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Mesobiliverdin IXα-enriched microalgae feed improves gut health in weaned piglets under LPS challenge

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Abstract: This study aimed to evaluate the effect of mesobiliverdin IXα-enriched microalgae (MBV-SP) on growth, diarrhoea prevalence, intestinal morphology, antioxidant capacity, and inflammatory cytokines in lipopolysaccharide (LPS)-induced enteritis in weaned piglets. Seventy-two 28-day-old piglets were randomly divided into four groups: control (NC), LPS, tylosin, and MBV-SP, with saline/LPS (100 μg/kg) administered intraperitoneally on day 14. Results showed reduced mortality and diarrhoea rates in the tylosin + LPS and MBV-SP + LPS groups compared to the LPS group. Histological analysis revealed improved villus morphology and decreased crypt depth in the MBV-SP group. Catalase activity was notably higher in the MBV-SP group. Both tylosin and MBV-SP supplementation reduced pro-inflammatory cytokines, with MBV-SP exhibiting a more pronounced effect. In conclusion, MBV-SP mitigated diarrhoea, improved antioxidant capacity, and modulated inflammatory cytokines in weaned piglets with LPS-induced enteritis, highlighting its potential as a dietary supplement for the gut health in piglets.

Keywords: lipopolysaccharide; mesobiliverdin IXα; microalgae; weaned piglets

Weaning is widely recognised as one of the most stressful stages in the pig industry. Several factors can contribute to the urgency of weaning, including changes in diet and exposure to environmental challenges. Weaned piglets face several challenges, such as an immature gastrointestinal tract, limited gastric acid secretion, poor enzyme activity, and reduced digestibility of carbohydrates and proteins in grain-based feeds (Miller et al. 1994). Furthermore, weaning stress can trigger the proliferation of pathogenic bacteria in the intestine and disrupt the beneficial microbial flora, leading to diarrhoea in piglets (Gresse et al. 2017). Enterotoxigenic *E. coli* is a critical factor that can colonise the intestines during diarrhoea and contribute to the high mortality rate of piglets (Gresse et al. 2017; Rhouma et al. 2017). Notably, the lipopolysaccharides (LPS) present in gram-negative bac-

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teria can bind to toll-like receptor 4 (TLR4) on the cell membrane, leading to the secretion of pro-inflammatory cytokines, such as interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumour necrosis factor-α (TNF-α). This process can disrupt tight junction proteins and increase intestinal permeability, thereby triggering intestinal inflammation (Drewe et al. 2001; Al-Sadi et al. 2009).

Mesobiliverdin IXα (MBV) occurs naturally in mammals and it is a structural analogue of anti-inflammatory biliverdin IXα (Ito et al. 2013; Takemoto et al. 2019). Both compounds are antioxidants. MBV can be generated in cell extracts of microalgae spirulina to give an MBV-enriched extract called MBV-SP (Chang et al. 2021; Liao et al. 2023). Providing broilers with feed containing 0.05% or 0.1% MBV-SP resulted in reduced levels of IL-6 and IL-1β pro-inflammatory cytokines in serum (Chang et al. 2021). Also, MBV-SP promotes intestinal villi and regulates intestinal microbiota with superior effects compared to spirulina in feed without MBV indicating that MBV-SP can promote chicken gut health and regulate gut flora (Chang et al. 2021). In addition, our previous study showed that feeding 0.5% MBV-SP decreased the level of IL-6 and TNF-α in intestinal tissues of weaned piglets to a greater extent than in the control group. MBV-SP may replace the antibiotics used in weanling piglets (Liao et al. 2023). The purpose of this study is to simulate inflammatory stress of weaned piglets with LPS challenge and to simultaneously add MBV-SP to the diet in order to investigate the abilities of MBV-SP to alleviate intestinal inflammation, diarrhoea, and mortality in a piglet enteritis model and to promote piglet gut health.

MATERIAL AND METHODS

Animal, feed and dietary treatments

The animal study was carried out on the farm of Ilan University in Wujie Township, Yilan County, Taiwan (24°40'11.8''N, 121°49'58.6''E). A total of seventy-two 28-day-old weaned piglets were randomly allocated to four groups, with 3 replicate pens and 6 piglets per pen. The groups were: 1) control group (NC), given a basal diet with saline challenge, 2) LPS group, given a basal diet with LPS challenge; 3) tylosin group, given a basal diet + 0.1% tylosin, and 4) MVP-SP group, given a basal diet + 1% MBV-SP. The saline and LPS challenges were administered by intraperitoneal injection (100 μg/kg body weight) on day 14, and intestinal sections were sampled following the blood collection on day 21. Basal diet was an isonitrogenous and isocaloric corn-soybean meal-based diet, formulated to meet the nutritional requirements of piglets (Table 1). Electric incandescent lights were used to maintain a warm temperature for the piglets. The basal diet composition is presented in Table 1. The diets were provided in mash form and given *ad libitum*, and the piglets had free access to tap water. MBV-SP was prepared according to methods previously described by Chang et al. (2021). The LPS used in this study was *Escherichia*

Table 1. The feed composition of animal experiment

Ingredients	% as fed basis
Corn meal	62.10
Soybean (CP 43%)	23.00
Fish meal (CP 60%)	3.50
Dried whey	5.00
Soybean oil	3.50
L-Lysin	0.45
DL-Methionine	0.10
Threonine	0.15
Tryptophan	0.10
$CaCO_3$	1.10
$CaHPO_4$	0.40
Choline-chloride 50%	0.12
Salt	0.30
Mineral premix[1]	0.10
Vitamin premix[2]	0.10
Total	100.00
Nutrient composition	
Crude protein	19.10
Crude fat	6.90
Crude fibre	3.60
Calcium	8.00
Phosphorus	6.60
Lysine	14.50
Methionine + cystine	6.50
ME (MJ/kg)	17.10

[1]Supplied per kg of diet: Cu, 20 mg; Fe, 140 mg; Zn, 100 mg; Mn, 100 mg; I, 0.2 mg; Mn, 4 mg; Se, 0.1 mg

[2]Supplied per kg of diet: Vit A, 6 000 IU; Vit D_3, 900 IU; Vit E, 30 IU; Vit K_3 3 mg; Vit B_2 6 mg; Vit B_6, 18 mg; Vit B_{12}, 30 μg; niacin, 60 mg; pantothenic acid, 18 mg

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coli serotype O55:B5 obtained from Sigma-Aldrich (St. Louis, MO, USA). The average body weight, average daily gain, average daily feed intake, and feed efficiency (total weight gain/total feed intake) were calculated from days 1 to 21. Diarrhoea scoring was conducted by observing the faecal consistency in each pen every morning, recording the occurrence of watery stools and diarrhoea, and calculating the diarrhoea rate. The formula used for calculating the diarrhoea rate was: number of diarrhoea events/days/number of pigs) × 100.

At the end of the experiment, the pigs were humanely euthanised with an anaesthetic and stunned with electricity. All research procedures were approved by the Ilan University Institutional Animal Care and Use Committee (IACUC Approval No. 110-1) prior to the start of data collection.

Histological examination

On day 21, intestinal samples from 2 piglets per replicate were freshly collected. Three replicates (6 pigs per treatment, n = 6) were used for histological examination. Intestinal proximal segment samples (approximately 2 cm in length) of the jejunum and ileum were excised and flushed with PBS to remove the residues. The intestinal samples were fixed in a 10% neutral formalin solution for histopathological examination. Tissues were embedded in paraffin wax blocks, sectioned at 5 μm thickness and stained with haematoxylin and eosin. The villus height was examined in six samples per group and each sample was photographed in four different fields randomly.

Catalase (CAT) and cytokine assays

At the end of experiments, serum samples from 2 piglets per replicate (6 pigs/treatment, n = 6) were collected from the jugular vein and separated by centrifugation at 2 500 × g for 20 minutes. The sera from different groups were used to measure antioxidant-related CAT enzyme activities using a commercial CAT assay kit (Cat. No. 707002; Cayman, Ann Arbor, MI, USA) and the manufacturer's assay procedure.

Pro-inflammatory intestinal tissue cytokines, IL-6 and tumour necrosis factor-alpha (TNF-α), were measured using commercial immunoassay kits (DY686 and DY690B, respectively, from R&D Systems, Minneapolis, MN, USA) using an ELISA microplate reader (Epoch2; BioTek Instrument, Inc., Winoosky, VT, USA).

Statistical analysis

The Kolmogorov-Smirnov test was used to test the normal distribution of the data before statistical analysis was performed. Statistical analyses were performed using the GraphPad software (v5.0). The collected data were tested by Student's t-test or by means of one-way ANOVA which is defined as follows (SST = sum of square total):

$$SST = \sum_{i=1}^{k}\sum_{j=1}^{n_i}\left(X_{ij} - \bar{X}_{overall}\right)^2 \quad (1)$$

where:

X_{ij} – the value of the j^{th} observation in the i^{th} group;

k – the number of replicates;

$\bar{X}_{overall}$ – the average of all observations;

n_i – the counts of observations in the i^{th} group.

The mean differences were compared using Tukey's multiple comparison test. Significance was declared at $P \leq 0.05$.

RESULTS

Growth performance and diarrhoea rates

The effects of MBV-SP on the growth performance of weaned piglets with LPS-induced enteritis are presented in Table 2. The growth performance results were divided into two periods: pre-trial period (days 1–14, before LPS injection) and post-trial period (days 14–21, after LPS injection). During the pre-trial period, the tylosin group had significantly higher body weight, average daily gain, and feed efficiency compared to the control group (NC) ($P < 0.05$). The MBV-SP group showed no significant difference in growth performance compared to the tylosin and NC groups. During the post-trial period, there were no significant differences in body weight, average daily gain, feed intake, and feed efficiency between the groups.

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Table 2. Growth performance of weaned piglets

Items	NC	LPS	Tylosin	MBV-SP	SEM	*P*-value
0–14 days, before LPS challenge						
BW at day 0 (kg)	7.47	7.49	7.49	7.50	0.01	0.448
BW at day 14 (kg)	9.74^{b}	10.3^{ab}	10.8^{a}	10.5^{ab}	0.22	0.052
ADG (g/d)	162^{b}	198^{ab}	235^{a}	214^{ab}	15.0	0.061
ADFI (g/d)	363	356	419	405	17.0	0.096
G : F	0.44^{b}	0.53^{ab}	0.56^{a}	0.53^{b}	0.02	0.019
14–21 days, after LPS challenge						
BW at day 21 (kg)	12.0	11.8	13.2	11.9	0.53	0.263
ADG (g/d)	327	220	353	201	62.0	0.292
ADFI (g/d)	473	412	493	413	53.0	0.627
G : F	0.69	0.53	0.71	0.47	0.10	0.290
Mortality rate (%)	0.00	22.0	5.00	5.00	–	0.185[1]

[1]*P*-value = effect of dietary treatment

Different letters indicate significantly different ($P < 0.05$) values by Tukey's test at the same sampling interval; Statistical analysis was conducted by χ2-test on mortality rate

ADFI = average daily feed intake (kg/pig/day); ADG = average daily gain (kg/pig/day); BW = body weight (kg); G : F = feed conversion ratio; LPS = LPS-challenged piglets fed basal diet; MBV-SP = LPS-challenged piglets fed basal diet plus 1% MBV-enriched microalgae; NC = non-challenged piglets fed basal diet; SEM = standard error of the means; Tylosin = LPS-challenged piglets fed basal diet plus 0.1% tylosin

Furthermore, within one day after LPS injection, the mortality rate was 22% in the LPS group, and 5% in the tylosin and MBV-SP groups.

For the result of diarrhoea scoring (Figure 1), in the pre-LPS period, the diarrhoea rates of the tylosin group and MBV-SP group decreased by approximately 8% and 11%, respectively, compared to the LPS group ($P < 0.1$ for the tylosin group, $P < 0.05$ for the MBV-SP group). In the post-LPS period, the diarrhoea rates of the tylosin group and MBV-SP group decreased by approximately 17% and 10%, respectively, compared to the LPS group ($P < 0.05$ for the MBV-SP group, $P < 0.01$ for the tylosin group).

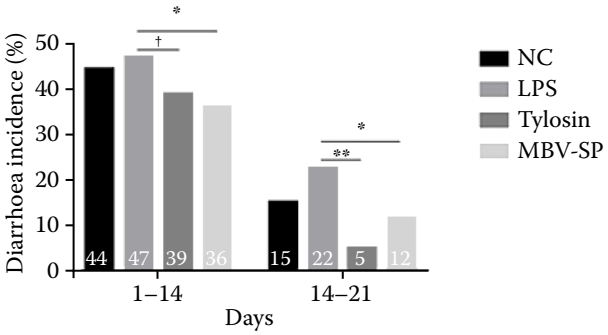

Figure 1. Effects of dietary supplementation of MBV-SP on diarrhoea incidence in weaned piglets

Incidence on day 1 to day 14 was calculated by treatment of 18 piglets; incidence on day 14 to day 21 was calculated by treatment of 14–18 piglets. Diarrhoea incidence (%) = (number of diarrhoeas recorded)/(number of pigs by treatment × total experimental days) × 100, where the number of diarrhoeas recorded was the sum of the numbers of pigs with diarrhoea observed each day for the experimental period. Statistical analysis was conducted by χ^2-test on diarrhoea incidences

$^{\dagger}P < 0.1$; $^{*}P < 0.05$; $^{**}P < 0.01$

LPS = LPS-challenged piglets fed basal diet; MBV-SP = LPS-challenged piglets fed basal diet plus 1% MBV-SP; NC = non-challenged piglets fed basal diet; Tylosin = LPS-challenged piglets fed basal diet plus 0.1% tylosin

Histological changes in the jejunum and ileum

The effects of tylosin and MBV-SP on the intestinal morphology of piglets challenged with LPS were investigated. Jejunal and ileal tissues from weaned piglets were examined for haematoxylin-eosin staining (Figure 2) to evaluate villus height, crypt depth, and the ratio of villus height to crypt depth. The results show no significant differences

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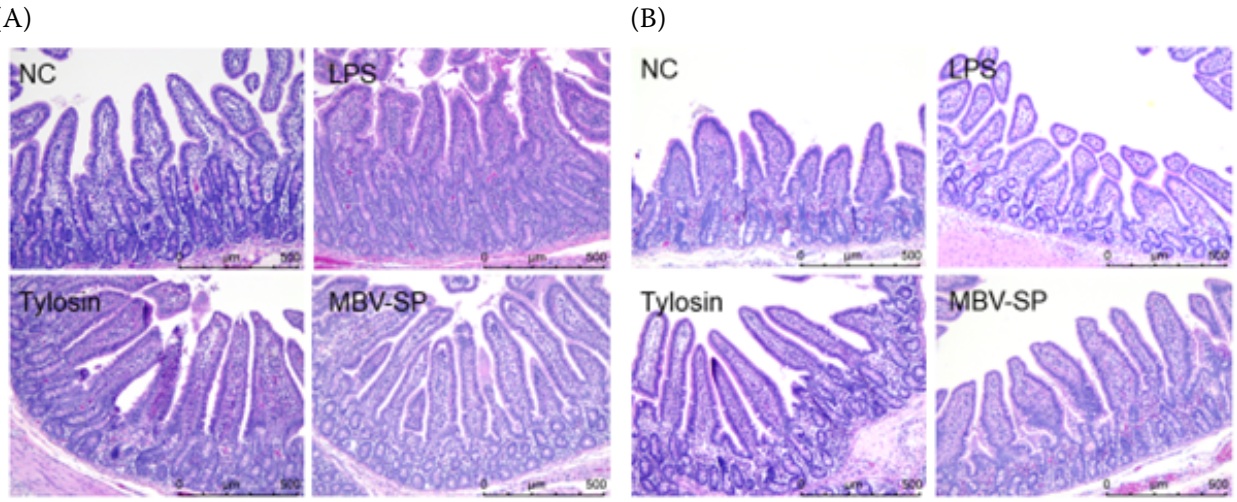

Figure 2. (A) H&E staining of the jejunum in LPS-challenged piglets; (B) H&E staining of the ileum in LPS-challenged piglets. The bar designates a length of 500 μm (X100)
LPS = LPS-challenged piglets fed basal diet; MBV-SP = LPS-challenged piglets fed basal diet plus 1% MBV-SP; NC = non-challenged piglets fed basal diet; Tylosin = LPS-challenged piglets fed basal diet plus 0.1% tylosin

Table 3. Effects of supplemental MBV-SP on the intestinal morphology of LPS-challenged piglets

Items	NC	LPS	Tylosin	MBV-SP	SEM	*P*-value
Jejunum						
VH (μm)	486	426	477	464	26.3	0.405
CD (μm)	229	255	222	216	13.3	0.193
VH : CD	2.19*	1.66	2.21*	2.22*	0.13	0.025
Ileum						
VH μm	429	404	485*	492*	20.6	0.017
CD μm	215	220	209	183†	9.80	0.069
VH : CD	2.06	1.92	2.42*	2.70**	0.11	0.003

†$P < 0.1$; *$P < 0.05$; **$P < 0.01$ compared to LPS group; Data are expressed as the mean ± SEM ($n = 6$)
CD = crypt depth; LPS = LPS-challenged piglets fed basal diet; MBV-SP = LPS-challenged piglets fed basal diet plus 1% MBV-SP; NC = non-challenged piglets fed basal diet; Tylosin = LPS-challenged piglets fed basal diet plus 0.1% tylosin; VH = villus height; VH : CD = villus height to crypt depth ratio

in villus height and crypt depth between the treatment groups in the jejunum (Table 3). However, compared to the LPS group, the NC, tylosin, and MBV-SP groups had significantly higher ratios of villus height to crypt depth ($P < 0.05$). In the ileum, the tylosin and MBV-SP groups had significantly higher villus heights compared to the LPS group ($P < 0.05$), and the MBV-SP group had significantly lower crypt depth compared to the LPS group ($P < 0.1$).

In addition, compared to the LPS group, both the tylosin group and the MBV-SP group had significantly higher ratios of villus height to crypt depth ($P < 0.05$; $P < 0.01$).

Serum CAT activities and intestinal inflammatory cytokine levels

Serum CAT antioxidant enzyme activity was significantly higher in the MBV-SP group compared to the LPS group ($P < 0.01$) (Figure 3A). LPS challenge significantly increased the intestinal concentrations of pro-inflammatory cytokines TNF-α and IL-6. Tylosin supplemental feeding decreased the concentrations of TNF-α and IL-6 ($P < 0.05$), which were even more pronounced with MBV-SP supplemental feeding ($P < 0.01$) (Figure 3B,C). This phenomenon was not observed in the duodenum and jejunum (data not shown).

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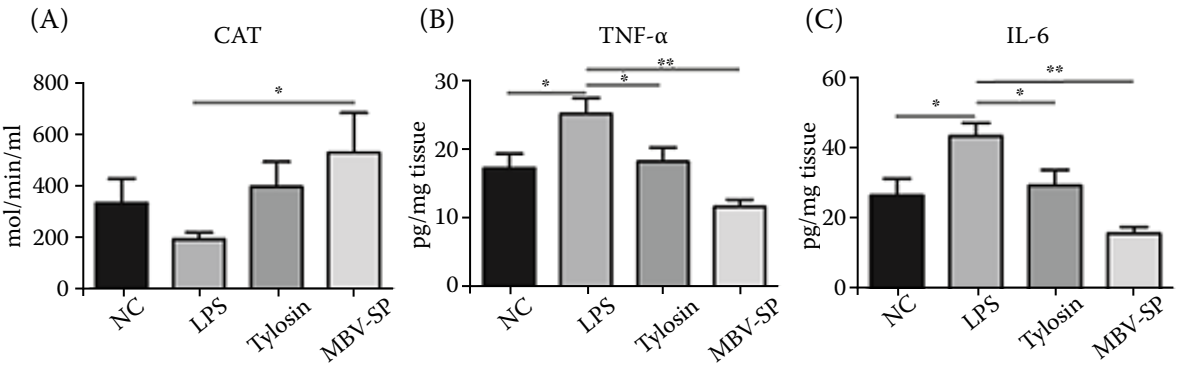

Figure 3. Effects of MBV-SP on antioxidant enzyme activity in serum plasma and pro-inflammatory cytokines in the jejunum of weaned pigs

(A) CAT (catalase) in plasma; (B) TNF-α (tumour necrosis factor α); (C) IL-6 (interleukin-6) in the intestinal tissue of weaned piglets

*P < 0.05; **P < 0.01 compared to LPS group; Data are expressed as the mean ± SEM (n = 6)

LPS = LPS-challenged piglets fed basal diet; MBV-SP = LPS-challenged piglets fed basal diet plus 1% MBV-SP; NC = non-challenged piglets fed basal diet; Tylosin = LPS-challenged piglets fed basal diet plus 0.1% tylosin

DISCUSSION

LPS administration to piglets (LPS group) resulted in sepsis with 22% mortality. In combination with the consumption of feed containing tylosin or MBV-SP, mortality decreased to 5%. In sepsis, LPS binds to TLR4 on cell membranes triggering the secretion of pro-inflammatory cytokines such as IL-6 and TNF-α. Excessive release of inflammatory cytokines like IL-1β and TNF-α leads to organ dysfunction and death (Merx and Weber 2007). In the study by Chang et al. (2021), feeding broilers with MBV-SP was found to reduce the concentrations of IL-6 and IL-1β in the plasma. It is therefore speculated that diets with MBV-SP may reduce the excessive release of pro-inflammatory cytokines into the circulatory system, thereby reducing the occurrence of sepsis and mortality. Consistently with the results of our study, previous studies on LPS-induced sepsis in pigs have shown that the intraperitoneal injection of 100 μg/kg LPS three to four times within a week can lead to reduced feed intake and growth retardation (He et al. 2017; Fan et al. 2019).

Post-weaning diarrhoea is a common condition that affects piglets due to various factors, such as diet and environmental stressors. This condition can be categorised as nutritional or bacterial diarrhoea, and it has been reported that up to 17% of piglets in Europe die due to diarrhoea (Lalles et al. 2007). The immature digestive system of piglets may result in insufficient acid secretion and enzyme activity, making it difficult to digest carbohydrates and proteins in feed and causing feed antigens in soybean meal to cause villous atrophy and enzyme secretion insufficiency (Miller et al. 1994). Furthermore, during the first week post-weaning, nutritional diarrhoea is more likely to occur due to factors such as long-distance transportation, exposure to a new environment, and changes in temperature and humidity. In this study, the results showed that both the tylosin group and the MBV-SP group had a significant effect in reducing the incidence of diarrhoea compared to the LPS group. Although the symptoms of nutritional diarrhoea tend to alleviate within a week as the piglet immunity improves, it may progress into bacterial diarrhoea if the environment is humid and unhygienic, allowing for the proliferation of enterotoxigenic *E. coli* and the production of toxins in the small intestine, resulting in dehydration and electrolyte imbalance (Gresse et al. 2017). Furbeyre et al. (2017) did not observe any improvement in diarrhoea with 1% spirulina in the piglet diet. In a subsequent study, feeding 385 mg/kg of spirulina by gavage significantly improved diarrhoea symptoms (Furbeyre et al. 2018). The authors explained that they improved the preparation of spirulina by avoiding a heat treatment that may affect bioactive substances. Subsequent studies did not confirm the efficacy of spirulina in alleviating diarrhoea (Furbeyre et al. 2018). The present study is the first to demonstrate that adding MBV-SP to the conservation piglet diet not only improves

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nutritional diarrhoea but also reduces the symptoms of diarrhoea.

The present study demonstrates that MBV-SP significantly enhances the activity of CAT, an antioxidant enzyme, in pigs, which in turn promotes pig growth and improves feed efficiency (Li et al. 2020). In addition, Takemoto et al. (2019) reported that MBV can inhibit *in vitro* lipid peroxidation and exhibits antioxidant activity similar to biliverdin IXα. The present study is the first research to report that MBV-SP enhances pig antioxidant capacity through its active component – MBV. Moreover, MBV, which has a similar structure to biliverdin IXα, can serve as substrate for biliverdin reductase activity. Therefore, MBV has the potential to regulate the downstream PI3K/AKt pathway upon binding to biliverdin reductase and consequently increase the expression of the anti-inflammatory cytokine IL-10 and decrease the expression of pro-inflammatory cytokines such as IL-1, IL-6, and TNF-α (Li et al. 2020). MBV-SP may regulate the nuclear factor and protein kinase in intestinal cells to reduce the expression of pro-inflammatory cytokines and alleviate the symptoms of diarrhoea in pigs during weaning. However, the exact mechanism of MBV anti-inflammatory pathway needs further verification in subsequent experiments. Among the indicators of the intestinal absorption capacity are the height, width, and surface area of the villi. Longer villi with larger surface areas indicate a greater capacity for nutrient absorption, while deeper crypts and increased cell division suggest the continuous tissue renewal and the generation of new villi (Pluske et al. 1997). No previous studies have investigated the effect of MBV on intestinal morphology in pigs, but Furbeyre et al. (2017) found that adding 1% spirulina to the diet of weaned piglets increased the jejunal villus length and improved the ratio of villus length to crypt depth. In addition, Chang et al. (2021) reported that adding 0.1% MBV-SP to the diet of broiler chickens improved the villus length more effectively than spirulina alone, suggesting that MBV-SP is more effective in improving the intestinal morphology. The stem cells in the crypts continually differentiate to replace old intestinal epithelial cells, thereby maintaining the integrity of the intestinal barrier and preventing the pathogen invasion. Therefore, piglets under weaning stress may use more protein and energy to renew intestinal epithelial cells, resulting in decreased energy for tissue and muscle growth. Our study demonstrates that the MBV-SP group piglets showed a significant increase in average body weight, as well as a marked improvement in the villus-to-crypt ratio and villus height, suggesting that MBV-SP may protect intestinal epithelial cells for nutrient absorption and promote pig growth by improving intestinal structure and reducing intestinal inflammation.

CONCLUSION

This study demonstrates that MBV-SP supplementation in weaned piglets with LPS-induced enteritis reduced mortality and diarrhoea rates comparably to tylosin treatment. MBV-SP improved intestinal villus morphology, decreased the crypt depth, enhanced catalase activity, and effectively reduced pro-inflammatory cytokines – with more pronounced anti-inflammatory effects than tylosin in some measures. These findings suggest MBV-SP can enhance antioxidant capacity, improve gut morphology, and modulate inflammatory responses in weaned piglets, making it a promising alternative to antibiotics for supporting the gut health in antibiotic-free pig husbandry.

Conflict of interest

The authors declare no conflict of interest.

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