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Effects of Low-Fish-Meal Diet Supplemented with Coenzyme Q10 on Growth Performance, Antioxidant Capacity, Intestinal Morphology, Immunity and Hypoxic Resistance of *Litopenaeus vannamei*

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Abstract: The aim of this study was to evaluate the effects of a low-fish-meal diet supplemented with coenzyme Q10 on the growth, antioxidant capacity, immunity, intestinal health and hypoxic resistance of *Litopenaeus vannamei*. *L.vannamei* with an initial weight of 0.66 g were fed with the experimental diets for 56 days. Diets D1 (20% FM level) and D2–D7 (15% FM level), supplemented with 0%, 0.002%, 0.004%, 0.006%, 0.008% and 0.01% coenzyme Q10 were formulated. In terms of growth performance, the weight gain and specific growth rate in the D2 diet were significantly lower than those in the D1 diet ($p < 0.05$). The final body weight, weight gain and specific growth rate in the D2–D7 diets had an upward trend, and the condition factor in the D2–D7 diets was lower than those in the D1 diet ($p < 0.05$). There were no significant differences in the crude protein and crude lipid levels in the whole body among all diet treatments ($p > 0.05$). In terms of hepatopancreas antioxidant parameters, the D5 and D6 diets significantly promoted the total antioxidant capacity and total superoxide dismutase activity, and significantly decreased the malondialdehyde content ($p < 0.05$). The expression levels of *cat*, *mnsod* and *gpx* in shrimp fed with the D5 and D6 diets were significantly higher than those of shrimp fed with the D2 diet ($p < 0.05$). In addition, the mRNA level of *ProPO* was increased in the D4 and D5 diets, and *LZM* expression was increased in the D6 diet compared with the D1 diet ($p < 0.05$). The villus height of shrimp fed with diets supplemented with coenzyme Q10 was significantly increased ($p < 0.05$), and the intestinal thickness and submucosal thickness of shrimp fed with the D6 diet were the highest ($p < 0.05$). After acute hypoxia stress, lethal dose 50 time in the D3–D7 diets was significantly increased compared with the D1 and D2 diets ($p < 0.05$), and the highest value was found in the D4 diet ($p < 0.05$). After stress, the expression levels of TLR pathway-related genes (*Toll*, *Myd88*, *Pelle*, *TRAF6* and *Dorsal)* in the D4 and D6 diets were significantly increased compared with the D2 diet. In general, *Litopenaeus vannamei* fed with the D6 diet achieved the best growth, antioxidant capacity, immunity, and intestinal morphology among all low FM diets and D4–D6 diets improved hypoxic resistance.

Keywords: white shrimp; coenzyme Q10; antioxidation property; immune response

Citation: Liu, Y.; Zhuang, Z.; Liao, Z.; Yao, R.; Chen, M.; Wei, H.; Zhao, W.; Niu, J. Effects of Low-Fish-Meal Diet Supplemented with Coenzyme Q10 on Growth Performance, Antioxidant Capacity, Intestinal Morphology, Immunity and Hypoxic Resistance of *Litopenaeus vannamei*. *Antioxidants* **2023**, *12*, 2042. https://doi.org/10.3390/antiox12122042

Academic Editor: Luca Tiano

Received: 19 September 2023
Revised: 15 November 2023
Accepted: 16 November 2023
Published: 24 November 2023

1. Introduction

Litopenaeus vannamei is one of the most important crustaceans in aquaculture. Its aquaculture industry is developing rapidly because of its adaptability to wide temperature and salt, fast growth rate, and large meat yield. In 2021, *Litopenaeus vannamei* is the largest cultured shrimp species in China, with an area of 178,043 hectares and a yield of 1,273,632 tons [1]. Fish meal (FM) is a vital ingredient in aquatic feed and the main source of animal protein [2]. Plenty

of studies have shown that *L. vannamei* has become one of the largest FM consumers [3,4]. Despite FM containing several beneficial amino acids, essential fatty acids, nucleotides, phospholipids, fats, minerals, and water-soluble vitamins, the price FM is continuously rising due to the rapid and influential expansions in the aquaculture sector [5–8]. Fluctuations in the supply, price, and quality of FM have become impending risks [9]. In recent years, there have been significant developments in research into FM replacement in aquaculture, but low-FM feed has several nutritional drawbacks [10–13], such as a worse growth performance, antioxidant capacity, immunity performance, etc. [14–16]. Sustainable alternative protein sources with lower market prices have partially or completely replaced FM for aquafeed. Nowadays, FM can be replaced by several sustainable protein sources like plant protein sources and animal protein sources [17]. But, compared with FM, these alternative protein sources have a number of disadvantages. Compared to plant protein, animal protein sources, such as meat and bone meal (MBM), blood meal (BM), insect meal, and poultry by-product meal (PBM), have the advantages of a higher protein and lipid content, a more suitable amino acid composition, and better palatability [9]. But some animal sources also have deficiencies or excesses in essential amino acids [18,19] (EAAs). The fluctuation of quality of animal protein sources depends on variability in raw material composition, processing and quality [20]. Although plant protein sources such as soybean meal (SBM), peanut meal (PM), and corn gluten meal (CGM) contain a high fiber content, they have a low protein content, a lack of one or more EAAs, low palatability and several antinutritional factors (ANFs), such as protease inhibitors, tannins, oligosaccharides and phytates, which reduce nutrient availability and digestibility of feed; however, they also have lower market prices, a large quantity in production and a stable quality, which make them suitable for FM replacement and reducing the cost of feeds [21–24]. To reduce the drawbacks, different functional additives are supplied in diets to maintain feed palatability, promote growth performance, or enhance immunity, aspects that are probably directly impacted by using FM replacement feeds [25–31].

Coenzyme Q10, also known as ubiquinone, is a hydrophobic molecule [32]. It is a naturally occurring compound whose properties are similar to vitamins (vitamin Q) [33,34]. As a cofactor in the mitochondrial electron transport chain (respiratory chain), coenzyme Q10 plays an important role in cellular bioenergetics and is critical for the production of ATP. Coenzyme Q10 acts as a mobile oxidant-reducing agent, shuttling electrons and protons in the electron transport chain. The redox function of coenzyme Q10 goes far beyond its form in mitochondria [35,36]. In addition, coenzyme Q10, as a reduced form of hydroquinone, serves as a potent antioxidant in mitochondria and lipid membranes, capable of recovering and regenerating other antioxidants, such as tocopherol and ascorbic acid [37]. Furthermore, coenzyme Q10 can also be involved in cell signaling and gene expression as a membrane stabilizer [38].

Coenzyme Q10 has been extensively studied for its strong antioxidant properties in humans and some animals [39–41]. Substantial studies show that coenzyme Q10 has enormous potential in the treatment of diseases, such as diabetes, obesity, muscular dystrophy, cancer, heart disease, oral wounds, Alzheimer's disease, Parkinson's disease, aging and other diseases [41–48]. In addition, coenzyme Q10 has been proven to have anti-inflammatory properties in vitro [49]. Coenzyme Q10 can effectively inhibit the oxidation of lipids and proteins, as well as DNA damage [50]. Due to its potential superior function in treating diseases and its advantages of easy synthesis by biological or chemical methods, coenzyme Q10 is a special material with great demand in the market. In recent years, coenzyme Q10 has attracted widespread attention as a feed additive for aquatic economic animals.

The aim of this study is to investigate the effect of supplementing coenzyme Q10 in low-fish-meal feed on the growth immunity, antioxidant status, intestinal morphology and acute hypoxic resistance of *L. vannamei*. The findings of this study will provide data support and a theoretical basis for the development of low-FM diets for *L. vannamei*.

2. Material and Methods

2.1. Ethics Approval

All experiments were conducted in accordance with the recommendations in the Guide for the Care and Use of Laboratory Animals of the National Institutes of Health (NIH). The study protocol and all experimental procedures were approved by the Institution Animal Care and Use Committee, Sun Yat-Sen University (approval code: SYSU-IACUC-2022-B0159, approval date: 4 March 2020).

2.2. Diets Design and Preparation

In this study, the shrimp were randomly divided into seven experimental groups, presented in Table 1. Among them, D1 contains 20% FM, and six other diets were prepared with 15% FM (25% of the FM replaced with corn gluten meal). Coenzyme Q10 in proportions of 0, 0.002, 0.004, 0.006, 0.008 and 0.01% were supplemented in D2, D3, D4, D5, D6, and D7 diets, respectively (0, 2, 4, 6, 8, 10 mg/kg of coenzyme Q10). The method of diet preparation was similar to that described by Liao et al. [51]. Dry ingredients were ground, weighed, combined and mixed well to homogeneity in a Hobart-type mixer (A-200T Mixer Bench Model unit, Resell Food Equipment Ltd., Ottawa, ON, Canada). Then, soy oil, fish oil and soybean lecithin were added and thoroughly mixed for 5 min. Water (40% dry ingredients mixture) was added and mixed well for 10 min. The 1.2 mm diameter pellets were extruded using a pelletizer (Institute of Chemical Engineering, South China University of Technology, Guangzhou, China), and heated in an electric oven at 80 °C for 1.5 h. All the diets were air-dried to 10% moisture and stored at −20 °C until used.

Table 1. Ingredients and proximate composition of experimental diets (% of dry matter).

Ingredients (%)	D1	D2	D3	D4	D5	D6	D7
Fish meal	20	15	15	15	15	15	15
Soybean meal	28	28	28	28	28	28	28
Peanut meal	12	12	12	12	12	12	12
Corn gluten meal	0	5	5	5	5	5	5
Wheat flour	23.85	23.25	23.248	23.246	23.244	23.242	23.24
Krill meal	2	2	2	2	2	2	2
Beer yeast	4	4	4	4	4	4	4
Fish oil	1.5	1.8	1.8	1.8	1.8	1.8	1.8
Soybean lecithin	1	1	1	1	1	1	1
Soy oil	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Vitamin premix [a]	1	1	1	1	1	1	1
Mineral premix [b]	1	1	1	1	1	1	1
Choline	0.5	0.5	0.5	0.5	0.5	0.5	0.5
$Ca(H_2PO_4)_2$	1.7	1.7	1.7	1.7	1.7	1.7	1.7
Lysine	0.29	0.53	0.53	0.53	0.53	0.53	0.53
Vitamin C	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Methionine	0.24	0.25	0.25	0.25	0.25	0.25	0.25
Threonine	0.32	0.37	0.37	0.37	0.37	0.37	0.37
Sodium alginate	1	1	1	1	1	1	1
Coenzyme Q10 [c]	0	0	0.002	0.004	0.006	0.008	0.01
Total	100	100	100	100	100	100	100
Proximate composition (%)							
Moisture	9.38	9.66	9.27	9.68	9.63	9.55	9.81
Crude protein	37.73	38.20	37.86	38.02	38.12	38.21	37.92
Crude lipid	6.96	7.24	7.02	7.12	7.32	7.18	7.07

Composition of vitamin premix (kg^{-1} of mixture): [a]: vitamin A, 250,000 IU; riboflavin, 750 mg; pyridoxine HCL, 500 mg; cyanocobalamin, 1 mg; thiamin, 500 mg; menadione, 250 mg; folic acid, 125 mg; biotin, 10 mg; a-tocopherol, 3750 mg; myo-inositol, 2500 mg; calcium pantothenate, 1250 mg; nicotinic acid, 2000 mg; vitamin D3, 45,000 IU; vitamin C, 7000 mg. [b]: Composition of mineral premix (kg^{-1} of mixture): Zn, 4000 mg; K, 22,500 mg; I, 200 mg; NaCl, 2.6 g; Cu, 500 mg; Co, 50 mg; $FeSO_4$, 200 mg; Mg, 3000 mg; Se, 10 mg. [c]: Coenzyme Q10 was provided by Zhejiang NHU Co., Ltd., Zhejiang, China.

2.3. Rearing Conditions and Sampling

An 8-week feeding experiment with *L. vannamei* was conducted in the Sanya experimental base of South China Sea Fisheries Research Institute (Sanya, China). Before the

experiment, all the shrimp were fed with commercial feed (crude protein content is 42%, crude fat content is 5%) and acclimated for 6 weeks. At the beginning of the experiment, 840 healthy shrimp with an average weight of 0.67 g ± 0.017 g were randomly distributed into 28 fiberglass tanks (400 L, 0.7 m^2 bottom, and 4 tanks per diet) at a density of 30 shrimp in each tank. All shrimp were fed to apparent satiation three times daily at 8:00, 15:00, and 22:00. During the period of the experiment, the conditions were as follows: PH: 7.7–8.2; water temperature: 29.2–30.0 °C; dissolved oxygen > 6.5 mg/L; salinity: 35‰. The normal natural light cycle was maintained throughout the experiment.

After the 8-week feeding experiment, all the shrimp were fasted for 24 h before sampling. Then, all the live shrimp in each tank were counted and weighed. A total of 5~8 shrimp in each tank were collected to analyze the proximate compositions of the whole shrimp body. The hepatopancreas of 4 shrimp were collected to measure enzyme activity and gene expression under aseptic conditions, then immediately placed in liquid nitrogen and stored at −80 °C. Two pieces of midgut tissue were obtained after dissection from 2 shrimp, which were fixed in 4% paraformaldehyde solution for 24 h, then transferred to 70% ethanol solution for fixation and stored at room temperature for subsequent HE staining section analysis.

2.4. Acute Hypoxic Stress Experiment

After sample collection, 10 shrimp were randomly selected from each tank and put into the original tank to calm down the stimulation for the subsequent acute low-dissolved-oxygen stress experiment. In the experiment, sample bags with unified specification were filled with the same amount of seawater, and the live shrimp in each tank were transferred to the corresponding sample bags and sealed. The number and time of dead shrimp in each group were recorded until half of them died, and the response time when half of them died was counted. Before the experiment, the dissolved oxygen in water was detected by the dissolved oxygen meter, and the dissolved oxygen before stress was approximately about 6 mg/L. The salinity was 35‰, and ammonia nitrogen level was not more than 0.1 mg/L.

2.5. Analysis of the Whole Body Proximate Composition

Moisture, crude lipid and crude protein in the diets were determined using standard methods (AOAC, 1995). The whole shrimp body was dried in the oven at 105 °C to constant weight. Meanwhile, moisture was determined. Crude protein was measured by the Kjeldahl method after acid digestion using an Auto Kjeldahl System (1030-Auto-analyzer; Tecator, Hoganos, Sweden). Crude lipid was determined by the ether-extraction method using a Soxtec System HT (Soxtec System HT6; Tecator, Sweden).

2.6. Intestinal Morphology Analysis

Two matching segments of midgut tissue were obtained after dissection from 2 shrimp and placed into 4% paraformaldehyde solution at room temperature for 24 h immediately, then were fixed in 70% ethanol as follows: The samples were dehydrated by a series of different graduation of ethanol and then embedded in paraffin. The paraffin-embedded blocks were cut into sections with a thickness of about 3–5 μm before being stained by using hematoxylin/eosin. The stained sections were observed and photographed with a Nikon upright microscope (Eclipse NI-E, Japan). The average intestinal villus height and submucosal thickness were randomly determined within 5 different fields and four replicates for each group.

2.7. Antioxidant Capacity Examination

About 0.6 g of the hepatopancreas tissue of *Litopenaeus vannamei* was homogenized with cold PBS (PH:7.4) according to the ratio of the sample weight: PBS volume (w:V) =1:9. Then, the homogenate was centrifuged (4000 rpm, 4 °C) for 20 min and the supernatant was used for determination. Total superoxide dismutase (T-SOD), total antioxidant capacity (T-AOC) and malondialdehyde (MDA) activities were analyzed using commercial kits

(T-SOD, A001-1-2; T-AOC, A015-3-1; Nanjing Jiancheng Bioengical Institute, Nanjing, China; MDA, S0131S; Beyotime Biotechnology Institute, Shanghai, China).

2.8. Quantitative Real-Time PCR Analysis

All gene expression levels in this study were detected using real-time quantitative PCR. Total hepatopancreas RNA was extracted using an RNAeasy™ Animal Long RNA Isolation Kit (Beyotime Biotechnology Institute, Shanghai, China) following the manufacturer's protocol. After the extraction, the concentration and quality of total RNA were determined using an ultrafine spectrophotometer Nanodrop-2000 (Thero Scientific, Waltham, MA, USA, A260: A280 nm). After this, the genomic DNA was removed by using an Evo M-MLV RT Kit with gDNA Clean for qPCR II (Accurate Biology, Changsha, China). The reaction condition was 42 °C for 2 min, and the DNA was stored at 4 °C after the reaction. Then, complementary DNA (cDNA) was synthesized using reverse transcription. The program was performed following the reaction conditions: 37 °C for 15 min, 85 °C for 5 s; it was then diluted to 200 µL with DEPC water and stored at −20 °C.

The qRT-PCR for the genes was performed on a LightCyler480 (Roche Applied Science, Basel, Switzerland). All the qRT-PCR primers for targeted genes, designed by SnapGene based on the published nucleotide sequences, are shown in Table 2. For each sample, three technical replications were run. The qRT-PCR reaction steps were as follows: 95 °C for 10 min, then 40 cycles subsequently (95 °C for 5 s, 60 °C for 30 s, 72 °C for 30 s), and finally cooled down at 4°C. Normalization of the gene expression was performed by a reference gene (β-actin), and expression levels were quantified using the $2^{-\Delta\Delta Ct}$ method.

Table 2. Primer information of quantitative real-time PCR.

Gene	Primer Sequence (5′ to 3′)	Genbank No.	Products Length
β-actin F	CTTGTGTGCGACAATGGCTC	XM_027364954.1	194
β-actin R	TCGATGGGGTACTTGAGGGT		
MnSOD F	TGTTGCACAAGCCATTGACG	XM_027381242.1	157
MnSOD R	ATCCTGGTTCTGGCAAGTGG		
CAT F	GCGACCAGAAACAACACACC	XM_027383071.1	166
CAT R	CTTGATGCCTTGGTCCGTCT		
GPX F	GGCACCAGGAGAACACTAC	XM_027368745.1	102
GPX R	CGACTTTGCCGAACATAAC		
ProPO F	TCCCGGACCGAGAAGATAGT	AY723296.1	105
ProPO R	TGTGGTATCATTCCCTGCGAG		
LZM F	CGATGATATCACGGAGGCCC	XM_027352857.1	111
LZM R	TTGCTGTTGTAAGCCACCCA		
Toll F	TTTCGGAGGATTGGAGTGCC	DQ923424.1	112
Toll R	GGTTTGTGAGGGAGTCCAGG		
Myd88 F	CCTCAGCCCAGCTTCTAAACA	JX073566.1	110
Myd88 R	CAGCCTGTTCTGCCAATCCT		
TRAF6 F	GGAGGTTGCAGGACACATGA	HM581680.1	132
TRAF6 R	TGTAGCTGCGTGGCTTGTAA		
Pelle F	CGTCAGTATTACGTCACGGC	KC346864	195
Pelle R	TGACTTCCAAGATGTGCGCT		
Dorsal F	CACGACCCATCAGAGTAGCC	XM_027382194.1	153
Dorsal R	AAACTGGAGGCTTCACAGCA		

2.9. Calculations and Statistical Analysis

The parameters were calculated as follows:

Initial body weight (IBW, g) = initial body wet weight (g);

Final body weight (FBW, g) = final body wet weight (g);

Weight gain rate (WG, %) = 100 × (final body weight − initial body weight)/initial body weight;

Specific growth rate (SGR, % day^{-1}) = 100 × (Ln (final mean weight) − Ln (initial mean weight))/number of days;

Feed conversion ratio (FCR) = feed consumed (g, dry weight)/weight gain (g, wet weight);

Condition factor (CF, g/cm^3) = 100 × (body weight, g)/(body length, cm)^3;

Survival rate (%) = 100 × (final number of shrimp)/(initial number of shrimp).

All the data were presented as the means with SEM. Data from each treatment were subjected to one-way analysis of variance (ANOVA) and Duncan's multiple tests. SPSS 22.0 statistical software was used to analysis the results. $p < 0.05$ was considered to indicate a statistically significant difference. A non-parametric Kruskal–Wallis test was applied when data did not have a homogeneous variance, followed by all pairwise multiple comparisons if there were significant differences ($p < 0.05$).

3. Results

3.1. Growth Performance and Feed Utilization

The growth performance and feed utilization of *L. vannamei* were shown in Table 3. After an eight-week feeding trial, the shrimp in all diets survived well (>85%), and there were no significant differences among all diets ($p > 0.05$). WG and SGR were influenced by dietary coenzyme Q10 levels. The WG and SGR of the shrimp fed with the D2 diet were significantly lower than the D1 group ($p < 0.05$). However, there were no significant differences between those fed with the D3, D4, D5, D6, and D7 diets and the D1 diet ($p > 0.05$). Shrimp fed with the D3, D4, D5, D6, and D7 diets had gradually increased FBW, WG and SGR with a rise in the coenzyme Q10 level. There were no significant differences in the FBW, FCR and Survival among all groups ($p > 0.05$). In addition, the groups fed with a lower FM level had a lower CF than D1 ($p < 0.05$), while there was no difference among the shrimp fed from diets D2 to D7 ($p > 0.05$).

Table 3. The effect of different coenzyme q10 levels on growth performance and feed utilization of *L. vannamei*.

Parameters	D1	D2	D3	D4	D5	D6	D7
IBW (g)	0.66 ± 0.01	0.67 ± 0.01	0.68 ± 0.00	0.66 ± 0.01	0.66 ± 0.00	0.68 ± 0.00	0.66 ± 0.01
FBW (g)	26.94 ± 0.78	24.71 ± 0.49	25.28 ± 0.47	25.71 ± 0.21	25.08 ± 1.17	26.08 ± 0.26	26.19 ± 0.77
WG (%)	3967.76 ± 120.48 $_{b}$	3606.94 ± 62.50 $_{a}$	3613.86 ± 70.97 $_{a}$	3790.40 ± 25.70 $_{ab}$	3708.63 ± 172.00 $_{ab}$	3749.86 ± 42.72 $_{ab}$	3899.68 ± 128.75 $_{ab}$
SGR (%, day^{-1})	5.88 ± 0.05 $_{b}$	5.73 ± 0.03 $_{a}$	5.74 ± 0.03 $_{a}$	5.81 ± 0.01 $_{ab}$	5.77 ± 0.07 $_{ab}$	5.79 ± 0.02 $_{ab}$	5.85 ± 0.05 $_{ab}$
FCR	1.46 ± 0.03	1.50 ± 0.03	1.48 ± 0.04	1.53 ± 0.09	1.56 ± 0.06	1.44 ± 0.03	1.51 ± 0.03
CF (g cm^{-3})	1.38 ± 0.03 $_{b}$	1.28 ± 0.04 $_{a}$	1.24 ± 0.03 $_{a}$	1.23 ± 0.02 $_{a}$	1.21 ± 0.02 $_{a}$	1.22 ± 0.02 $_{a}$	1.26 ± 0.01 $_{a}$
Survival (%)	89.17 ± 5.51	89.17 ± 4.38	86.67 ± 4.91	88.33 ± 5.18	88.33 ± 3.97	90.00 ± 1.36	87.50 ± 1.60

Abbreviation: IBW, initial body weight; FBW, final body weight; WG, weight gain; SGR, specific growth rate; FCR, Feed conversion ration; CF, condition factor; SR, survival rate. Values are mean ± SEM of four replicates (n = 4); a,b, shown on the right of SEM indicated the significant difference among groups; different letters displayed on top indicated significant difference ($p < 0.05$); same letters mean no significant difference ($p > 0.05$).

3.2. Whole-Body Proximate Composition

The moisture, crude protein and crude lipid levels of the whole body are presented in Table 4. The moisture parameter showed significant differences among all groups (Table 4). D2, D3, D6 and D7 had higher moisture values than D1, D4 and D5 ($p < 0.05$). Moreover, the moisture values of shrimp fed with the D3, D6, D7 diets were higher than the D2 diet ($p < 0.05$). However, the crude protein and crude lipid of shrimp were not influenced by the FM level or coenzyme Q10 level ($p > 0.05$).

Table 4. Whole-body proximate composition (%wet weight basis) of *L. vannamei fed* with different *level of coenzyme Q10.*

Parameter	D1	D2	D3	D4	D5	D6	D7
Moisture	72.77 ± 0.14 b	73.36 ± 0.37 ^{bc}	74.43 ± 0.53 ^{c}	71.06 ± 0.41 ^{a}	72.77 ± 0.67 ^{b}	74.06 ± 0.30 ^{bc}	73.00 ± 0.75 ^{bc}
Crude protein	19.23 ± 0.08	18.42 ± 0.08	18.46 ± 0.13	19.18 ± 0.42	18.05 ± 0.30	18.58 ± 0.30	19.10 ± 0.28
Crude lipid	1.75 ± 0.18	1.97 ± 0.05	1.90 ± 0.15	2.18 ± 0.12	2.02 ± 0.06	1.86 ± 0.11	2.01 ± 0.20

The results were expressed as mean ± standard error (Mean ± SEM); 4 replications in each group (n = 4); a,b,c, shown on the right of SEM indicate the significant differences among groups; different letters displayed on top indicated significant differences ($p < 0.05$); same letters mean no significant difference ($p > 0.05$).

3.3. Hepatopancreatic Antioxidant Enzyme Analysis

The results of the hepatopancreatic antioxidant enzyme activity of *L. vannamei* fed with different diets are shown in Figure 1. Results indicated that the T-AOC values of *L. vannamei* fed with the D2–D4 diets and the D7 diet were significantly lower than those fed the D1 diet ($p < 0.05$), but no significant differences among the D1, D5 and D6 diets ($p > 0.05$) were found. The T-SOD activity of shrimp fed with the D2 and D3 diets were remarkably lower than the D1 group ($p < 0.05$); on the contrary, no remarkable differences were found compared to the groups with a coenzyme Q10 level higher than 0.002% and the D1 group ($p > 0.05$). Analogously, the malondialdehyde (MDA) content of the shrimp fed with the D2 diet was the highest among all groups ($p < 0.05$), while those of the D5 and D6 diets were observably lower than D2–D4 diets ($p < 0.05$), and were no significant differences compared to the D1 diet ($p > 0.05$). Summarily, a certain extent of dietary coenzyme Q10 supplement can increase T-AOC and decrease MDA to improve the antioxidant capability of *L. vannamei*, but cannot affect the T-SOD activity of *L. vannamei*. Moreover, to a certain extent, *L. vannamei* fed a diet containing a low FM level (15%) with a coenzyme Q10 supplement can achieve the antioxidant capabilities of the shrimp fed with a high FM level (20%).

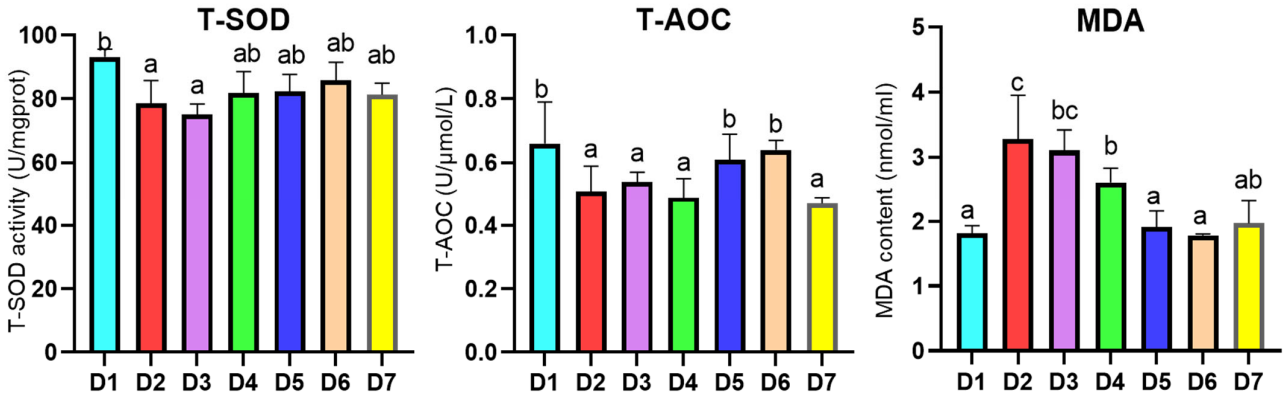

Figure 1. Effect of different diets on antioxidant capability in hepatopancreas of *L. vannamei*. Left: T-SOD, total superoxide dismutase; middle: T-AOC, total antioxidant capacity; right: MDA, malondialdehyde. The results are expressed as mean and error bar (SEM); 4 replications in each group (n = 4). a,b,c, shown above the error bars indicate a significant difference among groups; different letters displayed on top indicated significant difference ($p < 0.05$); same letters mean no significant difference ($p > 0.05$).

3.4. Relative Expression of Antioxidant and Immune Genes in Hepatopancreas

The results of the relative expression of antioxidant and immune genes in the hepatopancreas of *L. vannamei* were shown in Figure 2. The expressions of antioxidant genes are shown in Figure 2A. There were no significant differences among the shrimp fed with the D1 and D4–D7 diets in the *cat* mRNA expression level ($p > 0.05$), but the expression level in the D2 and D3 groups were significantly lower than the D1 group ($p < 0.05$). The results of the relative expression of *mnsod* mRNA indicated that it was distinctly lower in the D2 group compared with the D1 group ($p < 0.05$). In addition, the relative expression of *gpx* gene mRNA in D1 group was markedly higher than that in D2, D3, D4 and D7 groups ($p < 0.05$); however, there was no significant difference between the D1 group and the D5 and D6 groups ($p > 0.05$).

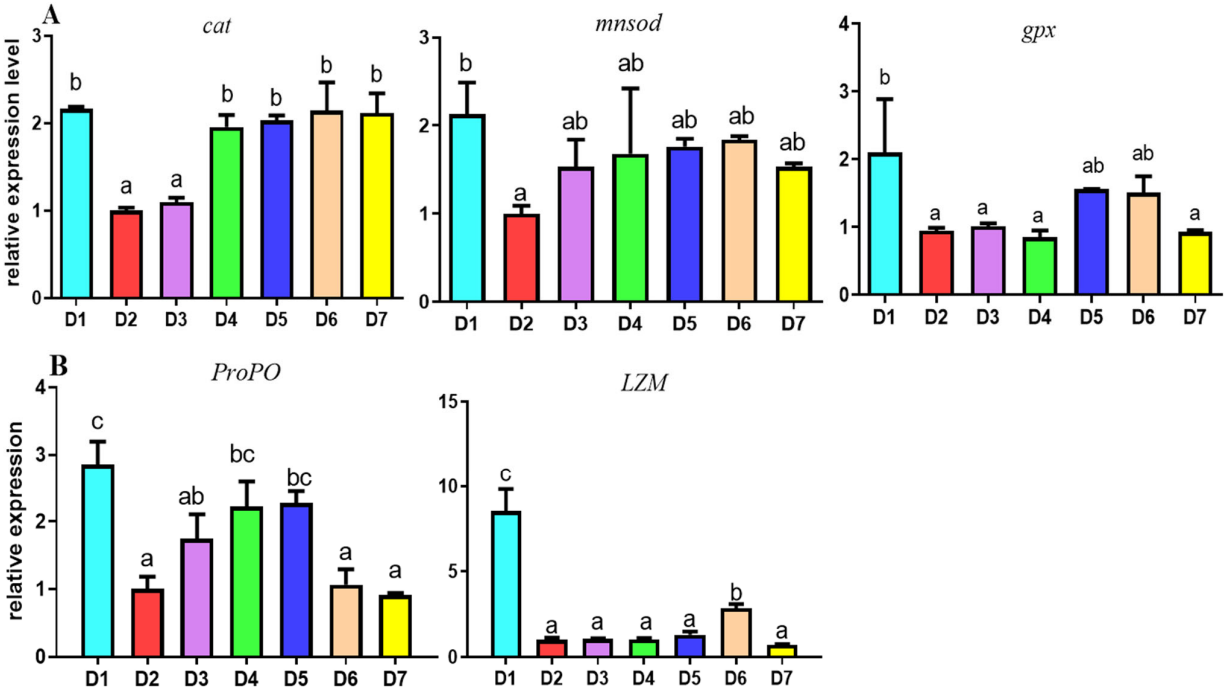

Figure 2. The relative antioxidant and immune-related gene expression levels in hepatopancreas of *L. vannamei* fed with different diets. (**A**) CAT, MnSOD, GPX, (**B**) ProPO, LZM genes of mRNA relative expression level, respectively. Abbreviation: CAT, Catalase; MnSOD, Manganese superoxide dismutase; GPX, Glutathione peroxidase; ProPO, Prophenoloxidase; LZM, Lysozyme. The results are expressed as mean and error bar (SEM); 4 replications in each group (n = 4); a,b,c, shown above the error bars indicate significant differences among groups; different letters displayed on top indicated significant difference ($p < 0.05$); same letters mean no significant difference ($p > 0.05$).

The expressions of immune genes in the hepatopancreas are shown in Figure 2B. The results indicated that the expression levels of *ProPO* mRNA were significantly higher in the D4 and D5 groups than the D2, D6 and D7 groups ($p < 0.05$), especially it was highest in the D1 group ($p < 0.05$); there were no significant differences between the D1, D4 and D5 groups. Moreover, the expression level of the *LZM* gene was highest in D1 group, and it was markedly higher than that in the D2–D7 groups ($p < 0.05$), but among the low-FM groups, it was highest in the D6 group ($p < 0.05$).

3.5. Intestinal Morphology Measurement

The intestinal morphology measurements of *L. vannamei* from each group are shown in Figure 3. The intestinal villus height and submucosal thickness of *L. vannamei* from each group were determined. According to the intestinal morphology of *L. vannamei* in each group, shown by intestinal HE staining sections (bottom of Figure 3), neither the FM level nor coenzyme Q10 addition level caused pathological changes in the *L. vannamei* intestinal morphology. Statistically speaking, the intestinal villus height and submucosal thickness showed significant differences among all treatment groups. The intestinal villi heights of groups D3–D7 were significantly higher than that of group D2 ($p < 0.05$), and the intestinal villi height of groups D3–D5 was significantly higher than that of group D1 ($p < 0.05$). There was no significant difference between groups D6 and D7 and group D1 ($p > 0.05$). The submucosal thickness in the D4, D5 and D6 groups was significantly higher than that in the D2, D3 and D7 groups ($p < 0.05$), but there was no significant difference in the submucosal thickness between the D4, D5 and D6 groups and the D1 group ($p > 0.05$).

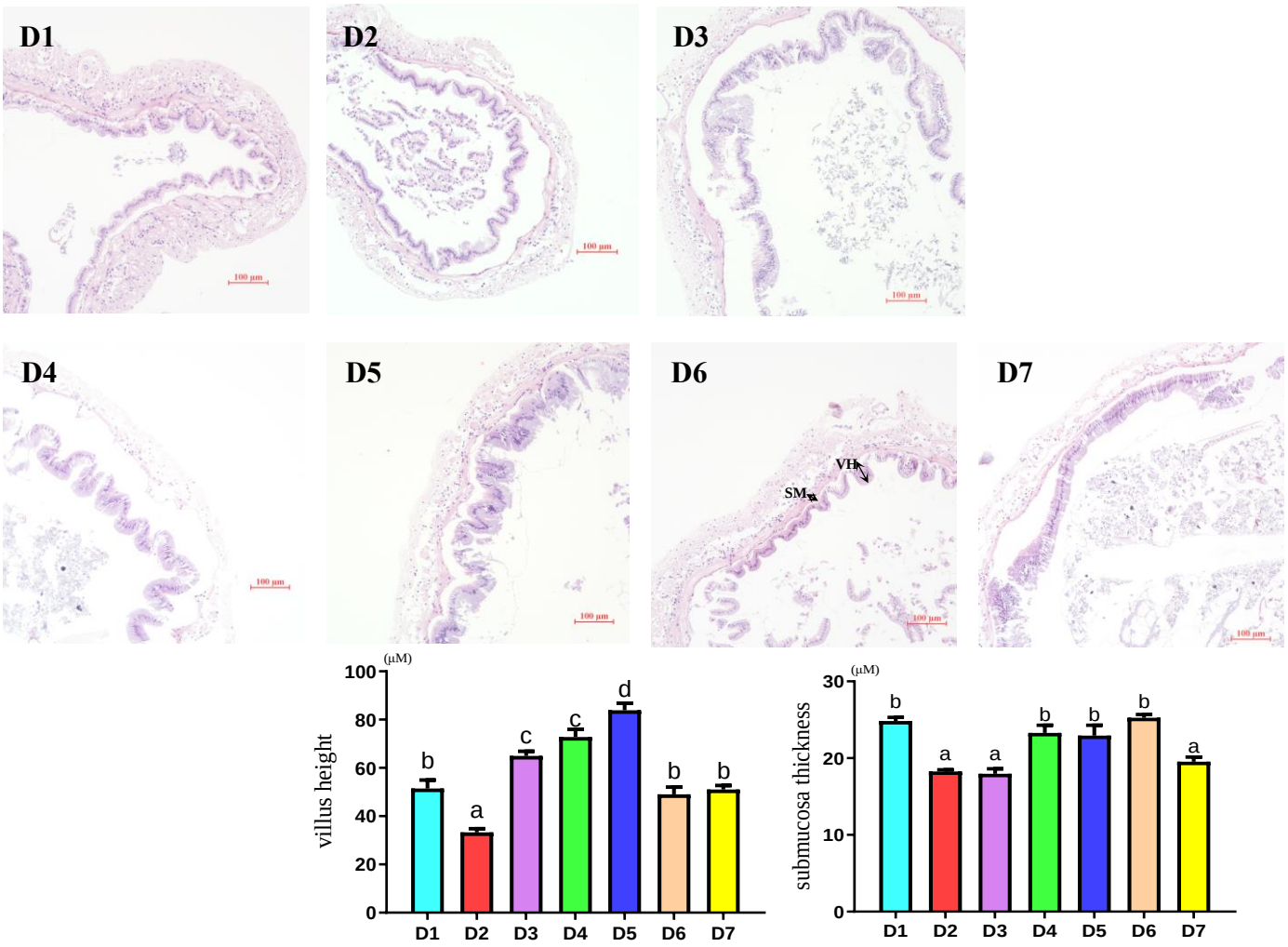

Figure 3. Effects of different supplemental levels of coenzyme Q10 on intestinal morphology of *L. vannamei.* Top: intestinal morphology; scale bar, 100 μm, original magnification ×10; VH: villus height; SM: submucosa thickness. Below: The results of villus height and submucosa thickness measurement. The average intestinal villus height and submucosal thickness were randomly determined within 5 different fields and four replicates for each group. The results were expressed as mean and error vertical bars (SEM); 4 replications in each group (n = 4). a,b,c,d shown above the error bars indicate significant differences among groups; different letters displayed on top indicated significant differences ($p < 0.05$); same letters mean no significant difference ($p > 0.05$).

3.6. Acute Hypoxia Stress

Figure 4 shows that the death time of half of *L. vannamei* under hypoxia stress was calculated between different treatment groups. According to the statistics in the figure, the median lethal time in the D3–D7 groups was significantly higher than that in the D1 and D2 groups ($p < 0.05$). Among all the treatment groups, the D4–D6 group had the longest half-death time, which was significantly higher than that of the D7 group ($p < 0.05$).

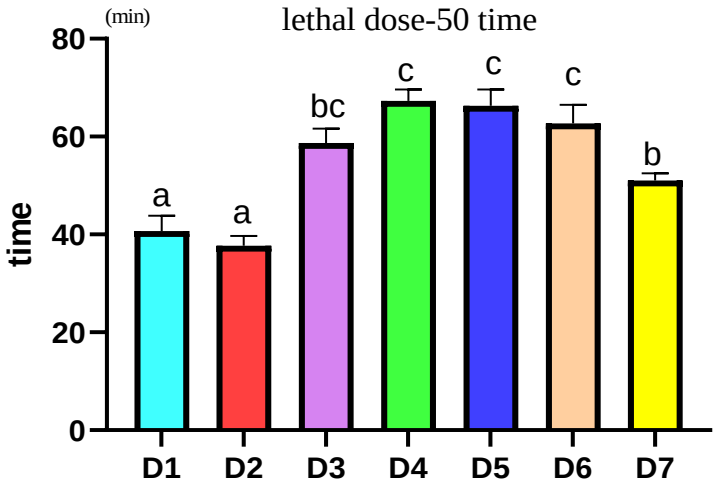

Figure 4. Effects of different supplemental levels of coenzyme Q10 on the lethal dose 50 time of *L. vannamei* under acute hypoxia stress. The results are expressed as the mean and error vertical bar (SEM); 4 replications in each group (n = 4). a,b,c, shown above the error bars indicate significant differences among groups; different letters displayed on top indicated significant difference ($p < 0.05$); same letters mean no significant difference ($p > 0.05$).

The results of antioxidant-related gene expression are presented in Figure 5. The *mnsod*, *cat* and *gpx* genes' relative expression were significantly upregulated after diets supplemented with coenzyme Q10. For the result of *cat*, those of D3–D6 were markedly higher than that of D2 ($p < 0.05$); in particular, the D5 group was the highest among them, with no significant differences compared with D1 ($p > 0.05$). Similarly, the results of *mnsod* and *gpx* gene relative expression showed that D5 was the highest among D2–D7 ($p < 0.05$). The expressions of these antioxidant-related genes were boosted after proper supplementation with coenzyme Q10.

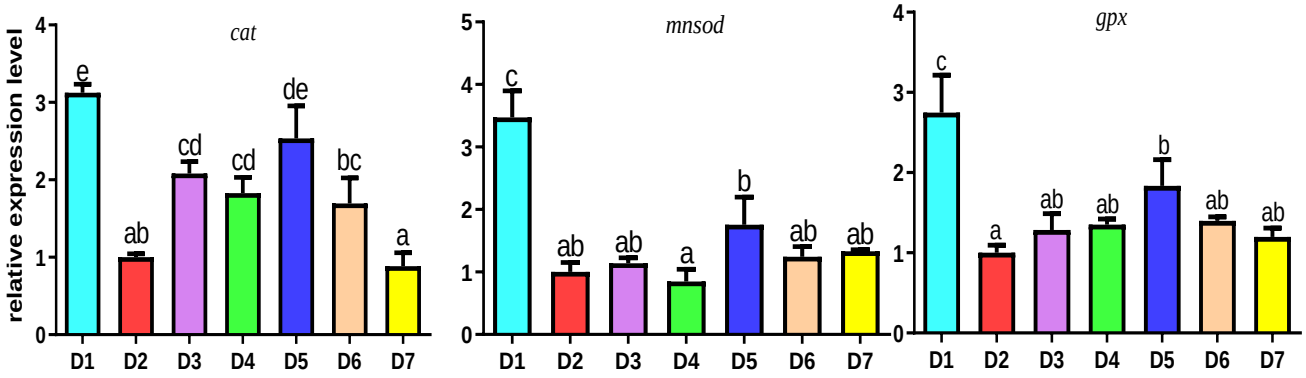

Figure 5. Effects of different supplemental levels of coenzyme Q10 on the expression of hepatopancreatic antioxidant-related genes of *L. vannamei* under acute hypoxia stress. The results are expressed as the mean and error vertical bar (SEM); 4 replications in each group (n = 4). a,b,c,d,e shown above the error bars indicate significant differences among groups; different letters displayed on top indicate significant differences ($p < 0.05$); same letters mean no significant difference ($p > 0.05$).

Figure 6 showed the partial immune-related gene expression of *Litopenaeus vannamei* under acute hypoxia stress in different treatment groups. The mRNA relative expression levels of a Toll-like receptor signaling pathway-related genes (*Toll*, *Myd88*, *Pelle*, *TRAF6* and *Dorsal*) in the D2–D7 group were significantly lower than those in the D1 group ($p < 0.05$). In the D2–D7 groups, with a 15% fish meal level, the *Toll* expression level in the D4 group was significantly higher than that in the D2 group ($p < 0.05$), but there was no significant difference between the D4 group and the other 15% fish meal groups

(D3, D5, D6 and D7) ($p > 0.05$). The expression levels of the *Myd88* gene in the D6 and D7 groups were significantly higher than that in the D2 group ($p < 0.05$), but there were no significant differences between the D2-D5 groups ($p > 0.05$). The *Pelle* gene expression level in the D4 and D6 groups was significantly higher than that in the D2 group ($p < 0.05$), but there were no significant differences between the D4, D5 and D7 groups and the D2 group ($p > 0.05$). The expression level of the *TRAF6* gene in the D4 group was significantly higher than that in the D2, D5 and D6 groups ($p < 0.05$), but there was no significant difference between the D4, D3 and D7 groups ($p > 0.05$). Interestingly, the *Dorsal* expression level in D4 was highest among D2–D7 ($p < 0.05$) and no remarkable discrepancy compared with D1 ($p > 0.05$).

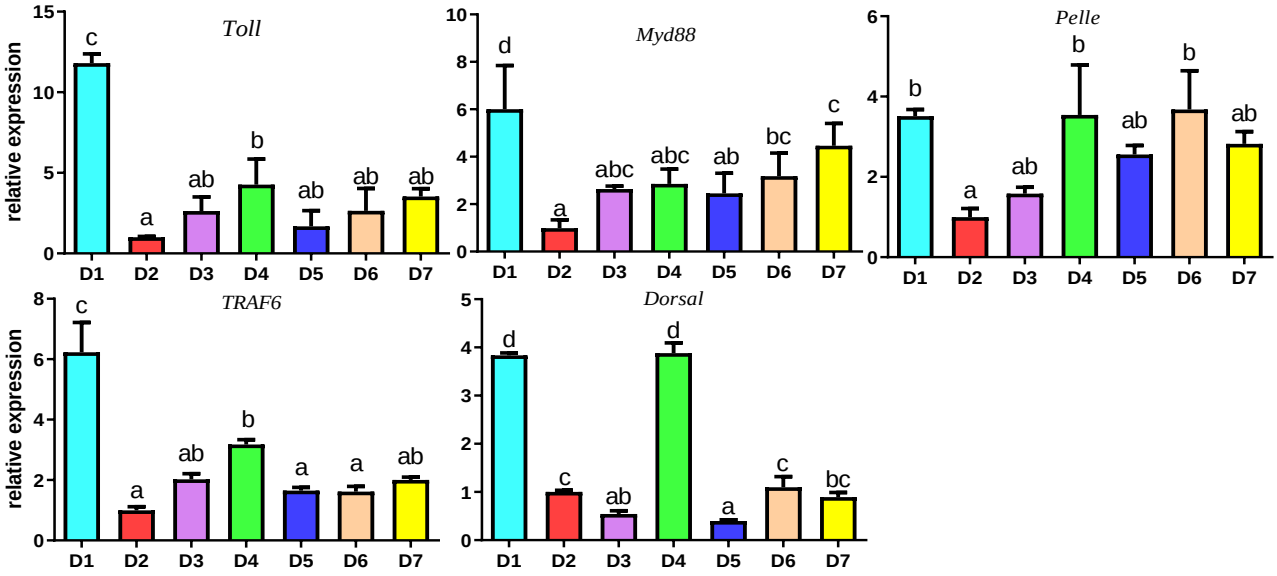

Figure 6. Effects of different supplemental levels of coenzyme Q10 on the expression of hepatopancreatic immune-related genes (Toll-like receptor signaling pathway) of *L. vannamei* under acute hypoxia stress. The results are expressed as the mean and error vertical bar (SEM); 4 replications in each group (n = 4). a,b,c,d shown above the error bars indicate significant differences among groups; different letters displayed on top indicated significant differences ($p < 0.05$); same letters mean no significant difference ($p > 0.05$).

4. Discussion

At present, FM is still the main source of protein in aquatic animal feed, but its price is increasing due to environmental impacts and overfishing [52,53]. Currently, FM levels in aquatic feed are usually reduced by substituting it with other protein sources. Diets with low fish meal levels, in particular, plant-based proteins (such as SBM, PM, CGM, dephenolized cottonseed protein, etc. [54–57]) are often less effective than high-fish-meal diets due to their high fiber content, low protein content, inappropriate amino acid composition, low palatability and the antinutritional factors of plant protein sources, which reduce the feed intake, nutrient availability and digestibility of feed, and influence the growth, antioxidant capacity and immunity of the shrimp [6,10–13]. In this study, CGM was used as an FM replacement and had a high content of non-soluble carbohydrates, which were hard for digestion and utilization and had adverse impacts on the shrimp [36,58]. In recent years, there have been an increasing number of studies focusing on low-FM feed for aquatic animals. In some cases, low-FM feed hindered the growth performances of aquatic animals such as turbot, rainbow trout, Atlantic Salmon, Nile tilapia, gilthead sea bream, *largemouth bass*, *L. vannamei*, black tiger shrimp, *Paralichthys olivaceus*, etc. [11,59–66]. A low-FM diet supplemented with functional additives to alleviate the growth retardation of aquatic animals has become a hot research objective in aquaculture. Coenzyme Q10, an inexpensive, obtainable, strong antioxidant dietary supplement, has been proven to

yield a broad range of advantageous impacts [67]. In this study, the addition of coenzyme Q10 also produced a good effect on *L. vannamei*. In terms of growth performance, weight gain rate (WG) and specific growth rate (SGR) increased with the addition of coenzyme Q10. Similarly, two studies by Basuini et al. indicated that the addition of coenzyme Q10 increased the growth, in terms of the WG and SGR, of Nile tilapia, which might be caused by the enhancement of the feed intake (FI) and the feed efficiency ratio (FER) with the dietary coenzyme Q10 supplement [68,69]. The findings of this study suggest that low-FM diets impair shrimp growth compared with high-FM diets, but dietary coenzyme Q10 supplementation can reverse the growth retardation caused by low-fish-meal diets. By adding coenzyme Q10, the results of intestinal villus height were enhanced compared to shrimp in the no-coenzyme-Q10 groups, which possibly promoted feed utilization, and this might be one of the reasons for the boosted growth performance.

Increased ROS (reactive oxygen species) levels cause oxidative damage to many important cellular macromolecules (lipids, proteins, carbohydrates, and nucleotides) [70]. As antioxidant enzymes in *L. vannamei*, SOD (superoxide dismutase), CAT (catalase) and GPX (glutathione peroxidase) can remove excessive ROS in vivo. They exist in approximately all aquatic animals and are normally used to assess the antioxidant capacity of organisms [71–73]. SOD is a cytosolic enzyme that can be detoxified using a superoxide radical (O^{2-}) converted to hydrogen peroxide and oxygen [74]. CAT (catalase) and GPX (glutathione peroxidase) can convert H_2O_2 into H_2O [75,76]. The findings of this study showed that added coenzyme Q10 slightly increased the relative expression level of *MnSOD*, the same as the result of T-SOD activity. Moreover, the expression level of *GPX* was mildly increased when supplemented with 6 and 8 mg/kg of coenzyme Q10. Similarly, *CAT* expression was upregulated with coenzyme Q10 by higher than 4 mg/kg. The T-AOC (total antioxidant capacity) and MDA (malondialdehyde) are both indicators of the antioxidant capacity and oxidant status of *L. vannamei*. T-AOC directly reflects antioxidant capacity overall, while MDA, as the end product of lipid peroxidation, is an important indicator of cell-membrane oxidative damage [77]. In the present study, it was observed that the shrimp fed with a 20% FM diet had a higher T-AOC and a lower MDA than those shrimp fed with a 15% FM diet, but the low-FM diets supplemented with 6 and 8 mg/kg coenzyme Q10 reversed the antioxidant inhibition caused by the FM-meal diets. When coenzyme Q10 was added to grouper sperm frozen medium [78], it was observed that oxidative stress was reduced, which significantly improved sperm motility and the fertilization rate. Homoplastically, in a previous study on *L. vannamei*, the T-AOC activity was increased and the *SOD* expression level was promoted by adding coenzyme Q10 under a low salt stress [79]. The results indicated that the antioxidant system of *L. vannamei* can be promoted by adding coenzyme Q10. Therefore, in the present study, it was found that coenzyme Q10 could improve the nutritional physiology of *L. vannamei*, which might be related to the strong antioxidant capacity of coenzyme Q10 alleviating the oxidative stress of the organism. In the human body, coenzyme Q10 has been used as an added supplement for the treatment of various diseases, and some of the help that coenzyme Q10 gives to human diseases is based on its strong antioxidant ability to clean up lipid peroxidation and enhance mitochondrial respiration [80].

Coenzyme Q10 also possesses the potential ability to activate the immune system. There is considerable evidence that coenzyme Q10 may influence immunity via different mechanisms, such as its effects on pro-inflammatory markers, mitochondria, lysosomes and peroxisomes [81]. For *L. vannamei*, the prophenoloxidase system (proPO-system) and lysozyme are the keys of the nonspecific immune system. Prophenoloxidase activation plays an important role as a recognition system through blood cell attraction and the induction of phagocytosis, melanization, cytotoxic reactant production, particle encapsulation and the formation of nodules and capsules [82]. ProPO is a crucial enzyme in the prophenoloxidase system, which transfers to catalytically activated phenoloxidase (PO). Lysozyme lyses bacteria by attacking the peptidoglycan of the bacterial cell wall [83]. Results have showed that a dietary supplement of 4 and 6 mg/kg of coenzyme Q10 enhanced the relative

expression level of *ProPO*, and 8 mg/kg of coenzyme Q10 upregulated lysozyme expression, which indicates the positive correlation between coenzyme Q10 and innate immunity. Coenzyme Q10 helps to maintain the acidic environment of the lysosomal lumen and also maintain the structural integrity of the peroxisome membrane from free-radical-induced oxidative damage, which may be one of the reasons why coenzyme Q10 enhances the innate immunity of *L. vannamei* [84,85].

Hypoxia is the main limiting factor in the crustacean aquaculture industry [78]. Both acute and chronic hypoxia stress can damage tissues in crustaceans [86,87]. The results indicated that coenzyme Q10 supplementation prolonged the semi-lethal time caused by acute hypoxic stress, which may be attributed to an improved health status and immunity. One of the deleterious consequences of hypoxia stress is the induction of ROS generation in aquatic animals [88]. Hypoxia increases ROS by transferring electrons from the ubisemiquinone to molecular oxygen at the Qo site of complex III of the mitochondrial electron transport chain [89]. Previous result have showed that hypoxia and subsequent reoxygenation induced high level of ROS in the hepatopancreas of *L.vannamei* [90]. In a study in Nile tilapia [91], the addition of coenzyme Q10 alleviated the oxidative stress caused by nickel to the brain, restored the activity of acetylcholinesterase, and alleviated the nerve damage caused by nickel to Nile tilapia. The results of this study showed that a proper coenzyme Q10 supplement enhanced the animals antioxidant capacity, and this will help to clarify the excess ROS that are being generated after hypoxia stress.

Hypoxia is known to hinder the nonspecific immunity system of crustaceans, which increases their susceptibility to pathogenic bacteria [92,93]. Hypoxia has been reported to reduce hemocyte counts and phagocytic activity, as well as reduce the bacteriolytic and antibacterial activity in the hemolymph of the southern king crab Lithodes santolla, giant freshwater prawn *Macrobrachium rosenbergii*, and white shrimp *L. vannamei* [78]. Hypoxia affects the expression of immune-related genes, but little is known about the mechanisms involved. The gills and hepatopancreas are the most sensitive organs in crustaceans and are susceptible to oxidative stress. In this study, the Toll-like receptor signaling pathway-related genes (*Toll*, *Myd88*, *Pelle*, *TRAF6* and *Dorsal*) were investigated after acute hypoxia stress. The Toll-like receptor signaling pathway plays a vital role in the innate immunity system, where it controls and clears invading pathogens [94,95]. Toll is a major pattern-recognition receptor of *L. vannamei*. It recruits the adaptor MyD88 through its own TIR domain, which then binds to the protein kinase Pelle to construct a complex that recruits other modulators. Phosphorylated Pelle induces the phosphorylation of tumor necrosis factor receptor-associated factor 6 (TRAF6), thereby inducing an immune response [94]. Dorsal, which belongs to the class II NF-κB family [96], is the critical regulator of the Toll-like receptor signaling pathway and is responsible for DNA binding, dimerization and interaction with the regulator proteins for the regulation of the expression of antimicrobial peptides [97]. The results of this study have shown that 4 mg/kg coenzyme Q10 supplementation enhanced the immunomodulatory effect of the Toll-like receptor signaling pathway after acute hypoxia stress, indicating that coenzyme Q10, which may help to enhance the animals antioxidant capability to fight oxidants that are generated after hypoxia stress, can help to improve the innate immune capacity of *L. vannamei*.

5. Conclusions

In this study, the results showed that dietary supplementation with an appropriate amount of coenzyme Q10 could enhance the nutritional physiological status of *Litopenaeus vannamei* fed on low-FM feed. In general, the optimum addition level of coenzyme Q10 was 0.008% for growth performance, antioxidant capacity, intestinal development, and immune performance. Dietary coenzyme Q10 supplementation in the amount of 0.004–0.008% improved the anti-hypoxic ability of *Litopenaeus vannamei*.

Author Contributions: The authors thank the participants who gave their time to the trial. J.N. and W.Z. designed the study. Z.Z. carried out the rearing trial and analyzed part of the results. Z.L., M.C., R.Y. and H.W. collected the trial samples. Y.L. carried out the rearing trial, analyzed the results and

wrote this paper. W.Z. revised the paper. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by the following project: Project of Science and Technology of Guangdong Province: 2021B0202050002; Project of China Agriculture Research System of MOF and MARA 48: CARS 48; The Central Government Guides Local Funds for Science and Technology Development of Science and Technology of Qinghai Province: 2023ZY015; Project of Science and Technology of Guangdong Province: 2019B110209005; The Fundamental Research Funds for the Central Universities, Sun Yat-sen University: 23ptpy26.

Institutional Review Board Statement: All experiments were conducted in accordance with the recommendations in the Guide for the Care and Use of Laboratory Animals of the National Institutes of Health (NIH). The study protocol and all experimental procedures were approved by the Institution Animal Care and Use Committee, Sun Yat-Sen University (approval code: SYSU-IACUC-2022-B0159, approval date: 4 March 2020).

Informed Consent Statement: Not applicable.

Data Availability Statement: The data presented in this study are available in the article.

Conflicts of Interest: The authors confirm that there are no conflicts of interest in this work.

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