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Exploring salinity adaptation in teleost fish, focusing on omics perspectives on osmoregulation and gut microbiota

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Teleosts are the most varied vertebrates. They inhabit various environments and are crucial to global fisheries, making them a focus of research using advanced omics approaches. These studies provide insights into the genetic factors, environmental adaptability, disease resistance, and metabolic processes, aiding aquaculture sustainability. Acclimation to salinity stress is complex, influenced by genetics and the environment. Although some species tolerate varying salinity levels, rapid shifts beyond their optimal tolerance cause stress. Euryhaline species experience stress at extreme salinities, whereas stenohaline species are sensitive to minor changes. Osmoregulation maintains homeostasis at varying salinities through acclimation in the intestine, kidney, and gills, ensuring survival in changing environments. Studies on gut microbiota and metabolomics have revealed how teleosts cope with salinity stress. This review delves into the acclimatization processes through transcriptomic, metabolomic, and gut microbiome analyses, which have shed light on the complex mechanisms that teleosts have evolved to cope with salinity stress. Transcriptomic analyses have identified key ion transport, osmoregulation, and stress response genes essential for adaptation, facilitating cellular adjustments and maintaining osmotic balance across habitats. Studies have revealed significant metabolite changes in energy production and osmolyte synthesis during stress, indicating metabolic reorganization for osmoregulation. Gut microbiota analysis highlights microbial diversity in regulating osmoregulatory functions, emphasizing microbiota's role in resilience. Although research on interactions between salinity, growth conditions, and gut microbiota in teleosts is limited, findings suggest a vital relationship that warrants further study. Understanding these mechanisms is essential for improving fish health and enabling sustainable aquaculture management under environmental fluctuations.

KEYWORDS

salinity adaptation, teleost fish, osmoregulation, gut microbiota, metabolomics

1 Introduction

The increasing global population has led to a higher demand for aquatic products, particularly in terms of the daily consumption of aquatic species (Cooney et al., 2021; Emerenciano et al., 2021; McLean et al., 2020; Yohana et al., 2023; Zarzar et al., 2023). Fish farming is the fastest-growing sector in the aquaculture industry, playing a crucial role in boosting food production, fostering local economic growth, and improving livelihoods (Chang et al., 2020; Mkulo et al., 2024; Yohana et al., 2024). However, wild and cultured aquatic species face stress from pollution, temperature, fluctuations in salinity, and elevated ammonia levels (Zarantoniello et al., 2021). Salinity fluctuations, often caused by extreme weather events, can involve changes of 5–10 ppt or more and rise to be harmful to many marine and freshwater species (Gonzalez, 2012b; Lee et al., 2022b; Röthig et al., 2023). Similarly, sudden temperature shifts exceeding 2–3°C can induce stress, particularly in species with narrow thermal tolerance ranges (Mugwanya et al., 2022). To exist in such environments, fish must actively regulate the balance of ions and water to maintain osmotic homeostasis, as their body fluids and external environments have distinct ionic and osmotic pressures (Ruiz-Jarabo et al., 2017; Soengas et al., 2019). Generally, to maintain osmotic equilibrium, fish rely on both active ion transport, which requires energy, and passive water movement driven by osmotic gradients across epithelial tissues, such as the gills, kidneys, and gut. Additionally, hormonal regulation and physiological adaptations contribute to maintaining a proper balance of salt and water in the body (Arjona et al., 2009; Evans, 2011; Gregório et al., 2013; Takei and Hwang, 2016). Therefore, fish performance can be significantly affected if they cannot efficiently acclimate to osmotic stress (Evans, 2010; Kültz, 2015; Tseng et al., 2022a). Understanding osmoregulatory mechanisms is increasingly essential in the context of the impact of changing climates and increasing salinity variations in aquatic ecosystems (Fridman, 2020; Tseng et al., 2022a; Tresguerres et al., 2023). Recent advances in molecular biology, particularly transcriptomics, metabolomics, and microbiota profiling, have greatly enhanced our knowledge of osmoregulation in response to environmental changes (Kim and Kültz, 2020; Mundy et al., 2020; Escobar-Sierra et al., 2024). Molecular techniques have been widely used to investigate the effects of how salinity changes have influenced fish physiology, metabolic pathways, and gene expression (Houde et al., 2019; Devlin et al., 2020; Rahi et al., 2021).

Teleosts are the most diverse vertebrates and serve as interesting models for osmoregulatory plasticity studies because of their broad tolerance to environmental changes (Takei et al., 2014; Perry et al., 2020). These fish have developed various morphological and physiological adaptations that allow them to thrive in changing environments within their habitats (Harrison and Whitfield, 2006; Christensen et al., 2019). The species that have been most extensively studied in terms of salinity acclimation belong to several families. These include the *Cyprinodontidae*, such as the sheepshead minnow *Cyprinodon variegatus*, mummichog *Fundulus heteroclitus*, and Arabian killifish *Aphanius dispar*; *Cichlidae*, such as black-chinned

tilapia *Sarotherodon melanotheron* and Mozambique tilapia *Oreochromis mossambicus*; and *Poeciliidae*, such as the sailfin molly *Poecilia latipinna*, on fish salinity adaptations (Gonzalez, 2012a). The intestine is crucial for osmoregulation, as it modulates ion transport, regulates gene expression, interacts with microbes, and facilitates water absorption to assist in adapting to changes in salinity (Chen et al., 2023b; Su et al., 2023a; Takei, 2021a). One crucial function of the gut is to regulate the immune system and create a healthy environment for fish by interacting with the gut microbiota. This interaction is essential for maintaining the overall health and well-being of fish (Diwan et al., 2023; Perry et al., 2020; Xia et al., 2022a; Gyan et al., 2024). Meanwhile, metabolomics explores the complete set of low molecular weight metabolites present in a cell or organism, providing insights into physiological and biochemical responses to stress (Nicholson et al., 1999; Cuykx et al., 2018). Transcriptomics, gut microbiota analysis, and metabolomics have offered valuable insights into the response of teleost fish species such as *Danio rerio* (Guh et al., 2015), *Salmo salar* (Tipsmark et al., 2002), and *Oreochromis mossambicus* (Richards et al., 2003) to salinity stress. Most studies have primarily examined short-term fluctuations in salinity, rather than long-term acclimation. The connection between changes in the gut microbiota and osmoregulatory mechanisms remains unclear, raising the question of whether microbial changes are adaptive responses or play a direct role in osmoregulation. This review explores the osmoregulatory responses of teleost fish to salinity changes, as well as the roles of gut microbiota, metabolomics, and transcriptomics in these responses. By integrating various approaches, we sought to enhance our understanding of how fish adapt to shifting aquatic environments. This review identifies key gaps in the current knowledge and proposes innovative research directions to advance scientific understanding in this field.

2 Interactive effects of salinity, temperature, pH, and oxygen on fish physiology

The interactive effects of environmental stressors, such as salinity, temperature, pH, and oxygen levels, significantly impact fish physiology by disrupting ion regulation, acid-base balance, hormone circulation, metabolic pathways, growth, and survival (Kaushal et al., 2010; Franklin and Edward, 2019; Wang et al., 2019; Mariu et al., 2023). Temperatures exceeding 30°C can impose severe stress and potentially lead to mortality, particularly in cold-water fish species (Jain et al., 2013; Mariu et al., 2023). Extremely high salinity and temperatures, above 35°C, can be lethal to most fish species within hours (He et al., 2017; Mariu et al., 2023; Vadboncoeur et al., 2023; Yang et al., 2023). Temperatures below 5°C can cause a decrease in metabolic rates and activity. Subzero temperatures can lead to bodily fluids freezing, which can result in tissue damage and hinder growth and reproduction (Mariu et al., 2023). In environments with low pH and salinity, aquatic organisms tend to allocate less energy to primary physiological functions to

focus on osmoregulation (Lin et al., 2013). A study was conducted to analyze the effects of salinity and temperature on cortisol and glucose concentrations in three different fish species: *Cottus bairdii*, *Catostomus platyrhynchus*, and *Oncorhynchus clarki pleuriticus*. The study findings indicated that temperature had the most significant impact, with the influence of salinity being influenced by temperature. Extended exposure to high salinity levels was seen to lower the baseline cortisol and glucose levels in the fish, leading to an increased stress response when exposed to high temperatures. This ultimately resulted in physiological suppression in the fish. These results highlighted the need for conservation strategies to mitigate the effects of temperature-dependent salinity stress on freshwater fish species, especially considering the expected increase in freshwater salinization and temperature levels (Walker et al., 2020).

The optimal pH range for most freshwater fish species falls between 6.5 and 9.0, promoting maximum growth and reproduction (McCormick and Bradshaw, 2006; Laycock and Meeran, 2012; McCormick et al., 2020). For saltwater species, the ideal pH range is 6.5–8.5, beyond which stress-related effects may become apparent. Fluctuations in pH levels can disrupt ion regulation, enzyme function, and metabolic processes, leading to a disturbance in homeostasis and impairing oxygen transport and enzyme activity. Deviations from optimal pH levels have the potential to alter enzyme configuration and decrease catalytic efficiency (Poff and Zimmerman, 2010; Mariu et al., 2023). Oxygen levels are critical for adaptation to salinity. Research on *Perca fluviatilis* shows oxygen uptake is minimized in brackish water, where osmotic stress is reduced, compared to freshwater and seawater (Ern et al., 2014). A study of six stenohaline Channel catfish *Ictalurus punctatus*, and goldfish *Carassius auratus* and euryhaline rainbow trout *Oncorhynchus mykiss*, brown trout *Salmo trutta*, striped bass *Morone saxatilis*, and Gulf sturgeon *Acipenser oxyrinchus* fish species examined variations in oxygen consumption across low salinity, highlighting differences in osmoregulatory strategies (Altinok and Grizzle, 2003). In *Oreochromis niloticus*, it has been observed that as salinity levels increase, there is a decrease in oxygen consumption and ammonia excretion rates. This may reflect a reduction in the energy demand for osmoregulation rather than a limitation in energy availability. The highest survival rates were found at a salinity level of 12 g/L, with the most optimal growth occurring between 6–12 g/L. Salinity levels and duration significantly impact metabolic oxygen consumption rates (MO₂), total ammonia excretion (Tamm), ammonia quotient (AQ), and oxygen-to-nitrogen ratio (O: N). Protein metabolism was found to contribute less than 14.74% of the total energy required for osmoregulation (Kombat et al., 2021). A study conducted on *Epinephelus malabaricus* revealed that fish exposed to a salinity level of 11 psu exhibited lower Na⁺/K⁺-ATPase transcript levels, decreased oxygen consumption, and increased growth rates. At 11 psu, the GH-IGF axis was upregulated, leading to improved food conversion efficiency and growth (Zhu et al., 2023b). These findings underscore the importance of taking a comprehensive approach when evaluating fish acclimation, highlighting the interconnected nature of these physiological

processes and the effects of salinity, temperature, pH, and oxygen availability on the resilience of aquatic species.

3 Osmoregulation mechanisms in teleost fish: the role of the gill, kidney, and intestine.

3.1 Gill

The gill is a remarkable organ that plays a crucial role in fish life and is a highly distinctive structure with multiple functions. Gills are essential respiratory structures in fish, responsible for respiratory gas exchange, ion and water transfer, filter feeding, ammonia nitrogen excretion, and osmoregulation (Figure 1) (Chen et al., 2023a). Gills have evolved complex morphological structures to perform their vital physiological functions. These structures, which are part of the branchial chamber to which the gills belong, include the gill operculum, filaments, arch, and rakers. Each of these components plays a crucial role in the respiratory process of aquatic organisms (Fiedler et al., 2020; Alsafy et al., 2023). These structures, except gill rakers, undergo morphological and functional modifications in response to variations in water flow, temperature, ion concentration, and salinity within the aquatic environment. One way in which organisms adapt to environmental stressors is by altering the length and surface area of their gill filaments. This adjustment allows for optimal gas exchange and osmoregulatory functions (Evans et al., 2005a; Foyle et al., 2020; Alsafy et al., 2023). Fish have strong ionic/osmotic gradients in their aquatic surroundings, and the methods by which they maintain internal homeostasis are more demanding than those of terrestrial vertebrates (Hwang et al., 2011; Tseng et al., 2022a). Ionocytes are specialized, mitochondria-rich epithelial cells (MR cells) involved in ion regulation and homeostasis in various tissues and organisms. They are primarily responsible for maintaining ionic equilibrium and regulating pH through active ion transport mechanisms. These cells are found in diverse locations, such as the gills of fish, the airway epithelium in mammals, and other organs like the kidney and salivary glands (Griffith, 2017; Guh et al., 2015; Tseng et al., 2022a). A substantial body of literature has proposed models for examining iono-osmoregulatory mechanisms in fish gills. Nevertheless, these models frequently present conflicting or unresolved issues due to variations in species-specific metabolic pathways, differences in experimental methodologies, and inherent limitations of current analytical techniques (Hwang et al., 2011). Recent research has shed light on the challenges of ion regulation and osmoregulation in teleost fish by utilizing cutting-edge molecular and cellular physiological techniques such as whole-body oxygen consumption measurements, ion flux assays, electrophysiology, and immunohistochemistry, as well as animal models like zebrafish (*Danio rerio*), rainbow trout (*Oncorhynchus mykiss*), and tilapia (*Oreochromis niloticus*). Freshwater Teleost gills contain a combination of ionocytes and pavement cells (PNA⁺) (Shih et al., 2023). Pavement cells, which make up approximately 90% of the gill surface, serve as the main

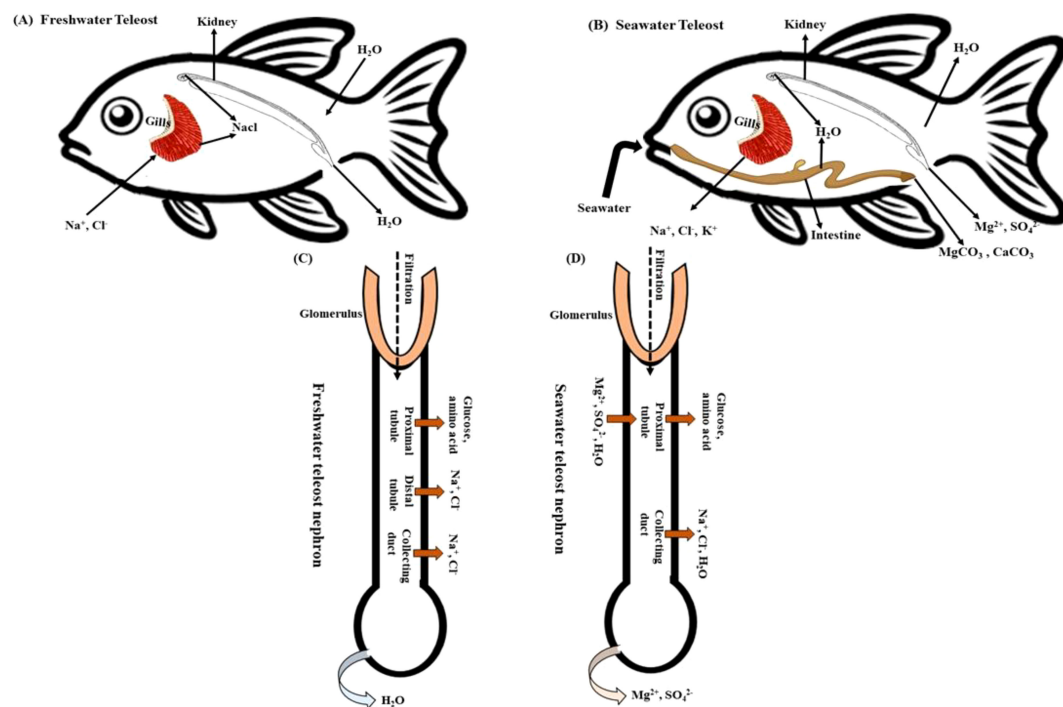


FIGURE 1

The acclimation process of teleost fishes to freshwater and seawater is crucial for regulating organ functions. This process involves the passage of ions and water through epithelial cells of the gill, kidney, and gut in both freshwater and seawater teleosts, referred to as (A, B). Additionally, the transport of ions and water in the nephrons of freshwater and marine teleosts is a significant aspect of acclimation (C, D). This process helps teleost fishes adapt to their environment and maintain organ function in varying salinity levels.

connection between the gills and water (Kovac and Goss, 2024). Ionocytes, primarily situated at the junction of gill filaments and lamellae, play a vital role in regulating ion transport to uphold osmotic balance. Their distribution is subject to alteration in response to environmental conditions; for instance, in fish inhabiting soft water environments, there may be an increase in the density of ionocytes within the lamellae. The apical surfaces of ionocytes vary among different species and environmental conditions, displaying features such as microvilli, a smooth finish, or a spongy texture (Masroor et al., 2019). In some species, ionocytes are situated within the epithelium, with their apical surfaces being partially obscured by pavement cells. The study conducted by (Shih et al., 2022), focused on freshwater teleost fish, particularly medaka (*Oryzias latipes*) and discovered and characterized the several types of ionocytes and ion transporters involved in the mechanisms of NaCl secretion, Na^+ uptake/acid secretion/ NH_4^+ excretion, Ca^{2+} uptake, and Cl^- uptake/base secretion. Additionally, this study also identified the key regulators involved in these processes, including Na^+/K^+ -ATPase (NKA) located in the basolateral membrane, which establishes the primary electrochemical gradient by actively transporting Na^+ out of the cell and K^+ into the cell. This gradient drives the movement of other ions through various transporters and co-transporters, the cystic fibrosis transmembrane conductance regulator (CFTR), the $\text{Na}^+/\text{K}^+/\text{2Cl}^-$ cotransporter (NKCC1), tight junction proteins such as claudins, and hormonal regulators like cortisol and prolactin, which collectively facilitate ion transport and osmoregulatory adaptations in teleost fish. Marine teleosts and

seawater-adapted euryhaline fish regulate ionic balance by actively excreting Na^+ and Cl^- , along with other minerals, through their gills (Figure 1). This process is facilitated by specialized mitochondrion-rich (MR) cells, also known as chloride cells. Several studies (Kolbadinezhad et al., 2018; Huang et al., 2020; Takvam et al., 2021a) have demonstrated that active trans epithelial Cl^- transport drives this process. Active chloride transport is accompanied by the passive flow of sodium ions across the paracellular space and tight junctions (Lavery and Skadhauge, 2012; Saint-Criq and Gray, 2017). The cellular process of chloride (Cl^-) secretion is comparable to that observed in several tissues, such as mammals' intestinal and airway epithelia (Rottgen et al., 2018; Shah et al., 2022; Becker and Seidler, 2024). Cl^- ions are initially transported across the basolateral membrane using the sodium-potassium-2 chloride (NKCC) transporter. This transporter depends on the Na^+/K^+ -ATPase to maintain a beneficial inward gradient for Na^+ ions. The overall impact of these transporters is to increase the concentration of intracellular Cl^- above electrochemical equilibrium (Janoš and Magistrato, 2021; Yurinskaya and Vereninov, 2021; Tseng et al., 2022a). Chloride ions are transported out of the cell by a specific channel called the cystic fibrosis transmembrane conductance regulator (CFTR) channel homolog. This process has been studied and documented by (Ferreira-Martins et al., 2021; Hanssens et al., 2021; Farinha et al., 2024). Several studies have explored the changes in the expression and function of transport components in response to osmoregulatory adaptations. In freshwater teleosts, water absorption and ion leakage through diffusion occur in the gills

(Figure 1A). Nevertheless, occludin and claudin proteins restrict the permeability of junctions between gill cells in these fish (Fridman, 2020). These junctions also contain negatively charged amino acid residues that bind to Ca^{2+} ions. Furthermore, mucosal cells located in the gills secrete mucus that contains charged glycoproteins and mucins. These substances can attract ions to the surface of the gills, aiding in the establishment of localized ionic gradients. This process effectively reduces passive ion loss through diffusion (Wilson and Laurent, 2002; Evans et al., 2005a).

In larval zebrafish, Na^+ uptake is mediated by Na^+/H^+ exchanger 3b (Nhe3b), electrogenic uptake driven by H^+ -ATPase in H^+ -ATPase-rich (HR) cells, and Na^+/Cl^- cotransporter (Ncc). However, when *slc9a3.2* (encoding *Nhe3b*) was knocked out using CRISPR/Cas9, Na^+ uptake remained unaffected, even in low Na^+ environments, indicating compensatory mechanisms. Neither H^+ -ATPase knockdown nor chloride absence influenced Na^+ uptake, highlighting zebrafish's adaptability and revealing gaps in understanding these processes (Zimmer et al., 2020). Prolactin (PRL), crucial for osmoregulation, was examined in zebrafish mutants deficient in PRL due to TALEN-induced mutations. These mutants couldn't survive in freshwater due to $\text{Na}^+/\text{K}^+/\text{Cl}^-$ uptake defects but thrived in brackish water, emphasizing PRL's vital role in ion balance (Shu et al., 2016). Investigation into carbonic anhydrase (*Ca17a*) demonstrated its significance in ion and acid-base equilibrium. CRISPR/Cas9 knockout of *ca17a* led to death by 19 days post-fertilization, with mutants showing increased Na^+ uptake and decreased Cl^- uptake, although overall ion content remained stable. Morpholino knockdown and pharmacological inhibition confirmed *Ca17a*'s involvement in Cl^- uptake, yet the exact cause of lethality remains unknown (Zimmer et al., 2021). These findings highlight the complexity of ion transport mechanisms in zebrafish, uncovering compensatory pathways and regulatory networks crucial for osmoregulation. Future research combining genetic and physiological methods will be essential to unravel these complex processes in freshwater and seawater teleosts. The zebrafish (*Danio rerio*) possesses five distinct ionocyte types: HR, NaR, NCC, SLC26, and KS cells, each with specific roles in ion transport. These regulatory mechanisms are governed by hormonal signaling pathways, which are mediated by isotocin, prolactin, cortisol, vitamin D, and calcitonin (Guh et al., 2015). These ionocytes play a crucial role in maintaining the osmotic balance within the fish. One key component of these ionocytes is the H^+ -ATPase (V-ATPase), located on the apical membrane (Davidson, 2024). This enzyme works to expel H^+ ions, creating an electric gradient that facilitates the entry of Na^+ through apical Na^+ channels (Davidson, 2024). This process is essential for regulating the fish's internal environment. Euryhaline teleosts have been extensively studied for their remarkable ability to adapt their ion and water regulation systems to withstand varying osmotic pressures (Agarwal et al., 2024). One critical system involved in these adaptations is the insulin-like growth factor (IGF) system. IGF-1 in particular plays a significant role in regulating myogenic cell proliferation and differentiation, as well as influencing osmoregulatory functions in fish gills by modulating plasma osmolality (Malone et al., 2015; McCormick and Regish, 2018).

Furthermore, Growth hormone (GH) has been found to enhance salinity tolerance in species like rainbow trout, Atlantic salmon, and killifish by stimulating gill Na^+/K^+ -ATPase (NKA) activity (Yada et al., 2012). This hormone plays a crucial role in helping these fish adapt to changing environmental conditions. Recent Genomic advances in salmonids have identified key transporters in ion-coupled fluid regulation, including NKA, Na^+/H^+ exchangers (NHEs), carbonic anhydrases, V-type H^+ -ATPase (V-ATPase), $\text{Na}^+/\text{HCO}_3^-$ co-transporters (NBCs), FXyDs, claudins, aquaporins (AQPs), $\text{Na}^+/\text{K}^+/\text{Cl}^-$ co-transporters (NKCCs), Na^+/Cl^- co-transporters (NCCs), and $\text{Cl}^-/\text{HCO}_3^-$ exchangers (SLC26A6) (Madsen, 2011). Among these transporters, Claudins maintain epithelial barrier integrity. For example, Zebrafish express claudin-15, while Atlantic salmon use claudin-30 to reduce sodium permeability in gill epithelia (Bagnat et al., 2007; Rosenthal et al., 2010; Amasheh et al., 2011; Englund and Madsen, 2011; Lingaraju et al., 2015). Identifying claudin-15 and claudin-25b in the salmon intestine has shed light on their specific osmoregulatory functions (Tipsmark, 2008; Tipsmark et al., 2010). Furthermore, in zebrafish, it has been studied that ion homeostasis is maintained through gill ionocytes expressing Na^+/K^+ -ATPase (NKA) and Na^+/Cl^- cotransporters (NCC) (Hwang and Chou, 2013). Under extreme ion deficiency, zebrafish increase expression of an NKA α -subunit (*zatp1a1a.5*), altering ATP hydrolysis efficiency (Esbaugh et al., 2019). Anadromous species such as Atlantic salmon undergo significant physiological changes during smoltification, enabling them to survive hypertonic seawater (Christensen et al., 2018; Morera et al., 2021; Morales-Rivera et al., 2022; Silva-Marrero et al., 2025). In freshwater environments, salmon gills exhibit high levels of NCC to absorb Na^+ and Cl^- . However, when transitioning to seawater, the expression of NCC decreases, while CFTR chloride channels and NKCCs increase. This shift promotes active salt excretion, which is essential for preventing dehydration (Yada et al., 2012; Lema et al., 2019; Inokuchi et al., 2022; Tümmeler, 2023). These discoveries shed light on the intricate molecular and physiological adaptations that contribute to salinity tolerance in teleost fish. Understanding these mechanisms is crucial for grasping their ecological resilience and potential applications in aquaculture.

3.2 Kidney

Fish kidneys are essential for regulating ions and water balance in freshwater (FW) (Figure 1A) and seawater (SW) (Figure 1B) environments. Glomerular filtration rate (GFR) as a key indicator of kidney function, representing the rate at which kidneys filter blood, is crucial in determining urine flow (Beyenbach, 2004; Takvam et al., 2023). However, the GFR of teleost fish exhibits considerable variability and is affected by factors such as glomerular intermittency, ambient salinity, renal perfusion pressure, and certain hormones including prolactin, atrial natriuretic peptide (ANP), cortisol, renin-angiotensin system (RAS) and arginine vasotocin (AVT) (Brown et al., 1990; Greenwell et al., 2003; McCormick, 2011). Hickman and Trump examined teleost kidneys'

evolutionary and anatomical features through microscopic observations and investigations of the isolated tubules, analyzing nephron components in euryhaline fish, including the glomerulus, aglomerular fish, proximal tubule, and collecting duct (Hickman and Trump, 1969). The morphological and regulatory characteristics of these kidney structures, such as the glomerulus, proximal tubule, and collecting duct, may vary depending on the acclimation of the fish to salinity or salinity fluctuations. Focusing on previous research conducted on aglomerular fish, which lack glomeruli or the distal tubule, resulting in limited urine dilution, researchers have studied aglomerular toadfish, a species with a lifespan of only three weeks in laboratory freshwater but can survive for months in 10% seawater. Toadfish experience increased metabolic activity when transitioning from seawater to a 10% solution, leading to a double increase in urine flow rate and a decrease in osmotic pressure. The kidneys excrete sodium, chloride, and sulfur at a ratio of 5:1:3, causing a decrease in plasma osmotic pressure (Lahlou et al., 1969; Baustian et al., 1997). To thrive in hypotonic environments, aglomerular toadfish must precisely regulate solute uptake through their branchial and intestinal cells while minimizing solute loss through their kidneys, as they are unable to produce dilute urine (Figures 1C, D) (Baustian et al., 1997).

The concentration of ions was notably low in the (FW) glomerulus of zebra fish and Nile tilapia. The glomerulus has evolved as an expression of the requirement for water excretion in freshwater animals. Dilute urine is regularly released because of the non-permeability of the distal tubule and downstream tissues, such as the collecting tubule/duct and bladder (Takvam et al., 2021a, 2023). The findings indicate that significant ions such as Na^+ , Mg^{2+} , SO_4^{2-} , Ca^{2+} , Cl^- , K^+ and HCO_3^- undergo reabsorption, whereas the osmotic reabsorption of water, which is present in combination with these ions, is restricted (Bates et al., 2018). Other reviews have provided evidence of this (Evans et al., 2005a; Hwang and Lee, 2007; Takvam et al., 2021a; Huang et al., 2023). Consequently, stenohaline (FW) and euryhaline (when in FW) fish continuously absorb water via their gills and skin while simultaneously losing significant ions through diffusion. To alleviate this phenomenon, the kidneys filter blood within the glomeruli (Loretz et al., 2009). The glomerular filtration rate (GFR) and urine flow rate (UFR) are consistently high, ranging from 4 to 16 ml/kg/h and 1 to 6 ml/kg/h, typically ranging from 20 to 50 mOsm/L (Hickman and Trump, 1969). Consequently, the organism displayed a significant release of diluted urine. This demonstrates the effectiveness of glomerular filtration and epithelial reabsorption of salt in maintaining osmotic balance in freshwater fish (Foskett et al., 1983). Generally, in (SW) conditions, where water conservation is of utmost importance, the renal system has a lower glomerular filtration rate (GFR) than the kidneys in freshwater (FW) environments (Nishimura and Imai, 1982; Ortiz et al., 2002). A low GFR causes the kidneys to filter blood at a lower rate, which preserves water and avoids excessive loss of vital ions. This adaptation facilitates the ability of organisms inhabiting salty habitats to acclimate to their surroundings and uphold internal homeostasis in the face of the difficulties presented by elevated salt concentration in the water. The greater part of sodium (99%), potassium (98%), and chloride (93%) obtained from ingesting

seawater are excreted through extrarenal pathways (mainly the gills, but also rectal fluid). The kidney has little or no role in osmoregulation (Evans, 2023).

3.3 Intestine

The intestine serves crucial roles in both digestion and osmoregulatory functions (Grosell, 2011; Rønnestad et al., 2017; de Oliveira et al., 2022) (Figure 1B). Specifically, the intestine plays a vital role in regulating the acid-base balance in marine and euryhaline teleosts, essential for maintaining osmoregulation. Efficient fluid absorption in the intestine is crucial for counteracting water loss in hypertonic environments (Carvalho et al., 2012; Whittamore, 2012). This absorption process is heavily influenced by osmotic gradients, particularly for sodium chloride (NaCl) absorption. The Na^+/K^+ pump, also known as NKA, plays a crucial role in the absorption of salts and water (Barany et al., 2021). Vertebrates, including fish, possess an impressive ability to absorb water through their digestive systems, effectively reclaiming fluids secreted by the stomach, small intestine, pancreas, and gall bladder. In fish, fluid absorption primarily takes place across the intestinal epithelium, aiding in osmoregulation and the regulation of internal water balance, particularly in hyperosmotic environments. Conversely, in freshwater environments, hydration primarily occurs through the gills (MacKay and Janicki, 1979; Ando, 1980; Ciccotti et al., 1993; Evans et al., 2005a; Takei, 2021a; Ciavoni et al., 2024). The intestine is integral to maintaining osmotic homeostasis in fish, particularly under conditions of salinity stress. This study examines the intricate mechanisms of osmoregulation in teleost fish, with a specific focus on the vital functions of the gill, kidney, and intestine. By analyzing the roles of these essential organs, we aim to advance our understanding of how teleost fish sustain their internal equilibrium of water and salts.

4 Effects of salinity stress on the gut microbiota of teleost fish

The fish intestine is a complex organ crucial for nutrient absorption, immune defense, and osmotic balance (Ciavoni et al., 2024). Along with the gills and kidneys, the gastrointestinal tract is vital for osmoregulation in teleost fish, managing water and electrolyte balance as they transition between FW and SW (Kolbadinezhad et al., 2018; Takvam et al., 2021a). Under hyperosmotic conditions, fish increase their water intake to counteract water loss, causing physiological changes in the intestine, including alterations in stomach acidity, digestive enzymes, and bile salts (Hieu et al., 2022). Environmental factors such as salinity and pollution significantly impact the gastrointestinal microbiota (GM), with salinity changes driving shifts in microbial community structure (Tolas et al., 2025). Microbial species adapted to low-salinity freshwater environments dominate the gut microbiota. Under hypersaline conditions, freshwater microbes with low salinity tolerance are eliminated,

whereas marine microbes with higher salinity tolerance thrive (Wang et al., 2018, 2021). The microbial community may also be affected by habitat-generalist bacteria, which possess the ability to thrive across a range of salinities and often become dominant in environments characterized by fluctuations. This phenomenon presents a compelling and significant area of investigation for researchers (Kivistik et al., 2020). Research on anadromous and euryhaline fish has shown that salinity changes shift gut microbiota, impacting microbial diversity (Lai et al., 2020). The properties of water influence the microbiota of tilapia larvae and are correlated with the microbiota present in water (Giatsis et al., 2015). Studies on stenohaline species gut microbiota, such as silver carp (*Hypophthalmichthys molitrix*), grass carp (*Ctenopharyngodon idella*), bighead carp (*Hypophthalmichthys nobilis*), and goldfish (*Carassius auratus*), which thrive in narrow salinity ranges, show restricted microbial changes under salinity stress. In contrast, euryhaline fish, such as *Oncorhynchus mykiss* (rainbow trout) and Asian sea bass, showed a strong correlation between gut and water microbiota when compared to the water microbiota of their natural habitats (Dehler et al., 2017; Zeng et al., 2020; Iehata et al., 2021; Lorgen-Ritchie et al., 2021; Morshed et al., 2023), suggesting that waterborne microbes may directly affect the gut microbiota.

Researchers have hypothesized that hypotonic stress leads to changes in the gill and gut microbiota of marine medaka (*Oryzias melastigma*), aiding salinity acclimation (Lai et al., 2022b) and decreasing bacterial diversity and increasing pathogenic bacteria in the yellowfin seabream (*Acanthopagrus latus*) (Lin et al., 2020). On the other hand, salinity stress in Nile tilapia (*Oreochromis niloticus*) increased opportunistic bacteria and decreased beneficial bacteria (Zhang et al., 2016). However, a study on *Poecilia mexicana* (Mexican mollies) found no such interaction, as key operational taxonomic units (OTUs) in the fish gut were absent in water, indicating that microbial colonization might be influenced by other factors such as host-specific mechanisms (Schmidt et al., 2015; Morshed et al., 2023). While many studies have shown that salinity changes influence the abundance and composition of gut microbiota in teleosts (Sullam et al., 2012; Lorgen-Ritchie et al., 2021; Morales-Rivera et al., 2022), others have reported minimal or no microbial shifts across salinity gradients (Schmidt et al., 2015; Sylvain et al., 2016). Understanding how teleost fish acclimate to extreme salinity is crucial for maintaining physiological homeostasis and ensuring successful osmoregulation. This insight is particularly crucial for enhancing the resilience of aquaculture and facilitating ecological adaptation.

Gut microbiota composition contributes to osmoregulation, affecting host metabolism and ion transport (Minich et al., 2020; Engevik and Engevik, 2021). In freshwater-adapted zebrafish, the microbiota primarily consists of *Aeromonas*, *Pseudomonas*, and *Vibrio*, which are members of the Proteobacteria phylum that contribute to development, immune responses, nutrient absorption, and ion homeostasis (Table 1) (Semova et al., 2012; Flores et al., 2020; Xia et al., 2022a). The gut microbiota of salmon undergoes significant changes during the transition to seawater, characterized by an increase in bacterial load and an increase in

Firmicutes, whereas *Actinobacteria* and *Proteobacteria* decrease. Research has shown that fluctuations in salinity have a profound effect on the richness, diversity, and taxonomic composition of salmon gut microbiota. Specifically, the study revealed that GSC and FD treatments led to an increase in microbiota diversity in salmon smolts. This suggests a potential correlation between the intestinal microbial community and the overall health of the fish during seawater transfer. These findings have important implications for monitoring the microbiome in smolt fish production, which could ultimately lead to improvements in salmon performance during transfer. By better understanding the relationship between intestinal microbiota and fish health, researchers and fish farmers can optimize the conditions for salmon production (Morales-Rivera et al., 2022). Additionally, core microbiota like *Lactobacillus* and *Clostridium* persist across salinity gradients, potentially aiding in osmoregulatory stability (Dehler et al., 2017; Bowman, 2024). Changes in microbial composition play a crucial role in enhancing ion transport mechanisms across the intestinal epithelia, highlighting their significance in maintaining homeostasis during salinity stress. These findings emphasize the complex interplay between the expression of ion transporters, the gut microbiota, and osmoregulatory functions in teleost fish.

As climate change continues to alter salinity gradients, it is essential to further investigate the adaptive mechanisms in these species using genomics, metabolomics, and microbiome profiling. Recent advancements in deep sequencing technology have revolutionized our understanding of the fish microbiota, enabling the study of microbial communities without the need for culturing. Overall, the relationship between microbial composition and ion transport mechanisms in teleosts is a critical area of research that can provide valuable insights into how these species adapt to changing environmental conditions (Tian et al., 2020). Quantitative real-time PCR (qPCR), denaturing gradient gel electrophoresis (DGGE), fluorescence *in situ* hybridization (FISH), temporal temperature gradient electrophoresis (TTGE), marker gene amplification and sequencing (e.g. ITS for fungi, 16S rRNA for bacteria and archaea), and metagenomics have improved our knowledge of fish gut microbiota composition, structure, and diversity (Ou et al., 2021). A metagenomic study of Nile tilapia exposed to acute high-salinity stress revealed significant changes in microbial communities, notably a shift from *Actinobacteria* to *Proteobacteria*, while fungal and phage communities remained stable. Functionally, intestinal bacteria show reduced activity in digestion and the nervous system, with increased energy metabolism. Key microbial genes, such as glutathione S-transferase, myo-inositol-1-monophosphatase, and glycine betaine/proline transporters, as well as specific carbohydrate-active enzyme families (*GT4*, *GT2*), were upregulated, whereas others (*GH15*, *GH23*) were downregulated (Gong et al., 2024). Studies using gnotobiotic fish models suggest that microbiota-derived short-chain fatty acids (SCFAs) influence ion transporter gene expression, affecting epithelial permeability and ion absorption (Lee et al., 2021; Xia et al., 2022a). These findings highlight the complex interactions between the host and the microbiota in

TABLE 1 The biological role of zebrafish and salmon fish gut microbiota.

Intestinal Bacteria Function	The biological function	Mechanism at the molecular level	References
<i>Aeromonas</i> , <i>Pseudomonas</i> , <i>Firmicutes</i> , <i>Actinobacteria</i> , <i>Proteobacteria</i> , <i>Clostridia</i> and <i>Lactobacillus</i>	Osmoregulation	<i>Aeromonas</i> and <i>Pseudomonas</i> in the gut microbiota of freshwater zebrafish may be associated with osmoregulation, assisting the fish in maintaining appropriate ion balance in their bodily fluids may also be associated with osmoregulation affecting the survival and growth of fish in the Atlantic salmon	(Flores et al., 2020; Xia et al., 2022a; Tolas et al., 2025)
<i>Pseudomonas fluorescens</i> , <i>Aeromonas veronii</i> biovar <i>sobria</i>	Development	Using specific host recognition mechanisms to promote intestinal epithelial maturation	(Bates et al., 2007; Butt and Volkoff, 2019)
<i>Vibrio</i> <i>Monospora</i> and <i>Enterobacteriaceae</i> , <i>Firmicutes</i> , <i>Actinobacteria</i> and <i>Proteobacteria</i>		In larval zebrafish, excessive <i>Vibrio</i> species proliferation prevents the establishment of adaptive immunity and affects the survival and growth of Atlantic salmon fish under salinity fluctuation	(Brugman et al., 2014; Tolas et al., 2025)
<i>Vibrio cholerae</i> : GFP ZWU0020, <i>Aeromonas veronii</i> : dTomato HM21		Essential for typical neurobehavioral development throughout the early life stages of zebrafish	(Cheesman et al., 2011; Phelps et al., 2017)
<i>Chryseobacterium</i> sp. ZOR0023, <i>Pseudomonas</i> sp. ZWU0006, <i>Exiguobacterium</i> sp. ZWU0009,	Metabolic Activity	Enhancing fatty acid absorption and lipid droplet deposition in intestinal epithelium and hepatic tissue	(Semova et al., 2012)
<i>Pseudomonas aeruginosa</i> strain PAK	Immunity	The regulation of the dynamic temporal and spatial activation of <i>NF-κB</i> transcription and subsequent up-regulation of target genes within the gastrointestinal tract.	(Kanter et al., 2011)
<i>Aeromonas veronii</i> biovar <i>sobria</i> , <i>Pseudomonas fluorescens</i> , <i>Streptococcus</i> , <i>Staphylococcus</i> , and <i>Vibrio</i>		Regulating host immunity via the control of <i>Myd88</i> and <i>TNF</i> receptor	(Cheesman et al., 2011; Brugman et al., 2014)

osmoregulation. Future research using gene knockout models and microbial colonization assays could provide deeper insights into the role of the microbiota in teleost salinity adaptation (Quan et al., 2021).

These advancements highlight the importance of the gut microbiota in the osmoregulation of euryhaline fish, where microbial changes are linked to osmoregulatory and energy metabolism alterations (Hu et al., 2017; Tseng et al., 2022a). However, much remains to be learned about microbial interactions and physiological changes that occur during salinity acclimation. The interaction between salinity stress and the gut microbiota in teleost fish is intricate and varies by species. Stenohaline species frequently encounter microbial instability when exposed to changes in salinity because their microbiota may experience significant fluctuations or a loss of stability. Conversely, euryhaline fish demonstrate more gradual and adaptive shifts in their microbiota, with alterations in the microbial community composition that facilitate osmoregulation. Gut microbiota responses to salinity stress highlight the balance between the host physiology and environmental factors. Future studies should use multi-omics approaches to clarify the role of gut microbes in salinity adaptation. Comparative research across teleost species

will reveal broader microbial patterns under stress, which is crucial for optimizing aquaculture, fish health, and microbiota stability under changing salinity.

5 Influence of salinity stress on metabolomics in teleost fish

Metabolomics, which involves studying all the low-molecular-weight metabolites present in a cell or organism, is known as metabolomics (Nicholson et al., 1999; Cuykx et al., 2018). By integrating metabolomics and transcriptomics, valuable insights can be gained into the effects of various stressors on fish, such as stickleback (Figure 2) (Divino, 2016; Abid et al., 2018; Meador et al., 2020; Iehata et al., 2021; Santos et al., 2023). Understanding the impact of environmental stress on fish can be achieved through comprehensive metabolomic analyses. Investigating the molecular mechanisms controlling teleost fish exposed to high salinity can greatly benefit metabolic analysis (Qin et al., 2022). The gills of euryhaline fish, which are highly oxidative tissues, regulate a variety of ion transporters and enzymes in response to changing salinities in an efficient and timely manner, requiring significant energy

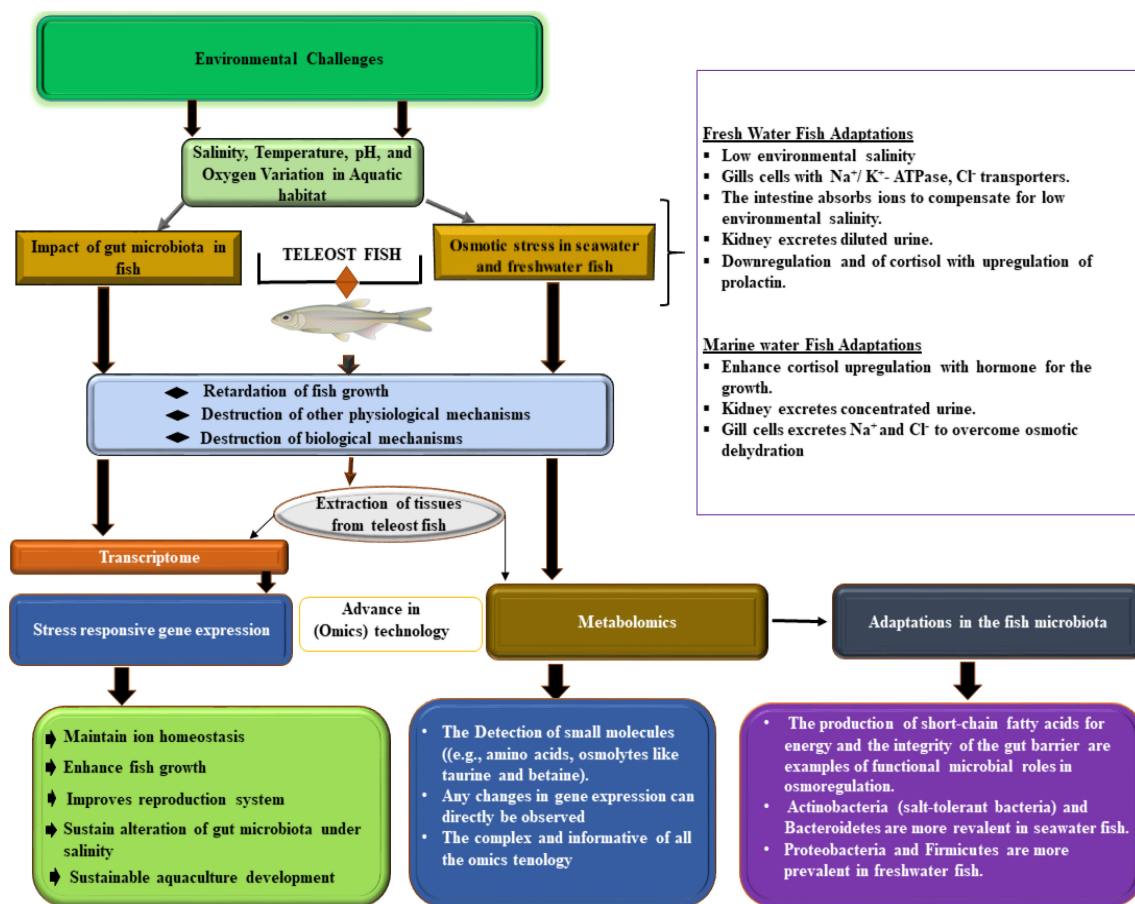


FIGURE 2

Displays salinity adaptation in teleost fish, covering environmental stressors, physiological osmoregulatory responses, and omics insights. The upper panel shows aquatic ecosystems and stressors, the central panel illustrates cellular osmoregulatory mechanisms in key organs, and the lower panel consolidates omics data, highlighting transcriptomic, metabolomic, and microbiome changes under different salinity conditions. The right panel summarizes the physiological adaptations, offering insights into the salinity management of teleost fish and its implications for aquaculture and conservation.

(Liu et al., 2023). Since fish ions and osmoregulation processes depend on energy availability for proper operation, this suggests that most metabolic and energy-related genes are expressed more when salinity is higher (Djiba et al., 2021). Hence, the study of Li et al. demonstrated how varying salinity concentrations affect gene expression and energy metabolism. Glycolysis and gluconeogenesis are crucial for generating energy and regulating glucose levels (Li et al., 2023). Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) is a glycolytic enzyme that plays a crucial role in carbon and energy metabolisms. Notably, studies have indicated that a decrease in GAPDH protein levels may facilitate the preservation of other glycolytic enzymes and redirect glucose flux through alternative metabolic pathways. This redirection potentially enhances glucose utilization under specific physiological conditions (Baumgarner et al., 2012; Lazarev et al., 2020). Upon the transfer of fish to seawater, the increased energy requirements in the gills may lead to enhanced reliance on anaerobic metabolism, specifically the conversion of pyruvate to lactate. Lactate dehydrogenase A (LDHA) plays a pivotal role in

facilitating this metabolic pathway (Vijayan et al., 1996). Advancements in metabolomics have opened new opportunities for understanding the complex physiological responses of teleost fish to changes in salinity (Ganguly et al., 2020). This emerging discipline focuses on the comprehensive characterization of metabolites, offering detailed insights into the biochemical changes and regulatory processes that enable teleost fish to thrive in variable environments (Alfaro and Young, 2018; Goode et al., 2020). Enhancing genetic traits or regulating nutrition through osmoregulation can significantly improve the ability of fish to adapt to different salinity levels. Metabolomic research on salinity adaptation in teleost fish is needed; however only a limited number of studies have been conducted on various species. Most fish species do not possess a strong ability to adjust to changes in salinity. Exposure to high salinity in their habitat has negative consequences such as stunted growth, susceptibility to diseases, and even mortality (Yamaguchi et al., 2018; Kujawa and Piech, 2022). This has impeded progress in aquaculture and poses a threat to fish biodiversity conservation. This offers a notable opportunity for

scientists to further investigate metabolic pathways and identify crucial biomarkers associated with osmoregulation (Liu et al., 2023). Using metabolomics, researchers have been able to identify metabolites from the intestine, hepatopancreas, and muscle of *Gymnocypris przewalskii* using LC-MS/MS, revealing 5,745 differentially expressed genes. Processes such as gluconeogenesis and long-chain fatty acid metabolism play crucial roles in maintaining glucose homeostasis and providing energy in cold-stressed fishes. Therefore, through the application of metabolomics, scientists can gain a comprehensive understanding of the molecular mechanisms by which teleost fish regulate ion balance, generate energy, and respond to stress (Liu et al., 2023).

Acquiring knowledge about the metabolites linked to optimal salinity adaptation is crucial for enhancing resilience and growth of fish in aquaculture settings (Figure 2). By identifying these key metabolites, specialized feeds and breeding programs can be developed to cultivate more resilient fish breeds (Raposo de Magalhães et al., 2022). In a recent study, researchers examined the stress proteome and metabolome of *Sparus aurata*, a fish species, in response to aquaculture challenges, including factors such as overcrowding, repetitive net handling, air exposure, and hypoxia. Their analysis revealed disrupted pathways in the fish liver, revealing a complex network of regulatory elements that impact cellular stress pathways. This study provides valuable insights into fish welfare (Raposo de Magalhães et al., 2022). Recent research has enhanced our understanding of teleost responses to saline-alkaline stress. Ding et al. examined the physiological and metabolic changes in Crucian carp (*Carassius auratus*) subjected to varying NaHCO_3 concentrations, identifying significant renal impairments such as glomerular atrophy, tubular degranulation, and renal cell proliferation (Ding et al., 2023). Furthermore, the study underscored disruptions in antioxidant systems, energy metabolism, and protein catabolism, indicating that *C. auratus* exhibits notable sensitivity to saline-alkali exposure. Conversely, comprehensive analyses of the annexin (*GpANN*) family in naked carp (*Gymnocypris przewalskii*), a species well-adapted to high-salinity and alkaline environments, revealed critical molecular adaptations. *GpANNs* displayed diverse functional motifs and tissue-specific expression profiles, with *GpANN2* and *GpANN3* demonstrating significant transcriptional and translational responses in kidney tissues under stress (Linlin et al., 2024). These findings suggest that, while *C. auratus* experiences stress-induced damage, *G. przewalskii* possesses evolved molecular mechanisms that enhance its resilience, offering a comparative model for understanding salinity adaptation in freshwater teleosts.

Metabolomics plays a vital role in promptly identifying stress and diseases in fish, allowing timely interventions to enhance their welfare (Low et al., 2017). By integrating metabolomic data with other omics approaches, we can gain a comprehensive understanding of adaptation mechanisms in fish (Jendoubi, 2021). Given the growing global demand for sustainable fish farming practices, it is essential to prioritize metabolomic research on teleosts fish is essential. Studying their adaptive abilities in response to salinity variations will not only deepen our knowledge, but also inspire innovative solutions for sustainable

aquaculture techniques. This will ultimately help the aquaculture business grow and become more resilient in the face of environmental challenges.

6 Influence of salinity stress on transcriptomics in teleost fish

Living species require adequate sensations, reactions, and adaptation to varying salinity conditions for development, reproduction, and survival. In recent decades, aquatic ecosystems have been facing elevated salinity stress due to road de-icing salts, rising sea levels, saltwater intrusion in coastal areas, and increased global temperature changes, affecting their biodiversity directly and indirectly (Cunillera-Montcusí et al., 2022). Salinization has been shown to affect ecological processes, trophic networks, functional trait variety, and community composition in several habitats (Cañedo-Argüelles et al., 2013; Hintz and Relyea, 2019; Tweedley et al., 2019; Röthig et al., 2023). The energy expenses associated with osmoregulation in fish, particularly the transfer of ions across cell membranes against a concentration gradient, can range from a few (‰) to up to 30 (‰) in salinities that differ from their body fluids (Figure 1) (Bœuf and Payan, 2001; Urbina and Glover, 2015). While teleost fish can temporarily adjust to changes in salinity circumstances (Jiang et al., 2019), it has been observed that excessive salinity levels hinder their growth (Zhao et al., 2022) and disrupt their regular metabolism (Jiang et al., 2019). Several physiological studies have been conducted on the osmoregulatory systems involved in the adaptation of fish to different salinity levels, such as freshwater or seawater, which can range from 0 to 38 ‰ (Evans et al., 2005a; Hwang and Lee, 2007; Lee et al., 2022a). The primary focus of their description was on osmoregulatory capabilities within this range of salinity. They provide information on various changes, such as alterations in electrolyte concentration in bodily fluids, remodeling of the epithelium, standard metabolic rates, hormonal regulation, expression patterns of specific genes involved in ion transport and osmoregulation, such as Na^+/K^+ -ATPase [NKA], $\text{Na}^+/\text{K}^+/\text{2Cl}^-$ cotransporter [NKCC], cystic fibrosis transmembrane conductance regulator [CFTR], aquaporins, and the use of high-throughput methods, such as RNA sequencing, to study osmoregulatory tissues (Figure 2). Studies that provide results for more than 40‰ salinity in fish are still uncommon (Lam et al., 2014; Su et al., 2022). The function of ion-transporters has been extensively studied in fish exposed to seawater challenges. The transfer of salmon, specifically *Onchorhynchus kisutch* or *Salmo salar*, and brown trout, known as *Salmo trutta*, in seawater led to a gradual acclimation of Na^+/K^+ -ATPase and $\text{Na}^+/\text{K}^+/\text{2Cl}^-$ cotransporter expression in the cells that make up the gills (Tipsmark et al., 2002). The mRNA levels of certain subunits of Na^+/K^+ -ATPase increased in response to changes in ambient salinity in the tissues of the tilapia *Oreochromis mossambicus* and rainbow trout *Onchorhynchus mykiss*. However, the mRNA levels of the other subunits decreased (Richards et al., 2003). In addition, studies have investigated the responses of fish to the challenges of freshwater environments by assessing and analyzing the expression of prolactin,

a hormone that plays a role in osmoregulation and adaptation to freshwater conditions. Prolactin is a key factor in the process of osmoregulation in freshwater fishes. It controls the movement of water and salt through the gills and kidneys by influencing changes in membrane permeability and creation of chloride cells (Forsyth and Wallis, 2002).

Previous studies have attempted to identify molecular processes, such as transcriptome analysis, to provide scientists with a useful set of data for developing specific interventions and management strategies that promote the survival and adaptation of fish populations in environments with different salinity levels (Table 2). Transcriptomics, which involves studying the expression of all genes at a specific time, has been utilized for more than ten years to understand the connections between the environment, genotype, and phenotype in natural populations (Li et al., 2024a). Transcriptomic profiling in animals lacking whole-

genome sequencing data is a powerful approach for investigating genomes and discovering functional genes (Escobar-Sierra et al., 2024). Transcriptomic analysis is a widely used technique to gain insights into the functional genomic components and reveal molecular mechanisms in cells and tissues of teleost fish (Figure 2). The transcriptome, consisting of both protein-coding messenger RNA (mRNA) and non-coding RNA (ncRNA), demonstrates heterogeneity in its response to developmental stage, physiological conditions, and external environment (Sun et al., 2020; Yi et al., 2021; Harshini et al., 2022; Ru et al., 2023). High-throughput sequencing technologies offer an opportunity to study changes in gene expression in organisms exposed to various environmental conditions. Transcriptome sequencing allows for comprehensive analysis of several physiological systems, such as metabolism, proteostasis, and osmoregulation (Vij et al., 2020; Escobar-Sierra et al., 2024; Li et al., 2024a).

TABLE 2 Provides an overview of studies that have conducted transcriptome analyses on teleost fish under salinity stress conditions.

Teleosts Species	Salinity environments	Discoveries from Transcriptome Analysis	References
<i>Fundulus heteroclitus</i> (killifish)	Freshwater to Saltwater	Ion transporters and osmosensory signaling genes are differentially expressed in osmoregulation.	(Scott et al., 2004; Whitehead et al., 2012)
<i>Lates calcarifer</i> (Asian seabass)	Freshwater to Seawater	An increase in the expression of genes associated with energy production, metabolism, osmoregulation, and the response to oxidative stress was observed.	(Xia et al., 2013; Vij et al., 2020)
<i>Oreochromis niloticus</i> (Nile tilapia)	Freshwater to hypersaline (above 35ppt)	The genes responsible for ion transport, osmotic regulation, and stress response are being upregulated.	(Ronkin et al., 2015; Liu et al., 2018; Zhao et al., 2020)
<i>Oncorhynchus mykiss</i> (Rainbow trout)	Freshwater to Seawater transition	Alterations in the transcriptome underscore the importance of ion channels and transporters in osmoregulatory adaptation.	(Leguen et al., 2010; Xiong et al., 2020; Liu et al., 2024; Pino-Martinez et al., 2024; Zuloaga et al., 2024)
Chinese Sea Bass (<i>Lateolabrax maculatus</i>)	freshwater (FW) to seawater (SW) but moderately adapt to highly alkaline water (AW)	Transcriptomic analysis reveals the unique cellular response in the gills when exposed to fluctuations in salinity and alkalinity.	(Zhang et al., 2017; Li et al., 2022a; Zhu et al., 2023a)
<i>Oreochromis mossambicus</i> (Mozambique tilapia)	Variable salinity (freshwater to seawater)	Various genes related to osmoregulation, stress response, prolactin receptors, and ion transport exhibit differential expression.	(Seale et al., 2014; Ronkin et al., 2015; Su et al., 2020; Inokuchi et al., 2021)
<i>Acanthopagrus schlegelii</i> (Black Sea bream)	Hypo- and hyper-saline conditions	Significant changes have been observed in the expression of genes related to metabolism, cellular stress, and ion transport.	(Chang et al., 2007; Li et al., 2022b; Nagarajan et al., 2023)
<i>Cyprinodon variegatus</i> (Sheepshead minnow)	freshwater to seawater)	Research has identified genes associated with immune response, stress response, and osmotic balance that exhibit changes in their transcriptomes.	(Simning et al., 2019)
<i>Dicentrarchus labrax</i> (European sea bass)	Euryhaline species with a Salinity gradient tolerating from FW up to 70 ppt	Differences were observed in the expression of genes associated with immune response, energy metabolism, and ion transport. These variances were crucial for maintaining distinct ecotypes during the early stages of reproductive isolation.	(Boutet et al., 2006; Masroor et al., 2019)

(Continued)

TABLE 2 Continued

Teleosts Species	Salinity environments	Discoveries from Transcriptome Analysis	References
<i>Danio rerio</i> (Zebrafish)	Freshwater fish	The stress response triggers alterations in gene expression, particularly in genes that contribute to developmental abnormalities in zebrafish. Furthermore, the research also pinpointed changes in gene expression associated with the regulation of post-embryonic development in response to salinity stress.	(Breves et al., 2013; Thompson et al., 2022; Seli et al., 2024)
<i>Gasterosteus aculeatus</i> (Three-spined stickleback)	Has a wide salinity tolerance from seawater to freshwater environments	Genes associated with energy metabolism, oxidative stress, and ion transport exhibit varying expression patterns.	(Jones et al., 2012; Taugbøl et al., 2022)

In the past years, there has been notable progress in understanding the transcript expression profile during salinity adaptation of various euryhaline teleost species using RNA-Seq, such as Nile tilapia (*Oreochromis niloticus*), Mozambique tilapia (*Oreochromis mossambicus*) (Table 2) (Ronkin et al., 2015), medaka (*Oryzias latipes*) (Lai et al., 2015), striped catfish (*Pangasianodon hypophthalmus*) (Thanh et al., 2015; Pasquier et al., 2016), and Asian seabass (*Lateolabrax japonicus*) (Xia et al., 2013). Multiple studies have demonstrated alterations in ion transporters, channels, and stress-related proteins, elucidating the physiological mechanisms by which fish can maintain a consistent internal environment under varying salinities. Transcriptomic analyses have recognized many genes involved in ion transport, water channels (aquaporins) (Riera Romo et al., 2016), and stress response pathways (Table 2) (Cutler et al., 2007). Tenuulosa ilisha (*Hilsa shad*), an anadromous fish, was examined in fresh, brackish, and marine water. The analysis revealed 3277 genes that were expressed differently (DEGs), with 232 being shared between marine and freshwater environments. Out of the 54 KEGG Pathways, the focal adhesion, adherens junction, tight junction, and PI3K-Akt signaling pathways were identified as the most significant. Various settings exhibited distinct expression patterns for 24 osmoregulatory genes that were differentially expressed in diverse habitats (Mohindra et al., 2023).

The gill transcriptome of *Odontesthes bonariensis*, a stenohaline freshwater species, demonstrates distinct gene expression patterns when exposed to high salinity, in contrast to *Odontesthes argentinensis*, a closely related euryhaline species capable of tolerating a broad range of salinities. This disparity underscores the unique molecular mechanisms that underpin salinity adaptation in species with differing osmoregulatory capacities (Hughes et al., 2017). An analysis was conducted on the transcriptomic data of the livers of juvenile *Scatophagus argus* following a sudden shift in salinity. The results revealed that this alteration led to the generation of 474 differentially expressed genes. The pathways associated with immune defense showed enrichment, including 'Antigen processing and presentation' and 'Phagosome', suggesting that *S. argus* may strengthen the immunological defense system. Low-salinity-induced oxidative stress led to the upregulation of several genes that encode antioxidant enzymes, such as HAO, Trx, and PHGPx. Downregulation

of *Cul3* could potentially enhance the activation of *Nrf2*, leading to the upregulation of antioxidant enzyme genes. The results suggested that *S. argus* could be used to confirm the effectiveness of the transcriptome as a molecular mechanism for resisting low salt stress (Sun et al., 2022). Furthermore, Lai et al. study investigates genetic responses to hypotonic conditions and gill microbiota dynamics in marine medaka following freshwater transfer. Using transcriptome and 16S rRNA sequencing, the study reveals 1,034 genes with altered expression and documents a microbial shift from *Vibrio* to *Pseudomonas* and *Cetobacterium*. The identification of overlapping pathways associated with glycosaminoglycan and chitin suggests significant host-microbiota interaction in gill adaptation, offering novel insights into osmoregulation during osmotic stress (Lai et al., 2022b).

7 Strengthening cross-omics correlation study

Variations in salinity levels stress aquatic organisms, disrupting homeostasis, metabolism, reproduction, and immune function (Leprêtre et al., 2025). Investigating teleost fish adaptation using high-throughput cross-optimal correlation analysis, including gut microbiota composition, metabolomics, and transcriptomics, elucidated salinity adaptation mechanisms (Figure 2). A challenge in gut microbiota studies is the contamination of metagenomic and metatranscriptomic data by host material and the overlap between host and microbial metabolites (Ou et al., 2021). Despite this, integrative omics approaches have advanced our understanding of host-microbiota interactions under stress. This review compiled research on microbial taxa, metabolic pathways, and gene expression interactions in response to salinity stress, offering insights into the adaptive strategies of teleost fish.

7.1 Gut microbiota and metabolomic interactions

Recent advancements in high-throughput chemical fingerprinting methods, such as metabolomics based on nuclear

magnetic resonance (NMR), have provided scientists with tools to delve deeper into the intricate interactions between the gut microbiota and host metabolism (van Ravenzwaay et al., 2007; Wei et al., 2018). Gut microbiota is a dynamic entity that evolves alongside the host and is influenced by many factors, including genetics, diet, and environment (Nicholson et al., 2012). Environmental fluctuations, particularly salinity variations, can profoundly affect the gut microbiome, which contains trillions of microorganisms and is considered to play a critical role in host digestion and metabolic homeostasis (Budd et al., 2020; Lai et al., 2022a; Liu et al., 2022). For example, a study on the wild yellowfin goby (*Acanthogobius flavimanus*) revealed seasonal and latitudinal changes in the metabolome, ionome, and microbiome, with salinity acting as a key regulator of gut microbial communities and homeostasis (Wei et al., 2018). Similarly, research on wild black Amur bream (*Megalobrama terminalis*) in China's drainage areas found higher alpha diversity in mainland populations than in those on Hainan Island. Geographic isolation and seasonal variations were found to have a significant effect on the gut microbiome, with distinct regulatory patterns observed in each population. This suggests that environmental factors and genotypes play a crucial role in shaping microbiome diversity in wild *M. terminalis* (Liu et al., 2022). In juvenile *M. salmoides*, exposure to 5‰ salinity increased superoxide dismutase activity, while 15‰ salinity elevated levels of aspartate aminotransferase, ALT, acid phosphatase, AKP activity, and total antioxidant capacity. Interestingly, the control group exhibited the highest levels of catalase and glutathione peroxidase activity, suggesting that a salinity of 5‰ enhances immune function. Analysis of paraffin sections revealed a decrease in villus length and an increase in epithelial cell expansion with increasing salinity levels. Furthermore, microbiota analysis showed shifts in dominant taxa, with an increase in *Bacillus* abundance at a salinity of 10‰. Salinity stress was found to affect lipid and amino acid metabolism, with the 15‰ salinity group showing enriched replication, recombination, and repair processes, as well as salinity stress response mechanisms (Sun et al., 2023). Additionally, different salinity levels were observed to affect the gut microbiota of Atlantic salmon, leading to alterations in microbial communities and an increase in specific taxa, such as *Vibrio*, *Pseudomonas*, *Acinetobacter*, *Corynebacterium*, *Alteromonas*, *Flavobacterium*, and *Micrococcus* (Ou et al., 2021). Furthermore, metabolomic profiling has demonstrated changes in key metabolites, particularly osmolytes such as taurine and betaine, as well as lipid derivatives (Tian et al., 2022; Li et al., 2024b). Metabolites are linked to osmoregulation and stress adaptation because taurine and betaine serve as compatible solutes that contribute to the stabilization of intracellular osmotic pressure, protection of cellular structures, and maintenance of enzyme activity under hyperosmotic conditions. Concurrently, alterations in lipid metabolism indicate the necessity for membrane remodeling and energy reallocation during salinity stress, both of which are crucial for sustaining homeostasis and physiological functions in dynamic environments. Restructuring of gut microbiota has also been observed in other teleost species, including golden pompano (*Trachinotus ovatus*) and wild Arctic

charr (*Salvelinus alpinus*), where salinity-induced changes affect amino acid, lipid, and carbohydrate metabolism, influencing host adaptation (Hamilton et al., 2019; Liu et al., 2019). This suggests that the gut microbiota plays a crucial role in maintaining the metabolic equilibrium of the host organism. Overall, these findings highlight the importance of the gut microbiota in maintaining metabolic equilibrium in the host organisms.

7.2 Metabolomics and transcriptomic integration

Through metabolomic and transcriptomic analyses, researchers have linked differentially expressed genes (DEGs) related to lipid metabolism, energy balance, and osmoregulation to metabolic alterations in response to salinity stress (Figure 2) (Kanika et al., 2025). A study of genetically improved farmed tilapia (GIFT) *Oreochromis niloticus*, identified osmoregulatory genes, such as aquaporin 3, Na⁺/K⁺-ATPase, Potassium channel subfamily K member, chloride channel 2, and solute carrier (SLC) transporters, showing differential expression across salinity conditions. The coordinated response between gene regulation and metabolic adaptation is demonstrated by the alignment of over-represented pathways, including UDP-N-acetyl-glucosamine synthesis, N-glycan biosynthesis, and lipid metabolism, all of which play a role in supporting osmoregulatory function. This coordinated response is further underscored by the metabolomic changes observed in osmolytes, such as 12-hydroxyeicosatetraenoic acid, choline, and adenine. These shifts in pathways and metabolites suggest a close connection between the activation of osmoregulatory genes and the metabolic adjustments required to maintain osmotic balance under salinity stress (Qin et al., 2022). This intricate relationship highlights the complex mechanisms at play in the cellular response to environmental challenges, shedding light on the adaptive strategies employed by organisms to survive and thrive in changing conditions. Transcriptomic analyses across various fish species have elucidated critical molecular adaptations to salinity stress, demonstrating how environmental changes influence gene expression and metabolic processes. In *Tenualosa ilisha*, key pathways related to cell adhesion, ion transport, and osmoregulation have been identified with KEGG pathways such as focal adhesion, tight junctions, and PI3K-Akt signaling being significantly enriched. Notably, the habitat-specific expression patterns of genes from the *slc16* and *slc2* families, as well as claudin genes (*cldn11*, *cldn10*), suggest that these genes play pivotal roles in acclimating to varying salinity conditions. Furthermore, protein-protein interaction (PPI) network analysis revealed that *fn1* interacts with genes involved in muscle structure development, underscoring the cellular and structural adjustments necessary for osmoregulation under stress (Mohindra et al., 2023). Similarly, in *Lates calcarifer*, the differential expression of osmoregulatory genes involved in tissue remodeling, circadian rhythms, and growth regulation indicates that salinity fluctuations not only drive acclimation to freshwater and seawater but also influence physiological behaviors such as migration (Vij et al., 2020). Additionally, in *Scatophagus argus*, transcriptome profiling

of brain tissue under high- and low-salinity conditions revealed metabolic reprogramming, with genes (*lipa*, *sle*, *acc*, *fas*, *bhmt*, *mpst*, *dnmt3a*, *mtr*, *hao2*, *LOC111225351*, *hmgcs1*, *hmgcr*, and *soat1*) related to lipid metabolism, steroid biosynthesis, and methylation pathways being significantly altered. These findings suggest that salinity stress affects both metabolic reprogramming and gene expression in the brain, particularly in processes that are vital for osmoregulation and stress adaptation (Lin et al., 2024). Collectively, these studies highlight the complex molecular responses to salinity stress, revealing how different fish species utilize distinct, yet interconnected, gene networks and metabolic pathways to adapt to their respective saline environments.

Alternative splicing (AS) has emerged as a critical post-transcriptional regulatory mechanism for salinity acclimation in teleosts. RNA-Seq analyses of Mozambique tilapia (*Oreochromis mossambicus*) and rainbow trout revealed significant results. In Mozambique tilapia, the process of differential alternative splicing (DAS) of genes associated with spliceosome assembly, RNA binding, and post-transcriptional processing reveals a highly regulated mechanism of gene expression in response to high-salinity conditions. This intricate regulation suggests that fish have evolved precise mechanisms to acclimate to environmental changes. The enrichment of DAS genes in mitochondrial energy metabolism, ribosomal protein synthesis, and cytoplasmic signal transduction indicates that fish may require rapid and energy-efficient cellular responses to cope with salinity stress, particularly in osmoregulatory tissues such as the gills (Huang et al., 2025). These acclimations likely help fish maintain ionic and osmotic balance when faced with fluctuations in salinity levels. Similarly, in rainbow trout, changes in gene expression related to taurine and glutamine metabolism have been observed, with shifts in metabolite concentrations confirmed using LC-MS/MS analysis. This highlights the importance of organic osmolytes in fish osmoregulatory processes, allowing them to stabilize cellular osmotic pressure without compromising essential cellular functions (Tian et al., 2022). Overall, these findings underscore the critical role of post-transcriptional regulation and compatible solute metabolism in the response of teleosts to salinity stress. By understanding these molecular mechanisms, we can gain insight into how these fish maintain their physiological resilience in challenging environments. Research on Nile tilapia and tongue sole has highlighted the role of amino acid accumulation in salinity adaptation (Jiang et al., 2019; Su et al., 2023b; Wang et al., 2024). KEGG pathway enrichment identified glycerophospholipid metabolism, bile acid biosynthesis, and amino acid metabolism as crucial for salinity adaptation, providing insights into fish osmoregulation. Integrating gut microbiota profiling, metabolomics, and transcriptomics enhances our understanding of salinity stress acclimation in teleosts. Salinity-induced gut microbial changes contribute to metabolic reprogramming, affecting the energy balance, osmoregulation, and immune responses. Transcriptomic analyses have highlighted differentially expressed genes, alternative splicing, and regulatory pathways involved in physiological adaptations. Future research

should validate omics predictions, characterize candidate genes, and elucidate host-microbiota interactions to improve the prediction and mitigation of environmental stress effects on aquatic organisms, thereby supporting sustainable fisheries and aquaculture.

We acknowledge the limitations of current research on salinity acclimation in teleost fish. The focus on short-term salinity stress studies has constrained our understanding of long-term acclimation and progressive physiological and microbiota changes. The causal relationship between gut microbiota alterations and osmoregulatory mechanisms remains ambiguous, requiring further functional validation to determine whether these changes are adaptive responses or active regulators. Multi-omics data integration presents technical challenges that affect functional interpretation. Many studies generalize findings across teleost species, overlooking the species-specific osmoregulatory strategies. Although transcriptomics and metabolomics provide valuable insights, experimental validation through *in vivo* functional studies is limited. Addressing these gaps will enhance our mechanistic understanding and broaden the applicability of our findings in aquaculture and ecological conservation.

8 Conclusion

Teleost fish are known for their ability to thrive in environments with varying salinity levels, requiring them to make precise physiological and molecular adjustments to maintain homeostasis. This review delves into the key osmoregulatory mechanisms found in the gills, kidneys, and intestinal tissues of these fish, highlighting the importance of transcriptomics, metabolomics, and gut microbiota in their ability to acclimate to changes in salinity. Transcriptomic analyses have revealed changes in gene expression related to ion transport, energy metabolism, and signaling pathways, providing insights into how teleost fish respond to salinity stress. Metabolomic studies have identified osmolytes and metabolites that play roles in maintaining cellular stability under these conditions. Furthermore, the gut microbiota of these fish affects their metabolic function and ability to acclimate to salinity fluctuations. By utilizing a combination of these multi-omics approaches, researchers have gained a comprehensive understanding of how teleost fish respond to changes in salinity levels. While these findings have the potential to improve aquaculture practices by enhancing stress resilience and health management, they also contribute to our broader understanding of fish physiology and environmental acclimatization.

Future perspectives

Future research should integrate transcriptomics, gut microbiota, and metabolomics to gain insights into the acclimatization of teleost fish to changes in salinity. Long-term studies will reveal the lasting effects and adaptations to fluctuating

salinities. Understanding these mechanisms can improve fisheries, enhance fish health, and optimize species-specific management strategies for aquaculture.

Author contributions

EMM: Conceptualization, Data curation, Methodology, Writing – original draft. LI: Methodology, Formal analysis, Writing – review & editing. MAY: Investigation, Writing – review & editing. AZ: Investigation, Writing – review & editing. JZ: Investigation, Writing – review & editing. MJ: Investigation, Writing – review & editing. FD: Software, Writing – review & editing. LW: Methodology, Writing – review & editing. HJZ: Validation, Writing – review & editing. BT: Investigation, Writing – review & editing. HZ: Investigation, Writing – review & editing. KA: Visualization, Project administration, Writing – review & editing. JH: Supervision, Writing – review & editing. BW: Resources, Writing – review & editing. ZW: Conceptualization, Funding acquisition, Methodology, Resources, Supervision, Writing – review & editing.

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Conflict of interest

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