International Journal of Entomology Research
www.entomologyjournals.com
ISSN: 2455-4758
Received: 17-09-2024, Accepted: 18-10-2024, Published: 02-11-2024
Volume 9, Issue 11, 2024, Page No. 26-30

Biochemical impacts and environmental risks of diclofenac in aquatic ecosystems: A comprehensive review

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Abstract
Diclofenac, a widely used non-steroidal anti-inflammatory drug (NSAID), has emerged as a significant contaminant in aquatic ecosystems due to its widespread use and insufficient removal in wastewater treatment. This review thoroughly examines diclofenac's biochemical effects on aquatic organisms, including oxidative stress, immune suppression, tissue damage, and endocrine disruption. Historical and recent literature reveals that these biochemical alterations can lead to severe ecological consequences such as reproductive failure and population declines. Case studies highlight the impact of diclofenac contamination in rivers and aquatic habitats. Regulatory challenges persist, with existing wastewater treatment technologies proving inadequate. Future strategies to mitigate diclofenac pollution are discussed, including advancements in wastewater treatment, the development of biodegradable pharmaceuticals, and enhanced regulatory measures. Addressing these challenges is crucial for protecting aquatic ecosystems from the long-term impacts of pharmaceutical pollution.

Keywords: Aquatic ecosystem, diclofenac, endocrine disruption, oxidative stress, pharmaceutical pollution, wastewater treatment

Introduction

Pharmaceutical pollutants, particularly non-steroidal anti-inflammatory drugs (NSAIDs), have become ubiquitous in aquatic environments, raising significant ecological concerns. Diclofenac, one of the most widely used NSAIDs globally, has been identified as a key contaminant in freshwater systems due to its extensive use in human and veterinary medicine. Its presence in surface waters can be attributed to improper disposal, excretion in unmetabolized forms, and inefficient removal during wastewater treatment processes (Vieno *et al.*, 2006; Fu *et al.*, 2016) [9, 30]. Recent studies have documented concentrations of diclofenac in rivers and lakes worldwide, with levels often exceeding ecologically safe limits (Fent *et al.*, 2006; Memmert *et al.*, 2013) [8, 18].

Despite its relatively low concentrations in aquatic environments, diclofenac's persistence, bioaccumulation, and chronic toxicity to non-target organisms have made it a pollutant of significant concern (Schwaiger *et al.*, 2004; Kuster *et al.*, 2020) [24]. Its biochemical effects, such as oxidative stress, immune system disruption, tissue damage, and endocrine interference, have been widely reported across various aquatic species, including fish, amphibians, and invertebrates (Triebskorn *et al.*, 2004; Hoeger *et al.*, 2005; Garcia-Cambero *et al.*, 2017) [10, 13, 28]. The long-term exposure of aquatic organisms to sub-lethal concentrations of diclofenac can lead to population declines and alterations in ecosystem dynamics (Bringolf *et al.*, 2019) [4].

The ecological impacts of diclofenac have been extensively studied in Europe, where it is a recognized environmental contaminant. For instance, the European Union has identified diclofenac as a priority substance under the Water Framework Directive since 2013, signalling the need for stringent regulatory control. However, despite these efforts, diclofenac continues to be detected in European water bodies at concentrations that pose a risk to aquatic life (Kuster *et al.*, 2020). Beyond Europe, the presence of diclofenac in aquatic environments has also been reported in other regions, including Asia and Africa, further highlighting the global scale of this environmental issue (Madikizela and Chimuka, 2017) [17].

This review aims to provide a comprehensive biochemical effects of diclofenac on aquatic organisms, highlighting key studies and emerging trends in the literature. It also explores the broader ecological implications of diclofenac contamination, particularly its effects on species interactions, population dynamics, and ecosystem health. Additionally, the review discusses regulatory challenges and future strategies for mitigating the environmental risks associated with diclofenac, including advancements in wastewater treatment technologies and the development of more environmentally friendly pharmaceuticals.

Biochemical pathways of diclofenac toxicity in aquatic organisms

Diclofenac exerts various biochemical effects on aquatic organisms, which can disrupt their normal physiological functions, potentially leading to population declines and long-term ecosystem imbalances. Below are some key biochemical alterations that have been observed in various aquatic species exposed to diclofenac.

1. Oxidative stress

Diclofenac-induced oxidative stress is well established. Early research demonstrated increased reactive oxygen species and oxidative damage in fish (Schwaiger *et al.*, 2004) [24]. Recent studies have reinforced these observations, showing reduced antioxidant enzyme activity and elevated lipid peroxidation markers, such as malondialdehyde (Garcia-Cambero *et al.*, 2017; Memmert *et al.*, 2013) [10, 18]. This oxidative damage impacts cellular membranes and overall organism health.

2. Immune system disruption

The impact of diclofenac on immune function has been observed since early studies, which showed impaired immune responses and increased susceptibility to pathogens in fish (Hoeger *et al*., 2005) [13]. Recent reviews reinforce these findings, indicating that diclofenac-induced immune suppression can significantly affect fish populations by reducing survival and reproductive success (Bringolf *et al*., 2019) [4].

3. Tissue damage and histopathology

Histopathological studies have consistently documented tissue damage due to diclofenac. Initial research revealed significant damage to fish liver and kidneys (Schwaiger *et al*., 2004) [24]. Subsequent studies provided further evidence of chronic tissue damage, including hepatocyte necrosis and gill impairment (Memmert *et al*., 2013; Perez *et al*., 2019) [18].

4. Endocrine disruption and reproductive effects

Diclofenac's endocrine-disrupting effects are well-documented. Early research demonstrated reduced estrogen levels and reproductive failure in fish (Triebskorn *et al*., 2004) [28]. More recent studies have confirmed these findings, linking diclofenac exposure to reduced fertility and abnormal development in various aquatic species (Kuster *et al*., 2020; Rivera-Hernandez *et al*., 2021) [20].

Biochemical Effects of diclofenac on aquatic organisms

1. Oxidative Stress and Tissue Damage

Several studies have demonstrated that diclofenac induces oxidative stress in aquatic organisms by increasing the production of reactive oxygen species and decreasing the activity of antioxidant defence systems (Triebskorn *et al*., 2004; Hoeger *et al*., 2005) [13, 28]. This oxidative stress leads to lipid peroxidation, protein oxidation, and DNA damage in various tissues, including the liver, gills, and kidneys of fish (Schwaiger *et al*., 2004) [24]. Chronic exposure to diclofenac has been linked to cellular apoptosis and tissue degeneration, manifesting as necrosis, fibrosis, and structural damage to vital organs (Garcia-Cambero *et al*., 2017) [10]. In particular, histopathological changes in the liver, such as hepatocyte vacuolation, inflammation, and necrosis, have been consistently reported in fish exposed to diclofenac.

2. Glucose and glycogen metabolism alterations

One of the significant biochemical disruptions caused by diclofenac exposure is the alteration of carbohydrate metabolism in aquatic organisms. Studies have shown that diclofenac can cause hyperglycemia in fish, which is a common stress response in vertebrates. This increase in glucose levels is often accompanied by a depletion of glycogen stores in the liver and muscle tissues. Glycogen, the primary storage form of glucose, is rapidly mobilized during stress conditions to provide energy, leading to its reduction in exposed organisms (Triebskorn *et al*., 2004) [28]. In *Oncorhynchus mykiss* exposed to diclofenac, significant reductions in hepatic glycogen levels were observed, indicating enhanced glycogenolysis due to oxidative stress and energy demand (Schwaiger *et al*., 2004) [24]. These disruptions in carbohydrate metabolism can weaken the organism's energy reserves, reducing its ability to cope with additional environmental stressors, such as temperature changes, hypoxia, or predation pressures.

3. Protein patterns and metabolic shifts

Diclofenac exposure also affects protein synthesis and metabolism in aquatic organisms. Changes in the expression of various proteins involved in stress responses, detoxification, and metabolic processes have been documented. These alterations are often observed as shifts in the protein profiles of exposed organisms, indicating that diclofenac interferes with normal protein turnover and synthesis pathways. One key observation is the reduction in total protein content in the tissues of exposed organisms, which can result from either protein degradation due to oxidative stress or impaired protein synthesis. In *Cyprinus carpio* (L.) and *Clarias gariepinus*, a decrease in muscle and liver protein content was reported after exposure to diclofenac (Hoeger *et al*., 2005; Madikizela and Chimuka, 2017) [13, 17]. This depletion of proteins not only structural and functional proteins but also enzymes crucial for metabolic processes. Alterations in the activity of enzymes involved in the urea cycle and ammonia detoxification have been linked to diclofenac exposure, further stressing the metabolic imbalance in these organisms (Garcia-Cambero *et al*., 2017) [10].

Additionally, stress-induced proteins, such as heat shock proteins are upregulated in response to diclofenac exposure, indicating that the organisms are mounting a cellular defense against drug-induced damage. However, prolonged exposure can overwhelm these protective mechanisms, leading to irreversible damage and impaired physiological functions.

4. Endocrine disruption and reproductive impairments

Diclofenac has also been implicated in endocrine disruption, particularly in fish species. It interferes with the hormonal regulation of reproductive processes, which can lead to impaired reproductive success. Studies have documented reduced levels of sex steroids, such as testosterone and estradiol, in fish exposed to diclofenac, resulting in decreased fertility, altered gonadal development, and reduced spawning activity (Kuster *et al*., 2020). This endocrine disruption may be mediated by diclofenac's interference with prostaglandin synthesis, a critical process in the regulation of reproductive functions in vertebrates.

5. Immune system suppression

The immunotoxic effects of diclofenac have also been well documented. In fish species *Oncorhynchus mykiss* and *Danio rerio*, exposure to diclofenac has been associated with a reduction in immune cell populations, such as macrophages and lymphocytes, leading to suppressed immune responses (Schwaiger *et al*., 2004) [24]. This immunosuppression makes the organisms more susceptible to infections, diseases, and parasitic infestations, further compromising their survival in polluted environments.

Recent case studies on diclofenac contamination in aquatic ecosystems

1. Diclofenac in the Rhine River, Germany

A recent study conducted by (Memmert *et al*., 2013) [18] investigated the chronic effects of diclofenac in the Rhine River, one of Europe's most industrialized waterways. The study revealed that diclofenac concentrations in the Rhine

frequently exceeded the threshold levels considered safe for aquatic organisms. Fish species, particularly *Oncorhynchus mykiss*, exhibited chronic kidney and liver damage, including hepatocyte necrosis and tubular degeneration, which were consistent with oxidative stress biomarkers. The study also observed reduced reproductive success in these fish populations, raising concerns about the long-term viability of fish populations in the river.

2. Diclofenac in the Yamuna River, India

The Yamuna River in India is notorious for high levels of pharmaceutical pollution, including diclofenac. A study by (Jain *et al*., 2020) [14] analyzed water samples from the Yamuna and found diclofenac concentrations ranging from 5 to 20 µg/L, well above safe ecological limits. Aquatic species, particularly native fish like *Labeo rohita*, showed signs of oxidative stress, increased mortality rates, and significant histopathological changes in the liver and gills. This study underscored the inadequacy of current wastewater treatment systems in India and the urgent need for regulatory reforms to address pharmaceutical contamination.

3. Amphibian vulnerability to diclofenac exposure in European wetlands

A study by (Rivera-Hernandez *et al*., 2021) [20] explored the effects of diclofenac on amphibian species in European wetlands, with a focus on the *Rana temporaria*. The research found that tadpoles exposed to environmentally relevant concentrations of diclofenac experienced developmental delays and abnormalities, including disrupted metamorphosis. Increased oxidative stress, reduced immune response, and higher mortality rates were observed, signalling the vulnerability of amphibians to diclofenac pollution. The study highlighted the need for stricter regulations to protect sensitive species in habitats that are already under threat from other environmental stressors.

4. Diclofenac contamination in South African Rivers

In South Africa, a study by (Madikizela and Chimuka, 2017) [17] revealed the presence of diclofenac in both wastewater treatment plant effluents and surface waters of local rivers. Concentrations of diclofenac were detected at levels between 0.5 and 8 µg/L in river water samples. The study focused on the effects of this contamination on native fish species, including *Clarias gariepinus*. The fish displayed histopathological changes in the liver and gills, as well as oxidative stress markers, indicating a high level of environmental stress due to pharmaceutical contamination. This study highlighted the global nature of the issue, as pharmaceutical pollution is not limited to highly industrialized countries but also affects developing nations with less stringent environmental controls.

Regulatory and environmental implications

Since diclofenac was designated a priority substance under the European Union Water Framework Directive in 2013, there has been increasing pressure to strengthen regulatory measures due to its persistent presence in surface waters. However, regulatory action remains insufficient, with numerous studies calling for more stringent limits and enhanced monitoring to protect aquatic ecosystems (Fent *et al.,* 2006; Bringolf *et al.,* 2019; Aus der Beek *et al.,* 2016) [2, 4, 8]. Recent research highlights the harmful effects of diclofenac on aquatic organisms, particularly fish and invertebrates, noting its potential to cause renal failure in fish and disrupt endocrine systems (Santos *et al.,* 2020; Zhang *et al.,* 2021) [22, 34]. These findings have intensified demands for regulatory updates to reduce diclofenac concentrations in water bodies. In parallel, wastewater treatment plants have struggled to effectively remove pharmaceuticals like diclofenac, leading to ongoing contamination of aquatic environments (Vieno *et al.,* 2007) [31]. While traditional treatment methods are insufficient, advancements such as ozonation and membrane bioreactors show promise in enhancing pharmaceutical removal (Memmert *et al.,* 2013; Sanderson *et al.,* 2004; Valcarcel *et al.,* 2021) [18, 21]. Despite scientific progress, regulatory bodies have been slow to implement stricter measures, with (Eggen *et al.,* 2020) [6] highlighting the widespread pharmaceutical use and the limitations of existing treatment technologies as major challenges to regulating diclofenac.

Future Directions

1. Advancements in wastewater treatment

Upgrading wastewater treatment technologies is crucial for managing diclofenac contamination, as traditional methods often fail to effectively remove pharmaceuticals from water. Several innovative approaches have shown promise in addressing this issue. Membrane filtration systems, such as ultrafiltration and nanofiltration, can efficiently remove micropollutants like diclofenac, although challenges like membrane fouling and high energy consumption still exist (Scheurell *et al.,* 2009) [23]. Advanced oxidation processes (AOPs) including ozonation and photocatalysis, are also effective at breaking down pharmaceutical compounds, with ozonation being particularly successful in degrading complex molecules like diclofenac through reactive hydroxyl radicals (Heberer, 2002) [12]. Some recent studies have investigated combining membrane filtration with AOPs to form hybrid systems, which improve removal efficiency and address the drawbacks of standalone technologies (Wang *et al.,* 2021) [33]. Additionally, electrochemical treatment methods have been found to degrade diclofenac via oxidation, though the energy requirements and longevity of the electrodes pose challenges for wider application (Sires *et al.,* 2014) [26]. These advancements offer the potential for more effective removal of diclofenac and reduced environmental contamination.

2. Development of eco-friendly pharmaceuticals

The development of eco-friendly pharmaceuticals is attracting growing attention as a way to mitigate the environmental impact of contaminants like diclofenac. Recent research has been focused on creating biodegradable alternatives that remain therapeutically effective but pose less risk to aquatic ecosystems. (Fu *et al.,* 2016) highlight the importance of employing "benign-by-design" strategies in drug development, ensuring that these compounds break down more easily in the environment without producing harmful by-products. In addition, green chemistry methods are being explored, such as altering the molecular structure of pharmaceuticals to improve their biodegradability while maintaining their medical effectiveness (Kummerer *et al.,* 2015) [16].

Further research suggests that future drug design should account for the entire life cycle of pharmaceuticals from production through to disposal to minimize environmental harm. (Escher *et al.,* 2011) [7] Advocate for the integration of environmental risk assessments early in the drug development process, which would help identify potential ecological risks before a drug is brought to market. Additionally, biocatalysis, which uses enzymes in the production process, is emerging as a promising method for creating more environmentally friendly pharmaceuticals that degrade quickly in natural environments (Sheldon and Brady, 2019) [25]

3. Monitoring and mitigation

Enhancing environmental monitoring is vital for tackling diclofenac contamination, particularly in developing countries where data on pharmaceutical pollution is often limited. (Crane *et al.,* 2006) [5] Highlight the global need for improved monitoring efforts to better understand the extent of diclofenac contamination and its impact on aquatic environments. Research indicates that diclofenac can persist in surface waters and bioaccumulate in aquatic organisms, potentially causing serious ecological damage, especially in areas lacking adequate wastewater treatment facilities.

Additionally, studies emphasize the importance of ecosystem-wide assessments to evaluate the long-term effects of diclofenac exposure. Prolonged exposure to diclofenac can negatively affect not only individual species but entire populations and food chains. (Hoeger *et al.,* 2005) [13] Reported that even at low concentrations, diclofenac can cause organ damage in fish, compromising their survival and reproductive abilities. Furthermore, (Gunnarsson *et al.,* 2012) [11] underscore the importance of examining the combined effects of diclofenac and other pollutants, as these interactions could intensify the harm done to aquatic ecosystems.

There is growing recognition that monitoring efforts should go beyond measuring contamination levels to also include tracking biological and ecological responses over time. Biomarker-based monitoring has been proposed as a method for detecting the sub-lethal effects of diclofenac and similar pharmaceuticals on wildlife, offering early indicators of ecological stress (Sumpter *et al.,* 2006) [27]. This strategy can help guide mitigation efforts by pinpointing vulnerable species and ecosystems that are at the highest risk of contamination.

4. Policy and regulation

The urgency for stricter national and international regulations to curb the discharge of diclofenac and other pharmaceuticals into the environment is becoming increasingly apparent. (Ankley *et al.,* 2007) [1] Stress the necessity of regulating pharmaceutical emissions, particularly from manufacturing facilities, to minimize the introduction of harmful substances into aquatic ecosystems. In regions with less rigorous regulations, significant pharmaceutical pollution has been reported, underscoring the inadequacies of current regulatory frameworks in controlling these discharges.

Another crucial recommendation from experts is to incorporate environmental risk assessments (ERAs) into the drug approval process. By doing so, potential environmental impacts would be evaluated before new pharmaceuticals reach the market. (Boxall *et al.,* 2012) [3] Note that conducting environmental risk assessments during the early stages of drug development can help prevent harmful substances, such as diclofenac, from becoming pervasive pollutants. These assessments can play a vital role in identifying and mitigating environmental risks, ultimately fostering the creation of more sustainable pharmaceuticals.

Additionally, international cooperation on regulatory standards is essential. (Kümmerer *et al.,* 2015) Argue that global collaboration is vital in tackling pharmaceutical pollution, as many drugs are produced and consumed worldwide. Aligning regulations across different countries could significantly diminish the environmental effects of pharmaceutical contaminants, particularly in regions where regulatory enforcement is weaker.

Furthermore, existing wastewater treatment regulations need to be updated to more effectively address pharmaceutical pollutants. (Verlicchi *et al.,* 2012) [32] Recommend that these regulations be revised to include specific requirements for the removal of pharmaceuticals like diclofenac from wastewater treatment facilities. Current treatment technologies often fall short of adequately filtering out these substances, allowing them to enter aquatic ecosystems and accumulate over time.

Conclusion

The extensive body of literature, from early reviews to recent studies, highlights the severe biochemical and ecological impacts of diclofenac on aquatic organisms. Addressing diclofenac contamination requires a multifaceted approach, including the implementation of advanced wastewater treatment technologies, the development of eco-friendly pharmaceuticals, and the enforcement of stricter regulatory frameworks. Furthermore, the integration of real-time monitoring systems to track pharmaceutical concentrations in water bodies can help ensure timely interventions. Public awareness campaigns about the environmental risks of improper pharmaceutical disposal, combined with take-back programs for unused medicines, can also significantly reduce the presence of pharmaceuticals like diclofenac in the environment. Incentivizing the pharmaceutical industry to invest in green chemistry and biodegradable drugs would further limit environmental damage. Collaborative efforts across government agencies, regulatory bodies, scientific institutions, and the pharmaceutical sector are essential for developing long-term, sustainable solutions. With continued research, improved monitoring, public engagement, and proactive policy reforms, it is possible to mitigate the risks of diclofenac and protect aquatic ecosystems from further pharmaceutical pollution, contributing to broader water quality improvement goals.

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