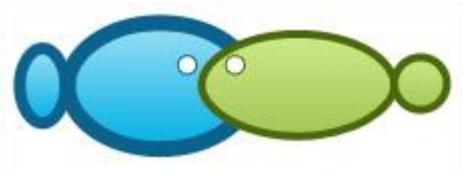

Evaluation of dietary α-lipoic acid effect on growth and antioxidative responses of striped catfish (*Pangasianodon hypophthalmus*)

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Abstract. This study aimed to evaluate the dietary supplementation of α-lipoic acid (ALA) on growth performance and antioxidative responses of striped catfish (*Pangasianodon hypophthalmus*). The striped catfish specimens, weighing 6.46±0.02 g, were stocked in 12 cages measuring 2x1x1.5 m^3, in a 200 m^2 pond. Each cage was supplied with thirty fish. Fish diet was supplemented with ALA (α-lipoic acid) at a level of 0.0, 0.8, 1.6, or 2.4 g kg^{-1} for each treatment. For 60 days, the fish were fed at satiation. The results demonstrated that supplementing ALA starting at 0.8 g kg^{-1} significantly improved survival, growth and protein efficiency ratios. The increase in ALA at 1.6 and 2.4 g kg^{-1} resulted in a growth performance that was not significantly different from ALA 0.8 g kg^{-1} diet. Moreover, treatments with ALA supplementations of 0.8 to 2.4 g kg^{-1} obtained higher levels of superoxide dismutase and liver glycogen than those of 0.0 g kg^{-1}. In contrast, those treatments resulted in lower malondialdehyde content and triglycerides. It can be concluded that the optimal dose of ALA for enhancing growth performance, antioxidative capacity and liver performance of striped catfish is 0.8 g kg^{-1}.
Key Words: growth, striped catfish, α-lipoic acid, antioxidant.

Introduction. In general, it is known that the use of feed in intensive aquaculture will increase waste, from both feed residues and the secretion of fish metabolic wastes. As a result, water quality suffers, increasing ammonia and nitrite content and decreasing dissolved oxygen content (Cao et al 2021). A drop in aquaculture water quality causes oxidative stress (Lushchak 2011), which is characterized by a decrease in superoxide dismutase (SOD) and an increase in malondialdehyde (MDA) in the fish liver (Maltez et al 2017). Increased liver oxidative stress can interfere with nutrient metabolism processes such as carbohydrate and lipid metabolism, reducing feed utilization efficiency and thus fish growth (Li et al 2015; Aroyape-Ospina et al 2021). Liver damage in fish that live in suboptimal conditions can be anticipated by administering antioxidants to mitigate the effect of increased lipid peroxidation due to exposure to stressors (Zhang et al 2017; Fratantonio et al 2018; Sena et al 2018).

As an antioxidant microbial sulfur compound, alpha-lipoic acid (ALA) is pentanoic acid 5-(1,2-dithiolan-3-yl) (Packer et al 1995). ALA is a water and fat-soluble molecule with two thiol groups reduced to form dihydrolipoic acid (DHLA) (Gorca et al 2011). Because they can react with free radicals such as reactive oxygen species (ROS) (Bast & Haenen 2010; Wang et al 2011; Oliva-Teles 2012; Moura et al 2015; Baeeri et al 2019), LA and DHLA can function as universal antioxidants (Packer et al 1995; Wollin & Jones 2003). Under hypoxia-reoxygenation conditions, ALA suppresses the occurrence of ROS by increasing SOD activity (Kütter et al 2012; Monserrat et al 2014) and glutathione transferase (GST) levels (Lobato et al 2018). As a powerful antioxidant, ALA can regenerate other antioxidants, such as vitamins C and E (Goraca et al 2012).

ALA plays a vital role in the interaction between insulin and cell receptors, present as a complex compound known as glucose tolerance factor (GTF), increasing insulin activity (Islam 2009). With lipolysis activity and beta-oxidation of fatty acids, ALA plays a critical role in fat metabolism, allowing protein requirements for growth to be maximized (Shi et al 2017). ALA also helps to increase insulin sensitivity (Serhiyenko et al 2018), which aids in the entry of glucose from the blood circulation into peripheral tissues (Anderson & Mertz 1997). Furthermore, ALA lowers cholesterol and triglycerides, while increasing lipolysis and oxidation of fatty acids (Xu et al 2019).

ALA has been studied as an antioxidant in various aquaculture commodities. According to Samuki et al (2020), adding ALA 0.6 g kg^{-1} feed increased SOD activity and optimized the growth of gourami (*Osphronemous gourami*) fry. Xu et al (2018a) discovered that ALA at a dose of 300 mg kg^{-1} of feed increased the SOD enzyme activity in the serum and liver of juvenile tilapia (*Oreochromis niloticus*). Siagian et al (2021) elaborated on the ALA supplementation: at a dose of 1.2 g kg^{-1}, reduced MDA levels resulted in optimal growth performance in African catfish (*Clarias gariepinus*). After 3 hours of hypoxia and 6 hours of anorexia, the addition of ALA to the feed provided antioxidant protection to vannamei juveniles (Lobato et al 2018). Kütter et al (2012) found that adding 316-524 mg kg^{-1} of ALA to feed improved the growth performance and antioxidant status of Plata Pompano (*Trachinotus marginatus*) juveniles. The addition of ALA 70 mg kg^{-1} to feed can reduce ROS levels in *Corydoras paleatus* (Monserrat et al 2008). Based on the findings of these studies, it appears that the need for ALA varies by fish species. On the other hand, because striped catfish, *Pangasianodon hypophthalmus*, is an air-breathing fish, intensive culture is typically carried out in less-than-optimal culture conditions, namely without aeration and water exchanges. Thus, the inclusion of ALA in catfish feed is thought to play an essential role in increasing antioxidant capacity, increasing growth, and feed efficiency. Thus, this study aimed to determine the influence of dietary ALA supplementation on the growth performance of *P. hypophthalmus*.

Material and Method

Experimental diet. The diet used in this study was a commercial diet with 30% protein content. This diet was supplemented with ALA as much as 0.0, 0.8, 1.6 or 2.4 g kg^{-1}. For 1 kg of diet, ALA was mixed with 30 g of chicken egg white, 0.9 g of egg yolk and 100 ml of water, blended in a blender to produce a suspension. The suspension was coated onto the feed until evenly distributed. The diet was then dried at 50°C (oven) for 3-4 hours and stored in an air-tight container until fed to the fish. Feed was analyzed proximately following the method of the Association of Official Analytical Chemists (AOAC 2012). The results of the proximate analysis are presented in Table 1.

Table 1

Proximate composition of experimental diets (%)

Nutrient	*α-lipoic acid supplementation (g kg^{-1} diet)*			
	0.0	*0.8*	*1.6*	*2.4*
Moisture	7.25	6.70	6.19	6.73
Ash	6.17	6.29	5.62	6.15
Lipid	4.99	4.36	4.57	4.59
Protein	30.06	30.24	30.26	30.38
Fiber	5.63	6.34	6.41	6.68
Carbohydrate	45.90	46.07	46.95	45.47
GE (kcal g^{-1})*	403.4	399.2	404.91	399.7

*GE-gross energy; 1 g protein-5.6 kcal;1 g lipid-9.4 kcal; 1 g carbohydrate-4.1 kcal (Watanabe 1988).

Fish rearing. *P. hypophthalmus* juveniles were obtained from a commercial hatchery in Bogor, West Java, Indonesia. After a week of adaptation, fish weighing 6.46±0.02 g were stocked in 12 cages measuring 2x1x1.5 m and transferred in a 200 m^2 pond at the Experimental Pond, Department of Aquaculture, IPB University. Each cage contained 30

fish, representing each replicate of the four treatments of ALA supplemented diets. For 60 days, fish were cultured. During the cultivation period, the fish were fed with ALA-supplemented diets at a dose of 0.0, 0.8 1.6, and 2.4 g kg^{-1} of diet, three times daily, at satiation. The total consumed diet was recorded to calculate the feed intake and feed conversion ratios.

Growth performance. On day 59 of culture, the fish were fed solely in the morning, followed by a 24-hour fast. On day 60, the fish were anesthetized, using clove oil at a dose of 0.1 mL L^{-1}, and their number was calculated to determine their survival rate. Furthermore, all fish were weighed to determine the total weight and individual weight. Fish weight data was used in calculating the feed conversion ratio, protein efficiency ratio and relative growth rate. The relative growth rate was calculated based on the following formula:

$$RGR = \frac{Wt - W0}{W0} \times 100$$

Where:
RGR - relative growth rate (%);
Wt - final fish weight average (g);
Wo - initial fish weight average (g).

Biochemical status. Weighing twelve unconscious fish from each cage was followed by blood collection using a 1 mL syringe rinsed with an anticoagulant. After removal, the fish liver was weighed. The hepatosomatic index (HSI) value was known from calculating the liver weight divided by body weight. Fish blood was centrifuged at 3,000 rpm for 5 minutes. Triglyceride levels in blood plasma were determined using the Liquiform triglyceride test kit (Laboratory test). The triglyceride concentration was determined from the absorbance value, using a spectrophotometer set to 505 nm. Fish livers were collected, immediately immersed in liquid nitrogen and then frozen at -80°C, until SOD, MDA and Glycogen levels were analyzed. The thiobarbituric acid test method determined the MDA levels using a lipid peroxidation kit (Abcam, Cambridge, UK). SOD analysis was performed using the SOD assay kit (Abcam, Cambridge, UK). Catfish liver glycogen levels followed the method of Watanabe (1988). Glycogen levels were measured based on the absorbance spectrophotometer, at a wavelength of 635 nm.

Statistical analysis. The research data were analyzed using Analysis of Variance (ANOVA) with SPSS ver.25.0 software at a 95% confidence interval. Significant differences between treatments were further tested using the Duncan multipage range test (DMRT).

Results. Growth performance of *P. hypophthalmus* cultured for 60 days on feed supplemented with ALA at various doses is presented in Table 2.

Table 2

Growth performance of *Pangasianodon hypophthalmus* cultured for 60 days

Parameter	*α-lipoic acid supplementation (g kg^{-1} diet)*			
	ALA 0.0	*ALA 0.8*	*ALA 1.6*	*ALA 2.4*
Initial individual weight (g)	6.5 ± 0.0^{a}	6.5 ± 0.0^{a}	6.5 ± 0.0^{a}	6.4 ± 0.0^{a}
Final individual weight (g)	73.6 ± 1.9^{a}	134.8 ± 5.5^{b}	120.4 ± 9.2^{b}	128.4 ± 4.1^{b}
Total final weight (g)	1815.9 ± 166.5^{a}	4042.8 ± 165.6^{c}	3438.7 ± 60.6^{b}	3594.1 ± 116.1^{b}
Feed intake (g/fish)	178.6 ± 15.8^{ab}	160.9 ± 0.4^{bc}	147.9 ± 22.2^{a}	163.3 ± 2.9^{b}
Feed conversion ratio	2.7 ± 0.2^{a}	1.3 ± 0.1^{b}	1.3 ± 0.1^{b}	1.3 ± 0.0^{b}
Relative growth rate (%)	1035.8 ± 32.1^{a}	1983.6 ± 93.1^{b}	1767.4 ± 147.7^{b}	1889.9 ± 68.1^{b}
Protein efficiency ratio (%)	1.3 ± 0.1^{a}	2.6 ± 0.1^{b}	2.6 ± 0.2^{b}	2.5 ± 0.0^{b}
Survival rate (%)	82.2 ± 6.9^{a}	100.0 ± 0.0^{b}	95.6 ± 7.7^{b}	93.3 ± 0.0^{b}

Values are presented as average ± standard deviation (n=3). Different superscript letters in the same line show a significant different value among treatments ($p<0.05$).

Fish that consumed feed starting with ALA 0.8 treatment had better growth performance than fish in ALA 0.0 treatment. The final individual weight values, survival and feed conversion ratio of fish in the ALA 0.8 treatment were not significantly different from those in ALA 1.6 and 2.4 treatments. However, the total weight of harvested fish and relative growth reached a maximum in the ALA 0.8 treatment. Fish in 1.6 and 2.4 treatments had a significantly higher total weight and relative growth than ALA 0.0 treatment.

The liver and blood biochemistry of *P. hypophthalmus* can be seen in Table 3. SOD levels were significantly higher in *P. hypophthalmus* treated with ALA 0.8 than those treated with ALA 0.0. The MDA level of the ALA 0.8 treatment was lower than for the ALA 0.0 treatment. The highest SOD level was obtained in the ALA treatment of 0.8. The HSI levels in the ALA treatments 0.8 and 1.6 were identical and both were lower than for other treatments. Increased ALA content in the diet enhanced liver glycogen, with the ALA 0.8 treatment having the highest glycogen content. Moreover, feed intake of ALA supplemented diets influenced the blood triglyceride level on fish. Treatment with ALA ≥0.8 could significantly reduce the triglyceride content in *P. hypophthalmus*. The lowest triglyceride was yielded in the ALA treatment of 0.8 g.

Table 3

Liver biochemistry and blood triglycerides of *Pangasianodon hypophthalmus* after 60 days of rearing

Parameter	*α-lipoic acid supplementation (g kg^{-1} diet)*			
	0.0	*0.8*	*1.6*	*2.4*
SOD (U g^{-1} Protein)	7.23±0.11^{a}	11.12±1.13^{d}	8.44±0.34^{c}	9.72±0.17^{b}
MDA (µMol L^{-1})	0.48±0.02^{a}	0.16±0.05^{b}	0.22±0.05^{b}	0.19±0.01^{b}
HSI (%)	1.96±0.17^{a}	0.92±0.15^{c}	1.20±0.07^{bc}	1.33±0.11^{b}
Glicogen (mMol g^{-1})	0.34±0.05^{a}	0.86±0.07^{c}	0.46±0.03^{b}	0.48±0.02^{b}
Triglyceride (mg dL^{-1})	383.9±10.9^{a}	316.6±2.0^{c}	342.9±7.5^{b}	344.1±16.4^{b}

Values are presented as average ± standard deviation (n=3). Different superscript letters in the same line show a significant different value among treatments ($p<0.05$). SOD- Superoxide dismutase; MDA- Malondialdehyde; HSI-Hepatosomatic Index.

Discussion. The results demonstrated that adding ALA to the diet could increase the growth of *P. hypophthalmus*. After being fed a diet supplemented with 0.8 g kg^{-1} ALA, the relative growth rate of catfish rose. Increased ALA doses induced growth at the same rate as the 0.8 g kg^{-1} dose. Growth enhancement caused by ALA supplementation was associated with a drop in the FCR value and an increased protein efficiency ratio. These conditions demonstrate that ALA is involved in metabolic processes and energy transformation in the *P. hypophthalmus* body (Trattner et al 2007) by encouraging the activation of 5'-activated adenosine monophosphate-kinase (AMPk) to maximize the glucose utilization as energy via the carbohydrate metabolism (Serhiyenko et al 2018). The increase in the protein-sparing effect of carbohydrates causes the protein to be used more efficiently for the growth process. Several studies have indicated that supplementing feed with ALA at certain levels will boost growth in certain species, including the giant gourami *Osphronemus gouramy* (Samuki et al 2020) at a dose of 0.6 g kg^{-1} diet. The optimal dose of ALA in African catfish is a 1.2 g kg^{-1} diet (Siagian et al 2021). ALA supplementation at a level of 0.4 g kg^{-1} diet can boost tilapia growth (Xu et al 2019). In contrast to the findings of Kütter et al (2012) and Zhang et al (2010), this study found that ALA supplementation at the highest level (2.4 g kg^{-1} diet) did not reduce the *P. hypophthalmus* growth.

The role of ALA in increasing the *P. hypophthalmus* growth can be recognized in the liver and blood biochemistry. ALA works as an antioxidant, protecting the liver as a detoxifying active site. As indicated by the HSI value, the enlarged liver size indicates the effect of a detoxifying burden on the liver. Numerous factors can contribute to elevated HSI value, including increased de novo fatty acid synthesis (lipogenesis) in the liver, reduced fatty acid oxidation in liver cells and an imbalance in triglyceride export from the

liver into the tissues (Heeren & Scheja 2021). In this study, ALA supplementation accelerated the catabolism and reduced the lipid synthesis in catfish, compared to a diet without supplementation. This is connected to the ALA's role in lipid metabolism via enhanced lipolytic activity for triglyceride transport from the liver to tissues and increased β-oxidation of fatty acids for the synthesis of ATP (Xu et al 2018b), through increased lipoprotein lipase (LPL) activity (Thirunavukkarasu et al 2004). The LPL is found in endothelial cells of muscle and adipose tissue. It is responsible for hydrolyzing triglycerides circulating in the blood and facilitating their delivery to muscle and adipose tissue (Heeren & Scheja 2021), resulting in a decrease in blood triglyceride levels following the ALA treatment of 0.8 g kg^{-1} diet. Xu et al (2018a) revealed a similar trend in the lipid transport profile in the blood, demonstrating that ALA supplementation in the diet reduced the triglyceride levels in GIFT tilapia liver, in giant gouramy (Samuki et al 2020), and in African catfish (Siagian et al 2021).

As previously stated, ALA serves as an antioxidant, thereby protecting the liver as a site of active detoxification from oxidative stress in cell membranes. In organisms, oxidative stress arises when reactive oxygen species (ROS) formation surpasses the antioxidant system's capacity (Matés et al 2008). ROS results in lipid peroxidation, which produces MDA as a final product (Fawole et al 2017). Sufficient ALA in the diet promotes the expression of antioxidant enzymes such as SOD (Moura et al 2015; Deng et al 2017), which react with reactive oxygen species such as superoxide radicals, hydroxyl radicals, hypochlorous acid, peroxyl radicals and singlet oxygen (Parker et al 1995), thereby reducing the occurrence of oxidative stress. In this study, starting from the ALA treatment of 0.8 g kg^{-1} of diet, there was an increase in SOD value and a decrease in MDA value. This condition implies that ALA plays an essential role in catfish antioxidative activity, allowing them to cope with oxidative stress (Kütter et al 2014). Catfish fed with ALA starting from 0.8 g kg^{-1} of diet could grow faster when exposed to oxidative stress. Our finding confirms the findings of Samuki et al (2020) on the giant gouramy and of Siagian et al (2021) on the African catfish. However, in the study of Siagian et al (2021), an increase in ALA above 1.6 g kg^{-1} lowered the antioxidative capacity, resulting in a rise in the liver MDA levels. This result implies that the antioxidative capacity conferred by ALA treatment varies between species.

It is known that the liver plays a vital role in the glucose metabolism. ALA can enhance blood glucose absorption by increasing the insulin activity (Henriksen et al 1997; Jacob et al 1996). In this study, the supplementation of ALA from 0.8 g kg^{-1} of diet enhanced the amount of glycogen in catfish liver, demonstrating that ALA can improve the glucose metabolism and absorption of blood glucose into the liver, as glycogen. Additionally, the high glucose utilization in the ALA treatment starting from 0.8 g kg^{-1} of diet proved an increase in the body's utilization of carbohydrates as a source of energy, resulting in improved fish growth.

Conclusions. This study found that dietary ALA has a positive effect on growth performance, such as daily growth rate, feed conversion ratio, and survival rate of *P. hypophthalmus*. Dietary ALA at a dose of 0.8 g kg^{-1} of feed was sufficient to improve growth performance of fish, due to the flat growth as ALA dose increase. The improvement of growth performance of fish was associated with a decrease in triglycerides and an increase in liver glycogen compared to ALA non-supplemented feed, and is an indication that ALA increases the utilization of carbohydrates as an energy source. ALA also acts as an antioxidant, characterized by a decrease in MDA and an increase in SOD in the liver. Thus, it can be concluded that dietary supplementation of ALA at 0.8 g kg^{-1} diet is the optimal dose to improve the growth performance and antioxidative responses in the *P. hypophthalmus*.

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Conflict of interest. The authors declare no conflict of interest.

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