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ORIGINAL ARTICLE

Effects of resveratrol on growth, antioxidative status and immune response of snakehead fish (*Channa argus*)

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Abstract

To explore the effects of resveratrol (RES) supplemented in diet, growth performance, levels of antioxidant activities and immune parameters of *Channa argus* were determined. Six experimental diets were formulated, which contain RES levels within 0–125 mg/kg diet. After feeding trial, the results of growth performance showed that feeding more than 75 mg RES/kg diet could significantly promote *C. argus* special growth rate (SGR, $p < .05$). The level of malondialdehyde (MDA) was not significantly changed in *C. argus* fed with RES supplement diet ($p > .05$). The levels of superoxide dismutase (SOD), catalase (CAT) and glutathione-*S*-transferase (GST) were significantly increased in tissues and serum of *C. argus* fed with RES supplement diet within 75–125 mg/kg ($p < .05$). Similarly, total antioxidant capacity (T-AOC) level was significantly increased in serum and tissues ($p < .05$) except liver and kidney ($p > .05$). Serum IgM level, important immune parameter, of 125 mg RES/kg diet was significantly higher than other doses ($p < .05$). There was no significant difference in complement 3 (C3), C4 and lysozyme (LYZ) levels of serum and tissues fed with 100 and 125 mg RES/kg diet ($p < .05$), and biochemical parameters related to immune responses were significantly increased. Moreover, qPCR results indicated that feeding 100 mg RES/kg diet could significantly upregulate immune gene expression in tissues ($p < .05$), containing interleukin-1β (IL-1β), interleukin-8 (IL-8), interleukin-10 (IL-10) and tumour necrosis factor-α (TNF-α). For culturing *C. argus*, feeding diet supplemented with 125 mg RES might improve growth, antioxidative status and immune responses.

KEYWORDS
antioxidative capacity, Chinese herbal extracts, immunity, resveratrol

1 | INTRODUCTION

Channa argus (snakehead fish) is one of the most economically important freshwater fishes (Jia & Guo, 2008; Jiang et al., 2016). In order to improve the health status of aquaculture fish, phytochemicals and plant-derived supplements have been used in diets and also could improve fish antioxidant capacity, anti-pathogenic activity and growth performance (Awad & Awaad, 2017; Bureau et al., 1998; Chakraborty & Hancz, 2011; Jodaa et al., 2016). The study of using phytochemicals and plant-derived bioactive component in aquaculture fish nutrition has more researchers' attention (Palsamy et al., 2010). Resveratrol (RES) is a polyphenolic phytoalexin and has been reported whose function of antioxidative effect and anti-inflammatory (Liu et al., 2015; Wilson et al., 2015). In a previous study, it has been reported that RES could improve fish growth performance and the fatty acid composition of rainbow trout (*Oncorhynchus mykiss*) (Jia et al., 2020; Torno et al., 2017). As previous studies reported, RES supplemented in dietary could alleviate lipid

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metabolic disease induced by HFD diet (Jia et al., 2019; Zhang, Kang, et al., 2017; Zhang, Yan, et al., 2017) and also increase antioxidant capacity for protecting tissues from oxidative damage (de la Lastra & Villegas, 2007). Those studies indicated that RES could be supplemented in dietary for improving fish antioxidant capacity and immune response.

As increased intensive culture model, *C. argus* is challenged by stress of various treatments. Superoxide dismutase (SOD), catalase (CAT) and glutathione (GSH) are the important enzymes for resisting oxidant stress (Li, Gao, et al., 2020; Li, Guo, et al., 2020). Innate immunity is the first barrier and is important for protecting fish against pathogen infection, and lysozyme (LYZ) level of activity is a key factor of innate immunity of fish (Saurabh & Sahoo, 2010). Biochemical parameters related to immune response, including IgM, complement 3 (C3) and C4, could effectively remove pathogenic microorganisms to improve fish immunity (Li et al., 2019). Similarly, immune genes are important for defence against pathogen infection. When pathogens infected body, macrophages could secrete interleukin-1β (IL-1β) and tumour necrosis factor-α (TNF-α), and TNF-α and IL-1β also regulate other inflammatory factors (Wei et al., 2009). Previous studies indicated that upregulated immune gene expression might promote fish immunity against pathogen infection (Kong et al., 2019; Tian et al., 2020; Zhang, Kang, et al., 2017; Zhang, Yan, et al., 2017). There were few studies to explore the effects of RES supplemented with diet on *C. argus*. In this study, growth performance, antioxidant activity levels and immune parameters were determined to assess suitable RES dose.

2 | MATERIALS AND METHODS

2.1 | Experimental diet

The formulation and nutrient content of the basal diet are shown in Table S1. As a previous study reported, the dietary nutriment of dry matter was as follows: crude protein 461.3 g/kg, crude lipid 113.5 g/kg, ash 133.1 g/kg, carbohydrate 20.93 g/kg and gross energy 18.9 kJ/g (Li, Gao, et al., 2020; Li, Guo, et al., 2020). Resveratrol (98% purity) was obtained from Tongze Biological Technology. The RES was mixed at room temperature into the basal diet for six levels: 0, 25, 50, 75, 100 and 125 mg/kg, dried under aseptic conditions, after pelleted the diet were stored at 4℃.

2.2 | Experimental fish and design

Healthy *C. argus* (body weight: 20.50 ± .55 g) were obtained from a commercial hatchery (Shandong, China) and acclimated into 350 L glass aquarium for 14 days. After acclimation, total of 900 *C. argus* were randomly selected and sorted into six groups (3 tanks per group, 50 fish per tank). The water temperature and pH were 28 ± 2℃ and 7.2–8.1, respectively. All fish were fed a rate of 3%–4% wet body weight at 08:00 and 16:00. All of the experimental fish were used in accordance with the NIH Guide for the Care, and all experimental protocols for this research were approved (22 September 2018) by the Regulations for Animal Experimentation of Jilin Agricultural University (JLAU20121008).

2.3 | Sampling

After 56 days of feeding experiment, 10 fish were randomly collected from each tank and anaesthetized with tricaine methanesulphonate (MS-222, 100 mg/ml; Darmstadt, Germany), blood was collected from caudal veins of sample fish, and serum was separated by centrifugation (3000 *g*, 4 ℃ for 12 min). All of the fish were dissected for the sampling of liver, spleen, kidney and intestine. All tissues were flash-frozen in liquid nitrogen for the measurement of enzymatic activity, genes relative expression and biochemical parameters.

2.4 | Analysis and measurement

2.4.1 | Antioxidant parameters

The activities of malondialdehyde (MDA), superoxide dismutase (SOD), catalase (CAT), total antioxidant capacity

TABLE 1 Primer sequences and annealing temperature for qPCR

Target gene	Sequence (5′–3′)	Annealing temp. (°C)	GenBank ID
IL-10 forward	AAGGCTTCCCTGTGAGAC	57	KP324788.1
IL-10 reverse	TGTTGGCAGAATGGTGTC		
TNF-α forward	ACAATACCACCCCAGGTCCCA	61	KF134538.1
TNF-α reverse	ACGCAGCATCCTCTCATCCAT		
IL-8 forward	GAGTCTGAGCAGCCTGGGAGT	61	HF585631
IL-8 reverse	CTGTTCGCCGGTTTTCAGTG		
IL-1β forward	GTTTACCTGAACATGTCGGCTTACG	59	JN085956.1
IL-1β reverse	AGGGTGCTGATGTTCAGCCCA		
β-actin forward	CACTGTGCCCATCTACGAG	57	EF452499
β-actin reverse	CCATCTCCTGCTCGAAGTC		

TABLE 2 Effects of RES levels in growth performance in *C. argus*

RES (mg kg dietry^{-1})	IW (g)	FW (g)	WGR (%)	SGR (%·day^{-1})	FCR	SR (%)
Control (0)	20.44 ± 0.11a	67.43 ± 0.31a	228.91 ± 3.25a	2.13 ± 0.17a	1.20 ± 0.01a	99.33 ± 1.15a
25	20.51 ± 0.11a	67.94 ± 0.16ab	231.31 ± 2.27ab	2.14 ± 0.12ab	1.20 ± 0.05a	98.00 ± 0.01a
50	20.47 ± 0.06a	68.07 ± 0.06b	232.53 ± 1.11ab	2.14 ± 0.02ab	1.18 ± 0.01a	98.67 ± 1.15a
75	20.52 ± 0.11a	68.40 ± 0.60b	233.29 ± 4.22b	2.15 ± 0.01b	1.17 ± 0.02a	99.33 ± 1.15a
100	20.497 ± 0.11a	68.50 ± 0.10b	234.64 ± 1.72b	2.16 ± 0.01b	1.17 ± 0.02a	98.67 ± 1.15a
125	20.50 ± 0.05a	68.77 ± 0.42b	235.479 ± 2.71b	2.16 ± 0.01b	1.18 ± 0.03a	99.33 ± 1.15a

Note: Data are expressed as the mean ± S.D. (n = 5). Values with different superscripts are significantly (p < .05).
Abbreviations: FW, final body weight; IW, initial body weight.

(T-AOC) and glutathione-*S*-transferase (GST) were determined in serum and tissues using commercial assay kits according to manufacturer's protocol (Nanjing Jiancheng Bioengineering Institute) as described by Li, Gao, et al. (2020) and Li, Guo, et al. (2020).

2.4.2 | Immunological parameters

Serum IgM level was determined using commercially available ELISA Kits (Jingmei Bioengineering Institute). Lysozyme (LYZ), complement 3 (C3) and complement 4 (C4) were measured according to the methods described by Xu et al. (2016).

2.4.3 | Quantitative real-time PCR

The primer sequences for determining gene expression in liver, spleen, kidney and intestine are shown in Table 1. Simply P Total RNA Kit (BioFlux Bioer) was used for total RNA extraction of all tissues. The concentration of RNA samples was examined using NanoDrop 2000c (Thermo Fisher Scientific), and the complementary DNA (cDNA) was synthesized using PrimeScript™ RT Reagent Kit with gDNA Eraser (Takara). The quantitative real-time PCR was performed with Applied Biosystems® 7500 Real-Time PCR Systems (Thermo Fisher Scientific), using SYBR Green Master Mix (Takara). The qPCR mixture was as follows: SYBR qPCR Mix (10 μl), the forward and reverse primers (10 mM, 1 μl, respectively), cDNA (1 μl) and RNase-free water (7 μl; TransGen Biotech Company). The qPCR

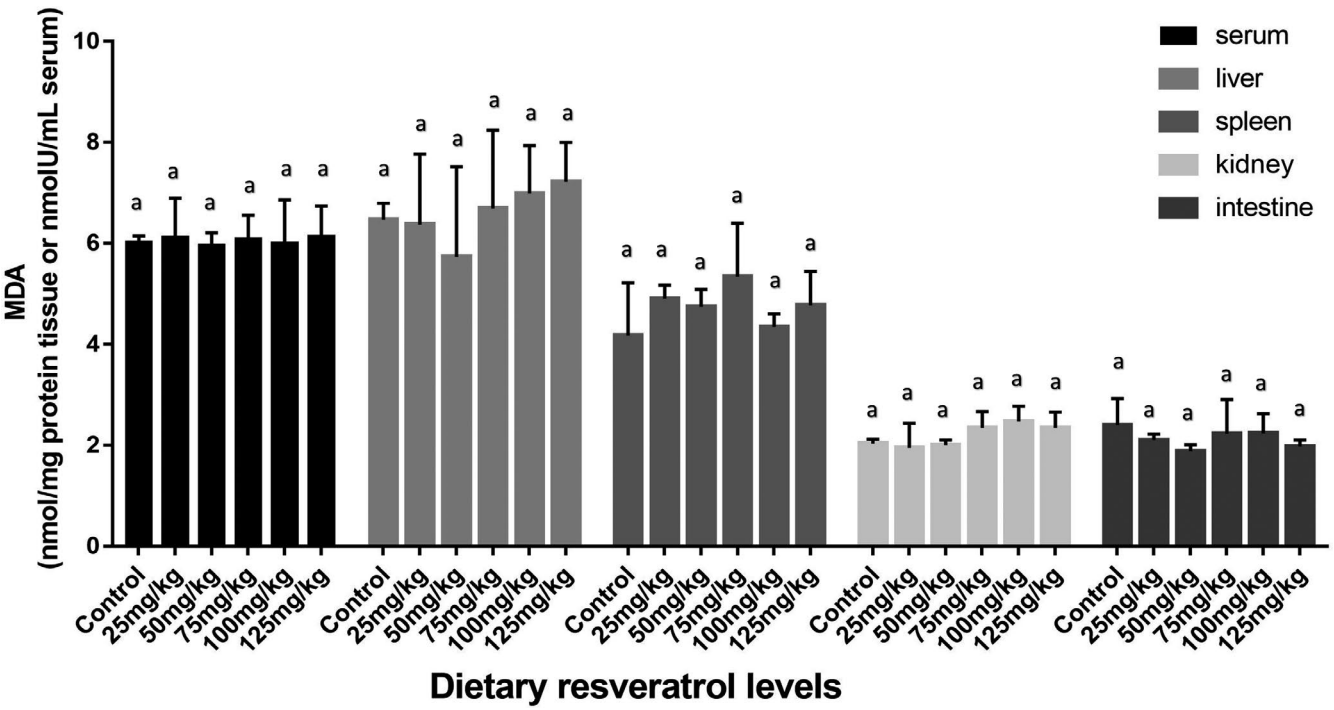

FIGURE 1 Malondialdehyde (MDA) in serum, liver, spleen, kidney and intestine of *Channa argus* fed diets supplemented with different RES levels. The values are normalized to control values and expressed as means ± SD (n = 5). Values with different letters denote significant differences between groups at the p < .05

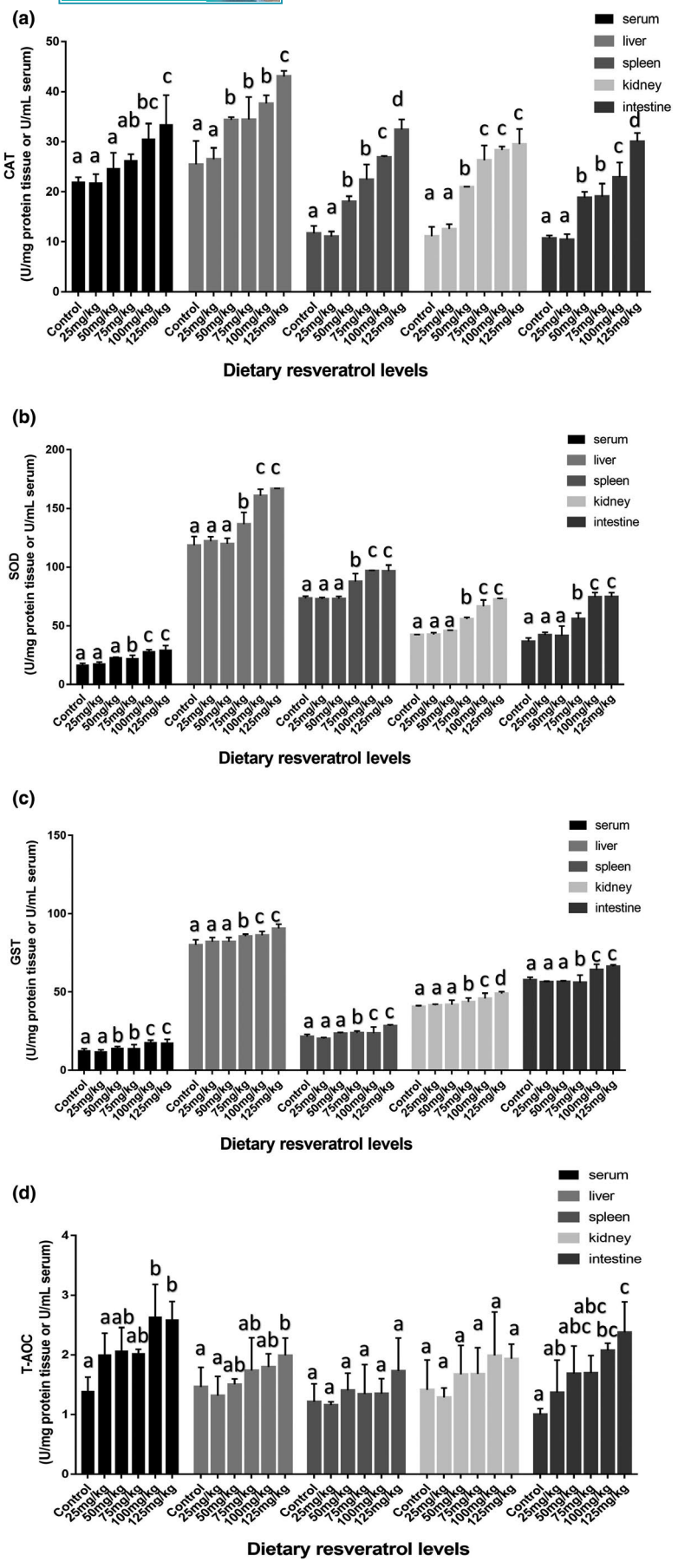

FIGURE 2 Catalase (CAT) (a), superoxide dismutase (SOD) (b), glutathione-*S*-transferase (GST) (c) and total antioxidant capacity (T-AOC) (d) in serum, liver, spleen, kidney and intestine of *Channa argus* fed diets supplemented with different RES levels. The values are normalized to control values and expressed as means ± SD (n = 5). Values with different letters denote significant differences between groups at the $p < .05$

conditions were as follows: 95℃ for 30 s, followed by 40 cycles of 95℃ for 5 s and annealing temperature for 35 s.

2.4.4 | Calculations and statistical methods

Growth parameters and body condition factors were calculated as follows:

$$\text{Survival rate (SR, \%)} = 100 \times \text{final fish number} / \text{initial fish number},$$

$$\text{Weight gain rate (WGR, \%)} = (\text{final body weight} - \text{initial body weight}) / \text{initial body weight} \times 100,$$

$$\text{Specific growth rate (SGR, \%/day)} = (\text{Ln final body weight} - \text{Ln initial body weight}) \times 100 / \text{days},$$

$$\text{Feed conversion ratio (FCR)} = \text{total diet fed (kg)} / \text{total wet weight gain (kg)}.$$

All results were presented as means and standard deviation (SD). Statistical analysis was performed using SPSS v16.0 software and GraphPad PRISM v5.0. All data were subjected to a one-way analysis of variance. In all cases, significant differences were considered as $p < .05$.

3 | RESULTS

3.1 | Growth performance

As shown in Table 2, after 56 days of feeding experiment, the final weight (FW) of *C. argus* fed with RES supplementation within 50–125 mg/kg was significantly higher than basal diet ($p < .05$), and there was no significant difference in FW of RES supplementation within 50–125 mg/kg ($p > .05$). Similarly, when the supplying RES dose was within 75–125 mg/kg, WGR and SGR were significantly higher than the basal diet group and other RES groups ($p < .05$). There was no significant difference in FCR and SR of all groups ($p > .05$).

3.2 | Antioxidant status

Antioxidant parameters in serum, liver, spleen, kidney and intestine were determined. The MDA levels are shown in Figure 1, and there was no significant difference in MDA levels in serum and tissues of *C. argus* fed with different doses of RES and basal dietary ($p > .05$, Figure 1). When the RES supplementation dose was more than 75 mg/kg, the activities of CAT, SOD and GST in serum and tissues were significantly increased than that fed with basal dietary ($p < .05$, Figure 2a–c). Moreover, those biochemical parameters related to antioxidant capacity, such as CAT, SOD, GST and T-AOC, were significantly increased in serum and tissues of *C. argus* fed with 125 mg/kg RES supplemented in dietary than basal dietary ($p < .05$, Figure 2a–d).

3.3 | Immune response

The serum IgM level of 125 mg/kg RES was significantly higher than other groups ($p < .05$, Figure 3). Compared with the control group, 125 mg/kg RES group significantly increased the level of LYZ, C3 and C4 in serum and tissues ($p < .05$, Figure 4a–c), while the level of LYZ in spleen and kidney was not significantly changed ($p > .05$). Moreover, the similar trends with antioxidant parameters showed that when the RES supplementation dose was more than 75 mg/kg in dietary, the level of C3 and C4 in serum and tissues was significantly increased than that fed with basal dietary ($p < .05$, Figure 4b,c). In addition, the level of C4 in *C. argus* spleen fed with different doses of RES was not significantly different ($p > .05$).

3.4 | qPCR analysis

The IL-10, IL-1β, IL-8 and TNF-α gene expression in tissues compared with β-actin was determined by qPCR with ABI 7500. The qPCR results are shown in Figure 5a–d. Compared with the control group, there was no significant difference in IL-10, IL-1β, IL-8 and TNF-α gene expression in tissues of *C. argus* fed with RES supplementation with 50 and 75 mg/kg ($p > .05$). Moreover, expression levels of the genes related to immune response were significantly increased in tissues of *C. argus* fed with 125 mg/kg RES than other doses ($p < .05$).

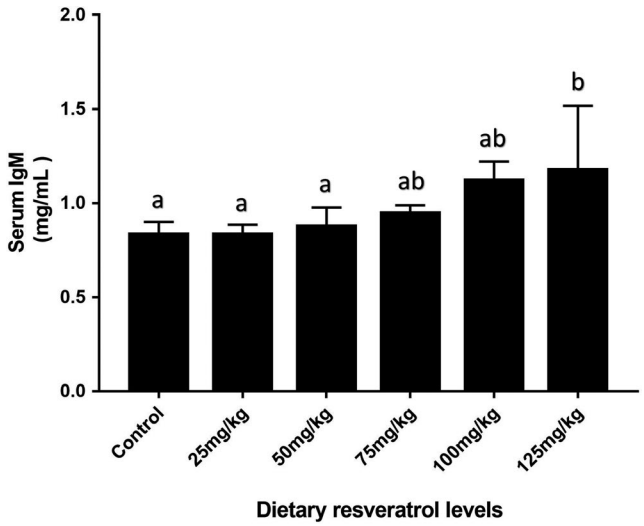

FIGURE 3 Serum IgM levels of *Channa argus* fed diets supplemented with different RES levels. The values are normalized to control values and expressed as means ± SD ($n = 5$). Values with different letters denote significant differences between groups at the $p < .05$

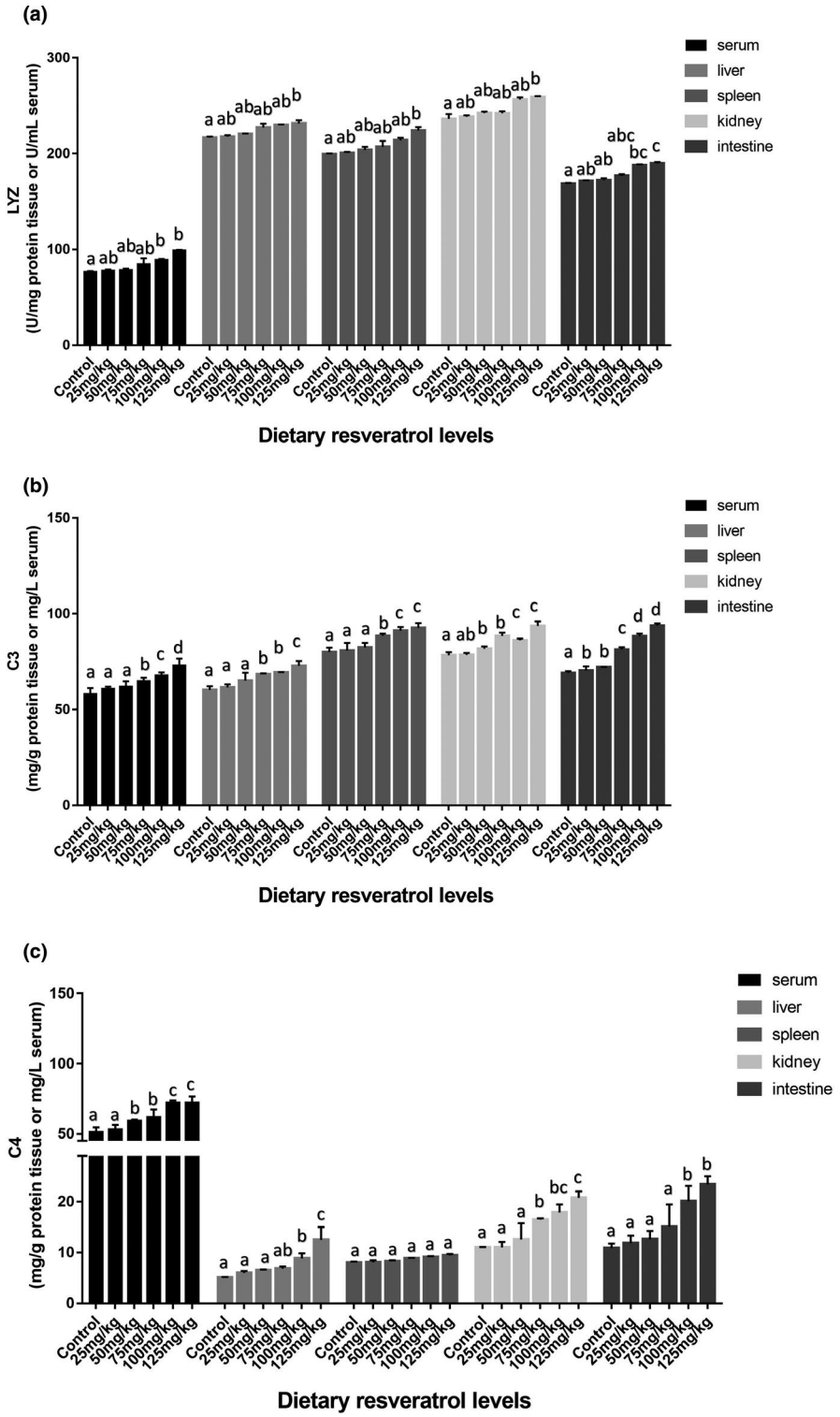

FIGURE 4 Lysozyme (LYZ) (a), complement 3 (C3) (b) and complement 4 (C4) (c) in serum, liver, spleen, kidney and intestine of *Channa argus* fed diets supplemented with different RES levels. The values are normalized to control values and expressed as means ± SD (n = 5). Values with different letters denote significant differences between groups at the $p < .05$

4 | DISCUSSION

As intensive aquaculture increased, aquaculture environment is more complex including various stressors could lead to organisms (such as fish, shellfish and crab) low immunity and oxidative stress state (Giri et al., 2015; Zheng & Wu, 2018). Chinese herbal extracts are environmentally friendly and exhibit wide biological activities (Sánchez-Fidalgo et al., 2010; Stojanovi et al., 2001; Yarahmadi et al., 2015).

To explore the supplementation dose of RES in diet, after fed with RES diet, growth performance, immune responses and antioxidant state of *C. argus* were determined. The results of growth performance showed that RES diets could stimulate the growth of *C. argus* within 8 weeks. And there was no significant difference in supplying RES dose within 75–125 mg/kg diet. In a previous study, diet supplemented with RES could increase the growth of southern flounder (Wilson et al., 2015). Meanwhile, more RES in

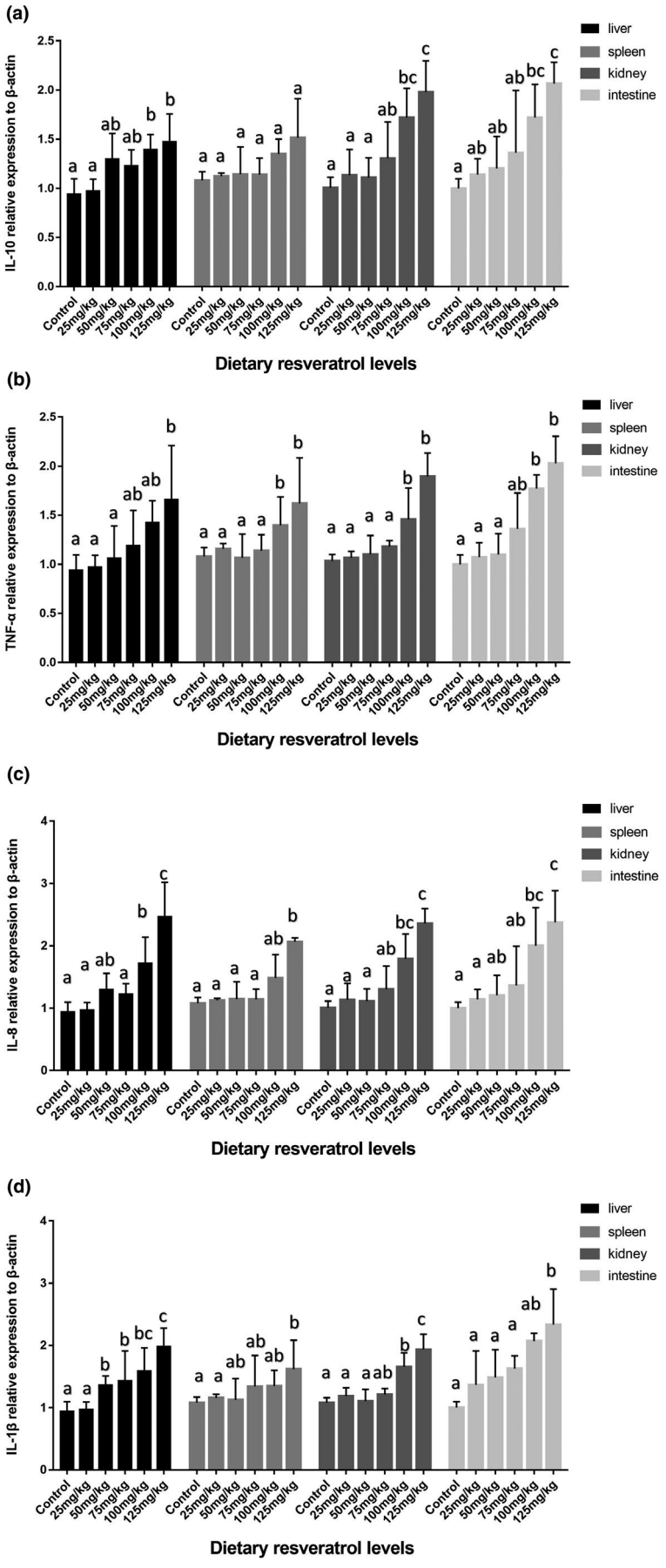

FIGURE 5 mRNA expression levels to β-actin of interleukin-10 (IL-10) (a), tumour necrosis factor-α (TNF-α) (b), interleukin-8 (IL-8) (c) and interleukin-1β (IL-1β) (d) in liver, spleen, kidney and intestine of *Channa argus* fed diets supplemented with different RES levels. The values are normalized to control values and expressed as means ± SD (n = 5). Values with different letters denote significant differences between groups at the $p < .05$

diet could inhibit the growth of blunt snout bream (Zhang, Kang, et al., 2017; Zhang, Yan, et al., 2017), and as academics conjectured, this phenomenon may relate to the mechanistic target of rapamycin (mTOR) signalling pathway (Liu & Liu, 2011). In this study, more than 75 mg/kg diet could significantly increase the growth of *C. argus*, and the supplementation dose of RES could not only increase growth performance. So, the antioxidant parameters and immune factors were determined for the evaluation of RES effects. MDA was a reliable indicator of oxidant stress (Liang et al., 2018). In this study, MDA levels of *C. argus* fed with RES supplement diet in tissues and serum were not significantly different, and those indicated that RES supplementatin dose within 0–125 mg/kg could not induce oxidant injury. Reactive oxygen species (ROS) homeostasis would injure cell structure and induce oxidant injury, and antioxidative enzymes are the first line of defences against ROS (Jaiswal, 2004). Previous studies reported resveratrol could improve antioxidative enzymes against oxidant stress (Zhou et al., 2014). In this study, CAT and SOD activities in serum and tissues of *C. argus* were significantly increased by feeding RES supplement diet. In the previous studies, RES could increase antioxidative enzyme activities against oxidant damage in aquaculture animals (Stojanovi et al., 2001; Yu & Li, 2012). GST activity plays an important role against oxidant damage induced by lipopolysaccharide (Li, Gao, et al., 2020; Li, Guo, et al., 2020). Different doses of RES could increase GST and T-AOC activities in tissues and serum, those indicated RES could protect fish against oxidant stress. Innate immune is important for defence against pathogen infection, and IgM is one of the most important immunoglobulins in fish (Tian et al., 2020; Zhang, Kang, et al., 2017; Zhang, Yan, et al., 2017). IgM, as an important immune index, could protect fish against pathogen infection. In this study, serum IgM level of *C. argus* fed with 125 mg RES/kg diet was significantly higher than other groups. It is assumed that RES could improve innate immunity through increased IgM level. Lysozyme, as an important bactericidal enzyme, could destroy pathogens and activate other immune molecules (Saurabh & Sahoo, 2010). In this study, lysozyme activities in serum and tissues were significantly increased by feeding RES supplement diet. Moreover, complements play a key role in innate immune system for protecting fish against pathogen and maintaining the health of fish (Ichiki et al., 2012; Ming et al., 2019). Our data revealed that the levels of C3 and C4 of serum and tissues in fish fed with RES supplement diet were significantly increased. Those results indicated RES could increase immune parameters and might enhance the immunity of *C. argus*.

Cytokines are key roles to regulate inflammatory process and are also one of the most important parameters in innate immune system, and IL-1β, IL-8 and TNF-α are the key immune factors for induction of other cytokines and defence against pathogen infection (Li et al., 2018; Tian et al., 2020; Wei et al., 2009). Our data showed that 125 mg RES/kg diet could significantly increase the expression of IL-1β, TNF-α and IL-8 in liver, spleen, kidney and intestine. Those results were similar to previous reports that *Lactobacillus casei* expressing immune protective protein could induce more IL-1β and TNF-α against *Aeromonas veronii* infection (Kong et al., 2019; Tian et al., 2020; Zhang, Kang, et al., 2017; Zhang, Yan, et al., 2017). IL-10 is a potent anti-inflammatory cytokine produced by monocytes, natural killer (NK) cells, macrophages and dendritic cells (Moore & O'Garra, 2001; Moore et al., 1993), and also could regulate inflammatory process. In this study, the expression of IL-10 and IL-8 was significantly increased in tissues fed with RES diet and that was similar to the previous study (Tian et al., 2020). RES could inhibit ROS and protect from oxidant damage, and also improve fish immunity against pathogen (Kumar et al., 2017). Rare study reported the effect of oxidant activity and immune factors of *C. argus* fed with different doses of RES.

5 | CONCLUSION

In conclusion, feeding more than 75 mg RES/kg diet could significantly promote *C. argus* growth performance, and 125 mg RES was significantly better than other doses. Similarly, antioxidant activities levels were significantly increased in *C. argus* tissues and serum fed with dietary supplemented with 125 mg RES. Feeding with dietary supplemented with 125 mg RES, it could active immune system to upregulate the expression of immune gene in tissues, and also increase the levels of serum immune parameters. This study indicated that the best RES supplementation dose was 125 mg/kg dietary and could improve *C. argus* antioxidant capacity and immune response to gain more benefit.

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CONFLICT OF INTEREST

None.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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