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Vitamin E: An assistant for black soldier fly to reduce cadmium accumulation and toxicity

Zhihui Shi [a], Yujia Wan [a], Miao Peng [a], Jie Zhang [a], Zhenghui Gao [b], Xiaoping Wang [c], Fen Zhu [a,c,*]

[a] Hubei International Scientific and Technological Cooperation Base of Waste Conversion by Insects, Huazhong Agricultural University, Wuhan 430070, China
[b] School of Engineering, Cardiff University, Cardiff CF24 3AA, UK
[c] Hubei Insect Resources Utilization and Sustainable Pest Management Key Laboratory, Huazhong Agricultural University, Wuhan 430070, China

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ABSTRACT

Cadmium (Cd) is a toxic heavy metal associated with osteoporosis, liver, and kidney disease. The black soldier fly (BSF) *Hermetia illucens* may be exposed to Cd during the transformation of livestock manure. The BSF has a high tolerance to Cd. In the previous work of the laboratory, we found that vitamin E (VE) may play a role in the tolerance of BSF to Cd exposure. The main findings are as follows: The BSF larvae pretreated with exogenous VE had heavier body weight, lower content and toxicity of Cd under similar Cd exposure. Even in high Cd exposure at the concentrations of 300 and 700 mg/kg, the BSF larvae pretreated with exogenous VE at a concentration of 100 mg/kg still reduced the Cd toxicity to 85.33 % and 84.43 %, respectively. The best-fitting models showed that metallothionein (MT) content, oxidative damage (8-hydroxydeoxyguanosine content, malondialdehyde content), antioxidant power (total antioxidant power, peroxidase activity) had a great influence on content and toxicity of Cd bioaccumulated in the larvae. The degree of oxidative damage was reduced in the larvae with exogenous VE pretreatments. This variation can be explained by their changed MT content and increased antioxidant power because of exogenous VE. These results reveal the roles of VE in insects defense against Cd exposure and provide a new option for the prevention and therapy of damage caused by Cd exposure.

1. Introduction

Cadmium (Cd), a toxic heavy metal with extensive environmental distribution, has been classified as the seventh most hazardous industrial carcinogen owing to its protracted half-life and high toxicity (Wang and Du, 2013; Zhang et al., 2023; Zhao et al., 2023). Multiple damages to organisms are caused by Cd exposure, such as chronic kidney, psoriatic, and diabetes diseases (Doccioli et al., 2024; Filippini et al., 2022; Wacewicz-Muczyńska et al., 2021). It exists a variety of toxicological effects in organism for Cd toxicity, e.g., Cd exposure inhibits growth (Rahman et al., 2023; Zheng et al., 2023), causes oxidative damage (Drzeżdżon et al., 2018; Qiu et al., 2023), and disrupts metabolism (Hong et al., 2021; Pietz et al., 2023). Biological exposure to Cd is mainly due to the polluted environment and food (Fu et al., 2013). It has been estimated that the biological intake of Cd from the environment could reach up to 10 % of the total intake (Yang et al., 2023).

Some carrion animals can reduce the content of heavy metal in the composts and should be used equally with plant or microbial treatments to manage the heavy metal pollution (Ahadi et al., 2020). The black soldier fly (BSF), *Hermetia illucens*, is currently the most popular carrion insect (van Huis et al., 2020), which could process diverse manure substrates including swine, chicken, quail, and cattle manure (Kaczor et al., 2023; Liu et al., 2020; Ur Rehman et al., 2023), mitigating manure Cd content and bioavailability through endogenous physiological/biochemical factors and gut microflora (Ao et al., 2021; Shi et al., 2022). It is known that BSF has thoroughly high tolerance to Cd (Diener et al., 2015; Wang et al., 2018).

Under Cd exposure, there are resistance mechanisms in organism. It is demonstrated that Vitamin E (VE) protect the health of tissues and organs under Cd exposure (Ayyat et al., 2017; Olaniyan et al., 2021; Ozovehe et al., 2021). However, it is far less descriptions and explanations of how VE helps organism defense against Cd exposure at the whole organism level. Vitamin E, a fat-soluble vitamin, possessed diverse bioactivities central to growth, development, and immunity.

* Corresponding author.
E-mail addresses: zhihuishi@webmail.hzau.edu.cn (Z. Shi), wanyujia@webmail.hzau.edu.cn (Y. Wan), pm@webmail.hzau.edu.cn (M. Peng), Peterzhang@webmail.hzau.edu.cn (J. Zhang), gaoz21@cardiff.ac.uk (Z. Gao), xpwang@mail.hzau.edu.cn (X. Wang), zhufen@mail.hzau.edu.cn (F. Zhu).

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Supplemental VE enhances swine growth and pork quality (Wang et al., 2022). Addition of VE could regulate the immune system such as platelets and coagulation system, anti-inflammatory and inhibit the formation of anti-atherosclerotic thrombus (Violi et al., 2022). VE also governs metabolic pathways including tryptophan, purine, and other intermediary metabolisms (Henderson et al., 2023). As a prototypical antioxidant, the free hydroxyl groups of VE scavenge free radicals and reactive oxygen species, thereby mitigating oxidative damage (Miyazawa et al., 2019; Szewczyk et al., 2021). Exceptionally high VE levels (248.8 ± 19.8 μg/g) occurred in BSF (Liland et al., 2017) has the potential to be a natural source. In summary, there are multiple pathways and influences of VE on organisms, and the significance of the multiple impact factors should be measured through datafication. The best-fitting model, which aims to find a parsimonious model that effectively captures the variance in the data by evaluating a series of models with predictors (Maestre et al., 2022), has become one of the most popular approaches of data analysis (Lubke and Campbell, 2016). Therefore, the best-fitting model is suit for this experiment.

Based on extraordinary Cd tolerance and abundant VE content in vivo, we hypothesized that VE plays an important role in assisting BSF to Cd exposure. We evaluated larval relative body weight ratio, Cd bioaccumulation and toxicity, MT content, oxidative damage, and antioxidant power with VE pretreatment under Cd exposure. In addition, we evaluated the important factors affecting Cd content and toxicity *via* weight sum of predictors in the best-fitting models. This study advances our basic understanding of the mechanisms of Cd tolerance in insects. More broadly, it further informs the development of insect-based bioremediation technologies for Cd pollution.

2. Materials and methods

2.1. Insects rearing

The BSF colony was maintained in a lab of Hubei International Scientific and Technological Cooperation Base of Waste Conversion by Insects, Huazhong Agricultural University. The adults were fed with water. Corrugated board was used to harvest the eggs. The larvae feed was wet wheat bran.

2.2. Feed allocation and larval treatment

Extraneous vitamin E (VE, Zhejiang Medicine Co., Ltd, China) was mixed into wet wheat bran to make the VE-added feed at concentrations of 0, 1, 10, and 100 mg/kg. The concentrations of VE treatments were referenced to Choi et al (2020). Extraneous $CdCl_2{\cdot}2.5H_2O$ (Sinopharm Chemical Reagent Co., Ltd, China) was used to prepare the tested Cd solution. They were added into wet wheat bran to make the Cd-polluted diet at concentrations of 0, 50, 300, and 700 mg/kg. According to sample surveys, Cd concentrations in soils from polluted areas could reach 1700 mg/kg or even higher (Bednarska et al., 2017), so the 700 mg/kg Cd exposure could be used as the highest treatment concentration. The 3-day experimental larvae were fed with the VE-added feed for 4 days. According to Braeckman *et al.*, 15 larvae were collected after 24 h, washed, paper-dried, and weighted before stored at −80 °C (Braeckman et al., 1999). The experiment was designed with triplicates.

2.3. Content and bioavailability investigation of Cd

The larvae were dried to a constant weight at 60 °C before being weighted for resolution. They were digested with 9 mL HNO_3 and 1 mL $HClO_4$, then fixed to 25 mL with 1 % HNO_3 solution. The resultant solution was filtered through a Φ13mm membrane for subsequent measurement. The contents of Cd were determined by an atomic absorption spectrophotometer (240FS AA; Agilent Technologies, USA).

To analysis the form of Cd, the larvae were extracted using the modified European Community Bureau of Reference (BCR) method according to Sutherland (Sutherland, 2010). Different forms of Cd were obtained in the following order: water-soluble (Aci), reducible (Red), oxidizable (Oxi), and residual (Res). The content of four forms of Cd was quantified using an atomic absorption spectrophotometer (240FS AA; Agilent Technologies, USA). The toxicity formula was as followed:

$$Toxicity(\%) = \frac{content(Aci) + content(Red)}{content(Aci) + content(Red) + content(Oxi) + content(Res)} \times 100\%$$

2.4. Detection of oxidative damage

The larvae were ground with beads on an automatic sample rapid grinder (Shanghai Jingxin Industrial Development Co., Ltd. Company, model: JXFSTPR-24). After centrifuging for 5 s on a mini centrifuge, 1 mL prechilled 0.9 % sterile normal saline (Shijiazhuang Four Medicine Co., Ltd., China) was added and mixed on a vortex. The homogenate was centrifuged at 3000 rpm for 10 min at 4 °C. The supernatants were collected and stored at −80 °C before subsequent tests.

Lipid peroxidation was monitored through the measurement of malondialdehyde (MDA) levels. Hydroxyl radical (–OH) and superoxide anion radical (O_2^-) were represented as oxygen radical capacity. The levels of 8-hydroxydeoxyguanosine (8-OHdG) were measured to evaluate oxidative DNA damage. All the tests were carried out with kits (A003-1–2, A018-1–1, A052-1–1, H165-1–1, Nanjing Jiancheng Bioengineering Research Institute, China).

2.5. Antioxidative activity and MT content assay

The total antioxidant power (T-AOC) and the activities of antioxidant enzymes, including superoxide dismutase (SOD), catalase (CAT), peroxidase (POD), and glutathione peroxidase (GSH-Px), as well as the content levels of non-enzymatic antioxidants such as glutathione (GSH) and vitamin C (VC) were measured. All the tests were carried out with kits (A015-1–2, A001-2–2, A007-1–1, A084-2–1, A005-1–2, A006-1–1, A009-1–1, Nanjing Jiancheng Bioengineering Research Institute, China).

The contents of metallothionein (MT) were detected by the kit (H132-1–2, Nanjing Jiancheng Bioengineering Research Institute, China).

2.6. Predictors of Cd content and toxicity

Two linear models "lm" function (y∼x) for Cd content and toxicity were constructed as Cd content ∼ VE pretreatment concentration+ 8-OHdG content + MT content + POD activity + MDA content + GSH-Px activity + VC content + T-AOC power; Cd toxicity ∼ VE pretreatment concentration+ 8-OHdG content + MT content + POD activity + MDA content + –OH content + T-AOC power. Using these models considering all predictors, we ran two models averaging procedure to select the set of predictors that best explained Cd content and toxicity, respectively. Then, we applied a multi-model inference procedure using the "MuMIn" R package. The AIC of each model was then transformed to ΔAIC, which is the difference between AIC of each model and the minimum AIC obtained. We retained all models with an AIC difference (ΔAIC) < 2, which we defined as best-fitting models.

Finally, we averaged predictor estimates selected across best-fitting models (those models selected within a ΔAIC < 2) using the conditional averaging approach in the function "model.avg" from the "MuMIn" R package. We fitted all models with "lm" function in the STATS package in R. The full results of the models averaging procedure, including R^2, AIC, predictor estimates, and P values of every model and the predictor importance based on sum of weights are available in table S1 and table S2.

2.7. Statistical analysis

Statistical analysis of the data was performed using one-way analysis of variance with SPSS 25.0 (IBM SPSS Statistics, USA). Data, obtained from four independent biological replicates, were expressed as mean ± standard error (mean ± S.E.). Radar charts were plotted by using the "fmsb" R packages and multivariate correlation analysis was plotted by "GGally" R packages.

3. Results

3.1. Effects of VE pretreatment on BSF relative body weight ratio under Cd exposure

Fig. 1 illustrated the effects of VE pretreatment on the relative body weight ratio of BSF larvae under Cd exposure. The relative body weight ratios of larvae with VE pretreatment were calculated using 0 mg/kg VE pretreatment as reference at all concentrations of Cd exposure. The relative body weight ratio of larvae with 0 mg/kg VE pretreatment under different concentrations of Cd exposure were calculated using 0 mg/kg Cd exposure as reference (Fig. S1). Relative body weight ratio showed a trend of significant rise followed by significant fall with Cd exposure concentration, 50 mg/kg Cd exposure significantly increased the relative body weight ratio of the larvae to 1.28, 300 and 700 mg/kg Cd exposure significantly decreased the Cd exposure of the larvae to 0.85 and 0.70, respectively. Without Cd exposure (Fig. 1A), 1, 10, and 100 mg/kg VE pretreatments all significantly increased relative body weight ratio to 1.13, 2.02, and 1.78. Under 50 mg/kg Cd exposure (Fig. 1B), 1 mg/kg VE pretreatment significantly decreased relative body weight ratio to 0.81. VE pretreatments of 10, 100 mg/kg significantly increased relative body weight ratio to 1.36 and 1.37. Under 300 mg/kg Cd exposure (Fig. 1C), 1 mg/kg VE pretreatment significantly decreased relative body weight ratio to 0.83. VE pretreatments of 10, 100 mg/kg significantly increased relative body weight ratio to 2.00 and 1.88. Under 700 mg/kg Cd exposure (Fig. 1D), 1 mg/kg VE pretreatment significantly decreased relative body weight ratio to 0.79. VE

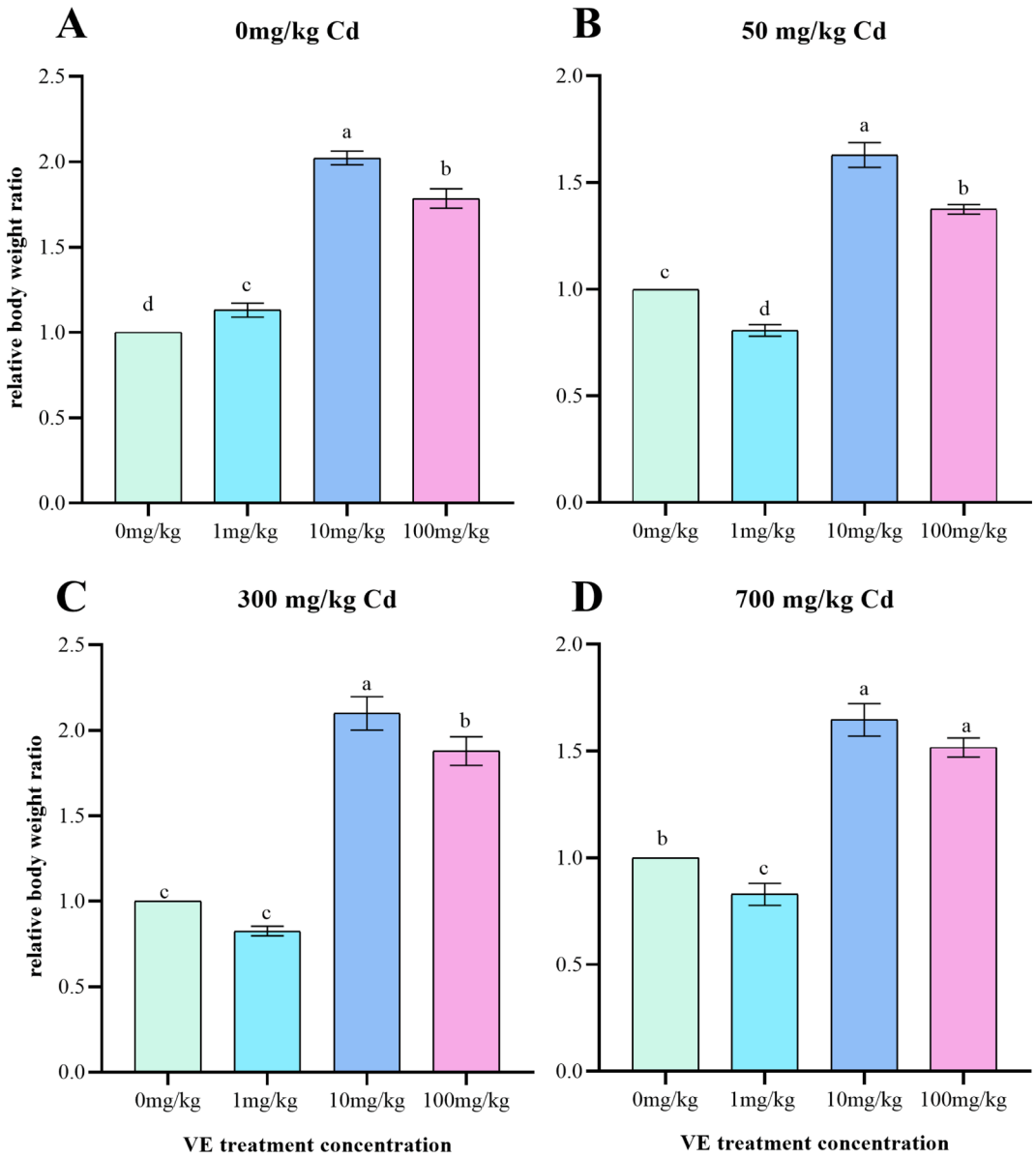

Fig. 1. Effects of VE pretreatment on relative body weight ratios under Cd exposure. A-D represented the relative body weight ratios under 0, 50, 300, and 700 mg/kg Cd exposure with different concentrations of VE pretreatment, using body weight of larvae at 0 mg/kg VE pretreatment as reference. Different letters a, b, c, d indicated inter-group variability, $p < 0.05$. VE, Vitamin E; Cd, cadmium.

pretreatments of 10, 100 mg/kg significantly increased relative body weight ratio to 1.72 and 1.52.

3.2. Effects of VE on Cd content and toxicity in BSF under Cd exposure

Fig. 2 displayed the effects of VE pretreatment on Cd accumulation and toxicity in BSF larvae across Cd exposures. The effects of 0 mg/kg VE pretreatment on Cd content and toxicity in larvae under different concentrations of Cd exposure were shown in Fig. S1 and S2. Without VE pretreatment, Cd content and toxicity of larvae increased significantly with the increases of Cd exposure concentration, and Cd toxicity reached a maximum value of 93.95 % at 300 mg/kg Cd exposure. What's more, Cd contents in larvae without VE pretreatment exceeded the treatment concentration in all Cd exposure concentrations. Without Cd exposure (Fig. 2A), Cd content was 8.83 mg/kg at 0 mg/kg VE pretreatment. 1, 10, and 100 mg/kg VE significantly decreased Cd contents to 1.79, 0.54, and 1.65 mg/kg, respectively. Under 50 mg/kg Cd exposure (Fig. 2B), Cd content and toxicity were 187.81 mg/kg and 81.07 % at 0 mg/kg VE pretreatment. 1, 10, and 100 mg/kg VE significantly decreased Cd contents to 141.11, 43.51, and 47.21 mg/kg. 10 mg/kg VE pretreatment significantly decreased Cd toxicity to 83.60 %. Under 300 mg/kg Cd exposure (Fig. 2C), Cd content and toxicity were 517.23 mg/kg and 92.14 % at 0 mg/kg VE pretreatment. 1, 10, and 100 mg/kg VE significantly decreased Cd contents to 389.43, 191.44, and 206.10 mg/kg. 10, and 100 mg/kg VE significantly decreased Cd toxicities to 91.28 % and 85.33 %. Under 700 mg/kg Cd exposure (Fig. 2D), Cd content and toxicity were 849.29 mg/kg and 90.44 % at 0 mg/kg VE pretreatment. 1, 10, and 100 mg/kg VE significantly decreased Cd contents to 707.77, 519.26, and 539.18 mg/kg, and 100 mg/kg VE pretreatment significantly decreased Cd toxicity to 84.43 % while 1 mg/kg VE pretreatment significantly increased Cd toxicity to 96.42 %.

3.3. Effects of VE pretreatment on MT contents under Cd exposure

Fig. 3 represented the effects of VE pretreatment on MT contents in BSF larvae across Cd exposures. Without Cd exposure (Fig. 3A), MT content was 55.77 ng/g at 0 mg/kg VE pretreatment, 1 mg/kg VE significantly increased MT content to 74.63 ng/g while 100 mg/kg VE significantly decreased MT content to 27.77 ng/g. Under 50 mg/kg Cd exposure (Fig. 3B), MT content was 66.07 ng/g at 0 mg/kg VE pretreatment, 10 and 100 mg/kg VE significantly decreased MT contents to 47.56 and 48.96 ng/g. Under 300 mg/kg Cd exposure (Fig. 3C), MT content was 56.81 ng/g at 0 mg/kg VE pretreatment, 100 mg/kg VE significantly increased MT content to 87.39 ng/g. Under 700 mg/kg Cd exposure (Fig. 3D), MT content was 46.93 ng/g at 0 mg/kg VE pretreatment, 1 and 10 mg/kg VE significantly increased MT contents to

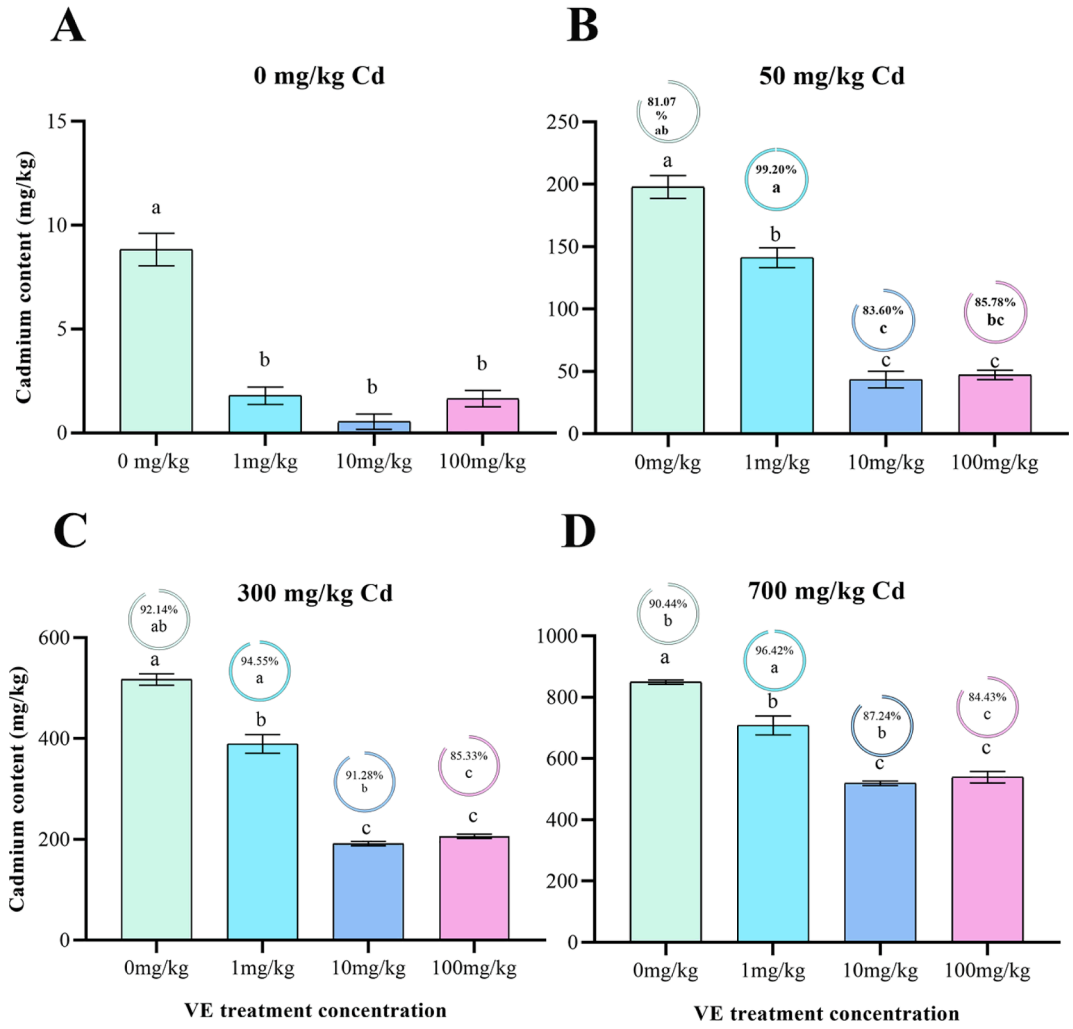

Fig. 2. Effects of VE pretreatment on Cd content and toxicity in larvae under Cd exposure. A-D represented the Cd content and toxicity under 0, 50, 300, and 700 mg/kg Cd exposure with different concentrations of VE pretreatment. Bar graphs indicated Cd content and pie charts indicated Cd toxicity. Because of non-reference value, Cd toxicity values were not presented under 0 mg/kg Cd exposure. Different letters a, b, c, d indicated inter-group variability, $p < 0.05$. VE, Vitamin E; Cd, cadmium.

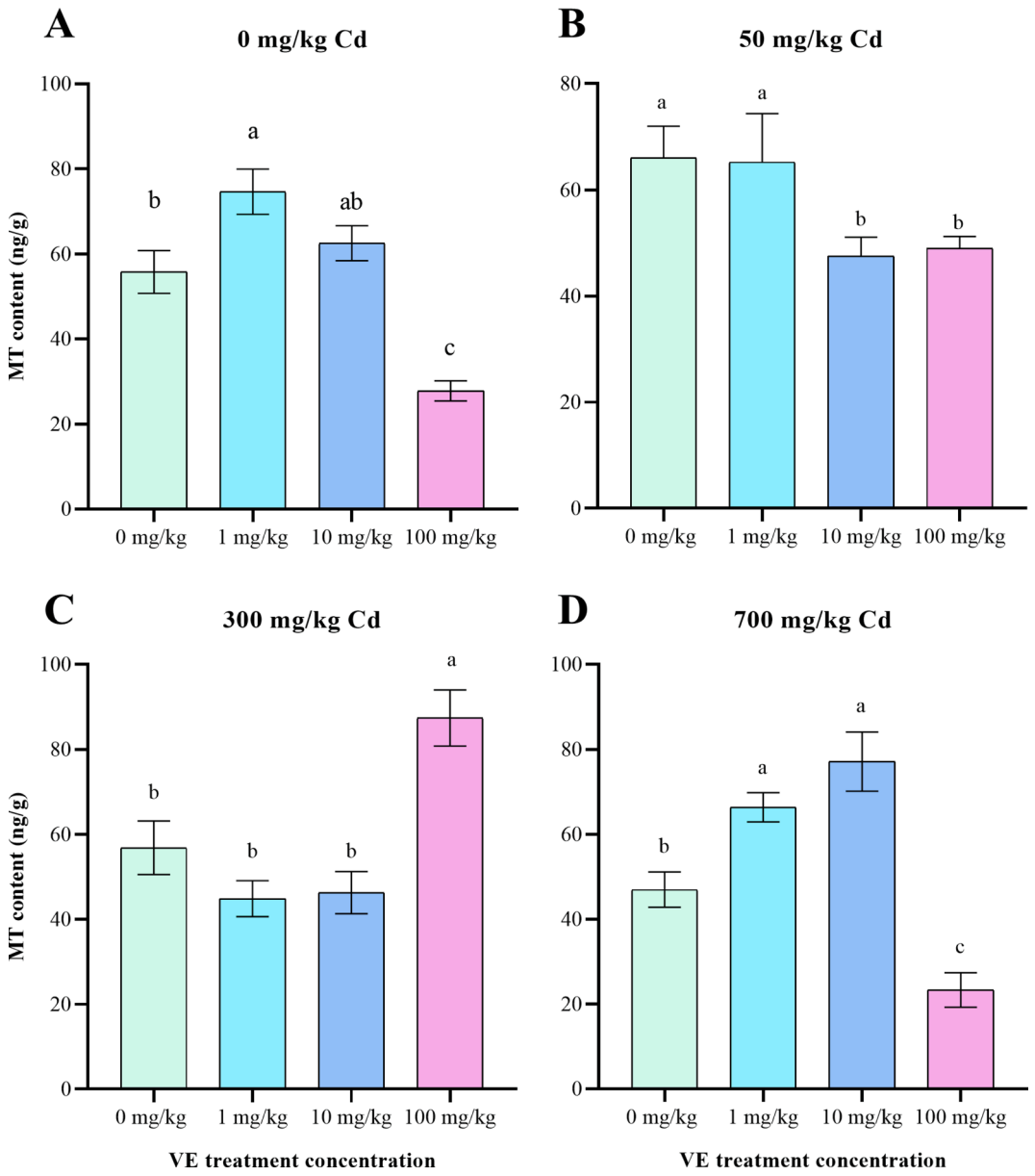

Fig. 3. Effects of VE pretreatment on MT content in larvae under Cd exposure. A-D represented the MT content under 0, 50, 300, and 700 mg/kg Cd exposure with different concentrations of VE pretreatment. Different letters a, b, c, d indicated inter-group variability, $p < 0.05$. VE, Vitamin E; Cd, cadmium; MT, metallothionein.

66.32 and 77.12 ng/g while 100 mg/kg VE pretreatment significantly decreased MT content to 23.30 ng/g in contrast.

3.4. Effects of VE pretreatment on oxidative damage in BSF under Cd exposure

Fig. 4 indicated the effects of VE pretreatment on four oxidative damage indexes under Cd exposure. Oxidative damage of larvae at 0 mg/kg VE pretreatment was used as reference. Radar charts were plotted by ratio approach due to the fact that the order of magnitude different between the values of indexes were so large. Without Cd exposure (Fig. 4A), 1 mg/kg VE pretreatment significantly increased the –OH, O_2^-, and 8-OHdG contents, with ratios of 2.12 ($P_{Cd=0,\ VE=1} = 0.006$), 2.97 ($P_{Cd=0,\ VE=1} = 0.047$), and 1.24 ($P_{Cd=0,\ VE=1} = 0.017$). 100 mg/kg VE pretreatment decreased O_2^- content with ratio of 0.73 ($P_{Cd=0,\ VE=100} = 0.038$). Under 50 mg/kg Cd exposure (Fig. 4B), 10 mg/kg VE pretreatment significantly reduced 8-OHdG content with ratio of 0.79 ($P_{Cd=50,\ VE=10} = 0.01$). Under 300 mg/kg Cd exposure (Fig. 4C), 1 mg/kg VE pretreatment reduced 8-OHdG content with ratio of 0.93 ($P_{Cd=300,\ VE=1} = 0.014$). 10 mg/kg VE pretreatment decreased O_2^-, –OH, and 8-OHdG content with ratios of 0.43 ($P_{Cd=300,\ VE=10} = 0.001$), 0.54 ($P_{Cd=300,\ VE=10} = 0.001$), and 0.91 ($P_{Cd=300,\ VE=10} = 0.004$). 100 mg/kg VE pretreatment significantly decreased –OH content with ratio of 0.45 ($P_{Cd=300,\ VE=100} = 0.001$), while it also increased MDA content and 8-OHdG content with ratios of 2.04 ($P_{Cd=300,\ VE=100} = 0.0041$) and 1.07 ($P_{Cd=300,\ VE=100} = 0.009$). Under 700 mg/kg Cd exposure (Fig. 4D), 10 mg/kg VE pretreatment significantly decreased –OH content with ratio of 0.63 ($P_{Cd=700,\ VE=10} = 0.0018$). 100 mg/kg VE pretreatment decreased O_2^- content with ratio of 0.50 ($P_{Cd=700,\ VE=100} = 0.005$).

3.5. Effect of VE pretreatment on antioxidant power in BSF under Cd exposure

The effect of VE pretreatment on antioxidant power of BSF under Cd exposure was showed in Fig. 5. Antioxidant power of larvae at 0 mg/kg VE pretreatment was used as reference. Radar charts were plotted by

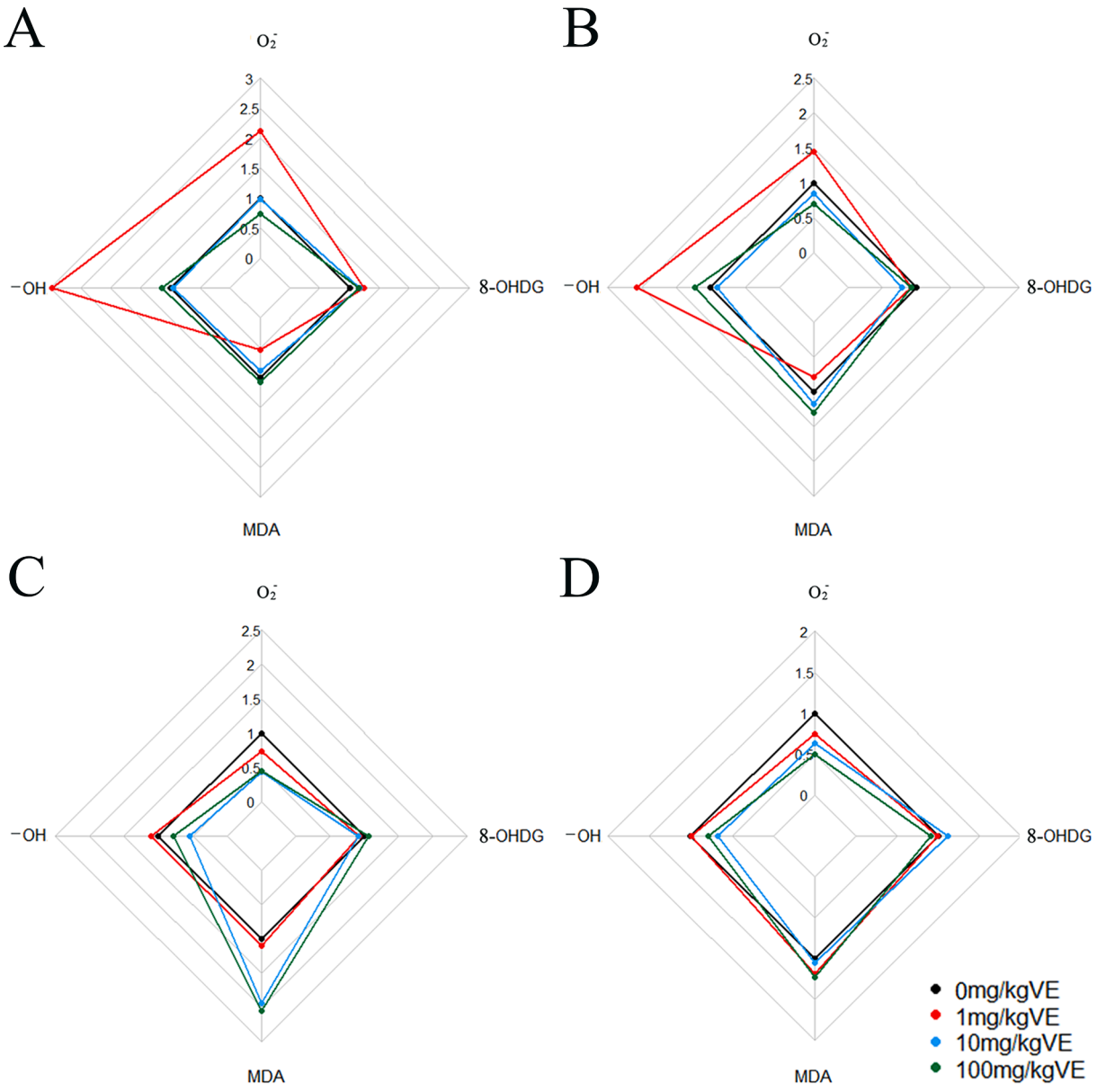

Fig. 4. Radar plots of the effects of VE pretreatment on oxidative damage in larvae under Cd exposure. A-D represented the effects of four oxidative damage index ratios of larvae pretreated with different concentrations of VE under 0, 50, 300, and 700 mg/kg Cd exposure, respectively. Oxidative damage of larvae at 0 mg/kg VE pretreatment was used as reference. MDA represented lipid peroxidation, 8-OHdG indicated DNA damage, O_2^- and –OH contents denoted the ability to inhibit oxygen radicals. Different letters a, b, c, d represented inter-group variability, $p < 0.05$. VE, Vitamin E; Cd, cadmium; MDA, malondialdehyde; 8-OHdG, 8-hydroxy-2 deoxyguanosine.

ratio approach due to the fact that the order of magnitude different between the values of indexed were so large. Without Cd exposure (Fig. 5A), 1 mg/kg VE pretreatment significantly reduced SOD, POD, CAT activities with ratios of 0.47 ($P_{Cd=0, VE=1} = 0.034$), 0.4719 ($P_{Cd=0, VE=1} = 0.0001$), and 0.44 ($P_{Cd=0, VE=1} = 0.018$), respectively. 10 mg/kg VE pretreatment reduced POD activity with ratio of 0.56 ($P_{Cd=0, VE=10} = 0.005$), while increasing GSH-Px activity with ratio of 2.49 ($P_{Cd=0, VE=10} = 0.002$). 100 mg/kg VE pretreatment reduced POD activity with ratio of 0.64 ($P_{Cd=0, VE=100} = 0.007$). Under 50 mg/kg Cd exposure (Fig. 5B), 1 mg/kg VE pretreatment significantly reduced POD activity with ratio of 0.23 ($P_{Cd=50, VE=1} = 0.001$). 10 mg/kg VE pretreatment significantly increased VC content with ratio of 1.53 ($P_{Cd=50, VE=10} = 0.003$) while decreased POD activity with ratio of 0.49 ($P_{Cd=50, VE=10} = 0.01$). 100 mg/kg VE pretreatment significantly increased VC content with ratio of 2.80 ($P_{Cd=50, VE=100} = 0.0001$). Under 300 mg/kg Cd exposure (Fig. 5C), 1 mg/kg VE pretreatment reduced POD activity with ratio of 0.55 ($P_{Cd=300, VE=1} = 0.0001$). 10 mg/kg VE pretreatment increased GSH, VC contents, SOD, CAT activities with ratios of 1.72 ($P_{Cd=300, VE=10} = 0.0001$), 1.51 ($P_{Cd=300, VE=10} = 0.0001$), 1.70 ($P_{Cd=300, VE=1} = 0.001$), 1.57 ($P_{Cd=300, VE=10} = 0.001$), respectively. 100 mg/kg VE pretreatment increased GSH, VC contents, SOD, POD, CAT activities with ratios of 2.30 ($P_{Cd=300, VE=100} = 0.0001$), 3.60 ($P_{Cd=300, VE=100} = 0.0001$), 1.52 ($P_{Cd=300, VE=100} = 0.004$), 1.18 ($P_{Cd=300, VE=100} = 0.032$), and 1.46 ($P_{Cd=300, VE=100} = 0.01$), respectively. Under 700 mg/kg Cd exposure (Fig. 5D), 1 mg/kg VE pretreatment significantly increased T-AOC capacity and GSH-Px activity with ratios of 3.34 ($P_{Cd=700, VE=1} = 0.025$) and 3.51 ($P_{Cd=700, VE=1} = 0.022$). 100 mg/kg VE pretreatment significantly increased GSH, VC contents, CAT activity with ratios of 1.51 ($P_{Cd=700, VE=100} = 0.036$), 2.17 ($P_{Cd=700, VE=100} = 0.0001$), and 1.50 ($P_{Cd=700, VE=100} = 0.032$), respectively.

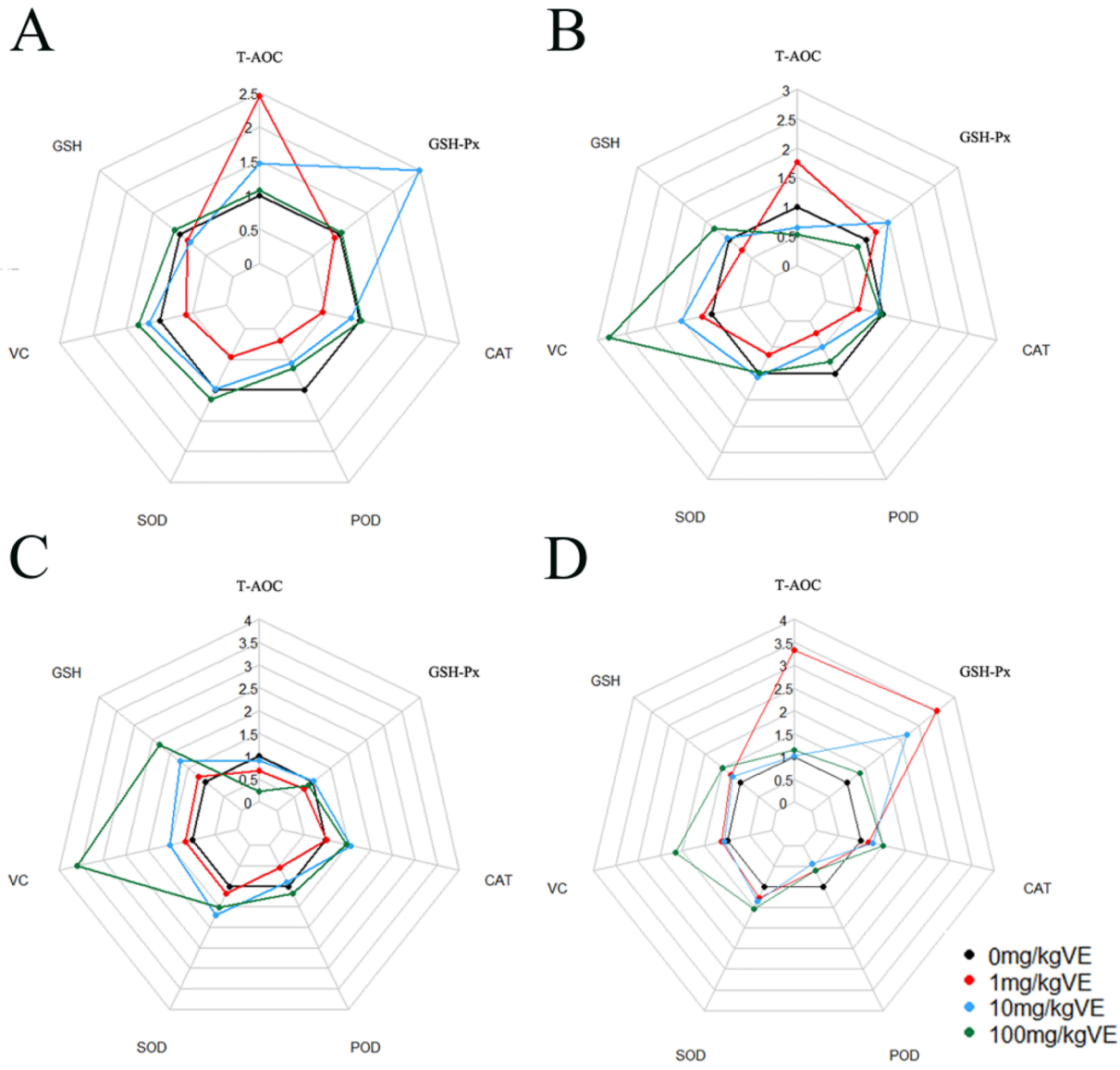

Fig. 5. Radar plots of the effects of VE pretreatment on antioxidant power in larvae under Cd exposure. A-D represented the effects of seven antioxidant power index ratios of larvae pretreated with different concentrations of VE under 0, 50, 300, and 700 mg/kg Cd exposure, respectively. Antioxidant power of larvae at 0 mg/kg VE pretreatment was used as reference. Different letters a, b, c, d represented inter-group variability, $p < 0.05$. VE, Vitamin E; Cd, cadmium; VC, Vitamin C; T-AOC, total antioxidant capacity; GSH, glutathione; CAT, catalase; POD, peroxidase; SOD, superoxide dismutase; GSH-Px, glutathione peroxidase.

3.6. Importance of predictors for Cd content and toxicity

The relative importance of predictors was averaged across the models (Table S1, S2) measured to compare their overall importance on Cd content and toxicity (Fig. 6). In best-fitting model of Cd content (Fig. 6A), a total of nine predictors were hypothesized based on multiple correlation analysis (Fig. S4), including VE pretreatment concentration, MT content, oxidative damage (8-OHdG content and MDA content), and antioxidant power (T-AOC power, VC content, POD, CAT, and GSH-Px activities). In descending order of importance, they were 8-OHdG content (weight sum = 1), POD activity (weight sum = 1), MT content (weight sum = 0.95), MDA content (weight sum = 0.93), GSH-Px activity (weight sum = 0.57), VC content (weight sum = 0.48), CAT activity (weight sum = 0.36), VE pretreat concentration (weight sum = 0.34) and T-AOC power (weight sum = 0.24). In best-fitting model of Cd toxicity (Fig. 6B), a total of seven predictors were hypothesized based on multiple correlation analysis (Fig. S5), including VE pretreatment concentration, MT content, oxidative damage (8-OHdG content and –OH content), and antioxidant power (T-AOC power, POD, and SOD activities). In descending order of importance, they were 8-OHdG content (weight sum = 1), –OH content (weight sum = 1), SOD activity (weight sum = 1), VE pretreatment concentration (weight sum = 1), T-AOC power (weight sum = 0.63), POD activity (weight sum = 0.58), and MT content (weight sum = 0.38).

4. Discussions

4.1. VE pretreatment promoted larval growth under Cd exposure

VE pretreatment enhanced larval relative body weight ratio under Cd exposure. In this study, 10 and 100 mg/kg VE pretreatment significantly increased larval relative body weight ratio under Cd exposure. Same results could be found in animal models (Li et al., 2023b; Tao et al., 2023). A case in point is that VE improved the growth rate of Nile tilapia under Cd exposure as a feed additive (Ayyat et al., 2017). It was hypothesized that there were three reasons for this result.

Firstly, VE mitigated oxidative damage due to its antioxidant properties. It is proved that the levels of oxidative stress affects the body

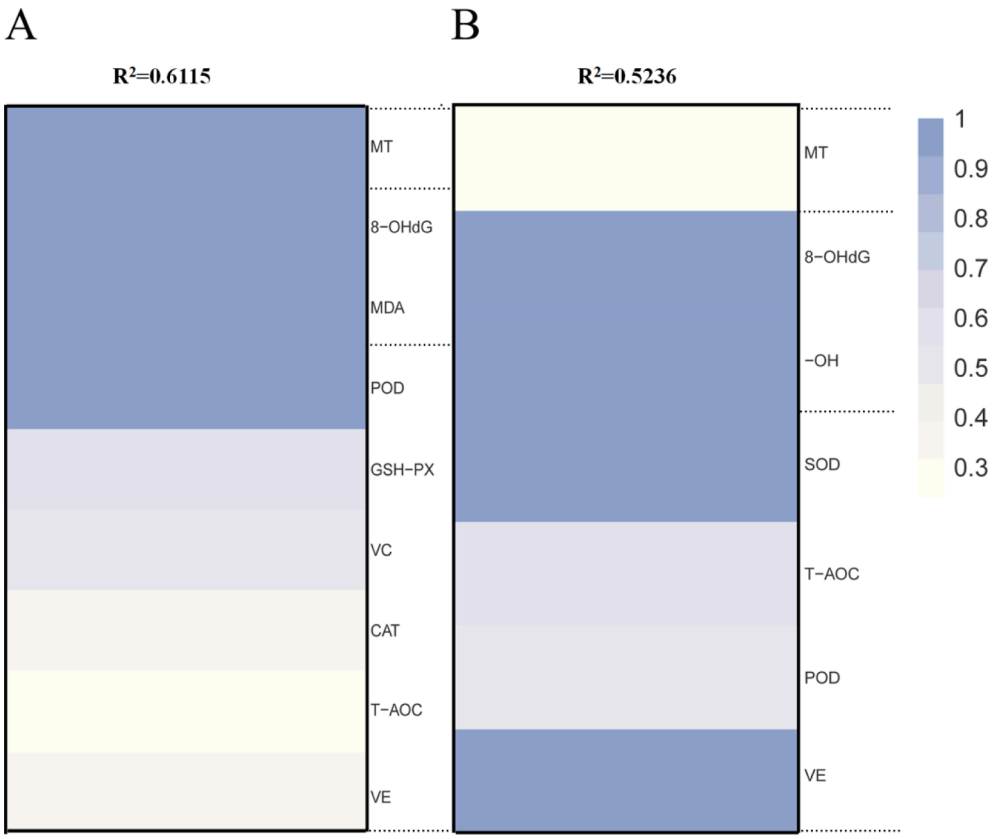

Fig. 6. Relative importance of predictors associated with Cd content and toxicity in the best-fitting models. Importance is quantified as the sum of the weights of all models that included the predictor of interest, considering the number of models in which each predictor appears. A-B represented the weighted sum of the predictors for Cd content and Cd toxicity, respectively. 8-OHdG: DNA damage; VE: Vitamin E; MT, metallothionein; MDA, malondialdehyde; VC, Vitamin C; T-AOC, total antioxidant capacity; POD, peroxidase; GSH-Px, glutathione peroxidase; CAT, catalase; SOD, superoxide dismutase. The numbers on right represented the weighted sum of predictors, with larger numbers and darker colors indicating more important predictors.

weight of organisms (Jakubiak et al., 2021), e.g. *Escherichia coli* infection in birds reduces weight by increasing oxidative damage (da Rosa et al., 2020). Not only did VE pretreatment reduce DNA damage but also oxygen radical capacity in this study, and larval weight gain was promoted by the reduced level of oxidative damage. The phenolic hydroxyl groups of VE may directly scavenge free radicals by hydrogen donation (Lo Fiego et al., 2004). Likewise, extracellular polysaccharides from *Aspergillus niger* reduces hydroxyl radicals and superoxide anion, conferring protection against Cd (Li et al., 2021). Similar antioxidant effects have been reported in zebrafish with VE attenuating Cd-induced elevations in superoxide and hydroxyl radicals (Dongwu et al., 2020). Secondly, VE attenuated Cd immune system damage. Stabilization of the immune system is precisely linked to biological weight (Cottam et al., 2022). Immunomodulatory effects of VE have been observed in animal models under disease conditions (Lee and Han, 2018). It is proved that VE could maintain normal immune function by modulating intestinal microbiota (Li et al., 2023a). Meanwhile, VE inhibits Cd-induced apoptosis in mammalian kidney and liver cells via Nrf2 pathway activation (Fang et al., 2021a; Fang et al., 2021b). Thirdly, VE sustained nutritional homeostasis by governing lipid and energy metabolism under Cd exposure. Substance metabolism affects the growth of organisms (Liu et al., 2023). It is illustrated that VE's key role in mitigating the deleterious effects of lipid metabolic dysregulation induced by external stressors (Liang et al., 2021).

In addition, 100 mg/kg VE pretreatment was less effective on larval relative body weight ratio than 10 mg/kg VE pretreatment at 50 and 300 mg/kg Cd exposure. The reason for the above results was mainly due to the fact that 100 mg/kg VE treatment maybe cause accumulation of pro-oxidant, which could reduce or eliminate the positive effects of VE (Azzi and Stocker, 2000; Poljšak et al., 2012). Similar results can be found in the application of VE to fish culture, such as pandani (Mete and Tulin, 2019).

4.2. *VE pretreatment altered MT content to reduce Cd content under Cd exposure*

VE pretreatment significantly decreased Cd bioaccumulation under Cd exposure. In this study, 10, 100 mg/kg VE pretreatment significantly reduced Cd contents under Cd exposure, which is the similar result to the reduction of Cd content with VE in a rat model (Chen et al., 2022). MT content was highly important in best-fitting model of Cd content (Fig. 6A). MT is mainly responsible for the transportation of Cd ions in larvae (Talukder et al., 2021; Nordberg and Nordberg, 2022; Ghouri et al., 2023).

Under 0 and 50 mg/kg Cd exposure, VE pretreatment resulted in a decrease in both Cd and MT contents. There is a positive relationship between MT content and Cd content (Cenov et al., 2018). The decrease of MT content led to a decrease in the ability of larvae to enrich Cd followed by a decrease in Cd content. MT synthesis is affected by oxidative stress (Stangl et al., 2000), which was in agreement with the result that O_2^- content was significantly correlated with MT content (Fig. S4). In this study, VE pretreatment reduced MT content by mitigating oxidative damage. Conversely, the trends of Cd content and MT content with VE pretreatment were opposite under 300 and 700 mg/kg Cd exposure. The combined effects of VE and MT helped larvae resist the high Cd exposure. In *Cideopharyngodon idellus*, the combination of VE and MT significantly reduces the Cd content and toxicity (Duan et al., 2018). Besides, the MT content did not exceed 80 ng/g in all the

treatment groups which was mainly due to the fact that the MT reaches the chelated state at 50 mg/kg of Cd in the BSF (Gao et al., 2017). MT may not be the main mode of detoxification in larvae under high Cd exposure in consequence (Toušová et al., 2016). Antioxidant power played an important role on Cd content in best-fitting models. In summary, VE pretreatment might also infect Cd bioaccumulation through other ways, e.g., metal-rich granules (Wallace et al., 2003) and high molecular proteins (Long et al., 2011). The reduction of Cd content is the key method of curing Cd poisoning (Liu et al., 2022).

4.3. VE pretreatment reduced Cd toxicity through antioxidant and detoxification pathways

Not only did consider the bioaccumulation of Cd to organisms, but also its toxicity. The biotoxicity of Cd is closely linked to its morphology (Yang et al., 2018). VE pretreatment reduced Cd toxicity under Cd exposure. In this study, 10, 100 mg/kg VE pretreatment significantly reduced Cd toxicity under Cd exposure. The underlying mechanisms likely involved antioxidant and detoxification pathways of VE modulation, which was found in best-fitting model of Cd toxicity such as 8-OHdG content and T-AOC power. The similar mechanisms could be found in the silicon and selenium elements reduction of Cd toxicity in plants (Naeem et al., 2018; Zhang et al., 2020; El-Saadony et al., 2021).

VE-induced elevations in VC and GSH alleviates Cd toxicity in Cd-stressed mice (Anna et al., 2022; Averill-Bates, 2023; Paunović et al., 2017). In this study, not only did VE pretreatment increase non-enzymatic antioxidant substances but also antioxidant enzymes activities under Cd exposure in best-fitting models. Similar enhancement of SOD, CAT and GSH-Px activities by VE are observed in other animals exposed to Cd toxicity (Mashkoor et al., 2023; Mondal et al., 2023). Enhancing antioxidant enzyme activities (SOD, CAT) alleviates Cd toxicity in *Sedum alfredii* and *Glycine* max by mitigating oxidative damage (Zhou et al., 2022; Hu et al., 2023). Additionally, VE may reduce Cd toxicity by regulating amino acids. For instance, the amino acid threonine increases the abundances of *E.coli* to reduce Cd toxicity (Li et al., 2023c).

4.4. Optimum concentration exists for VE pretreatment

There was an optimum concentrations of VE pretreatment under different Cd exposure. In this study, 10 mg/kg VE pretreatment assisted larvae to resist low Cd (50 mg/kg) exposure most effectively, and 100 mg/kg VE pretreatment was most effective under middle (300 mg/kg) and high (700 mg/kg) Cd exposure. The effects of Cd on organisms are dose-dependent (Zhan et al., 2021). The higher the concentration, the more serious the damage is (Liang et al., 2019). Therefore, high concentration of VE pretreatment is more effective under high Cd exposure. Similar results could be found in biochar (Kováčik et al., 2022), selenium (Hussain et al., 2020; Wang et al., 2023), and other substances (Hasan et al., 2019; Wang et al., 2021; Xu et al., 2023) that assist organisms in resisting Cd exposure. However, 1 mg/kg VE pretreatment had the opposite effects on body weight, Cd toxicity, and oxidative stress under Cd exposure, which was detrimental to the larval health. It was hypothesized that the low concentration of VE pretreatment could not effectively counteract the damage caused by Cd exposure, while it worked together to cause negative effects. There is a range of effective concentrations for VE treatment (Azzi et al., 2016), e.g., high VE intake slows down cellular senescence, whereas low VE intake accelerates cellular senescence (Corina et al., 2018).

5. Conclusion

In summary, 10, 100 mg/kg VE pretreatment promoted larval weight gain by reducing oxidative damage under Cd exposure, and mitigated Cd bioaccumulation through modulating MT contents. At the same time, 10, 100 mg/kg VE pretreatment enhanced antioxidant activity power to decrease Cd toxicity. The optimal concentration of VE pretreatment for alleviating Cd exposure varied under different Cd exposure conditions. Furthermore, we summarized the importance of VE pretreatment-affected indexes of MT content, oxidative damage, and antioxidant power on Cd content and toxicity. Our findings suggested that VE pretreatment with appropriate concentrations represented a promising avenue for alleviating Cd damage in BSF.

CRediT authorship contribution statement

Zhihui Shi: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation. **Yujia Wan:** Writing – review & editing, Validation, Methodology. **Miao Peng:** Writing – review & editing, Visualization, Methodology, Data curation. **Jie Zhang:** Validation, Investigation, Formal analysis. **Zhenghui Gao:** Investigation, Formal analysis. **Xiaoping Wang:** Investigation, Formal analysis. **Fen Zhu:** Writing – review & editing, Visualization, Supervision, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2024.108547.

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