EFFECTS OF PROBIOTICS ON ANTIOXIDANT DEFENSE IN FARMED FISH: RECENT ADVANCES

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Abstract

The intensification of aquaculture exposes farmed fish to environmental and chemical stressors that can disrupt redox homeostasis. This narrative review synthesizes recent studies, primarily published from 2020 onward, on probiotic-mediated antioxidant protection in cultured fish. Evidence was assessed across environmental and chemical challenges, with emphasis on antioxidant enzymes, oxidative damage markers and molecular pathways. Probiotics generally reduced oxidative damage and supported redox homeostasis, either by restoring suppressed antioxidant defenses or by normalizing compensatory enzyme overactivation. Effects depended on strain, dose, host species and stressor. Collectively, current evidence suggests that probiotics can strengthen antioxidant defense and improve fish resilience to stress, with efficacy depending on strain, dose and challenge conditions.

Key words: *probiotics; aquaculture; oxidative stress; antioxidant defense; redox homeostasis*

INTRODUCTION

Aquaculture has become a major component of global food production and an increasingly important contributor to food security and nutrition. In 2022, global aquaculture production reached 130.9 million tonnes, including 94.4 million tonnes of aquatic animals. For the first time, farmed aquatic animals accounted for 51% of global aquatic animal production, surpassing capture fisheries [1]. Continued expansion of the sector, however, is occurring under increasing pressure from climate change, water scarcity, pollution and other forms of environmental degradation, making the maintenance of fish health and physiological resilience increasingly important for sustainable production [1].

Fish are continuously exposed to the physicochemical characteristics of their surrounding water and are therefore particularly sensitive to environmental fluctuations. Changes in temperature, dissolved oxygen, salinity, pH and pollution load can disturb normal physiological function and promote excessive production of reactive oxygen species (ROS) [2]. When ROS generation exceeds the capacity of endogenous antioxidant defenses, cellular redox homeostasis is disrupted, potentially affecting growth, reproduction, immunity and overall performance [2].

In addition to culture-related environmental stressors, farmed fish may be exposed to a broad range of chemical contaminants. Global pesticide use reached 3.92 million tonnes of active ingredients in 2024, representing an 18% increase over the previous decade and more than twice the amount reported in 1990 [3]. Pesticides can contaminate aquatic environments and

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affect non-target organisms, while exposure in fish has been associated with oxidative damage and altered antioxidant responses [3,4]. Heavy metals constitute another persistent concern, as industrial activity, wastewater and agricultural runoff can increase their environmental availability and facilitate their accumulation in aquatic food chains [5]. Aquaculture environments may additionally contain microplastics, antibiotics, persistent organic pollutants, bisphenol A, per- and polyfluoroalkyl substances and other emerging contaminants [6]. Even recirculating aquaculture systems are not exempt, with microplastics, heavy metals, antibiotics and antibiotic resistance genes reported within these production environments [6,7].

Despite their different origins, many of these stressors converge on oxidative imbalance. Fish rely on enzymatic and non-enzymatic defenses, including superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx) and glutathione-dependent systems, to limit ROS accumulation and oxidative damage [2,4]. Redox-sensitive pathways such as Nrf2–Keap1 also contribute to the regulation of this response [4]. Importantly, antioxidant changes are not always unidirectional: moderate stress may stimulate compensatory antioxidant activity, whereas prolonged or severe exposure may overwhelm these defenses. Consequently, antioxidant status should be interpreted in relation to oxidative damage, stress intensity and molecular regulation rather than from changes in a single biomarker alone.

Within this context, probiotics have gained increasing attention as a nutritional strategy capable of supporting redox homeostasis and improving stress resilience in farmed fish. The present review critically examines recent evidence on probiotic-mediated antioxidant defense, with emphasis on endogenous antioxidant systems, Nrf2–Keap1 signaling, gut microbiota and microbial metabolites, direct limitation of ROS accumulation, contaminant detoxification and inflammation–redox interactions. Particular attention is given to probiotic efficacy under major aquaculture stressors, including ammonia, hypoxia, thermal and salinity stress, as well as exposure to heavy metals, pesticides and emerging aquatic contaminants. By comparing biochemical, transcriptional and mechanistic evidence, the review aims to clarify how probiotic strain, dose, host species and challenge conditions influence antioxidant responses in cultured fish.

MATERIAL AND METHOD

For this narrative review, a literature search was conducted using Web of Science, Scopus, PubMed, ScienceDirect and Google Scholar to identify recent studies on probiotic-mediated antioxidant responses in farmed fish. The search was updated through October 2026. Search terms included combinations of “probiotics”, “fish”, “aquaculture”, “oxidative stress”, “antioxidant”, “SOD”, “CAT”, “GPx”, “Nrf2”, “ammonia”, “hypoxia”, “temperature”, “salinity”, “heavy metals”, “pesticides”, “microplastics” and related contaminants. Priority was given to studies published from 2020 onward involving cultured fish species, live probiotic supplementation and direct assessment of antioxidant or oxidative-stress markers. Studies involving non-farmed model fish, non-fish experimental systems, paraprobiotics, combined interventions in which the probiotic effect could not be separated, or studies lacking relevant antioxidant endpoints were considered only when they provided specific mechanistic context and were interpreted separately from direct evidence in cultured fish. Reference lists of relevant reviews and original articles were also screened to identify additional studies.

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MECHANISMS OF PROBIOTIC-MEDIATED ANTIOXIDANT DEFENSE IN FARMED FISH

The mechanisms through which probiotics modulate antioxidant defense in fish are complex and remain only partially elucidated. Earlier evidence suggested that probiotic-mediated antioxidant protection may involve metal ion chelation, modulation of the intestinal microbiota, production of antioxidant metabolites, and limitation of reactive oxygen species generation [8]. More recent studies have expanded this framework, reporting effects on endogenous antioxidant systems, redox-sensitive signaling pathways, particularly the Nrf2–Keap1 pathway, as well as interactions involving microbial metabolism and host immune responses [9–11]. However, the magnitude and nature of these effects remain strongly dependent on probiotic strain, dose, fish species, tissue, environmental conditions, and experimental design. The main mechanisms currently associated with probiotic-mediated antioxidant defense in farmed fish are discussed below.

Modulation of endogenous antioxidant defense

One of the most consistently reported effects of probiotic supplementation in fish is the modulation of the endogenous antioxidant defense system. This system relies mainly on enzymatic components, including superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx) and glutathione S-transferase (GST), together with non-enzymatic antioxidants such as reduced glutathione (GSH). These components act sequentially to neutralize reactive oxygen species (ROS): SOD catalyzes the dismutation of superoxide radicals, whereas CAT and GPx contribute to the removal of hydrogen peroxide and organic hydroperoxides. Consequently, strengthening these endogenous defenses can limit ROS accumulation and reduce oxidative damage to cellular lipids and other macromolecules.

Several recent studies in farmed fish support this response. Dietary supplementation with compound probiotic cultures containing *Bacillus subtilis*, *Lactobacillus plantarum* and *Saccharomyces cerevisiae* increased hepatic T-AOC, CAT, GPx and T-SOD activities in juvenile largemouth bass, together with increased transcription of the antioxidant-related genes *SOD1*, *SOD2*, *CAT*, *GPx* and *GST* [12]. Similarly, a multispecies probiotic administered to striped catfish increased hepatic CAT, SOD and GPx activities while simultaneously decreasing malondialdehyde (MDA), indicating improved antioxidant capacity accompanied by reduced lipid peroxidation [13]. In Nile tilapia, dietary mixed *Bacillus* strains also increased hepatic and splenic CAT and SOD activities and reduced MDA levels, further supporting the ability of probiotics to reinforce endogenous antioxidant defenses [14].

Comparable responses have been reported in other cultured species. In grass carp, dietary supplementation with *B. subtilis* and *L. plantarum* significantly improved SOD and CAT activities and reduced MDA concentrations [15]. In yellow catfish, *Bacillus amyloliquefaciens* increased both SOD activity and total antioxidant capacity [16]. Likewise, supplementation with *Saccharomyces cerevisiae*, *Lactobacillus bulgaricus*, or their combination in *Mugil capito* enhanced hepatic SOD, CAT and GPx activities, while reducing thiobarbituric acid reactive substances, indicating lower lipid peroxidation [17]. Long-term dietary administration of *L. plantarum* or *B. subtilis* also improved hepatic antioxidant capacity in olive flounder under commercial farming conditions [18].

The protective role of this mechanism becomes particularly evident under oxidative challenge. In common carp exposed to waterborne cadmium, oxidative stress was characterized by reduced CAT, GSH-Px and SOD activities together with increased ROS and MDA levels. Dietary *Bacillus coagulans*

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SCC-19 largely restored antioxidant enzyme activities and reduced ROS and MDA accumulation, demonstrating that probiotics can restore an antioxidant system impaired by environmental stress [19]. A similar pattern was observed in Asian seabass: dietary quorum-quenching probiotics increased SOD and CAT before bacterial challenge and were associated with higher antioxidant activities and lower MDA levels following *Vibrio alginolyticus* infection [20].

Taken together, these findings indicate that probiotics can modulate endogenous antioxidant defense in fish by increasing or restoring the activity of key enzymatic systems, particularly SOD, CAT and GPx, and by influencing glutathione-dependent defenses such as GSH and GST. This coordinated response enhances the detoxification of superoxide radicals, hydrogen peroxide and organic hydroperoxides, thereby helping to maintain cellular redox homeostasis. The concomitant reduction in MDA or TBARS reported in several studies should be interpreted as evidence of lower lipid peroxidation and oxidative damage rather than as a component of the antioxidant defense system itself. Importantly, most studies demonstrate this mechanism primarily at the biochemical level. Stronger mechanistic evidence is available when changes in enzyme activity are accompanied by transcriptional regulation. In juvenile *Micropterus salmoides*, probiotic supplementation increased the expression of *SOD1*, *SOD2*, *CAT*, *GPx* and *GST* together with their corresponding antioxidant activities, indicating regulation of endogenous antioxidant defense at both biochemical and transcriptional levels [12].

Activation of the Nrf2–Keap1 antioxidant signaling pathway

The Nrf2–Keap1 pathway is emerging as one of the better-supported molecular routes through which probiotics may influence antioxidant defense in fish. Nrf2 regulates the transcription of several genes involved in redox homeostasis, whereas Keap1 acts as its main negative regulator. Changes in this signaling system can therefore affect the expression of enzymes involved in ROS detoxification, including SOD, CAT, GPx and GST. In probiotic-fed fish, modulation of this pathway has increasingly been reported alongside changes in antioxidant enzyme activity, suggesting that at least part of the response occurs at the transcriptional level.

One of the clearest examples was reported in juvenile *Micropterus salmoides* fed a compound probiotic culture containing *Bacillus subtilis*, *Lactobacillus plantarum* and *Saccharomyces cerevisiae*. Supplementation increased *Nrf2* expression, reduced *Keap1* expression and upregulated *SOD1*, *SOD2*, *CAT*, *GPx* and *GST*. These transcriptional changes were accompanied by higher T-AOC, SOD, CAT and GPx activities, providing a relatively consistent link between Nrf2–Keap1 modulation and the antioxidant phenotype [12].

Evidence from single-strain supplementation points in the same direction, although the magnitude of the response differs between probiotic species and tissues. In *M. salmoides*, dietary *B. subtilis* significantly increased intestinal *Nrf2* expression and reduced *keap1*, together with higher expression of *SOD1*, *GPX* and *CAT* [21]. In a subsequent study on the same fish species, both *B. subtilis* and *Lactobacillus reuteri* affected the hepatic Nrf2–Keap1 pathway and increased the expression of *Nrf2*, *SOD1*, *SOD2*, *GST* and *CAT*. However, the biochemical response was more pronounced with *B. subtilis*, which also increased hepatic T-AOC, SOD and CAT activities [22]. This difference is important, because comparable transcriptional changes do not necessarily result in an identical antioxidant response.

The pathway also appears to participate in probiotic protection during oxidative challenge. In *Cyprinus carpio* exposed to *Aeromonas hydrophila*, dietary

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Lactobacillus delbrueckii increased *nrf2*, *sod*, *cat*, *gpx* and *gst* expression while decreasing *keap1a* relative to infected fish without probiotic supplementation. The same treatment reduced oxidative damage and improved several components of the glutathione-dependent antioxidant system, including GPx, GST and GR activity [23]. The authors therefore linked the improved antioxidant response to modulation of Nrf2 signaling, although the study still relied mainly on gene-expression data rather than direct assessment of Nrf2 activation.

Recent evidence from juvenile GIFT *Oreochromis niloticus* further supports transcriptional regulation of antioxidant defense by *B. subtilis*. Dietary supplementation significantly increased *nrf2*, *sod*, *gst*, *gsh-px* and *cat* expression in both the intestine and liver, with the strongest overall response generally observed around 1 × 10^9 CFU/kg diet [24]. The non-linear response across supplementation levels also suggests that stimulation of antioxidant signaling may depend on an optimal probiotic dose rather than increasing continuously with bacterial concentration.

Not all studies, however, provide equally direct evidence for Nrf2–Keap1 involvement. In Nile tilapia, *B. subtilis* DSM 32315 improved antioxidant capacity and resistance to acute ammonia exposure, with the effective supplementation level differing before and during the ammonia challenge. The study is valuable in showing that probiotic effects on redox status are strongly influenced by nutritional background and environmental stress, but it provides less direct mechanistic support for Nrf2–Keap1 than studies specifically examining coordinated pathway and downstream gene responses [25].

Additional observations come from preparations derived from probiotic bacteria, although these should be interpreted separately from evidence obtained with live probiotics. In black sea bream, an inactivated *L. plantarum* preparation alone reduced *Keap1b*, whereas the combination of inactivated *L. plantarum* and berberine increased *Nrf2* and further reduced *Keap1b*. Because the study did not include a berberine-only treatment, the specific contribution of the bacterial preparation to Nrf2 activation cannot be separated from the effect of berberine [26]. Likewise, heat-killed *Lactiplantibacillus plantarum* VSG3 increased antioxidant enzyme activities and altered hepatic *Nrf2* and *Keap1* expression in *C. carpio*, but this represents a paraprobiotic rather than a conventional live probiotic intervention [27]. These studies broaden the biological picture, but they should not be treated as equivalent evidence for mechanisms mediated by viable probiotics.

A further distinction is needed for *Clostridium butyricum* DMZ-SG06. This live probiotic increased SOD, CAT and GSH-Px activities and reduced MDA in *M. salmoides*. The authors proposed that butyrate generated by the strain may contribute to antioxidant protection through Keap1–Nrf2 signaling, but Nrf2–Keap1 activation itself was not directly measured in the experiment [28].

Current studies therefore indicate a recurring association between probiotic supplementation, modulation of *Nrf2*/*Keap1* expression and increased transcription of downstream antioxidant genes. The evidence is strongest when molecular changes are accompanied by higher antioxidant enzyme activity and reduced oxidative damage, as seen in several studies with *B. subtilis* and *L. delbrueckii*. Nevertheless, most experiments still rely on mRNA expression as a surrogate for pathway activation. Measurements of Nrf2 protein stabilization, nuclear translocation, Keap1 protein abundance or direct ARE activation remain uncommon. This limitation is important, because increased *Nrf2* transcription alone does not fully demonstrate functional activation of the pathway.

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Modulation of gut microbiota and microbial metabolites

Probiotics may influence antioxidant defense by reshaping the intestinal microbiota and, consequently, the metabolic environment of the gut. The most convincing evidence comes from studies showing that microbial changes are accompanied not only by improved antioxidant markers, but also by changes in metabolites that could plausibly mediate the response.

In largemouth bass, *Clostridium butyricum* increased intestinal acetate, propionate and butyrate together with T-AOC, CAT, SOD and GSH-Px, while reducing MDA [29]. The authors linked these effects to changes in microbial composition and microbial functions involved in nutrient and energy metabolism, suggesting that SCFA production may help create a more favorable intestinal environment and support redox homeostasis. A similar mechanism was proposed for *C. butyricum* LZK-08, which showed a strong capacity to produce butyrate and simultaneously improved intestinal antioxidant status and microbial composition [30]. Here, however, butyrate production was demonstrated mainly in vitro, so its direct contribution to the antioxidant response in vivo remains inferential.

Metabolomic studies provide further support for this idea. *Bacillus tequilensis* Bt-CO altered both intestinal microbiota and metabolite profiles, including pathways related to glutamine and glutamate metabolism, which the authors associated with free-radical scavenging and oxidative stress control [31]. They therefore proposed that probiotic-induced changes in microbial metabolism may contribute to the observed improvement in antioxidant capacity. Likewise, *Bacillus velezensis* YFI-E109 modified the gut microbiome and host metabolic pathways while reducing hepatic MDA at appropriate inclusion levels [32]. Importantly, excessive supplementation reversed part of this benefit, showing that microbial and antioxidant responses depend strongly on dose.

Other studies support the same relationship, although less directly. *Bacillus subtilis* FZU103 enriched *Lactobacillus* and improved hepatic SOD and GPx while reducing MDA; *Lactobacillus* abundance was positively correlated with the antioxidant enzymes [33]. The authors interpreted this as a possible functional connection between microbiota remodeling and redox status, but correctly noted that correlation does not prove causality. Under pollutant exposure, *Lactobacillus rhamnosus* also partially restored dysbiotic microbial communities while improving antioxidant responses in zebrafish exposed to PFOA and PFOS [34], suggesting that preservation of microbial balance may contribute to protection when oxidative stress is externally induced.

Beyond SCFAs, recent studies suggest that other microbiota-derived metabolites may also connect probiotic supplementation with antioxidant protection. In common carp, *Lactobacillus plantarum* and *Bacillus licheniformis* reshaped the gut microbiota and bile acid profile while activating hepatic FXR/SHP signaling, alongside improved antioxidant capacity [35]. This suggests that the gut microbiota–bile acid axis may represent an additional route through which probiotics influence redox homeostasis. Another possible pathway involves microbial tryptophan metabolism. In zebrafish, *Akkermansia muciniphila* increased several indole derivatives and activated AhR/IL-22 signaling, while antibiotic pretreatment partly abolished the probiotic effects, providing stronger evidence that the response depended on the gut microbiota [36]. These findings broaden the current view of probiotic action, indicating that the antioxidant effect may involve not only SCFAs, but also other microbiota–host signaling axes. However, direct causal validation of these pathways remains limited.

The evidence therefore supports a microbiota–metabolite contribution to

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probiotic-mediated antioxidant protection, particularly through SCFAs and shifts in microbial metabolic pathways. Still, most studies demonstrate parallel changes rather than a complete causal chain. The mechanism is therefore biologically well supported, but the specific metabolites responsible for triggering the host antioxidant response remain only partly defined.

Direct scavenging and limitation of ROS production

In addition to stimulating the host antioxidant system, some probiotics appear to possess intrinsic antioxidant activity. Microbial cells or compounds released during their growth may therefore interact directly with reactive species and contribute to reducing the oxidative burden.

Most direct evidence for this mechanism comes from in vitro studies. Probiotic candidates isolated from hybrid grouper showed antioxidant activity across several complementary assays, including DPPH, ABTS, superoxide and hydroxyl radical scavenging, ORAC, reducing activity and Fe^{2+} chelation [37]. These findings are particularly relevant because they indicate that the microorganisms themselves possess antioxidant properties, rather than merely stimulating host antioxidant enzymes. In addition to neutralizing existing radicals, Fe^{2+} chelation may also limit ROS formation by reducing the availability of redox-active iron involved in Fenton-type reactions and, consequently, the generation of highly reactive hydroxyl radicals [37]. However, this mechanism has so far been demonstrated mainly in vitro. A similar intrinsic antioxidant capacity was observed for *Bacillus cereus* fkW8-1-2, whose intact cells showed strong DPPH removal and superoxide-anion scavenging activity [38]. Fish-derived *Bacillus* strains also displayed DPPH and ABTS scavenging, β-carotene bleaching inhibition and reducing activity [39].

The antioxidant effect may not be restricted to the microbial cell itself. In lactic acid bacteria isolated from tilapia, both intact cells and cell-free supernatants showed DPPH-scavenging activity [40], suggesting that extracellular compounds released during bacterial growth may also contribute to radical neutralization. Cell extracts from several *Lactiplantibacillus plantarum* strains similarly showed ABTS- and DPPH-scavenging activity, with clear differences among strains [41]. This variability indicates that intrinsic antioxidant activity is strongly strain dependent rather than a general property of all probiotics. Probiotic yeasts may act in a similar way. *Rhodotorula paludigena* CM33 showed direct DPPH-scavenging activity in vitro and improved antioxidant responses after dietary supplementation in fish [42]. The yeast is also known to produce carotenoids, particularly β-carotene, which could provide an additional antioxidant contribution; however, this mechanism was not directly demonstrated in the feeding trial.

Evidence that these intrinsic properties translate into lower oxidative burden in vivo is less direct. In hybrid grouper fed oxidized fish oil, *Lactobacillus pentosus* reduced both reactive oxygen radicals and MDA in muscle [43]. Likewise, *Lactobacillus rhamnosus* reduced ROS accumulation in zebrafish larvae exposed to microcystin-LR, while increasing GSH content and CAT activity [44]. Under ammonia exposure, *Bacillus licheniformis* Dahb1 reduced lipid peroxidation and DNA damage [45]. In these studies, however, the reduction in oxidative damage occurred together with stimulation of endogenous antioxidant defenses, making it difficult to determine how much of the protection resulted from direct scavenging by the probiotic itself.

Overall, direct radical scavenging appears to be a plausible component of probiotic-mediated antioxidant protection, particularly where intact cells, cell extracts or cell-free supernatants show measurable radical-scavenging activity. However, most direct evidence remains in vitro, whereas in vivo studies generally demonstrate reduced ROS

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accumulation or oxidative damage without clearly separating direct microbial scavenging from stimulation of host antioxidant systems. These mechanisms are therefore likely complementary, but their relative contribution in fish remains difficult to define.

Binding and detoxification of pro-oxidant contaminants

A further mechanism by which probiotics may protect fish from oxidative damage is by reducing exposure to the pro-oxidant contaminant itself. This is particularly relevant for heavy metals, which can promote ROS generation after absorption and accumulation in tissues. In this context, probiotics may act upstream of the host antioxidant system by binding or immobilizing metal ions in the intestinal environment, reducing their bioavailability and subsequent tissue accumulation.

Evidence for this mechanism is particularly strong for cadmium. In common carp, *Bacillus coagulans* SCC-19 showed Cd-removal capacity and reduced Cd accumulation in the liver and kidney, together with lower ROS and MDA and restoration of antioxidant enzyme activities [19]. A complementary study using the same strain further showed reduced intestinal Cd accumulation and improved expression of tight-junction genes under Cd exposure [46]. The authors proposed that Cd binding in the gut lowers its bioavailability and consequently limits intestinal uptake, thereby protecting both the intestinal barrier and downstream tissues. This provides a plausible mechanistic sequence in which probiotic-mediated metal sequestration occurs before the antioxidant response: metal binding → reduced absorption and tissue burden → lower ROS generation → reduced oxidative damage.

More direct evidence for microbial metal binding was obtained with *Lactococcus lactis* in common carp exposed to a mixture of Cr, Cd and Cu [47]. This distinction is mechanistically important because metal sequestration does not necessarily require bacterial colonization or active metabolism. The comparable binding observed with live and non-viable biomass suggests that cell-surface adsorption may represent an initial physicochemical barrier to metal uptake [47]. The strain showed metal-binding activity in vitro and markedly reduced metal accumulation in vivo, while increasing SOD and decreasing MDA. The authors related this binding capacity to negatively charged components of the bacterial surface, particularly peptidoglycan and teichoic acids, which can interact with positively charged metal ions through ion exchange, complex formation and surface precipitation. Interestingly, similar metal-binding capacities were observed for live and non-viable bacterial biomass in vitro, suggesting that the initial sequestration step may be largely physicochemical rather than dependent on active bacterial metabolism. However, the dietary intervention itself involved live probiotics, and additional effects on the intestinal environment may have contributed to the protection observed in vivo.

A comparable pattern has been reported for copper exposure. In Nile tilapia, dietary Lactobacillus-based probiotics reduced Cu accumulation in the gonads at the higher exposure levels and simultaneously lowered MDA [48]. This is consistent with reduced metal bioavailability, although Cu binding by the administered strains was not directly measured in the fish. Therefore, the decrease in tissue accumulation supports, but does not by itself prove, an intestinal sequestration mechanism.

Reduced contaminant accumulation may also involve preservation of the intestinal barrier and changes in the surrounding microbial community. In common carp exposed to Pb, *Rhodobacter sphaeroides* SC01 colonized the intestine, reduced Pb accumulation in intestinal contents, intestine, liver, kidney and blood, and improved hepatic resistance to oxidative stress [49]. Active

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microbial processes may also contribute to metal detoxification. *R. sphaeroides* SC01 has previously been reported to remove Pb from solution through lead-phosphate bioprecipitation, although whether this process occurs to a relevant extent in the fish intestine remains unresolved [49]. The probiotic also preserved intestinal barrier function and altered microbial and metabolic profiles, changes that could further limit Pb absorption. A subsequent study in grass carp using the same strain reported lower Pb levels in the intestine, gills and kidney, together with increased abundance of several bacterial taxa described as Pb-adsorbing and improved tight-junction responses [50]. These findings suggest that detoxification may involve both the probiotic itself and a broader microbiota-mediated capacity to retain or transform metals within the intestinal environment.

However, these studies also illustrate an important limitation of the available evidence. The two *R. sphaeroides* SC01 studies involve the same probiotic strain and closely related experimental systems, and therefore should not be interpreted as fully independent confirmation of the mechanism. Moreover, reductions in tissue metal concentration can result from several processes, including decreased absorption, enhanced fecal elimination, altered intestinal permeability or changes in metal transport and metabolism. Direct demonstration of metal binding within the fish intestine remains uncommon.

The interpretation is further complicated when the probiotic is combined with another active antioxidant component. In *Luciobarbus capito*, selenium-enriched *Lactobacillus plantarum* reduced Cd accumulation and improved antioxidant responses [51]. Although these findings are consistent with contaminant detoxification, selenium itself can interact with Cd and participate in antioxidant defense. Consequently, the contribution of the probiotic cannot be separated clearly from that of selenium in this model. Similar effects may extend beyond heavy metals. *Bacillus coagulans* and *Clostridium butyricum* markedly reduced glyphosate concentrations in the intestine, brain and muscle of exposed crucian carp [52]. However, the study primarily linked protection to restoration of the intestinal microbiota and metabolite profiles, and neither direct glyphosate binding nor microbial degradation was demonstrated. Thus, for organic contaminants, evidence for probiotic-mediated reduction of internal exposure is emerging, but the underlying detoxification processes remain less clearly defined than for metal ions.

The available evidence supports contaminant sequestration and reduced bioavailability as an upstream mechanism of probiotic-mediated antioxidant protection. The strongest support comes from heavy-metal models in which reduced tissue accumulation occurs together with direct in vitro binding capacity and lower oxidative damage. Nevertheless, decreased contaminant burden should not automatically be interpreted as proof of direct microbial binding, because intestinal barrier preservation, microbiota remodeling, altered transport and enhanced elimination may produce similar outcomes. Distinguishing among these processes will require studies that directly trace contaminant–microbe interactions and quantify absorption and excretion alongside oxidative endpoints.

Modulation of inflammation–redox crosstalk

Oxidative stress and inflammation are closely interconnected processes, and probiotics may influence antioxidant defense by modulating this interaction. Excessive ROS production can activate redox-sensitive inflammatory pathways such as NF-κB, whereas sustained inflammatory signaling can further increase oxidative pressure through cytokine production and activation of immune cells. Probiotics may therefore interrupt this self-amplifying cycle by simultaneously limiting excessive

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inflammatory signaling and restoring antioxidant capacity.

Strong evidence for this coordinated regulation was recently reported in zebrafish exposed to permethrin. Dietary *Lactobacillus casei* suppressed activation of the TLR4/NF-κB inflammatory axis while restoring AKT/Nrf2-dependent antioxidant signaling, accompanied by lower inflammatory cytokine expression and improved redox status [53]. Importantly, these effects were supported not only by transcriptomic and qPCR data, but also by protein-level analyses and pharmacological manipulation of the pathways. The study further showed increased Nrf2 activity and reduced NF-κB signaling after probiotic supplementation, while heat-killed *L. casei* failed to reproduce the protective effect. This provides comparatively strong evidence that viable probiotic activity can coordinate inflammatory and antioxidant responses rather than merely altering isolated biochemical markers.

A related interaction between oxidative stress and inflammatory signaling was observed with *Pediococcus pentosaceus* YC in Nile tilapia exposed to dietary gossypol. Probiotic supplementation reduced intestinal ROS and MDA while increasing SOD and GSH-Px activities and simultaneously decreasing the expression of pro-inflammatory cytokines, including *il-1β*, *il-6* and *il-8* [54]. RNA sequencing and in vivo siRNA interference supported the involvement of the NLRC3/NF-κB/IL-1β pathway in the inflammatory response, while fecal microbiota transplantation showed that changes in the intestinal microbiota contributed to the protective phenotype. However, the siRNA experiment primarily established regulation of the inflammatory pathway and did not directly demonstrate that suppression of this pathway was responsible for the reduction in ROS. The study therefore supports a mechanistic association between redox regulation and inflammation, but does not fully establish their causal direction.

Evidence that improved antioxidant status may itself contribute to attenuation of inflammation was provided in Nile tilapia receiving *Bacillus amyloliquefaciens* SS1 under a high-carbohydrate dietary challenge. The probiotic reduced hepatic ROS and MDA and increased SOD, GSH and total antioxidant capacity, while suppressing NF-κB/IL-1β signaling [55]. In vitro experiments further showed antioxidant activity associated with microbiota-derived acetate, leading the authors to propose that improved antioxidant capacity contributed to the reduction of hepatic inflammation. However, because acetate activity was examined separately from the in vivo inflammatory response, its specific contribution to NF-κB regulation in fish remains inferential.

The reciprocal regulation of antioxidant and inflammatory pathways has also been observed under contaminant-induced stress. In male zebrafish exposed to microcystin-LR, *Lactobacillus rhamnosus* GG reduced ROS and MDA, restored SOD and CAT activities and modulated genes associated with the Nrf2/ARE antioxidant pathway, while simultaneously affecting the TLR4/NF-κB inflammatory pathway [56]. Concurrent regulation of Nrf2-related antioxidant responses and NF-κB-associated inflammation was also reported for *Lactobacillus delbrueckii* during *Aeromonas hydrophila* challenge in common carp [23]. In both cases, however, much of the pathway evidence was based on transcriptional changes rather than direct manipulation of the interaction between the two signaling systems. These studies therefore support coordinated regulation more strongly than strict causality.

Additional physiological support comes from *Lactobacillus plantarum* SHY21-2, which protected zebrafish against *A. hydrophila* infection by reducing intestinal and muscular inflammation while improving hepatic antioxidant enzyme activities and lowering MDA [57]. These parallel responses are consistent with inflammation–redox

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crosstalk, although the study did not identify a specific signaling pathway directly linking the inflammatory and antioxidant effects.

An important distinction is that probiotic-mediated control of oxidative stress should not be interpreted as generalized suppression of ROS production. ROS generated during the respiratory burst are an important component of antimicrobial defense. Indeed, *B. amyloliquefaciens* SS1 improved antioxidant status while increasing respiratory burst activity of head-kidney leukocytes following *A. hydrophila* challenge [55]. This suggests that probiotics may limit excessive or damaging ROS accumulation while preserving, or even enhancing, localized ROS-dependent immune functions.

Current evidence therefore supports inflammation–redox crosstalk as an additional route through which probiotics may contribute to antioxidant protection in fish. The strongest mechanistic support comes from studies combining biochemical endpoints with protein-level measurements and pathway manipulation [53], whereas many others still demonstrate simultaneous changes in oxidative and inflammatory markers without establishing which process is upstream. The direction and relative importance of this interaction are therefore likely to depend on the stressor, tissue and probiotic strain. The main mechanisms currently proposed to explain probiotic-mediated antioxidant protection in farmed fish are summarized in Figure 1.

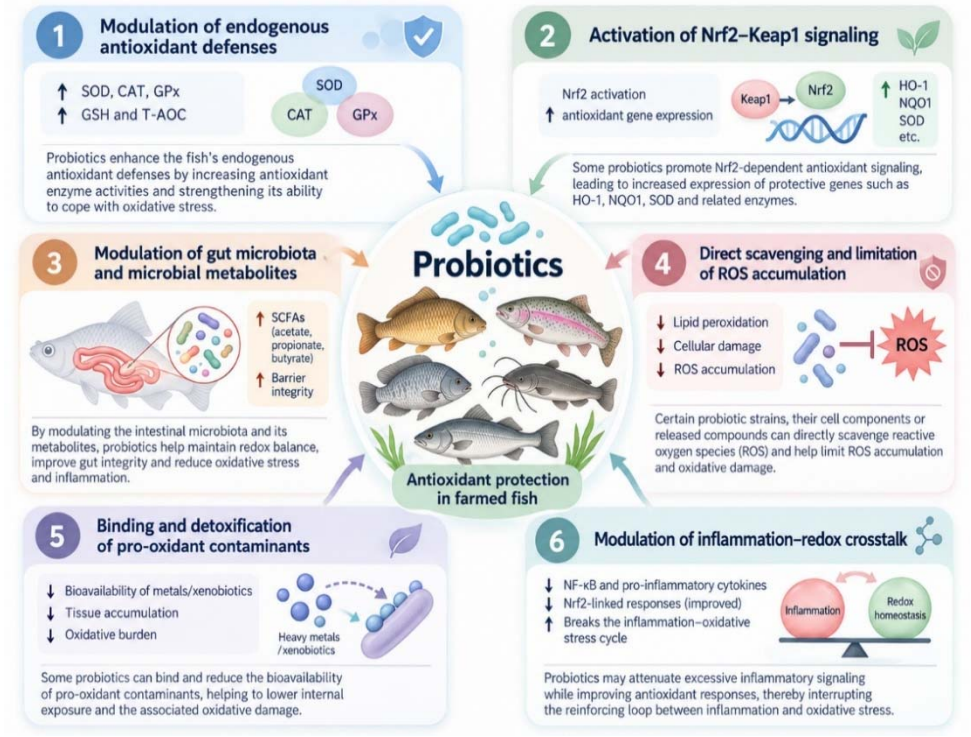


Figure 1. Proposed mechanisms of probiotic-mediated antioxidant protection in farmed fish.
Abbreviations: CAT, catalase; GPx, glutathione peroxidase; GSH, reduced glutathione; NF-κB, nuclear factor kappa B; Nrf2, nuclear factor erythroid 2-related factor 2; ROS, reactive oxygen species; SCFAs, short-chain fatty acids; SOD, superoxide dismutase; T-AOC, total antioxidant capacity.
Note: This figure was created with the assistance of generative AI and subsequently reviewed and edited by the authors.

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PROBIOTIC-MEDIATED ANTIOXIDANT PROTECTION UNDER MAJOR AQUACULTURE STRESSORS

Environmental stressors

Fish reared under intensive aquaculture conditions are frequently exposed to fluctuations in environmental parameters that can disturb physiological homeostasis and compromise health and performance [58]. Among the most relevant stressors are changes in water temperature, dissolved oxygen, pH, salinity and nitrogenous waste compounds such as ammonia and nitrite [2,58]. When these conditions exceed the adaptive capacity of the fish, they can promote excessive ROS production and disrupt cellular redox balance, leading to oxidative damage and impaired physiological function [2]. Because oxidative stress is a common component of the response to several environmental challenges, probiotics have increasingly been investigated as a nutritional strategy to improve antioxidant capacity and stress resilience under suboptimal rearing conditions [11].

Ammonia stress

Ammonia accumulation can disturb redox balance and promote oxidative damage in intensively farmed fish. In Nile tilapia, a *Bacillus subtilis–B. licheniformis* mixture improved antioxidant enzyme activity, reduced MDA and supported Nrf2-related responses during acute ammonia exposure [59]. Similar protection was observed in yellow catfish supplemented with *Lactobacillus amylovorus*, where lower ROS and MDA were accompanied by higher SOD, CAT, GSH and T-AOC, increased NRF2 and GPX4 protein expression, and improved survival [60]. Probiotic protection may also involve reducing the ammonia burden itself. Under chronic ammonia stress, *Cetobacterium somerae* ceto lowered serum and hepatic ammonia concentrations and promoted ureagenesis, while the stress-induced antioxidant response was reduced, consistent with lower oxidative pressure [61]. The magnitude of protection also appears to depend on probiotic strain and dose. Different *Bacillus subtilis* strains produced distinct responses in hybrid grouper exposed to ammonia-nitrogen stress [62], while *Lactobacillus paracasei* N1115 improved hepatic antioxidant status in hybrid sturgeon and increased subsequent survival during ammonia challenge, with the strongest response occurring at an intermediate dietary dose [63].

Hypoxia and thermal stress

Low dissolved oxygen and temperature fluctuations can rapidly alter fish metabolism and increase oxidative pressure. In rainbow trout exposed to acute hypoxia, dietary *Bacillus subtilis* MS.45 improved T-AOC and SOD and limited lipid peroxidation, together with changes in hypoxia-related signaling [64]. Similarly, *Bacillus amyloliquefaciens* AV5 enhanced CAT, SOD and T-AOC in Nile tilapia exposed to hypoxia as well as low- and high-temperature stress, with the higher dietary dose generally producing the strongest response [65].

Probiotic effects under thermal stress also appear to depend on dose and formulation. In heat-stressed Nile tilapia, a mixture of *B. subtilis*, *B. licheniformis* and *B. pumilus* reduced MDA and increased SOD and CAT, with the lower supplementation level showing the most consistent antioxidant response [66]. In the same species, supplementation with *Saccharomyces boulardii* and *Bifidobacterium bifidum* improved SOD, CAT and GPx activity, while the combined treatment was associated with higher survival following heat exposure [67]. In rohu maintained at 36°C, a multispecies probiotic containing *B. subtilis*, *Lactobacillus plantarum* and *L. buchneri* improved the expression of antioxidant-related genes, including *SOD* and *GPx* [68].

These findings support a protective role of probiotics under oxygen and temperature

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stress, while indicating that the magnitude of the response varies with probiotic composition, dose and stress conditions.

Salinity stress.

Salinity changes can disturb redox homeostasis by increasing the energetic demand for osmoregulation. In *Labeo rohita*, a multispecies probiotic containing *Bacillus subtilis*, *B. licheniformis* and *Clostridium butyricum* reduced oxidative stress and improved antioxidant defenses under 6 and 12 ppt salinity [69]. Similar protection was observed during long-term rearing at approximately 6.1 ppt, where supplementation reduced ROS and TBARS and supported SOD, CAT, POD and GSH responses [70]. In common carp, selenium-enriched *Lactobacillus plantarum* attenuated liver injury and modulated Nrf2-related antioxidant genes under salinity stress [71]. A subsequent study at 12 ppt also showed higher CAT, SOD, GSH-Px and T-AOC, lower MDA, and involvement of glutathione metabolism and ferroptosis-related pathways [72]. However, the effects cannot be attributed to the probiotic alone, since selenium was also an active component; therefore, the observed reduction in salinity stress likely reflects the combined action of the probiotic and selenium.

Additional challenge studies showed improved salinity tolerance in common carp supplemented with *Pediococcus acidilactici*, particularly when combined with formic acid [73], and in juvenile *Pagrus major* receiving *Bacillus amyloliquefaciens* [74]. Overall, probiotics appear to improve resilience to salinity stress, although differences in formulation and experimental design limit direct comparison among studies. To facilitate comparison across different challenge conditions, representative studies on probiotic-mediated antioxidant protection in farmed fish under major aquaculture stressors are summarized in Table 1

Table 1. Representative studies on probiotic-mediated antioxidant protection in farmed fish under major aquaculture stressors

Stressor	Fish species / probiotic	Challenge	Dose	Main antioxidant response		Reference
				Control	Probiotic	
Ammonia	*Oreochromis niloticus*	5 mg TAN/L, 72 h	0.012 g/m³ water	MDA ≈18.4 nmol/mL; GPx ≈12.2 U/mL; CAT ≈10.0 U/mL	MDA ≈14.4 nmol/mL; GPx ≈13.1 U/mL; CAT ≈10.4 U/mL	[59]
	B. subtilis + *B. licheniformis*					
	Pelteobagrus fulvidraco	125 mg/L TAN, 14 days	1 × 10⁸ CFU/g feed	MDA ≈11.0 nmol/mg protein; T-AOC ≈2.2 U/mg protein; SOD ≈41 U/mg protein; CAT ≈41 U/mg protein	MDA ≈7.5 nmol/mg protein; T-AOC ≈3.7 U/mg protein; SOD ≈46 U/mg protein; CAT ≈47 U/mg protein	[60]
	L. amylovorus					
	Pelteobagrus fulvidraco	25 mg/L TAN, 6 weeks	1 × 10⁸ CFU/mL water	T-AOC 12.70 ± 0.19 U/mL; SOD 61.69 ± 0.65 U/mL; CAT 16.68 ± 1.19 U/mL	T-AOC 2.10 ± 0.43 U/mL; SOD 52.81 ± 0.48 U/mL; CAT 13.67 ± 0.17 U/mL	[61]
	C. somerae ceto					
Hypoxia	*Oncorhynchus mykiss*	DO 2 mg/L, reached after ~6 min acute hypoxia	10⁹ CFU/g feed	T-AOC ≈1.7 mmol/mL; SOD ≈8.2 U/mg; MDA ≈50 nmol/g	T-AOC ≈2.2 mmol/mL; SOD ≈11.1 U/mg; MDA ≈35 nmol/g	[64]
	Bacillus subtilis MS.45					

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	Oreochromis niloticus *B. amyloliquefaciens AV5*	Hypoxia, 20 h	1 × 10^8 CFU/g feed	CAT 81.55 ± 2.10 U/mL; SOD 140.33 ± 1.30 U/mL; T-AOC 15.36 ± 1.20 U/mL	CAT 121.33 ± 3.60 U/mL; SOD 216.39 ± 2.60 U/mL; T-AOC 25.38 ± 1.60 U/mL	[65]
Heat stress	*Oreochromis niloticus* *B. subtilis + B. licheniformis + B. pumilus*	36 ± 0.5°C, 2 h	0.5 g/kg diet	Liver: MDA ≈89 nmol/mg protein; SOD ≈130 U/mg protein; CAT ≈4.5 U/mg protein	Liver: MDA ≈73 nmol/mg protein; SOD ≈180 U/mg protein; CAT ≈10 U/mg protein	[66]
Salinity	*Labeo rohita* *B. subtilis + B. licheniformis + C. butyricum*	12 ppt, 60 days	2% diet	Liver: ROS 0.40 ± 0.02; TBARS 37.06 ± 1.30; GSH 3.93 ± 0.09 µmol/g; SOD 3.25 ± 0.17 U/mg; CAT 3.23 ± 0.02 U/min	Liver: ROS 0.20 ± 0.06; TBARS 26.66 ± 1.52; GSH 4.95 ± 0.09 µmol/g; SOD 3.63 ± 0.01 U/mg; CAT 3.35 ± 0.05 U/min	[69]
	Cyprinus carpio *Se-enriched Lactobacillus plantarum*	12 ppt, 8 weeks	1 × 10^5 CFU/g feed + 1 ppm Se-NPs	Liver: SOD ≈98 U/mg; CAT ≈150 U/mg; GSH-Px ≈44 U/mg; T-AOC ≈3.5 U/mg; MDA ≈9.4 U/mg	Liver: SOD ≈145 U/mg; CAT ≈200 U/mg; GSH-Px ≈73 U/mg; T-AOC ≈5.8 U/mg; MDA ≈5.5 U/mg	[72]
Transportation	*Oreochromis niloticus* *B. subtilis + B. megaterium + B. licheniformis*	4 h transport	1 × 10^6 CFU/g preparation; 0.5 mL/L water weekly, 120 days	MDA at 72 h post-transport ≈ 90 µmol/L	MDA at 72 h post-transport ≈ 63 µmol/L	[75]
Crowding	*Cyprinus carpio* *L. acidophilus*	80% water-level reduction, 6 h	1.5 × 10^7 CFU/g feed, 60 days	MDA 45.23 ± 1.17 nmol/mL; SOD 24.66 ± 1.92 U/mL; CAT 100.00 ± 4.04 U/mL; GPx 132.00 ± 1.52 U/mL	MDA 39.13 ± 1.84 nmol/mL; SOD 26.43 ± 0.69 U/mL; CAT 114.70 ± 3.46 U/mL; GPx 139.00 ± 2.30 U/mL	[76]

Note: CAT – catalase; CFU – colony-forming units; DO – dissolved oxygen; GPx – glutathione peroxidase; GSH-Px – glutathione peroxidase; GSH – reduced glutathione; MDA – malondialdehyde; ppm – parts per million; ppt – parts per thousand; ROS – reactive oxygen species; Se-NPs – selenium nanoparticles; SOD – superoxide dismutase; T-AOC – total antioxidant capacity; TAN – total ammonia nitrogen; TBARS – thiobarbituric acid-reactive substances.

CHEMICAL STRESSORS

Heavy metal exposure

Heavy-metal exposure consistently disturbed antioxidant homeostasis across the available studies, although the magnitude and pattern of probiotic protection varied with the metal, tissue and formulation used. Cadmium provides the most coherent example. In common carp, *Bacillus coagulans* SCC-19 restored hepatic CAT, GSH-Px and SOD activities while reducing ROS and MDA and limiting Cd accumulation [19]. A second study with the same strain reproduced most of this pattern in the intestine, where SOD and CAT increased and both ROS and MDA

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decreased, although GSH-Px was not significantly improved [46]. The two studies therefore support a consistent protective effect, but they should not be viewed as fully independent confirmation because they used the same probiotic strain and host species. In *Luciobarbus capito*, selenium-enriched *Lactobacillus plantarum* also counteracted Cd-induced declines in CAT, SOD and GSH-Px and reduced MDA, while restoring Nrf2-related gene expression [77]. The broader molecular response observed here is noteworthy, but its interpretation is less straightforward because selenium itself contributes to antioxidant protection and its effect cannot be separated from that of the probiotic.

The Pb studies show a similarly consistent relationship between metal removal and antioxidant recovery, but with somewhat stronger cross-species support. In common carp, *Rhodobacter sphaeroides* SC01 reduced hepatic MDA by almost 50% and improved T-AOC, GSH-Px and SOD while simultaneously lowering Pb accumulation [49]. In grass carp, the same strain again reduced tissue Pb burden and MDA, while improving T-AOC, GSH-Px, CAT, SOD and GSH responses [50]. Compared with the Cd studies, this provides stronger evidence that the response can be reproduced across different cultured fish species. At the same time, both studies still rely on the same bacterial strain, so the available evidence supports the effectiveness of SC01 more clearly than it supports a general effect of probiotics against Pb.

Responses to Hg were more heterogeneous. Selenium-rich *Bacillus subtilis* improved several antioxidant indices in common carp, including SOD, CAT and GSH-related responses, and reduced MDA [78]. Unlike the selenium-enriched *L. plantarum* study, this experiment included separate Se and *B. subtilis* treatments, and the combined formulation produced stronger antioxidant-related changes than either component alone. This supports a combined effect, but still does not justify attributing the full response to the probiotic itself. A less conventional pattern was reported in African catfish, where *Lactococcus lactis* reduced Hg accumulation but increased both GSH and MDA relative to Hg-exposed fish [79]. This makes the antioxidant interpretation less clear than in the Cd and Pb studies. In Nile tilapia, however, a multispecies probiotic shifted Hg-induced SOD and CAT overexpression back toward control levels [80]. Rather than stimulating antioxidant defenses further, the probiotic appeared to reduce the oxidative pressure that had triggered their upregulation, illustrating that successful protection does not necessarily mean higher antioxidant enzyme expression.

Evidence for Cu and mixed-metal exposure is more limited, but it broadly fits the same pattern. In Nile tilapia, *Lactobacillus*-based supplementation reduced Cu accumulation and lowered gonadal MDA at the higher exposure levels [48]. In common carp exposed simultaneously to Cr, Cd and Cu, *Lactococcus lactis* was more effective than *Enterococcus faecium* or the combined treatment in reducing metal accumulation and was associated with the lowest MDA levels across several tissues [47]. Interestingly, lower SOD values were also observed in the *L. lactis* group and were interpreted by the authors as reflecting reduced ROS generation rather than impaired antioxidant capacity, again showing that antioxidant protection should not be judged solely by increases in enzyme activity.

Altogether, the studies point to a common outcome rather than a single antioxidant mechanism: probiotics tend to reduce metal accumulation and lipid peroxidation while shifting antioxidant responses toward a less stressed state. This pattern is most consistent for Cd and Pb,

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whereas the Hg data are more variable and more sensitive to formulation and biomarker selection. The current evidence is also limited by repeated use of the same probiotic strains, the predominance of cyprinid models and, in some of the strongest studies, the inclusion of selenium as an additional active component.

Pesticide exposure

Pesticide-induced oxidative stress shows a less uniform response to probiotic supplementation than heavy-metal toxicity, particularly because the direction of antioxidant change differs markedly among compounds and experimental models. Among organophosphates, chlorpyrifos provides a clear example of partial rather than complete protection. In common carp, exposure reduced SOD, GPx and GR activities and total antioxidant capacity while increasing MDA, whereas Protexin restored SOD and GR and lowered lipid peroxidation without fully recovering GPx or CAT [81]. The effect also depended on exposure intensity, as some protective responses became less evident at the higher chlorpyrifos concentration, suggesting that probiotic efficacy may decline as toxic pressure increases.

Two studies with Sumithion further illustrate why increased antioxidant activity cannot always be interpreted as the expected sign of protection. In striped catfish, a sublethal exposure of 0.6 mg/L, approximately one tenth of the reported 96-h LC_{50}, increased GPx expression but suppressed SOD and CAT. The multispecies probiotic restored SOD toward control values and prevented the increase in GPx, whereas CAT showed only partial recovery [82]. In Nile tilapia, however, Sumithion produced the opposite transcriptional pattern, with marked upregulation of SOD and CAT, while probiotic treatment reduced both toward control levels [83]. Rather than being contradictory, these findings suggest that probiotics may either reinforce impaired antioxidant defenses or reduce the need for compensatory antioxidant activation, depending on how the pesticide initially disturbs redox homeostasis.

Malathion adds another dimension because protection was evaluated during both exposure and recovery. At 0.5 × LC_{50}, malathion increased serum MDA and suppressed *sod-2* and *cat* expression in the liver, spleen and intestine of Nile tilapia [84]. Probiotic-fed fish showed stronger antioxidant gene expression during exposure and lower MDA during recovery. Nevertheless, untreated fish also returned toward control values after pesticide withdrawal, meaning that the probiotic accelerated and strengthened recovery rather than being solely responsible for it. The relatively severe challenge is also relevant: although formally sublethal, 0.5 × LC_{50} produced appreciable mortality, showing that "sublethal" exposure does not necessarily represent mild oxidative stress.

Responses to other insecticides were similarly incomplete or endpoint-dependent. In African catfish exposed for 30 days to thiamethoxam at 0.5 × LC_{50}, *Bacillus subtilis* reduced the pesticide-induced increases in MDA and GST, but neither marker returned fully to control levels [85]. The magnitude of protection was also comparable to that obtained with *Thymus vulgaris* essential oil tested in parallel, so the experiment supports a protective probiotic effect without demonstrating clear superiority over other dietary interventions. Fipronil produced a different pattern in Nile tilapia, increasing hepatic SOD expression while suppressing GPx in a concentration-dependent manner [86]. *Saccharomyces cerevisiae* clearly ameliorated several physiological and histological effects of fipronil, but the antioxidant evidence itself is less robust because it relies mainly on transcriptional endpoints and does not demonstrate the same clear restoration across both antioxidant genes.

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Differences in efficacy are also evident among studies using defined fractions of LC_{50}. In common carp challenged with acetamiprid at 25% of LC_{50}, dietary *Lactobacillus sakei* increased SOD activity, especially at the higher probiotic dose, but changes in MDA and GPx were modest and CAT remained unaffected [87]. Hawthorn extract tested in the same experiment produced a clearer reduction in lipid peroxidation and stronger GPx responses, indicating that the antioxidant contribution of the probiotic was comparatively limited. In rainbow trout exposed to butachlor at only 12.5% of LC_{50}, the same probiotic species produced a more coherent antioxidant response: SOD recovered to values comparable with the control and MDA fell markedly below the butachlor-only group, whereas CAT showed little additional improvement [88]. The contrast between these two studies is notable because it suggests that even the same probiotic species does not produce a fixed antioxidant profile; pesticide identity and challenge intensity appear to matter as much as the probiotic itself.

Herbicide studies provide stronger evidence for specific molecular pathways. In Nile tilapia challenged with glyphosate at 1/20 of LC_{50}, following an eight-week feeding period, *S. cerevisiae* reversed the suppression of hepatic *nrf2* and *sod* and counteracted the increase in *keap1* [89]. This points more directly toward Nrf2/Keap1 regulation, although the antioxidant assessment remained predominantly molecular. Mechanistic support is strengthened by a recent zebrafish study using an environmentally relevant permethrin concentration corresponding to 1/20 of the 96-h LC_{50} [53]. Permethrin increased ROS and MDA while reducing T-AOC, SOD, CAT and GSH-Px; viable *Lactobacillus casei* restored these indices in a dose-dependent manner and also reactivated AKT/Nrf2 signaling and the GPX4/SLC7A11 ferroptosis-protective axis. Importantly, heat-killed bacteria failed to reproduce the effect, providing unusually direct evidence that probiotic viability contributed to protection.

A consistent picture emerges in which probiotic protection against pesticide-induced oxidative stress is evident, but strongly conditioned by the intensity and design of the toxic challenge. Most studies deliberately used sublethal exposures, ranging from approximately 1/20 to 1/2 of the reported LC_{50}, rather than truly lethal concentrations. At the lower end of this range, such as glyphosate, permethrin and butachlor, probiotic supplementation frequently restored antioxidant indices close to control values. At higher fractions of LC_{50}, protection was more often partial, as seen with thiamethoxam and malathion, while the chlorpyrifos study similarly showed weaker protection at the higher pesticide concentration. This pattern should nevertheless be interpreted cautiously, since exposure duration, pesticide chemistry, tissue and endpoint differ substantially among experiments and prevent a direct dose-response comparison across studies. What is more consistent is that probiotic protection does not always manifest as increased antioxidant activity: depending on the initial toxic response, successful intervention may restore suppressed defenses, reduce lipid peroxidation, or normalize compensatory enzyme overexpression. Future comparisons would therefore benefit from standardized sublethal challenge levels and simultaneous assessment of oxidative damage, enzyme activity and antioxidant signaling rather than reliance on a single biomarker.

Other aquatic contaminants

Emerging aquatic contaminants provide additional evidence that probiotic-mediated antioxidant protection is highly dependent on the nature and duration of the toxic challenge. Micro- and nanoplastics are currently the most extensively investigated within this group, but even closely related

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plastic particles do not elicit a uniform antioxidant response. In Nile tilapia exposed to 1 mg/L PS microplastics, hepatic SOD, CAT, GST and GPx activities increased markedly, while plasma MDA increased and total antioxidant capacity declined [90]. Pretreatment with the multispecies AquaStar® Growout probiotic at 3 or 6 g/kg reduced MDA, restored T-AOC and moderated the excessive antioxidant enzyme response, with the higher inclusion level also producing the clearest histological protection. The reduction in enzyme activities toward control values therefore appears to reflect relief of the oxidative challenge rather than suppression of antioxidant capacity, particularly because it occurred together with lower lipid peroxidation and improved liver integrity. The probiotic contained viable *Bacillus subtilis, Enterococcus faecium, Lactobacillus reuteri* and *Pediococcus acidilactici*, with the two dietary treatments corresponding to approximately 4.3×10^8 and 7.5×10^8 CFU/g diet. A less complete response was observed in grass carp exposed to polystyrene nanoplastics. Fish were pre-fed *B. subtilis, B. velezensis, L. reuteri* or *Lactococcus lactis* at 5×10^8 CFU/g before a five-day exposure to 100 µg/L PS-NPs [91]. Probiotic-treated fish initially showed increased CAT, SOD and MPO activities, but this antioxidant advantage diminished as exposure continued. *B. velezensis* and *L. lactis* produced the clearest reduction in intestinal damage, yet protection against oxidative stress and microbiota disruption remained incomplete. This temporal pattern is particularly relevant because it suggests that probiotic pretreatment can strengthen the early antioxidant response without necessarily maintaining complete protection during continued nanoplastic exposure. Thus, persistence of the contaminant may be as important as probiotic strain selection in determining the final redox outcome. A similar normalization of stress-induced antioxidant activation was reported in Nile tilapia exposed for six weeks to 10 mg/L polyamide microplastics. In this model, microplastic exposure markedly increased hepatic *sod* and *cat* expression, whereas the multispecies probiotic returned both transcripts to values statistically comparable with the control [92]. As observed with some pesticide challenges, this reduction should not be interpreted as inhibition of antioxidant defense. Instead, the return of SOD and CAT expression toward basal levels, together with improvement in other stress-related and intestinal endpoints, is more consistent with normalization of a compensatory antioxidant response once the severity of the challenge was reduced.

Plastic-associated chemicals can produce the opposite antioxidant pattern. In crucian carp (*Carassius auratus*) exposed to 1 µmol/L mono-(2-ethylhexyl) phthalate (MEHP) for 30 days, CAT, GSH-Px and T-SOD activities were significantly suppressed while MDA increased, indicating direct impairment of hepatic antioxidant defenses rather than compensatory activation [93]. Dietary *Lactobacillus brevis* Lb-0401 reversed this pattern, restoring antioxidant enzyme activities toward control values and reducing lipid peroxidation, alongside substantial improvement in liver morphology and metabolic alterations. This contrasts with the microplastic models above and reinforces the idea that successful probiotic protection may appear either as attenuation of excessive antioxidant activation or as restoration of previously suppressed defenses, depending on the initial redox disturbance produced by the contaminant.

Engineered nanomaterials extend this response beyond the liver and intestine. In common carp exposed orally to carbon quantum dots (CQDs), brain SOD and GSH-Px activities declined while MDA

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increased, together with histological brain damage, impaired blood–brain barrier integrity and behavioral disturbances [94]. Probiotic supplementation with *L. acidophilus, B. subtilis* and *Phaffia rhodozyma* attenuated these changes and also reduced the associated inflammatory, apoptotic and microbiota disturbances. The study therefore links antioxidant protection with the broader microbiota–gut–brain axis rather than treating oxidative stress as an isolated response. However, CQDs were administered by repeated oral gavage at 20 mg/kg body weight for five weeks, making this model more useful for identifying protective mechanisms than for estimating the magnitude of protection under typical waterborne exposure conditions.

A recent study with cadmium telluride quantum dots provides an even broader multi-organ perspective. Common carp exposed to 1 or 10 mg/kg body weight CdTe QDs showed reduced SOD activity and GSH, increased MDA and suppression of Nrf2/HO-1 signaling in the intestine, liver and brain [95]. The consistency of the response across several organs strengthens the mechanistic link between probiotic-mediated redox regulation and preservation of barrier function. Nevertheless, the exposure doses were deliberately selected to induce measurable subchronic toxicity without acute lethality, and the authors themselves note the uncertainty surrounding environmentally realistic concentrations of quantum dots. Accordingly, the CdTe QD model is particularly informative at the mechanistic level, especially with regard to Nrf2/HO-1 signaling and barrier protection, whereas its relevance to field exposure remains uncertain because the doses were selected to produce measurable subchronic toxicity under controlled conditions.

Across the available studies, probiotic-mediated redox protection appears to be highly context-dependent rather than uniformly stimulatory. Microplastic exposure often elicited compensatory activation of antioxidant defenses, which probiotics subsequently brought closer to basal levels, whereas MEHP and quantum dots primarily suppressed enzymatic defenses and increased lipid peroxidation, requiring restoration of antioxidant capacity. The persistence of the challenge also influenced efficacy: early or shorter-term responses could approach control values, while prolonged nanoplastic exposure remained only partially corrected. Differences in exposure route and contaminant burden further limit direct comparison, particularly for orally administered nanomaterials. The most convincing evidence therefore comes from studies in which changes in oxidative damage markers are accompanied by coordinated recovery of antioxidant enzymes, signaling pathways and tissue integrity, rather than from the direction of any single biomarker alone. Table 2 provides an overview of the main antioxidant responses associated with probiotic supplementation under different chemical stressors.

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Table 2. Representative studies on probiotic-mediated antioxidant protection in farmed fish under major chemical stressors

Stressor	Fish species / probiotic	Challenge	Dose	Main antioxidant response		Reference
				Control	Probiotic	
Cadmium	*Cyprinus carpio* / *Bacillus coagulans* SCC-19	0.5 mg/L Cd, 60 days	1 × 10^8 CFU/g feed	Liver: SOD ≈100 U/mg protein; CAT ≈32 U/mg; GSH-Px ≈28 U/mg; MDA ≈23 nmol/mg	Liver: SOD ≈170 U/mg; CAT ≈62 U/mg; GSH-Px ≈55 U/mg; MDA ≈13 nmol/mg	[19]
Chromium + Cadmium + Copper	*Cyprinus carpio* / *Lactococcus lactis*	0.8 mg/L Cr + Cd + Cu mixture, 28 days	>1 × 10^7 CFU/g feed	Kidney: SOD ≈34 U/mg protein; MDA ≈35 nmol/mg protein	Kidney: SOD ≈22 U/mg; MDA ≈18 nmol/mg	[47]
Lead	*Cyprinus carpio* / *Rhodobacter sphaeroides* SC01	1 mg/L Pb, 50 days	1 × 10^8 CFU/g feed	MDA ≈0.62 nmol/mg protein; T-AOC ≈0.30 U/mg protein; GSH-Px ≈35 U/mg protein; SOD ≈180 U/mg protein	MDA ≈0.32 nmol/mg protein; T-AOC ≈0.60 U/mg protein; GSH-Px ≈45 U/mg protein; SOD ≈210 U/mg protein	[49]
Copper	*Oreochromis niloticus* / *Lactobacillus*-based probiotic	3 mg/L Cu, 15 days	25 mL/kg feed (1 × 10^8 CFU/mL)	Gonad MDA 1.54 ± 0.01 μM/mL	Gonad MDA 1.42 ± 0.01 μM/mL	[48]
Mercury	*Oreochromis niloticus* / *B. subtilis* + *L. plantarum* + *L. buchneri*	0.03 mg/L Hg, 42 days	1.0 mL/L water	CAT mRNA ≈1.25-fold; SOD mRNA ≈1.50-fold	CAT mRNA expression ≈0.83-fold; SOD mRNA expression ≈1.15-fold	[80]
Chlorpyrifos	*Cyprinus carpio* / Protexin	40 μg/L chlorpyrifos, 30 days	4 × 10^9 cells/g feed	SOD ≈0.65 U/g protein; MDA ≈9.6 μmol/g tissue; TAO ≈135 μmol/g protein	SOD ≈1.48 U/g protein; MDA ≈4.0 μmol/g tissue; TAO ≈175 μmol/g protein	[81]
Sumithion	*Pangasianodon hypophthalmus* / *B. subtilis* + *L. plantarum* + *L. buchneri*	0.6 mg/L Sumithion, 42 days	1 mL/L water	GPx mRNA ≈3.4-fold; SOD mRNA ≈0.6-fold; CAT mRNA ≈0.1-fold	GPx mRNA ≈1.5-fold; SOD mRNA ≈1.1-fold; CAT mRNA ≈0.4-fold	[82]
Thiamethoxam	*Clarias gariepinus* / *Bacillus subtilis*	5 mg/L TMX, 30 days	1000 ppm feed	MDA 37.13 ± 1.11 U/mL; GST 29.61 ± 1.85 U/mL	MDA 27.65 ± 0.47 U/mL; GST 22.58 ± 1.61 U/mL	[85]
Polystyrene microplastics (PS-MPs)	*Oreochromis niloticus* / *B. subtilis* + *E. faecium* + *L. reuteri* + *P. acidilactici*	1 mg/L, 0.5 μm PS-MPs, 14 days	6 g/kg feed (7.5 × 10^8 CFU/g diet)	Liver SOD ≈75 U/mg protein; CAT ≈7.7 U/mg protein; plasma MDA ≈6.0 μM	Liver SOD ≈37 U/mg protein; CAT ≈3.8 U/mg protein; plasma MDA ≈3.4 μM	[90]
Polystyrene nanoplastics (PS-NPs)	*Ctenopharyngodon idella* / *Bacillus velezensis*	100 μg/L PS-NPs, 5 days after 14-day probiotic pre-feeding	5 × 10^8 CFU/g feed	At 24 h: intestinal CAT ≈11 U/mg protein	At 24 h: CAT ≈14 U/mg protein; antioxidant advantage declined with prolonged exposure	[91]
Polyamide microplastics (PA-MPs)	*Oreochromis niloticus* / *B. subtilis* + *L. plantarum* + *L. buchneri*	10 mg/L PA-MPs, 42 days	1 mL/L water	SOD mRNA ≈3.0-fold; CAT mRNA ≈2.9-fold	SOD mRNA ≈1.6-fold; CAT mRNA ≈1.1-fold	[92]

Note: CAT – catalase; CFU – colony-forming units; GPx – glutathione peroxidase; GSH-Px – glutathione peroxidase; GST – glutathione S-transferase; MDA – malondialdehyde; mRNA – messenger RNA; SOD – superoxide dismutase; T-AOC – total antioxidant capacity; TAO – total antioxidant capacity; TMX – thiamethoxam; PS-MPs – polystyrene microplastics; PS-NPs – polystyrene nanoplastics; PA-MPs – polyamide microplastics; Cd – cadmium; Cr – chromium; Cu – copper; Pb – lead; Hg – mercury.

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CONCLUSIONS

Current evidence supports probiotics as promising modulators of redox homeostasis in farmed fish, but their antioxidant effects cannot be reduced to a uniform increase in antioxidant enzyme activity. Depending on the nature and intensity of the challenge, probiotic supplementation may restore suppressed antioxidant defenses, reduce lipid peroxidation and ROS accumulation, or normalize compensatory overactivation of antioxidant enzymes once oxidative pressure is alleviated. These responses are strongly influenced by probiotic strain and dose, host species, tissue, administration strategy, exposure duration and the specific stressor involved. Consequently, antioxidant protection is best evaluated through coordinated changes in oxidative damage markers, enzymatic and non-enzymatic defenses, molecular signaling and tissue integrity rather than through the direction of a single biomarker.

The available evidence indicates that probiotic-mediated protection involves complementary mechanisms, including modulation of endogenous antioxidant systems, regulation of Nrf2–Keap1 signaling, remodeling of the gut microbiota and its metabolites, reduction of contaminant bioavailability, and interaction with inflammation–redox pathways. Direct radical-scavenging activity may also contribute, although its importance in vivo remains less clearly established. Responses to pesticides, micro- and nanoplastics and other emerging contaminants remain more heterogeneous and are frequently incomplete. Future studies should prioritize standardized challenge models, clearly characterized viable probiotic strains, environmentally relevant exposure levels, integrated biochemical and molecular assessment, causal mechanistic approaches and farm-scale validation. Overall, probiotics represent a promising component of oxidative-stress management in aquaculture, but their efficacy should be regarded as strain-, dose- and context-dependent rather than as a universal antioxidant effect.

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