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REVIEW

Plant-based materials as protective agents against nanoparticle-induced toxicity, with emphasis on fish: a mechanistic review

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Abstract

The present review paper explores the protective effects of phytochemicals against nanoparticle (NP)-induced toxicity in fish, with a focus on underlying molecular mechanisms. Nanoparticles (NPs) are widely utilized across various industrial and technological sectors. However, their release into aquatic environments may pose significant ecological concerns, particularly for aquatic organisms such as fish. Due to their small size and high surface reactivity, NPs can accumulate in fish tissues and disrupt physiological processes. The toxic effects of NPs include oxidative stress, inflammation, genotoxicity, mitochondrial dysfunction, and apoptosis. These effects are influenced by the physicochemical properties of the nanoparticles and surrounding environmental conditions, making toxicity assessment complex. Phytochemicals such as polyphenols (curcumin, resveratrol, quercetin) have demonstrated strong antioxidant, anti-inflammatory, and detoxifying capabilities. These compounds can modulate key molecular signaling pathways, including Nrf2/Keap1, NF-κB, and JAK/STAT, to reduce cellular damage. Additionally, they stabilize mitochondrial function, inhibit pro-apoptotic signaling, and support immune responses in fish exposed to NPs. Plant-based chelators further contribute by reducing NP bioavailability and tissue accumulation, thus lowering overall toxicity. While laboratory studies show encouraging results, real-world applications remain limited. Challenges such as low bioavailability, variability in phytochemical content, and incomplete understanding of their interactions with NPs still need to be addressed. Moreover, synergistic effects with other mitigation strategies and long-term ecological impacts require further study. Future research should emphasize high-throughput screening methods, nano-formulation improvements, and in vivo validation under realistic environmental conditions.

Keywords Nanoparticle toxicity · Phytochemicals · Aquaculture · Oxidative stress · Fish

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Introduction

Nanoparticles (NPs) are ultra-small particles with dimensions typically ranging between 1 and 100 nm. Due to their tiny size and large surface area, they exhibit unique physical, chemical, and biological properties compared to bulk materials (Khan et al. 2019). Application of NPs has rapidly advanced across various fields, including medicine, electronics, cosmetic industry, and water treatment. In medicine, they are used for targeted drug delivery, imaging, and cancer treatment (Wang et al. 2012; Bobo et al. 2016; Utreja et al. 2020). In electronics, nanoparticles enhance the performance of batteries, sensors, and semiconductors (Nazir et al. 2024). The cosmetic industry employs nanoparticles in sunscreens and skincare products for better absorption and UV protection (Sharma et al. 2012; Gupta et al. 2022; Piluk et al. 2024). Additionally, they are utilized in environmental science for water purification and pollutant removal (Kumari et al. 2019). Despite the positive impacts of nanoparticles in various fields, their environmental and ecological effects remain uncertain. Short-term and long-term consequences of nanoparticle exposure on ecosystems and biodiversity are not fully understood (MacCormack and Goss 2008; Kefeni et al. 2017; Kumari et al. 2019; Punia et al. 2021). In aquatic environments, the potential toxicity of nanoparticles can significantly impact the ecosystems by harming marine organisms and disrupting ecological balance. They can accumulate in aquatic species, causing oxidative stress, cellular damage, and altered reproductive or behavioral patterns. Over time, this toxicity may lead to biodiversity loss and destabilization of the food chain (Guerranti and Renzi 2015). Nanoparticles enter aquatic ecosystems primarily through industrial wastewater, agricultural runoff, and household products. These tiny particles can accumulate in water bodies, altering water quality and posing risks to aquatic organisms including fish (Brar et al. 2010; Batley et al. 2013; Khabbazi et al. 2015; Hoseini et al. 2016; Mirghaed et al. 2018; Ghafarifarsani et al. 2023; Gong et al. 2023). NPs can bioaccumulate in fish through ingestion or absorption from their environment. Once inside the body, they may cause oxidative stress, inflammation, immunosuppression, and damage to vital organs like the liver and gills (Baker et al. 2014; Mirghaed et al. 2018; Brandts et al. 2022; Ghafarifarsani et al. 2023). Over time, NPs may bioaccumulate in the food chain, affecting ecosystem balance and potentially harming human health (Callaghan and MacCormack 2017; Gupta et al. 2017). NPs, due to their small size and large surface area, can interact with biological systems in unique and potentially harmful ways (Zoroddu et al. 2014). These interactions may result in toxic effects that impact fish health and the surrounding ecosystem. One primary concern is the bioaccumulation of NPs in fish tissues. When introduced into aquatic environments, NPs may enter the food chain through waterborne exposure, ingestion, or gill uptake (Xiao et al. 2020). For instance, metallic NPs like silver (AgNPs) or titanium dioxide (TiO_2) can accumulate in organs such as the liver, kidney, and gills, disrupting cellular processes (Osborne et al. 2015; Carmo et al. 2019). NPs may induce oxidative stress by generating reactive oxygen species (ROS), which can damage DNA, proteins, and lipids in fish cells (Reeves et al. 2008; Carrillo et al. 2015; Subaramaniyam et al. 2023). This oxidative stress has been linked to inflammation, impaired immune responses, and organ dysfunction (Jovanović and Palić, 2012). Furthermore, NPs may disrupt endocrine systems, affecting growth, reproduction, and behavior. The toxicity of NPs is influenced by their size, shape, surface charge, and concentration. Smaller particles tend to penetrate biological membranes more easily, while surface coatings can alter their reactivity and toxicity (Zoroddu et al. 2014; Egbuna et al. 2021). Environmental factors, such as pH, temperature, and salinity, also affect behavior of NPs, complicating toxicity assessments (Kim et al. 2012; Majedi et al. 2014).

Plant-based materials including extracts, essential oils, and their bioactive compounds derived from them (i.e., phytochemicals) play a vital role in promoting aquatic health by enhancing immunity, improving growth, and protecting against diseases in aquatic organisms. As natural alternatives to synthetic chemicals and antibiotics, phytochemicals are gaining popularity in aquaculture for their effectiveness and sustainability (Nik Mohamad Nek Rahimi et al. 2022; Naiel et al. 2023). Phytochemicals such as alkaloids, flavonoids, tannins, saponins, and essential oils exhibit growth-promoting, antimicrobial, antioxidant, and anti-inflammatory properties. These compounds help boost the innate and adaptive immune responses of fish and shellfish, making them more resilient to bacterial, viral, and fungal infections (Chakraborty and Hancz 2011; Chakraborty et al. 2014; Naiel et al. 2023). Extracts, essential oils, and phytochemicals have also shown potential in mitigating the adverse effects of NP toxicity in fish (Zadmajid and Mohammadi 2017; Giordo et al. 2020; Hamed and Abdel-Tawwab 2021; Mahboub et al. 2022; Noureen et al. 2023; Farag et al. 2024). These natural substances contain compounds with strong antioxidant properties, such as flavonoids, phenolics, and tannins, which are able to neutralize ROS and thus protect cells from oxidative damage (Engwa 2018). In addition, plant-based products and their derivatives protect vital organs such as the liver (Yin et al. 2011; Jannu et al. 2012; Jia et al. 2019; Oliveira et al. 2024) and are also recognized to have immunomodulatory properties, boosting fish immune defenses compromised by nanoparticle exposure (Awad and Awaad 2017; Giordo et al. 2020; Mahboub et al. 2022; Noureen et al. 2023). Given the demonstrated protective and immunomodulatory effects of plant-based compounds on fish exposed to nanoparticles, it is crucial to comprehensively examine the broader implications of nanoparticle toxicity and the mechanisms by which phytochemicals counteract these effects. In this context, the present review article aims to discuss the toxicity of NPs on fish health, the importance of phytochemicals, and the mechanisms underlying their protective role in mitigating this toxicity. Finally, it seeks to highlight the knowledge gaps in this area that could serve as potential subjects for future studies.

Natural sources of nanoparticles

NPs in aquatic environments arise from both natural processes and anthropogenic activities. These particles can influence water chemistry, ecological balance, and aquatic health, with their impact depending on their type, origin, and behavior (Krzyżewska et al. 2016). The natural sources of NPs primarily include weathering and erosion, biogenic processes, volcanic eruptions, and atmospheric deposition (Buzea and Pacheco 2017). Geological processes release natural NPs such as silica, clay minerals, and iron oxides into water bodies (Sharma et al. 2015). Biological activities, including microbial metabolism and decomposition of organic matter, generate biogenic NPs like calcium carbonate and organic nanomaterials (Griffin et al. 2017). Also, volcanic ash and dust contribute to nanoparticle inputs, which settle in aquatic environments through rainfall or air deposition (Tepe and Bau 2014; Ermolin et al. 2018). Also, the anthropogenic sources of NPs primarily include industrial effluents, agricultural runoff, urban wastewater, and aquaculture practices (Buzea and Pacheco 2017). NPs used in fish feed, water treatment, and disease management can accumulate in aquaculture ponds and surrounding waters. NPs exist in various forms, including metal and metal oxides, carbon-based NPs, polymeric NPs, and naturally occurring NPs such as clay, silica, and organic NPs derived from natural sources (Raut et al. 2024).

Nanoparticle toxicity in fish

NPs can cause toxicity in fish through various biological and physicochemical interactions, including oxidative stress, bioaccumulation, membrane damage, immune system impairment, endocrine disruption, neurotoxicity, and interaction with environmental factors, which often disrupt vital physiological processes (Khan et al. 2015; Cazenave et al. 2019). The toxicity of NPs in fish is influenced by multiple factors, including the physicochemical properties of NPs (i.e., size, shape, surface charge, coating and functionalization and solubility), environmental conditions, and the biological characteristics of fish (i.e., species-specific sensitivity, life stage, exposure route, accumulation and detoxification ability) and concentration and duration of exposure.

Certain fish species are more vulnerable to NP toxicity due to their physiological traits, life stages, and ecological niches. Zebrafish (*Danio rerio*) are highly sensitive because of their rapid embryonic development, transparent embryos, and permeable skin, making them widely used in NP toxicity studies (Chakraborty et al. 2016; Haque and Ward 2018; Cazenaveet al. 2019). Changes in water pH can alter the stability, aggregation, and reactivity of NPs, affecting their bioavailability and toxicity (Fernando and Zhou 2019). In marine and brackish environments, higher salinity can lead to NP aggregation, potentially reducing toxicity (Petosa et al. 2010). Elevated temperatures may also increase metabolic rates in fish and nanoparticle reactivity, intensifying toxicity (Zhang et al. 2022). Additionally, organic matters in water can bind to NPs, reducing their bioavailability but potentially forming harmful complexes (Yu et al. 2018).

Accurately detecting and quantifying NPs in aquatic systems and fish tissues is essential for understanding their environmental behavior and toxicological impact. Several advanced analytical techniques such as dynamic light scattering (DLS) are commonly used to measure particle size distribution in water samples, although it has limitations in complex matrices (Naiim et al. 2015). Transmission electron microscopy (TEM) and scanning electron microscopy (SEM) provide high-resolution imaging to assess NP morphology and aggregation states (Dini et al. 2015). For quantitative analysis, inductively coupled plasma mass spectrometry (ICP-MS) and single-particle ICP-MS (spICP-MS) are widely used to determine metal-based NP concentrations in both water and biological tissues with high sensitivity (Peters et al. 2015). These methods can distinguish between ionic and particulate forms, which is crucial for risk assessment. Additionally, X-ray diffraction (XRD) and Fourier-transform infrared spectroscopy (FTIR) are applied to identify crystalline structures and chemical bonds of NPs, respectively (Robinson 2012; Pasieczna-Patkowska et al. 2025). In fish tissues, sample preparation typically involves digestion, separation, or fractionation techniques such as ultracentrifugation or filtration before analysis. Despite progress, challenges remain due to NP transformation in the environment, low concentrations, and interference from natural organic matter. Therefore, method development and standardization continue to be active areas of research in nanotoxicology.

Phytochemicals: classification and therapeutic roles

Phytochemicals are mainly categorized into several groups, each with distinct structural features and biological activities. The primary classes include polyphenols, alkaloids, terpenoids, organosulfur compounds, and saponins (Thacker and Ram (2024). Polyphenols are perhaps the most extensively studied group, encompassing flavonoids (e.g., quercetin, catechins, and anthocyanins), phenolic acids (e.g., caffeic and gallic acid), and stilbenes (e.g., resveratrol) (Bravo 1998). These compounds exhibit potent antioxidant properties by scavenging reactive oxygen species (ROS), thereby mitigating oxidative stress—a key factor in chronic disease progression (Li et al. 2014). Flavonoids also modulate immune responses by regulating cytokine production and enhancing natural killer (NK) cell activity. Alkaloids, such as berberine, caffeine, and morphine, are nitrogen-containing compounds that have demonstrated anti-inflammatory and immunomodulatory effects (Burkard et al. 2017; Oo et al. 2022). For instance, berberine has been shown to inhibit pro-inflammatory pathways like NF-κB signaling and to modulate macrophage activity (Jia et al. 2017). Terpenoids, including carotenoids (e.g., β-carotene, lycopene) and essential oils, exhibit significant antioxidant activity. Carotenoids protect cellular membranes from lipid peroxidation and support immune function by influencing T cell proliferation and enhancing antibody production (Jyonouchi et al. 1994; Gruszecki and Strzałka 2005). Organosulfur compounds, primarily found in allium and cruciferous vegetables, such as allicin and sulforaphane, play a critical role in detoxification pathways and oxidative stress reduction (Petropoulos et al. 2017). These compounds activate the Nrf2 signaling pathway, which upregulates the expression of antioxidant enzymes (Egbujor et al. 2022). Saponins, glycoside compounds found in legumes and various herbs, exhibit both anti-inflammatory and immunostimulatory properties (Gurfinkel 2000). They enhance immune function by increasing lymphocyte proliferation and modulate inflammatory markers such as TNF-α and IL-6 (Bhardwaj et al. 2014). In the following section, an attempt is made to explore some of the major protective mechanisms of phytochemicals. Particular emphasis is placed on how these compounds mediate cellular defense against oxidative stress and inflammation.

Protective mechanisms of plant-based materials against nanoparticle toxicity

The mechanisms of action of phytochemicals are summarized in Fig. 1. In general, phytochemicals exert their protective role mainly through reducing the bioavailability of NPs, immunogenic and antioxidant effects, altering cell signaling pathways, and apoptosis.

Reducing nanoparticle bioavailability

Phytochemicals play a significant role in reducing the bioavailability of toxic nanoparticles (NPs). These plant-derived compounds can bind to NPs in the digestive tract, limiting their absorption and systemic distribution. By enhancing gut barrier integrity and promoting excretion pathways, phytochemicals reduce NP accumulation in vital organs (Wang et al. 2024; Sousa et al. 2025). Additionally, their antioxidant and anti-inflammatory properties help protect tissues from NP-induced damage (Martins-Gomes et al. 2024). Certain plant

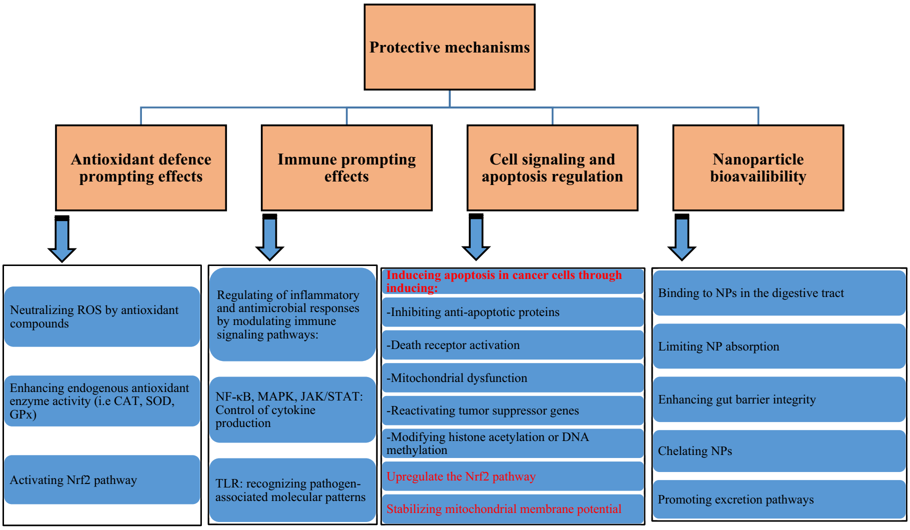

Fig. 1 Schematic diagram of the mechanisms of the protective effect of phytochemicals against nanoparticle toxicity

extracts enhance intestinal mucosal defenses or upregulate efflux transporters (e.g., P-gp) and detox enzymes (e.g., CYP450), effectively reducing NP translocation from the gut into systemic circulation (Martins-Gomes and Silva 2023). Bioactive molecules like tannins form complexes with NP-bound metal ions, reducing their solubility and uptake. Analogous to how humic acids protect fish gills from silver NP toxicity, plant chelators may similarly immobilize NPs in the gastrointestinal milieu.

Natural products as a tool to modulate the activity and expression of multidrug resistance proteins of intestinal barrier.

Antioxidant prompting effects and detoxification

The plant-based supplements and their bioactive compounds, phytochemicals, have garnered attention for their protective properties against the toxicity of NPs in aquatic environments. Their antioxidant, anti-inflammatory, and detoxifying mechanisms provide a natural defense system for fish exposed to the adverse effects of NPs (Mihailovic et al. 2021; Noureen et al. 2023). NPs possess unique properties that enable their widespread use, but their toxicity to aquatic organisms, particularly fish, is a growing concern. NPs can generate ROS, causing oxidative stress, inflammation, and cellular damage in fish (Aziz and Abdullah 2022). The enzymatic and non-enzymatic antioxidant defense system is the first line of defense against oxidative stress caused by pollutants, especially nanoparticles. In fish, the antioxidant responses against nanoparticle toxicity have been reported in many studies (Khoei 2021; Mansour et al. 2021; Kumar et al. 2022; Temiz and Kargın, 2022; Ghafarifarsani et al. 2023).

Plant extracts, essential oils, and phytochemicals have emerged as effective natural mitigators of such toxicity, with their antioxidant properties being a key mechanism of protection. Phytochemicals like flavonoids, phenolics, and tannins are powerful antioxidants

Table 1 Impact of representative plant-based materials on immune and antioxidant related components in the fish exposed to nanoparticle-induced toxicity

Nanoparticle type	Phytochemical	Fish	Results	Ref.
TiO_2-NPs	*Moringa oleifera* leaf extract	*Oreochromis niloticus*	↑ Immunity; ↓ Oxidative stress	Kandeil et al. (Kandeil 2019)
ZnO-NPs	*Allium hirtifolium* extract	*Cyprinus carpio*)	↑ Antioxidant parameters ↑ Biochemical parameters (TP, Alb, Glo) ↓ Biochemical parameters (Trig, Chol, Cort, Glu, Creat and Urea)	Mahboub et al. (2022)
TiO_2-NPs	*Ginkgo biloba*	*Oncorhynchus mykiss*	↓ Oxidative stress (lipid peroxidation (LPO), ↑glutathione peroxidase (GPx), and catalase (CAT), ↑ immunity	Hajirezaee et al. (2023)
ZnO-NPs	*Allium hirtifolium* extract	*Cyprinus carpio*	↑ Immunity (serum and mucus)	Rashidian et al. (2022)
Fe_2O_3-NPs	*Pomegranate peel* extract	*Cyprinus carpio*	↓ Hepatotoxicity; ↑ Antioxidant status	Abd El-Aziz et al. 2022
ZnO-NPs	*Hyssopus officinalis* extract	*Oreochromis niloticus*	↑Oxidative stress; changes in the expression of inflammatory genes and the antioxidant system	
ZnO-NPs	*Allium hirtifolium* extract	Common carp (*Cyprinus carpio*)	↑ Antioxidant gene expression (CAT, SOD and GPx)	Mahboub et al. 2022
CuO-NPs	*Trigonella foenum-graecum* seeds	*Cyprinus carpio*	↑ Oxidative stress (lipid peroxidation (LPO), glutathione (GSH), and catalase (CAT)	Noureen et al. (2022)
ZnO-NPs	*Allium hirtifolium* extract	Common carp (*Cyprinus carpio*)	↑ Inflammatory responses (TNF-α, IL-1β and IL-8)	Rashidian et al. (2022)
ZnO-NPs	*Moringa oleifera* leaf extract	*Penaeus vannamei*	↑ Immunity (activity of profenoloxidase II, alpha-2-macroglobulin, penaidin2, anti-lipopolysaccharide factor, krustin, lysozyme, glutathione peroxidase and superoxide dismutase)	
ZnO-NPs	*Moringa oleifera*	*Oreochromis niloticus*	↑ Growth Improved final body weight (FBW), survival rate (SR), specific growth rate (SGR), weight gain (WG), and feed conversion ratio (FCR)	

ZnO-NPs: Zinc oxide nanoparticles, Total protein (TP), Albumin (Alb), Globulin (Glo), Triglyceride (Trig), Cholesterol (Chol), Cortisol (Cort), Glucose (Glu), Creatinine (Creat)

found in plant extracts (Bravo 1998; Banjarnahor and Artanti 2014; Altemimi et al. 2017). These compounds neutralize ROS by donating electrons, thereby preventing oxidative damage to cellular components such as lipids, proteins, and DNA. Essential oils, rich in terpenoids and polyphenols, similarly combat oxidative stress by inhibiting ROS formation and enhancing endogenous antioxidant enzyme activity (Saleh et al. 2010). NPs can disrupt fish cell membranes through lipid peroxidation caused by oxidative stress (Aziz and Abdullah 2022). The compounds such as β-carotene, resveratrol, curcumin, and quercetin stabilize the lipid bilayer, preserving membrane integrity and preventing cell death (Liang et al. 2012; Margina et al. 2012; Neves et al. 2015; Simonyan et al. 2022). Many plant-based compounds, including flavonoids and phenolics, activate the nuclear factor erythroid 2–related factor 2 (Nrf2) pathway, promoting the expression of antioxidant enzymes like superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) (Alrawaiq et al. 2014; Wu et al. 2014). Plant extracts and phytochemicals can enhance the activity of the antioxidant enzymes in fish exposed to nanoparticles (Table 1). These enzymes play a critical role in detoxifying ROS and maintaining cellular redox balance. The fish liver and kidneys, primary sites for detoxification (Topić Popović et al. 2023), are particularly vulnerable to NP-induced oxidative damage (Velma and Tchounwou 2013; Correia et al. 2020). Phytochemicals such as resveratrol and quercetin protect these organs by reducing ROS levels, enhancing antioxidant defenses, and minimizing inflammation. The liver, as the central organ for detoxification, plays a critical role in metabolizing and eliminating xenobiotics, including NPs (Carmo et al. 2019). Phase I (e.g., cytochrome P450 enzymes) and Phase II (e.g., glutathione-S-transferase, UDP-glucuronosyltransferase) enzymes are crucial for detoxifying and facilitating the excretion of harmful substances (Monostory et al. 1996). Plant-derived materials have been found to modulate these enzymes, enhancing the detoxification capacity of the liver and other tissues (Burkina et al. 2015). Resveratrol and quercetin have been shown to activate the Nrf2 (nuclear factor erythroid 2-related factor 2) pathway, which regulates the expression of several detoxification enzymes (Farkhondeh et al. 2020; Sharma et al. 2020). Nrf2 activation leads to the upregulation of phase II enzymes such as glutathione-S-transferase (GST), quinone reductase, and glutamate-cysteine ligase (GCL), which are involved in conjugating toxic metabolites to hydrophilic molecules for easier excretion (Lee and Johnson 2004). By stimulating the expression and activity of these detoxification enzymes, plant-derived materials help to enhance the body's ability to break down and eliminate toxic NPs, thus reducing their harmful effects.

Certain plant-derived materials possess the ability to chelate and sequester metal NPs, preventing their cellular uptake and reducing their bioavailability (Andal et al. 2022). This is especially relevant for metal-based NPs, such as silver or gold NPs, which can accumulate in organs like the liver and kidney. Resveratrol has been shown to bind metal ions and metal-containing NPs, reducing their toxicity (Gülçin 2010; Bardestani et al. 2021). The ability of pectin to form complexes with heavy metals may help mitigate the bioaccumulation and subsequent toxic effects of metal-based NPs (Wang et al. 2019a, b). Polyphenolic compounds like tannins are known to have metal-binding properties (Borowska et al. 2018), which may contribute to the sequestration and elimination of toxic metal NPs from the body. These plant-based chelators provide an additional layer of defense against nanoparticle toxicity by reducing nanoparticle accumulation in critical organs and facilitating their safe elimination.

Immune prompting effects

NPs can disrupt the immune system of fish, leading to increased susceptibility to infections and reduced ability to recover from environmental stressors (Rastgar et al. 2022). The immune system of fish can be also influenced by nanoparticle toxicity (Ates et al. 2016; Thummabancha et al. 2016; Wang et al. 2019a, b; Mahboub et al. 2022; Rashidian et al.

2022; Rastgar et al. 2022; Hedayati et al. 2024). Plant extracts, essential oils, and phytochemicals have demonstrated immunogenic properties that help mitigate these effects, providing a natural and sustainable approach to protecting fish health (Rashidian et al. 2022; Abou-Zeid et al. 2023; Noureen et al. 2023; Farag et al. 2024). These compounds enhance both innate and adaptive immunity, reduce inflammation, and restore immune homeostasis. Stimulation of innate immunity, modulation of inflammatory responses, enhancement of adaptive immunity, antimicrobial effects, reduction of oxidative stress on immune cells, improvement of gut-associated immunity, anti-stress effects, and protection of immune organs are among the main functions suggested for plant-based materials and compounds (PBMCs) in the fish immune system (Chakraborty and Hancz 2011; Elumalai et al. 2020; Taştan and Salem 2021). Considering the innate immune system, plant supplements have been shown to have a boosting effect on components of innate immunity. Table 1 presents the effects of representative plant supplements, including extracts, essential oils, and phytochemicals, on innate immune responses of the fish exposed to NPs. NPs often trigger excessive inflammatory responses, damaging tissues and suppressing immunity (Goncalves et al. 2011). According to the literature, modulation of immuno-signaling pathways seems to be the most important mechanism behind the effects of PBMCs on immune responses (Merecz-Sadowska et al. 2020; Jiang et al. 2021). Plant-based materials and phytochemicals play a pivotal role in modulating immune signaling pathways such as Toll-like receptor (TLR), Nuclear factor kappa B (NF-κB), Janus kinase/signal transducer and activator of transcription (JAK/STAT), and Mitogen-Activated Protein Kinase (MAPK) pathways. These natural compounds enhance both innate and adaptive immune responses by influencing key cellular signaling mechanisms. Their bioactive properties regulate cytokine production, transcription factor activity, and cellular communication, leading to improved immune responses (Merecz-Sadowska et al. 2020). Toll-like receptors (TLRs) are a crucial component of the innate immune system in fish, playing a pivotal role in recognizing pathogen-associated molecular patterns (PAMPs) and initiating immune responses (Fan ZeJun et al. 2015). These transmembrane receptors are evolutionarily conserved and are found on the surfaces of immune cells, such as macrophages, dendritic cells, and epithelial cells (UeMatsu and Akira 2008). TLRs enable fish to detect a wide range of microbial threats, including bacteria, viruses, fungi, and parasites, triggering a cascade of signaling pathways that lead to pathogen elimination. Activation of PAMPs, cytokine production, and antimicrobial responses are among the consequences that result from the activation of the TLR pathways (Fan ZeJun et al. 2015). Plant-derived compounds stimulate TLR pathways to increase the production of antimicrobial peptides (Hong-Geller et al. 2008; Liu et al. 2011). It also appears that the NF-κB, Mitogen-Activated Protein Kinase (MAPK), and JAK/STAT signaling pathways are among the pathways that can be modulated by phytochemicals (Shin et al. 2020; Haftcheshmeh et al. 2022). These pathways play a significant role in the control of cytokine responses, and phytochemicals, by modulating these pathways, are capable of balancing inflammatory responses (Shin et al. 2020). The JAK/STAT pathway regulates the production of pro-inflammatory (TNF-α, IFN-γ, IL-6, IL-12) and anti-inflammatory (IL-10) cytokines (Pfitzner et al. 2004; Malemud and Pearlman 2009). The MAPK pathway regulates cytokine production at both the transcriptional and post-transcriptional levels. Similar to the JAK/STAT pathway, the MAPK pathway also controls inflammatory responses through the production of inflammatory and anti-inflammatory cytokines (Manzoor and Koh 2012). The role of cytokines in macrophage and complement system activity has been demonstrated in fish and other vertebrates (Grayfer et al. 2018; Sakai et al. 2021). For example, the cytokine IFN-γ binds to its receptor on macrophages and activates the expression of genes involved in antimicrobial defense (e.g., inducible nitric oxide synthase

[iNOS], which generates nitric oxide), antigen presentation (Bancroft et al. 1987; Salim et al. 2016). IFN-γ also upregulates TNF-α production, amplifying macrophage activation (Shakhov et al. 1996). Additionally, IL-10, as an anti-inflammatory cytokine, binds to its receptors on macrophages and dampens macrophage activation through activating the JAK/STAT3 pathway (Riley et al. 1999).

Cell signaling and apoptosis regulation

A key mechanism through which nanoparticle toxicity manifests is apoptosis, a tightly regulated process of programmed cell death critical for maintaining cellular and organismal health (Paunovic et al. 2020). In fish, exposure to NPs can induce apoptosis in various tissues, including gills (Taju et al. 2014), liver (Wang et al. 2019a, b), kidneys (Abdel-Latif et al. 2021), and intestine (Wang et al. 2015), leading to physiological and developmental abnormalities. NPs can induce apoptosis in fish through several interrelated mechanisms, including oxidative stress, mitochondrial dysfunction, DNA damage and genotoxicity, activation of apoptotic signaling pathways, and disruption of calcium homeostasis (Zhao et al. 2016; Hu et al. 2021; Vineetha et al. 2021). NPs generate ROS either directly (due to their surface reactivity) or indirectly by interacting with cellular components (Horie and Tabei 2021). ROS damage proteins, lipids, and DNA, triggering apoptosis (Redza-Dutordoir and Averill-Bates 2016). NPs interact with mitochondrial membranes, causing depolarization of the mitochondrial membrane potential (MMP) and opening of the mitochondrial permeability transition pore (MPTP). These events lead to the release of pro-apoptotic factors, such as cytochrome c and apoptosis-inducing factor (AIF), into the cytoplasm, triggering caspase activation and cell death (Wu et al. 2020). NPs can also disrupt intracellular calcium levels, which play a key role in regulating apoptosis. Nanoparticle-induced release of calcium from the endoplasmic reticulum (ER) into the cytoplasm causes ER stress and mitochondrial calcium overload, promoting the activation of apoptotic factors, such as cytochrome c and caspases (Zhang et al. 2012; Morales-Cruz et al. 2014; Cao et al. 2017). The effects of plant-based supplements on apoptosis are complex and context-dependent, often exhibiting both beneficial and harmful roles depending on factors such as dosage, cellular environment, and the type of cells targeted (healthy *versus* cancerous). One of the most promising aspects of herbal supplements is their ability to selectively induce apoptosis in cancer cells through inducing mitochondrial dysfunction, death receptor activation, inhibiting anti-apoptotic proteins, modifying histone acetylation or DNA methylation, and reactivating tumor suppressor genes (Khursheed 2016; Tao et al. 2019). However, while promoting apoptosis in cancer cells is beneficial, herbal supplements must avoid triggering apoptosis in healthy cells, as this could lead to tissue damage and adverse effects. Many plant-based compounds exhibit protective properties that prevent unnecessary apoptosis in normal cells, often through their antioxidant and anti-inflammatory effects (Chor et al. 2005; Ahmad et al. 2010; Kumar and Khanum 2013). Polyphenols (e.g., curcumin, resveratrol, quercetin) are potent antioxidants that neutralize ROS, the main agent inducing apoptosis (Barclay et al. 2000; Gülçin 2010; Zhang et al. 2011).

In fish, some studies have shown mitigating effects of plant-based supplements on apoptosis, which were attributed to the antioxidant, anti-inflammatory, and cytoprotective properties of phytochemicals in their biochemical composition (Tan et al. 2018; Khafaga et al. 2020; Li et al. 2020). For example, dietary *Origanum vulgare* essential oil attenuated cypermethrin-induced apoptosis and reduced DNA damage in common carp, *Cyprinus carpio* (Khafaga et al. 2020). Li et al. (2020) showed that the use of 4.0 g ethyl acetate extract of *Angelica sinensis* in the diet of common carp reduces trichlorfon-induced apoptosis in the gills and erythrocytes of the fish. Also, dietary ginkgo biloba leaf extract down-regulated the expression of apoptosis-related genes in hybrid grouper (*Epinephelus lanceolatus*♂ × *Epinephelus fuscoguttatus*♀) fed high lipid diets (Tan et al. 2018). The mitigating effects of phytochemicals on apoptosis induced by nanoparticle toxicity have also been demonstrated (Bhatti et al. 2022; Li et al. 2022). Furthermore, dietary curcumin (200–800 mg/kg) attenuated lipopolysaccharide-induced apoptosis in snakehead fish, *Channa argus* over 8-week feeding period (Li et al. 2022).

Plant-derived antioxidants upregulate the Nrf2 (nuclear factor erythroid 2-related factor 2) pathway (Stefanson and Bakovic 2014; Akbari et al. 2022), which controls the transcription of genes encoding antioxidant and detoxification enzymes (Lee and Johnson 2004). Activation of Nrf2 restores redox balance, reducing apoptosis (Jenkins and Gouge 2021). Mitochondrial dysfunction plays a central role in nanoparticle-induced apoptosis, as NPs disrupt mitochondrial membrane potential (MMP) and promote the release of pro-apoptotic factors like cytochrome c (Wu et al. 2020). Plant-derived compounds such as curcumin, silymarin, and resveratrol stabilize MMP by preventing mitochondrial oxidative damage (Dave et al. 2008; Jat et al. 2013; Surai 2023). NPs also induce inflammation, which exacerbates apoptosis by promoting the release of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 (Goncalves et al. 2011). These cytokines activate death receptors, leading to apoptosis via the extrinsic pathway (Aggarwal 2000; Sano et al. 2021). Anti-inflammatory phytochemicals such as curcumin (Singh and Aggarwal 1995; Kahkhaie et al. 2019), resveratrol (Ma et al. 2015; de Sá Coutinho et al. 2018), gingerol (Yücel et al. 2022), and quercetin (Granado-Serrano et al. 2012; Chen et al. 2020) inhibit pro-inflammatory pathways, including NF-κB and AP-1 signaling, reducing cytokine production.

The formation of chelate is one of the other mechanisms of plants-derived materials that reduce the availability of NPs to cells (Susan et al. 2019; Vishnu and Dhandapani 2021). Polyphenols and polysaccharides, such as pectin and tannins, chelate metal-based NPs (Kharissova et al. 2013; Amini and Akbari 2019), preventing cellular uptake and toxicity. In conclusion, plant-derived compounds offer significant protective effects against nanoparticle-induced apoptosis in fish by modulating oxidative stress, stabilizing mitochondrial function, inhibiting caspase activation, and reducing inflammation.

Discussion

The growing integration of NPs into industrial, pharmaceutical, and agricultural applications has inevitably led to their release into aquatic ecosystems. Numerous studies have confirmed that NPs, due to their minute size and high surface reactivity, can accumulate in fish and exert toxic effects (Khan et al. 2015; Zhao et al. 2016; Cazenave et al. 2019; Hu et al. 2021; Vineetha et al. 2021). However, despite significant advances, the current landscape of toxicological studies on NPs still presents notable limitations. Most studies have relied heavily on short-term, acute exposure models that do not accurately reflect chronic, low-dose exposures typically seen in natural environments. These models often fail to consider the complexity of ecological interactions, co-contaminants, and environmental modulators such as pH, salinity, or temperature, all of which influence NP behavior and toxicity (Kim et al. 2012; Majedi et al. 2014). Moreover, toxicity data tend to be species-specific (Paparella et al. 2021), making cross-species extrapolation difficult and potentially misleading. Also, the variability in NP properties such as size, shape, surface charge, coating, and solubility adds another layer of complexity (Luyts et al. 2013). Even within a single NP type (e.g., AgNPs), variations in synthesis method and environmental conditions can lead to drastically different toxicological outcomes. Analytical limitations also persist. The detection and quantification of NPs in biological matrices such as fish tissues require high-resolution and sensitive methods like single-particle ICP-MS, electron microscopy, and advanced imaging techniques, which are not universally available or standardized. Therefore, establishing standardized protocols for NP characterization and toxicity testing in aquatic organisms, prioritizing long-term, environmentally relevant exposure models that include chronic and sub-lethal endpoints, incorporating multi-species, trophic-level interactions to better simulate ecological dynamics, investing in advanced detection technologies and inter-laboratory calibration to improve data accuracy and reproducibility, and expanding research to include understudied NP types and exploring their interactions with co-pollutants are essential in order to gain a comprehensive understanding of NPs, its toxicity, and its effects on aquatic life. Future research on NPs and their effects on aquatic organisms can be directed in two key areas. The first is focused on NP formulation and reducing inherent toxicity, where green-synthesized nanoparticles represent a promising solution. Green-synthesized nanoparticles (green NPs) have emerged as a promising alternative to conventional engineered NPs, offering reduced toxicity and greater environmental compatibility (Kirubakaran et al. 2025). Green NPs are typically synthesized using biological materials such as plant extracts, algae, fungi, or bacteria as reducing and capping agents (Hussain et al. 2016). This eco-friendly synthesis method not only avoids the use of hazardous chemicals but also imparts biofunctional properties to the nanoparticles, contributing to their biocompatibility and reduced ecotoxicity. The toxicity of traditional NPs in aquatic systems often stems from their physicochemical instability, high surface reactivity, and uncontrolled release of toxic ions (Krzyżewska et al. 2016). In contrast, green NPs tend to be more stable in aqueous environments due to their bio-organic coatings derived from natural compounds such as polyphenols, flavonoids, and proteins (Mohammadi and Amini 2024). These surface-bound phytochemicals not only enhance NP dispersion but also serve as antioxidants and anti-inflammatory agents, thereby mitigating oxidative stress when the particles interact with fish tissues. Mechanistically, green NPs reduce oxidative stress by generating fewer reactive oxygen species (ROS) and by carrying intrinsic antioxidant properties from the bioactive molecules used in their synthesis (Yang et al. 2021). Additionally, they exhibit lower tendencies to bioaccumulate in fish organs such as the liver, gills, and kidneys, thereby minimizing long-term toxicological effects (Rasool et al. 2022; Badran and Hamed 2024). The capping layers derived from plant metabolites may also act as biological barriers, hindering ion dissolution (e.g., Ag^{+} from AgNPs), a major factor contributing to NP toxicity. Green NPs also support immune homeostasis by reducing pro-inflammatory responses and maintaining the integrity of epithelial tissues, especially in gills and the gastrointestinal tract (Liu et al. 2019; Agarwal and Shanmugam 2020). Furthermore, their controlled release properties make them ideal carriers for therapeutic agents, including vaccines and antioxidants in aquaculture, offering targeted delivery with minimal side effects. For example, studies on *Oreochromis niloticus* (Girilal et al. 2015) have shown that green NPs synthesized from *Salacia reticulate* are significantly less toxic compared to their chemically synthesized counterparts. As a result, green nanotechnology offers a sustainable and safer pathway for harnessing the benefits of nanoparticles while minimizing ecological and biological risks in aquaculture.

Phytochemicals have shown considerable promise as natural mitigators of NP-induced toxicity in aquatic species. Their antioxidant, anti-inflammatory, immunostimulatory, and chelating properties make them attractive alternatives to synthetic chemicals for use in aquaculture (Nik Mohamad Nek Rahimi et al. 2022; Naiel et al. 2023). Compounds such as curcumin, quercetin, resveratrol, and tannins have demonstrated the ability to reduce reactive oxygen species (ROS), stabilize membranes, support detoxification pathways, and enhance immune responses. However, despite the positive findings, several challenges constrain the widespread use of phytochemicals. A major issue is the variability in phytochemical content due to plant species, growing conditions, harvest timing, and extraction methods. Also, different extraction techniques (e.g., solvent extraction, supercritical fluid extraction) yield extracts with varying phytochemical profiles (Bitwell et al. 2023). These make it difficult to reproduce results across different studies or scale up for commercial use (Gololo 2018). In addition, only a small fraction of the thousands of known phytochemicals have been tested for their protective effects against NPs. The mechanisms of action for many remain unclear, and potential synergistic or antagonistic effects among compounds within crude extracts are not well understood. In addition, current screening methods for identifying bioactive phytochemicals are limited, slow, and resource-intensive. To improve the identification of promising plant sources, future research may utilize bioinformatics and chemoinformatics platforms. Techniques such as chemotaxonomic clustering can categorize plants based on shared phytochemical traits, aiding in the strategic selection of species (Liu et al. 2017). In silico tools, including molecular docking and QSAR modeling, can predict interactions between phytochemicals and oxidative or immune-related targets (Rana et al. 2019). Structural features such as hydroxylation patterns in polyphenols may also serve as selection criteria due to their known antioxidant activity (Fujimoto and Gotoh 2023). Integration with machine learning algorithms trained on toxicological and chemical datasets could further refine predictions (Grenet et al. 2018). In addition, databases like ChEMBL**,** NPASS, and PubChem offer valuable resources for compound pre-screening (Wassermann and Bajorath 2011). Ultimately, combining these digital approaches with experimental validation can accelerate the discovery of effective, plant-based protective agents against nanoparticle-induced toxicity in aquatic systems.

Another key limitation is bioavailability. Many phytochemicals are poorly absorbed in the fish gastrointestinal tract, unstable in water, or rapidly metabolized and excreted (Wang et al. 2014). This limits their efficacy unless appropriate delivery systems such as encapsulation or nanoformulations are employed. We believe that utilizing advanced phytochemical profiling (e.g., HPLC, LC–MS) to standardize extracts and identify bioactive constituents, expanding screening libraries using bioinformatics and machine learning tools to predict candidate compounds with strong protective potential, investigating synergistic phytochemical interactions through factorial design experiments and omics-based approaches, developing improved delivery systems, such as liposomal carriers or biopolymer-based encapsulations, to enhance stability and absorption in fish, and collaborating with ethnobotanists to explore traditional medicinal plants that may harbor potent unexplored phytochemicals could be suitable solutions for identifying phytochemicals and discovering their therapeutic potentials in aquatic animals.

Understanding the mechanisms through which phytochemicals exert their protective effects against NP-induced toxicity is crucial for targeted application and optimization. Current evidence indicates that these compounds act through several major pathways: antioxidant defense via the Nrf2/Keap1 axis, modulation of inflammatory responses through NF-κB and JAK/STAT signaling, immunoregulation via cytokine pathways, and control of apoptosis through mitochondrial stabilization and caspase inhibition. However, the precise molecular mechanisms of these compounds in mitigating NP toxicity remain poorly understood (Bhatti et al. 2022), especially in fish. For instance, the influence of phytochemicals on autophagy, DNA repair, calcium signaling, or endoplasmic reticulum stress pathways in the context of NP toxicity is largely unstudied. In addition, pathway-specific data in aquatic species, particularly non-model organisms, are limited, making it difficult to generalize findings across diverse aquaculture settings. Further complicating the matter is the dual nature of some phytochemicals. While they may exhibit protective effects at certain doses, high concentrations could paradoxically induce toxicity (Molyneux et al. 2007; Huang and Bu 2022). We believe that these limitations can be overcome by performing multi-omics studies (transcriptomics, proteomics, metabolomics) to comprehensively map the molecular targets and pathways modulated by phytochemicals in NP-exposed fish, using CRISPR and RNAi technologies in model species to validate specific pathway involvement (e.g., knockdown of Nrf2 to confirm antioxidant mechanism), investigating the dose–response relationships of phytochemicals to define therapeutic windows and avoid adverse effects, exploring novel protective pathways beyond the classical oxidative stress/inflammation axis, such as mitochondrial biogenesis or gut microbiota modulation, and incorporating in vitro–in vivo correlation models to bridge mechanistic insights with whole-organism outcomes.

Conclusion

NP-induced toxicity poses a growing threat to aquatic ecosystems, particularly to fish, which are highly vulnerable due to their physiological traits and environmental exposure. The toxic effects of NPs ranging from oxidative stress, inflammation, genotoxicity, and mitochondrial dysfunction to apoptosis highlight the urgent need for effective mitigation strategies. This review underscores the potential of plant-derived materials, especially phytochemicals, as eco-friendly agents that can counteract such toxic impacts. Phytochemicals such as polyphenols, flavonoids, tannins, alkaloids, and terpenoids exhibit significant antioxidant, anti-inflammatory, immunomodulatory, and detoxifying properties. These bioactive compounds work through well-defined molecular mechanisms, including the modulation of Nrf2/Keap1, NF-κB, and JAK/STAT pathways, stabilization of mitochondrial function, and reduction of pro-apoptotic signaling. Furthermore, their ability to chelate metals and reduce nanoparticle bioavailability adds another layer of protection. Despite their promise, several challenges hinder widespread application. Phytochemicals often suffer from poor solubility and low bioavailability, and their effects may vary due to inconsistencies in extraction, plant source, and environmental conditions. Moreover, most current studies are confined to laboratory settings, limiting real-world applicability. Understanding the synergistic interactions between various phytochemicals and nanoparticles also remains an underexplored area. Addressing these limitations requires advancements in phytochemical standardization, nano-formulation technologies for improved delivery, and comprehensive in vivo studies that reflect realistic environmental exposures. The development of high-throughput screening methods and in silico models may accelerate the identification of potent phytochemicals and optimize their application in aquaculture systems. The integration of phytochemicals with sustainable aquaculture practices could transform nanoparticle toxicity management, ensuring fish welfare, environmental integrity, and food safety. Their use may also complement or replace synthetic additives, contributing to greener aquaculture. Future studies should explore long-term ecological impacts, optimal dosing strategies, and potential applications of phytochemical-enriched feeds and water treatments.

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Data availability No datasets were generated or analysed during the current study.

Declarations

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References

Abdel-Latif HM, Shukry M, El Euony OI, Mohamed Soliman M, Noreldin AE, Ghetas HA, ..., Khallaf MA (2021) Hazardous effects of SiO2 nanoparticles on liver and kidney functions, histopathology characteristics, and transcriptomic responses in Nile Tilapia (Oreochromis niloticus) Juveniles. Biology 10(3):183

Abd El-Aziz YM, Hendam BM, Al-Salmi FA, Qahl SH, Althubaiti EH, Elsaid FG et al (2022) Ameliorative effect of pomegranate peel extract (PPE) on hepatotoxicity prompted by iron oxide nanoparticles (Fe2O3-NPs) in mice. Nanomaterials 12(17):3074

Abou-Zeid SM, Zheng C, Khalil SR, Farag MR, Elsabbagh HS, Siddique MS, Mawed SA, Azzam MM, Di Cerbo A, Elkhadrawey BA (2023) Thymol-enriched diet alleviates the toxic impacts of zinc oxide nanoparticles on growth performance, blood biochemistry, oxidant/antioxidant status and stress-related genes and histology of liver and gills in Oreochromis niloticus. Aquac Rep 33:101750

Agarwal H, Shanmugam V (2020) A review on anti-inflammatory activity of green synthesized zinc oxide nanoparticle: mechanism-based approach. Bioorg Chem 94:103423

Aggarwal BB (2000) Tumour necrosis factors receptor associated signalling molecules and their role in activation of apoptosis, JNK and NF-κB. Ann Rheum Dis 59(suppl 1):i6–i16

Ahmad R, Javed S, Bhandari U (2010) Antiapoptotic potential of herbal drugs in cardiovascular disorders: an overview. Pharm Biol 48(4):358–374

Akbari B, Baghaei-Yazdi N, Bahmaie M, Mahdavi Abhari F (2022) The role of plant-derived natural antioxidants in reduction of oxidative stress. Biofactors 48(3):611–633

Alrawaiq N, Abdullah AZMAN (2014) Dietary phytochemicals activate the redox-sensitive transcription factor Nrf2. Int J Pharm Pharm Sci 6:11–16

Altemimi A, Lakhssassi N, Baharlouei A, Watson DG, Lightfoot DA (2017) Phytochemicals: extraction, isolation, and identification of bioactive compounds from plant extracts. Plants 6(4):42

Amini SM, Akbari A (2019) Metal nanoparticles synthesis through natural phenolic acids. IET Nanobiotechnol 13(8):771–777

Andal V, Kannan K, Selvaraj V, Suba K (2022) Plant-derived nanoparticles for heavy metal remediation. In: Phytonanotechnology. Springer Nature Singapore, Singapore, pp 59–76

Ates M, Demir V, Arslan Z, Kaya H, Yılmaz S, Camas M (2016) Chronic exposure of tilapia (*Oreochromis niloticus*) to iron oxide nanoparticles: effects of particle morphology on accumulation, elimination, hematology and immune responses. Aquat Toxicol 177:22–32

Awad E, Awaad A (2017) Role of medicinal plants on growth performance and immune status in fish. Fish Shellfish Immunol 67:40–54

Aziz S, Abdullah S (2022) Toxicity of metal oxide nanoparticles in freshwater fish. Nanomaterials in the battle against pathogens and disease vectors. CRC Press, pp 257–282

Badran SR, Hamed A (2024) Is the trend toward a sustainable green synthesis of copper oxide nanoparticles completely safe for *Oreochromis niloticus* when compared to chemical ones?: using oxidative stress, bioaccumulation, and histological biomarkers. Environ Sci Pollut Res Int 31(6):9477–9494

Baker TJ, Tyler CR, Galloway TS (2014) Impacts of metal and metal oxide nanoparticles on marine organisms. Environ Pollut 186:257–271

Bancroft GJ, Schreiber RD, Bosma GC, Bosma MJ, Unanue ER (1987) AT cell-independent mechanism of macrophage activation by interferon-gamma. J Immun 139(4):1104–1107

Banjarnahor SD, Artanti N (2014) Antioxidant properties of flavonoids. Med J Indones 23(4):239–244

Barclay LRC, Vinqvist MR, Mukai K, Goto H, Hashimoto Y, Tokunaga A, Uno H (2000) On the antioxidant mechanism of curcumin: classical methods are needed to determine antioxidant mechanism and activity. Org Lett 2(18):2841–2843

Bardestani A, Ebrahimpour S, Esmaeili A, Esmaeili A (2021) Quercetin attenuates neurotoxicity induced by iron oxide nanoparticles. J Nanobiotechnol 19:1–33

Batley GE, Kirby JK, McLaughlin MJ (2013) Fate and risks of nanomaterials in aquatic and terrestrial environments. Acc Chem Res 46(3):854–862

Bhardwaj J, Chaudhary N, Seo HJ, Kim MY, Shin TS, Kim JD (2014) Immunomodulatory effect of tea saponin in immune T-cells and T-lymphoma cells via regulation of Th1, Th2 immune response and MAPK/ERK2 signaling pathway. Immunopharmacol Immunotoxicol 36(3):202–210

Bhatti R, Shakeel H, Malik K, Qasim M, Khan MA, Ahmed N, Jabeen S (2022) Inorganic nanoparticles: toxic effects, mechanisms of cytotoxicity and phytochemical interactions. Adv Pharm Bull 12(4):757

Bitwell C, Indra SS, Luke C, Kakoma MK (2023) A review of modern and conventional extraction techniques and their applications for extracting phytochemicals from plants. Sci Afr 19:e01585

Bobo D, Robinson KJ, Islam J, Thurecht KJ, Corrie SR (2016) Nanoparticle-based medicines: a review of FDA-approved materials and clinical trials to date. Pharm Res 33:2373–2387

Borowska S, Brzoska MM, Tomczyk M (2018) Complexation of bioelements and toxic metals by polyphenolic compounds–implications for health. Curr Drug Targets 19(14):1612–1638

Brandts I, Cánovas M, Tvarijonaviciute A, Llorca M, Vega A, Farré M, Pastor J, Roher N, Teles M (2022) Nanoplastics are bioaccumulated in fish liver and muscle and cause DNA damage after a chronic exposure. Environ Res 212:113433

Brar SK, Verma M, Tyagi RD, Surampalli RY (2010) Engineered nanoparticles in wastewater and wastewater sludge–evidence and impacts. Waste Manag 30(3):504–520

Bravo L (1998) Polyphenols: chemistry, dietary sources, metabolism, and nutritional significance. Nutr Rev 56(11):317–333

Burkard M, Leischner C, Lauer UM, Busch C, Venturelli S, Frank J (2017) Dietary flavonoids and modulation of natural killer cells: implications in malignant and viral diseases. J Nutr Biochem 46:1–12

Burkina V, Zlabek V, Zamaratskaia G (2015) Effects of pharmaceuticals present in aquatic environment on phase I metabolism in fish. Environ Toxicol Pharmacol 40(2):430–444

Buzea C, Pacheco I (2017) Nanomaterial and nanoparticle: origin and activity. In: Ghorbanpour M, Manika KH, Varma A (eds) Nanoscience and plant–soil systems. Springer International Publishing, Cham, pp 71–112

Callaghan NI, MacCormack TJ (2017) Ecophysiological perspectives on engineered nanomaterial toxicity in fish and crustaceans. Comp Biochem Physiol C Toxicol Pharmacol 193:30–41

Cao Y, Long J, Liu L, He T, Jiang L, Zhao C, Li Z (2017) A review of endoplasmic reticulum (ER) stress and nanoparticle (NP) exposure. Life Sci 186:33–42

Carmo TL, Siqueira PR, Azevedo VC, Tavares D, Pesenti EC, Cestari MM, Carmo TLL, Martinez CBR, Fernandes MN (2019) Overview of the toxic effects of titanium dioxide nanoparticles in blood, liver, muscles, and brain of a Neotropical detritivorous fish. Environ Toxicol 34(4):457–468

Carrillo Y, Torres-Duarte C, Oviedo MJ, Hirata GA, Huerta-Saquero A, Vazquez-Duhalt R (2015) Lipid peroxidation and protein oxidation induced by different nanoparticles in zebrafish organs. Appl Ecol Environ Res 13(3):709–723

Cazenave J, Ale A, Bacchetta C, Rossi AS (2019) Nanoparticles toxicity in fish models. Curr Pharm Des 25(37):3927–3942

Chakraborty SB, Hancz C (2011) Application of phytochemicals as immunostimulant, antipathogenic and antistress agents in finfish culture. Rev Aquacult 3(3):103–119
Chakraborty SB, Horn P, Hancz C (2014) Application of phytochemicals as growth-promoters and endocrine modulators in fish culture. Rev Aquacult 6(1):1–19
Chakraborty C, Sharma AR, Sharma G, Lee SS (2016) Zebrafish: a complete animal model to enumerate the nanoparticle toxicity. J Nanobiotechnol 14:1–13
Chen T, Zhang X, Zhu G, Liu H, Chen J, Wang Y, He X (2020) Quercetin inhibits TNF-α induced HUVECs apoptosis and inflammation via downregulating NF-kB and AP-1 signaling pathway in vitro. Medicine (Baltimore) 99(38):e22241
Chor SY, Hui AY, To KF, Chan KK, Go YY, Chan HLY, Chan HL, Leung WK, Sung JJ, Sung JJY (2005) Anti-proliferative and pro-apoptotic effects of herbal medicine on hepatic stellate cell. J Ethnopharmacol 100(1–2):180–186
Correia AT, Rodrigues S, Ferreira-Martins D, Nunes AC, Ribeiro MI, Antunes SC (2020) Multi-biomarker approach to assess the acute effects of cerium dioxide nanoparticles in gills, liver and kidney of *Oncorhynchus mykiss*. Comp Biochem Physiol C Toxicol Pharmacol 238:108842
Dave M, Attur M, Palmer G, Al-Mussawir HE, Kennish L, Patel J, Abramson SB (2008) The antioxidant resveratrol protects against chondrocyte apoptosis via effects on mitochondrial polarization and ATP production. Arthritis Rheum 58(9):2786–2797
de Sá Coutinho D, Pacheco MT, Frozza RL, Bernardi A (2018) Anti-inflammatory effects of resveratrol: mechanistic insights. Int J Mol Sci 19(6):1812
Dini L, Panzarini E, Mariano S, Passeri D, Reggente M, Rossi M, Vergallo C (2015) Microscopies at the nanoscale for nano-scale drug delivery systems. Curr Drug Targets 16(13):1512–1530
Egbujor MC, Petrosino M, Zuhra K, Saso L (2022) The role of organosulfur compounds as Nrf2 activators and their antioxidant effects. Antioxidants 11(7):1255
Egbuna C, Parmar VK, Jeevanandam J, Ezzat SM, Patrick-Iwuanyanwu KC, Adetunji CO, ..., Ibeabuchi CG (2021) Toxicity of nanoparticles in biomedical application: nanotoxicology. J Toxicol 2021(1):9954443
Elumalai P, Kurian A, Lakshmi S, Faggio C, Esteban MA, Ringø E (2020) Herbal immunomodulators in aquaculture. Rev Fish Sci Aquac 29(1):33–57
Engwa GA (2018) Free radicals and the role of plant phytochemicals as antioxidants against oxidative stress-related diseases. Phytochemicals: source of antioxidants and role in disease prevention. BoD–Books on Demand 7:49–74
Ermolin MS, Fedotov PS, Malik NA, Karandashev VK (2018) Nanoparticles of volcanic ash as a carrier for toxic elements on the global scale. Chemosphere 200:16–22
Fan ZeJun FZ, Zou PengFei ZP, Yao CuiLuan YC (2015) Toll-like receptors (TLR) and its signaling pathway in teleost. Sci China Life Sci 68(7):1889–1911
Farag MR, El Behery EI, Nouh DS, Attia YA, Alhotan RA, Alagawany M, Di Cerbo A, Hassan MA (2024) Chamomile essential oil improves the growth, immunity, and antioxidant status of Nile tilapia exposed to nanosized alumina. Aquacult Int 32(2):1613–1628
Farkhondeh T, Folgado SL, Pourbagher-Shahri AM, Ashrafizadeh M, Samarghandian S (2020) The therapeutic effect of resveratrol: focusing on the Nrf2 signaling pathway. Biomed Pharmacother 127:110234
Fernando I, Zhou Y (2019) Impact of pH on the stability, dissolution and aggregation kinetics of silver nanoparticles. Chemosphere 216:297–305
Fujimoto T, Gotoh H (2023) Feature selection for the interpretation of antioxidant mechanisms in plant phenolics. Molecules 28(3):1454
Ghafarifarsani H, Hedayati SA, Yousefi M, Hoseinifar SH, Yarahmadi P, Mahmoudi SS, Van Doan H (2023) Toxic and bioaccumulative effects of zinc nanoparticle exposure to goldfish, *Carassius auratus* (Linnaeus, 1758). Drug Chem Toxicol 46(5):984–994
Giordo R, Nasrallah GK, Al-Jamal O, Paliogiannis P, Pintus G (2020) Resveratrol inhibits oxidative stress and prevents mitochondrial damage induced by zinc oxide nanoparticles in zebrafish (*Danio rerio*). Int J Mol Sci 21(11):3838
Girilal M, Krishnakumar V, Poornima P, Fayaz AM, Kalaichelvan PT (2015) A comparative study on biologically and chemically synthesized silver nanoparticles induced heat shock proteins on fresh water fish *Oreochromis niloticus*. Chemosphere 139:461–468
Gololo SS (2018) Effects of environmental factors on the accumulation of phytochemicals in plants. In: Chukwuebuka E, Chinenye Ifemeje J, Kumar SH, Sharif N (eds) Phytochemistry. Apple Academic Press, Florida, pp 267–278
Goncalves DM, De Liz R, Girard D (2011) The inflammatory process in response to nanoparticles. Sci World J 11:2442

Gong H, Li R, Li F, Guo X, Xu L, Gan L, Yan M, Wang J (2023) Toxicity of nanoplastics to aquatic organisms: genotoxicity, cytotoxicity, individual level and beyond individual level. J Hazard Mater 443:130266

Granado-Serrano AB, Martín MÁ, Bravo L, Goya L, Ramos S (2012) Quercetin attenuates TNF-induced inflammation in hepatic cells by inhibiting the NF-κB pathway. Nutr Cancer 64(4):588–598

Grayfer L, Kerimoglu B, Yaparla A, Hodgkinson JW, Xie J, Belosevic M (2018) Mechanisms of fish macrophage antimicrobial immunity. Front Immunol 9:1105

Grenet I, Yin Y, Comet JP, Gelenbe E (2018) Machine learning to predict toxicity of compounds. In: Artificial neural networks and machine learning, ICANN 2018: 27th international conference on artificial neural networks, Rhodes, Greece, October 4–7, 2018, Proceedings, Part I 27. Springer International Publishing, pp 335–345

Griffin S, Masood MI, Nasim MJ, Sarfraz M, Ebokaiwe AP, Schäfer KH, Masood M, Nasim M, Ebokaiwe A, Keck C, Jacob C (2017) Natural nanoparticles: a particular matter inspired by nature. Antioxidants 7(1):3

Gruszecki WI, Strzałka K (2005) Carotenoids as modulators of lipid membrane physical properties. Biochimica Et Biophysica Acta (BBA)-Mol Basis Dis 1740(2):108–115

Guerranti C, Renzi M (2015) Ecotoxicity of nanoparticles in aquatic environments: a review based on multivariate statistics of meta-data. J Environ Anal Chem 2(04):1000149

Gülçin İ (2010) Antioxidant properties of resveratrol: a structure–activity insight. Innov Food Sci Emerg Technol 11(1):210–218

Gupta GS, Shanker R, Dhawan A, Kumar A (2017) Impact of nanomaterials on the aquatic food chain. Nanosci Food Agric 5:309–333

Gupta V, Mohapatra S, Mishra H, Farooq U, Kumar K, Ansari MJ, Ansari M, Aldawsari M, Alalaiwe A, Mirza M, Iqbal Z (2022) Nanotechnology in cosmetics and cosmeceuticals—a review of latest advancements. Gels 8(3):173

Gurfinkel DM (2000) The bioactivity of saponins: triterpenoid and steroidal glycosides. Drug Metab Drug Interact 17(1–4):211–236

Haftcheshmeh SM, Abedi M, Mashayekhi K, Mousavi MJ, Navashenaq JG, Mohammadi A, Momtazi-Borojeni AA (2022) Berberine as a natural modulator of inflammatory signaling pathways in the immune system: focus on NF-κB, JAK/STAT, and MAPK signaling pathways. Phytother Res 36(3):1216–1230

Hajirezaee S, Rafieepour A, Khanjani MH (2023) Ameliorating effects of gingko, *Ginkgo biloba* extract on waterborne toxicity of titanium dioxide nanoparticles (TiO_2) in the rainbow trout, *Oncorhynchus mykiss*: growth, histology, oxidative stress, immunity, antioxidant defense and liver function. Aquac Rep 31:101635

Hamed HS, Abdel-Tawwab M (2021) Dietary pomegranate (*Punica granatum*) peel mitigated the adverse effects of silver nanoparticles on the performance, haemato-biochemical, antioxidant, and immune responses of Nile tilapia fingerlings. Aquaculture 540:736–742

Haque E, Ward AC (2018) Zebrafish as a model to evaluate nanoparticle toxicity. Nanomaterials 8(7):561

Hedayati A, Mazandarani M, Jafar A, Bagheri T (2024) Dietary effect of molasses supplement on some hematological indices of common carp (*Cyprinus carpio*) exposed to titanium oxide nanoparticles. Journal of Aquaculture Development 18(1):29–41

Hong-Geller E, Chaudhary A, Lauer S (2008) Targeting toll-like receptor signaling pathways for design of novel immune therapeutics. Curr Drug Discov Technol 5(1):29–38

Horie M, Tabei Y (2021) Role of oxidative stress in nanoparticles toxicity. Free Radic Res 55(4):331–342

Hoseini SM, Hedayati A, Mirghaed AT, Ghelichpour M (2016) Toxic effects of copper sulfate and copper nanoparticles on minerals, enzymes, thyroid hormones and protein fractions of plasma and histopathology in common carp *Cyprinus carpio*. Exp Toxicol Pathol 68(9):493–503

Hu Q, Wang H, He C, Jin Y, Fu Z (2021) Polystyrene nanoparticles trigger the activation of p38 MAPK and apoptosis via inducing oxidative stress in zebrafish and macrophage cells. Environ Pollut 269:116075

Huang Y, Bu Q (2022) Adverse effects of phytochemicals. In: Zhang L (ed) Nutritional toxicology. Springer Nature Singapore, Singapore, pp 355–384

Hussain I, Singh NB, Singh A, Singh H, Singh SC (2016) Green synthesis of nanoparticles and its potential application. Biotechnol Lett 38:545–560

Jannu V, Baddam PG, Boorgula AK, Jambula SR (2012) A review on hepatoprotective plants. Int J Drug Dev Res 4(3):1–8

Jat D, Parihar P, Kothari SC, Parihar MS (2013) Curcumin reduces oxidative damage by increasing reduced glutathione and preventing membrane permeability transition in isolated brain mitochondria. Cell Mol Biol (Noisy-Le-Grand) 59(2):1899–1905

Jenkins T, Gouge J (2021) Nrf2 in cancer, detoxifying enzymes and cell death programs. Antioxidants 10(7):1030

Jia XJ, Li X, Wang F, Liu HQ, Zhang DJ (2017) Berbamine exerts anti-inflammatory effects via inhibition of NF-κB and MAPK signaling pathways. Cell Physiol Biochem 41(6):2307–2318

Jia R, Gu Z, He Q, Du J, Cao L, Jeney G, Xu P, Yin G (2019) Anti-oxidative, anti-inflammatory and hepatoprotective effects of *Radix Bupleuri* extract against oxidative damage in tilapia (*Oreochromis niloticus*) via Nrf2 and TLRs signaling pathway. Fish Shellfish Immunol 93:395–405

Jiang L, Zhang G, Li Y, Shi G, Li M (2021) Potential application of plant-based functional foods in the development of immune boosters. Front Pharmacol 12:637782

Jovanović B, Palić D (2012) Immunotoxicology of non-functionalized engineered nanoparticles in aquatic organisms with special emphasis on fish—review of current knowledge, gap identification, and call for further research. Aquat Toxicol 118:141–151

Jyonouchi H, Zhang L, Gross M, Tomita Y (1994) Immunomodulating actions of carotenoids: enhancement of in vivo and in vitro antibody production to T-dependent antigens. Nutr Cancer 21(1):47–58. https://doi.org/10.1080/01635589409514303

Kahkhaie KR, Mirhosseini A, Aliabadi A, Mohammadi A, Mousavi MJ, Haftcheshmeh SM, Sathyapalan T, Sahebkar A (2019) Curcumin: a modulator of inflammatory signaling pathways in the immune system. Inflammopharmacology 27:885–900

Kandeil MA, Mohammed ET, Hashem KS, Aleya L, Abdel-Daim MM (2020) Moringa seed extract alleviates titanium oxide nanoparticles (TiO2-NPs)-induced cerebral oxidative damage, and increases cerebral mitochondrial viability. Environ Sci Pollut Res 27(16):19169–19184

Kefeni KK, Mamba BB, Msagati TA (2017) Application of spinel ferrite nanoparticles in water and wastewater treatment: a review. Sep Purif Technol 188:399–422

Khabbazi M, Harsij M, Hedayati SAA, Gholipoor H, Gerami MH, Ghafari Farsani H (2015) Effect of CuO nanoparticles on some hematological indices of rainbow trout *Oncorhynchus mykiss* and their potential toxicity. Nanomedicine J 2(1):67–73

Khafaga AF, Naiel MA, Dawood MA, Abdel-Latif HM (2020) Dietary *Origanum vulgare* essential oil attenuates cypermethrin-induced biochemical changes, oxidative stress, histopathological alterations, apoptosis, and reduces DNA damage in Common carp (*Cyprinus carpio*). Aquat Toxicol 228:105624

Khan MS, Jabeen F, Qureshi NA, Asghar MS, Shakeel M, Noureen A (2015) Toxicity of silver nanoparticles in fish: a critical review. J Bioenviron Sci 6(5):211–227

Khan I, Saeed K, Khan I (2019) Nanoparticles: properties, applications and toxicities. Arab J Chem 12(7):908–931

Kharissova OV, Dias HR, Kharisov BI, Pérez BO, Pérez VMJ (2013) The greener synthesis of nanoparticles. Trends Biotechnol 31(4):240–248

Khoei AJ (2021) Evaluation of potential immunotoxic effects of iron oxide nanoparticles (IONPs) on antioxidant capacity, immune responses and tissue bioaccumulation in common carp (*Cyprinus carpio*). Comp Biochem Physiol C Toxicol Pharmacol 244:109005

Khursheed A (2016) Plant-based natural compounds and herbal extracts as promising apoptotic agents: their implications for cancer prevention and treatment. Adv Biomed Pharm 03(04):225–248

Kim HA, Choi YJ, Kim KW, Lee BT, Ranville JF (2012) Nanoparticles in the environment: stability and toxicity. Rev Environ Health 27(4):175–179

Kirubakaran D, Wahid JBA, Karmegam N, Jeevika R, Sellapillai L, Rajkumar M, SenthilKumar KJ (2025) A comprehensive review on the green synthesis of nanoparticles: advancements in biomedical and environmental applications. Biomed Mater Devices. https://doi.org/10.1007/s44174-025-00295-4

Krzyżewska I, Kyzioł-Komosińska J, Rosik-Dulewska C, Czupioł J, Antoszczyszyn-Szpicka P (2016) Inorganic nanomaterials in the aquatic environment: behavior, toxicity, and interaction with environmental elements. Arch Environ Prot. https://doi.org/10.1515/aep-2016-0011

Kumar KH, Khanum F (2013) Hydroalcoholic extract of *Cyperus rotundus* ameliorates H_2O_2-induced human neuronal cell damage via its anti-oxidative and anti-apoptotic machinery. Cell Mol Neurobiol 33:5–17

Kumar M, Gupta G, Muhammed NP, Varghese T, Srivastava PP, Bhushan S, R K, Shukla SP, Krishna G, Gupta S (2022) Toxicity ameliorative effect of vitamin E against super-paramagnetic iron oxide nanoparticles on haemato-immunological responses, antioxidant capacity, oxidative stress, and

metabolic enzymes activity during exposure and recovery in *Labeo rohita* fingerlings. Aquacult Int 30(4):1711–1739
Kumari P, Alam M, Siddiqi WA (2019) Usage of nanoparticles as adsorbents for waste water treatment: an emerging trend. Sustain Mater Technol 22:e00128
Lee JM, Johnson JA (2004) An important role of Nrf2-ARE pathway in the cellular defense mechanism. BMB Rep 37(2):139–143
Li AN, Li S, Zhang YJ, Xu XR, Chen YM, Li HB (2014) Resources and biological activities of natural polyphenols. Nutrients 6(12):6020–6047
Li HT, Wu M, Wang J, Qin CJ, Long J, Zhou SS, Yuan P, Jing XQ (2020) Protective role of *Angelica sinensis* extract on trichlorfon-induced oxidative damage and apoptosis in gills and erythrocytes of fish. Aquaculture 519:734895
Li M, Kong Y, Wu X, Guo G, Sun L, Lai Y, Zhang J, Niu X, Wang G (2022) Effects of dietary curcumin on growth performance, lipopolysaccharide-induced immune responses, oxidative stress and cell apoptosis in snakehead fish (Channa argus). Aquac Rep 22:100981
Liang R, Liu Y, Fu LM, Ai XC, Zhang JP, Skibsted LH (2012) Antioxidants and physical integrity of lipid bilayers under oxidative stress. J Agric Food Chem 60(41):10331–10336
Liu X, Zheng J, Zhou H (2011) TLRs as pharmacological targets for plant-derived compounds in infectious and inflammatory diseases. Int Immunopharmacol 11(10):1451–1456
Liu K, Abdullah AA, Huang M, Nishioka T, Altaf-Ul-Amin M, Kanaya S (2017) Novel approach to classify plants based on metabolite-content similarity. Biomed Res Int 2017(1):5296729
Liu Y, Kim S, Kim YJ, Perumalsamy H, Lee S, Hwang E, Yi TH (2019) Green synthesis of gold nanoparticles using *Euphrasia officinalis* leaf extract to inhibit lipopolysaccharide-induced inflammation through NF-κB and JAK/STAT pathways in RAW 264.7 macrophages. Int J Nanomed 14:2945–2959
Luyts K, Napierska D, Nemery B, Hoet PH (2013) How physico-chemical characteristics of nanoparticles cause their toxicity: complex and unresolved interrelations. Environ Sci Process Impacts 15(1):23–38
Ma C, Wang Y, Dong L, Li M, Cai W (2015) Anti-inflammatory effect of resveratrol through the suppression of NF-κB and JAK/STAT signaling pathways. Acta Biochim Biophys Sin 47(3):207–213
MacCormack TJ, Goss GG (2008) Identifying and predicting biological risks associated with manufactured nanoparticles in aquatic ecosystems. J Ind Ecol 12(3):286–296
Mahboub HH, Rashidian G, Hoseinifar SH, Kamel S, Zare M, Ghafarifarsani H, ... and Van Doan H (2022) Protective effects of Allium hirtifolium extract against foodborne toxicity of zinc oxide nanoparticles in common carp (Cyprinus carpio). Comparative Biochemistry and Physiology Part C: Toxicology and Pharmacology 257:109345
Majedi SM, Kelly BC, Lee HK (2014) Role of combinatorial environmental factors in the behavior and fate of ZnO nanoparticles in aqueous systems: a multiparametric analysis. J Hazard Mater 264:370–379
Malemud CJ, Pearlman E (2009) Targeting JAK/STAT signaling pathway in inflammatory diseases. Curr Signal Transduct Ther 4(3):201–221
Mansour WA, Abdelsalam NR, Tanekhy M, Khaled AA, Mansour AT (2021) Toxicity, inflammatory and antioxidant genes expression, and physiological changes of green synthesis silver nanoparticles on Nile tilapia (*Oreochromis niloticus*) fingerlings. Comp Biochem Physiol C Toxicol Pharmacol 247:109068
Manzoor Z, Koh YS (2012) Mitogen-activated protein kinases in inflammation. J Bacteriol Virol 42(3):189–195
Margina D, Ilie M, Manda G, Neagoe I, Mocanu M, Ionescu D, ... and Ganea C (2012) Quercetin and epigallocatechin gallate effects on the cell membranes biophysical properties correlate with their antioxidant potential. Gen Physiol Biophys 31(1):47–55
Martins-Gomes C, Silva AM (2023) Natural products as a tool to modulate the activity and expression of multidrug resistance proteins of intestinal barrier. J Xenobiotics 13(2):172–192
Martins-Gomes C, Nunes FM, Silva AM (2024) Natural products as dietary agents for the prevention and mitigation of oxidative damage and inflammation in the intestinal barrier. Antioxidants 13(1):65
Merecz-Sadowska A, Sitarek P, Śliwiński T, Zajdel R (2020) Anti-inflammatory activity of extracts and pure compounds derived from plants via modulation of signaling pathways, especially PI3K/AKT in macrophages. Int J Mol Sci 21(24):9605
Mihailovic V, Katanic Stankovic JS, Selakovic D, Rosic G (2021) An overview of the beneficial role of antioxidants in the treatment of nanoparticle-induced toxicities. Oxid Med Cell Longev 2021(1):7244677

Mirghaed AT, Yarahmadi P, Craig PM, Farsani HG, Ghysvandi N, Eagderi S (2018) Hemato-immunological, serum metabolite and enzymatic stress response alterations in exposed rainbow trout (*Oncorhynchus mykiss*) to nanosilver. Int J Aquat Biol 6(4):221–234
Mohammadi E, Amini SM (2024) Green synthesis of stable and biocompatible silver nanoparticles with natural flavonoid apigenin. Nano-Structures & Nano-Objects 38:101175
Molyneux RJ, Lee ST, Gardner DR, Panter KE, James LF (2007) Phytochemicals: the good, the bad and the ugly? Phytochemistry 68(22–24):2973–2985
Monostory K, Jemnitz K, Vereczkey L (1996) Xenobiotic metabolizing enzymes in fish: diversity, regulation and biomarkers for pollutant exposure. Acta Physiol Hung 84(4):369–382
Morales-Cruz M, Figueroa CM, González-Robles T, Delgado Y, Molina A, Méndez J, ..., Griebenow K (2014) Activation of caspase-dependent apoptosis by intracellular delivery of cytochrome c-based nanoparticles. J Nanobiotechnology 12:1–11
Naiel MA, El-Kholy AI, Negm SS, Ghazanfar S, Shukry M, Zhang Z, Naiel MAE, Ahmadifar E, Abdel-Latif HMR, Abdel-Latif HM (2023) A mini-review on plant-derived phenolic compounds with particular emphasis on their possible applications and beneficial uses in aquaculture. Ann Anim Sci 23(4):971–977
Naiim M, Boualem A, Ferre C, Jabloun M, Jalocha A, Ravier P (2015) Multiangle dynamic light scattering for the improvement of multimodal particle size distribution measurements. Soft Matter 11(1):28–32
Nazir S, Zhang JM, Junaid M, Saleem S, Ali A, Ullah A, and Khan S (2024) Metal-based nanoparticles: basics, types, fabrications and their electronic applications. Z Phys Chem 238(6):965–995
Neves AR, Nunes C, Reis S (2015) New insights on the biophysical interaction of resveratrol with biomembrane models: relevance for its biological effects. J Phys Chem B 119(35):11664–11672
Nik Mohamad Nek Rahimi N, Natrah I, Loh JY, Ervin Ranzil FK, Gina M, Lim SHE, Lai K-S, Chong CM (2022) Phytocompounds as an alternative antimicrobial approach in aquaculture. Antibiotics 11(4):469
Noureen A, De Marco G, Rehman N, Jabeen F, Cappello T (2022) Ameliorative hematological and histomorphological effects of dietary trigonella foenum-graecum seeds in common carp (Cyprinus carpio) exposed to copper oxide nanoparticles. Int J Environ Res Public Health 19(20):13462
Noureen A, Jabeen F, Wajid A, Kazim MZ, Safdar N, Cappello T (2023) Natural bioactive phytocompounds to reduce toxicity in common carp *Cyprinus carpio*: a challenge to environmental risk assessment of nanomaterials. Water 15(6):1152
Oliveira MIB, Brandão FR, Tavares-Dias M, Barbosa BCN, Rocha MJS, Matos LV, Souza DCM, Majolo C, Oliveira MR, Chaves FCM, Chagas EC (2024) Essential oils of *Ocimum gratissimum*, *Lippia grata* and *Lippia origanoides* are effective in the control of the acanthocephalan *Neoechinorhynchus buttnerae* in *Colossoma macropomum*. Aquaculture 578:740043
Oo AM, Nor MNM, Lwin OM, Simbak N, Adnan LHM, Rao USM (2022) Immunomodulatory effects of apigenin, luteolin, and quercetin through natural killer cell cytokine secretion. J Appl Pharm Sci 12(9):121–126
Osborne OJ, Lin S, Chang CH, Ji Z, Yu X, Wang X, Xia T, Nel AE (2015) Organ-specific and size-dependent Ag nanoparticle toxicity in gills and intestines of adult zebrafish. ACS Nano 9(10):9573–9584
Paparella M, Scholz S, Belanger S, Braunbeck T, Bicherel P, Connors K, ..., Walter-Rohde S (2021) Limitations and uncertainties of acute fish toxicity assessments can be reduced using alternative methods. Altex 38(1):20–32
Pasieczna-Patkowska S, Cichy M, Flieger J (2025) Application of Fourier transform infrared (FTIR) spectroscopy in characterization of green synthesized nanoparticles. Molecules 30(3):684
Paunovic J, Vucevic D, Radosavljevic T, Mandić-Rajčević S, Pantic I (2020) Iron-based nanoparticles and their potential toxicity: focus on oxidative stress and apoptosis. Chem Biol Interact 316:108935
Peters R, Herrera-Rivera Z, Undas A, van der Lee M, Marvin H, Bouwmeester H, Weigel S (2015) Single particle ICP-MS combined with a data evaluation tool as a routine technique for the analysis of nanoparticles in complex matrices. J Anal At Spectrom 30(6):1274–1285
Petosa AR, Jaisi DP, Quevedo IR, Elimelech M, Tufenkji N (2010) Aggregation and deposition of engineered nanomaterials in aquatic environments: role of physicochemical interactions. Environ Sci Technol 44(17):6532–6549
Petropoulos S, Di Gioia F, Ntatsi G (2017) Vegetable organosulfur compounds and their health promoting effects. Curr Pharm des 23(19):2850–2875
Pfitzner E, Kliem S, Baus D, Litterst MC (2004) The role of STATs in inflammation and inflammatory diseases. Curr Pharm Des 10(23):2839–2850

Piluk TD, Faccio G, Letsiou S, Liang R, Freire-Gormaly M (2024) A critical review investigating the use of nanoparticles in cosmetic skin products. Environ Sci Nano 11:3674–3692

Punia P, Naagar M, Chalia S, Dhar R, Ravelo B, Thakur P, Thakur A (2021) Recent advances in synthesis, characterization, and applications of nanoparticles for contaminated water treatment-a review. Ceram Int 47(2):1526–1550

Rana S, Dixit S, Mittal A (2019) In silico target identification and validation for antioxidant and anti-inflammatory activity of selective phytochemicals. Braz Arch Biol Technol 62:e19190048

Rashidian G, Mahboub HH, Hoseinifar SH, Ghafarifarsani H, Zare M, Punyatong M, Van Doan H (2022) *Allium hirtifolium* protects *Cyprinus carpio* against the detrimental responses mediated by foodborne zinc oxide nanoparticle. Aquaculture 555:738252

Rasool S, Faheem M, Hanif U, Bahadur S, Taj S, Liaqat F, Pereira L, Liaqat I, Shaheen S, Shuaib M, Gulzar S (2022) Toxicological effects of the chemical and green ZnO NPs on *Cyprinus carpio* L. observed under light and scanning electron microscopy. Microsc Res Tech 85(3):848–860

Rastgar S, Alijani Ardeshir R, Segner H, Tyler CR, JGM Peijnenburg W, Wang Y, ..., Movahedini A (2022) Immunotoxic effects of metal-based nanoparticles in fish and bivalves. Nanotoxicology 16(1):88–113

Raut SS, Singh R, Lekhak UM (2024) Naturally occurring nanoparticles (NONPs): a review. Next Sustainability 3:100037

Redza-Dutordoir M, Averill-Bates DA (2016) Activation of apoptosis signalling pathways by reactive oxygen species. Biochimica Et Biophysica Acta (BBA)-Molecular Cell Research 1863(12):2977–2992

Reeves JF, Davies SJ, Dodd NJ, Jha AN (2008) Hydroxyl radicals (OH) are associated with titanium dioxide (TiO2) nanoparticle-induced cytotoxicity and oxidative DNA damage in fish cells. Mutat Res-Fundam Mol Mech Mutagen 640(1–2):113–122

Riley JK, Takeda K, Akira S, Schreiber RD (1999) Interleukin-10 receptor signaling through the JAK-STAT pathway: requirement for two distinct receptor-derived signals for anti-inflammatory action. J Biol Chem 274(23):16513–16521

Robinson I (2012) Nanoparticle structure by coherent X-ray diffraction. J Phys Soc Jpn 82(2):021012

Sakai M, Hikima JI, Kono T (2021) Fish cytokines: current research and applications. Fish Sci 87:1–9

Saleh MA, Clark S, Woodard B (2010) Antioxidant and free radical scavenging activities of essential oils. Ethn Dis 20:78–82

Salim T, Sershen CL, May EE (2016) Investigating the role of TNF-α and IFN-γ activation on the dynamics of iNOS gene expression in LPS stimulated macrophages. PLoS One 11(6):e0153289

Sano E, Kazaana A, Tadakuma H, Takei T, Yoshimura S, Hanashima Y, Ozawa Y, Yoshino A, Suzuki Y, Ueda T (2021) Interleukin-6 sensitizes TNF-α and TRAIL/Apo2L dependent cell death through upregulation of death receptors in human cancer cells. Biochimica Et Biophysica Acta (BBA)-Molecular Cell Research 1868(7):119037

Shakhov AN, Woerly G, Car BD, Ryffel B (1996) Interferon-gamma enhances tumor necrosis factor-alpha production by inhibiting early phase interleukin-10 transcription. Eur Cytokine Netw 7(4):741–750

Sharma A, Kumar S, Mahadevan N (2012) Nanotechnology: a promising approach for cosmetics. Int J Recent Adv Pharm Res 2(2):54–61

Sharma VK, Filip J, Zboril R, Varma RS (2015) Natural inorganic nanoparticles–formation, fate, and toxicity in the environment. Chem Soc Rev 44(23):8410–8423

Sharma A, Parikh M, Shah H, Gandhi T (2020) Modulation of Nrf2 by quercetin in doxorubicin-treated rats. Heliyon. https://doi.org/10.1016/j.heliyon.2020.e03803

Shin SA, Joo BJ, Lee JS, Ryu G, Han M, Kim WY, Park HH, Lee JH, Lee CS (2020) Phytochemicals as anti-inflammatory agents in animal models of prevalent inflammatory diseases. Molecules 25(24):5932

Simonyan R, Simonyan G, Babayan M, Simonyan M (2022) Membrane stabilizing effect of curcumin on chronic cadmium intoxication. Ajastan Kensabanakan Handes 74(4):64–68

Singh S, Aggarwal BB (1995) Activation of transcription factor NF-κB is suppressed by curcumin (diferuloylmethane)(*). J Biol Chem 270(42):24995–25000

Sousa A, Kämpfer AA, Schins RP, Carvalho F, Fernandes E, Freitas M (2025) Protective effects of quercetin on intestinal barrier and cellular viability against silver nanoparticle exposure: insights from an intestinal co-culture model. Nanotoxicology. https://doi.org/10.1080/17435390.2025.2450372

Stefanson AL, Bakovic M (2014) Dietary regulation of Keap1/Nrf2/ARE pathway: focus on plant-derived compounds and trace minerals. Nutrients 6(9):3777–3801

Subaramaniyam U, Allimuthu RS, Vappu S, Ramalingam D, Balan R, Paital B, Panda N, Rath PK, Ramalingam N, Sahoo DK (2023) Effects of microplastics, pesticides and nano-materials on fish health, oxidative stress and antioxidant defense mechanism. Front Physiol 14:1217666

Surai PF (2023) Silymarin as a vitagene modulator: effects on mitochondria integrity in stress conditions. In: Ostojic SM (ed) Molecular nutrition and mitochondria. Academic Press, New York, pp 535–559

Susan A, Rajendran K, Sathyasivam K, Krishnan UM (2019) An overview of plant-based interventions to ameliorate arsenic toxicity. Biomed Pharmacother 109:838–852

Taju G, Majeed SA, Nambi KSN, Hameed AS (2014) In vitro assay for the toxicity of silver nanoparticles using heart and gill cell lines of *Catla catla* and gill cell line of *Labeo rohita*. Comp Biochem Physiol C Toxicol Pharmacol 161:41–52

Tan X, Sun Z, Liu Q, Ye H, Zou C, Ye C, Wang A, Lin H (2018) Effects of dietary *ginkgo biloba* leaf extract on growth performance, plasma biochemical parameters, fish composition, immune responses, liver histology, and immune and apoptosis-related genes expression of hybrid grouper (*Epinephelus lanceolatus*♂× *Epinephelus fuscoguttatus*♀) fed high lipid diets. Fish Shellfish Immunol 72:399–409

Tao F, Zhang Y, Zhang Z (2019) The role of herbal bioactive components in mitochondria function and cancer therapy. Evidence-Based Complementary and Alternative Medicine 2019(1):3868354

Taştan Y, Salem MOA (2021) Use of phytochemicals as feed supplements in aquaculture: a review on their effects on growth, immune response, and antioxidant status of finfish. Journal of Agricultural Production 2(1):32–43

Temiz Ö, Kargın F (2022) Toxicological impacts on antioxidant responses, stress protein, and genotoxicity parameters of aluminum oxide nanoparticles in the liver of *Oreochromis niloticus*. Biol Trace Elem Res 200(3):1339–1346

Tepe N, Bau M (2014) Importance of nanoparticles and colloids from volcanic ash for riverine transport of trace elements to the ocean: evidence from glacial-fed rivers after the 2010 eruption of Eyjafjallajökull Volcano, Iceland. Sci Total Environ 488:243–251

Thacker H, Ram V (2024) Medicinal properties of phytochemicals: a review. J Pharmacogn Phytochem 13(2):78–82

Thummabancha K, Onparn N, Srisapoome P (2016) Analysis of hematologic alterations, immune responses and metallothionein gene expression in Nile tilapia (*Oreochromis niloticus*) exposed to silver nanoparticles. J Immunotoxicol 13(6):909–917

Topić Popović N, Čižmek L, Babić S, Strunjak-Perović I, Čož-Rakovac R (2023) Fish liver damage related to the wastewater treatment plant effluents. Environ Sci Pollut Res 30(17):48739–48768

Uematsu S, Akira S (2008) Toll-like receptors (TLRs) and their ligands. Toll-like receptors (TLRs) and innate immunity. Handb Exp Pharmacol 183:1–20

Utreja P, Verma S, Rahman M, Kumar L (2020) Use of nanoparticles in medicine. Current Biochemical Engineering 6(1):7–24

Velma V, Tchounwou PB (2013) Oxidative stress and DNA damage induced by chromium in liver and kidney of goldfish, *Carassius auratus*. Biomark Insights 8:BMI-S11456

Vineetha VP, Devika P, Prasitha K, Anilkumar TV (2021) *Tinospora cordifolia* ameliorated titanium dioxide nanoparticle-induced toxicity via regulating oxidative stress-activated MAPK and NRF2/Keap1 signaling pathways in Nile tilapia (*Oreochromis niloticus*). Comp Biochem Physiol C Toxicol Pharmacol 240:108908

Vishnu D, Dhandapani B (2021) A review on the synergetic effect of plant extracts on nanomaterials for the removal of metals in industrial effluents. Curr Anal Chem 17(2):260–271

Wang AZ, Langer R, Farokhzad OC (2012) Nanoparticle delivery of cancer drugs. Annu Rev Med 63(1):185–198

Wang S, Su R, Nie S, Sun M, Zhang J, Wu D, Moustaid-Moussa N (2014) Application of nanotechnology in improving bioavailability and bioactivity of diet-derived phytochemicals. J Nutr Biochem 25(4):363–376

Wang T, Long X, Liu Z, Cheng Y, Yan S (2015) Effect of copper nanoparticles and copper sulphate on oxidation stress, cell apoptosis and immune responses in the intestines of juvenile *Epinephelus coioides*. Fish Shellfish Immunol 44(2):674–682

Wang R, Liang R, Dai T, Chen J, Shuai X, Liu C (2019) Pectin-based adsorbents for heavy metal ions: a review. Trends Food Sci Technol 91:319–329

Wang T, Wen X, Hu Y, Zhang X, Wang D, Yin S (2019) Copper nanoparticles induced oxidation stress, cell apoptosis and immune response in the liver of juvenile *Takifugu fasciatus*. Fish Shellfish Immunol 84:648–655

Wang C, Huang C, Cao Y (2024) Epigallocatechin gallate alleviated the in vivo toxicity of ZnO nanoparticles to mouse intestine. J Appl Toxicol 44(5):686–698

Wassermann AM, Bajorath J (2011) BindingDB and ChEMBL: online compound databases for drug discovery. Expert Opin Drug Discov 6(7):683–687

Wu KC, McDonald PR, Liu J, Klaassen CD (2014) Screening of natural compounds as activators of the KEAP1-NRF2 pathway. Planta Med 80(01):97–104

Wu D, Ma Y, Cao Y, Zhang T (2020) Mitochondrial toxicity of nanomaterials. Sci Total Environ 702:134994

Xiao B, Wang X, Yang J, Wang K, Zhang Y, Sun B, Zhang T, Zhu L (2020) Bioaccumulation kinetics and tissue distribution of silver nanoparticles in zebrafish: the mechanisms and influence of natural organic matter. Ecotoxicol Environ Saf 194:110454

Yang P, Zhang J, Xiang S, Jin Z, Zhu F, Wang T, Duan G, Liu X, Gu Z, Li Y (2021) Green nanoparticle scavengers against oxidative stress. ACS Appl Mater Interfaces 13(33):39126–39134

Yin G, Cao L, Xu P, Jeney G, Nakao M (2011) Hepatoprotective and antioxidant effects of *Hibiscus sabdariffa* extract against carbon tetrachloride-induced hepatocyte damage in *Cyprinus carpio*. In Vitro Cellular & Developmental Biology-Animal 47:10–15

Yu S, Liu J, Yin Y, Shen M (2018) Interactions between engineered nanoparticles and dissolved organic matter: a review on mechanisms and environmental effects. J Environ Sci (China) 63:198–217

Yücel Ç, Karatoprak GŞ, Açıkara ÖB, Akkol EK, Barak TH, Sobarzo-Sánchez E, Aschner M, Shirooie S (2022) Immunomodulatory and anti-inflammatory therapeutic potential of gingerols and their nanoformulations. Front Pharmacol 13:902551

Zadmajid V, Mohammadi C (2017) Dietary thyme essential oil (*Thymus vulgaris*) changes serum stress markers, enzyme activity, and hematological parameters in gibel carp (*Carassius auratus gibelio*) exposed to silver nanoparticles. Iran J Fish Sci 17(3):1063–1084

Zhang M, Swarts SG, Yin L, Liu C, Tian Y, Cao Y, Okunieff P et al (2011) Antioxidant properties of quercetin. In: Joseph C, LaManna MA, Puchowicz KX, Harrison DK, Bruley DF (eds) Oxygen transport to tissue XXXII. Springer US, Boston, pp 283–289

Zhang R, Piao MJ, Kim KC, Kim AD, Choi JY, Choi J, Hyun JW (2012) Endoplasmic reticulum stress signaling is involved in silver nanoparticles-induced apoptosis. Int J Biochem Cell Biol 44(1):224–232

Zhang H, Chen Y, Wang J, Wang Y, Wang L, Duan Z (2022) Effects of temperature on the toxicity of waterborne nanoparticles under global warming: facts and mechanisms. Mar Environ Res 181:105757

Zhao X, Ren X, Zhu R, Luo Z, Ren B (2016) Zinc oxide nanoparticles induce oxidative DNA damage and ROS-triggered mitochondria-mediated apoptosis in zebrafish embryos. Aquat Toxicol 180:56–70

Zoroddu MA, Medici S, Ledda A, Nurchi VM, Lachowicz JI, Peana M (2014) Toxicity of nanoparticles. Curr Med Chem 21(33):3837–3853

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