Dose-Dependent Effects of Histamine on Growth, Immunity and Intestinal Health in Juvenile Grouper (*Epinephelus coioides*)

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A 56 day feeding trial was conducted to examine the effects of different levels of dietary histamine on growth performance, immune response, and intestinal health of grouper (*Epinephelus coioides*). Seven isonitrogenous (46%), isolipidic (10%) diets were prepared with histamine supplement levels of 0 (T0), 0.05% (T1), 0.1% (T2), 0.15% (T3), 0.2% (T4), 0.25% (T5), and 0.3% (T6), respectively. The results showed that histamine supplementation had no significant effects on weight gain rate (WGR), specific growth rate (SGR), feed conversion rate (FCR), hepatosomatic index (HSI), and survival rate (SR) at the initial feeding period (day 0–28), but WGR and SGR had negative linear responses to the dietary histamine level at the whole feeding period (day 0–56), and a significant decrease was observed in groups T5 and T6 compared with T0 ($P < 0.05$). Supplementation of histamine decreased antioxidant capacity, immune response, the contents of serum interleukin-1 beta (IL-1β), intestinal-type fatty acid-binding protein (FABP2) and intestinal trefoil factor (ITF), and caused serious damage of intestine with significantly decreased VH and MFH of grouper, especially in fish fed with diets supplemented with high doses of histamine (0.25 and 0.3%). The intestinal microbial communities in treatments were different clearly with the control (T0), in terms of beta (β)-diversity boxplots and UPGMA phylogenetic tree based on unweighted unifrac distance. At the phylum level, the relative abundance of *Fusobacteria* was lower in group T0, while the abundance of *Firmicutes* was significantly lower in groups T5 and T6 ($P < 0.05$). At the genus level, the relative abundance of uncultured_bacterium_f_*Bacteroidales*_S24-7_group, uncultured_bacterium_f_*Lachnospiraceae,* and *Ruminiclostridium* were significantly higher in the control, while the abundance of *Cetobacterium* was significantly higher in groups T5 and T6 ($P < 0.05$). In conclusion, the present study suggested that up to 0.2% of dietary histamine did not result in a remarkable reduction in growth, immune response, and intestinal health; however, 0.25% or more dietary histamine could cause significant negative effects on growth performance, immune response, and intestinal health in *E. coioides*.

Keywords: histamine, growth performance, immune response, intestinal health, *Epinephelus coioides*

INTRODUCTION

With the rapid development of aquaculture industry worldwide in recently years, the quality of fish meal (FM), which served as the most primary protein source in aquatic feeds, has received more and more attention (Li et al., 2018; Wang et al., 2019; Ye et al., 2020; Zhai et al., 2020). High levels of histamine are usually presented in poor quality FM due to difference of original fish species, suboptimal conditions of preparation and transportation, improper storage, and so on (Higgs et al., 1995; Anderson et al., 1997; Visciano et al., 2012), resulting in a series of negative effects in aquatic animals, such as suppression of growth performance, reduction of feed utilization, inflammatory reaction, and intestinal diseases (Aksnes et al., 1997; Aksnes and Mundheim, 1997; Caballero et al., 1999; Tapia-Salazar et al., 2004). Therefore, histamine level is a useful and widely recognized parameter to assess FM quality and also as a vital safety indicator for food (Pike and Hardy, 1997; Tapia-Salazar et al., 2001; Tao et al., 2011; Biji et al., 2016).

The effects of dietary histamine exhibited variation in humans and different animal species. In humans, it was found that high dose of histamine (exceed 0.75 mg/kg body weight) may significantly enhance the risk of poisoning (Doeun et al., 2017). The European Union set regulatory ensures of histamine level below 0.2 g/kg in fresh fish and 0.4 g/kg in seafood products (Visciano et al., 2014). Moreover, suppression of growth, reduction of feed utilization and survival rate (Harry et al., 1975; Zhao et al., 2012), and gizzard lesions (Harry and Tucker, 1976) have been reported in chickens suffering from high doses of dietary histamine. The dietary histamine supplementation exerts detrimental effects in mysis (*Neomysis awatschensis* and *Neomysis japonica Nakazawa*) (Yang et al., 2010), rainbow trout (*Oncorhynchus mykiss*) (Moghaddam et al., 2015), and American eel (*Anguilla rostrata*) (Zhai et al., 2020). Li et al. (2018) found digestive system damage and liver inflammation in yellow catfish (*Pelteobagrus fulvidraco*) fed a diet supplemented with 0.1% histamine. Zhao et al. (2016) reported that high levels of histamine (4 g/kg) decreased the activity of digestive enzymes and exerted great damage to the morphology of the intestine and hepatopancreas in Chinese mitten crab (*Eriocheir sinensis*); however, dietary histamine supplementation had no significant effect on growth performance. In rainbow trout (*O. mykiss*), digestive tract damage was observed in fish fed diet containing 2 g/kg histamine (Watanabe et al., 1987; Fairgrieve et al., 1994), and dietary supplementation of histamine (2 g/kg) (Fairgrieve et al., 1994) or putrescine (13.3 g/kg) (Cowey and Cho, 1992) decreased feed consumption. Interestingly, Tapia-Salazar et al. (2001) reported that diet supplemented with 1.2–2.4 g/kg histamine/diet had a positive effect on weight gain in blue shrimp (*Litopenaeus stylirostris*).

Groupers as typical marine carnivorous fish have been widely cultured in several regions of China and Southeast Asia with the development of the intensive aquaculture industry. In China, annual production of groupers reached 183,127 tons in 2019 (China Fishery and Statistics Yearbook, 2020), for its fast growth, rich nutrition, high economic value, and consumer demand. To the best of our knowledge, study on the effects of dietary histamine on the performance of grouper is lacking, and its impact on intestinal health of fish is less reported (Zhao et al., 2016). Therefore, the present study was conducted to evaluate the effects of different doses of dietary histamine on growth performance, immune response, and intestinal health of grouper (*Epinephelus coioides*).

MATERIALS AND METHODS

Experimental Diets

A basal diet (T0; non-supplemented with histamine), served as control, was formulated (**Table 1**) based on nutritional requirements of grouper (*E. coioides*) as recommended by Yang et al. (2019). The experimental diets were prepared by supplementing the basal diet with 0.05% (T1), 0.1% (T2), 0.15% (T3), 0.2% (T4), 0.25% (T5), and 0.3% (T6) histamine (S20188; histamine [$C_5H_9N_3$] $\geq$ 98.0%; 111.15 g/mol; Shanghai yuanye Bio-Technology Co., Ltd., China). All the dietary ingredients were crushed to powders and through 60 mesh sieve and thoroughly mixed using the progressive enlargement method, then added the premixed fish oil, soybean oil and lecithin; subsequently, water with/without histamine was supplemented

TABLE 1 | Ingredients and proximate nutrient composition of the basal diet (% dry matter).

Ingredients	Content (%)
White fish meal[a]	43.0
Shrimp head meal	3.0
Soybean meal	16.88
Vital wheat gluten	7.00
Fish oil[b]	2.5
Soybean oil	2.5
Lecithin	2.0
Wheat meal	20.0
Choline chloride[c]	0.5
Vitamin premix[d]	0.5
Mineral premix[e]	0.5
Ca(H$_2$PO$_4$)$_2$	1.5
Antifungal agent	0.10
Antioxidant	0.02
Proximate nutrients composition	
Crude protein	45.90
Crude fat	10.32
Crude ash	9.17

[a]*White fish meal was obtained from Jiakang Feed Co., Ltd., Xiamen, China, imported from Peru (crude protein 68.34%, crude lipid 9.06%).*
[b]*Fish oil were obtained from Jiakang Feed Co., Ltd., Xiamen, China.*
[c]*Cholesterol was produced by Baiwei Biotechnology Holdings Co., Ltd., Hebei, China, which is extracted from pig, cattle, or sheep brain, and the minimum level is higher than 95%.*
[d]*Vitamin premix (mg kg^{-1} diet): vitamin A, 15; vitamin D3, 15; vitamin E, 75; vitamin K3, 50; vitamin B1, 50; vitamin B2, 75; vitamin B6, 75; vitamin B12, 0.3; nicotinic acid, 200; inositol, 350; D-calcium pantothenate, 200; folic acid, 9; D-biotin, 0.5.*
[e]*Mineral premix (mg kg^{-1} diet): FeSO$_4$·7H$_2$O, 278; CuSO$_4$·5H$_2$O, 41; ZnSO$_4$·7H$_2$O, 463; MnSO$_4$·4H$_2$O, 57; MgSO$_4$·7H$_2$O, 2009; CoSO$_4$·7H$_2$O, 3; Na$_2$SeO$_3$ 0.6, Ca (IO$_3$)$_2$, 5.*

slowly and kept stirring until forming a dough. After pelletized, the diets were packed in plastic bags and stored at refrigerator (−20°C) until subsequent use. The histamine level in the basal diet was determined to be 158.7 mg/kg.

Animals and Experimental Conditions

The procedures for care and use of animals were approved by the Animal Care and Use Committee of Jimei University, China. The feeding trial was conducted in a recirculating water system and healthy grouper (*E. coioides*) were obtained from the Haikang Aquaculture Research Base of Dabeilong Aquaculture group. The whole study followed a strict series of rules and regulations promulgated by animal care and use committee of Jimei University, China. After acclimation (2 weeks), 30 fish (29 ± 0.52g; mean ± SE) were randomly allocated to each tank (containing 300 L seawater) and three tanks for each treatment were served as replicate, and thus 21 tanks (seven groups, and three repeats in each group) and 630 fish were used in the feed trial. Fish were hand fed one of seven diets for 56 days to apparent satiation two times daily at 08:30 and 18:30, respectively, and approximately 60% seawater was replaced daily. During the trial period, rearing water environment were monitored daily and maintained in a suitable range (temperature: 20–26°C; salinity: 30–32 g/L, pH: 7.5–8.2, dissolved oxygen [DO]: ≥7.5 mg/L; and total ammonia concentration: <0.2 mg/L).

Sample Collection

To determine the growth performance, 10 fish were randomly collected from each tank (three tanks for each treatment) after starvation for 24 h at days 28 and 56 respectively, thus 30 fish for each treatment were collected at each time point, batchwise anesthetized by 2-phenoxyethanol, and single-weighed for calculation of growth performance. Blood samples were taken from the caudal vein of 10 fish in each tank, immediately transferred into 1.5 mL Eppendorf tubes and held at 4°C overnight. Then, serum was collected and pooled following centrifugation at 10,000 r/min at 4°C for 10 min and stored in 1.5 mL Eppendorf tubes at −80°C for further analysis. Liver and intestine samples were dissected, weighed, and frozen immediately in liquid nitrogen and stored at −80°C for subsequent analysis. Foregut were randomly sampled from four fish in each tank, fixed with Bouin's fixative solution (75 ml saturated aqueous solution of picric acid, 25 ml formalin, 5 ml glacial acetic acid) for morphological determination. Intestine samples were collected from one fish per tank for intestinal microbiota analysis at day 56.

Measurement of Serum and Liver Biochemical Parameters

The total antioxidant capacity (T-AOC) and activities of alkaline phosphatase (AKP), acid phosphatase (ACP), and superoxide dismutase (SOD) in serum were evaluated spectrophotometrically using commercial kits (Nanjing Jiancheng Bioengineering Institute, Nanjing, China) according to the manufacturer's instructions as previously described (Hu et al., 2019).

The liver sample was homogenized in ice-cold 0.86% physiological saline (pH: 7.2–7.4; w: v = 1:9), centrifuged at 3,000 rpm at 4°C for 10 min and the supernatant was collected. Protein concentration of the supernatant was determined with Coomassie brilliant blue method described by Hu et al. (2019). Malondialdehyde (MDA) level and activities of glutamic oxaloacetic transaminase (GOT) and glutamic propylic transaminase (GPT) of the supernatant were estimated using commercial kits (Nanjing Jiancheng Bioengineering Institute, Nanjing, China) following the manufacturer protocol.

Serum and Intestinal Inflammatory Factors

Interleukin-1 beta (IL-1β), serum amyloid A (SAA), and C-reactive protein (CRP) in serum were analyzed by enzyme-linked immunosorbent assay (ELISA) kits (Nanjing Jiancheng Bioengineering Institute, Nanjing, China). An ELISA kit was purchased from Shanghai Jianglai Biotechnology Co., Ltd. (Shanghai, China) for determination of fatty acid-binding protein 2 (FABP2) in serum, according to the manufacturer's instruction.

Intestinal samples were rinsed in 0.86% physiological saline of precooling (pH: 7.2–7.4; w: v = 1:9), homogenized and centrifuged (3,000 rpm, 4°C for 10 min). Protein concentration of the supernatant was measured by Coomassie brilliant blue method. Intestinal trefoil factor (ITF) was estimated by ELISA Kit provided by Shanghai Jianglai Biotechnology Co., Ltd. (Shanghai, China). The content of ITF was expressed as "pg per mg of protein."

Intestinal Morphology

Analysis of intestinal morphology by making Hematoxylin and Eosin (H&E)- stained sections as described in our previous study (Zhang J. J. et al., 2020). Briefly, the pre-fixed anterior intestinal samples with Bouin's fixative solution were subsequently dehydrated with a graded series of ethanol and cleared in xylene, then embedded in paraffin, finally sectioned at 6 um thickness. After that, sections were stained using Hematoxylin and Eosin (H&E) and mounted on glass slides. The sections were observed with positive fluorescence microscope (Leica TM 820, Nussloch, Germany), and muscular thickness (MT) and mucosal fold height (MFH) were measured using Image-Pro Plus 6.0 software (Media Cybernetics, Silver Spring, MD, United States) as described in our previous study (Zhang J. J. et al., 2020).

Intestinal Microbiota Analysis

Total DNA of intestinal samples was extracted using a DNA extraction kit, and DNA integrity and quality were measured by electrophoresis on a 1% agarose gel. Then, the V3 + V4 regions of the 16S rRNA gene of intestinal bacteria was amplified with the forward primer 338F (5′-ACTCCTACGGGAGGCAGCA-3′) and the reverse primer 806R (5′-GGACTACHVGGGTWTCTAAT-3′) by Polymerase Chain Reaction (PCR). The PCR product purity and concentration were determined with Nano-Drop®ND-1000 spectrophotometer (Nano-Drop Technologies, Wilmington, DE, United States). Subsequently, high-throughput sequencing was performed on an

Illumina HiSeq platform (Beijing Biomarker Biotechnology Co., Ltd., Beijing, China). The sequencing data have been uploaded to GenBank (Accession number, PRJNA718150). Analysis of intestinal microbiota abundance and diversity was performed using BMKCloud[1]. The detailed protocols were described in our earlier study (Yang et al., 2019).

Calculations and Statistical Analysis

The following formulas were used to calculate growth performances and feed utilization parameters: Weight gain rate (WGR,%) = 100 × (final body weight–initial body weight)/initial body weight; Specific growth rate (SGR,%/d) = 100 × (ln final body weight–ln initial body weight)/days of feeding trial; Feed conversion rate (FCR) = feed intake/(final body weight–initial body weight); Hepatosomatic index (HSI,%) = 100 × (liver weight/body weight); Survival rate (SR,%) = 100 × number of survived fish in sampling/initial number of fish allocated.

All data were subjected by one-way analysis of variance (ANOVA) followed by Duncan's multiple-range test, which was conducted to examine significant differences among treatments using SPSS statistical package version 22.0 (SPSS Inc., Chicago, United States). The results are presented as mean values followed by the standard error of the mean (Mean ± SE) and significance was declared at the $P < 0.05$.

RESULTS

Growth Performance

The growth performance of grouper is presented in **Table 2**. With increasing histamine level, WGR and SGR tend to decrease, while FCR showed an increase trend, but no significant difference was observed at the initial feed period (day 0–28). Compared with group T0, significant increased FCR and decreased WGR and SGR were observed in the groups T5 and T6 at the whole feeding period (day 0–56) ($P < 0.05$). Neither HSI nor SR statistically differed across dietary treatments at the initial feed period (day 0–28) and the whole feeding period (day 0–56) ($P > 0.05$), and the SR were above 95.56% in all groups.

Serum Non-specific Immune Parameters

The serum non-specific immune parameters are presented in **Table 3**. At days 28 and 56, the serum ACP activities in fish fed the histamine supplemented diets were lower than those fed the control diet (T0), and significant difference was observed in fish fed the diet T6 ($P < 0.05$). Fish fed the diets T4, T5, and T6 at days 28 and 56 showed significant decreased AKP activities compared to those fed the diet T0 ($P < 0.05$), while fish fed the diet T6 exhibited the lowest AKP activity. Serum SOD activity decreased with the increment of dietary histamine in experimental diets and a significant decrease was observed in the treatment T6 compared with the T0 at days 28 and 56 ($P < 0.05$). The T-AOC activities in the histamine treatments at day 28 was significantly lower than that in the control ($P < 0.05$), with the exception of the group T2. T-AOC

activity was affected negatively by all histamine treatments at day 56, while significant decrease was only observed in fish fed the diet T6 ($P < 0.05$).

Liver Biochemical Indices

The results of the liver biochemical parameters are displayed in **Table 4**. The MDA contents of fish fed the histamine supplemented diets (except for diet T1) at day 28 were significantly higher than those fed the diet T0 ($P < 0.05$). Meanwhile, compared with the group T0, significantly decreased activities of GOT and GPT were observed in group T6 ($P < 0.05$). At day 56, the MDA content in liver of fish fed diets T5 and T6 increased statistically compared with the control ($P < 0.05$). Moreover, GOT and GPT activities in groups T5 and T6 were significantly lower than those in group T0 ($P < 0.05$).

Inflammation Markers in Serum and Intestine

As can be seen from **Table 5**, serum amyloid A (SAA) and C-reactive protein (CRP) contents did not vary statistically in all dietary treatments at days 28 and 56. Compared with the control, the serum IL-1β content of fish fed diet T6 increased significantly at day 28 ($P < 0.05$). At day 56, serum IL-1β contents of fish fed the histamine supplemented diets increased statistically compare with those fed the diet T0 ($P < 0.05$), while the treatment T6 showed the highest value. In groups T4, T5, and T6, the contents of serum fatty acid-binding protein 2 (FABP2) and intestinal trefoil factor (ITF) increased significantly at day 28 as compared to the control and the highest values exhibited in fish fed diet T6 ($P < 0.05$). At day 56, the contents of serum FABP2 and intestinal ITF in group T6 were significantly higher than that in the control ($P < 0.05$).

Intestinal Morphology

Intestinal morphometrical parameters of grouper fed different diets at days 28 and 56 are shown in **Table 6**. There was a significant reduction of muscular thickness (MT) in fish fed diets T5 and T6 at days 28 and 56 compared with those fed the diet T0 ($P < 0.05$). In addition, the mucosal fold height (MFH) in groups T4, T5, and T6 at day 28 was lower significantly than the control, while the significant decrease was only observed in group T6 ($P < 0.05$). The intestine section of fish fed with diet supplemented with histamine displayed an inflammation and damage, characterized by a thin MT, reduced MFH, while the most serious impairment was observed in fish fed diets T5 and T6 with higher doses of histamine (0.25 and 0.3%) (**Figures 1**, **2**).

Intestinal Microbiota

The phylum level analysis demonstrated that *Proteobacteria*, *Firmicutes*, *Bacteroidetes*, *Actinobacteria*, *Fusobacteria*, *Chloroflexi,* and *Acidobacteria* constituted common predominant bacterial phylum in all groups, and histamine supplemented diets significantly reduced the relative abundance of *Firmicutes* and *Bacteroidetes*, significantly increased the relative abundance of *Proteobacteria* and *Fusobacteria*, especially in groups T5

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[1]www.biocloud.net

TABLE 2 | Effects of histamine on growth performance of grouper (*Epinephelus coioides*).

		Groups						
		T0	T1	T2	T3	T4	T5	T6
0–28 d	WGR (%)	138.59 ± 17.48	124.55 ± 3.90	122.56 ± 6.49	121.07 ± 8.27	120.24 ± 9.42	120.01 ± 8.60	119.05 ± 3.67
	SGR (%)	3.09 ± 0.25	2.89 ± 0.06	2.85 ± 0.10	2.83 ± 0.13	2.81 ± 0.16	2.81 ± 0.14	2.80 ± 0.06
	FCR	1.06 ± 0.08	1.13 ± 0.04	1.14 ± 0.06	1.20 ± 0.02	1.17 ± 0.10	1.18 ± 0.08	1.20 ± 0.04
	HSI (%)	2.24 ± 0.24	1.92 ± 0.23	1.78 ± 0.12	2.15 ± 0.28	2.09 ± 0.24	2.07 ± 0.16	2.03 ± 0.18
	SR (%)	98.89 ± 1.11	100.00 ± 0.00	96.67 ± 1.92	97.78 ± 2.22	97.78 ± 1.11	98.89 ± 1.11	97.78 ± 1.11
0–56 d	WGR (%)	235.43 ± 9.40[a]	231.62 ± 8.41[a]	228.60 ± 15.57[ab]	217.59 ± 19.83[ab]	216.57 ± 7.52[ab]	214.08 ± 5.86[ab]	210.51 ± 9.90[b]
	SGR (%)	2.16 ± 0.05[a]	2.14 ± 0.04[a]	2.12 ± 0.09[ab]	2.06 ± 0.11[ab]	2.06 ± 0.04[ab]	2.04 ± 0.03[b]	2.02 ± 0.06[b]
	FCR	1.01 ± 0.06[a]	1.10 ± 0.06[ab]	1.13 ± 0.03[abc]	1.13 ± 0.07[abc]	1.13 ± 0.02[abc]	1.19 ± 0.04[bc]	1.26 ± 0.01[c]
	HSI (%)	2.44 ± 0.14	2.28 ± 0.17	2.00 ± 0.15	2.37 ± 0.12	2.02 ± 0.12	2.34 ± 0.14	2.06 ± 0.11
	SR (%)	98.89 ± 1.11	95.56 ± 1.11	95.56 ± 2.22	96.67 ± 1.92	95.56 ± 1.11	95.56 ± 1.11	95.56 ± 1.11

Different characters in the same row data indicate significant differences (P < 0.05).

TABLE 3 | Effects of histamine on serum immune parameters of grouper (*Epinephelus coioides*).

		Groups						
		T0	T1	T2	T3	T4	T5	T6
28 d	ACP (U/100 mL)	7.34 ± 0.23[a]	7.16 ± 0.15[a]	7.03 ± 0.29[a]	7.11 ± 0.14[a]	6.80 ± 0.19[ab]	6.72 ± 0.24[ab]	6.19 ± 0.42[b]
	AKP(U/100 mL)	30.50 ± 2.88[a]	26.44 ± 2.87[ab]	25.73 ± 1.84[ab]	25.18 ± 0.44[ab]	22.43 ± 1.26[b]	22.33 ± 1.88[b]	21.06 ± 1.20[b]
	SOD (U/mL)	182.44 ± 3.38[a]	180.57 ± 4.10[a]	179.70 ± 3.69[a]	155.58 ± 5.80[b]	167.50 ± 9.46[ab]	157.66 ± 3.99[b]	131.83 ± 5.65[c]
	T-AOC (mM)	1.56 ± 0.11[a]	1.25 ± 0.13[b]	1.29 ± 0.06[ab]	1.23 ± 0.04[b]	1.15 ± 0.03[bc]	0.87 ± 0.17[c]	1.12 ± 0.06[bc]
56 d	ACP (U/100 mL)	7.15 ± 0.04[a]	7.09 ± 0.06[a]	7.15 ± 0.16[a]	6.98 ± 0.22[a]	6.88 ± 0.08[ab]	6.84 ± 0.09[ab]	6.60 ± 0.05[b]
	AKP(U/100 mL)	27.21 ± 0.46[a]	25.39 ± 0.70[ab]	25.21 ± 1.44[ab]	24.43 ± 0.42[b]	22.08 ± 0.34[c]	21.13 ± 0.36[c]	20.56 ± 0.72[c]
	SOD (U/mL)	155.14 ± 4.28[a]	153.68 ± 6.56[a]	149.19 ± 9.28[ab]	143.08 ± 12.03[ab]	142.79 ± 9.48[ab]	143.25 ± 9.17[ab]	123.26 ± 4.23[b]
	T-AOC (mM)	1.66 ± 0.13[a]	1.60 ± 0.07[a]	1.59 ± 0.22[a]	1.44 ± 0.04[ab]	1.40 ± 0.20[ab]	1.19 ± 0.08[ab]	1.09 ± 0.18[b]

Different characters in the same row data indicate significant differences (P < 0.05). ACP, acid phosphatase; AKP, activities of alkaline phosphatase; SOD, superoxide dismutase; T-AOC, total antioxidant capacity.

TABLE 4 | Effects of histamine on liver biochemical indices of grouper (*Epinephelus coioides*).

		Groups						
		T0	T1	T2	T3	T4	T5	T6
28 d	MDA (nmol/gprot)	2.37 ± 0.74[a]	3.39 ± 1.86[a]	8.83 ± 2.31[b]	8.59 ± 2.43[b]	9.66 ± 0.95[b]	11.01 ± 0.62[b]	11.13 ± 1.54[b]
	GOT(U/gprot)	40.19 ± 0.87[a]	39.90 ± 2.42[a]	39.68 ± 1.20[ab]	34.35 ± 2.54[ab]	39.13 ± 1.62[ab]	37.32 ± 2.95[ab]	33.16 ± 1.15[b]
	GPT(U/gprot)	97.04 ± 8.11[a]	96.49 ± 13.12[a]	85.78 ± 6.75[ab]	73.61 ± 3.73[ab]	75.09 ± 3.12[ab]	85.18 ± 8.41[ab]	62.55 ± 8.84[b]
56 d	MDA (nmol/Gprot)	5.95 ± 1.11[a]	8.21 ± 1.87[ab]	8.22 ± 1.55[ab]	8.51 ± 0.49[ab]	8.78 ± 1.25[ab]	11.19 ± 1.78[b]	11.00 ± 1.73[b]
	GOT(U/gprot)	39.57 ± 1.08[a]	37.04 ± 1.44[ab]	36.41 ± 1.64[ab]	37.38 ± 1.17[ab]	36.35 ± 0.91[ab]	34.74 ± 1.41[b]	35.19 ± 1.21[b]
	GPT(U/gprot)	95.21 ± 7.11[a]	78.40 ± 6.39[ab]	87.18 ± 3.46[ab]	80.32 ± 5.36[ab]	80.11 ± 7.28[ab]	71.73 ± 3.05[b]	73.61 ± 4.56[b]

Different characters in the same row data indicate significant differences (P < 0.05). MDA, Malondialdehyde; GOT, glutamic oxaloacetic transaminase; GPT, glutamic propylic transaminase.

and T6 (*P* < 0.05) (**Figure 3A** and **Table 7**). At the genus level, enhanced abundance of *Cetobacterium* was observed in all treatments (except T3) compared with the control (T0), as well as decreased abundances of *Ruminiclostridium* and uncultured *Bacteroidales*_S24-7_group and *Lachnospiraceae*, while significant changes were observed in high histamine groups (0.25 and 0.3%) (*P* < 0.05) (**Figure 3B** and **Table 7**).

The Beta (β)-diversity boxplots and UPGMA phylogenetic tree based on binary_jaccard distance were used to analyze the microbial similarities among different groups. From the data in **Figure 4A**, a clear separation was observed between histamine treated groups and the control (T0) at phylum level, suggesting that supplementation of histamine changed the intestinal microbial community in *E. coioides*, especially in groups T5 and T6. However, no significant differences were found for the intestinal microbial β-diversity in different treatments, although apparent difference was observed in groups T5 and T6 (**Figure 4B**).

TABLE 5 | Effects of histamine on inflammation markers of grouper (*Epinephelus coioides*).

		Groups						
		T0	T1	T2	T3	T4	T5	T6
28 d	IL-1β (ng/L)	57.69 ± 8.45[a]	71.20 ± 0.62[a]	73.67 ± 4.32[ab]	79.99 ± 3.54[ab]	73.85 ± 1.51[ab]	80.20 ± 0.90[ab]	101.79 ± 9.50[b]
	SAA (μg/mL)	8.12 ± 0.43	8.80 ± 1.04	9.15 ± 1.25	8.80 ± 0.67	9.11 ± 1.02	8.95 ± 0.63	9.51 ± 0.83
	CRP (μg/mL)	7.61 ± 0.26	8.13 ± 0.40	8.12 ± 0.32	8.23 ± 0.21	8.27 ± 0.23	8.37 ± 0.15	8.40 ± 0.07
	ITF (pg/mgprot)	175.08 ± 5.71[a]	204.53 ± 5.87[abc]	201.15 ± 8.63[abc]	194.40 ± 14.51[ab]	213.74 ± 2.92[bc]	225.38 ± 16.09[c]	231.18 ± 4.13[c]
	FABP2 (ng/mL)	15.79 ± 1.06[a]	16.73 ± 1.98[a]	18.96 ± 0.16[ab]	19.25 ± 1.65[ab]	21.45 ± 0.38[b]	20.49 ± 1.13[b]	21.91 ± 0.19[b]
56 d	IL-1β (ng/L)	49.96 ± 9.51[a]	77.62 ± 2.98[b]	76.50 ± 3.00[b]	78.92 ± 2.95[b]	81.20 ± 4.96[b]	74.92 ± 1.78[b]	82.57 ± 4.33[b]
	SAA (μg/mL)	7.39 ± 0.52	8.83 ± 0.71	9.28 ± 0.91	9.26 ± 1.06	8.13 ± 1.00	9.82 ± 1.08	10.14 ± 0.89
	CRP (μg/mL)	7.47 ± 0.40	7.72 ± 0.92	8.20 ± 0.51	7.95 ± 0.13	7.62 ± 1.10	8.25 ± 0.13	8.33 ± 0.88
	ITF (pg/mgprot)	153.51 ± 4.15[a]	163.06 ± 9.67[ab]	166.04 ± 1.76[ab]	186.50 ± 7.44[bc]	175.19 ± 9.39[abc]	174.55 ± 10.87[abc]	190.87 ± 3.65[c]
	FABP2 (ng/mL)	10.97 ± 0.98[a]	11.50 ± 0.79[a]	12.27 ± 1.09[a]	12.14 ± 0.83[a]	13.11 ± 0.91[ab]	13.81 ± 0.10[ab]	15.51 ± 1.28[b]

Different characters in the same row data indicate significant differences ($P < 0.05$). IL-1β, Interleukin-1 beta; SAA, serum amyloid A; CRP, C-reactive protein; ITF, intestinal trefoil factor; FABP2, intestinal-type fatty acid-binding protein.

DISCUSSION

An initial objective of the present study was to evaluate the effect of graded levels of dietary histamine on performance of grouper (*E. coioides*). In the present study, the SR was unaffected by dietary histamine, which is in line with the result of previous studies (Watanabe et al., 1987; Fairgrieve et al., 1994; Tapia-Salazar et al., 2001; Zhai et al., 2020). Furthermore, we have demonstrated that the growth performance was not statistically different among the dietary treatments at initial feeding period (0–28 days), whereas dietary histamine suppressed growth performance at the whole feeding period (0–56 days), especially when histamine supplementary doses were 0.25 and 0.3%. Similar results were reported in Nile tilapia (*Oreochromis niloticus*) (Reyes-Sosa and Castellanos-Molina, 1995), Atlantic halibut (*Hippoglossus hippoglossus*) (Aksnes and Mundheim, 1997), Atlantic salmon (*Salmo salar* L.) (Opstvedt et al., 2000), Japanese seabass (*Lateolabrax japonicus*) (Hu et al., 2013), and American eel (*A. rostrata*) (Zhai et al., 2020). In Chinese mitten crab (*E. sinensis*), however, histamine supplementation (1, 2, 4 g/kg) did not affect the growth performance (Zhao et al., 2016). Tapia-Salazar et al. (2001) studied the effect of dietary histamine supplementation in blue shrimp *Litopenaeus stylirostris* and observed that a quadratic effect between weight gain and histamine supplementation levels, while the optimum dietary histamine supplementation levels (1,200 and 2,400 mg/kg), had favorable effects on growth performance. He et al. (2018) also reported that optimum dietary histamine level (18 mg/kg) significantly improved growth performance of yellow catfish (*Pelteobagrus fulvidraco*). Diamine oxidase (DAO) is one of the crucial enzymes in charge of the exogenous histamine metabolizing and scavenging system in organisms (Smolinska et al., 2014). Several studies suggested that DAO activity exists diversity in animals due to different contents of histamine and histidine infeed (Waton, 1963; Yang et al., 2010), which is a major reason for the difference in histamine intolerance. It is possible, therefore, that the sensitivities of fish and shrimp to histamine are highly species-specific, which partly explained the discrepancy

of growth performance, although the information is lacking in aquatic animals.

Serum non-specific immune parameters served as important indexes that reflect health status of animals (Yu et al., 2019; Zhai et al., 2020). AKP and ACP, two important phosphatase enzymes, play a key role in clearing extracellular invaders and immune defense (Ellis et al., 2011; Matozzo et al., 2011; Tripathi et al., 2012). In the current study, serum ACP and AKP activities decreased significantly in fish fed 0.25 and 0.3% histamine containing diets, suggesting suppressed immune response. In accord with our results, Zhai et al. (2020) noticed the reduction of serum ACP and AKP activities in American eel (*A. rostrata*) fed commercial diet (containing 217 mg/kg histamine) supplemented 300 mg/kg histamine. Another study in Chinese mitten crab (*E. sinensis*) had reported that after 6 h of histamine injection, ACP and AKP activities in the 1 and 50 mg/g (body weight) histamine treated groups were significantly lower than those in the control (Zhao et al., 2012). However, contrary results were reported that improvement of lysozyme activity in histamine treated *Tetrahymena* (Kovacs and Csaba, 1990) and increased AKP activities were observed in all histamine treated groups (50, 100, and 200 μg/kg) in rabbits (Tripathi et al., 2012). Phosphatase activity enhanced significantly during incubation of *Tetrahymena pyriformis* in histamine-supplemented cultures, and histamine was identified as a phagocytic stimulus affecting phosphatase synthesis and phagocytosis of hemocytes (Kovacs and Csaba, 1990; Ellis et al., 2011; Matozzo et al., 2011). These inconsistent effects of histamine may be due to the different administration regimes and species specificity. Generally, the serum T-AOC and SOD activities can provide an indication of the antioxidant status of organisms, while higher serum T-AOC and SOD activities might indicate higher antioxidant capacity (Reddy et al., 1991). In the present study, the significant reduction of serum T-AOC and SOD activity might indicate a diminished antioxidant capability by high dose of histamine (0.25 and 0.3%). However, Zhao et al. (2012) reported that injected histamine could increase SOD activity at 6–24 h in *E. sinensis*. In an *in vitro* study, enhancement of peroxide activity and superoxide anion production were observed in whole hemolymph of Sydney

TABLE 6 | Effects of histamine on foregut muscular thickness and mucosal fold height of grouper (*Epinephelus coioides*).

		Groups						
		T0	T1	T2	T3	T4	T5	T6
28 d	MT (µm)	101.31 ± 8.00^{a}	88.34 ± 2.43^{ab}	86.02 ± 7.08^{ab}	85.12 ± 4.55^{ab}	84.37 ± 3.87^{ab}	78.99 ± 3.83^{b}	72.31 ± 8.73^{b}
	MFH (µm)	251.63 ± 9.84^{a}	215.99 ± 20.34^{ab}	204.28 ± 20.07^{ab}	208.27 ± 15.74^{ab}	198.15 ± 16.86^{b}	173.30 ± 10.40^{b}	179.96 ± 13.60^{b}
56 d	MT (µm)	106.12 ± 9.63^{a}	98.00 ± 5.46^{ab}	84.72 ± 7.91^{ab}	85.74 ± 7.37^{ab}	97.28 ± 4.94^{ab}	83.34 ± 6.96^{b}	77.62 ± 6.29^{b}
	MFH (µm)	262.21 ± 17.60^{a}	221.55 ± 18.30^{ab}	213.96 ± 22.81^{ab}	217.76 ± 19.32^{ab}	216.79 ± 24.97^{ab}	214.41 ± 20.99^{ab}	194.50 ± 15.70^{b}

Different characters in the same row data indicate significant differences ($P < 0.05$). MT, muscular thickness; MFH, mucosal fold height.

rock oysters (*Saccostrea glomerata*) after treatment for 30 min with noradrenaline, another biogenic amine (Aladaileh et al., 2008). These paradoxes may be explained in that short-term histamine stress can rapidly improve the antioxidant capacity by compensatory mechanism; however, long-term dietary histamine damage the ability to respond to reactive oxygen intermediates, which subsequently result in oxidative damage and cause the noticed decline with T-AOC and SOD activities.

Liver biochemical indices provide generally effective information about the function and health status of liver. Malondialdehyde (MDA), an endogenous genotoxic product of enzymatic and oxygen radical-induced lipid peroxidation, is commonly used as a bioindicator of oxidative injury. Additionally, the reduction of liver GPT and GOT activities suggested probable liver damage or dysfunction (Zhang J. Z. et al., 2020). In this study, histamine was noticed to cause higher MDA level and lower activities of GPT and GOT in liver. In accordance with our results, histamine-rich diets resulted in liver injury with a significant improvement in plasma GOT and GPT activities (Li et al., 2018; Zhai et al., 2020). Study done in immunized rabbits observed that histamine may cause hepatic damage at different dosage by determining the characteristic ratios and changes in serum GPT and GOT activities (Tripathi et al., 2012). However, different from the above studies, dietary supplementation with 10 g/kg histamine did not significantly affect the plasma GOT and GPT activities in rainbow trout (Shiozaki et al., 2004). The reason for these controversial results is unclear but it may have something to do with different degree of histamine intolerance in rearing species. Interestingly, grouper fed diets supplemented low dose histamine (0.1, 0.15, and 0.2%) at day 28 showed significantly lower antioxidative capacity (estimating by determining the activity of SOD, the T-AOC, and the level of MDA) compared with those fed the control diet (T0), but no significant differences were observed at day 56. This suggested that grouper had the capacity to adapt their antioxidative physiology changes caused by a long-term exposure to low dose of dietary histamine to some degree.

It has been evidenced extensively that the enhancement of pro-inflammatory factors (e.g., IL-1β, ITF, and FABP2) sharpens the inflammatory extent and results in intestinal and local tissue injury in organisms (Andre et al., 2000; Sharma et al., 2004; Levy et al., 2009; Overland et al., 2009; Skov et al., 2012; Venold et al., 2012; Song et al., 2013; Couto et al., 2014; Lee et al., 2017; Impellizzeri et al., 2018). The present study showed that dietary histamine increased the intestinal ITF and serum IL-1β and FABP2 levels at days 28 and 56, especially in the high dose group (0.3% histamine), illustrating that supplementation of histamine induced inflammation in grouper. In line with our results, Zhai et al. (2020) reported that high level of dietary histamine resulted in liver inflammation and oxidative damage in juvenile American eel (*A. rostrata*). These results confirmed that histamine is biologically active in fish with regulating the inflammatory response (Mulero et al., 2007). Interestingly, the contents of intestinal ITF and serum IL-1β and FABP2 at day 56 were lower than those at day 28, indicating that grouper adapted to dietary histamine gradually during the long-term feeding period. CRP and SAA are two key acute phase proteins associated with an
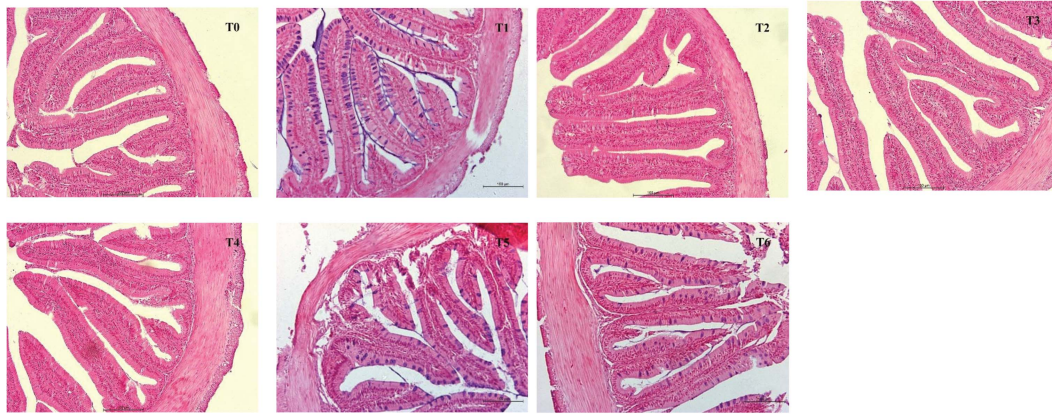
FIGURE 1 | The foregut morphological images from H&E-stained section of *E. coioides* fed the experimental diets for 28 days (100×).
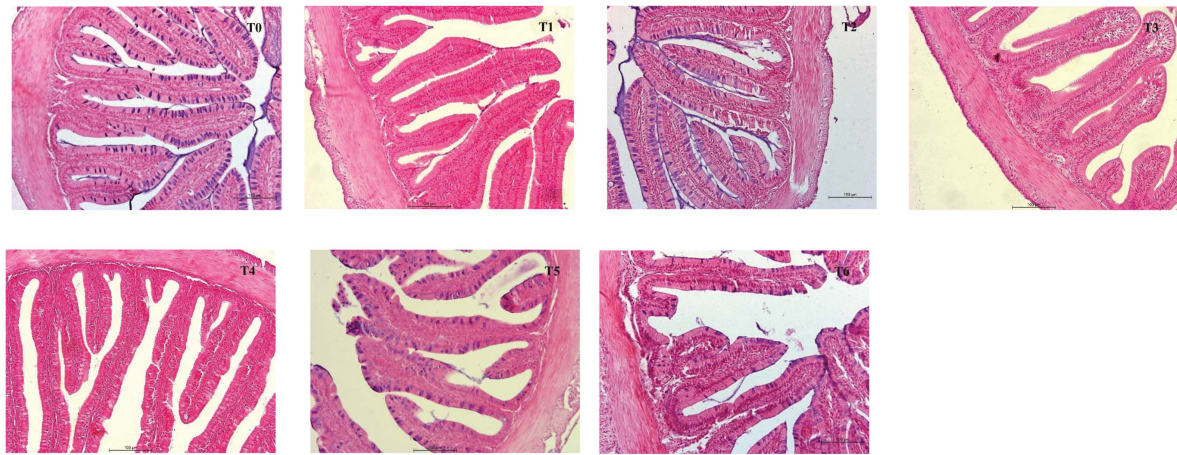

FIGURE 2 | H&E stained anterior intestine morphological sections of *E. coioides* fed the experimental diets for 56 days (100×).
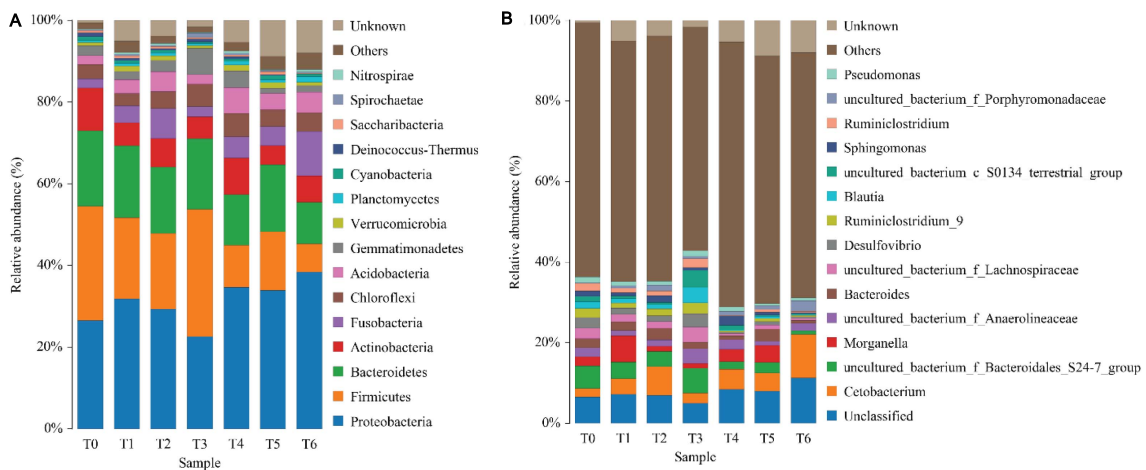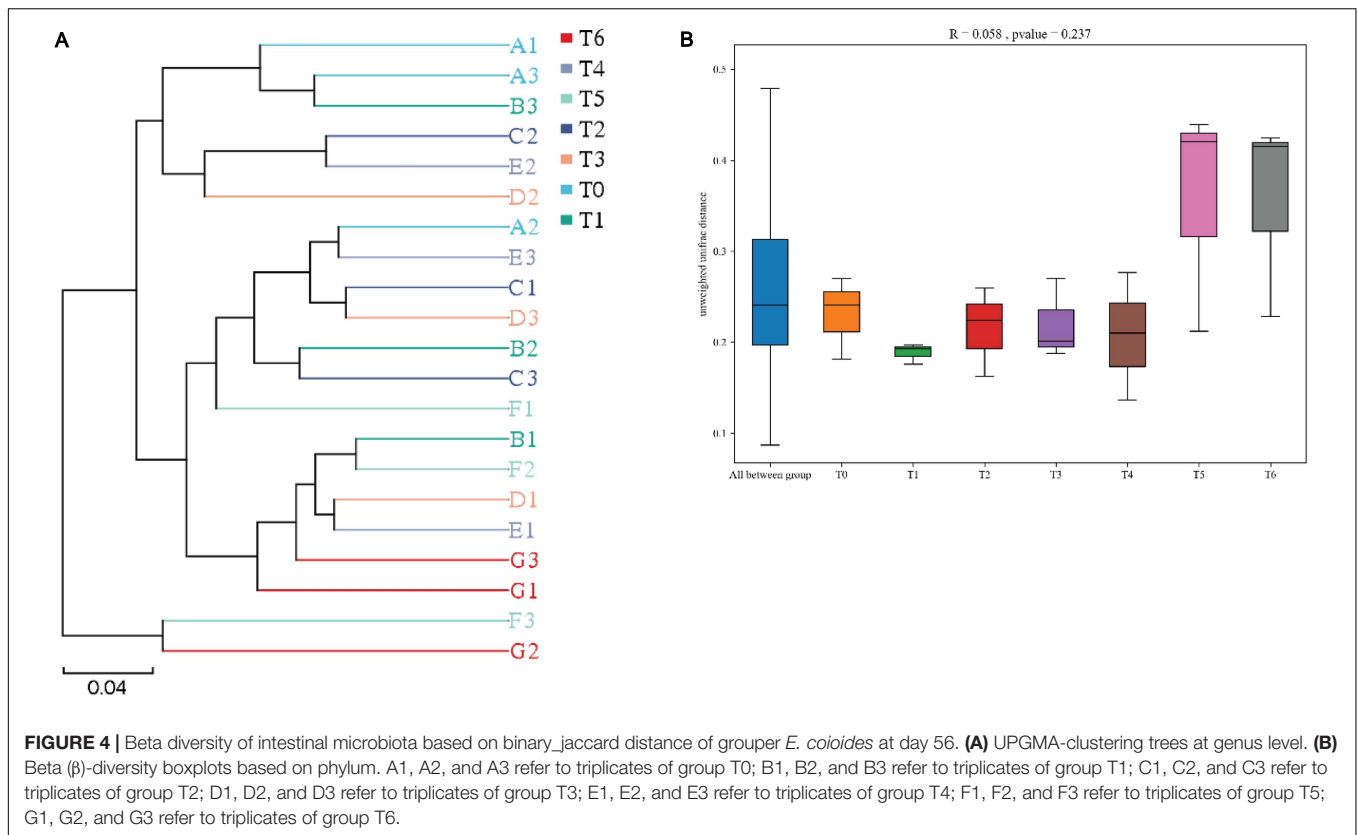

FIGURE 3 | Taxonomy classification of reads from 16 S rRNA V3–V4 regions at the phylum **(A)** and genus **(B)** taxonomic levels in intestinal microbiota of grouper *E. coioides* at day 56. Only top 15 most abundant (based on relative abundance) bacteria phylum and genus were exhibited in **(A,B)**, and other phylum and genus were all classified as "others."

TABLE 7 | MetaStat analysis of the abundance of intestinal bacterial phyla and genera ($\times 10^{-4}$) of grouper at day 56.

	Groups						
	T0	T1	T2	T3	T4	T5	T6
Phylum							
Proteobacteria	2040.69 ± 57.82[c]	3130.35 ± 403.20[bc]	2886.99 ± 91.96[abc]	2251.97 ± 350.30[ab]	3351.02 ± 150.71[a]	3326.06 ± 133.75[a]	3761.60 ± 644.49[a]
Firmicutes	3700.38 ± 58.19[a]	1961.52 ± 734.61[bc]	1766.59 ± 757.48[bc]	2805.52 ± 150.27[ab]	994.64 ± 192.88[c]	1409.50 ± 182.22[c]	705.21 ± 182.13[c]
Bacteroidetes	1847.51 ± 400.61[a]	1738.90 ± 86.25[a]	1576.15 ± 296.27[ab]	1724.92 ± 154.73[a]	1191.04 ± 135.70[ab]	1600.42 ± 124.50[ab]	986.52 ± 159.10[b]
Actinobacteria	525.29 ± 5.24	552.38 ± 28.50	700.10 ± 176.10	526.15 ± 45.14	897.58 ± 229.03	464.96 ± 4.42	703.75 ± 430.76
Fusobacteria	313.50 ± 164.16[b]	410.21 ± 196.24[b]	1100.79 ± 479.88[b]	256.0 ± 132.49[b]	618.42 ± 31.93[b]	542.80 ± 51.75[b]	2067.00 ± 380.63[a]
Genus							
Cetobacterium	21.73 ± 1.80[b]	385.95 ± 184.59[b]	739.99 ± 584.86[b]	250.28 ± 130.14[b]	460.92 ± 128.02[b]	432.86 ± 109.06[b]	2060.84 ± 379.77[a]
uncultured_bacterium_f _Bacteroidales_S24-7_group	561.79 ± 181.85[ab]	402.64 ± 104.45[abc]	360.75 ± 191.52[abc]	613.14 ± 31.71[a]	177.56 ± 89.43[bc]	255.64 ± 78.10[abc]	95.32 ± 34.33[c]
uncultured_bacterium_f _Anaerolineaceae	224.24 ± 87.73	128.02 ± 64.75	145.84 ± 28.56	361.63 ± 58.64	255.06 ± 172.24	92.03 ± 15.37	175.60 ± 67.39
Bacteroides	229.35 ± 42.64	217.53 ± 25.86	283.48 ± 158.23	162.93 ± 13.33	89.13 ± 38.18	304.73 ± 76.47	69.01 ± 23.18
uncultured_bacterium_f _Lachnospiraceae	368.89 ± 8.84[a]	184.39 ± 97.95[ab]	153.00 ± 97.84[ab]	364.77 ± 105.68[a]	52.77 ± 16.05[b]	98.91 ± 27.92[b]	49.87 ± 9.64[b]
Desulfovibrio	259.41 ± 124.74[ab]	152.03 ± 103.67[ab]	136.93 ± 79.53[ab]	331.51 ± 38.64[a]	36.54 ± 14.25[b]	86.27 ± 49.10[b]	46.22 ± 15.91[b]
Ruminiclostridium_9	233.07 ± 107.88[ab]	121.92 ± 90.05[ab]	160.40 ± 93.50[ab]	264.29 ± 36.80[a]	32.87 ± 13.49[b]	42.70 ± 11.07[b]	33.69 ± 1.35[b]
Blautia	169.80 ± 80.76[ab]	109.18 ± 68.33[b]	105.18 ± 71.42[b]	374.90 ± 175.21[a]	22.85 ± 13.58[b]	55.73 ± 20.30[b]	29.77 ± 7.38[b]
uncultured_bacterium_c _S0134_terrestrial_group	132.51 ± 60.92[ab]	59.73 ± 44.25[b]	49.68 ± 10.66[b]	411.16 ± 218.66[a]	116.70 ± 82.22[ab]	26.90 ± 14.61[b]	12.21 ± 4.20[b]
Sphingomonas	131.44 ± 66.12	84.96 ± 17.95	168.32 ± 82.38	75.30 ± 18.66	149.41 ± 38.94	69.58 ± 1.89	30.13 ± 9.64
Ruminiclostridium	280.56 ± 2.83[a]	110.24 ± 76.35[bc]	111.06 ± 69.88[bc]	218.30 ± 12.36[ab]	17.46 ± 9.36[c]	70.66 ± 26.14[c]	26.85 ± 6.28[c]
Bradyrhizobium	21.77 ± 8.28[b]	55.43 ± 5.41[b]	140.10 ± 84.68[b]	30.20 ± 8.15[b]	336.43 ± 131.07[a]	108.38 ± 45.62[b]	28.93 ± 9.39[b]

Different characters in the same row data indicate significant differences (P < 0.05).

FIGURE 4 | Beta diversity of intestinal microbiota based on binary_jaccard distance of grouper *E. coioides* at day 56. **(A)** UPGMA-clustering trees at genus level. **(B)** Beta (β)-diversity boxplots based on phylum. A1, A2, and A3 refer to triplicates of group T0; B1, B2, and B3 refer to triplicates of group T1; C1, C2, and C3 refer to triplicates of group T2; D1, D2, and D3 refer to triplicates of group T3; E1, E2, and E3 refer to triplicates of group T4; F1, F2, and F3 refer to triplicates of group T5; G1, G2, and G3 refer to triplicates of group T6.

acute inflammatory response, with a significant enhancement of serum CRP and SAA levels following organism inflammation, injury, or infection (Pepys et al., 1978; Lindhorst et al., 1997; Pepys and Hirschfield, 2003; MacCarthy et al., 2008; Rosani et al., 2016; Franco-Martinez et al., 2019; Bello-Perez et al., 2020; Gursky, 2020; Williams et al., 2020). Derebe et al. (2014) reported that vitamin A deficiency may lead to an immune deficiency in mice with decreasing the abundances of SAAs in small intestine and liver. Another study in mice also demonstrated that animals may against lipopolysaccharides (LPS)-induced inflammation and tissue injury through increasing content of serum acute-phase SAA (Cheng et al., 2018). On the other hand, MacCarthy et al. (2008) reported that serum CRP-like protein level improved several folds in common carp (*Cyprinus carpio*) challenged with the pathogen *Aeromonas hydrophila*. A study done in rainbow trout showed that serum CRP concentration rose to a maximum at 6 or 9 days after exposure to formalin for 3.5 h at 300 ppm or 9.5 h at 30 ppm, respectively, and subsequently it began to decline until below normal at day 18 (Kodama et al., 2004). Kodama et al. (2004) also reported that the CRP content enhanced significantly to a maximum at day 3 after exposure to metriphonate (9.9 times higher than normal), then reduced to below normal. Interestingly, the present study showed that dietary histamine did not markedly affect serum CRP and SAA contents at days 28 and 56, although slight enhancement was observed in histamine-supplemented groups. A possible explanation for this might be that serum acute phase proteins (CRP and SAA) contents had recovered in some extent after starvation for 24 h. Unfortunately,

serum CRP and SAA contents have not been immediately measured after feeding in this study. Taken together, exogenous high dose histamine not only causes liver oxidative damage but also induces inflammation on the digestive tract in both terrestrial and aquatic animals.

Intestinal morphometrical change is a helpful indicator of gut inflammation and health status (Venold et al., 2012). Intestinal integrity is mainly referred by MT, MFH, and abundance of goblet cells (Garcia-Ortega et al., 2016). Generally, higher MT and MFH indicated healthier intestinal structure, strongly linked to the suppression of enteritis and nutrient transport capacity. In this study, the reduction of MT and MFH demonstrated high doses of histamine (0.25 and 0.3%) exert harmfulness effect on intestinal morphology of grouper. Similar results were reported that high dose of histamine (103.5 mg/kg or more) may result in destruction of gastric and intestinal mucosal barrier in yellow catfish (*P. fulvidraco*) (He et al., 2018). As far as we know, to date, information about the effects of histamine on intestinal morphology in fish remains limited. Several studies indicated that histological and morphological pathology of digestive systems appeared in both rainbow trout and chicks when dietary histamine content exceeded 2 g/kg (Watanabe et al., 1987; Fairgrieve et al., 1994).

It has been extremely reported that intestinal microbiota might be of crucial importance to host health by improving intestinal morphology (Lee et al., 2014; Sayyaf Dezfuli et al., 2018; Torraca and Mostowy, 2018; Cani et al., 2019; Liu et al., 2019; Ortega et al., 2019), modulating metabolic, physiological,

and immunological processes (Al-Fataftah and Abdelqader, 2014; Reda and Selim, 2015; Wang et al., 2018; Heiss and Olofsson, 2019; Deng et al., 2020), and which is highly sensitive to dietary ingredients and components (Ringø et al., 2016). In the current study, the intestinal microbiota of grouper was dominated by *Proteobacteria*, *Firmicutes*, *Bacteroidetes,* and *Actinobacteria*, which is in keeping with our previous studies in grouper (Yang et al., 2019). Dietary 0.3% histamine significantly enhanced relative abundance of *Fusobacteria* compared with the control. Bacteria from this phylum includes several common pathogens in human (Tahara et al., 2014; Han, 2015; Harrandah et al., 2021) and aquatic animals (Meng et al., 2021; Wang et al., 2021), which can cause tissue necrosis and inflammatory response of the host. The relative abundances of *Firmicutes* and *Bacteroidetes* in histamine supplemented groups were lower than those in the control, and it has been reported that members of these phyla improve the functions of intestinal mucosal barrier and non-specific immunity of fish (Costantini et al., 2017; Duan et al., 2018; Wang et al., 2019; Meng et al., 2021). These results may partly explain why the growth performance and non-specific immunity of grouper in the control group were higher than those in histamine supplemented groups. Although significant difference was not observed in intestinal microbial diversity of grouper, higher histamine-treated diets changed bacterial composition in the intestine and increased its diversity, such as increased relative abundances of *Cetobacterium*, as well as decreased abundances of *Ruminiclostridium*, uncultured_bacterium_f_*Lachnospiraceae,* and uncultured_bacterium_f_ *Bacteroidetes*_S24-7_group. In accord with our study, Ye et al. (2020) reported that chilled trash fish generally contain high levels of biogenic amines (such as histamine) (Zhao et al., 2012, 2016), led to significantly decreased intestinal beneficial bacteria (e.g., *Bacteroidetes*_S24-7_group and *Lachnospiraceae*, etc.) in hybrid grouper (*Epinephelus fuscoguttatus* ♀ × *Epinephelus lanceolatus* ♂), paralleled with suppression of growth performance. As for horse study, supplementation of *Saccharomyces cerevisiae* (*S. cerevisiae*) modulated positively the overall structure of intestinal microbiota with increased relative abundance of *Lachnospiraceae* (Garber et al., 2020), which is a family of butyrate-producing bacteria (Nicholson et al., 2012; Hamilton et al., 2020). On the other hand, high fat diet resulted in a reduction of the relative abundance of the *Bacteroidetes*_S24-7_group and *Lachnospiraceae* in mice, which might be one of the primary etiological mechanisms underlying obesity (Li et al., 2020). Similar to this study, the lower relative abundance of *Cetobacterium* is accompanied by greater growth performance in tilapia (*O. niloticus*) (Standen et al., 2015; Li et al., 2019). Moreover, combined with the poor growth performance and increased relative abundances of *Cetobacterium* in the soybean meal (SM) group, Wang et al. (2020) speculated that *Cetobacterium* may exert a harmful effect in bullfrog (*Lithobates catesbeianus*). However, these results are contrary to that of Meng et al. (2021) who suggested *Cetobacterium* has a beneficial effect on the production of vitamin B-12 in common carp (*Cyprinus carpio* L.). In the present study, combined with the results of intestinal morphology and inflammation markers, the increase of intestinal microbial diversity by supplemented histamine may be adverse to maintain homeostasis of intestine, indicating a tendency to induce inflammation, which is in line with previous study (Reveco et al., 2014). The above data suggested that the intestinal microbiota composition of grouper was greatly shaped by supplementation of high dose of histamine, which might negatively affect the growth performance, immune function, and intestinal morphology.

CONCLUSION

Diet supplemented with no more than 0.2% histamine did not negatively affect the growth performance, immune response, and intestinal health in grouper, while high doses (0.25 and 0.3%) of dietary histamine exert apparently negative effects on growth performance, immune response, and intestinal health in grouper. This study lays the foundation for future studies on exploring effective strategies to eliminate the adverse effects of histamine in marine fish.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found below: NCBI [accession: PRJNA718150].

ETHICS STATEMENT

The animal study was reviewed and approved by the Animal Care and Use Committee of Jimei University.

AUTHOR CONTRIBUTIONS

Z-YL: investigation and original draft. H-LY: data analysis and writing. L-HH: investigation and data analysis. WY: feed preparation and animal trial. C-XA: review and editing. Y-ZS: supervision, project administration, funding acquisition, review and editing. All authors contributed to the article and approved the submitted version.

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