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Hormesis in metal oxide nanoparticles: a review of efficacy in controlling infectious agents and toxicology in aquatic organisms

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Abstract

The aquaculture industry faces persistent threats from bacterial (*Aeromonas hydrophila* and *Streptococcus iniae*) and fungal (*Fusarium solani*) pathogens. Metal oxide nanoparticles, particularly copper oxide (CuO NPs) and zinc oxide (ZnO NPs), have emerged as promising broad-spectrum antimicrobial agents. *In vitro* studies demonstrated potent antimicrobial activity, with CuO NPs showing superior efficacy against *F. solani*. However, *in vivo* investigations revealed a critical limitation: the effective dose falls dangerously close to the lethal dose for host organisms. In crustacean models, the therapeutic : lethal dose ratio approached 1:1, with dose increases from 25 to 40 mg/l reducing survival from 93.3% to 66.7%. Similarly, in fish models, minimum inhibitory concentrations (MIC) overlap with lethal concentration ranges. This narrow therapeutic window, characteristic of an inverted bell-shaped dose-response relationship, currently precluded systemic use of free nanoparticles. However, non-systemic applications, including short-term baths, dietary supplementation, and filter loading, may represent safer alternatives. Overall, the available evidence indicated that CuO NPs and ZnO NPs have strong antimicrobial potential but may also cause dose-dependent toxicity, highlighting the importance of controlling exposure and optimizing formulation. Future research should focus on surface engineering, biocompatible coatings, oral formulations, and comprehensive ecological risk assessment.

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Introduction

The aquaculture industry, as one of the pillars of food security, is constantly threatened by infectious agents including bacterial, viral, parasitic, and fungal pathogens. Disease-causing agents such as *Fusarium solani* (the causative agent of fusariosis in crustaceans), *Aeromonas hydrophila*, and *Streptococcus iniae* (agents of septicemia in fish) are considered serious challenges in this field (Salighehzadeh *et al.,* 2019; Shiry and Akhlaghi, 2026). Numerous reports of fungal fusariosis infections in various crab species have been documented (Melendre *et al.,* 2006; Mahmoud, 2019). Moreover, the concurrent infection of *F. solani* and *A. hydrophila* in the freshwater long-arm crab in Iran has been reported for the first time (Salighehzadeh *et al.,* 2019). *Fusarium* infections, particularly fusariosis caused by the *F. solani* species complex, along with other opportunistic pathogens that induce severe inflammatory responses and tissue melanization (blackening) in crustaceans, have been recognized over the past two decades as among the most significant infectious diseases. Due to their high virulence, these infections can lead to substantial mortality, population decline in susceptible hosts, and even extinction (Fisher *et al.,* 2012).

Conventional disinfectants such as formalin, chloramine-T (sodium tosylchloramide), potassium permanganate, methylene blue, and malachite green, although effective (Chacko and Sekharan, 2022; Siramshetty *et al.,* 2022), are associated with issues including toxicity to aquatic organisms and consumers, occupational hazards, environmental residues, and the emergence of drug resistance (Melendre *et al.,* 2006; Yang *et al.,* 2025). Formalin remains widely used as an effective fungicide in aquaculture. The U.S. Food and Drug Administration has approved the use of formalin in water baths for controlling external parasites on fish and shrimp, as well as certain fungal infections on fish eggs (FDA, 2025). However, due to its cytotoxicity and carcinogenic effects, its use is legally restricted in many countries, making the search for safer alternatives a necessity (Melendre *et al.,* 2006; Kouba *et al.,* 2010). These limitations have created strong motivation to identify safer and more effective substitutes (Swain *et al.,* 2014).

Nanotechnology, through the introduction of metal oxide nanoparticles, has opened a new horizon in this field. Due to their small size (below 100 nm) and high surface-to-volume ratio, nanoparticles exhibit exceptional chemical and biological reactivity (Shiry and Akhlaghi, 2026). In recent years, metal nanoparticles have emerged as novel antimicrobial agents with high potential for use in aquaculture (Swain *et al.,* 2014). Copper oxide (CuO NPs) and zinc oxide nanoparticles (ZnO NPs) are among the most extensively studied nanoparticles, owing to their broad-spectrum antimicrobial activity, thermal stability, and relatively low production cost, making them highly promising for aquaculture applications (Shiry and Akhlaghi, 2026). CuO NPs, due to their high surface-to-volume ratio and ability to release copper ions, have demonstrated notable antibacterial and antifungal activities (Ramezani *et al.,* 2020; El-Abeid *et al.,* 2024). ZnO NPs have also shown significant reduction in fungal growth in studies on crabs infected with *F. solani* (Mahmoud, 2019).

Despite the growing number of studies investigating disinfectants and nanoparticles against aquatic pathogens, the available evidence remains scattered across different pathogens, nanoparticle types, aquatic species, and experimental conditions. Accordingly, this review summarizes and critically discusses the available evidence on the antimicrobial efficacy, toxicity, dose-response characteristics, and potential applications of metal oxide nanoparticles, particularly CuO NPs and ZnO NPs, in aquaculture. Particular attention was given to the relationship between antimicrobial efficacy and host toxicity, with the aim of identifying potential applications and the major limitations that should be addressed before practical use.

In vitro efficacy: overcoming infectious agents

In a study on bacterial pathogens of fish, the susceptibility of *S. iniae, Lactococcus garvieae, Yersinia ruckeri*, and *A. hydrophila* to CuO NPs and ZnO NPs was evaluated using well-diffusion and microdilution methods (Shiry and Akhlaghi, 2026). The findings indicated that CuO NPs and ZnO NPs significantly inhibited the growth of *S. iniae* at concentrations of 0.18 and 0.24 µg/ml and above. This level of efficacy was comparable to that of the reference antibiotic florfenicol. Based on the findings of that study, the primary

mechanism of CuO NPs and ZnO NPs is the disruption of the cell wall, and Gram-negative bacteria exhibit greater susceptibility to this destructive mechanism (Heinlaan *et al.,* 2008). The metal nanoparticles examined possessed growth-inhibitory capacity against the target bacteria, and by killing them through cell wall disruption, alteration of osmotic pressure, and the resulting plasmolysis, they contribute to the control of biofilm populations.

A comparison of the minimum inhibitory concentration (MIC) values of ZnO NPs for *S.iniae* reported by Mohammadbeigi *et al*. (2016) with similar quantitative measurements indicates that the strain isolated from northern regions of the country (Tehran, Mazandaran, and Golestan provinces) exhibited greater sensitivity than the isolate from Fars province.

In a study conducted on the freshwater long-arm crab, the efficacy of seven different compounds-including potassium permanganate, sodium chloride, methylene blue, chloramine-T, 37% formalin, ketoconazole, and CuO NPs-was compared against a clinical isolate of *F. solani* using the disk diffusion method at a concentration of 50 ppm (Shiry *et al.,* 2026). The results clearly demonstrated the superiority of CuO NPs. Copper nanoparticles produced an inhibition zone of 28.5 mm, showing markedly better performance than all conventional compounds. This finding confirms the intrinsic resistance of *Fusarium* species to this class of drugs (Yang *et al.,* 2025) and further highlights the necessity of identifying new alternatives. It is also fully consistent with previous studies reporting significant antifungal activity of CuO NPs against *Fusarium* isolates (Ramezani *et al.,* 2020; Kamel *et al.,* 2022; El-Abeid *et al.,* 2024). In a study evaluating the antifungal activity of CuO NPs against *F. solani*, it was shown that the fungus exhibited greater sensitivity at concentrations above 50 mg/ml, with an inhibition zone of 18 mm at 100 mg/ml (Ramezani *et al.,* 2020). Additionally, CuO NPs synthesized using *Zizyphus spina* leaf extract demonstrated notable antifungal activity against this fungus (El-Abeid *et al.,* 2024).

The superiority of CuO NPs can be attributed to their dual mechanism of action: first, the release of copper ions (Cu^{2+}), which generate reactive oxygen species (ROS) that damage the fungal cell membrane and cause leakage of cytoplasmic contents; second, the direct interaction of nanoparticles with the fungal cell wall due to their high surface-to-volume ratio, which disrupts membrane permeability (Shiry and Akhlaghi, 2020; Shiry *et al.,* 2026). These features make CuO NPs as an attractive alternative to conventional compounds, especially considering the increasing resistance of *F. solani* to azole drugs such as ketoconazole, which poses serious concerns in the aquaculture industry (Yang *et al.,* 2025).

Literature search and review approach

This review was developed to summarize and critically discuss available evidence on the antimicrobial efficacy, toxicity, dose-response characteristics, and potential applications of metal oxide nanoparticles, particularly CuO NPs and ZnO NPs, in aquatic organisms. Relevant studies addressing aquatic pathogens, antimicrobial activity, toxicity, therapeutic and lethal concentrations, dose-response relationships, and nutritional or non-systemic applications were considered. Particular attention was given to experimental studies involving fish and crustacean models and to studies evaluating CuO and ZnO nanoparticles. The available evidence was organized thematically according to antimicrobial efficacy, toxicity, hormesis and dose-response characteristics, nutritional applications, and potential practical applications. Because this article is a narrative review rather than a systematic review with a predefined protocol and formal screening process, PRISMA-based study selection and quantitative meta-analysis were not performed.

Toxicity mechanisms in the host

Nanoparticle toxicity in the host primarily arises from the same potent antimicrobial mechanisms. Excessive ROS production in vital tissues such as the gills and hepatopancreas leads to lipid peroxidation, DNA damage, and protein denaturation (Khosravi-Katuli *et al.,* 2018). The resulting acute inflammatory response and oxidative stress explain the observed clinical signs, including lethargy, abnormal swimming, increased mucus secretion, and ultimately death (Shiry and Akhlaghi, 2020).

Numerous studies have shown that metal oxide nanoparticles can induce toxic effects in aquatic organisms and disrupt ecological balance (Adam *et al.,* 2015; Khosravi-Katuli *et al.,* 2018). Their toxicity depends on factors such as the type of metal oxide, nanoparticle size, surface charge, and behavior in aquatic environments (Adam *et al.,* 2015). Review studies have indicated that silver nanoparticles exhibit the highest toxicity among nanoparticles, followed by zinc oxide, copper, copper oxide, and titanium dioxide (Swain *et al.,* 2014; Khosravi-Katuli *et al.,* 2018).

The most significant pathological complication observed in poisoned fish and crabs is respiratory impairment, which can be the primary cause of mortality (Shiry and Akhlaghi, 2020; Shiry *et al.,* 2026). This has been confirmed in previous studies demonstrating changes in gill filament morphology and suppression of ion-transport gene expression in zebrafish gill cells (Griffitt *et al.,* 2009), bioaccumulation in the primary gill lamellae of rainbow trout (Scown *et al.,* 2010), physiological hypoxia in European perch (Bilberg *et al.,* 2010), inhibition of Na^+/K^+-ATPase in zebrafish gill cells (Khosravi-Katuli *et al.,* 2014), and severe fusion of secondary lamellae in Caspian kutum (Khosravi-Katuli *et al.,* 2018).

The contradiction between efficacy and toxicity

The most critical-and perhaps alarming-aspect of the studies lies in the *in vivo* findings. At this stage, it becomes evident that the potent antimicrobial activity observed in laboratory plates does not necessarily translate into a successful and safe treatment within a living organism (Shiry and Akhlaghi, 2020; Shiry *et al.,* 2026).

The concept of a "narrow therapeutic window"

The most prominent concept emerging from the studies is the "narrow therapeutic window." This refers to the small gap between the effective therapeutic dose and the toxic dose. In simple terms, the dose that kills the pathogen is not far from the dose that poisons the host (Shiry and Akhlaghi, 2020).

Crustacean model (Shiry *et al.*, 2026): In the acute toxicity test, the 24-hour median lethal concentration (LC_{50}-24 hours) of CuO NPs was calculated as 44.5 mg/l. Meanwhile, the effective *in vitro* concentration was approximately 50 mg/l. This near 1:1 ratio was a serious warning sign. In the therapeutic experiment, a dose of 25 mg/l was identified as the optimal point, resulting in 93.3% survival. However, increasing the dose to 40 mg/l (still below the LC_{50}) not only failed to improve efficacy but, due to toxicity, reduced survival to 66.7% and increased lesion severity. In the crab model, the observed nonlinear dose-response pattern was consistent with an inverted bell-shaped response; however, this observation was based on a single experimental study and should not be generalized across aquatic organisms.

Fish model (Shiry and Akhlaghi, 2020): A similar pattern was observed. The LC_{50}-96 hours values for CuO NPs and ZnO NPs were reported as 102.3 and 107.4 µg/l, respectively. Comparing these values showed that, unlike their antibacterial effect, CuO NPs possess greater toxic capacity. Although these concentrations were very low, their MIC values against bacteria fall within the same range or even lower. This dangerous overlap confirmed that direct use of nanoparticles for treating systemic infections in fish can rapidly lead to fatal poisoning. The researchers explicitly warned that applying the effective concentration of these nanoparticles could cause mortality due to toxicity in fish (Table 1).

The hormesis phenomenon

One of the notable phenomena in nanoparticle toxicity studies is hormesis. Hormesis refers to a biphasic dose-response in which low doses of a toxic substance may have beneficial or stimulatory effects, whereas high doses are harmful (Calabrese and Baldwin, 2002). Recent studies have shown that nanoparticles can induce hormesis-like biphasic responses in a wide range of biological cell types, and these responses can be highly dependent on the physicochemical properties of the agent (Iavicoli *et al.,* 2014). In aquatic ecosystems, hormetic effects may occur at low doses and promote organismal growth rather than causing harm. This phenomenon adds further complexity to ecological risk assessment of nanoparticles (Iavicoli *et al.,* 2018).

In the crab study, the response pattern to CuO NPs deviated from classical sigmoidal curves and followed an inverted bell-shaped curve with high determination coefficients for survival (R^2 = 0.91) and lesion severity (R^2 = 0.89) (Shiry *et al.,* 2026). This nonlinear, dose-dependent pattern-where 25 ppm emerged as the optimal point with 93.3% survival, but 40 ppm resulted in reduced survival (66.7%) and increased lesion severity-indicated the presence of a narrow therapeutic window. The steep slope between 25 and 40 ppm (a 26.6% drop in survival) showed that even minimal dose increases near the toxicity threshold can have irreversible consequences. This phenomenon was likely due to oxidative stress and inflammatory responses triggered by copper ion accumulation in gill and hepatopancreatic tissues at higher doses.

Table 1. Study nanoparticle model/target main finding Key safety finding.

Study	Nanoparticle	Model/Target	Main finding	Key safety finding
Shiry and Akhlaghi (2020)	CuO NPs	Rainbow trout / bacterial pathogens	Demonstrated antibacterial activity against fish pathogens	LC_{50}-96 hours: 102.3 µg/l
Shiry and Akhlaghi (2020)	ZnO NPs	Rainbow trout / bacterial pathogens	Demonstrated antibacterial activity against fish pathogens	LC_{50}-96 hours: 107.4 µg/l
Shiry *et al.* (2026)	CuO NPs	*Astacus leptodactylus* / *Fusarium solani*	25 mg/l produced effective control with 93.3% survival	LC_{50}-24 hours: approximately 44.5 mg/l
Swain *et al.* (2014)	ZnO NPs	Nile tilapia / *Citrobacter freundii*	200 mg/kg feed reduced mortality to 10% and RPS reached 80%	No histopathological alterations reported at this dose
Rehman *et al.* (2026)	CuO NPs + vitamin C	Indian carp	Vitamin C partially mitigated CuO NP-related adverse effects	Suggests potential for reducing nanoparticle-associated toxicity

Integrated analysis and model comparison

Comparing studies across two different animal models revealed valuable insights:

(1) The problem of pervasive toxicity: The issue of a narrow therapeutic window is not limited to a single aquatic species or nanoparticle type. Whether in bony fish (rainbow trout) or crustaceans (crabs), and whether using copper oxide or zinc oxide nanoparticles, this common pattern is observed. This indicates an inherent challenge in the use of free metal oxide nanoparticles in aquatic environments (Adam *et al.,* 2015).

(2) Species sensitivity: Sensitivity to nanoparticle toxicity can vary among species. The LC_{50} of CuO NPs for rainbow trout is in the microgram-per-liter range (102.3 µg/l), whereas for crabs it is in the milligram-per-liter range (44.52 mg/l) (Shiry and Akhlaghi, 2020; Shiry *et al.,* 2026). Although direct comparison is challenging, this 1000-fold difference suggests that crabs (as chitinous exoskeleton-bearing crustaceans) may exhibit relatively greater resistance to acute nanocopper toxicity compared to rainbow trout. However, review data indicate that crustaceans are generally more sensitive to metal oxide nanoparticles than fish (Swain *et al.,* 2014). This point may be useful in designing species-specific therapeutic strategies.

(3) The pathogen–host paradox: An interesting contradiction is observed in antifungal efficacy. While CuO NPs at 25 mg/l effectively controlled the fungus within the crab (Shiry *et al.,* 2026), their direct antibacterial effect under laboratory conditions was excellent for fish (Shiry and Akhlaghi, 2020). This suggests that certain eukaryotic pathogens (fungi) may be inhibited within the host at concentrations lower than the lethal threshold for the host itself (Melendre *et al.,* 2006). This provides a promising outlook for treating external localized fungal infections (such as shell and gill infections).

Nutritional applications and alternative approaches

In addition to direct therapeutic applications, the use of metal oxide nanoparticles as dietary supplements has also gained attention (Swain *et al.,* 2014). In a study on Nile tilapia (*Oreochromis niloticus*) infected with *Citrobacter freundii*,

supplementation of ZnO NPs at 200 mg/kg feed reduced mortality to 10% and increased the relative percent survival (RPS) to 80%, whereas mortality in the positive control group was 50% (Swain *et al.,* 2014). Histopathological examinations showed no tissue alterations in groups fed 200 mg/kg ZnO NPs. Furthermore, ZnO NPs upregulated immune‑related genes such as IL‑10 and complement 5 (C5). These findings indicate that oral administration of nanoparticles at controlled doses may be a safer strategy for managing bacterial infections.

In another study, the effect of vitamin C as an antioxidant in reducing copper oxide nanoparticle toxicity in Indian carp (*Catla catla*) was investigated (Rehman *et al.,* 2026). The results showed that vitamin C could partially mitigate the toxic effects of CuO NPs on body composition and digestive enzyme activity. Although the exact protective mechanism is not yet fully understood, this approach highlights the potential of antioxidant compounds in reducing nanoparticle toxicity in aquatic organisms.

Future perspectives and recommended strategies

Current evidence indicates that CuO NPs and ZnO NPs have substantial antimicrobial potential, but their nonspecific toxicity and narrow therapeutic window remain important limitations for direct systemic application in aquaculture. Therefore, future research should focus on the following priorities:

Localized and limited applications: Controlled-dose, short-duration baths may be more appropriate for external fungal infections of eggs and shells than systemic administration. Surface disinfection of hatchery equipment and other aquaculture facilities should also be investigated (Melendre *et al.,* 2006; Shiry *et al.,* 2026).

Surface engineering and formulation: Surface coating and formulation of nanoparticles with biocompatible materials should be investigated to reduce nonspecific toxicity and control metal ion release (Adam *et al.,* 2015).

Oral formulations: Low-dose dietary formulations require further investigation, particularly regarding long-term safety, tissue accumulation, and therapeutic efficacy (Swain *et al.,* 2014).

Combination with antioxidants: The combined use of nanoparticles with antioxidant compounds such as vitamin C may help reduce nanoparticle-induced oxidative stress and potentially improve the therapeutic window (Rehman *et al.,* 2026).

Environmental monitoring and standardization: Treatment protocols should include monitoring of physicochemical water parameters, including temperature, pH, and hardness, because these factors can influence nanoparticle bioavailability and toxicity. Standardized toxicity-testing protocols are also needed to improve comparability among studies (Adam *et al.,* 2015).

Ecological risk assessment: Comprehensive ecological risk assessment is necessary because nanoparticles may enter aquatic environments. Cumulative effects, low-dose responses, and long-term effects on aquatic microbiomes require further investigation (Adam *et al.,* 2015; Khosravi-Katuli *et al.,* 2018).

Nanoparticle loading on filters: Loading ZnO or CuO nanoparticles onto filtration systems may represent an alternative approach to reduce the use of conventional disinfectants, provided that acute and chronic toxicity and residue risks are adequately evaluated (Shiry and Akhlaghi, 2020).

In conclusion, the available evidence indicates that CuO and ZnO nanoparticles have considerable antimicrobial potential against aquatic pathogens, but their practical use is limited by a narrow therapeutic window. In fish and crustacean models, concentrations associated with antimicrobial activity may approach concentrations associated with host toxicity. In the crab model, a dose of 25 mg/l resulted in 93.3% survival, whereas increasing the dose to 40 mg/l reduced survival to 66.7%, indicating a clear dose-dependent toxic response (Shiry *et al.,* 2026).

The observed nonlinear response in this model is consistent with an inverted bell-shaped dose-response pattern; however, this finding is based on a limited experimental evidence base and should not be generalized to all aquatic organisms.

The evidence also suggests that nanoparticle type, species, exposure conditions, and formulation can substantially influence both antimicrobial efficacy and toxicity. Therefore, direct comparison of toxicity values between different species should be interpreted cautiously. Dietary administration and localized or non-systemic applications may offer safer alternatives to systemic exposure, but their long-term safety and efficacy require further investigation.

This review has several limitations. The available studies differ substantially in experimental models, nanoparticle characteristics, exposure conditions, target pathogens, and outcome measures, which limits direct comparison among studies. In addition, the available evidence on hormesis and therapeutic windows in aquatic organisms remains limited. Therefore, the current findings should be considered as a basis for future experimental research rather than definitive evidence for clinical application. Future studies should prioritize standardized toxicity protocols, nanoparticle surface engineering, controlled-dose formulations, long-term safety assessment, and ecological risk evaluation.

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Conflict of Interest

There are no conflicts to declare.

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