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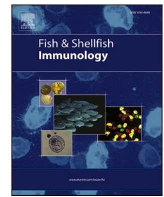

Full length article

Modulatory role of dietary curcumin and resveratrol on growth performance, serum immunity responses, mucus enzymes activity, antioxidant capacity and serum and mucus biochemicals in the common carp, *Cyprinus carpio* exposed to abamectin

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ABSTRACT

In this study, we investigate the potentials of dietary curcumin and resveratrol on blood biochemistry, immune responses and resistance to the toxicity of the pesticide, abamectin. 540 common carps (30.78 ± 0.17 g) were randomly distributed into 18 tanks (30 fish per tank), as six experimental groups (T1: non-supplemented and on-exposed fish, T2: 300 mg/kg curcumin, T3: 300 mg/kg resveratrol, T4: 12.5% LC_{50} of abamectin, T5: 300 mg/kg curcumin +12.5% LC_{50} of abamectin, T6: 300 mg/kg resveratrol + 12.5% LC_{50} of abamectin). Use of 300 mg/kg resveratrol in the diet of non-abamectin exposed fish improved the growth performance ($P < 0.05$), while such effects were not observed for curcumin ($P > 0.05$). There were no differences in the final weight (FW), feed conversion ratio (FCR) and weight gain (WG) between control and fish of the treatments, resveratrol + abamectin and curcumin + abamectin ($P < 0.05$). The immune components in blood [lysozyme, complement activity, Total immunoglobulin (total Ig), protease, myeloperoxidase (MPO), nitro-blue-tetrazolium (NBT), peroxidase, albumin] and mucus [acid phosphatase (ACP), alkaline phosphatase (ALP), esterase, antiprotease)] and antioxidant enzymes [(superoxide dismutase (SOD), glutathione peroxidase (GPx)] exhibited various change patterns compared to the control group, however, these components were almost all higher in fish supplemented with curcumin and resveratrol in an abamectin-free medium than in control and other groups ($P < 0.05$). In most cases, the levels of immune and antioxidant components in the control did not show significant difference with the treatments, resveratrol + abamectin and curcumin + abamectin ($P > 0.05$). Abamectin induced oxidative stress in fish, as the malondialdehyde (MDA) levels significantly increased in the exposed fish compared to non-exposed groups ($P < 0.05$). It appears that neither curcumin nor resveratrol were as effective in preventing oxidative stress, because MDA levels were higher in exposed fish (abamectin, curcumin + abamectin, resveratrol + abamectin) than in control and non-exposed individuals ($P < 0.05$). Curcumin and resveratrol also showed

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protective effects on liver, since the levels of liver metabolic enzymes [aspartate transaminase (AST), ALP, lactate dehydrogenase (LDH)] were lower in the supplemented fish in a abamectin-free medium than in control ($P < 0.05$). Curcumin and resveratrol also mitigated the stress responses in the exposed fish, as cortisol and glucose levels showed significant decreases in the supplemented fish ($P < 0.05$). In conclusion, this study revealed that abamectin can depress the growth and immunity in the common carp. Although, both resveratrol and curcumin were mitigated the toxic effects of abamectin, it seems that resveratrol be more effective than curcumin.

1. Introduction

The development of agricultural activities has been accompanied by a significant elevation in the use of insecticides in farms to control pests [1,2]. However, the use of insecticides has always been a matter of environmental and human health concern. Aquatic ecosystems are no exception, as insecticides or their derivatives mainly enter the water through run-off or drainage, threatening the lives of aquatic organisms [3]. In aquatic ecosystems, insecticides may be also transmitted and biomagnified throughout the food chain, which intensifies their toxicity, especially in final consumers [4–7]. Fish are among the organisms that are negatively affected by insecticides and pesticides in aquatic ecosystems [8]. Some studies have shown that the use of dietary supplements with immune-stimulating properties can reduce the toxic effects of pesticides on fish [9–15]. Among them, medicinal plants and their derivatives have received a lot of attention over the last decade due to their antioxidant and immunogenic properties [16–25]. In this regard, some studies have shown that medicinal plants and their derivatives can have a protective effect against the toxicity of pesticides in fish [11–14, 26]. *Curcuma longa* is one of the well-known medicinal plants, which its rhizomes are used to treat different diseases in China and India [27–29].

Curcumin or diferuloymethane, is a yellow pigment derived from *C. longa*, with antibacterial, anti-inflammatory, immunomodulatory and antioxidant functions [30–32]. There are many studies reporting the immune-stimulating properties of curcumin in fish [33–38].

Resveratrol is another plant-derived polyphenolic compound with antioxidant and anti-inflammatory functions (A [39–42]. The antioxidant and immune-stimulating effects of resveratrol has been also reported in fish [43–49]. Although the immunogenic and antioxidant function of curcumin and resveratrol have been reported in fish, very little is known about their effects on the immunotoxic and oxidative stress-induced by pesticides.

In this study, we investigated the modulatory role of dietary curcumin and resveratrol on growth performance, immune system, and resistance against toxicity induced by the pesticide, abamectin in the common carp, *Cyprinus carpio*. Abamectin is the most compound of avermectins (macrocyclic lactone compounds extracted from the fungus *Streptomyces avermitilis*), which used for both agricultural and pharmaceutical purposes. Abamectin is a neurotoxic insecticide that acts through the glutamate and γ-amino butyric acid-gated chloride channels in brain [50,51]. Although abamectin is relatively safe for human, its toxic effects on fish have been reported in various studies [52–55]. The results of this study may suggest a natural way to enhance the immune system of carp against abamectin induced toxicity.

2. Materials and methods

2.1. Fish and experiment design

600 juvenile common carps with an average weight of 27.18 ± 0.2 g were prepared from a local farm in Isfahan province, Iran and adapted to laboratory conditions for 2 weeks at a water temperature of 24–25 °C. In this period, the fish were daily fed *ad libitum* with a basic food (Table 1). After the adaptation period, fish (n = 540, mean weight: 30.78 ± 0.17 g) were randomly distributed into 18 tanks (30 fish per tank), as six experimental treatments with three replicates. The experimental groups were: control (T1): non-supplemented fish cultured in an abamectin-free medium, T2: 300 mg/kg curcumin supplemented fish cultured in an abamectin-free medium, T3: 300 mg/kg resveratrol supplemented fish cultured in an abamectin-free medium, T4: non-supplemented fish cultured in a medium containing 12.5% LC_{50} of abamectin, T5: 300 mg/kg curcumin supplemented fish cultured in a medium containing 12.5% LC_{50} of abamectin, T6: 300 mg/kg resveratrol supplemented fish cultured in a medium containing 12.5% LC_{50} of abamectin. During the experiment period, 75% of the water was daily exchanged and the abamectin concentration was adjusted accordingly. The tanks were continuously aerated, the suspended particles siphoned daily, and the biomass of each tank was weighed every two weeks to adjust the feeding rate. The water quality parameters were daily checked, which included: temperature: 24 ± 0.5 °C, dissolved oxygen 6.5 ± 0.78 mg/l (Portable Dissolved Oxygen Meter, Hanna, HI9146, Hanna instruments CO., UK), pH: 7.3 ± 0.2 (pH meter, Hanna-HI 98128, Hanna instruments CO., UK) and non-ionized ammonia 0.03 ± 0.025 mg/l (Hi-700 Ammonia Low Range Colorimeter – Checker, Hanna instruments CO., UK). Feeding was done twice a day at satisfaction [56].

2.2. Preparation of experimental diets

Curcumin [820354, purity: ≥ 75%] and resveratrol (R5010, purity: ≥ 99%) were provided from Merck CO., and Sigma Aldrich CO., respectively. In order to prepare experimental diets, firstly, food ingredients were prepared and after weighting, they were mixed well together. In the next step, some water along with the supplements at adjusted levels were added to form a dough. The dough was then pelleted by a meat grinder and the pellets dried at 37 °C and stored at 4 °C [56,57].

Table 1
Feedstuffs and compositions of the basal diet.

Ingredients	g/kg	Proximate composition	% in dry basis
Fishmeal[a]	160	Crude protein	393
Soybean meal [b]	170	Crude lipid	88.7
Wheat flour (Res or cur)	381	ash	62.1
Poultry meal[c]	150	Dry matter	908
Wheat gluten[d]	100		
Phytase[e]	5		
Fish oil	10		
Lysine [f]	6		
Soybean oil	10		
Methionine[f]	3		
Mineral mix[g]	2.5		
Vitamin mix[h]	2.5		
Total	1000		

[a] Peygir Co (crude protein 55.8%).
[b] Soyabean Co (crude protein 45.5%).
[c] Peygir Co (crude protein 50.0%).
[d] Shahdineh Aran Co (crude protein 78.3%).
[e] CheilJedang Co.
[f] Golbid Co (10,000 IU).
[g] The premix provided following amounts per kg of diet: Mg: 350 mg; Fe:13 mg; Co: 2.5 mg; Cu: 3 mg; Zn: 60 mg; NaCl: 3 g; dicalcium phosphate: 10 g.
[h] The premix provided following amounts per kg of feed: A: 1,000 IU; D3: 5,000 IU; E: 20 mg; B5: 100 mg; B2: 20 mg; B6: 20 mg; B1: 20 mg; H: 1 mg; B9: 6 mg; B12: 1 mg; B4: 600 mg; C: 50 mg.

2.3. Determination of acute toxicity of abamectin and exposure trial

Before the main exposure test, it is first necessary to know the lethal range and acute concentration of abamectin for common carp to select appropriate doses. Therefore, after the adaptation period, common carp were exposed to different concentrations of abamectin to obtain its lethal range. For this purpose, fish (n = 30, 10 fish per replicates) were exposed to concentrations of 0 (control), 0.25, 0.5, 1, 1.5, 2 and 4 mg/l abamectin to determine the LC_{50} according to the standard method [58] during 96 h. The fish mortality was recorded at 24, 48, 72 and 96 h post exposure. Finally, based on the probit statistical analysis method, the values of LC_{10}, LC_{30}, LC_{50}, LC_{70}, and LC_{90} were calculated at 24, 48, 72 and 96 h (Table 2).

2.4. Sampling

At the end of the 30th day, the fish were fed for 24 h, anesthetized with eugenol solution (100 mg/l) and the growth and nutritional indices were calculated through biometry of fish and determination of the feed consumed according to following formulas [59]:

Weight gain (WG; g) = Final weight (FW) – Initial weigh (IW).

Specific growth rate (SGR; %) = 100 × [(ln FW – ln IW)/d],

Feed conversion ratio (FCR) = Feed intake/(FW-IW).

Survival rate (SR; %) = (number of alive fish/total number of fish) × 100.

To evaluate the serum immune parameters, three fish were anesthetized from each tank using eugenol solution (100 mg/l) [59]. Blood samples were taken from the caudal vein using a 2 ml syringe. The blood samples were poured into tubes and kept at room temperature for 2 h. Then, the serum samples were separated using centrifugation (3000×*g* for 10 min at 4 °C). The obtained serum was stored at −70 °C until the biochemical assays. To collect the mucus samples, three fish were randomly caught from each tank and transferred to polyethylene bags containing 10 ml of 50 mM saline solution. After 3 min, the mucus was centrifuged (2500×*g* for 10 min at 4 °C) and the supernatant was stored at −80 °C [60].

2.5. Serum and mucus immune assays

Serum and mucus lysozyme activity were measured based on turbidity method described by Ellis [61] using *Micrococcus lysodeikticus* in phosphate buffer (0.2 mg/ml in a 0.05 M sodium phosphate buffer (pH 6.2) as target. Total serum immunoglobulin (total Ig) (mg/dL) was assayed based on the amount of protein before and after the addition of polyethylene glycol. The concentration of serum complement components (C3 and C4) (mg/dL) was determined by ELISA [(ELX800), Bio-Tek, Vermont, USA)] using commercial assay kit (Pars Azmun Co., Tehran, Iran). The alternative complement activity (ACH_{50}) was evaluated based on the method described by Yano [62]. In this method, sheep red blood cells in the vernal buffer containing EGTA and Mn, were considered as targets. The different concentrations of serum samples (0.312, 0.625, 1.25, 2.5, 5 and 10%) were prepared and then 25 μl serum was mixed with 125 ml of the buffer containing 50 μl of blood cells. After 2 h incubation, the mixture was centrifuged (13000×*g* for 5 min) and kept at room temperature, then the absorption rate was recorded at 412 nm.

Mucus protease activity was measured based on the method described by Ref. [63]. In this method, 100 μl of mucus was mixed with 100 μl ammonium bicarbonate buffer (100 mM) containing 0.7% azocasein solution and then incubated at 30 °C for 20 h. The reaction was stopped using trichloroacetic acid and the supernatant was separated by centrifugation (15000×*g* for 5 min). The supernatant was then mixed with 0.5 N hydroxide and the absorption rate was recorded at 450 nm.

Serum peroxidase activity was measured using Hank's buffer (HBSS) at a wavelength 450 nm based on the method suggested by Quade and Roth [64].

Mucus alkaline phosphatase activity was assayed using Pars Azmun commercial assay kits (Pars Azmun Co., Tehran, Iran) according to manufacturer's protocol.

Serum nitro-blue-tetrazolium (NBT) was assayed using the method of [65]. Briefly, 100 μl of blood was added to 100 μl of 0.2% NBT and the mixture was incubated for 25 min at 25 °C. The resulting 50 μl suspension was added to 1 ml N, N-dimethyl formamide, centrifuged at 3000×*g* for 5 min, and the adsorption of the supernatant was recorded at 540 nm.

Serum myeloperoxidase (MPO) activity was measured by Quade and Roth [64] method. In this method, a mixture of 10 μl serum and 90 μl of Na^{+} and Mn^{2+} without Hank's balanced salt solution (HBSS) was added to the wells of a 96-well microplate reader (Thermo Fisher Scientific, Inc., USA). Then 35 μl of tetramethylbenzidine hydrochloride (TMB) system was added to the wells. The color change was stopped by the addition of 35 μl sulfuric acid (0.5 M) and the absorption rate was recorded at 450 nm.

Mucus acid phosphatase (ACP) activity was assayed at 37 °C in 0.1 M acetate buffer (pH 5.0) using p-nitrophenyl phosphate as substrate as previously reported by Garen and Levinthal, [66].

Total antiprotease activity was measured based on the ability of mucus to inhibit trypsin activity [67]. Briefly, 10 μl of mucus was incubated with 5 mg trypsin at 22 °C for 10 min. Then 100 μl ammonium bicarbonate (100 mM) and 125 μl of azocasein 0.7% were added to the mixture. Samples were incubated for 2 h at 30 °C and then 250 μl of trichloroacetic acid was added. The mixture was then centrifuged at 6000×*g* for 10 min. The supernatant was poured into the wells of the 96-well microplate reader containing 100 μl of sodium peroxide and the absorption rate was read at 450 nm.

Esterase activity was measured based on Guardiola [67]. In this method, an equal volume of mucus and 0.4 mM nitrofenyl meristate in ammonium bicarbonate buffer containing 0.5% Triton X100 was incubated at 30 °C and the absorption rate was read at 405 nm.

2.6. Serum and mucus biochemical parameters

Serum and mucus cortisol levels (ng/ml) was assayed by ELISA using a commercial assay kit (IBL Co., Gesellschaft für Immunchemieund Immunbiologie, Germany). The serum and mucus glucose (mg/dL) concentrations were determined by commercial assay kit (Pars Azmun Co., Tehran, Iran). The serum glutathione peroxidase (GPx) (U/ml) and superoxide dismutase (SOD) (U/ml) activities were assayed through measuring the oxidation rate of glutathione oxide and reduction rate of cytochrome C, respectively (ZellBio GmbH, Veltinerweg, Germany). The serum catalase (CAT) activity (U/ml) was calculated by estimating the decomposition rate of H_2O_2, as described by Goth [68]. The lipid peroxidation indicator, malondialdehyde (MDA) was evaluated by thiobarbituric acid (TBARS) method using commercial assay kit (ZellBio GmbH, Veltinerweg, Germany). The activity of ALP, AST and alanine aminotransferase (ALT) and lactate dehydrogenase (LDH) (U/l) enzymes in serum were measured using commercial assay kits (Pars Azmun CO., Tehran, Iran) by a biochemical autoanalysis (Beckman Coulter, Avanti J-26 XPI, CA, USA).

Table 2
Lethal Concentrations ($LC_{10\text{-}90}$) of Abamectin depending on time (24–96h) for *Cyprinus carpio* (mean ± SE).

Point	Concentration (ppm) (95% of confidence limits)			
	24h	48h	72h	96h
LC_{10}	0.95 ± 0.38	0.84 ± 0.33	0.70 ± 0.33	0.62 ± 0.41
LC_{30}	1.24 ± 0.38	1.15 ± 0. 33	1.01 ± 0.33	0.87 ± 0.41
LC_{50}	**1.45 ± 0.38**	**1.37 ± 0. 33**	**1.22 ± 0.33**	**1.04 ± 0.41**
LC_{70}	1.65 ± 0.38	1.59 ± 0. 33	1.43 ± 0.33	1.22 ± 0.41
LC_{90}	1.95 ± 0.38	1.91 ± 0. 33	1.74 ± 0.33	1.47 ± 0.41

2.7. Data analysis

Data of the present study was analyzed by SPSS software. After evaluation of data normality by Kolmogorov-Smirnov test. One-way analysis of variance (ANOVA) was conducted to determine the differences between the means and then the means compared by Tukey test ($P < 0.05$). Data in figures and table are presented as Mean ± SE.

3. Results

3.1. Growth performance

The values of FW significantly were higher in the treatment T3 (300 mg/kg resveratrol), compared to control after 30 days feeding (Table 3, $P < 0.05$). Also, the values of FW were higher in T2 than in those in T5 (Table 3, $P < 0.05$). The FW showed no significant differences between other groups (Table 3, $P > 0.05$). The WG values significantly increased in T3 compared to control, while the lowest WG values observed in T4 (Table 3, $P < 0.05$). There were no significant differences in WG between control and other groups (Table 3, $P > 0.05$). The lowest and highest values of FCR were observed in T3 and T4 respectively (Table 3, $P < 0.05$). In comparison with control, the FCR value in T3 showed significant decreases, while it increased in T4 (Table 3, $P < 0.05$). There were no significant differences in FCR betweenT3, T5 and T6 (Table 3, $P > 0.05$). The SGR value was significantly lower in T4 compared to other experimental groups (Table 3, $P < 0.05$). The other groups showed no significant differences in SGR (Table 3, $P > 0.05$). There were no significant differences in SR between all groups (Table 3, $P > 0.05$).

3.2. Serum immune components

The lysozyme activity significantly increased in the treatments, T2 and T3 compared to control and other groups (Table 4, $P < 0.05$). There were no significant differences in lysozyme activity between control and other groups (Table 4, $P > 0.05$). The ACH_{50} activity in T2 and T4 significantly showed higher and lower activities than in control respectively (Table 4, $P > 0.05$). The ACH_{50} activity in other groups exhibited no significant differences with control (Table 4, $P > 0.05$). The total Ig concentrations significantly increased in the treatment, T3 compared to control (Table 4, $P < 0.05$). The total Ig concentrations in control showed no significant differences with other groups (Table 4, $P > 0.05$). There were no significant differences in total Ig concentration between T2, T3 and T6 and also between T5 and T6 (Table 4, $P > 0.05$). The activity of protease significantly increased in the treatment, T2 compared to control (Table 4, $P < 0.05$). The protease activity in control exhibited no significant differences with other groups (Table 4, $P > 0.05$). There were no significant differences in protease activity between T3 and T5 and also between T4, T5 and T6 (Table 4, $P > 0.05$). The MPO activity in control showed no significant differences with other groups (Table 4, $P > 0.05$). However, MPO activity was significantly higher in T2 than in T4 (Table 4, $P < 0.05$). The NBT activity significantly increased in the treatments, T3 and T6 compared to control (Table 4, $P < 0.05$). There were no significant differences in NBT activity between T3 and T6 and also between control, T2, T4 and T5 (Table 4, $P > 0.05$). The peroxidase activity significantly increased in the treatment, T3 compared to control (Table 4, $P < 0.05$). Furthermore, peroxidase activity was significantly higher in T2 than in T4 and T5 (Table 4, $P < 0.05$). The activity of C3 significantly increased in the treatment, T2 and T3 compared to control (Table 4, $P < 0.05$). Also, the C3 activity in T2 exhibited higher levels than those in T4 and T5 (Table 4, $P > 0.05$). There were no significant differences in C3 activity between control and T4, T5 and T6 (Table 4, $P > 0.05$). Although C4 activity in the treatment, T3 was higher than T4, no significant differences in this component were observed between control and other groups (Table 4, $P > 0.05$).

Table 3
The growth and survival of the common carp, *Cyprinus carpio* over 30 days feeding with experimental diets: T1: non-supplemenetd and non-abamectin exposed fish, T2: non-abamectin exposed fish supplemented with 300 mg/kg curcumin, T3: non-abamectin exposed fish supplemented with 300 mg/kg resveratrol, T4: non-supplemenetd fish exposed to 12.5% LC_{50} of abamectin, T5: 300 mg/kg curcumin supplemented fish exposed to 12.5% LC_{50} of abamectin, T6: 300 mg/kg resveratrol supplemented fish exposed to 12.5% LC_{50} of abamectin. Data are presented as mean ± SE. Different letters in the same row show significant differences ($P < 0.05$).

Parameters	T1 (control)	T2	T3	T4	T5	T6
IW (g)	30.43 ± 0.34^{a}	31.43 ± 0.47^{a}	30.93 ± 0.43^{a}	30.46 ± 0.43^{a}	30.83 ± 0.72^{a}	30.60 ± 0.20^{a}
FW (g)	46.66 ± 0.72^{bcd}	49.83 ± 0.92^{ab}	50.16 ± 0.72^{a}	43.36 ± 0.44^{d}	46.46 ± 0.77^{cd}	46.73 ± 0.53^{bc}
WG (g)	16.23 ± 0.39^{b}	18.40 ± 0.49^{ab}	19.23 ± 0.88^{a}	12.90 ± 0.66^{c}	15.63 ± 0.36^{bc}	16.13 ± 0.72^{b}
FCR	1.54 ± 0.04^{b}	1.38 ± 0.03^{bc}	1.29 ± 0.04^{c}	1.86 ± 0.05^{a}	1.46 ± 0.06^{bc}	1.51 ± 0.06^{bc}
SGR (%/d)	1.42 ± 0.01^{ab}	1.53 ± 0.01^{ab}	1.61 ± 0.07^{a}	1.17 ± 0.06^{c}	1.36 ± 0.04^{bc}	1.41 ± 0.05^{abc}
SR (%)	96.33 ± 2.02^{a}	97.33 ± 1.33^{a}	98.66 ± 1.33^{a}	93.00 ± 1.73^{a}	95.00 ± 1.00^{a}	96.33 ± 2.02^{a}

*IW: initial weigh; FW: final weight; WG: weight gain; FCR: feed conversion ratio; SGR: specific growth rate; SR: survival rate.

Table 4
The serum immune components of the common carp, *Cyprinus carpio* over 30 days feeding with experimental diets: T1: non-supplemenetd and non-abamectin exposed fish, T2: non-abamectin exposed fish supplemented with 300 mg/kg curcumin, T3: non-abamectin exposed fish supplemented with 300 mg/kg resveratrol, T4: non-supplemenetd fish exposed to 12.5% LC_{50} of abamectin, T5: 300 mg/kg curcumin supplemented fish exposed to 12.5% LC_{50} of abamectin, T6: 300 mg/kg resveratrol supplemented fish exposed to 12.5% LC_{50} of abamectin. Data are presented as mean ± SE. Different letters in the same row show significant differences ($P < 0.05$).

Parameters	T1 (control)	T2	T3	T4	T5	T6
Lysozyme (U/ml)	22.60 ± 1.51^{cd}	28.93 ± 0.86^{ab}	31.36 ± 1.19^{a}	18.76 ± 0.72^{d}	22.10 ± 1.15^{cd}	25.23 ± 0.67^{bc}
ACH_{50} (U/ml)	106.50 ± 3.29^{b}	123.50 ± 2.46^{a}	118.03 ± 1.88^{ab}	92.33 ± 3.48^{c}	106.73 ± 2.74^{b}	104.63 ± 3.44^{bc}
Protease (%)	5.73 ± 0.66^{bc}	8.33 ± 0.48^{a}	7.93 ± 0.52^{ab}	3.76 ± 0.43^{c}	6.13 ± 0.49^{abc}	5.23 ± 0.43^{c}
Total Ig (mg/ml)	17.50 ± 0.81^{bc}	21.43 ± 0.80^{ab}	22.23 ± 1.01^{a}	13.36 ± 0.78^{c}	7.33 ± 1.20^{bc}1	18.50 ± 0.73^{ab}
MPO (OD 450)	1.23 ± 0.20^{ab}	2.21 ± 0.34^{a}	1.63 ± 0.24^{ab}	1.00 ± 0.17^{b}	1.50 ± 0.15^{ab}	1.30 ± 0.17^{ab}
NBT (OD 540)	1.21 ± 0.11^{b}	1.56 ± 0.22^{ab}	2.48 ± 0.20^{a}	2.15 ± 0.23^{ab}	2.11 ± 0.27^{ab}	2.58 ± 0.29^{a}
Peroxidase (U/ml)	7.83 ± 0.46^{bc}	10.06 ± 0.58^{ab}	11.83 ± 0.89^{a}	6.20 ± 0.62^{c}	6.43 ± 0.47^{c}	8.16 ± 0.52^{bc}
C3 (g/dL)	29.33 ± 1.14^{cd}	34.60 ± 0.87^{ab}	38.93 ± 1.21^{a}	24.70 ± 0.94^{d}	28.43 ± 1.31^{cd}	30.83 ± 1.01^{bc}
C4 (g/dL)	15.16 ± 1.01^{ab}	15.86 ± 1.04^{ab}	16.80 ± 0.69^{a}	12.03 ± 0.57^{b}	12.70 ± 1.20^{ab}	13.16 ± 0.88^{ab}

*ACH_{50}: alternative complement activity; Total Ig: total immunoglobulin; MPO: myeloperoxidase; NBT: nitro-blue-tetrazolium; C3 and C4: concentration of serum complement components.

3.3. Mucus immune components

The protease activity showed significant decreases in the treatment T4 compared to T3 (Fig. 1A, $P < 0.05$). Other groups had no significant differences in protease activity with control (Fig. 1A, $P > 0.05$). There were no significant differences in lysozyme activity between all groups (Fig. 1B, $P > 0.05$). The ACP activity exhibited significant increases T2 and T3 compared to control (Fig. 1C, $P > 0.05$). There were no significant differences in ACP activity between control and the treatments, T4, T5 and T6 (Fig. 1C, $P > 0.05$). The ALP activity significantly elevated in T3 compared to control (Fig. 1D, $P > 0.05$). The other groups showed no significant differences in ALP activity with control (Fig. 1D, $P > 0.05$). The esterase activity significantly elevated in the treatment, T2 compared to control (Fig. 1E, $P > 0.05$). No significant differences were observed in esterase activity between control and other groups (Fig. 1E, $P > 0.05$). Also, the activity of esterase was significantly lower in the treatment T4 than those in T3 (Fig. 1E, $P > 0.05$). The antiprotease activity exhibited significant increases T3 compared to control (Fig. 1F, $P > 0.05$). Also, the treatment, T2 showed higher antiprotease activity than in T4, T5 and T6 (Fig. 1F, $P > 0.05$). There were no significant differences in antiprotease activity between control and the treatments, T4, T5 and T6 (Fig. 1F, $P > 0.05$). In addition, no significant differences were observed in antiprotease activity between T4, T5 and T6 (Fig. 1F, $P > 0.05$).

3.4. Serum biochemicals

CAT activity showed no significant differences between the experimental groups after feeding period (Table 5, $P > 0.05$). The SOD activity was significantly higher in T3 than those in T4 (Table 5, $P < 0.05$). No significant differences were observed in SOD activity between control and other groups (Table 5, $P < 0.05$). GPx activity significantly increased in T3 compared to control (Table 5, $P < 0.05$). There were no significant differences in GPx activity between control and other groups (Table 5, $P > 0.05$). The MDA levels significantly elevated in the treatments, T4, T5 and T6 compared to control and other groups (Table 5, $P < 0.05$). No significant differences were observed in MDA between control, T2 and T3 and also between T4, T5 and T6 (Table 5, $P > 0.05$). The liver metabolic enzymes in serum were influenced by experimental diets (Table 6, $P < 0.05$). The levels of ALT significantly decreased in the treatment T3 compared to control (Table 6, $P < 0.05$). No significant differences were observed in ALT levels between control and other groups (Table 6, $P > 0.05$). The ALP and AST levels in control showed no significant differences with other groups (Table 6, $P > 0.05$). However, the ALP levels in T3 significantly decreased compared to T4 (Table 6, $P < 0.05$). The LDH levels showed significant decreases in the treatments, T2 and T3 compared to control (Table 6, $P > 0.05$). There were no significant differences in LDH activity between control and other groups (Table 6, $P > 0.05$).

Total protein and globulin concentrations exhibited no significant differences between the experimental groups after feeding period (Table 7, $P > 0.05$). The albumin levels significantly increased in T3 compared to control (Table 7, $P < 0.05$). There were no significant differences in albumin concentration between control and other groups

Table 5
The serum antioxidant enzyme activity in the common carp, *Cyprinus carpio* over 30 days feeding with experimental diets: T1: non-suplemenetd and non-abamectin exposed fish, T2: non-abamectin exposed fish supplemented with 300 mg/kg curcumin, T3: non-abamectin exposed fish supplemented with 300 mg/kg resveratrol, T4: non-suplemenetd fish exposed to 12.5% LC_{50} of abamectin, T5: 300 mg/kg curcumin supplemented fish exposed to 12.5% LC_{50} of abamectin, T6: 300 mg/kg resveratrol supplemented fish exposed to 12.5% LC_{50} of abamectin. Data are presented as mean ± SE. Different letters in the same row show significant differences ($P < 0.05$).

Parameters	T1 (control)	T2	T3	T4	T5	T6
CAT (U/ml)	100.16 ± 3.89^{a}	103.66 ± 5.19^{a}	105.00 ± 3.75^{a}	92.86 ± 3.19^{a}	93.90 ± 3.03^{a}	95.93 ± 2.52^{a}
SOD (U/ml)	25.33 ± 1.16^{ab}	26.43 ± 1.65^{ab}	29.40 ± 1.05^{a}	21.33 ± 0.99^{b}	24.63 ± 1.24^{ab}	25.46 ± 1.31^{ab}
MDA (nmol/ml)	35.56 ± 1.66^{b}	31.80 ± 1.47^{b}	28.63 ± 1.12^{b}	45.43 ± 1.65^{a}	44.06 ± 1.76^{a}	43.33 ± 1.45^{a}
GPx (U/ml)	150.33 ± 3.17^{b}	154.00 ± 2.30^{ab}	165.50 ± 3.04^{a}	142.50 ± 2.35^{b}	148.33 ± 2.89^{b}	152.83 ± 2.45^{ab}

*CAT: catalase; SOD: superoxide dismutase; MDA: malondialdehyde; GPx: glutathione peroxidase.

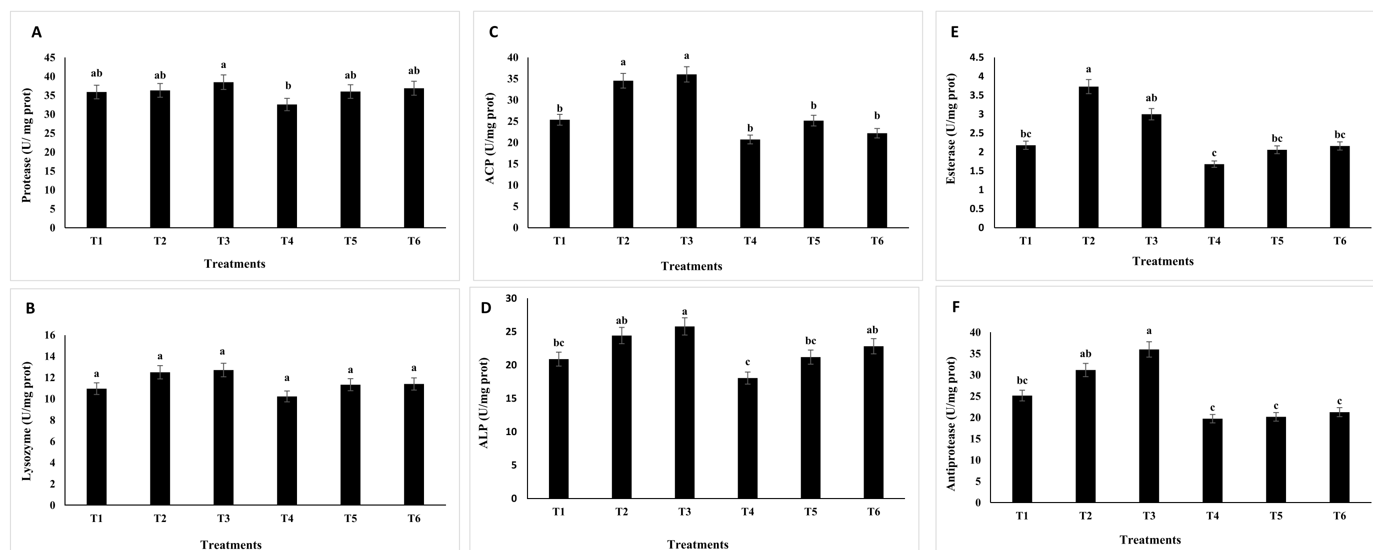

Fig. 1. The immune components in the mucus of the common carp, *Cyprinus carpio* over 30 days feeding with experimental diets: T1: non-suplemenetd and non-abamectin exposed fish, T2: non-abamectin exposed fish supplemented with 300 mg/kg curcumin, T3: non-abamectin exposed fish supplemented with 300 mg/kg resveratrol, T4: non-suplemenetd fish exposed to 12.5% LC_{50} of abamectin, T5: 300 mg/kg curcumin supplemented fish exposed to 12.5% LC_{50} of abamectin, T6: 300 mg/kg resveratrol supplemented fish exposed to 12.5% LC_{50} of abamectin. (ACP: acid phosphatase; ALP: alkaline phosphatase). Data are presented as mean ± SE. Different letters in the same row show significant differences ($P < 0.05$).

Table 6
The activity of liver metabolic enzymes in serum of the common carp, *Cyprinus carpio* over 30 days feeding with experimental diets: T1: non-supplemenetd and non-abamectin exposed fish, T2: non-abamectin exposed fish supplemented with 300 mg/kg curcumin, T3: non-abamectin exposed fish supplemented with 300 mg/kg resveratrol, T4: non-supplemenetd fish exposed to 12.5% LC_{50} of abamectin, T5: 300 mg/kg curcumin supplemented fish exposed to 12.5% LC_{50} of abamectin, T6: 300 mg/kg resveratrol supplemented fish exposed to 12.5% LC_{50} of abamectin. Data are presented as mean ± SE. Different letters in the same row show significant differences ($P < 0.05$).

Parameters	T1 (control)	T2	T3	T4	T5	T6
ALT (U/l)	21.53 ± 1.01[ab]	18.66 ± 0.88[bc]	17.10 ± 0.51[c]	24.90 ± 0.60[a]	20.50 ± 0.76[bc]	21.26 ± 0.89[ab]
AST (U/l)	80.40 ± 1.53[a]	78.16 ± 2.16[a]	80.16 ± 2.20[a]	86.10 ± 1.93[a]	81.20 ± 1.74[a]	84.40 ± 1.81[a]
ALP (U/l)	107.16 ± 4.18[ab]	98.83 ± 4.20[b]	95.50 ± 2.59[b]	116.23 ± 3.03[a]	104.50 ± 2.59[ab]	98.50 ± 2.75[b]
LDH (U/l)	287.00 ± 3.78[a]	274.00 ± 2.30[b]	270.83 ± 1.58[b]	292.20 ± 1.74[a]	288.83 ± 2.74[a]	290.83 ± 1.48[a]

*ALT: alanine aminotransferase; AST: aspartate transaminase; ALP: alkaline phosphatase; LDH: lactate dehydrogenase.

Table 7
The biochemicals in the serum of the common carp, *Cyprinus carpio* over 30 days feeding with experimental diets: T1: non-supplemenetd and non-abamectin exposed fish, T2: non-abamectin exposed fish supplemented with 300 mg/kg curcumin, T3: non-abamectin exposed fish supplemented with 300 mg/kg resveratrol, T4: non-supplemenetd fish exposed to 12.5% LC_{50} of abamectin, T5: 300 mg/kg curcumin supplemented fish exposed to 12.5% LC_{50} of abamectin, T6: 300 mg/kg resveratrol supplemented fish exposed to 12.5% LC_{50} of abamectin. Data are presented as mean ± SE. Different letters in the same row show significant differences ($P < 0.05$).

Parameters	T1 (control)	T2	T3	T4	T5	T6
Total Protein (g/dL)	3.00 ± 0.17[a]	3.40 ± 0.26[a]	3.95 ± 0.27[a]	2.90 ± 0.18[a]	2.86 ± 0.20[a]	3.03 ± 0.29[a]
Albumin (g/dL)	1.30 ± 0.05[ab]	1.46 ± 0.17[ab]	1.63 ± 0.13[a]	1.05 ± 0.10[b]	1.36 ± 0.08[ab]	1.43 ± 0.08[ab]
Globulin (g/dL)	1.70 ± 0.11[a]	1.93 ± 0.08[a]	2.31 ± 0.18[a]	1.85 ± 0.08[a]	1.50 ± 0.28[a]	1.60 ± 0.25[a]
Glucose (g/dL)	81.76 ± 1.67[ab]	74.16 ± 2.45[bc]	67.50 ± 2.17[c]	85.50 ± 1.89[a]	83.10 ± 1.93[ab]	76.86 ± 1.27[ab]
Cortisol (ng/ml)	93.50 ± 1.89[b]	86.76 ± 1.29[bc]	81.26 ± 1.75[c]	105.16 ± 2.61[a]	93.50 ± 1.32[b]	91.40 ± 1.66[b]

(Table 7, $P > 0.05$). The glucose concentrations significantly decreased in T3 compared to control (Table 7, $P < 0.05$). The other groups showed no significant differences in glucose concentration with control (Table 7, $P > 0.05$). In comparison with control, the cortisol levels in T3 significantly decreased, while its levels increased in T4 (Table 7, $P < 0.05$). There were no significant differences in cortisol levels between control, T5 and T6 (Table 7, $P > 0.05$).

3.5. Mucus biochemicals

The cortisol levels significantly decreased in the treatments, T3 compared to control and the treatments, T4, T5 and T6 (Fig. 2A, $P < 0.05$). There were no significant differences in cortisol levels between control and other groups (Fig. 2A, $P < 0.05$). The glucose concentrations were significantly higher in the treatment, T4 than those in T4 (Fig. 2B, $P < 0.05$). There were no significant differences in glucose concentration between control and other groups (Fig. 2B, $P < 0.05$). The lactate concentrations exhibited no significant differences between the experimental groups after feeding period (Fig. 2C, $P > 0.05$).

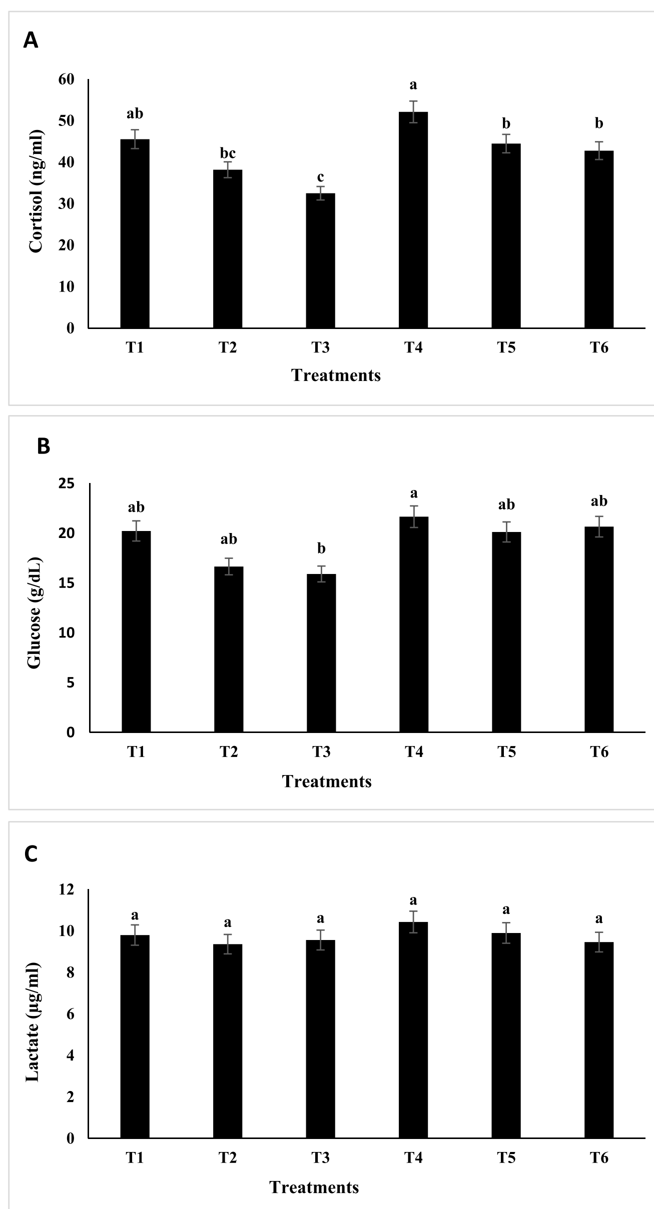

Fig. 2. The biochemicals in the mucus of the common carp, *Cyprinus carpio* over 30 days feeding with experimental diets: T1: non-supplemenetd and non-abamectin exposed fish, T2: non-abamectin exposed fish supplemented with 300 mg/kg curcumin, T3: non-abamectin exposed fish supplemented with 300 mg/kg resveratrol, T4: non-supplemenetd fish exposed to 12.5% LC_{50} of abamectin, T5: 300 mg/kg curcumin supplemented fish exposed to 12.5% LC_{50} of abamectin, T6: 300 mg/kg resveratrol supplemented fish exposed to 12.5% LC_{50} of abamectin. Data are presented as mean ± SE. Different letters in the same row show significant differences ($P < 0.05$).

4. Discussion

In the present study, use of 300 mg/kg resveratrol in the diet of non-abamectin exposed fish considerably improved the growth performance, as the values of FW and WG increased and the FCR decreased in this treatment compared to other groups. Such effects were not observed for curcumin, since the growth performance in the treatment 300 mg/kg curcumin was similar to those in control. The growth prompting effects of resveratrol and curcumin and resveratrol have been widely reported in fish [31,36,40,47,49,57,69–75]. However, the growth results may be

different depending on fish species, the dietary level of the supplements, and the duration of feeding and experimental conditions. For example, a combination of resveratrol (400–800 mg/kg) and the probiotics, *Lactobacillus acidophilus* and *Bifidobacterium bifidum* in the diet of rainbow trout improved the fish growth and immunity [49].

In crucian carp, *Carassius auratus*, the growth indices improved in the fish supplemented with 5 g/kg feed curcumin, which be attributed to the enhanced activity of digestive enzymes in the supplemented fish [69]. In grass carp, *Ctenopharyngodon idella*, curcumin at dietary levels of 438.20 mg/kg diet prompted the fish growth, which be related to the improved immune and antioxidant system in the curcumin supplemented fish [36]. Similar results obtained in the study of Ashry et al. [73], where inclusion of 2–3% curcumin improved the growth performance of gilthead seabream, *Sparus aurata*. Li et al. [72] showed that curcumin may prompted the growth in grass carp by improving intestinal growth and development and the capabilities of intestine in absorption and transportation of amino acids. Curcumin may also increase the feed intake in fish due to its attractive flavor as well [31,76]. Like curcumin, resveratrol had also beneficial effects on in turbot, *Scophthalmus maximus* [47] and southern flounder, *Paralichthys lethostigma* [40], pacu, *Piaractus mesopotamicus* [71] and snakehead fish, *Channa argus* [74]. The prompting effects of resveratrol on fish growth are mainly exerted through restoring of intestinal damages [47], reducing protein degradation [40], improving antioxidant defense [71] and lipid and glucose metabolism [77]. In this study, the growth was reduced in the fish exposed to abamectin free supplementation, as previously reported in other studies [78,79]. Pesticides including abamectin usually reduce growth in fish by reducing food intake, suppressing digestive enzymes and growth hormone, inducing intestinal tissue damages and following disruptions in digestion and absorption of nutrients and disrupting liver function [55,80–87]. In this study, the FW showed higher values in fish of the treatment, 300 mg/kg curcumin compared to the treatment, 300 mg/kg curcumin +12.5% LC_{50} of abamectin. In addition, we observed no differences in the FW, FCR and WG between control and fish of the treatments, resveratrol + abamectin and curcumin + abamectin, which may suggest an ameliorating functions for the supplements on the growth depressing effects of the abamectin.

In this study, the immune components in blood (lysozyme, C3, ACH_{50}, total Ig, protease, MPO, NBT, peroxidase, albumin) and mucus (ACP, ALP, esterase, antiprotease) and antioxidant enzymes (SOD, GPx) showed various changes compared to the control group, however, these components were almost all higher in fish supplemented with curcumin and resveratrol in a abamectin-free medium than in control and other groups. In line with our results, many studies have demonstrated the immune-stimulating effects of curcumin and resveratrol in fish [33,35,38,44,74,88–91]. Although the mechanism of action of curcumin and resveratrol in fish is still unknown, studies in other vertebrates have shown that those may be involved in the immune system by affecting the production of cytokines and modulating of inflammatory responses [92–94].

The antioxidant system in fish is the first line of defense against free radicals caused by oxidative stress. In this study, abamectin stimulated oxidative stress in fish, because MDA levels, as the indicator of oxidative stress, showed a significant increase in the exposed fish. Curcumin and resveratrol are known to have a scavenging effect on free radicals generated upon oxidative stress [95–97]. This scavenging function has been also reported in fish [45,98,99]. Therefore, both the supplements can strengthen the immune system in this way. However, it appears that neither curcumin nor resveratrol were as effective in preventing oxidative stress, because MDA levels were higher in the treatments, abamectin only and supplement + abamectin than in control and non-exposed fish supplemented with curcumin and resveratrol.

In this study, in most cases, the levels of immune and antioxidant components in the control did not show significant difference with the groups, resveratrol + abamectin and curcumin + abamectin, which may indicate the moderating action of these supplements on the immunotoxic effects of abamectin.

Elevated levels of hepatic metabolic enzymes (LME) in blood may have a variety of causes and may not necessarily be a specific symptom, but they usually indicate liver disorders and damage [100,101]. In fish, elevated levels of LME in the blood have been reported after exposure to contaminants, especially pesticides, which have been attributed to liver damage caused by toxins [102–104]. In our study, the levels of LME in the blood of the control group did not show a significant difference with the abamectin exposed ones, which could indicate the non-significant effect of the pesticide at a dose of 12.5% LC_{50} on the liver. In non-abamectin exposed fish, the levels of ALT, LDH and ALP in resveratrol-supplemented fish and LDH in those supplemented with curcumin showed significant decreases compared to control, which may suggest a protective role for the supplements with liver.

Cortisol, as the most important stress hormone, is secreted into the bloodstream in response to stressors and breaks down glycogen in the liver to produce glucose to provide the energy needs of stressful conditions [105]. In this study, the cortisol levels increased in non-supplemented fish after exposure to abamectin, indicating stress inducing effect of the pesticide, as previously reported for other pesticides in fish [106–110]. Based on our results, the cortisol and glucose levels showed significant decreases in non-exposed fish supplemented with resveratrol, suggesting a stress mitigating effect for resveratrol. In addition, the glucose and cortisol levels in control were similar to those in resveratrol + abamectin and curcumin + abamectin, which may support this mitigating effect.

5. Conclusion

In conclusion, the results of this study revealed that abamectin can reduce the growth and immunity of the common carp. Although, both resveratrol and curcumin were able to mitigate the abamectin induced disruptions, it seems that resveratrol be more effective than curcumin. In addition, although abamectin reduced the growth and immunity in non-supplemented treatments, it had no significant effect on fish survival rate.

Ethical approval

In this study, all stages of sampling and manipulation of animals have been performed in accordance with ethical standards.

Compliance with ethical standards

The authors declare that they have no competing interests.

CRediT authorship contribution statement

Martina Kurnia Rohmah: Conceptualization, Writing – original draft. **Omar Dheyauldeen Salahdin:** Data curation, Writing – review & editing. **Reena Gupta:** Formal analysis, Writing – review & editing. **Khursheed Muzammil:** Funding acquisition. **Maytham T. Qasim:** Investigation. **Zahraa Haleem Al-qaim:** Project administration. **Nada Fadhil Abbas:** Resources. **Mohammed Abed Jawad:** Supervision. **Ghulam Yasin:** Visualization, Writing – review & editing. **Yasser Fakri Mustafa:** Writing – original draft. **Aadel Heidary:** Methodology, Field Study and Sampling. **Safoura Abarghouei:** Methodology, Field Study and Sampling.

Declaration of competing interest

The authors have no conflict of interest.

Data availability

Data will be made available on request.

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