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Sanat Chandravanshi
Department of Aquatic Animal Health Management, College of Fisheries, CAU (I) Lembucherra, Agartala, Tripura, India

Leena Thakur
Fish Processing Technology, Kerela University of fisheries and Oceans Studies, Kochi, Kerala, India

Joshi Sharon J
West Bengal University of Animal and Fishery Sciences, Chakgaria, Kolkata, West Bengal, India

Parlapalli Tharun Kumar Reddy
College of Fishery Science, Andhra Pradesh Fisheries University, SPSR Nellore, Andhra Pradesh, India

Kadam Bihari
College of Fisheries ANDUAT, Kumarganj, Ayodhya, Uttar Pradesh, India

Pranay Kumar Rai
Fisheries Resource Management, College of Fisheries Lembucherra, CAU, Agartala, Tripura, India

Corresponding Author:
Pranay Kumar Rai
Fisheries Resource Management, College of Fisheries Lembucherra, CAU, Agartala, Tripura, India

Sustainable health management in freshwater aquaculture: Integrating Omics, green therapeutics, and nanotechnology

Sanat Chandravanshi, Leena Thakur, Joshi Sharon J, Parlapalli Tharun Kumar Reddy, Kadam Bihari and Pranay Kumar Rai

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Abstract
Freshwater aquaculture is a critical component of global food security, yet its sustainability is threatened by infectious disease outbreaks exacerbated by intensive farming practices. Traditional chemical therapeutics, while initially effective, pose significant environmental and safety concerns, including non-target toxicity, pathogen resistance, and regulatory restrictions. This comprehensive review synthesizes recent advances in sustainable disease management strategies, emphasizing the role of omics technologies in elucidating host-pathogen interactions, the application of green therapeutics and immunostimulants, and the emerging potential of nanotechnology. Through a systematic analysis of 40 omics-based studies, we highlight key bacterial, viral, and parasitic pathogens that affect major freshwater species and detail the molecular mechanisms underlying disease progression and immunity. We further explore how nanotechnology—particularly nano-vaccines, selenium nanoparticles, and chitosan-based nanocomposites—offers innovative solutions for targeted therapy, enhanced nutrition, and environmental remediation. The integration of these approaches within a proactive health management framework is essential for advancing ecological safety, host resilience, and economic viability in aquaculture. We conclude that the future of sustainable aquaculture depends on the synergistic application of omics-driven insights, green chemistry, and nano-enabled technologies, supported by global cooperation in biosecurity and policy implementation.

Keywords: Freshwater aquaculture, sustainable disease management, Omics technologies, green therapeutics, nanotechnology in aquaculture, host-pathogen interactions

1. Introduction

The complex interactions among host, pathogen, and environment influence fish health. This balance is often disturbed in intensive culture systems due to high stocking densities, deteriorating water quality, and inadequate nutrition (Mishra *et al.*, 2017; Snieszko, 1974) [23, 31]. As a result, a wide range of infectious diseases has emerged as significant threats to production. In Indian freshwater aquaculture, bacterial diseases such as Motile Aeromonad Septicemia (MAS) and *Edwardsiellosis*, along with parasitic diseases like Argulosis and *Ichthyophthiriasis*, frequently cause high morbidity, mass mortalities, and economic losses (Mishra *et al.*, 2017; Sahoo *et al.*, 2013) [23, 28]. Additionally, parasitic conditions such as velvet disease, caused by Amyloodinium and Piscinoodinium, continue to affect both freshwater and marine aquaculture globally, including ornamental fish culture, resulting in significant financial losses (Lieke *et al.*, 2020) [20].

To manage these infections, aquaculture has traditionally relied on chemical therapeutics such as copper sulphate, formalin, and triphenylmethane dyes like malachite green (Lieke *et al.*, 2020) [20]. Although effective in the short term, these chemicals are non-specific, toxic to non-target organisms, stressful to fish, and environmentally persistent (Lieke *et al.*, 2020; Sudova *et al.*, 2007) [20]. Their prolonged use has also contributed to pathogen resistance, while increasing regulatory restrictions—particularly in the European Union—have limited their availability due to concerns over food and environmental safety (Lieke *et al.*, 2020) [20].

These limitations have created a pressing need for sustainable disease management solutions. Current global efforts emphasize a shift from reactive, chemical-based treatments to proactive strategies focusing on ecological safety and host resilience (Lieke *et al.*, 2020) [20].

Promising "green" therapeutics, such as hydrogen peroxide and peracetic acid, offer effective pathogen control while breaking down into harmless byproducts. At the same time, the use of immunostimulants and functional feeds, including prebiotics, probiotics, synbiotics, and humic substances, has gained attention for their ability to enhance immunity, reduce stress, and improve overall health (Lieke *et al.*, 2020; Dawood *et al.*, 2018) [20, 7].

Given this backdrop, a comprehensive understanding of emerging sustainable fish health management strategies is essential for guiding future aquaculture practices. This review focuses on evaluating major freshwater fish diseases, limitations of conventional chemical treatments, and recent advancements in green therapeutics and immunomodulatory approaches for sustainable aquaculture.

2. Methodology

A systematic review was conducted in accordance with the PRISMA guidelines to ensure a transparent and structured synthesis of the literature related to infectious diseases in freshwater aquaculture. A comprehensive search was conducted in Scopus, Web of Science, and PubMed for studies published up to December 2023. The search terms used were: ("freshwater aquaculture" OR "freshwater fish") AND ("disease" OR "infection") AND (bacterial OR viral OR parasitic OR fungal), ensuring wide coverage of disease-related research in freshwater systems.

Studies were included if they were original research articles, focused on freshwater farmed fish species, investigated bacterial, viral, parasitic, or fungal diseases, and applied omics-based approaches. Review articles, non-English papers, studies unrelated to freshwater aquaculture, and research lacking omics analysis were excluded.

The initial search yielded 350 records, and 75 duplicates were removed. Titles of 275 studies were screened, and 90 were excluded for irrelevance. Abstract screening of 185 studies led to the exclusion of 110 papers based on species, pathogen type, article type, or language. A full-text assessment was performed on 75 articles, and 35 were excluded because they did not utilize omics techniques or lacked sufficient data. Finally, 40 studies met all criteria and were included in this review. The selection process is summarized in the PRISMA flow diagram (Figure 1).

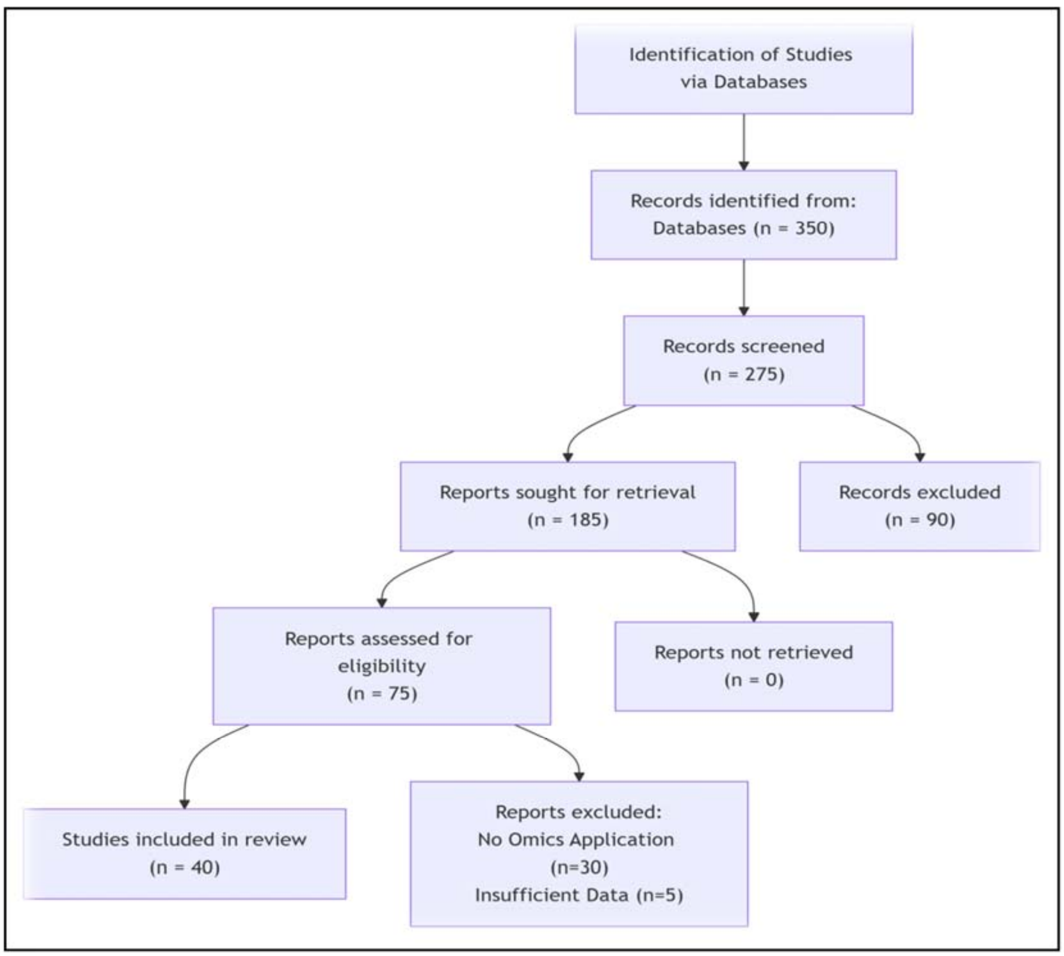

Fig 1: PRISMA Flow Diagram

3. Major Pathogens in Freshwater Aquaculture

A diverse array of infectious diseases critically constrains the productivity of freshwater aquaculture. The systematic review of the selected literature highlights bacterial pathogens as the most extensively studied, followed by viral and parasitic agents, reflecting their significant economic impact on major freshwater species such as carp, tilapia, trout, and catfish.

3.1 Bacterial Pathogens

Bacterial diseases constitute the most frequent and devastating challenge in freshwater systems. Aeromoniasis, caused by *Aeromonas hydrophila* and related species, emerged as a predominant threat, leading to *motile aeromonad septicemia* (MAS) in a wide range of species, including common carp *(Cyprinus carpio)* and tilapia (*Oreochromis niloticus*) (Di *et al.*, 2017; Sherif & Mahfouz, 2019) [8, 29]. Infections are often characterized by hemorrhagic septicemia, dermal ulcers, and high mortality, particularly under stressful conditions.

Another significant bacterial disease is streptococcosis, primarily caused by Streptococcus iniae and S. agalactiae. This pathogen is a significant concern for tilapia aquaculture globally, causing meningoencephalitis, exophthalmia, and erratic swimming behavior (Zhu *et al.*, 2015; Zhao *et al.*, 2015) [40, 37]. The reviewed omics studies consistently show a strong inflammatory and immune response in tilapia liver and spleen upon infection.

Furthermore, edwardsiellosis, caused by *Edwardsiella tarda* and *E. ictaluri*, is a severe disease affecting catfish and carp, resulting in granulomatous lesions in internal organs and septicemia (Guo *et al.*, 2015; Xiong *et al.*, 2020) [13, 35]. Columnaris disease, caused by Flavobacterium columnare, is a significant issue in channel catfish *(Ictalurus punctatus)* and other species, characterized by gill necrosis and skin lesions that can result in rapid mortality (Geng *et al.*, 2015) [11].

3.2 Viral Pathogens

Viral diseases in freshwater aquaculture are often highly contagious and lack effective treatments. The *Cyprinid herpesviruses* (CyHVs) are of particular importance. CyHV-3 (*Koi Herpesvirus)* causes massive mortality in common carp and koi, targeting the gills, skin, and kidneys (Lee *et al.*, 2016) [19]. Another notable virus is the *Spring Viremia of Carp Virus* (SVCV), a rhabdovirus that causes a severe hemorrhagic disease in common carp, often with seasonal occurrence (Zhang *et al.*, 2017) [8].

In salmonid aquaculture, primarily conducted in freshwater stages, viruses like the Infectious Hematopoietic Necrosis Virus (IHNV) and Viral Hemorrhagic Septicemia Virus (VHSV) cause significant losses, affecting hematopoietic tissues and leading to high mortality in juvenile rainbow trout *(Oncorhynchus mykiss)* and other species (Jones *et al.*, 2020; Hart *et al.*, 2017) [16, 14].

3.3 Parasitic and Fungal Pathogens

While less represented in omics studies compared to bacteria and viruses, parasites remain a substantial burden. The ciliate *Ichthyophthirius multifiliis*, which causes "white spot" or ich, is a ubiquitous ectoparasite that infests the gills and skin of virtually all freshwater fish, leading to respiratory distress and high mortality if left untreated (Syahputra *et al.*, 2019) [33]. Monogenean worms, such as *Dactylogyrus* and *Gyrodactylus* species, are also common gill and skin flukes that cause significant damage, especially in intensive culture systems.

Fungal infections, often secondary to physical injury or stress, are typically caused by water molds, such as *Saprolegnia* spp. Although they were not the primary focus of the selected omics studies, they represent a consistent management challenge in hatcheries and during handling.

The persistent and severe impact of these pathogens underscores the limitations of traditional chemical and antibiotic treatments. This has accelerated the adoption of omics technologies to decipher the molecular basis of host immunity and pathogen virulence, paving the way for novel and sustainable disease control strategies.

4. The Omics Revolution in Understanding Host-Pathogen-Environment Interactions

The limitations of conventional disease management have catalyzed a shift towards a more fundamental, molecular understanding of aquatic diseases. Omics technologies *(genomics, transcriptomics, proteomics, metabolomics)* are now pivotal in deconstructing the complex interplay between the host, pathogen, and environment—the very triad identified as central to disease onset (Snieszko, 1974) [31]. By providing system-level data, these approaches move beyond descriptive pathology to reveal the mechanistic underpinnings of infection and immunity.

4.1 Deciphering Host Immune Responses through Transcriptomics and Proteomics

Proteomic and transcriptomic analyses have been widely employed to map the host's immune landscape during infection. Transcriptome analyses of tilapia *(Oreochromis niloticus)* challenged with *Streptococcus agalactiae* consistently show a strong upregulation of inflammatory response-related genes in the spleen and head kidney, including cytokines such as TNF-α and IL-1β, as well as various chemokines (Zhu *et al.*, 2015; Zhao *et al.*, 2015) [40, 37]. This pro-inflammatory cascade is a double-edged sword; while crucial for pathogen clearance, its dysregulation can contribute to tissue damage and mortality, highlighting potential targets for immunomodulation.

Similarly, proteomic profiling of carp (*Cyprinus carpio*) infected with Aeromonas hydrophila has identified key proteins involved in acute-phase response (e.g., C-reactive protein), complement activation, and iron metabolism as critical components of the defense mechanism (Di *et al.*, 2017) [8]. These findings are corroborated by studies on other species, such as channel catfish *(Ictalurus punctatus),* which respond to *Flavobacterium columnare*, where pathways related to phagocytosis and oxidative burst are prominently activated (Geng *et al.*, 2015) [11]. The convergence of these responses across species and pathogens points to conserved defense mechanisms that could be broadly enhanced through nutritional or environmental strategies.

4.2 Unveiling Viral Strategies and Host Vulnerabilities

Omics have been particularly revealing in viral diseases, where direct treatments are unavailable. Genomic studies of Cyprinid Herpesvirus 3 (CyHV-3) have identified a repertoire of viral genes involved in immune evasion, including those that inhibit antigen presentation and the interferon response (Lee *et al.*, 2016) [19]. Concurrent host transcriptomic studies during CyHV-3 infection reveal the suppression of k y adaptive immune genes in carp, which explains the virus's devastating effectiveness and provides a rationale for the development of potent vaccines that can overcome this immunosuppression (Lee *et al.*, 2016; Zhang *et al.*, 2017) [19, 8].

In rainbow trout *(Oncorhynchus mykiss)*, research on the Infectious Hematopoietic Necrosis Virus (IHNV) has utilized transcriptomics to demonstrate how the virus preferentially targets and replicates in hematopoietic tissues, leading to widespread apoptosis and immunosuppression (Hart *et al.*, 2017; Jones *et al.*, 2020) [14, 16]. This detailed understanding of viral tropism and pathogenesis is crucial for breeding programs that aim to select for resistant stock and for designing targeted antiviral therapies.

4.3 Probing Parasite Pathogenesis and Host-Parasite Dynamics

While fewer in number, omics studies on parasitic infections are providing unprecedented insights. Genomic sequencing of the ciliate *Ichthyophthirius multifiliis* has uncovered numerous proteases and adhesion molecules essential for its attachment and feeding on fish skin and gills (Syahputra *et al.*, 2019) [33]. On the host side, transcriptomic analysis of fish responding to *I. multifiliis* infection shows an apid mucosal immune response, characterized by the upregulation of immunoglobulin genes (particularly IgT), mucins, and a suite of innate immune receptors (Syahputra *et al.*, 2019) [33]. This highlights the crucial role of mucosal surfaces as the primary line of defense, informing the development of treatments that can enhance barrier immunity.

4.4 Integrating Multi-omics for a Holistic View

The most powerful applications come from integrating multiple omics layers. For example, a study on *Edwardsiella tarda* infection in fish might combine genomic data on bacterial virulence factors (Guo *et al.*, 2015) [13] with host transcriptomic data showing immune pathway activation and metabolomic data revealing shifts in energy metabolism in the liver (Xiong *et al.*, 2020) [35]. This integrated analysis can construct a comprehensive model of the infection process, from initial pathogen recognition to systemic physiological changes, revealing novel, network-level targets for intervention that would be invisible to single-platform studies.

5. Nanotechnology: A Frontier for Sustainable Disease Management and Enhanced Health

The quest for sustainable disease control, driven by the limitations of conventional chemicals and the detailed mechanistic insights from omics, has ushered in a new frontier: nanotechnology. Defined as the science of materials at the nanoscale (1-100 nm), nanotechnology offers a novel and versatile toolkit to address multiple challenges in aquaculture simultaneously, from pathogen control to nutrition and water quality (Nasr-Eldahan *et al.*, 2021) [25]. Its application represents a paradigm shift from bulk, non-specific treatments to targeted, efficient, and environmentally friendlier interventions.

5.1 Nanoparticles as Immunonutrition and Growth Pro oters

The integration of nanoscale elements into fish feed has shown remarkable potential to enhance growth and bolster innate immunity, acting as a proactive health management strategy. For instance, dietary supplementation with selenium nanoparticles (SeNPs) has been extensively studied. In crucian carp (*Carassius auratus gibelio*), SeNPs significantly boosted final weight, relative growth rate, and the activity of the antioxidant enzyme glutathione peroxidase, while also increasing muscle selenium concentration more effectively than organic selenomethionine (Zhou *et al.*, 2009) [39]. This enhanced antioxidant status is crucial for mitigating oxidative stress induced by high stocking densities or pathogen challenge. Similar benefits have been reported in Nile tilapia, where nano-chitosan supplementation improved growth performance, feed utilization, and stimulated key immune parameters such as lysozyme activity and respiratory burst (Abdel-Tawwab *et al.*, 2019; Wang & Li, 2011) [1, 34]. These findings are complemented by earlier reports of significantly faster growth rates (24-30%) in young carp and sturgeon fed iron nanoparticles (ETC, 2003). The high bioavailability and low toxicity of nanoparticles, compared to their bulk counterparts, make them superior candidates for functional feeds designed to enhance host resilience.

5.2 Nanovaccinology: Revolutionizing Prophylaxis

The most transformative application of nanotechnology in aquatic he lth is in the field of vaccinology. Conventional vaccines, although effective for certain diseases, face challenges such as the limited immunogenicity of subunit antigens, the need for booster doses, and the requirement for a cold chain (Plant & LaPatra, 2011) [26]. Nanovaccines, which consist of antigens encapsulated in or conjugated to nanoparticles, overcome these hurdles (Zhao *et al.*, 2014) [38].

The advantages are multifold. First, nanoparticles act as potent adjuvants; their similar size to pathogens allows for enhanced recognition and uptake by antigen-presenting cells, such as macrophages, leading to a more robust activation of both cellular and humoral adaptive immunity (Mamo & Poland, 2012; Smith *et al.*, 2013) [22, 30]. Second, they protect the antigen from degradation, ensuring its stable delivery to the target site. Third, they can facilitate controlled release, potentially eliminating the need for multiple booster vaccinations (Gheibi Hayat & Darroudi, 2019) [12]. For example, chitosan nanoparticles have been successfully used for the oral delivery of DNA vaccines in Asian sea bass against Vibrio anguillarum (Rajeshkumar *et al.*, 2008) [27], demonstrating the potential for non-stressful, mass vaccination methods. This technology directly addresses the need for effective prophylaxis against stubborn pathogens, such as Streptococcus and Cyprinid Herpesviruses, aligning with the omics-driven goal of eliciting precise immune responses.

5.3 Nanotechnology in Diagnostics and Environmental Management

Beyond treatment and vaccination, nanotechnology offers tools for prevention and monitoring. Nanosensors can be developed for the rapid, early detection of specific pathogens in water, enabling preemptive action before an outbreak occurs (Nasr-Eldahan *et al.*, 2021) [25]. Furthermore, nanomaterials are increasingly used for water remediation in aquaculture systems. Nanoparticles of metal oxides (e.g., ferric oxides, titanium oxides) and chitosan-based nanocomposites are highly effective in adsorbing and removing heavy metals and organic pollutants from water, thereby improving overall water quality and reducing one of the key environmental stressors that predispose fish to disease (Hua *et al.*, 2012; Futalan *et al.*, 2011) [15, 10].

5.4 Balancing Promise with Prudence: The Nanosafety Imperative

Despite the immense promise, the application of nanotechnology in aquaculture necessitates a cautious approach regarding nanosafety. Particle size, shape, surface charge, concentration, and the species of the target organism are only a few of the many variables that interact to affect the ecological and health effects of nanoparticles (Khosravi-Katuli *et al*., 2017) [17]. Unintentional toxicity to aquatic organisms that are not the intended target, bioaccumulation in the food chain, and unanticipated long-term health impacts on the cultivated species themselves are examples of potential danger. Therefore, before nano-based products are widely used, thorough toxicity research encompassing the whole life cycle of farmed animals is crucial. Regulatory frameworks must be developed in parallel to ensure the safe and sustainable integration of nanotechnology into aquaculture practices.

6. Conclusion and Synthesis: An Integrated Path Forward

The journey through the landscape of freshwater aquaculture diseases reveals a sector at a critical juncture. The classical reliance on broad-spectrum chemicals is untenable due to the development of resistance, environmental damage, and consumer demand for safer alternatives. The omics revolution has provided an unprecedented, deep understanding of host-pathogen interactions, revealing the molecular blueprints of immunity and pathogenesis. This knowledge is the foundation upon which the next generation of sustainable aquaculture health strategies must be built.

The path forward is not reliant on a single solution but on the integration of multiple, synergistic approaches. The future lies in:

1. **Proactive Health Management:** Shifting the focus from treatment to prevention through robust biosecurity, improved nutrition, and stress reduction.
2. **Precision Intervention:** Using omics data to develop targeted therapies, innovative vaccines, and selective breeding programs for disease resistance.
3. **Sustainable Technologies:** Embracing the potential of nanotechnology for advanced vaccine delivery, immunonutrition, and environmental management, while rigorously evaluating its safety.
4. **Global and Regional Cooperation:** Strengthening surveillance networks, harmonizing diagnostic protocols, and implementing international guidelines and national strategies.

By weaving together the threads of advanced molecular biology, cutting-edge material science, and prudent management frameworks, the global aquaculture sector can navigate the persistent challenge of disease. This integrated approach will secure its role as a vital, sustainable, and resilient source of protein for a growing global population, transforming a major constraint into a manageable component of a productive and responsible industry.

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