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Invited Review Article

Dietary amelioration of lead toxicity in fish- A review

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Abstract

Due to anthropogenic activities, lead (Pb) contamination in aquatic environment has become rampant, and fish are especially vulnerable to bioaccumulation and bio-magnification. As a result, Pb, a serious pollutant of the aquatic environment, continually endangers both farmed fish and fish eaters. Pb, an industrial pollutant and immunotoxin, is likely to harm both human and animal health and result in a variety of physiological, biochemical, and neurological dysfunctions. Lead exposure even to low levels has been linked to long-lasting immunological changes, oxidative stress, nephro-toxicity, hepato-toxicity, gastric enzyme dysfunctions, growth impairments, lower fertility, a delay in sexual maturity, irregular estrus, and a reduction in the number of corpora lutea in both human and test animals, and many more. For fish with persistent Pb toxicity, there is no such therapy strategy available. Amelioration modes and methods are thus reviewed for better understanding of the subject and future studies.

Key words: Amelioration, Fish, Heavy metals, Lead, Pb toxicity

Highlights

- Lead (Pb) is a potent toxicant for fish and its consumers.
- No treatment as such thus requires amelioration.
- Plant based pro & pre-biotics and algal agents are more explored.
- Others agents includes chelators, antioxidants, vitamin-minerals etc.
- Dietary amelioration of Pb toxicity proved to be effective.

INTRODUCTION

Aquaculture is a very promising industry and contributes immensely to the growth of the economy in our nation. Aquaculture has experienced an excellent annual average growth of more than 10%, contributing to the sector's overall robust growth of roughly 8% (DOF, 2020). The total inland fish production in 2019-20 in West Bengal was 16.19 lakh tons, while for the country, it was 104.37 lakh tons. Environmental pollutants including metals, pesticides, and other chemicals pose serious threat to the aquatic creatures, including fish. Fish are widely used to evaluate the health of aquatic ecosystems because toxins build up in the food chain and have detrimental effect and are responsible for death of animal in the aquatic ecosystems. (Farkas *et al.*, 2002). Heavy metal pollution of water has become one of the most significant threats in recent years due to the discharge of agricultural, industrial, and urban wastes produced by diverse human activities into water resources (Giri *et al.*, 2021). Many researchers have focused on the negative impacts of various heavy metal toxicants on aquatic life, especially fish, because fish cannot resist these pollutants' negative effects. In addition to economic loss to aquaculture, heavy metal contamination in aquaculture poses great risks to human health because it can accumulate and enter the food chain of human. These heavy metals are dangerous as they are not degraded,

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and they have the ability to bioaccumulation. Lead (Pb) is one of the most harmful heavy metal contaminants with fatal consequences for both people and animals. It is considered as a potent occupational toxin and poses worldwide threat to the environment. Due to Pb's strong antagonistic effects on calcium, exposure to Pb in fish can interfere with salt and chloride metabolism (Hashish *et al.*, 2015). Fish exposed acutely to waterborne Pb also experience haemoglobin alteration, black tail illness, and spinal abnormalities (Sherif, 2020). Additionally, fish intestines can collect higher levels of Pb, suggesting a location of dietary Pb uptake. Lead has been identified as one of the most widespread heavy metals with unknown biological functions and has been recognized as human carcinogen by the International Agency for Research on Cancer (IARC). In aquatic environments, Pb can easily enter the bloodstream of fish, build up in their organs, and ultimately infect people through consumption. Moreover, the presence of more heavy metals in the food chain has led to numerous toxicological issues, which have a negative economic impact on aquaculture and constitute a risk to food safety. Therefore, the need for cost-effective and environmentally benign methods of reducing heavy metal (Pb) pollution in aquaculture is growing. The topic of lead poisoning and its relief has been extensively studied and frequently published, yet full control and prevention of lead exposure still seem to be a long way off. The objective of this study is thus to explore and summarize extant research works related to amelioration modes and methods of lead toxicity through dietary supplementation in fish.

Lead toxicity in aquaculture

Lead is a non-biodegradable intrinsic persistent contaminant with accumulating behaviour and occurs naturally in earth's crust. It can enter into the water bodies through geologic weathering and volcanic action or by various anthropogenic activities such as burning of fossil fuels, automobile exhausts, metal coating and paints, effluents from storage battery industries, agricultural runoff including fertilizers, pesticides and from additives in pigments and gasoline (Said *et al.*, 2017). Lead's toxicological effects are widely understood due to its strength as an occupational hazard. The Environmental Protection Agency has designated Pb as one of the 129 priority pollutants (El-Fahla *et al.*, 2022a). Many steps have been taken to reduce the Pb industrial effluents and agricultural runoff into water bodies. Despite this, various number of pollution incidents have been reported in aquatic ecosystems such as ponds, lakes, rivers, and seas throughout the world in recent times, indicating that the aquatic environments are seriously threatened by this toxic metal. Bioaccumulation of lead in finfish and shellfish occurs due to discharges from different sources mentioned above. The heavy metal toxicants like Pb, after entering into the aquatic environment, accumulate in the kidneys, liver, spleen, gonad, brain, gills and muscles of aquatic organisms. The amount of accumulation depends on ecological, physical, chemical and biological conditions and the kind of element as well as physiological condition of that organisms. Pb can enter into the fish body by feed intake through gastrointestinal tract and from through gills. Moreover, after exposure liver bind Pb to steroids in bile, then bile metal complexes either reabsorbed by intestinal lining or excrete through feces. Hence, Pb enters into fish body via circulatory system through liver and gills.

Due to continuous waterborne Pb exposure to the cultivable fish species; the reproductive, neurological, immunological, hepatic, and renal toxicities occur including genotoxicity which enhance the mortality of the culture population leading to the economic loss of fish farmers. Moreover, Pb can easily be accumulated and magnified into the food chain causing a great concern for human health and posing a threat to food safety (Zhai *et al.*, 2017). Several studies demonstrated that exposure to lead is a major health problem impacting mostly on human nervous system. Therefore, researchers now-a-days pay more attention to lead toxicity. Chronic Pb exposure in fish causes ion regulatory disruption having disturbance on homeostasis and induce physiological stress which reduce food consumption and assimilation. A detail account of bioaccumulation, oxidative stress, neurotoxicity, immune response of lead exposure in fish is reviewed (Lee *et al.*, 2019).

Amelioration of lead toxicity

Lead (Pb) contamination in the environment has increased over the years due to anthropogenic activities and fishes are most susceptible for bioaccumulation and bio-magnification. Pb, as a potent pollutant of the aquatic environment, is thus constantly endangering cultured fish as well as fish consumers. Being an immunotoxicant and an industrial contaminant, Pb may have a negative impact on both human and animal health, causing a wide spectrum of physiological, biochemical, and neurological dysfunction. In both humans and test animals, early exposure to low amounts of lead was found to cause long-lasting cognitive and neurobehavioural deficits, persistent immunological alterations, decreased fertility, a delay in sexual maturity, irregular estrus, and a decrease in the number of corpora lutea. No such treatment protocol is available for chronic Pb poisoning in fish. Various ameliorating agents were thus tried to reduce Pb accumulation in different fish species. A brief account of ameliorating studies is presented in Table 1 for better understanding.

Table 1. Summary of ameliorating agents against lead exposure in fishes

Ameliorating agents	Fishs pecies	Lead form and dose	Effects	Reference
Spirulina algae (*Arthrospira platensis;* 5 and 10 g/kg BW; 12 wks)	Nile tilapia *(Oreochromis niloticus)*	Lead nitrate (10% of the LC50, 143.3 mg/L)	-RBC, PCV, MCV, MCH, and MCHC values improved -Liver enzymes AST, ALT, MT increased by lead exposure were stabilized-Stabilized Increasing GPx and CAT level -Reduced cumulative mortality rate -Improved immunity	(Sherif *et al.*, 2020)
Spirulina (*Spirulina platensis*; 0.25% and 0.5%; 4 wks)	Catfish*(Clarius gariepinus)*	Lead nitrate (1 mg/L)	-Serum electrolyte imbalance corrected -Improved LDH, AChE, SOD, CAT, GST, TAC level -MDA level reduced - Best result in 4th week	(Sayed *et al.*, 2017)
Spirulina (*Spirulina platensis*; 0.25%	Catfish*(Clarius gariepinus)*	Lead nitrate (1 mg/L)	-Suppress cytotoxicity and genotoxicity -Repair of damaged DNA	(Hamed *et al.*, 2019)

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Ameliorating agents	Fishs pecies	Lead form and dose	Effects	Reference
and 0.5%; 4 wks)			-Inhibit the poikilocytosis of erythrocytes	
Spirulina (*Spirulina* sp.; 500 mg/fish)	*Labeo rohita*	Lead acetate (0.017 mg/L)	-Liver alkaline phosphatase and acid phosphatase improved	(Vetrivel *et al.*, 2014)
Indian lotus leaves, (*Nelumbo nucifera*) (0.2-0.4%; 45 days)	Nile tilapia *(Oreochromis niloticus)*	Lead acetate (1/20 of the 96 h of the LC50), 9.12 mg/L	-Serum MDA, CAT, SOD, and GPx activities reduced -Hepatic metallothionein reduced -Serum alanine, aspartate, creatinine, and urea declined	(Abdel Rahman *et al.*, 2019)
Coriander (*Coriandrum sativum*) seeds powder (20, 30 mg/kg) and extracts (20 mg/kg) diet; 45 days	Nile tilapia *(Oreochromis niloticus)*	Lead acetate20.2 mg/L	-Higher serum lysozyme activity in coriander extract supplemented group -Increased nitric oxide level supplemented groups(CE20>CP30>CP20) -Serum bactericidal activity increased by both coriander extract and powder -IL-1β mRNA level effectively controlled	(Ahmed *et al.*, 2020)
Curcumin(15 g/kg; 8 weeks)	Common carp (*Cyprinus carpio*)	Waterborne lead (1 mg/L)	-PWG, FI and SGR increased, FCR reduced -Reduced Pb accumulation in gill, spleen, liver, intestine -RBC, Hct, Hb, serum protein, and albumin levels in blood restored -Increased AST, ALT, LDH, MDA by Pb exposure, restored -Decreased ALP, SOD, GPx, GST, G-Rd by Pb exposure, recovered -Elevated level of TNF-α, IL-1β (liver tissue), NFκBp65, IκB-α (liver), HSP70 (liver+kidney) -Suppressed level of IL-10	(Giri *et al.*, 2021)

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Ameliorating agents	Fishs pecies	Lead form and dose	Effects	Reference
			(liver+ kidney), Nrf2 (liver + kidney), CYP450 1A (liver+ kidney) restored by dietary CUR	
Powdered flower of*M. oleifera* (15% of diet; 30 days)	Nile tilapia *(Oreochromis niloticus)*	Lead nitrate(4.02 mg/L, 10% of 96 hr-LC50)	-BWG, SGR, PER higher and lower FCR-Reversal of histopathological changes in liver -Recovery in hematological values -Reduced level of ALT, AST, cortisol and glucose -Regulated the expression of three antioxidant genes such as Cu- Zn-SOD, CAT, and GPx1 in lead exposure near to normal level	(Kiran Kumar *et al.*, 2021)
Garlic (*Allium sativum*) (2%) and Fu-ling (*Poria cocos*) (1%)	Grass carp (*Ctenopharyngodon idella*)	Lead nitrate (3.5 mg/L; 8 weeks)	-Growth performance improved -Muscle level of Pb decreased-Stabilised the antioxidant enzymes like SOD and CAT as well as GSH -Gene expression of metal-binding proteins (TF and MT-2) upregulated -Stabilised expression of HSP30 and HSP60 as well as TNF-α and IL 1β	(Liu *et al.*, 2021)
Cinnamon (*Cinnamomum zeylanicum*) powder (10 g/ kg diet; 60 days	Nile tilapia fingerlings *(Oreochromis niloticus)*	Lead nitrate (7.94 mg Pb/ L)	-Improved feed intake, body weight, specific growth rate -Hematological parameters like WBC, RBC, Hb, hematocrit value increased -MCV and MCH hemoglobin decreased	(Hamed *et al.*, 2022)

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Ameliorating agents	Fishs pecies	Lead form and dose	Effects	Reference
			-Blood cortisol, glucose, total cholesterol level, total lipid, total protein, albumin, globulin stabilized-SOD, CAT, TAC, LYZ, RBA and total Ig level improved -Decreased MDA and DNA fragmentation %	
Lactobacillus plantarum CCFM8610(10^8 CFU/g)	Nile tilapia *(Oreochromis niloticus)*	Pb (1 mg/L; 4 wks)	-Pb accumulation in kidney, liver, gonad, brain, gills and muscle reduced - Increased MDA and decreased GSH levels and decreased GPx and T-AOC activity restored -Nuclear abnormalities in peripheral blood erythrocytes due to PB exposure were significantly lower -Inhibited activity of blood ALAD and decreased level of enzymes related to innate immunity like lysozyme and MPO was reversed on probiotic supplementation	(Zhai *et al.*, 2017)
Lactobacillus reuteri P16 (10^8 CFU/g)	Freshwater fish*(Cyprinus carpio)*	Pb (1 mg/L; 6wks)	-Strongly reduce Pb tissue accumulation -Alleviated oxidative	(Giri *et al.*, 2018)

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Ameliorating agents	Fishs pecies	Lead form and dose	Effects	Reference
			stress -Gut microbial population and intestinal enzymatic activities re-established-Reversed the inhibition of expression of TNF-α, IL-1β and HSP70	
Beta-MOS®(0.3%; for 60 days)	Nile tilapia (*Oreochromis niloticus*)	Pb acetate (10 mg/L)	-Increased body weight-Higher RBC & Hb values-Serum creatinine reduced-Reversed renal histopathological changes	(El-Fahla, *et al.*, 2022b)
Beta-MOS®(0.3%; for 60 days)	Nile tilapia (*Oreochromis niloticus*)	Pb acetate (10 mg/L)	-Improved body weight and GSI -Improved level of estradiol, testosterone, gonadal antioxidant enzymes-Reduced the elevated cortisol, glucose, and gonadal MDA	(El-Fahla *et al.*, 2022a)
Selenium (sodium selenite, 4 mg/kg dry diet) and α-tocopherol (200 mg/kg dry diet)	Nile tilapia *(Oreochromis niloticus)*	Pb acetate (73.40 mg/L; 10 wks)	-Improved ALT, AST and serum protein level -Improved serum urea and creatinine level -Improved serum electrolytes (Ca, P, Mg) level to normal-Liver and kidney MDA decreased, SOD & GSH increased	(Elgaml *et al.*, 2015)
Selenium (sodium selenite, 4 mg/kg dry diet) and α-tocopherol (200 mg/kg dry diet)	Nile tilapia *(Oreochromis niloticus)*	Pb acetate (73.40 mg/L; 10 wks)	- Serum calcium, magnesium and phosphorus level were increased - Serum creatinine was decreased -Kidney antioxidants, SOD, GSH level were increased by both mixed or separate application -Reduction in MDA level	(Hashish *et al.*, 2015)

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Ameliorating agents	Fishs pecies	Lead form and dose	Effects	Reference
Organic selenium (2.50 mg/kg)	Common carp (*Cyprinus carpio*)	Lead nitrate (1.5 mg/L; 14 days)	-GSH-Px, GST activities, and levels of GSH with MDA in liver and brain tissues stabilized	(Özkan-Yilmaz *et al.*, 2014)
Thiamin hydrochloride (4 mg/kg)	Fresh water fish (*Tilapia zilli*)	Pb acetate (8.3 mg/L; 32 days)	-Pb accumulation in kidney, liver, gonad, brain, gills and muscle reduced -Hb and RBC level restored -Survival rate higher	(Ghazaly, 1991)
Quercetin (800 & 1600 mg quercetin/ kg added with diet; 28 days)	Juvenile tilapia (*Oreochromis niloticus*)	Dietary Lead (800 mg/kg)	-Mitigated growth retardation and restored FCR -Reduced SOD & CAT activity -Reduced GPx level	(Zhai *et al.*, 2014)
$CeCl_3$ (1.5 mg/kg, i/p; 28 days)	Silver crucian carp (*Carassius auratus gibelio*)	$PbCl_2$ (10, 20, or 30 mg/kg wet, i/p; 14 days)	-Increased wet weight & HSI -SOD, CAT, APx values improved -Ascorbate to dehydroascorbate & glutathione to oxidized glutathione ratio, stabilised	(Ling & Hong, 2010)
Zeolite (50 mg/ L/day, 35 days; 20 mg/L/day, 120 days)	Cat fish (*Heteropneustes fossilis*)	$Pb(NO_3)_2$ (60 mg/L/day, 35 days; 20 mg/ L/day, 120 days)	-Body weight, protein, glycogen and RNA content improved -Cholesterol level decreased	(Jain, 1999)
Clinoptilolite (50 mg/L; 35 days)	Common carp (*Cyprinus carpio*)	Lead nitrate (60 mg/L)	-Reduced total ammonia nitrogen, cholesterol & LDH level - Soluble protein, glycogen and RNA content improved	(Tepe, 2004)
Natural zeolite, (Clinoptilolite; 1,3,5%; 45 days)	Nile tilapia (*Oreochromis niloticus)*	Lead acetate (7.34 mg/L; 21 days)	-Serum glucose, ALT, AST, cholesterol restored -Decreased CAT, SOD & TAC	(Abbas *et al.*, 2021)

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Ameliorating agents	Fishs pecies	Lead form and dose	Effects	Reference
			-Zero lead residue in muscle -Increased protein & albumin level	
Montmorillonite (0.5% with basal diet; 60 days)	Nile tilapia *(Oreochromis niloticus)*	Lead nitrate (100 mg/kg)	-Reduced accumulation of Pb in kidney and blood -DNA damage decreased in peripheral blood cells	(Dai *et al.*, 2010)
Bentonite, Mannan Oligosaccharide (MOS), organic selenium (OS) or vitamin C (40 g, 4 g, 0.3 mg, 50 mg /kg diet, respectively; 16 weeks)	Nile tilapia *(Oreochromis niloticus)*	Pb acetate (50 ppm)	-Enhancement in the growth performance, highest in MOS> OS>VitC -Improved FCR -Total protein & albumin improved, best in bentonite supplementation -Creatinine, urea, AST, ALT level restored -Decrease in Hb and RBCs and increase in WBCs due to Pb toxicity, controlled by supplementation -Lead residue in fish body eliminated	(Ayyat *et al.*, 2020)
Magnetic silica; SiMag & Nanoporous silica; SiNPs(400 and 600 mg/kg diet, respectively; 56 days)	Nile tilapia (*Oreochromis niloticus*)	Lead For 30 days	-Max. growth, FCR, biochemical parameter observed through SiMag & SiNP administration in diet -Pb residue declined in gill, liver, kidney, muscle by supplementation - Down-regulation of P450, caspase -3 and HSP-70 and MT were observed in groups received 600 mg/kg diet of Si-Mag or Si-NPs.	(Alandiyjany *et al.*, 2022)

RBC- Red blood cell, PCV- Packed cell volume, MCV- Mean corpuscular volume, MCH- Mean corpuscular hemoglobin, MCHC- Mean corpuscular hemoglobin concentration, AST- Aspartate amino transferase, ALT- Alanine amino transferase, MT- Metallothionein, GPx- Glutathione peroxidase, SOD- Superoxide dismutase, GST- Glutathione S-transferase, G-Rd- Glutathione reductase, CAT- Catalase, LDH- Lactate dehydrogenase, ALP- Alkaline phosphatase, CE- Coriander extract, CP- Coriander powder, PWG- Percent weight gain, FI- Feed intake, SGR- Specific growth rate, FCR- Feed conversion ratio, LYZ- Lysozyme, TAC- Total antioxidant capacity, RBA- Respiratory burst activity, T-AOC- Total antioxidant capacity, MPO- Myelopeoxidase, ALAD- δ-aminolevulinic acid dehydratase, Beta-MOS- beta glucan- mannan oligosaccharide, GSI- Gonado-somatic index, HIS- Hepato-somatic index, APx- Ascorbate peroxidase, AChE- Acetylcholinesterase

Spirulina: In the recent past, natural products and feed additives have been tried for amelioration of Pb toxicity in fish. Algae like spirulina was tested in different fish species, viz. carp, catfish, and Nile tilapia, with promising results. Spirulina, a blue-green filamentous marine algae, produced commercially for years for human consumption, was thought to be an immune-enhancing antioxidant that regulates infectious agents and toxicants and the immune-enhancing characteristics were due to its high content of vitamins, minerals, phycocyanin, beta-carotene, and algal polysaccharides (Khan *et al.*, 2005; Raja and Hemaiswarya, 2010; Ragap *et al.*, 2012; Sherif *et al.*, 2020). On Nile tilapia, exposed to lead nitrate at the rate of 10 percent of LC50, use of spirulina algae (*Arthrospira platensis*) in diet produced promising ameliorating results. Pb exposure was related to anaemia with lower RBC, PCV, MCV, MCH, MCHC, Hb, and Hct. The spirulina supplemented groups after 12 weeks of study were significantly ameliorated with enhanced hemoglobin. Significant increase in values of ALT, AST and MT indicating liver damage and higher values of GPx and CAT indicating oxidative stress in case of Pb exposure, were also improved by spirulina supplementation (Sherif *et al.*, 2020). Similar hematological responses were seen in case of catfish (*Clarias gariepinus*) exposed to lead nitrate also (Hamed *et al.*, 2019) Improvement in liver alkaline phosphatase and acid phosphatase was reported in carp (*Labeo rohita*) supplemented with spirulina after exposure to lead acetate (Vetrivel *et al.*, 2014). In catfish *(Clarius gariepinus)*, *Spirulina platensis* was reported to ameliorate lead nitrate-induced cytotoxity and genotoxicity and for that - indices like poikilocytosis, apoptosis, micronuclei (cytotoxicity studies) and DNA damage (genotoxic studies) were assessed. Micronuclei percentage and apoptosis percentage were significantly increased in lead-treated groups. However, co-treatment with either 0.25% or 0.5% spirulina significantly decreased the values, which were although still higher than the control groups. Similarly, DNA damage measured by % TDNA, TL, and olive tail moment was recovered to normal by spirulina supplementation (Hamed *et al.*, 2019). In similar experimental condition, by significantly lowering the lipid peroxidation biomarker, the level of MDA, and increasing the level of total antioxidant capacity as well as the activity of the enzymes LDH, AChE, SOD, CAT, and GST, spirulina produced extraordinary hepato-protective effects. Concentration and time dependency were also observed with best result in 4th week (Sayed *et al.*, 2017). A significant enhancement in immune status in Nile tilapia supplemented with spirulina was observed. Serum bactericidal activity and oxidative burst activity were decreased in lead nitrate exposure, and dietary spirulina supplementation reversed the condition (Sherif *et al.*, 2020).

Lotus leaves: Different parts like flower, leaves, rhizomes, and seeds of Indian lotus (*Nelumbo nucifera*) among other natural products demonstrated antioxidant, antibacterial, and immuno-stimulatory characteristics because it contains beneficial elements such as alkaloids, steroids, triterpenoids, and polyphenols (Mukherjee *et al.*, 2010; Kim and Shin, 2012; Mehta *et al.*, 2013). To find the potential use of lotus leaves against environmental pollutants like lead acetate, Nile tilapia was used as a selected species of fish. It has been suggested that antioxidant status was improved, as represented by the reduced levels of enzymes like MDA, CAT, SOD, and GPx. The hepatoprotective effect was majorly contributed by the polyphenols (phenolic acids and flavonoids). Hepatic metallothionein has a positive relationship with Pb, which was reduced when lotus leaves were added to the diet. Protection against nephrotoxicity was also evident, along with other positive effects of lotus leaves against heavy metals in Nile tilapia (Abdel Rahman *et al.*, 2019).

Coriander: Through its effects on humoral B cells, T cells, natural killer cells, cytokine profiles, chemotaxis, phagocytosis, and nitric oxide production, lead poisoning has the potential to modulate the immune systems of both humans and animals (Singh *et al.*, 2003).

The dried seed of coriander (*C. sativum*) showed ameliorative properties against metal toxicity. In a study to assess particularly the immunomodulation by coriander powder and extracts in Nile tilapia, indicators like serum lysozyme activity, nitric oxide level, etc. were inspected. Serum lysozyme activity was reduced by Pb exposure, which was further improved by using coriander extracts. Nitric oxide levels were also increased with supplementation of both coriander powder and extract. Similar results were achieved in the case of serum bactericidal activity in supplemented groups. Furthermore, the coriander extract supplemented group (30 mg/kg) had better results and lower mortality than the coriander powder supplemented groups. The level of IL-1β mRNA was increased more in the Pb exposed control group, and again, the most effective results in IL-1β mRNA level were seen in the coriander extract supplemented group (30 mg/kg) (Ahmed *et al.*, 2020).

Turmeric: Another traditional herb, turmeric (*Curcuma longa*) is well known for its curcumin (diferuloymethane), extracted from the rhizome. Strong anti-inflammatory, antioxidant, anti-tumor, and antidepressant properties are displayed by curcumin. Waterborne lead-exposed common carps when supplemented with curcumin, improved growth parameters, hematological indices, oxidative enzymes, immunological parameters, and gene expression, thereby mitigating the negative effects of heavy metal toxicity. Curcumin supplemented animals had lower mortality and feed conversion ratios, as well as higher specific growth rates, feed intake, and percent weight gain. Curcumin alleviated the increased mRNA expression of IL-1β in liver and kidney tissue (Giri *et al.*, 2021).

Moringa: Drumstick trees (*Moringa oleifera)* are reported to have wide utility contributed by different parts of the plant, like leaves, flowers, etc. The main flavonoid components identified from Moringa, are quercetin, isoquercetin, rutin, Moringa isothiocyanate, kaempferol, etc., have been shown to be free-radical scavengers and antioxidants that can up-regulate the expression of genes of antioxidant enzymes (Amaglo *et al.*, 2010). Overall growth was improved through lower FCR, higher body weight gain, specific growth rate, and protein efficiency ratio in Nile tilapia supplemented with dried moringa flower powder exposed to lead nitrate (10% of 96 hr LC50). Significant hepato-pathological lesions, oxidative stress, and other hematological signs were caused by Pb toxicity; however, moringa supplementation alleviated these symptoms. ALT and AST enzyme levels in the blood were reduced, as were cortisol and glucose levels, indicating physiological stress leading to gluconeogenesis. Upregulation of antioxidant genes such as Cu-Zn-SOD, CAT, and GPx1 was also reported in the case of moringa dried flower powder supplementation (Kiran Kumar *et al.*, 2021).

Garlic: Its rich phytochemical profile makes this herb (*Allium sativum*) a superfood. It has good vitamin, mineral, and amino acid content along with other phytochemicals of medicinal importance. Garlic, alone or in combination with other herbs such as Fu-ling (*Poria cocos*, around two thousand years old Chinese traditional medicine, an edible medicinal fungus), has been shown to significantly reduce lead toxicity in grass carps. Chelating-related genes (TF and MT-2) in the liver of the grass carp were measured by quantitative real-time PCR (qRT-PCR) and were relatively higher in the garlic and fu-ling mixed diet group. Goblet cells (immune cells of intestine), intestinal trypsin, amylase were relatively higher and alkaline phosphatase (ALP) and low-density lipoprotein (LDL-C) were found relatively lower. Enzyme activity of SOD and the content of GSH (non-enzymatic substances) in the liver which can protect against the overproduction of reactive oxygen species (ROS), was increased by garlic supplementation because of antioxidant components, flavonoids and sulfur-containing compounds (diallyl disulfide and s-allyl cysteine) present in it. Relative expressions of heat stress protein genes (HSP30 and HSP60) present higher value in supplemented experimental group and immune-related genes such as TNF-α, IL-1β was higher in both garlic and combination groups. Lead residue in liver and muscle was least in case of garlic and fu-ling mixed diet group and overall growth performance was best in this group (Liu *et al.*, 2021).

Cinnamon: The common spice cinnamon (*Cinnamomum zeylanicum*) is well known for its use as a potent anti-emetic, anti-diarrheal, and anti-flatulent. In aquatic animals, dietary supplementation with cinnamon is helpful as an antioxidant, an immunity booster, as well as a performance enhancer (Ahmad *et al.*, 2011). Nile tilapia *(Oreochromis niloticus)* fingerlings given with dietary cinnamon powder (10 g/kg diet), improved feed intake as well as body weight and specific growth rate. Growth performance is an important indicator reflecting the fish health. Hematological parameters like WBC, RBC, hemoglobin, and hematocrit value which were decreased and mean corpuscular volume, and mean corpuscular hemoglobin which were increased due to lead exposure, were stabilized by inclusion of cinnamon in the diet. Lead exposure also increased blood cortisol, glucose and total cholesterol level and decreased total lipid, total protein, albumin and globulin level. Fishes fed with dietary cinnamon reversed the values improving the overall hematological parameters. The same study reported that DNA fragmentation percentage, level of malondialdehyde, hepatic superoxide dismutase, catalase, and total antioxidant activity as well as blood lysozyme, respiratory burst activity, and total immunoglobulin level which were decreased in lead toxicity, were further improved by cinnamon supplementation (Hamed *et al.*, 2022).

Probiotics: Probiotics are a well-researched and widely acknowledged approach for reducing antibiotic misuse in aquatic feed. Probiotic dietary supplementation has been shown to be useful in enhancing fish growth, controlling immunological response, modifying intestinal microbiota, and preventing pathogen infection. Probiotics are also found effective as ameliorating agent against heavy metals. Tilapia exposed to waterborne Pb at the rate of 1 mg/L were supplemented with *Lactobacillus plantarum* mixed in feed as a phosphate-saline buffer to get a final bacterial concentration of 10^8 CFU/g. Lead accumulation in kidney, liver, gonad, brain, gills and muscles was reduced by using probiotics. Pb toxicity led increased MDA and decreased GSH levels, and decreased GPx and T-AOC activity were also restored. Nuclear abnormalities in peripheral blood erythrocytes of tilapia due to PB exposure like micronuclei, kidney-shaped nuclei, blebbed nuclei, lobed nuclei, hook-shaped nuclei and bilobed nuclei were significantly lowered in probiotic supplemented group. The study also reported reversed values for inhibited activity of blood δ-aminolevulinic acid dehydratase (ALAD) and decreased level of enzymes related to innate immunity like lysozyme and myeloperoxidase (MPO) on probiotic supplementation (Zhai *et al.*, 2017). For the purpose of using lactobacillus strains as dietary supplements to reduce Pb contamination in aquaculture, *L. reuteri* P16 also gave effective results, which has high antioxidative and Pb-binding properties (Giri *et al.*, 2018)**.** With other beneficial effects, this probiotic in freshwater carp (*C. carpio*) reduced the Pb-exposure-induced expression of heat shock proteins, TNF-α and IL-1β. Monocytes and macrophages are the main producers of the cytokines IL-1 and TNF, which control various elements of the immune response. When there is inflammation, TNF- impacts the tissue vasculature and also causes the liver to produce acute phase proteins. Thus, immune compromised and inflammatory condition was induced by Pb exposure which further was reversed by probiotic supplementation (Giri *et al.*, 2018).

Prebiotics: Among other functional dietary supplements to ameliorate Pb toxicity in fish, prebiotics like mannan oligosaccharide (MOS) and beta glucans (βG) were tested in tilapia. Prebiotic supplements have been shown to be successful in altering the gut beneficial flora (Andrews *et al.*, 2009), boosting growth performance and immune response (Selim and Reda, 2015), increasing nutritional availability, and preventing pathogen infection in fish (Abu-Elala *et al.*, 2018). In tilapia exposed to Pb in water (10 mg/L) the efficacy of supplementing a combined product of mannan oligosaccharide and beta glucans (Beta-MOS®) was tested. In comparison to the control, the lead acetate significantly reduced final body weight, weight increase, red blood cell count, and hemoglobin concentration. Additionally, there were regressive changes in the histological sections of the lead group and a significant rise in creatinine compared to the control group. However, all of the lead-induced perturbations in the evaluated parameters were reduced by dietary Beta-MOS® (El-Fahla *et al.*, 2022b). In similar experimental conditions, reproductive performances were also evaluated. Pb exposure reduced the weight and gonado-somatic index as well as the levels of testosterone, estradiol, GSH, and MDA. Pb exposed group also expressed atrophy and degeneration in the gonads along with higher cortisol, glucose, and MDA levels. The Beta-MOS supplementation ameliorated the adverse effects of Pb toxicity in tilapia. The stress-relieving and antioxidant actions of beta-MOS that enhanced gonadal sex steroids and pathologies may be responsible for the ameliorative effect of pb-induced reproductive deficits (El-Fahla *et al.*, 2022a).

Minerals and vitamins: Protection against the negative consequences of oxidative stress depends on the cooperative interplay of endogenous and dietary antioxidants (Jacob, 1995). Thus, vitamins and minerals may play their role in amelioration of lead toxicity in fish. In Nile tilapia exposed to lead acetate severe congestion of the dorsal area, caudal peduncle, and internal organs, as well as occurrence of hemorrhagic anus was observed. Significant reduction in the ionic reabsorption in kidney and disturbance of homeostasis was also seen as nephrotoxic effect of Pb intoxication. On supplementation of sodium selenite and alpha tocopherol serum calcium, magnesium and phosphorus level was increased, and serum creatinine was decreased. However, serum phosphorus and magnesium level improvement were more in alpha tocopherol than sodium selenite and serum creatinine level lowering was higher in mixed use of sodium selenite and alpha tocopherol. Kidney antioxidants, superoxide dismutase (SOD, first line of cell defence against reactive oxygen species), and glutathione (GSH, biomarker of oxidative stress), level was increased by both mixed or separate application, but α-toc showed greater result than selenium. Significant reduction in MDA (end product of lipid peroxidation) level was indicative of effectiveness of using sodium selenite and alpha tocopherol against Pb intoxication (Hashish *et al.*, 2015). Similar study also indicated improved ALT, AST and serum protein, serum urea and creatinine level during mixed supplementation. Pb intoxication induced serum electrolytes (Ca, P, Mg) imbalance was reported to be normal. Meanwhile, liver and kidney MDA level was decreased, and SOD & GSH level was increased (Elgaml *et al.*, 2015). In another study, common carp exposed to lead nitrate, supplied with organic selenium the toxicity induced glutathione peroxidase (GSH-Px), glutathione S-transferase (GST) activities, and levels of reduced glutathione (GSH) with malondialdehyde (MDA) in liver and brain tissues were stabilized (Özkan-Yilmaz *et al.*, 2014). Thiamin supplemented as thiamin hydrochloride in pb exposed *Tilapia zilli* showed better ameliorating results. The bioaccumulation of Pb in kidney, liver, gonads, brain, gills, and muscle was reduced in the thiamin-supplemented group. Fishes also showed better survival, and meanwhile, reduced hemoglobin and RBC levels in cases of Pb intoxication were effectively restored (Ghazaly, 1991).

Antioxidants: Quercetin is a potent antioxidant and is rapidly absorbed, deposited in aglycone form, and expressed its effects in tilapia. (Park *et al.*, 2008). In a 28-day study on tilapia, quercetin was looked at to see if it could help fish that have been exposed to lead. It was concluded that dietary quercetin effectively normalised the antioxidant status in the hepatopancreas of tilapia and restored the FCR (Zhai *et al.*, 2014). Cerium, the most abundant rare earth metal, was also used as an antioxidant for ameliorating heavy metal toxicity.

Experimental fish were first intoxicated with $PbCl_2$ through intra-peritoneal injection for 14 days and then given with $CeCl_3$ through the same route. After 28 days of the cerium injection, the net increase in fish body wet weight was higher than that of fish injected with Pb alone, and the hepatosomatic index (HIS) was reduced. Antioxidant enzymes SOD, CAT, and APx (ascorbate peroxidase) values decreased due to intoxication and were controlled by cerium injection. Ratios of ascorbic acid to dehydroascorbic acid (ASA/DHASA) and ratios of glutathione to oxidised glutathione (GSH/GSSG) in fish liver were stabilised by cerium (Ling and Hong, 2010).

Chelating and other agents: In both short-term and long-term studies conducted on catfish intoxicated by lead nitrate, zeolite (sodium aluminum silicate) was found to give better ameliorating results like restoration of soluble protein, RNA, and glycogen content. Zeolite has a high cation exchange capacity, which means that ionic lead may replace other cations there and become less accessible to fish (Jain, 1999). Given its selectivity for heavy metal cations like lead, cadmium, and nickel, clinoptilolite is likely the most prevalent of the more than 40 natural zeolite species. According to reports, of all the heavy metals, clinoptilolite has the highest affinity for lead (Vaca Mier *et al.*, 2001). By reducing the negative effects of lead nitrate, clinoptilolite therapy was able to shield common carps from lead toxicity. Clinoptilolite supplementation considerably decreased the total ammonia nitrogen and cholesterol concentrations that were increased by lead exposure from diet. Clinoptilite decreased the LDH level, a sign of hepatocellular damage that was almost two times higher after lead exposure. RNA, soluble protein, and glycogen content were all increased (Tepe, 2004). Natural zeolite was discovered to be efficient in restoring serum glucose, cholesterol, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) levels in a different investigation on tilapia. Pb exposure increased these levels, and zeolite supplementation through food decreased them. In the cases of CAT, SOD, and TAC levels, comparable patterns were seen. Zero Pb residues were found in muscle, while levels of albumin and protein were elevated in the blood (Abbas *et al.*, 2021).

The primary component of bentonite is often montmorillonite (MMT), a subset of aluminosilicate clay. Given its greater cation exchange capacity and greater specific surface area, MMT is known to have excellent adsorptive characteristics. For the treatment of dietary Pb toxicity in aquatic animals, the adsorption of Pb onto MMT can be an alluring and affordable solution (He *et al.*, 2000).

The effectiveness of using magnetic silica, also known as SiMag and nanoporous silica, or SiNPs, to reduce lead (pb) toxicity in Nile tilapia was the subject of a different study. In groups who received SiMag or SiNPs, serum antioxidant enzyme levels as well as their transcriptional levels in muscle and liver were increased. Pb residue in gill, liver, kidney, and muscle was reduced and max growth and FCR was observed in supplemented groups. Increased level of P53 in liver and gills due to Pb intoxication was reduced by Si-Mag or Si-NP supplementation (Alandiyjany *et al.*, 2022).

Conclusion

The topic requires more extensive studies particularly based on natural ameliorating agents. However, among different ameliorating agents plant-based products, algae, probiotics, prebiotics, antioxidants, chelating agents etc. were found promising to combat lead toxicity in fish by dietary means. Recent trend for eco-friendly feed supplements to attenuate the harmful effects of various pollutants, including heavy metals like Pb, would be beneficial not only for fish and its consumers but also for the environment.

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Author's contribution: SD, SM, HD, PNC: Wrote the manuscript. All authors read and approved the manuscript.

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