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REVIEW ON THE IMPACT OF ELEVATED TEMPERATURES ON THE IMMUNE SYSTEM OF FRESHWATER FISH IN THE CONTEXT OF CLIMATE CHANGE

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Abstract

Climate change has significant effects on aquatic ecosystems, including the health and immunity of freshwater fish. As ectotherms, fish rely on the surrounding environment to regulate their body temperature. Elevated water temperatures impose physiological stresses, and prolonged heat exposure can compromise their immune system, making them more susceptible to infections and mortality. The capacity of fish to cope with these elevated temperatures depends on prior acclimation, but once the thermal threshold is surpassed, the stress becomes critical and may lead to local extinction in vulnerable species. This review analyses the effects of elevated temperatures on fish immune mechanisms. It highlights how rising temperatures influence inflammatory responses, increase pathogen susceptibility, and alter immune gene expression. Additionally, it discusses changes in physiological barriers and adaptive responses essential for fish survival in warming environments. The paper underscores the importance of studying fish immunity in the context of climate change, emphasizing the need for strategies to preserve aquatic biodiversity. Understanding how elevated temperatures impact fish immunity is important for developing sustainable resource management practices.

Key words: *Danube River, fish health, immune system, pathogen susceptibility, thermal stress.*

INTRODUCTION

Global temperature is the primary driver of climate change, directly and significantly influencing the evolution and behavior of the entire climate system. Rising global temperatures represent one of the most visible and extensively studied effects of climate change. Reports from the United Nations (https://www.un.org/en/climatechange/science/causes-effects-climate-change) and the Copernicus Climate Change Service (https://climate.copernicus.eu/climate-bulletins) highlight a marked increase in extreme heat events, with heatwaves and scorching days becoming more frequent and intense, accompanied by a rise in destructive storms. These temperature shifts trigger significant transformations in natural environments, particularly aquatic ecosystems (EPA, 2021; Stroe et al., 2024), with such changes being deeply interconnected and self-perpetuating (Lenton et al., 2008; Bennett et al., 2019; IPCC, 2021).

For instance, elevated temperatures exacerbate pollution (Sinha et al., 2017; Latiu et al., 2022; Balaci et al., 2024) and dissolved oxygen levels (Ficke et al., 2007; Sindler et al., 2024), combined with rising water temperatures (Ambrosetti & Barbanti, 1999; Livingstone, 2003; Friedrichs-Manthey et al., 2024), declining freshwater levels (Vorosmarty et al., 2000), and changes in precipitation patterns. Moreover, the intensification of extreme weather events can spread pollutants over long distances (IPCC, 2013). A combination of these factors contributes to an increase in disease prevalence and further weakens the health of aquatic ecosystems.

Numerous studies have shown that the proliferation of opportunistic pathogens such as *Aeromonas hydrophila* (Stanier, 1943) (Shimizu, 2013; Awan et al., 2018) or *Vibrio* spp. (Colwell, 1996; Johnson et al., 2012; Vezzulli et al., 2016; Totoiu et al., 2018) is facilitated by climate change, particularly by rising water temperatures (Stroe et al., 2022).

This rise in diseases within aquatic ecosystems has implications not only for biodiversity but also for commercial fishing and aquaculture, leading to significant economic losses. Exploring the effects of rising temperatures on aquatic ecosystems and adaptation strategies is therefore essential for conserving resources and maintaining ecological balance.

Fish, as integral components of these ecosystems, are particularly susceptible to temperature variations. Being poikilothermic organisms, they lack efficient internal mechanisms to maintain a constant body temperature, and their physiological processes are closely tied to environmental conditions (Alborali, 2006; D'Abramo & Slater, 2019; Islam et al., 2022). Furthermore, metabolic rates accelerate under high-temperature conditions, depleting the energy reserves necessary for efficient immune responses (Bowden, 2008). Even minor environmental changes can make fish vulnerable (Alborali, 2006; Uiuiu et al., 2019) to stress, while the prevalence of diseases in aquatic ecosystems continues to rise (Austin & Austin, 2016; Sheikh et al., 2022).

This paper analyzes the impact of elevated temperatures on the immune system of freshwater fish in the Danube River, in the context of climate change. By reviewing recent literature, it seeks to highlight how increased temperatures affect fish health, pathogen proliferation, and aquatic ecosystems.

While there is substantial research on the effects of temperature on ecosystems, studies on its direct impact on fish immunity are limited. Furthermore, research on the effects of thermal stress on species in the Danube River is even more limited. This paper aims to fill this gap through an in-depth analysis of the existing literature and to highlight areas requiring further research.

MATERIALS AND METHODS

The paper presents a review based on the analysis of published studies investigating the response of the immune system of freshwater fish to high temperatures.

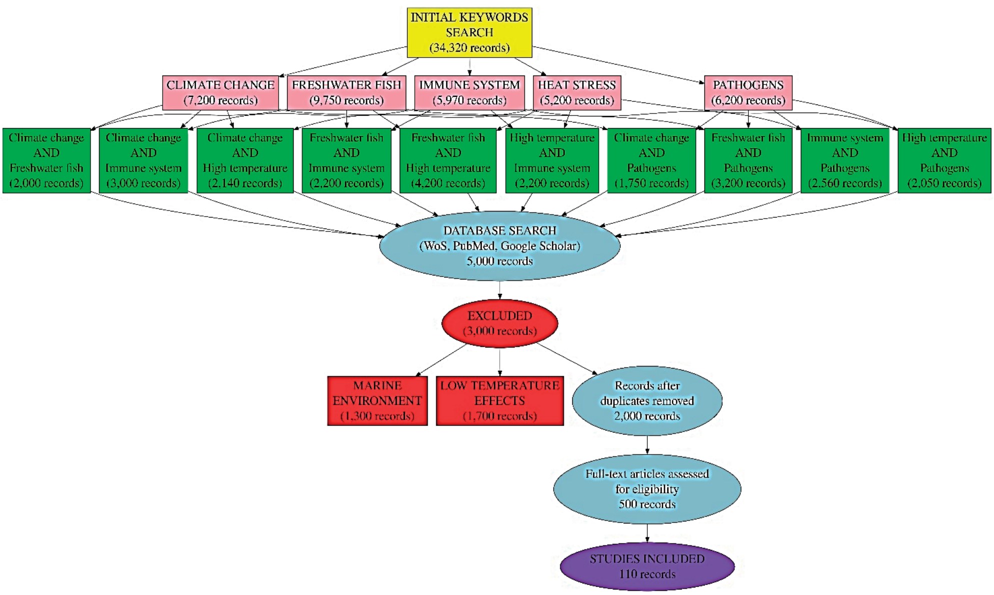

Figure 1. PRISMA flow diagram used in the analysis of relevant literature (Source: original)

The review was conducted using the PRISMA method (Preferred Reporting Items for Systematic Reviews and Meta-Analyses), ensuring a rigorous and transparent selection process of relevant studies (Moher et al. 2009; Alfonso et al., 2023). These studies, sourced from reputable scientific journals and databases like PubMed, Web of Science, and Google Scholar, focus on climate change, high temperatures, and their effects on the immune system of freshwater fish (Figure 1). Studies addressing marine ecosystems, unrelated diseases caused by thermal stress or low temperature were excluded to maintain the relevance of the analysis.

The PRISMA diagram was generated using R software version 4.4.2, providing a visual representation of the study selection process. Additionally, R software was used to create a diagram of the immune system and its associated functions, highlighting the intricate interactions and processes that influence fish immunity under the conditions of climate change. This visualization aids in understanding the mechanisms through which temperature fluctuations impact immune responses in fish.

The analysis of hydrological parameters of the Danube River focused on the Romanian section, extending from km 1075 at the Baziaș entry point to its discharge into the Black Sea. This study relied on data from the National Institute of Hydrology and Water Management, with atmospheric data provided by the National Meteorological Administration. Annual and seasonal averages were computed, and the Pearson correlation coefficient was applied to examine the relationships between hydrological and atmospheric parameters.

RESULTS AND DISCUSSIONS

The complexity of the Danube River ecosystem arises from its unique combination of biodiversity (Ibănescu et al., 2016), its crucial role in supporting local communities, and the anthropogenic pressures it faces as it flows through 19 countries over its 2,857 km course (Schmid et al., 2023). Moreover, the Danube River is considered "A Green Wildlife Corridor" (https://danube-region.eu/protecting-life-in-danube-region/) for 102 native fish species inhabiting this ecosystem (Kottelat and Freyhof, 2007), including 30 endemic species, and serves as the last refuge for some sturgeons (Schmid et al., 2023).

Effects of climate change on Danube's hydrological parameters

Current climate change models predict significant effects on water resources and the ecological status of the Danube River due to rising air temperatures and alterations in the hydrological cycle. These changes will not only affect water flows but also the stability of aquatic ecosystems. According to a study by the International Commission for the Protection of the Danube River (ICPDR), climate change is expected to lead to significant shifts in temperature and precipitation patterns within the Danube basin. The increasing water temperature will alter aquatic biochemical processes and amplify the impact of pollution on water quality, with serious consequences for biodiversity and the health of this ecosystem (ICDPR, 2012).

A key factor in this context is the strong correlation of 0.85 observed between air temperature and water temperature (Figure 2), which indicates a direct link between atmospheric temperature variations and changes in Danube water temperature.

This correlation suggests that significant changes in air temperature are strongly correlated with aquatic environmental conditions, as emphasized by Scharsack & Franke (2022). These environmental modifications directly affect the health of organisms within these ecosystems, particularly through prolonged exposure to elevated temperatures, which weakens their immune systems. Furthermore, Ferreira et al. (2023) observed significant transcriptional changes in sturgeons *Acipenser gueldenstaedtii* (Brandt & Ratzeburg, 1833) exposed to prolonged thermal stress. These changes include upregulation and downregulation of genes involved in immune responses, metabolic pathways (Dobrota et al., 2022; Nica et al., 2023), and protein synthesis, which are directly linked to the physiological impacts of thermal stress.

The immune system of fish is strongly influenced by ambient temperatures (Rohlenová et al., 2011), exhibiting particular sensitivity to climatic fluctuations. Wild fish are exposed to various biological stressors (e.g., escaping predators) and environmental stressors (e.g., extreme temperatures, low dissolved oxygen), which can impact their health and survival (Boyd & Tucker, 1998; Arlinghaus et al., 2007). These conditions can become more severe during extreme events, such as prolonged hot summers, or when fish face increased predation pressure.

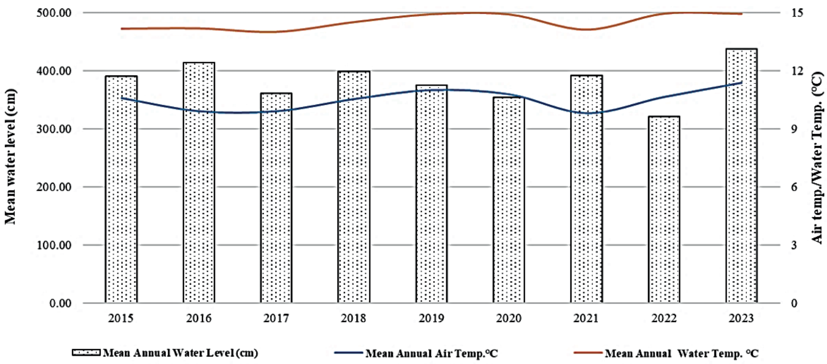

Figure 2. Evolution of environmental parameters between 2015 and 2023 (Source: original)

An even more concerning aspect is that this upward temperature trend does not occur in isolation: pollution by, for example, increases of harmful algal blooms, hypoxia, and high salinity are just some of the effects caused by elevated temperatures in aquatic environments, triggering a chain reaction in immune responses. Therefore, as global warming progresses, it is crucial to understand how these temperature changes affect aquatic organisms in the Danube River.

The immune system of fish

The immune system has the following components: the innate immune system and the adaptive immune system, each playing a specific role in maintaining the fish's well-being (Figure 3). These systems work closely together to detect, eliminate, and prevent pathogenic threats.

Through a rapid response to stress factors, the innate immune system (nonspecific) serves as the first line of defence (Turvey et al., 2010; Mokhtar et al., 2023). Using physical or surface barriers, humoral and cellular factors (Magnadóttir, 2006; Uribe et al., 2011), the innate immune system plays a crucial role in preventing and delaying the entry of pathogens (Patriche, 2008; Duan et al., 2022). It recognizes pathogen-associated molecular patterns (PAMPs) through Toll-like receptors (TLRs) (Akira et al., 2006; Mogensen, 2009; Silva-Gomes et al., 2015). Maintaining the integrity of physical barriers (epidermis, mucus, gills, and gastrointestinal tract) is vital for preserving osmotic balance and eliminating microorganisms (Patriche, 2008; Sveen et al., 2020; Mokhtar et al., 2023). Additionally, effector cells such as macrophages, neutrophils, dendritic cells, and natural killer (NK) cells eliminate pathogens through phagocytosis, cytotoxicity, and secretion of pro-inflammatory cytokines (Iwasaki & Medzhitov, 2004; Duan et al., 2022).

Activated after infection or vaccination, the adaptive immune system is characterised by T lymphocytes, responsible for cell-mediated immunity; B lymphocytes, involved in humoral-mediated immunity; and immune memory (Patriche, 2008; Dash et al., 2014). T lymphocytes are divided into T-helper lymphocytes (CD4+) and cytotoxic T lymphocytes (CD8+). They coordinate immune responses through cytokine secretion and eliminate infected cells. B lymphocytes produce specific antibodies targeting pathogens, while memory lymphocytes ensure faster and stronger responses upon repeated exposure.

In the Danube ecosystem (Figure 4), where water temperature fluctuates considerably depending on the season and weather conditions (especially due to climate change), fish are frequently exposed to thermal stress conditions (Rohlenová et al., 2011).

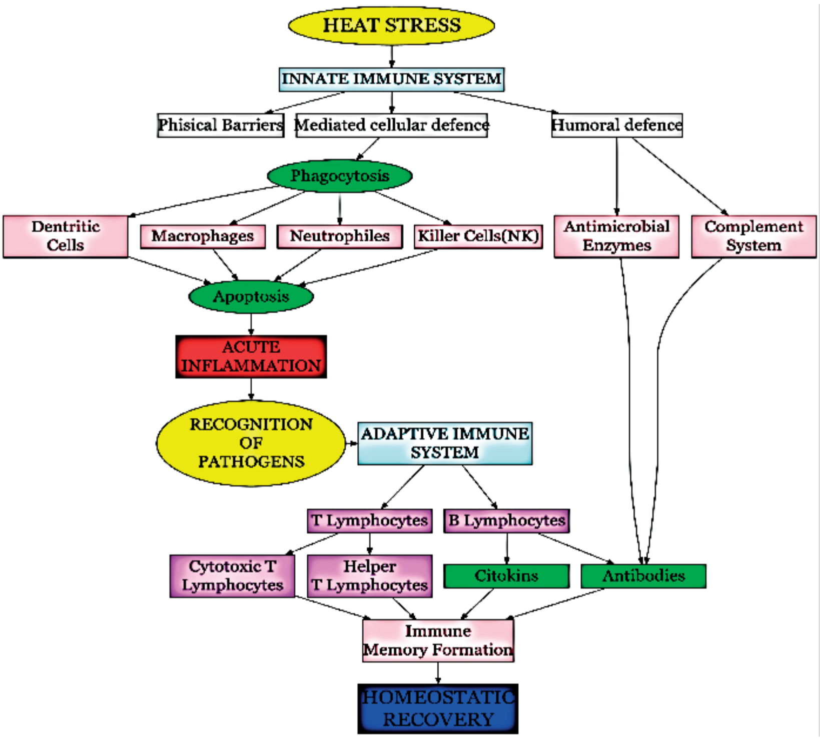

Figure 3. The structure of the Fish Immune System (Source: original)

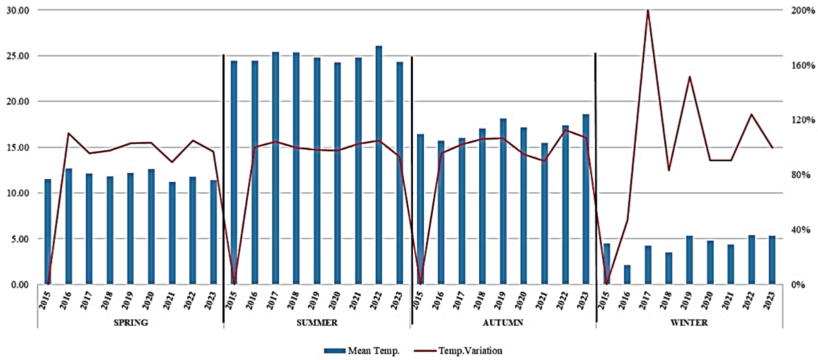

Figure 4. Seasonal variations in water temperature of the Danube River (2015-2023) (Source: original)

Overactivation of the innate immune system and suppression of the adaptive immune system

At high temperatures, particularly during summer months, the adaptive immune response is inhibited, while the innate immune response becomes overactive (Scharsack & Franke, 2022). Consequently, fish rely more on innate immunity than on adaptive immunity under elevated temperatures (Bowden, 2008). Castellano et al. (2017) and, later, Ferreira et al. (2023) observed a reduction in ACP (acid phosphatase) and ceruloplasmin activity, alongside upregulation of lysozyme in the acute phase of thermal stress in sturgeon.

Thermal stress alters the activity of immune cells, such as B and T lymphocytes, which play a crucial role in combating microbial infections (Secombes & Fletcher, 1992; Marnila & Lilius, 2015), affecting fish health and contributing to the emergence of opportunistic infections, including bacteria and parasites, which thrive under thermal stress conditions (Barton, 2002). Coupled with overstimulation of the innate immune system, prolonged effects can be harmful, leading to liver inflammation or tissue damage (Ferreira et al., 2023), a reaction known as the *"inflammatory cascade"* (Lalles, 2019; Daskalaki et al., 2021), a general immune mechanism observed across multiple species, including *Huso huso* (Linnaeus, 1754) or *Cyprinus carpio* (Linnaeus, 1758).

High temperatures can trigger exaggerated expression of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6, resulting in a systemic inflammatory response in great sturgeons or common carp (Lalles, 2019), tilapia and other freshwater species (Reyes-Cerpa et al., 2012; Wang & Secombes, 2013; Suvra et al., 2017). This leads to immune cell recruitment to affected areas (Zou & Secombes, 2016), which, if uncontrolled, can cause tissue damage (Wang & Secombes, 2013) and further contribute to autoimmune diseases, disrupting immune homeostasis (Daskalaki et al., 2021).

Moreover, these conditions of thermal stress can disrupt the way phagocytes handle oxygen, leading to the activation of leukocytes respiratory burst, also known as oxidative burst. The respiratory burst is a process where immune cells, such as neutrophils and macrophages, release reactive oxygen species (ROS), superoxide anion ($O_2^{\bullet -}$) and hydrogen peroxide (H_2O_2). This can lead to increased oxidative stress, which, despite its role in combating pathogens, can also cause cellular damage, impairing healthy tissues and disrupting normal cell functions (Thomas, 2017; Biller & Takahashi, 2018).

Wang et al. (2016) observed that thermal stress induced a significant increase in the splenic macrophage respiratory burst activity, serum superoxide dismutase (SOD) activity, and serum malondialdehyde (MDA) levels, indicating the presence of oxidative stress and cellular damage in rainbow trout (*Oncorhynchus mykiss*, Walbaum, 1792).

In the Danube River, these effects may be exacerbated by various types of pollution, including nutrient pollution (such as nitrogen and phosphorus), industrial discharges, and chemical contaminants, as well as climatic variability (https://www.icpdr.org/danube-basin/countries/romania). These factors significantly reduce the fish's capacity to protect themselves against pathogens, impairing their immune system and overall health. Nutrient pollution, particularly from agricultural runoff, leads to eutrophication, while industrial discharges introduce hazardous substances that further stress aquatic ecosystems.

Heat Shock Proteins (HSP) and Osmoregulation

The hyperactivation of the innate immune system caused by high temperatures can lead to osmoregulatory difficulties due to increased gill permeability. Warm water, with lower dissolved oxygen levels and higher salinity, exacerbates stress conditions, especially for fish already fatigued by excessive physical activity (Somero & Hofmann, 1997; Bartholomew & Bohnsack, 2005). This results in hypertonic stress, where water moves out of the cells via osmosis, causing cellular dehydration, as found in Nile tilapia by Zhang et al. (2024).

In response, the synthesis of osmotic stress proteins, such as Heat Shock Proteins (HSPs), activates stress-response mechanisms to stabilize cellular structures (Dawood et al., 2020; Somero, 2020; Elbahnaswy et al., 2024). Ferreira et al. (2023) observed an upregulation of these proteins in Russian sturgeon, while Zarei et al. (2024) reported fluctuations in HSP27, HSP70 and HSP90 expressions in the liver, gill, and kidney cells of sterlet sturgeons influenced by high levels of salinity. Chen et al. (2021) reported similar changes in pikeperch *Sander lucioperca* (Linnaeus, 1758). Additionally, the production or accumulation of compatible osmolytes, such as glycine, proline, or trehalose, is initiated to maintain osmotic balance without disrupting cellular functions (Steinberg, 2012).

Zhang et al. (2024) argued that hypertonic stress triggers an exaggerated immune response in fish, including the excessive activation of T cells and an increase in the production of pro-inflammatory cytokines. This adversely impacts their ability to combat bacterial infections effectively.

Antibodies and Humoral Immune Response

Prolonged exposure to high temperatures has a direct impact on antibody production and can reduce the expression of certain proteins associated with adaptive immunity (Franke et al., 2024), which are involved in the recognition and processing of antigens by immune cells, thus affecting the adaptive immune response. These proteins include, among others, T-cell receptors (TCR) and B-cell co-receptors, which are essential for the activation and proliferation of T and B lymphocytes. Additionally, proteins involved in the antigen presentation process, such as MHC II (Major Histocompatibility Complex), may be affected by thermal stress (Scharsack & Franke, 2022).

In complex aquatic ecosystems, such as the Danube, serum proteins, such as immunoglobulins produced at the ribosome level in plasma cells and lymphocytes, play a crucial role in protecting fish from pathogens (Patriche, 2008). In a study conducted on carp *Cyprinus carpio*, Rohlenová et al. (2011) observed high levels of IgM during adaptation periods to environmental parameter changes, namely the beginning of summer and early autumn, but lower levels during the "hot" season. This response was also observed by Ferreira et al. (2023) in sturgeon *Acipenser gueldenstaedtii*. In addition, the works of Bowden (2008), Magnadóttir (2006), and Castellano et al. (2017) highlighted the reduced effectiveness of serum proteins under prolonged exposure to high temperatures. This phenomenon compromises the efficiency of the adaptive immune response, making fish more vulnerable to bacterial infections.

An important effect on variations in immunoglobulin levels under thermal stress conditions is cortisol (Rohlenová et al., 2011). Castellano et al. (2017) observed low cortisol concentrations in sturgeons due to chronic stress, following prolonged exposure to high temperatures in the summer season. While cortisol levels might rise initially in response to stress (as is typical in many animals), this increase is not sustained in the long term.

The Impact of Thermal Stress on Cellular Homeostasis

In areas with higher water temperatures, such as the southern and central sectors of the Danube, the process of oxidative stress becomes more pronounced. High temperatures promote the production of reactive oxygen species (ROS) (Elbahnaswy et al., 2024), which, if not balanced by spontaneous and enzymatic antioxidants, have toxic effects on cellular biomolecules (proteins, lipids, and DNA), and consequently on their functions (Achard-Joris et al., 2006; Qiu et al., 2011; Alfons & Badr, 2018; Sheikh et al., 2022).

This oxidative stress exacerbates the health of freshwater fish, having a direct impact on their ability to defend against infections, as documented in species such as *Cyprinus carpio* or *Oreochromis niloticus* (Linnaeus, 1758) (Alfonso et al., 2021, 2023).

Extended oxidative stress can have severe effects on cellular signaling, leading to significant DNA damage and the induction of apoptosis (programmed cell death). These processes are essential for maintaining homeostasis and immune responses. Thermal stress amplifies these processes, thus contributing to the elimination of infected or damaged cells, playing a crucial role in protecting the organism from autoimmunity and regulating inflammation.

In this context, apoptosis plays an important role in the immune response, helping to prevent autoimmune disorders and inhibiting pro-inflammatory cytokines (Chandra et al., 2000; Gao et al., 2013; Luzio et al., 2013; Luo et al., 2017). Studies have shown that acute thermal stress in pikeperch activates the mitochondrial apoptosis pathway mediated by the protein p53, generating inflammation and oxidative stress in the liver (Liu et al., 2022). At 34°C, severe liver damage was observed, including increased activity of genes associated with programmed cell death, such as bax (pro-apoptotic regulator), caspase-3, and caspase-9 (key enzymes involved in apoptosis) (Liu et al., 2022). Additionally, markers of oxidative stress like MDA (a by-product of lipid damage) and antioxidant enzymes such as T-SOD and CAT were significantly elevated (Luo et al., 2015; Kostić et al., 2017; Chen et al., 2021). This sustained oxidative stress was accompanied by prolonged inflammation, creating a harmful cycle where oxidative stress exacerbates inflammation, worsening liver damage.

In the context of these liver disorders, albumin, cholesterol, and triglyceride levels decreased as temperatures continued to rise, as lipid resources were depleted to meet increased energy demands (Li et al., 2019). The same study showed in pikeperch, an increase in the number of leukocytes (WBC), as the cellular immunity of the fish was affected.

The Impact of Climate Change on the Prevalence of Aquatic Pathogens

Pathogenic infections are significantly accelerated at higher temperatures. For instance, pathogens such as *Ichthyophthirius multifiliis* (Fouquet, 1876) in *Abramis brama* (Linnaeus, 1758)*, Leuciscus idus* (Linnaeus, 1758)*, Rutilus rutilus* (Linnaeus, 1758)*, Sander lucioperca, Esox lucius* (Linnaeus, 1758)*, Perca fluviatilis, Neogobius fluviatilis* (Pallas, 1814) (Matvienko et al., 2020) or *Edwardsiella tarda* in European eels and crucian carp (Alcaide et al., 2006; Jiang et al., 2019), *Flavobacterium columnare* in carp, catfish, and perch (Dong et al., 2016; Mitiku, 2018), *Aeromonas hydrophila* in cyprinids and sturgeons (Matvienko et al., 2020; Semwal et al., 2023), show accelerated development under elevated temperatures.

Furthermore, these pathogens display enhanced genetic adaptability to temperature fluctuations, leading to the emergence of more virulent and treatment-resistant strains (Shimizu, 2013; Awan et al., 2018). Takahara (2014) highlighted the heightened vulnerability of carp to viral infections caused by Cyprinid herpesvirus-3 (CyHV-3) at water temperatures between 23°C and 28°C. Similarly, Borzym and Maj-Paluch (2015) reported increased virulence and rapid progression of ranaviruses (e.g., ENV - haematopoietic necrosis virus) in European perch *Perca fluviatilis* (Linnaeus, 1758) under elevated thermal conditions. Keymer & Read (1991), Zuk & Stoehr (2002), Rohlenová et al. (2011) mentioned the energy consumption that occurs when the immune system of hosts infected is activated, while other physiological tasks (e.g. growth, reproduction, even survival) are neglected. Thus, pathogens not only encounter an individual already vulnerable due to environmental stressors, but they also contribute to worsening the host's health by redirecting energy resources to fight the infection (Franke et al., 2024).

For example, Chen et al. (2020) found that *Aeromonas hydrophila* infection in common carp induces high levels of oxidative stress in the serum, liver, intestines, and gills, indicating systemic damage caused by the infection. In addition, lipid peroxidation leads to elevated levels of malondialdehyde (MDA), reflecting the severity of cellular damage caused by oxidative stress. Moreover, a significant decrease in the activity of antioxidant enzymes, especially in the advanced stages of infection, suggests the exhaustion of the organism's antioxidant mechanisms.

In this context, the ability of fish to survive these threats depends on their resistance and tolerance to pathogens (Soares et al., 2017; Cascarano et al., 2021), especially those that thrive in heat conditions, while fish become more prone to developing infections (Rohlenová et al., 2011; Sheikh et al., 2022). Additionally, they may favor the spread of pathogen species that were not naturally present in this ecosystem (Cavicchioli et al., 2019). Moreover, these energy-consuming adaptive processes can lead to increased levels of lipids, reactive oxygen species, and reactive aldehyde derivatives, with inflammatory effects on cells (Ferreira et al., 2023).

CONCLUSIONS

Climate change has a significant impact on aquatic ecosystems, particularly on fish health. Rising water temperatures affect the functioning of the immune system of fish, weakening their natural defence and making them more vulnerable to infections. These infections, become more frequent and severe under high temperature conditions, which can lead to a decline in biodiversity and significant economic losses in the fishing and aquaculture industries.

Exposure to high temperatures triggers an excessive activation of the innate immune system in fish, while the adaptive immune response is inhibited. This makes them more prone to infections, which develop rapidly under continuous thermal stress. Thus, the health of fish becomes increasingly fragile, and the long-term effects on the aquatic ecosystem can be devastating.

Protecting aquatic biodiversity is very important in a context where climate change threatens already vulnerable species. It is important to understand how temperature fluctuations affect fish immunity and to implement effective conservation measures. Continuous monitoring of water temperature and the health status of sensitive species can help prevent large losses and maintain ecological balance.

Future studies should focus on the long-term effects of climate change on fish immunity, including its impact on genetic diversity, epigenetic responses, and ecosystem functioning. At the same time, research is needed to find solutions to mitigate these changes, such as developing water management techniques and preventing pollution, to protect fish health and aquatic ecosystems.

Another area of interest should be the study of the impact of climate change on species in the Danube basin. These species are particularly vulnerable to high temperatures and other effects of climate change, and research in this area could provide valuable insights for protecting biodiversity in this region.

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