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Microbiome Engineering for Healthier Fish and Sustainable Aquaculture

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Aquaculture has become a cornerstone of global food security, yet the industry faces persistent challenges from disease outbreaks, antibiotic dependence, and environmental stressors. Recent advances in microbiome science have revealed that the fish gut microbiome plays a crucial role in nutrient utilization, immune regulation, disease resistance, and overall host health. Microbiome engineering has emerged as a promising approach to harness these beneficial microbial communities for improving aquaculture sustainability. Through targeted interventions such as probiotics, prebiotics, synbiotics, microbiota transplantation, and genetically engineered microbial consortia, researchers are developing strategies to enhance fish growth, strengthen immunity, and reduce reliance on antibiotics. Advances in multi-omics technologies, artificial intelligence, and synthetic biology are further accelerating the design of precision microbial solutions tailored to specific host species and farming conditions. This article explores the principles, technologies, applications, and future prospects of gut microbiome engineering, highlighting its potential to transform aquaculture into a more resilient, productive, and environmentally sustainable food production system.

Key words: Eubiosis, dysbiosis, gut microbiota, sustainable aquaculture

Introduction

Aquaculture is very embedded within our global food systems today. In 2022, global aquatic animal production was 223.2 million tonnes with 130.9 million tonnes from farmed animals comprising 51% of this total. It is worthy to note that farmed fish production has surpassed capture fisheries since 2016 (FAO, 2024) and aquatic products contribute a major source of protein for more than 3.2 billion people worldwide, providing up to 20% of their animal protein intake.

Therapeutic methods that control infections and diseases have shifted over time from the use of antibiotics and other chemicals towards an approach rooted in microbiome and holobiont research. The holobiont integrates the host organism along with its associated microbial communities to develop insights into how these microbes interact with the host and influence immunity, metabolism and overall host health. The progress of probiotics, synbiotics, microbiome transplantation and the development of synthetic microbial communities to control disease have facilitated the development of strategies to increase disease resistance while decreasing antibiotic usage in fish production, improving the long-term sustainability of aquaculture.

Recent developments and technological advancements include the development of 'gut microbiome design to introduce good intestinal microbial communities. Such communities support overall host health via effects on growth and nutrient utilization and also provide enhanced stress tolerance and health resilience. These biological tools have been developed through the use of multi-omics, synthetic biology and high-throughput sequencing technologies. They include the use of probiotics, prebiotics, phage therapy, genetic design and other approaches to create disease-resilient aquatic hosts that are also sustainable (Ma et al., 2025; Tayyab et al., 2025).

Composition and Function of the Fish Gut Ecosystem

The fish gut microbiome is a highly diverse ecosystem that differs from terrestrial livestock due to continuous interaction with the aquatic environment. Unlike mammals, where Firmicutes and Bacteroidetes commonly dominate, fish gut communities are enriched with Proteobacteria, Fusobacteria, Firmicutes, Actinobacteria, and Bacteroidetes (Ma *et al*., 2025). Comparative studies across 25 fish gut communities revealed substantial variation among species, highlighting the influence of habitat and ecological niche on microbial composition. Proteobacteria frequently dominate and contribute to nutrient metabolism and host interactions, whereas Fusobacteria, particularly *Cetobacterium*, support vitamin B12 synthesis and energy metabolism (Ma *et al*., 2025; Llewellyn *et al*., 2014; Sugita *et al*., 1991). These variations reflect adaptation to different habitats and dietary patterns.

Beyond digestion, gut microbiota contributes to immune maturation, nutrient absorption, pathogen resistance, and physiological regulation. They support the development of gut-associated lymphoid tissue (GALT) and provide colonization resistance against pathogens (Ma *et al*., 2025). Microbial communities also aid nutrient assimilation through enzyme production and participate in host development through cooperative host–microbe interactions (Perez *et al*., 2010; Nayak, 2010). Increasing evidence supports a gut–brain axis in fish, where intestinal microbes influence feeding behavior, stress responses, and neuroendocrine signalling. In zebrafish, microbiome enrichment has been associated with reduced anxiety-like behavior and lower cortisol levels (Ma *et al*., 2025).

The composition of fish gut microbial communities is shaped by diet, developmental stage, host genetics, and environmental microbiota. Fish harbour both allochthonous (transient) microbes from food and water and autochthonous (resident) microbes that establish stable intestinal associations (Ringø *et al*., 2016). Diet strongly influences microbial function and composition, while microorganisms from surrounding water and sediment continuously contribute to gut colonization, making the fish intestine a dynamic ecosystem influenced by both host and environmental factors (Ma *et al*., 2025; Muegge *et al*., 2011).

Technologies for Targeted Manipulation

In aquaculture, host-derived precision probiotics tailored to host intestinal conditions are being introduced to replace broad-spectrum commercial probiotics. Probiotic bacteria of beneficial taxa such as Cetobacterium and Weissella have been identified using advancements such as metagenomics and multi-omics. These bacteria were selected based on characteristics such as suppression of pathogens, production of bacteriocin, generation of metabolites, adherence to epithelial cells and resilience to stress (Tayyab et al., 2025). These next-generation probiotics aim to efficiently colonize and provide specific benefits in the host intestine. Microbial compounds such as bacteriocin and SCFAs are known to modulate host health and improve immunity, providing enhanced disease resistance.

Developed synbiotics include specifically selected probiotics with supporting prebiotics, designed to improve microbe persistence and functional synergy. Some rationally formulated combinations like chitosan oligosaccharides with Lactiplantibacillus plantarum and king oyster mushroom extracts can provide enhanced immune function, a stable microbiome and inhibition of pathogens (Tayyab et al., 2025).

Faecal microbiota transplantation is gaining attention as a way to re-establish a balanced gut microbiome through transplanting healthy communities into dysbiotic hosts. In aquaculture, FMT is being investigated to restore gut microbial diversity following administration of antibiotics, diseases or environmental stress, and therefore boost the immune system and disease resistance (Tayyab et al., 2025).

In recent years, novel approaches to targeted manipulation of the microbiome have been developed with the assistance of advances in synthetic biology and genetic engineering. For instance, gene editing technologies including CRISPR-Cas systems can be utilized to specifically edit metabolic pathways or virulence genes in microorganisms (Tayyab et al., 2025). Cetobacterium somerae XMX-1, edited with CRISPR, led to a nearly 75% decrease in viral mortality in zebrafish (Tayyab et al., 2025). Furthermore, recombinant cyanobacteria are also being utilized as oral delivery vehicles for vaccines and immunomodulatory agents and contribute to precision microbiome engineering in aquaculture.

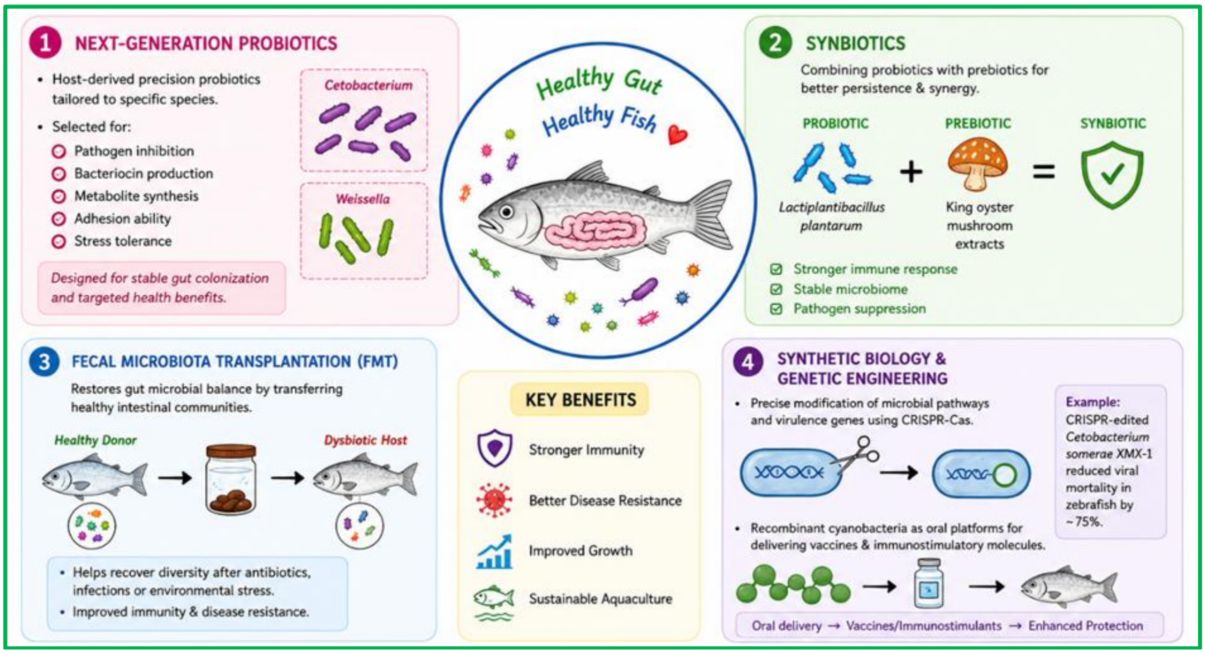


Figure 1. Technologies for Targeted Manipulation

The Multi-Omics Revolution

Metagenomics for Biomarker Discovery

Advances in metagenomics and high-throughput sequencing have revolutionized our ability to study host-microbe interaction through detailed characterization of the microbial community structure and determination of microbial signatures related to the disease and healthy state of the host (Human Microbiome Project Consortium, 2012; Gilbert et al., 2016; Integrative HMP Research Network Consortium, 2019; Wang et al., 2024). These approaches provide a means for more profound analysis of microbial diversity, functional capacity and host-related ecological phenomena in a wide array of organisms and biological systems. By applying the sequencing technologies of 16S rRNA gene profiling and shotgun metagenomics, microbial changes and the corresponding key species contributing to the illness and progression of disease can be readily identified (Tayyab et al., 2025). Elevated levels of opportunistic pathogens like Vibrio and Aeromonas alongside a decreased proportion of beneficial commensal bacteria have been observed as the early signs of intestinal disturbance. By employing the multi-omics approach, ratios such as the changes in Vibrio/Photobacterium ratio were identified as markers of stress-induced intestinal imbalance and disruption of immune homeostasis in shrimp at an early stage, before the appearance of symptoms and spread of disease (Tayyab et al., 2025).

Metabolomic Insights

The functional significance of microbial metabolite- host crosstalk has become increasingly apparent from metabolomics research and its effects on host physiology and immunity. While SCFAs such as butyrate are well-established as energy sources, their role as immune mediators through HDAC inhibition and G-protein-coupled receptor signalling is being unveiled (Tayyab et al., 2025). *Clostridium butyricum* supplementation was demonstrated to be capable of producing favorable metabolites and promoting mucosal immunity in aquatic organisms. It has been known that metabolites like indole-3-acetic acid (IAA) and other bacterial-derived bioactive compounds have a direct antimicrobial role. They can maintain intestinal homeostasis by inhibiting the growth of pathogens, as well as participate in intestinal immune signalling. Analysis of metabolites has also exposed intricate host-microbe relationships associated with bile acid metabolism, amino acid metabolism and stress-related signalling pathways.

Host Transcriptomics

Transcriptomics have unravelled the mechanisms through which the gut microbiota regulate the host gene expression and trigger the host protective pathways related to immunity and stress tolerance. Probiotics and the microbial metabolites help in upregulating the expression of genes involved in innate immune response, antioxidant production and anti-microbial mechanisms. Beneficial microbes have been shown to induce immune signalling pathways such as Toll, Imd and NLRP3 pathways and boost the expression of anti-microbial peptides and immune effectors (Tayyab et al., 2025). Probiotics also upregulate genes such as Crustin, Penaeidin-3, proPO and lysozyme and help to enhance the immune capacity and resistance against diseases of crustaceans (Cheng et al., 2024). Transcriptomic under stress also indicates up-regulation of pathways such as antioxidant pathways, glutathione metabolic pathway and the systems involved in energy management to combat against environmental and pathogenic stresses.

Impact on Health and Nutrition

Disease Resistance

Modulation of the microbiome has been demonstrated as an effective strategy to increase resistance to common aquaculture pathogens via regulation of microbial equilibrium, immune responses, and the processes of pathogen exclusion (Ring et al., 2016; Hoseinifar et al., 2018; Nayak, 2010). Research has identified that application of host-derived probiotics and microbiome engineering can successfully improve survival against disease such as Acute Hepatopancreatic Necrosis Disease caused by *Vibrio parahaemolyticus* and bacterial infection by *Streptococcus agalactiae*. In an experimental study, a gut-derived *Weissella paramesenteroides* isolated from *Penaeus vannamei* administration caused decrease in the abundance of V. Parahaemolyticus and an increased shrimp survival rate from 23.3% to 63.3% after AHPND challenge (Qin et al., 2026). The probiotic also enhanced the activity of antioxidant enzymes (SOD, AKP, T-AOC) and up-regulated antimicrobial peptide genes, such as Crustin and Penaeidin-3.

Growth and Feed Efficiency

Besides disease prevention, the proper balance of gut microbiota can obviously and positively influence the performance of growth and the utilisation efficiency of feed. A well-balanced intestinal microbial community can contribute to the synthesis of digestive enzymes, increase the availability of nutrients in feed and raise the feed conversion ratio (FCR) through digestion and metabolism of carbohydrates, protein and lipids (Ma et al., 2025). Moreover, intestinal integrity and energy harvesting capacity can also be ameliorated by microbial products, especially short-chain fatty acids (SCFAs), thereby reducing nutritional stress in intensive culture conditions and guaranteeing the growth of the host (Ring et al., 2016).

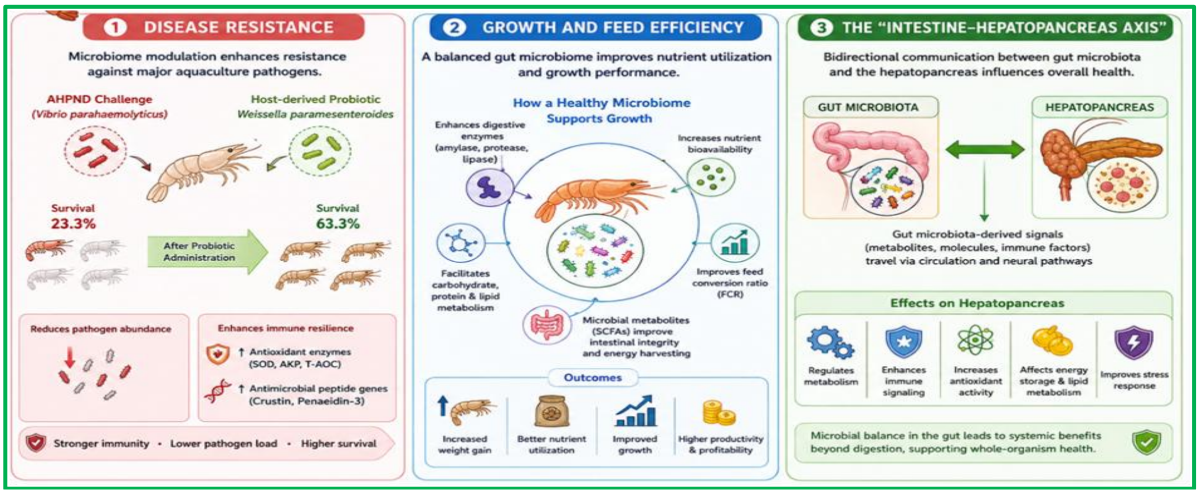


Figure 2. Impact of microbiome modulation on health and nutrition

The "Intestine–Hepatopancreas Axis"

There is increasing evidence in crustaceans supporting the idea of an intestine-hepatopancreas axis, where communication occurs bidirectionally between the intestinal microbes and the hepatopancreas, which is known to be the key metabolic and immune organ. The composition of intestinal bacteria can have a direct effect on hepatopancreatic metabolism, signalling and immune function, and antioxidant capabilities as well as energy storage processes. Shifts in the intestinal microflora have a direct impact on lipid metabolism, partitioning of nutrients and also stress responses, and clearly gut microbial change does affect physiological function elsewhere in the whole animal (Wang et al., 2026). Furthermore, the data from transcriptome analysis, alongside that of microbiome analysis, indicates that hepatopancreatic functions pertaining to metabolism and host defense are mediated by gut-derived signals.

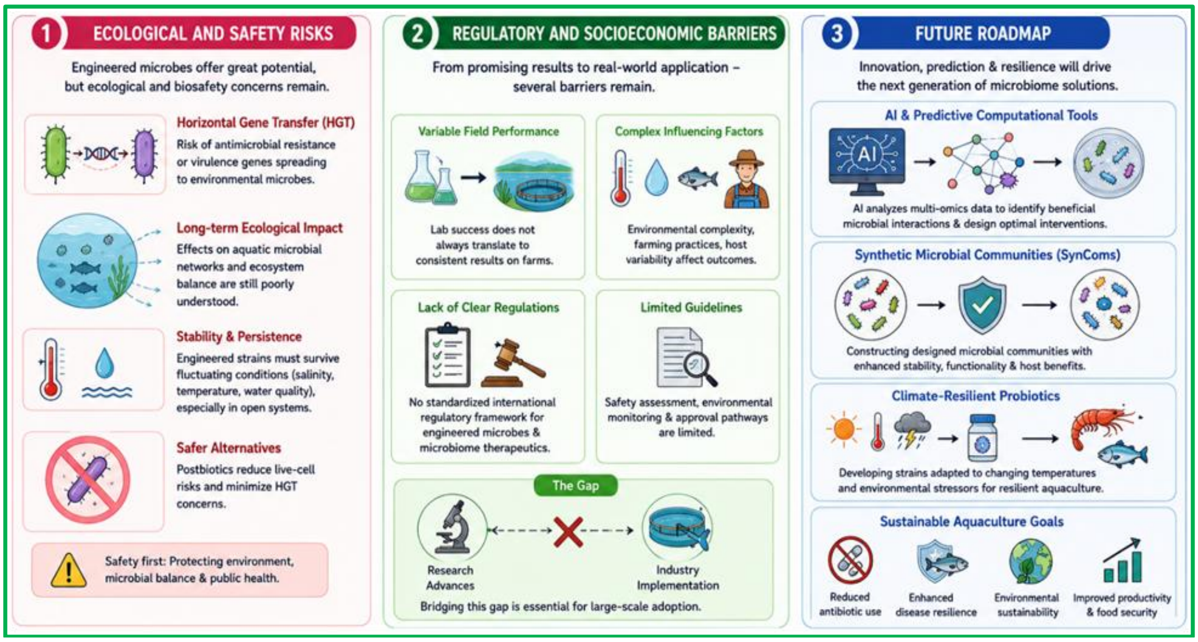
Challenges, Safety, and the Path to Commercialization

Ecological and Safety Risks

Although microbiome engineering has potential, challenges remain in ecological and bio-safety aspects. Deployment of engineered microbes in open aquaculture may be associated with risks of HGT of genes related to antimicrobial resistance and/or pathogenicity into microbial populations within the environment (Tayyab et al., 2025). The long-term ecological impacts of introducing engineered microbes into aquatic microbial networks are largely unknown. Sustainability and persistence of engineered microbes in dynamic environments with varying salinity, temperature, and water quality present further challenges, especially in open-water culture. Postbiotic systems are considered to avoid risks related to viable cell populations and eliminate HGT potential (Vinderola et al., 2022).

Regulatory and Socioeconomic Barriers

While laboratory-based outcomes using microbiome interventions appear positive, practical applications in commercial aquaculture face significant obstacles. Several promising probiotic and synbiotic applications exhibit inconsistent performance in commercial settings where complexity of environments, farming practices, and variation within host animals influence performance (Negi and Chen, 2026). Similarly, variation in species, cultivation methods and varying degrees of environmental stressors may contribute to inconsistent performance between farms. Lack of a globally accepted regulatory strategy for manufactured microbial products and microbiome-based therapeutic treatments delays large-scale applications. Clear guidelines for safety assessment, environmental impact evaluation, and the approval processes have not yet been fully developed or adopted widely.



Engineered microbes offer great potential, but ecological and biosafety concerns remain.

Horizontal Gene Transfer (HGT): Risk of antimicrobial resistance or virulence genes spreading to environmental microbes.

Long-term Ecological Impact: Effects on aquatic microbial networks and ecosystem balance are still poorly understood.

Stability & Persistence: Engineered strains must survive fluctuating conditions (salinity, temperature, water quality), especially in open systems.

Safer Alternatives: Postbiotics reduce live-cell risks and minimize HGT concerns.

Safety first: Protecting environment, microbial balance & public health.

From promising results to real-world application – several barriers remain.

Variable Field Performance: Lab success does not always translate to consistent results on farms.

Complex Influencing Factors: Environmental complexity, farming practices, host variability affect outcomes.

Lack of Clear Regulations: No standardized international regulatory framework for engineered microbes & microbiome therapeutics.

Limited Guidelines: Safety assessment, environmental monitoring & approval pathways are limited.

Bridging this gap is essential for large-scale adoption.

Innovation, prediction & resilience will drive the next generation of microbiome solutions.

AI & Predictive Computational Tools: AI analyzes multi-omics data to identify beneficial microbial interactions & design optimal interventions.

Synthetic Microbial Communities (SynComs): Constructing designed microbial communities with enhanced stability, functionality & host benefits.

Climate-Resilient Probiotics: Developing strains adapted to changing temperatures and environmental stressors for resilient aquaculture.

Figure 3. Challenges, Safety, and the Path to Commercialization

Future Roadmap

The future of microbiome engineering will use AI and predictive computational approaches for the design of precise microbial applications. AI will use multi-omics information to predict beneficial microbial interactions and design robust, functionally capable SynComs that can be incorporated into farming applications (Tayyab et al., 2025). These will also allow prediction of host-microbe interactions under different farming circumstances and aid in designing desired formulations of microbes for farming applications. Similarly, as climate change increases stresses such as variable temperature conditions and other environmental pressures for aquaculture, development of stress-tolerant, resilient probiotics suited for various farming conditions will become increasingly important (Negi and Chen, 2026). Both applications closely correlate with global sustainability aims of reduced antibiotic use and enhanced resistance to disease and a more sustainable production system.

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