there were no significant differences in these growth performance indices between the SAN and antibiotic groups ($P>0.05$). 2) Compared with the control group, the villus height and villus height/crypt depth (V/C) ratio in the duodenum and jejunum of the SAN and antibiotic groups were significantly or extremely significantly increased ($P<0.05$ or $P<0.01$), but there were no significant differences in these indices between the SAN and antibiotic groups ($P>0.05$); whereas the ileal villus height and V/C ratio in the SAN group were significantly higher than those in the other two groups ($P<0.05$). 3) Compared with the control group, the contents of immunoglobulin A, immunoglobulin G, and immunoglobulin M in the duodenal, jejunal, and ileal mucosa of the SAN and antibiotic groups were significantly or extremely significantly increased (except for duodenal mucosal immunoglobulin G and jejunal mucosal immunoglobulin M) ($P<0.05$ or $P<0.01$); however, there were no significant differences in these indices between the SAN and antibiotic groups (P>0.05). In conclusion, dietary supplementation with SAN can improve intestinal mucosal morphology, enhance small intestinal mucosal immune function, and thereby improve the growth performance of weaned piglets, achieving effects comparable to those of antibiotics.

Full Text

Effects of Dietary Sanguinarine on Growth Performance, Intestinal Mucosal Morphology and Immune Function of Small Intestinal Mucosa of Weaned Piglets

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Abstract: This experiment was conducted to investigate the effects of sanguinarine (SAN) on growth performance, intestinal morphology, and small intestinal mucosal immune function in weaned piglets. Thirty-six healthy "Duroc × Landrace × Yorkshire"crossbred piglets (23 days old, initial weight (6.55±0.18) kg) were randomly allocated to three groups (12 replicates per group, one pig per replicate) based on similar body weight and equal gender ratio. The groups were fed either a basal diet (control group), basal diet + 75 mg/kg chlortetracycline (antibiotic group), or basal diet + 50 mg/kg SAN (SAN group) for a 21-day experimental period. The results showed that: 1) Compared with the control group, both SAN and antibiotic groups exhibited significantly higher average daily gain (ADG) and average daily feed intake (ADFI) (P<0.05), and significantly lower feed-to-gain ratio (F/G) and diarrhea rate (P<0.05). However, no significant differences were observed between the SAN and antibiotic groups for these growth performance parameters (P>0.05). 2) The villus height and villus height-to-crypt depth ratio (V/C) in the duodenum and jejunum were significantly or extremely significantly increased in both SAN and antibiotic groups compared with the control group (P<0.05 or P<0.01), with no significant differences between the SAN and antibiotic groups (P>0.05). The SAN group showed significantly higher ileal villus height and V/C ratio than the other two groups (P<0.05). 3) The contents of immunoglobulin A (IgA), immunoglobulin G (IgG), and immunoglobulin M (IgM) in the duodenal, jejunal, and ileal mucosa were significantly or extremely significantly elevated in both SAN and antibiotic groups compared with the control group (except for duodenal IgG and jejunal IgM) ($P<0.05$ or $P<0.01$), with no significant differences between the SAN and antibiotic groups ($P>0.05$). In conclusion, dietary SAN supplementation can improve intestinal mucosal morphology and enhance small intestinal mucosal immune function, thereby improving the growth performance of weaned piglets with effects comparable to antibiotics.

Keywords: sanguinarine; weaned piglets; growth performance; intestinal morphology; immunoglobulin

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In modern swine production, early weaning has long been adopted to improve sow reproductive efficiency and reduce disease transmission between sows and piglets. However, the sudden changes in physiology, nutrition, and environment cause decreased feed intake, frequent intestinal diseases, growth retardation, and increased mortality in weaned piglets, collectively known as weaning stress syndrome. Although dietary antibiotics can partially alleviate weaning stress syndrome by improving growth performance and disease resistance, their extensive use and even abuse have led to dramatically increased bacterial resistance in the gastrointestinal tract, along with drug residues and environmental pollution, threatening animal-derived food safety and directly impacting human health and environmental security. Therefore, developing new green alternatives without drug residues, pollution, or resistance is urgently needed.

Sanguinarine is a benzophenanthridine isoquinoline alkaloid isolated from *Macleaya cordata*, characterized by easy degradation and low environmental pollution, with unique composition and mechanisms. Sanguinarine and its derivatives possess strong cell permeability and exhibit potent inhibitory effects against pathogenic bacteria such as *Salmonella*, *Staphylococcus aureus*, and *Escherichia coli*. Sanguinarine also demonstrates multiple pharmacological effects including anti-tumor, immune enhancement, anti-inflammatory, and antioxidant activities, highlighting its potential as a novel green feed additive. As sanguinarine finds widespread application in human clinical practice, its use in livestock and poultry production has attracted increasing attention. Kosina et al. reported that supplementing weaned piglet feed with 3.75 mg/kg SAN from *Macleaya cordata* alkaloids stimulated appetite and increased feed intake, protected essential amino acids from degradation in the intestine, and consequently promoted animal growth. Lee et al. and Liu Jing demonstrated that combined use of sanguinarine and organic acids in broiler diets improved intestinal structure and microbiota balance, achieving growth-promoting effects. Yun Long found that dietary sanguinarine significantly increased serum immunoglobulin M (IgM) content and improved intestinal morphology in yellow-feathered broilers, promoting their growth performance. While the exact mechanisms underlying sanguinarine' s growth-promoting effects in livestock remain unclear, most studies suggest they may be related to improved intestinal health. However, research on sanguinarine’ s effects on intestinal morphology and immune function in weaned piglets has not been reported. Therefore, this experiment investigated the effects of dietary sanguinarine supplementation on growth performance, intestinal morphology, and small intestinal mucosal immune function in weaned piglets, aiming to provide theoretical basis and reference for developing safe, efficient, and antibiotic-free diets.

1.1 Experimental Materials

Sanguinarine preparation: Sanguinarine concentration of 1.5%, provided by Hunan Micolt Bioresource Co., Ltd. Chlortetracycline content of 15%, commercially available product.

1.2 Experimental Animals and Design

Thirty-six healthy “Duroc × Landrace × Yorkshire” crossbred weaned piglets (23 days old, average weight (6.55±0.18) kg) were randomly divided into three groups according to similar body weight and equal gender ratio. The groups were fed a basal diet (control group), basal diet + 75 mg/kg chlortetracycline (antibiotic group), or basal diet + 50 mg/kg sanguinarine (sanguinarine group). Each group had 12 replicates with one pig per replicate, and the experimental period lasted 21 days.

1.3 Experimental Diets and Management

The basal diet was formulated according to NRC (2012) standards, with composition and nutrient levels shown in Table 1 . The experiment was conducted in the animal housing facility at the Institute of Subtropical Agriculture, Chinese Academy of Sciences. Piglets were housed individually in stainless steel cages and fed three times daily at 07:30, 12:00, and 18:30 with free access to feed and water. Mash feeding was employed with the principle of no leftover feed in troughs. Daily feed intake was accurately recorded for each piglet, and health status was monitored throughout the experiment. Routine disinfection and cleaning procedures were followed, and the pig house was maintained ventilated and clean.

Table 1 Composition and nutrient levels of the basal diet (as-fed basis)

Items	Content
Ingredients	
Corn grain	
Soybean meal	
Full-fat soybean powder	
Fish meal	
Whey powder	
Soybean oil	

Items	Content
L-Lys (98%)	
DL-Met	
CaHPO	
Limestone	
NaCl	
Premix[1]	
Total	
Nutrient levels[2]	
DE (MJ/kg)	
Crude protein CP	
Lysine Lys	
Methionine Met	
Methionine + Cysteine Met+Cys	
Threonine Thr	
Tryptophan Trp	
Available phosphorus AP	

[1]The premix provided the following per kg of diet: VA 10,800 IU, VD 4,000 IU, VE 40 IU, VK 3.4 mg, VB 1.6 mg, VB 12 mg, VB 6 mg, VB   0.05 mg, biotin 0.2 mg, folic acid 2 mg, niacin 50 mg, D-calcium pantothenate 25 mg, Fe 80 mg, Cu 100 mg, Mn 50 mg, Zn 90 mg, Co 1 mg, Se 0.17 mg, I 0.15 mg.
[2]Nutrient levels were calculated values.

1.4 Sample Collection

At the end of the experiment, after 12 hours of fasting, all pigs were intravenously anesthetized with 150.00 mg/kg pentobarbital sodium and slaughtered following conventional procedures. Small intestine segments (duodenum at ~10 cm from pylorus, jejunum at mid-section, and ileum at ~5 cm from ileocecal junction) were collected (2.5 cm each) and fixed in 10% neutral formalin for paraffin sectioning and hematoxylin-eosin (HE) staining to examine intestinal morphology. The remaining portions of each segment were gently opened (approximately 10 cm), rinsed with sterile phosphate-buffered saline (PBS), and dried with filter paper. Intestinal mucosa was scraped with glass slides, wrapped in aluminum foil, snap-frozen in liquid nitrogen, and stored at -80°C for subsequent analysis.

1.5.1 Growth Performance

Initial body weight was recorded on the morning of day 1 after overnight fasting. Final body weight was measured at the end of the feeding trial to calculate average daily gain (ADG). Daily feed allowance and refusals were recorded to determine average daily feed intake (ADFI) and feed-to-gain ratio (F/G). Formulas were as follows:

ADG = (final body weight - initial body weight) / experimental days
ADFI = total feed intake / experimental days
F/G = ADFI / ADG

Fecal consistency was observed daily at 08:00 to record diarrhea incidence and duration. Diarrhea rate was calculated as:

Diarrhea rate (%) = 100 × [(number of diarrheic pigs × diarrhea days) / (total pigs × experimental days)]

1.5.2 Intestinal Morphology

Fixed intestinal tissues were dehydrated, paraffin-embedded, sectioned, and HE-stained. Villus height and crypt depth in duodenum, jejunum, and ileum were measured using Motic Images Advanced 3.2 software. Ten fields per slice were observed, and villus height-to-crypt depth ratio (V/C) was calculated.

1.5.3 Small Intestinal Mucosal Immunoglobulin Content

Following the method of Wang et al., duodenal, jejunal, and ileal mucosa were dissolved in 2 mL PBS (pH 7.4) and centrifuged at 3,500 × g for 5 minutes to collect supernatant. Immunoglobulin G (IgG), immunoglobulin A (IgA), and IgM contents were determined using porcine enzyme-linked immunosorbent assay (ELISA) kits according to the manufacturer’ s instructions (Nanjing Senbeijia Biological Technology Co., Ltd.).

1.6 Statistical Analysis

Data were preliminarily processed using Excel 2013 and analyzed with SPSS 20.0 software. Duncan’ s multiple comparison test was used for significance testing. Diarrhea rate was analyzed using non-parametric Kruskal-Wallis test. Results were expressed as mean ± standard error. $P<0.01$ was considered extremely significant, $P<0.05$ significant, and 0.05 $P<0.10$ indicative of a trend.

2.1 Effects of Sanguinarine on Growth Performance of Weaned Piglets

As shown in Table 2 , compared with the control group, ADG and ADFI were significantly increased ($P<0.05$), while F/G and diarrhea rate were significantly decreased ($P<0.05$) in both sanguinarine and antibiotic groups. No significant differences were observed between sanguinarine and antibiotic groups for these growth performance parameters ($P>0.05$). These results indicate that dietary sanguinarine supplementation can improve growth performance in weaned piglets with efficacy comparable to antibiotics.

Table 2 Effects of sanguinarine on growth performance of weaned piglets

Items	Control group	Antibiotic group	Sanguinarine group	P-value
Initial weight (kg)	6.56±0.16	6.55±0.11	6.57±0.13	
Final weight (kg)	11.89±0.33	12.41±0.26	13.03±0.47	
ADG (g)	254.52±14.67	294.28±3.29	307.62±15.33	
ADFI (g)	465.16±13.47	486.55±14.31	501.29±17.32	
F/G	1.82±0.13	1.65±0.11	1.62±0.09	
Diarrhea rate (%)	3.57±0.89	1.06±0.18	1.11±0.17	

In the same row, values with no letter or the same small letter superscripts indicate no significant difference (P>0.05), different small letters indicate significant difference (P<0.05), and different capital letters indicate extremely significant difference (P<0.01). The same applies below.

2.2 Effects of Sanguinarine on Small Intestinal Morphology of Weaned Piglets

As shown in Figure 1 [Figure 1: see original paper] and Table 3 , compared with the control group, villus height and V/C ratio in duodenum and jejunum were significantly increased in both sanguinarine and antibiotic groups (P<0.05 or P<0.01), with no significant differences between these two groups (P>0.05). However, ileal villus height and V/C ratio in the sanguinarine group were significantly higher than in the other two groups (P<0.05). These findings suggest that dietary sanguinarine supplementation can increase intestinal mucosal surface area, thereby enhancing nutrient absorption efficiency.

Figure 1 Detection of small intestine morphology of weaned piglets (100×)

Table 3 Effects of sanguinarine on small intestinal morphology of weaned piglets

Items	Control group	Antibiotic group	Sanguinarine group	P-value
Villus height (m)				
Duodenum	509.31±13.49	554.27±31.21	562.48±30.20	
Jejunum	500.83±18.78	539.94±24.45	543.87±11.94	
Ileum	499.16±16.85	515.39±33.74	589.56±19.68	

Items	Control group	Antibiotic group	Sanguinarine group	P-value
Crypt depth (m)				
Duodenum	307.55±16.33	305.87±18.68	300.21±25.57	
Jejunum	296.37±18.41	287.49±17.56	280.43±13.99	
Ileum	271.58±19.27	270.33±10.26	257.59±28.12	
Villus height/Crypt depth (V/C)				
Duodenum	1.66±0.09	1.81±0.11	1.88±0.05	
Jejunum	1.69±0.04	1.96±0.12	2.08±0.11	
Ileum	1.78±0.07	1.89±0.18	2.11±0.11	

2.3 Effects of Sanguinarine on Immunoglobulin Content in Small Intestinal Mucosa of Weaned Piglets

As shown in Table 4 , compared with the control group, duodenal IgA and IgM contents were significantly ($P<0.05$) and extremely significantly ($P<0.01$) increased, respectively, in both sanguinarine and antibiotic groups. Jejunal IgA and IgG contents were significantly elevated ($P<0.05$), while ileal IgG and IgM contents were significantly increased ($P<0.05$) and IgA content was extremely significantly elevated ($P<0.01$). No significant differences were observed between sanguinarine and antibiotic groups for these parameters ($P>0.05$). These results indicate that dietary sanguinarine supplementation can enhance intestinal immunity in weaned piglets.

Table 4 Effects of sanguinarine on immunoglobulin contents in small intestinal mucosa of weaned piglets

Items	Control group	Antibiotic group	Sanguinarine group	P-value
IgA				
Duodenum	1.87±0.13	2.11±0.09	2.15±0.12	
Jejunum	1.74±0.08	2.18±0.10	2.49±0.18	
Ileum	1.62±0.16	2.00±0.09	2.36±0.12	
IgG				
Duodenum	1.28±0.11	1.44±0.09	1.17±0.11	
Jejunum	1.97±0.13	1.62±0.12	1.54±0.16	
Ileum	2.16±0.11	2.37±0.21	2.65±0.32	
IgM				
Duodenum	1.93±0.21	1.60±0.15	1.59±0.22	
Jejunum	2.11±0.09	2.27±0.18	2.29±0.13	
Ileum	2.16±0.11	2.37±0.21	2.48±0.24	

3 Discussion

Sanguinarine is a novel plant-derived alkaloid with potential as a feed additive, primarily developed as an antibiotic alternative in animal nutrition. Long-term, large-scale antibiotic use causes enhanced pathogen resistance, disruption of normal gut microbiota structure, and drug residues, posing potential threats to human health. Safety assessment studies in rats demonstrated that high-dose, long-term (90 days) feeding of sanguinarine and its derivatives caused no tissue damage, with no parent compound or metabolites retained in the body. Numerous studies have reported significant growth-promoting and diarrhea-reducing effects of sanguinarine in livestock and poultry. Rao et al. found that dietary sanguinarine significantly increased ADG and ADFI while reducing diarrhea rate and alleviating weaning stress in piglets, with no significant differences compared to chlortetracycline supplementation. Dai Bo similarly reported that sanguinarine reduced diarrhea rate in weaned piglets. Kantas et al. demonstrated that 50 mg/kg dietary sanguinarine increased body weight and ADG in weaned piglets. Vieira et al. reported improved growth performance in turkeys fed 50 mg/kg sanguinarine. The present study found that 50 mg/kg dietary sanguinarine significantly improved ADG and ADFI, reduced diarrhea rate, and achieved effects comparable to antibiotics, consistent with previous research. The growth-promoting mechanisms may involve: 1) Sanguinarine' s structural similarity to tryptophan, allowing it to inhibit aromatic amino acid decarboxylase activity, reduce aromatic amino acid degradation, and improve utilization efficiency of tryptophan and phenylalanine in the small intestine, thereby increasing protein deposition; 2) Its antioxidant function reducing muscle antioxidant response and oxidative stress; and 3) Increased relative length of jejunum and ileum and altered intestinal morphology, promoting efficient nutrient absorption and diet digestibility.

The small intestine serves as the primary site for digestion and absorption in animals and is a key indicator of digestive function. The integrity of small intestinal mucosal morphology is crucial for ensuring digestive and absorptive capacity. Villus height, villus width, crypt depth, and V/C ratio are the most direct indicators of small intestinal mucosal structure and functional integrity. Greater villus height increases absorptive surface area; deeper crypts and wider villi reduce digestive function; higher V/C ratios indicate stronger digestive capacity. Lee et al. reported that dietary sanguinarine increased relative length of jejunum and ileum in broilers. He Xi et al. demonstrated that *Macleaya cordata* alkaloids significantly increased V/C ratio in yellow-feathered broilers. The present results showed that sanguinarine significantly increased villus height and V/C ratio while tending to reduce jejunal crypt depth, consistent with its growth-promoting effects. This indicates that sanguinarine improves intestinal mucosal morphology development, enhancing nutrient digestion and absorption capacity, thereby improving growth performance. Li et al. reported that sanguinarine at 0.00625–0.1 g/mL significantly promoted proliferation of porcine intestinal epithelial cells (IPEC-1), suggesting that sanguinarine may enhance intestinal digestion, absorption, immune barrier function, and stress response by promoting intestinal cell proliferation and differentiation. Additionally, sanguinarine' s beneficial effects on intestinal morphology may relate to its antimicrobial activity, which inhibits pathogen colonization (e.g., *E. coli*) and increases *Lactobacillus* populations, thereby protecting intestinal mucosa. In this study, no significant differences were observed between sanguinarine and antibiotics regarding intestinal development. While antibiotics effectively inhibit pathogen proliferation, they disrupt gastrointestinal microbiota structure. Sanguinarine protects intestinal microbiota structure by competitively inhibiting harmful pathogens, which may partially explain its diarrhea-reducing effects. Further research is needed to investigate sanguinarine's effects on gut microbiota structure and intestinal development in weaned piglets.

Animal studies have demonstrated that *Macleaya cordata* possesses immunoenhancing properties, increasing serum albumin/globulin ratio and stimulating T and B lymphocyte functions. As the main active component, sanguinarine has been incorporated into feed by Chinese veterinary companies as an immune enhancer. Man Yi et al. reported that dietary *Macleaya cordata* extract increased serum IgG content, improved immune function, enhanced disease resistance, and improved growth performance in weaned piglets, with superior effects compared to oxytetracycline. The present results showed that dietary sanguinarine significantly increased small intestinal mucosal IgA, IgG, and IgM contents, achieving effects comparable to antibiotics, consistent with reports by Yun Long and He Xiayang.

4 Conclusion

Dietary sanguinarine supplementation improves intestinal mucosal morphology and enhances small intestinal mucosal immune function, thereby improving growth performance in weaned piglets with efficacy comparable to antibiotics. These results suggest that sanguinarine can effectively alleviate weaning stress and may be used to reduce or replace antibiotics in weaned piglet diets.

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Note: Figure translations are in progress. See original paper for figures.