

# Microplastic-Induced Gut Microbiome–Immune Crosstalk in Nile Tilapia (*Oreochromis niloticus*): Molecular Mechanisms, Biomarkers, Multi-Omics Insights and Mitigation Strategies for Sustainable Aquaculture

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## Abstract

Microplastics (MPs) are widespread pollutants in freshwater aquaculture systems, entering through the degradation of pond linings and nets, contaminated aquafeeds, agricultural runoff and atmospheric deposition. Nile tilapia (*Oreochromis niloticus*) an omnivorous and intensively farmed fish, is heavily exposed to MPs however, the interaction between MPs, gut microbiota and mucosal immunity in this species has not been comprehensively assessed. In this review, we summarize recent evidence on the sources, uptake and accumulation of MPs and on how MP exposure causes gut dysbiosis, characterized by decreased alpha diversity, increased abundance of Proteobacteria and reduced levels of beneficial Firmicutes and Fusobacteria, which may affect short chain fatty acid biosynthesis. We then examine how dysbiosis and barrier dysfunction are linked to activation of the TLR4/MyD88/NF- $\kappa$ B, MAPK, JAK/STAT, Nrf2/Keap1 and NLRP3 inflammasome pathways and to oxidative and histopathological damage in the intestine and liver. Special attention is given to age dependent susceptibility, as juvenile fish show dysregulated inflammatory genes under conditions in which no effects are observed in adults. Candidate molecular, biochemical, hematological and non-invasive mucus-based biomarkers are discussed alongside the feasibility of multi omics approaches (metagenomics, transcriptomics, proteomics and metabolomics) for resolving host microbiota environment interactions. Mitigation strategies, including multi species probiotics, algal supplements, engineered biochar, feed management and biodegradable materials, are also evaluated. Key knowledge gaps remain in chronic low dose exposure, mixture effects, nanoplastics, reversibility of dysbiosis and methodological standardization. Addressing these gaps will be essential for developing resilient and sustainable tilapia aquaculture.

**Keywords:** Microplastics; *Oreochromis niloticus*; gut microbiome; immune response; oxidative stress; multi-omics; aquaculture sustainability.

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## 1. INTRODUCTION

Annual global production of plastics is more than 400 million metric tons, out of which a significant number gets into the freshwater and marine ecosystem as MPs, which are referred to as plastic particles having less than 5 mm in size (Wu *et al.*, 2023; Qasim *et al.*, 2025).

The aquaculture freshwater systems with a focus on intensive farming of Nile tilapia (*Oreochromis niloticus*) are considered a vital sink for MPs. Due to its omnivorous benthic feeding habits and formulated feeds containing plastic pollutants, the fish is exposed to MPs (Lu *et al.*, 2022; Wu *et al.*, 2022). Teleost fish GI tract acts as the primary point of contact between the host and

various environmental insults. In this environment, constant communication takes place between the gut microbiome and the mucosal immune system which is referred to as gut microbiome-immune crosstalk (Bereded *et al.*, 2021; Ather *et al.*, 2026). Emerging studies have revealed that microplastics (MPs) interfere with this balance leading to dysbiosis and causing an inflammatory response, oxidative stress, and metabolic disorders (Zheng *et al.*, 2024; Amin *et al.*, 2025; Chaudhary *et al.*, 2025; Ijaz *et al.*, 2024; Nabeel *et al.*, 2026). A critical observation by Kardgar *et al.* (2024) further complicates this narrative: while juvenile Nile tilapia exhibited significant alterations in inflammatory gene expression after 30 days of dietary MP exposure, adult fish exposed for 7 days showed no significant effects on intestinal barrier function, oxidative stress, or histopathology. This age-dependent divergence underscores the necessity of life-stage-specific risk assessments in aquaculture toxicology. Despite considerable progress achieved in understanding the toxicity of MPs on marine organisms, existing literature on the interactions among MPs, gut microbiome, and the immune system in economically significant freshwater fish farming still lacks coherence. Previous reviews have generally focused on MP pollution in aquaculture (Wu *et al.*, 2023), or MP effects on fish health (Subaramaniyam *et al.*, 2023); yet, there exists a lack of comprehensive research on the molecular regulation of the gut-immune dysfunction in Nile tilapia. Such a lack in existing literature is crucially important for developing specific mitigative measures in intensive tilapia farming.

**The objectives of this review are fourfold:** To synthesize current knowledge on MP sources, uptake, and accumulation in *O. niloticus*;

1. To critically evaluate the mechanisms of MP-induced gut dysbiosis and its interplay with host immunity, with particular attention to age-dependent vulnerabilities;
2. To identify reliable molecular and histological biomarkers and assess the utility of multi-omics approaches; and

3. To evaluate sustainable mitigation strategies. By adopting a critical and analytical lens, this review aims to provide a comprehensive, publication-quality framework that advances our understanding of MP ecotoxicology and informs resilient aquaculture practices.

## 2. Microplastics in Freshwater Aquaculture

### 2.1 Classification and Sources

The microplastics have been operationally classified based on their source as primary microplastics, which are manufactured in the microscopic form (such as microbeads), and secondary microplastics, which form due to the degradation of plastic litter in a bigger size (Wu *et al.*, 2022). The secondary microplastics prevail in the freshwater aquaculture systems. The sources include the degradation of the lining of the ponds, the deterioration of the nets for aquaculture, wear and tear by the hull of the boat, atmospheric deposition and the utilization of contaminated agricultural runoff (Wu *et al.*, 2023). An important but often overlooked source is the aquafeed, where microplastics have been detected in the commercial pelleted feed, probably due to their contamination either during production, packaging, or because of the contamination of the feed ingredients (Alberghini *et al.*, 2022).

### 2.2 Occurrence and Fate

The concentration of MPs in freshwater aquaculture ponds is highly variable and depends on geographical location, level of farming operations, and distance from urban or industrial areas. The levels of MPs in Chinese aquaculture systems have been described as being similar to, or even higher than, levels in natural freshwater ecosystems (Wu *et al.*, 2022). The most common plastics in terms of types are polystyrene (PS) and polyethylene (PE) due to their mass production and slow degradation processes. Sediments in such systems can serve as ultimate accumulators, and from there, bottom-feeders like tilapia can suspend and ingest particles.

**Table 1: Classification of microplastics**

| Classification Basis | Category                                 | Description                                     | Examples                             |
|----------------------|------------------------------------------|-------------------------------------------------|--------------------------------------|
| Origin               | Primary                                  | Intentionally manufactured at microscopic sizes | Microbeads, nurdles, plastic pellets |
|                      | Secondary                                | Resulting from fragmentation of larger plastics | Plastic fragments, fibers, films     |
| Size                 | Microplastics                            | Particles 1 µm – 5 mm                           | Small fragments, fibers              |
|                      | Nanoplastics                             | Particles < 1 µm (typically < 100 nm)           | Degradation products, engineered NPs |
| Polymer Type         | Common MPs                               | High production volume polymers                 | PS, PE, PP, PVC, PET                 |
| Shape                | Fragments, Fibers, Films, Foams, Spheres | Influences uptake and toxicity                  | Irregular, filamentous, spherical    |

**Table 2: Major sources of microplastics in freshwater aquaculture**

| Source                        | Primary Mechanism                           | Typical Polymer Types        | References                                             |
|-------------------------------|---------------------------------------------|------------------------------|--------------------------------------------------------|
| Pond Linings & Infrastructure | Physical weathering, UV degradation         | PVC, PE                      | (Wu <i>et al.</i> , 2023)                              |
| Aquaculture Nets & Gear       | Abrasion, mechanical wear                   | Nylon (PA), HDPE             | (Wu <i>et al.</i> , 2022)                              |
| Aquafeed & Feed Ingredients   | Processing contamination, packaging         | PS, PE fragments             | (Alberghini <i>et al.</i> , 2022)                      |
| Agricultural Runoff           | Irrigation water, plastic mulch degradation | PE, PP                       | (Wu <i>et al.</i> , 2023)                              |
| Atmospheric Deposition        | Airborne fibers and particles               | Synthetic textiles (PET, PA) | (Fred-Ahmadu <i>et al.</i> , 2024)                     |
| Wastewater Effluent           | Direct discharge of untreated water         | Mixed polymers               | (Wu <i>et al.</i> , 2022; Qasim <i>et al.</i> , 2026a) |

### 3. Characteristics of Nile Tilapia Gut Microbiome

Nile tilapia's gut microbiome is a complex ecosystem, which carries out important functions in the process of digestion, vitamin synthesis, and the initiation of immunity response. The core microbiota has been analyzed through the use of high-throughput sequencing technology, revealing Proteobacteria, Firmicutes, Fusobacteria and Bacteroidetes as the dominating phyla, but their relative abundance can be affected strongly by diet, genetics and environmental factors (Bereded *et al.*, 2020, 2021; Zhu *et al.*, 2022). The diet plays a critical role in determining microbial community structure. Diets based on fish meal promote growth of the phylum Fusobacteria including the genus Cetobacterium that plays an important role in protein fermentation. On the other hand, plant-based diets lead to higher proportions of the phyla Firmicutes and Proteobacteria (Li *et al.*, 2025; Qasim *et al.*, 2026b; Haidri *et al.*, 2026). Moreover, there are notable distinctions between luminal and mucosal communities as well as along the entire length of the GI tract (Bereded *et al.*, 2020; Qasim *et al.*, 2026). The plasticity of the system has its pros and cons. The ability of the fish to feed on diverse food sources due to the flexibility of the gut microbiota increases its susceptibility to dysbiosis due to xenobiotic disturbance of the intestine environment (in particular, because of MPs). The stability of the ecosystem depends on the factors provided by the host (e.g., mucus and antimicrobial peptides), microbial competition, and nutrition.

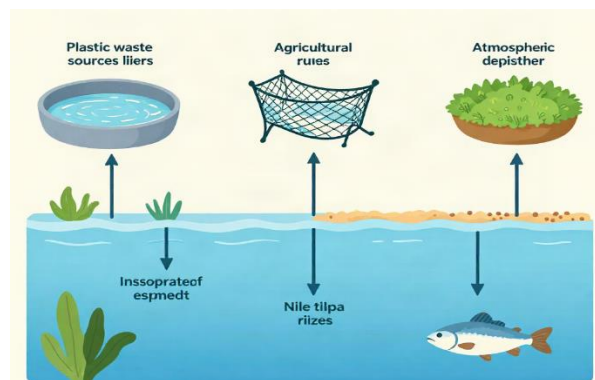
### 4. Microplastic Uptake and Distribution

#### 4.1 Uptake Pathways

Nile tilapia is exposed to MPs accidentally through eating and breathing. The nonselective feeding nature of these fish results in easy intake of MPs that are suspended in the water or attached to other particles in the diet. After oral exposure, MPs are transported through the esophagus to the stomach and intestines. Size is one of the main factors influencing bioavailability of MPs. NP is able to cross the intestinal barrier and enter systemic circulation, while MPs do not exceed the gastrointestinal tract or pass out through feces (Deng *et al.*, 2017; Sefiloglu *et al.*, 2025).

#### 4.2 Tissue Distribution and Accumulation

Patterns of accumulation in *O. niloticus* indicate an apparent hierarchy that is specific to each organ type. The gut and liver act as the initial targets for accumulation because of their direct contact and function in processing xenobiotics, respectively. It has been observed that nano-polystyrene particles accumulate in Nile tilapia after exposure through water, resulting in adverse effects on the health of the gut and liver by causing endoplasmic reticulum stress and changing the microbiome (Ding *et al.*, 2023). Outside the GIT, distribution in gills, brain, and muscle has also been observed in fish species, indicating the potential risk of MP transfer to consumers along with their chemical additives (Alberghini *et al.*, 2022; Ghosh *et al.*, 2024).

**Figure 1: Sources, transport, and exposure pathways of microplastics in freshwater aquaculture**

This diagram illustrates primary and secondary MP sources (pond infrastructure, aquafeed, agricultural runoff, atmospheric deposition), their transport via water

and sediment and their ultimate exposure to Nile tilapia through ingestion and respiration. Biofilm-coated MPs represent an important vector for pathogen co-transport.

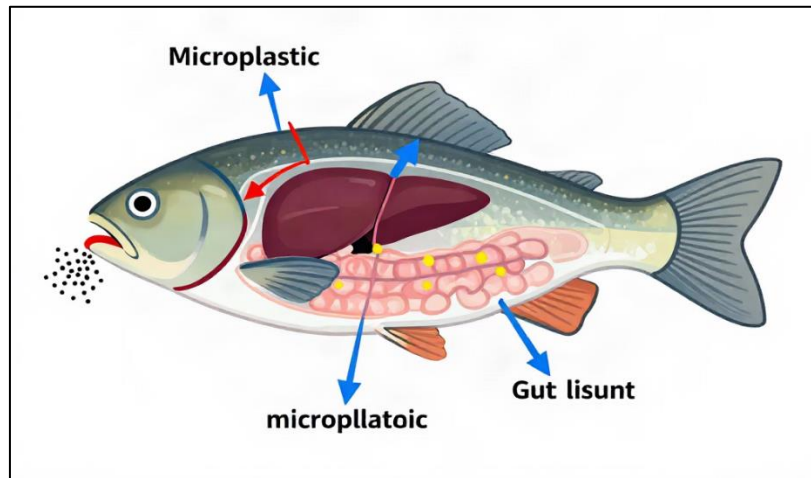


**Figure 2: Microplastic uptake, translocation, and accumulation in Nile tilapia**

Schematic showing MPs ingested via the oral route, accumulation in the gastrointestinal tract, and potential translocation across the epithelial barrier to the liver and other distal organs. Size-dependent barriers and the role of the mucus layer are indicated.

## 5. Gut Dysbiosis Caused by Microplastics

### 5.1 Shifts in Microbial Composition

Dysbiosis of gut flora due to MP ingestion is perhaps the most prevalent phenomenon in teleosts' toxicology research. Dietary administration of polyethylene MPs in *O. niloticus* has been demonstrated to induce substantial changes in the composition and diversity of gut microbiota together with suppressed growth parameters and lower digestive enzymes activity (Lu *et al.*, 2022). Overall, MP ingestion causes the decrease in the level of alpha-diversity (richness and Shannon indices). In the phylum level, MPs cause an increase in Proteobacteria which include many opportunistic pathogens and a reduction in Firmicutes

and Fusobacteria, which are fermentative bacteria and are beneficial (Lu *et al.*, 2022; Zheng *et al.*, 2024). This imbalance, which manifests itself as an increasing Proteobacteria to Firmicutes ratio, is known as a marker of dysbiosis in both mammals and fish. (Zhu *et al.*, 2022) further showed that this imbalanced state in GIFT tilapia causes impacts on the microbiome and its functions across multiple kingdoms

### 5.2 Functional Consequences

The changes in taxonomy due to MPs are reflected in severe functional disruptions. Lower numbers of Firmicutes and Fusobacteria tend to correlate with reduced SCFA production, specifically butyrate production, since butyrate is the main energy source for colonocytes and an important regulator of immune tolerance. At the same time, Proteobacteria enrichment may increase the risk of LPS-induced endotoxemia in case the intestinal barrier is damaged.

**Table 3: Studies reporting gut microbiome alterations in *O. niloticus* after microplastic exposure**

| Study                      | Exposure Type                                | Concentration/Duration            | Major Taxonomic Changes                                         | Reported Outcomes                                                          |
|----------------------------|----------------------------------------------|-----------------------------------|-----------------------------------------------------------------|----------------------------------------------------------------------------|
| Lu <i>et al.</i> , 2022    | Dietary PE MPs                               | 0.1–0.4% diet; 8 weeks            | Downward Diversity; shifts in Firmicutes/Proteobacteria         | Depressed growth, reduced digestive enzymes, intestinal and hepatic damage |
| Ding <i>et al.</i> , 2023  | Waterborne nano-PS                           | 0.1–10 mg/L; 45 days              | Microbiome alterations linked to ER stress                      | Hepatic steatosis, intestinal barrier dysfunction                          |
| Zheng <i>et al.</i> , 2024 | Dietary MPs (+ <i>Chlorella</i> remediation) | MP-induced damage baseline        | Restoration of beneficial taxa by <i>Chlorella</i>              | Alleviation of intestinal damage, anti-inflammatory effect                 |
| Zhu <i>et al.</i> , 2022   | Long-term dietary (GIFT tilapia)             | 180-day faba bean diet            | Core phyla shifts (Fusobacteria, Bacteroidetes, Proteobacteria) | Metabolic reprogramming linked to diet-microbiome interactions             |
| Amin <i>et al.</i> , 2025  | Dietary PA MPs (+ probiotics)                | Environmentally relevant; 8 weeks | Modulation by multi-species probiotics                          | Reduced inflammation, restored growth, histopathological recovery          |

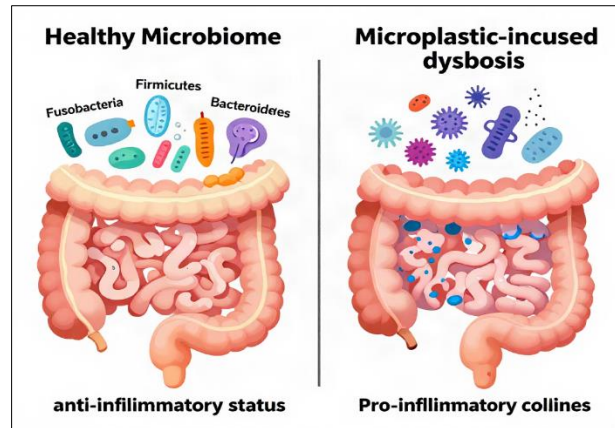


Figure 3: Healthy versus microplastic-induced dysbiotic gut microbiome in Nile tilapia

Comparison of a balanced symbiotic state (rich in *Firmicutes* and *Fusobacteria*, high SCFA production, intact mucus layer, anti-inflammatory milieu) versus a dysbiotic state (*Proteobacteria* enrichment, pathogen bloom, mucus erosion, inflammation).

## 6. Gut Microbiome–Immune Crosstalk

### 6.1 The Intestinal Barrier as a Sentinel

The intestinal epithelium of teleost fish, like that of mammals, provides a physical and biochemical barrier separating the internal milieu from the luminal environment. This barrier comprises a single layer of epithelial cells joined by tight junction (TJ) proteins (e.g., occludin, claudins, zonula occludens-1), overlaid by a protective mucus gel secreted by goblet cells. MPs have been shown to downregulate the expression of tight junction proteins and damage the mucus layer, effectively increasing intestinal permeability (Zhang *et al.*, 2023; Jia *et al.*, 2023). Contradictory results, however, have also been found. For instance, in an extensive study using Ussing chamber analysis, adult Nile tilapia exposed to dietary MPs for 7 days showed no significant changes in TER, TEP or SCC, implying that there were

no functional impairments to the barrier in this particular group (Kardgar *et al.*, 2024). The difference could be attributed to varying exposure time, developmental stages or the kind of polymers used in different studies.

### 6.2 Bidirectional Communication

The intestinal microbiome and the immune system of the host are engaged in an intricate communication process. Commensal microbes promote the growth of gut-associated lymphoid tissue (GALT) and educate the innate immune cells. In response to this, the immune system of the host influences the microbiota by producing antimicrobial peptides (AMPs), IgT and mucus glycoproteins. In the case of dysbiosis induced by MPs, the balance is broken. Inactivation of the useful bacteria will lower their competitive exclusion over the opportunistic pathogen. At the same time, the damage to the barrier leads to exposure of bacterial components (like lipopolysaccharides and flagellin) to lamina propria, which activates the PRRs on the macrophages and epithelial cells. This activation leads to production of pro-inflammatory cytokines like IL-1 $\beta$ , TNF- $\alpha$ , and IL-6.

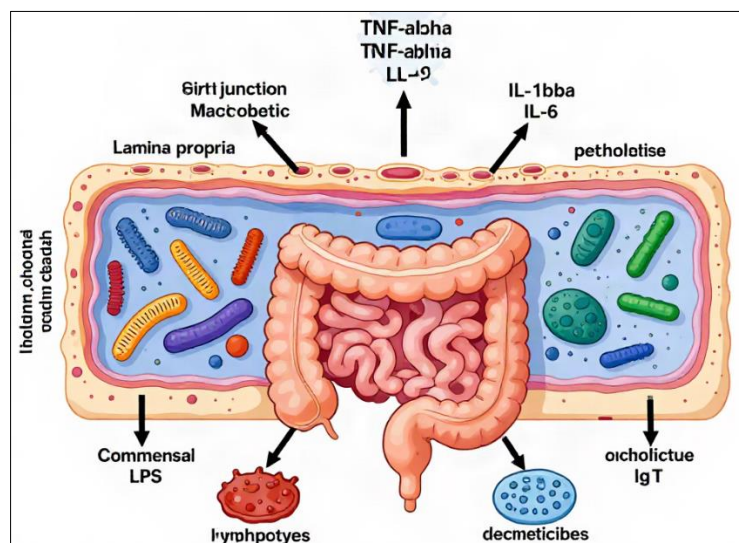


Figure 4: Gut microbiome–immune crosstalk under microplastic stress

Illustration of the interaction between dysbiotic microbiota, compromised tight junctions, immune cell activation (macrophages, lymphocytes) and the release of cytokines. The role of MAMPs (microbe-associated molecular patterns) and mucosal IgT is emphasized.

## 7. Molecular Mechanisms

The detrimental effects of MPs on the tilapia gut-immune axis are orchestrated by several highly conserved molecular signaling pathways.

### 7.1 TLR/NF- $\kappa$ B Pathway

The TLRs are responsible for being the first line of innate immunity. TLR4, specifically, binds to the LPS of Gram-negative bacteria. Activation of TLR4 activates MyD88, resulting in a signaling pathway that ends with NF- $\kappa$ B activation. NF- $\kappa$ B is normally present in the cytoplasm in an inactive form bound by inhibitors (I $\kappa$ Bs). MP-induced bacteria translocation and oxidative stress activate I $\kappa$ B phosphorylation and release of NF- $\kappa$ B into the nucleus to initiate the transcription of inflammatory genes such as TNF- $\alpha$ , IL-1 $\beta$ , IL-6, and IL-8 (Zhang *et al.*, 2023; Fan *et al.*, 2025).

### 7.2 MAPK and JAK/STAT Pathways

Similarly, MAPK pathways (ERK, JNK, p38), which become active upon cellular stress and cytokines, work in concert with the NF- $\kappa$ B transcription factor. The regulation of various biological processes, such as inflammation, cell proliferation, and apoptosis, is

controlled by kinases. The JAK/STAT signaling pathway acts as an amplifier of the inflammatory process following interferon and interleukin stimulation. Studies conducted on Nile tilapia exposed to a combination of MPs and pesticides showed a pronounced dysregulation of genes involved in the immune system functioning through the described signaling pathways (Hossain *et al.*, 2025).

### 7.3 Nrf2/Keap1 and Oxidative Stress Signaling

However, due to the generation of ROS by MPs, Nrf2, which is a redox-sensitive transcription factor, dissociates from its repressor, Keap1, and moves to the nucleus. At the nucleus, Nrf2 attaches to AREs to increase the expression of defensive genes including SOD, CAT, and GPx. Although this represents a defensive mechanism, excessive MP exposure may saturate the process and result in oxidative stress to lipids, proteins, and DNA (Wang *et al.*, 2022; Subaramaniam *et al.*, 2023).

### 7.4 Inflammasome and Apoptotic Pathways

The NLRP3 inflammasome is stimulated by MPs together with associated pollutants. In the case of stimulation of NLRP3, pro-caspase-1 is converted into its active form and, therefore, pro-IL-1 $\beta$  and pro-IL-18 are processed into their active forms. Overstimulation of the inflammasome may cause pyroptosis, an inflammatory form of programmed cell death, resulting in erosion and leakiness of the gut (Meng *et al.*, 2022).

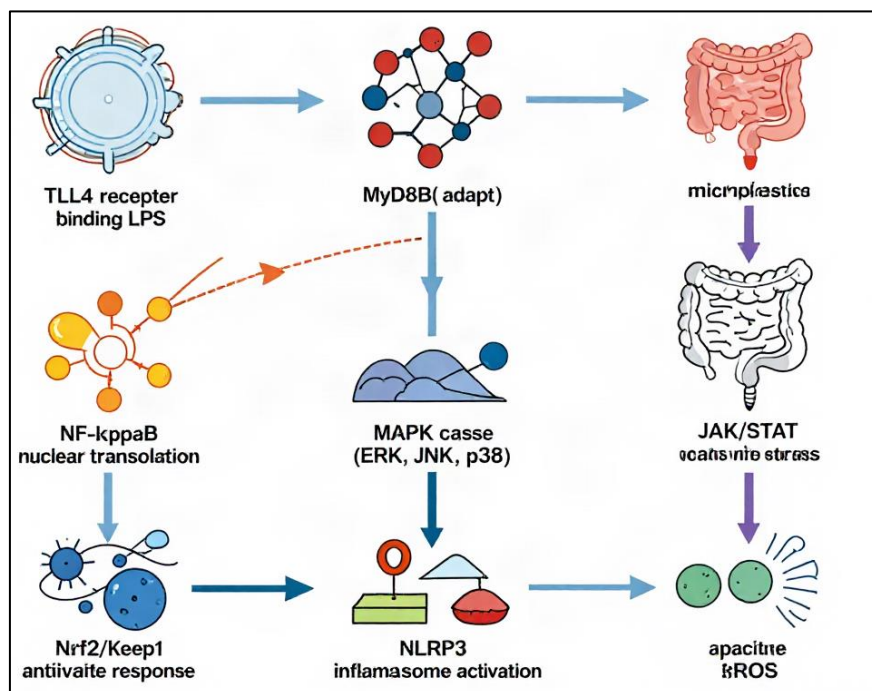


Figure 5: Molecular signaling pathways activated by microplastics in Nile tilapia intestinal epithelium

A detailed schematic of the TLR4/MyD88/NF- $\kappa$ B, MAPK, JAK/STAT, Nrf2/Keap1, and

NLRP3 inflammasome pathways. The diagram illustrates how MPs initiate ROS production and MAMP

recognition, leading to inflammation, oxidative stress responses, and apoptosis.

## 8. Oxidative Stress and Inflammation

### 8.1 ROS Generation and Antioxidant Response

The microplastics cause the formation of oxidative stress due to the overproduction of the reactive oxygen species (ROS), which include  $\text{O}_2^{\bullet-}$ ,  $\text{H}_2\text{O}_2$  and  $\text{OH}^{\bullet}$ . This is because of the damage caused by the mitochondria and activation of the NADPH oxidase enzymes. In this case, there will be lipid peroxidation, which is measured using malondialdehyde (MDA) levels. High MDA levels, together with increased activities of antioxidant enzymes like SOD and CAT, have been found in Nile tilapia fish after exposure to polypropylene (PP) microplastics (Nair *et al.*, 2024). Nevertheless, continuous exposure to MPs will eventually cause exhaustion of these antioxidant enzymes, resulting in cumulative damage to cells. According to (Atamanalp *et al.*, 2022), the presence of high ROS and MDA levels in fish exposed to MPs causes

oxidative stress, especially when combined with other stressors.

### 8.2 Inflammatory Mediators

The inflammatory response in MP-exposed tilapia is characterized by the upregulation of key cytokines. Pro-inflammatory cytokines such as TNF- $\alpha$ , IL-1 $\beta$ , and IL-6 orchestrate the acute phase response, recruiting leukocytes to the site of injury. Simultaneously, anti-inflammatory cytokines like IL-10 and transforming growth factor- $\beta$  (TGF- $\beta$ ) attempt to resolve inflammation. A dysregulated balance, skewed towards chronic pro-inflammatory signaling, is a hallmark of MP toxicity. Importantly, (Kardgar *et al.* 2024) found that although there were no significant differences between the expression of inflammatory genes in adult tilapia during short-term exposure, juveniles demonstrated increased expression of hepatic and intestinal inflammatory genes following 30 days of exposure. Age-dependent sensitivity is of critical importance in aquaculture, where juvenile fish are the most susceptible life stage.

**Table 4: Changes in immune-related genes and cytokines in *O. niloticus* exposed to microplastics**

| Molecule           | Type                             | Direction of Change                 | Exposure Context                                 | References                                                   |
|--------------------|----------------------------------|-------------------------------------|--------------------------------------------------|--------------------------------------------------------------|
| TNF- $\alpha$      | Pro-inflammatory cytokine        | Upregulated                         | Juvenile, 30-day dietary MP; Co-exposure studies | (Kardgar <i>et al.</i> , 2024; Hossain <i>et al.</i> , 2025) |
| IL-1 $\beta$       | Pro-inflammatory cytokine        | Upregulated                         | Co-exposure with sumithion; Juvenile exposure    | (Hossain <i>et al.</i> , 2025)                               |
| IFN- $\gamma$      | Pro-inflammatory cytokine        | Upregulated                         | Immune dysregulation in co-exposure              | (Hossain <i>et al.</i> , 2025)                               |
| IL-10              | Anti-inflammatory cytokine       | Variable (context-dependent)        | Limited direct evidence; requires further study  | To be determined                                             |
| TLR4               | Pattern Recognition Receptor     | Upregulated                         | PS-MP induced tissue injury                      | (Zhang <i>et al.</i> , 2023)                                 |
| MyD88              | Adaptor Protein                  | Upregulated                         | TLR4-mediated signaling                          | (Fan <i>et al.</i> , 2025)                                   |
| NF- $\kappa$ B p65 | Transcription Factor             | Nuclear translocation increased     | Multiple MP polymer types                        | (Zhang <i>et al.</i> , 2023)                                 |
| Nrf2               | Antioxidant transcription factor | Upregulated (nuclear translocation) | Oxidative stress response                        | (Wang <i>et al.</i> , 2022)                                  |
| IgT                | Mucosal Immunoglobulin           | Variable                            | Dependent on exposure duration                   | Limited data in tilapia                                      |

**Table 5: Oxidative stress and antioxidant biomarkers in fish exposed to microplastics**

| Biomarker | Biological Function                        | Direction in Response to MPs           | References                                                  |
|-----------|--------------------------------------------|----------------------------------------|-------------------------------------------------------------|
| MDA       | Lipid peroxidation end-product             | Increase                               | (Nair <i>et al.</i> , 2024; Atamanalp <i>et al.</i> , 2022) |
| SOD       | Dismutates superoxide radicals             | Increase (acute) / Depletion (chronic) | (Nair <i>et al.</i> , 2024; Wang <i>et al.</i> , 2022)      |
| CAT       | Decomposes hydrogen peroxide               | Increase (acute) / Depletion (chronic) | (Nair <i>et al.</i> , 2024)                                 |
| GPx       | Reduces peroxides using GSH                | Variable                               | (Subaramaniyam <i>et al.</i> , 2023)                        |
| GSH       | Major intracellular antioxidant            | Decrease                               | (Subaramaniyam <i>et al.</i> , 2023)                        |
| Nrf2      | Transcription factor (antioxidant defense) | Upregulated (nuclear translocation)    | (Wang <i>et al.</i> , 2022)                                 |

## 9. Histopathological Alterations

Histopathological analysis offers physical proof of MP-caused damage. For the Nile tilapia, prolonged exposure to MPs causes considerable morphological changes in both the intestines and the liver. Intestines generally show signs of villous atrophy, sloughing off of the epithelium, necrosis, inflammation with lymphocytes and neutrophils, and increased production of goblet cells (Lu *et al.*, 2022; Amin *et al.*, 2025). Steatosis (fatty liver disease), vacuolization, hepatocyte necrosis, and sinusoidal congestion are often observed in liver tissues. This is because of the functions of the liver as a detoxifying organ and as the second site of accumulation for MPs after translocation. (Ding *et al.* 2023) found the

accumulation of nano-PS in hepatic steatosis and endoplasmic reticulum stress of Nile tilapia. According to (Kardgar *et al.*, 2024), there was no observable difference in the histopathology of intestinal tissues from the controls, kaolin (as the natural particle control) and MPs regardless of whether these were the juveniles or adults. This disconnect between the molecular and the histological endpoints could mean that changes in the expression of genes could be an early sensitive indicator of stress. The degree of the lesion is dependent on the MP concentration in a dose-dependent manner, although the effect of particle size, polymer type, and exposure period needs to be standardized among other studies.

**Table 6: Summary of histopathological changes observed in Nile tilapia exposed to microplastics**

| Organ     | Lesion Type             | Description                                    | Associated Studies                                   |
|-----------|-------------------------|------------------------------------------------|------------------------------------------------------|
| Intestine | Villous Atrophy         | Shortening and blunting of villi               | (Lu <i>et al.</i> , 2022)                            |
|           | Epithelial Desquamation | Loss of apical enterocytes                     | (Lu <i>et al.</i> , 2022; Amin <i>et al.</i> , 2025) |
|           | Inflammatory Infiltrate | Lymphocyte and neutrophil accumulation         | (Lu <i>et al.</i> , 2022)                            |
|           | Goblet Cell Hyperplasia | Increased mucus secretion (defensive response) | (Jia <i>et al.</i> , 2023)                           |
| Liver     | Steatosis               | Lipid accumulation in hepatocytes              | (Ding <i>et al.</i> , 2023)                          |
|           | Vacuolization           | Cytoplasmic degeneration                       | (Lu <i>et al.</i> , 2022)                            |
|           | Hepatocyte Necrosis     | Cell death, nuclear pyknosis                   | (Amin <i>et al.</i> , 2025)                          |
|           | Sinusoidal Congestion   | Blood vessel engorgement                       | (Nair <i>et al.</i> , 2024)                          |

## 10. Biomarkers

Reliable biomarkers are essential for the early detection of MP toxicity in aquaculture settings, enabling proactive management before clinical mortality occurs.

### 10.1 Molecular Biomarkers

The gene expression profiles exhibit high sensitivity. The activation of TNF- $\alpha$ , IL-1 $\beta$ , IL-8, and TLR4 RNA indicates an early indication of non-lethal inflammation. Likewise, the nuclear translocation of NF- $\kappa$ B and the expression of genes targeted by Nrf2 such as HO-1 and SOD1 suggest oxidative and inflammatory dysfunction. This study conducted by (Kardgar *et al.*, 2024) provides a good example in this context because even though there were no pathological changes in the body tissues, changes in the inflammatory gene expression profiles were observed in juveniles of the tilapia.

### 10.2 Biochemical and Hematological Biomarkers

In terms of proteins and metabolites, MDA level and SOD/CAT activity ratio are reliable markers of oxidative balance. (Compaa *et al.* (2024) performed a meta-analysis showing that MPs always trigger oxidative stress in marine and freshwater fish, which proves that these markers have universal value across species. Besides, some hematological factors like decrease in red blood cells count and changes in leukocytes differentiation serve as additional markers (Nair *et al.*, 2024). Wu *et al.* (2024) developed an innovative technique for non-invasive testing, including epidermal

mucus metabolomics which allows one to identify metabolic disorders caused by nano- and microplastic polypropylene in Nile tilapia.

## 11. Multi-Omics Approaches

Dysregulation of gut immunity due to MP exposure is complicated enough to warrant a holistic approach. With multi-omics techniques, one can analyze the genome, transcriptome, proteome, and metabolome at once.

### 11.1 Metagenomics and Transcriptomics

Sequencing of the 16S rRNA gene and metagenomics sequencing provide an exhaustive characterization of the taxonomic and functional capabilities of the microbiome of the gut. Metagenomics in MP-exposed tilapia enables the detection not only of changes in the structure of the microbial community but also of the pathways involved, including carbohydrate metabolism and LPS synthesis. Transcriptomics (RNA-seq) provides insights into the transcriptional responses of the host, with the upregulation of genes associated with immunity and stress.

### 11.2 Proteomics and Metabolomics

Quantitative proteomics (such as LC-MS/MS) finds differentially expressed proteins that are associated with maintaining the barrier function, immune responses, and metabolism. Non-invasive metabolomics, which focuses on metabolites within epidermal mucus of organisms, is one such technique that has helped identify

metabolic disturbance due to nano and micro-plastic contamination of polypropylene in Nile tilapia (Wu *et al.*, 2024). Multi-omics correlation analysis can help

create these molecular networks of microbial dysbiosis and host traits.

**Table 7: Multi-omics techniques and their applications in microplastic research on Nile tilapia**

| Omics Layer            | Technique                                     | Application/Output                                  | Advantages                                       | Limitations                                               |
|------------------------|-----------------------------------------------|-----------------------------------------------------|--------------------------------------------------|-----------------------------------------------------------|
| <b>Metagenomics</b>    | 16S rRNA sequencing; Shotgun sequencing       | Taxonomic profiling; Functional gene prediction     | High throughput; Cost-effective for 16S          | 16S lacks strain resolution; DNA doesn't reflect activity |
| <b>Transcriptomics</b> | RNA-Seq (bulk or single-cell)                 | Differential gene expression; Pathway mapping       | Genome-wide coverage; Quantitative               | Snapshot in time; RNA instability                         |
| <b>Proteomics</b>      | LC-MS/MS, iTRAQ/TMT                           | Protein abundance; Post-translational modifications | Functional readout closer to phenotype           | High cost; Complex data analysis                          |
| <b>Metabolomics</b>    | GC-MS, LC-MS, NMR; Non-invasive mucus probing | Metabolite profiles; Biomarker discovery            | Highly sensitive; Non-invasive sampling possible | Metabolite identification challenging                     |
| <b>Integration</b>     | Multi-omics networks                          | Host-microbe interaction models                     | Holistic understanding                           | Computationally intensive; Requires expertise             |

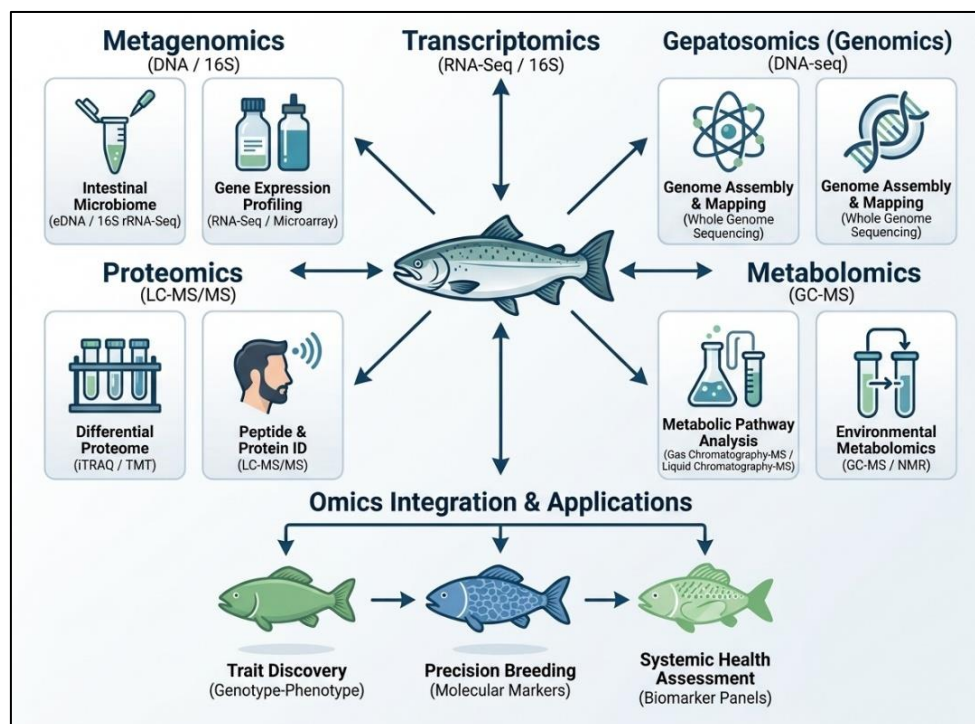


**Figure 6: Integrated multi-omics workflow for studying microplastic-induced gut-immune dysregulation**

Schematic showing sample collection (intestine, liver, mucus), parallel processing for DNA, RNA, protein, and metabolite extraction, bioinformatics pipelines, and the generation of a unified systems biology model.

## 12. Mitigation Strategies

Sustainable mitigation of MP impacts must address both environmental remediation and host resilience.

### 12.1 Probiotic and Prebiotic Supplementation

Probiotics offer some of the most promising bioremediation approaches. Probiotic combinations of multiple species have been found to alleviate MP-induced stress and growth inhibitions in Nile tilapia fish by controlling immune response, restoring the normal morphology of the intestine and alleviating any histopathological damages (Amin *et al.*, 2025). Similarly, dietary administration of *Spirulina platensis* and *Chlorella* has been found effective in the mitigation of MP-induced growth inhibitions and intestinal injuries

through antioxidants and anti-inflammatory effects (Zheng *et al.*, 2024).

### 12.2 Biochar and Filtration Technologies

Engineered biochar has emerged as a sustainable, multifunctional adsorbent for the removal of MPs from aquatic systems (Qasim *et al.*, 2026c). Its high surface area and porosity allow for the physical trapping of plastic particles, while surface functionalization can enhance pollutant adsorption. Recent reviews highlight the integrated assessment of engineered biochars for aquatic microplastic remediation, emphasizing their

potential as a practical, scalable approach to reducing MP bioavailability in pond-based aquaculture systems.

### 12.3 Feed Management and Policy Interventions

Elimination of MP contamination at the feed production stage represents the most direct preventive measure. Quality control protocols, including the sourcing of plastic-free ingredients and improved packaging materials, are essential. The development of biodegradable alternatives to conventional plastics and the enforcement of stringent regulations on plastic waste management are critical complementary strategies.

**Table 8: Mitigation strategies for microplastic toxicity in aquaculture**

| Strategy                                                            | Proposed Mechanism                                              | Advantages                                     | Limitations                                                     | Future Potential                                          |
|---------------------------------------------------------------------|-----------------------------------------------------------------|------------------------------------------------|-----------------------------------------------------------------|-----------------------------------------------------------|
| <b>Multi-species Probiotics</b>                                     | Competitive exclusion; Immune modulation; Barrier reinforcement | Natural; Safe for consumption; Cost-effective  | Strain-specific effects; Shelf-life stability                   | Genetically engineered probiotics; Synbiotic formulations |
| <b>Algal Supplements</b><br>( <i>Chlorella</i> , <i>Spirulina</i> ) | Antioxidant delivery; Anti-inflammatory; Microbiome modulation  | High nutritional value; Sustainable production | Variable bioactive content; Extraction costs                    | Nanocapsulated algal extracts                             |
| <b>Engineered Biochar</b>                                           | Physical adsorption of MPs; Trapping in sediments               | Low-cost; Scalable; Carbon sequestration       | Requires periodic replacement; Standardization needed           | Functionalized magnetic biochar for recovery              |
| <b>Feed Quality Control</b>                                         | Elimination of MP contamination at source                       | Prevents exposure directly; Immediate impact   | Requires industry-wide compliance; Cost of implementation       | Blockchain tracking of feed ingredients                   |
| <b>Biodegradable Polymers</b>                                       | Reduction of persistent plastic load                            | Addresses root cause of pollution              | Degradation rate in water; Cost barriers; Mechanical durability | Aquaculture-specific biodegradable gear and liners        |

### 13. Knowledge Gaps

Despite significant advances, numerous critical gaps persist in our understanding of MP toxicity in Nile tilapia:

- Age-Dependent Vulnerability:** The differential sensitivity between juvenile and adult tilapia, as demonstrated by Kardgar *et al.* (2024), remains poorly characterized at the mechanistic level. Juvenile fish appear substantially more susceptible to inflammatory dysregulation, yet the developmental windows of highest vulnerability remain undefined.
- Chronic Low-Dose Effects:** The majority of studies employ acute or sub-acute exposures at concentrations exceeding environmentally realistic levels. Long-term, multi-generational studies at low, chronic doses are urgently needed to assess population-level impacts and establish no-observed-adverse-effect concentrations (NOAECs).
- Mixture Toxicology:** MPs in the environment co-occur with pesticides, heavy metals, and pathogenic bacteria. Hossain *et al.* (2025) provided important initial evidence of synergistic toxicity between polyamide MPs and the organophosphate pesticide sumithion,

but the broader toxicological interaction space remains largely unexplored.

- Nanoplastics vs. Microplastics:** While research on microplastics has intensified, the behavior and toxicity of nanoplastics ( $< 1 \mu\text{m}$ ) in the tilapia gut are less understood, particularly regarding their enhanced ability to penetrate cellular membranes, enter the bloodstream, and cross biological barriers (Ding *et al.*, 2023).
- Reversibility and Microbiome Restoration:** Research is needed to determine whether fecal microbiota transplantation, probiotic administration, or dietary intervention can reverse established MP-induced dysbiosis in farmed fish, and what timeframes are required for recovery.
- Methodological Standardization:** There is a profound lack of consistency across studies. Variations in polymer type, particle size, concentration, exposure route, fish developmental stage, and analytical endpoints make cross-study comparisons and meta-analyses challenging.
- Climate Change Nexus:** The interaction between rising water temperatures, hypoxia,

acidification, and MP toxicity is a nascent but critical area of research, as climate stressors may exacerbate MP-induced immunosuppression and oxidative stress.

#### 14. Future Perspectives

The field of MP toxicology in aquaculture stands at an important inflection point. Future research should prioritize environmentally realistic exposure scenarios, life-stage-specific vulnerability assessments, and the integration of non-invasive biomonitoring tools such as epidermal mucus metabolomics (Wu *et al.*, 2024). The application of artificial intelligence and machine learning to multi-omics datasets holds promise for identifying predictive biomarker signatures and modeling complex host-microbe-environment interactions. From a management perspective, the development of precision aquaculture approaches combining real-time water quality monitoring, probiotic delivery systems, and biochar-based filtration offers a tangible pathway toward MP-resilient production systems. Ultimately, safeguarding Nile tilapia aquaculture against the invisible threat of microplastics will require unprecedented collaboration among toxicologists, microbiologists, immunologists, engineers and policymakers.

#### 15. CONCLUSIONS

Microplastic pollution represents a significant, multifaceted threat to Nile tilapia aquaculture, operating at the critical nexus of gut microbiome integrity and host immune function. This review has demonstrated that MP exposure induces profound gut dysbiosis, compromises the intestinal barrier, and activates conserved inflammatory and oxidative stress pathways (TLR/NF- $\kappa$ B, MAPK, Nrf2/Keap1). The consequences histopathological damage, growth depression, metabolic dysregulation, and immunomodulation pose substantial risks to the sustainability and economic viability of tilapia farming. Critical findings, such as the age-dependent vulnerability of juvenile tilapia to inflammatory gene dysregulation (Kardgar *et al.*, 2024) and the pioneering application of non-invasive mucus metabolomics for biomonitoring (Wu *et al.*, 2024), highlight both the complexity of the challenge and the innovative solutions emerging to address it. Moving forward, the integration of multi-omics approaches will be essential to decode the complex host-microbe-environment interactions governing MP toxicity. However, technological advancement must be matched by practical mitigation. The incorporation of probiotics, functional feeds (e.g., *Chlorella*, *Spirulina*), and engineered biochar filtration offers a tangible path toward resilient aquaculture systems. Ultimately, safeguarding Nile tilapia production against the invisible threat of microplastics will require a concerted effort encompassing rigorous scientific inquiry, technological innovation, and robust environmental policy.

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