IJPSR (2021), Volume 12, Issue 10 (Review Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 04 August 2020; received in revised form, 22 June 2021; accepted, 23 June 2021; published 01 October 2021

IMPACTS OF HUMAN PHARMACEUTICALS ON FISH HEALTH

Bhawna Srivastava [1] and P. B. Reddy [*2]

Department of Zoology [1], DAV College, Kanpur - 208001, Uttar Pradesh, India.
Government PG College [2], Ratlam - 457001, Madhya Pradesh, India.

Keywords:

Freshwater, Fish health, Pharmaceuticals, Surface waters, Toxic responses

Correspondence to Author:
P. B. Reddy

Professor,
Government PG College, Ratlam - 457001, Madhya Pradesh, India.

E-mail: reddysirr@gmail.com

ABSTRACT: Human pharmaceuticals and their metabolites affect the endocrine system and physiology of aquatic wildlife, which is an important global ecological concern. The published data from open-source toxicology and worldwide web resources reveal about 175 pharmaceuticals that can affect estrogen pathways to disrupt the endocrine system and metabolism. Such studies demand additional investigations on fish and wildlife. As predicted, the use of therapeutic drugs is expected to progressively increase over the coming years, following increased discharge in a freshwater environment. The widespread use and their incorrect dumping procedures have made these chemicals as contaminants of emerging concern (CEC). Particularly, the active pharmaceutical ingredients (APIs) are universally identified in surface water and soil, where they execute negative effects in living organisms. The associated presence of different drugs may undergo bioaccumulation, which causes potential toxicological effects on behaviour, histopathological alterations, reproductive and immunotoxic responses in fish and wildlife. However, the results of published literature revealed that the intensity of impacts is mostly regulated by the concentration of active pharmaceutical compounds, time of exposure, and some abiotic factors like photoperiod and nutrient availability. The response of species to these active pharmaceutical substances may be noticeably different from species type. Therefore, it is necessary to continue systematic research on active metabolites and drug detection methods, check the great number of active pharmaceuticals in drinking water, surface, and groundwater, and assess the environmental risks arising from their increased presence in the freshwater environment.

INTRODUCTION: All living beings are composed of water, and it is very difficult to imagine life without water. The presence of several cocktails of contaminants, including human pharmaceuticals and their metabolites and other pollutants, are major concerns of the world today [1-3]. A few numbers of these environmental pollutants are omnipresent and cannot be removed from water treatment plants. Indeed, such pollutants can bioaccumulate in the tissues of aquatic organisms and pose a number of health risks.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.12(10).5185-94

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.12(10).5185-94

The majority of pollutants undergo biotic and abiotic degradation in order to safeguard freshwater environments and their organisms. Wastewater usually contains a multifaceted mixture of pharmaceuticals, xenobiotics and microbes of human and animal origin.

In the past, pharmaceuticals pollution was not considered a major issue of the release of drugs into the environment. Nevertheless, the current modern research shows that certain pharmaceutical manufacturing units can cause environmental contamination at levels way above standards [4]. The living organisms found around such ecosystems may experience adverse effects as reflections. Published literature evidently reveals that certain aquatic plants can absorb these pharmaceuticals and their metabolites and pass these harmful pollutants to all the organisms at various food chain levels [5, 6]. Pharmaceutical contamination has become an inevitable global ecological issue. As roughly $800 billion worth of medicines are sold globally, and more and more pharmaceuticals are being discharged into the environment [7]. Of the 175 potential drugs, around one-third were recognized as estrogen agonists, and two-thirds were acknowledged as estrogen antagonists. The global use of medicines and drug use has continued to elevate, with Americans filling 5.8 billion recommendations in 2018 with an increase of 2.7% over the previous year. In 2018, growth on expenditures on pharmaceuticals in the United States bounced back to 4.5% on a net basis with an estimated $61 billion market. It is expected that in the next five years, the net medicine expenses in the United States alone will enhance from $344 billion in 2018 to $420 billion in 2023 [8]. The sales growth was witnessed parallel with the advancement in medical technology and enhanced spending on health care.

The Indian sub-continent is the major contributor to generic drugs, bulk drugs, intermediates, drug formulations, and herbal products, and surgical internationally. The country's pharmaceutical sector provides over 50 percent of worldwide demand for various medicines and 40 percent of generic demand in the US. The Indian pharmaceutical sector is projected to grow up to US$ 100 billion by 2025. The revenue of the nation's domestic pharmaceutical bazaar reached Rs 1.4 lakh crore (US$ 20.03 billion) in 2019, which is 9.8% raise compared to Rs 129,015 crore (US$ 18.12 billion) in 2018 [9].

The commonly found pharmaceuticals and their metabolites in freshwater environments reach water bodies through a variety of pathways. Direct dumping of household leftover drugs, excretion in faeces/urine after medicinal use, incomplete effluent treatment from the manufacturing units [10] handling and prophylaxis through the water in farms aquaculture farms [11], and livestock treatment and petcare [11] are found to be major pathways to reach the aquatic environment. In general, the detected levels of pharmaceuticals concentrations in the freshwater environment are comparatively low. Usually, they lie between in the ng L^{-1} to µg L^{-1} range [12], but in some nations like India and China, these concentrations are comparatively high due to feeble legislative regulations [13]. Potential risks associated with the releases of pharmaceuticals into the environment have become an increasingly important issue for environmental regulators and the pharmaceutical industries. This concern has been driven by prevalent exposure of pharmaceuticals in environmental samples due to improved analytical capabilities and the charging of focused field surveys. Pharmaceutical pollutants are biologically active substances intended to interact with a definite physiological pathway in the target organisms. Accordingly, they symbolize a class of emerging pollutants competent enough to affect particular physiological functions like growth, development, defense and reproduction at ecologically pertinent concentrations [14].

The long-term studies of Grzesiuk *et al.*, [5] evidently discovered that the chronic exposure of pharmaceuticals (fluoxetine, ibuprofen, and propranolol) on *Acutodesmus obliquus* and *Nannochloropsis limnetica* for 30 generations exhibited decreased in cell number, increased carotenoid to chlorophyll ratio, and affected their consumer feeding. Notably, pharmaceuticals are specifically designed to correct definite physiological functions. This is different from most other pollutants entering the freshwater environment, where biological effects usually happen as an unintentional effect of their principal function [15]. Therefore, many pharmaceuticals designed to provoke a result in humans or livestock have a high possibility of being biologically active in wildlife species. Supporting this statement, the study of Gunnarssan *et al.,* [16] conclude that zebrafish possesses orthologs to 86% of 1318 tested human gene-drug targets [17, 18].

Besides, the biological target system in wildlife species is somewhat different or is more susceptible to the effects of certain pharmaceuticals than in livestock and humans or livestock animals [16]. For example, the diclofenac, a non-steroidal anti-inflammatory drug, exhibited a severe effect on kidney function in *Gyps* vulture species and has resulted in their extensive decline and even extinctions [16]. Another example is that the β-blocker drug, which mainly targets the adrenergic function, is believed to be involved in melanophore function in fish [19] are not, observed in humans.

The most significant adverse effects of pharmaceuticals include their capability to interfere with the endocrine system altering hormone secretion required for fundamental physiological functions. The most effective drugs are synthetic steroid estrogens, for instance, 17β-estradiol (E2), estrone (E1) and 17 α-ethinyl-estradiol (EE2). A number of laboratory investigations offer confirmation that exposure to these compounds can lead to anomalous change or disruption of growth and reproduction in fish and aquatic wildlife. In a study, exposure to the pharmaceutical mixtures of Tb (1, 10, and 50 ng/L) and EE2 (2 and 5 ng/L) on juvenile zebrafish (*Danio rerio*) for 20 and 60 days caused sexual disruption, masculinization effects, and intersex condition [20]. Additionally, a reduction in reproductive function [21, 22], reduced fecundity and/or fertility [23, 24,] and alterations to gonadal maturation [25] are among the most frequently observed effects.

Pharmaceuticals are potentially competent to modify homeostasis and critical functions and mechanisms of an organism. In some cases, they may act as endocrine-disrupting chemicals and affect the hormone secretions. Altogether, the measurable effects of pharmaceuticals on physiological, biochemical, or behavioral modifications can be successfully applied as biomarkers in biomonitoring approaches [14]. The current appraisal could offer implications to advance the global pharmaceutical ecological management globally for effective monitoring systems in the release of pharmaceutical compounds in manufacturing units as well as from landfill effluent. Another area with a need for additional research is green chemistry, which could decrease or even remove the probable hazards of pharmaceutical substances that enter the environment. Fish and other aquatic animals are known to be more vulnerable to water pollution. The role of human pharmaceuticals in the endocrine disruption in the fish and the wild is very difficult to assess. In this document, we sincerely evaluate the probable biological impacts of pharmaceuticals discharged into the freshwater environment in fish due to their ecological position and many resemblances with mammalian species in physiological processes. Besides, fish species are perhaps the most credible vertebrate species to be affected by pharmaceuticals in the freshwater environment. Therefore, this document positively assesses the potential for ecological impacts of pharmaceuticals in the freshwater environment on fish health by drawing on comparisons between effects observed in the laboratory and concentrations measured in the field and assessing the scale of the (potential) problem. The Food and Drug Administration (USFDA, 2017) has approved about 10,000 pharmaceuticals and 3,000 ingredients for the treatment and are regular human applications. However, much amount of pharmaceutical waste is generated by improper disposal by patients, veterinary drug additives, and agrarian wastes, which are ultimately released into the freshwater environment. The extensive usage and inappropriate dumping of pharmaceutical drugs cause the spreading of multi-drug-resistant pathogens. As there are no specific guidelines on the antibiotic residue discharge limits, the effluents produced from these industries are treated as per the Central Pollution Control Board (CPCB) guidelines on wastewater, which unfortunately do not include antibiotic residues. As a consequence, they are not monitored in the pharmaceutical industry effluents. Besides, we advocate that pharmaceutical industries should utilize the best available and advanced technology to tackle pharmaceutical contamination in India.

MATERIALS AND METHODOLOGY: The present study is based on a systematic survey of the literature. The literature survey was executed on publications acquired for the data related to the impacts of pharmaceuticals on fish health and ecotoxicity. Web searches began with Google Scholar and Web of Science and using key terms "pharmaceuticals," "drugs in the water" "aquaculture," and "fish health." Supplementary data were obtained from the reference sections of each article. Information was also acquired from news media and periodicals. We reviewed and included the most recent peer-reviewed academic literature for the present study, and 72 key sources are cited in the manuscript to demonstrate key issues and emphasize key research gaps still awaiting attention in future studies.

RESULTS AND DISCUSSION:

Pharmaceuticals in Freshwater Aquatic System:

Globally, every year, several tons of pharmaceutical, chemical substances are produced and used. Pharmaceuticals are an important class of emerging environmental micropollutants and their occurrence in the freshwater environment is an increasing environmental concern. Nevertheless, most of these drugs may undergo biotic or abiotic degradation and finally accumulate in the tissues of fish and other aquatic organisms to induce potential toxicological effects like behaviour, histopathology, reproductive disruption, and immunotoxic responses.

Behavioral Responses: Behavioural alterations are the reflections of early toxicity signs, as they offer integrative actions of neurotoxicity [27]. Several aquatic organisms in general exposed to various pharmaceutical wastewater. Fish and other organisms potentially exhibit defense behaviour to combat any overall effect. Species may exhibit asymmetrical behavioral effects to pharmaceutical contamination, which vary with the concentration of the drug [28]. Many pharmaceuticals and their metabolites can accumulate in aquatic food webs and alter innate and vital behaviors in fish [29-32]. However, the behavioral effects of drugs in freshwater ecosystems depend on species-specific interactions and abiotic interactions [30]. For example, in an experiment, the fish *Lepomis gibbosus* (pumpkin-seed sunfish) was exposed to three anti-anticonvulsant drugs (diazepam, carbamazepine, and phenytoin) exhibited a significant increase in time spent in motion behavior [33].

Another laboratory study of McCallum *et al*., [34] demonstrated reduced aggressive behaviour and misplace their nesting site, which is an important behaviour in round goby (*Neogobius melanostomus*) exposed to wastewater with pharmaceutically active compounds. The study of Lagesson [30] confirmed that the anxiety drug (Oxazepam) has the potential to alter the growth and behaviour in *Perca fluviatilis (perch)* but not in *Esox lucius* (pike) in the presence of temperature and predators as additional stressors. The experiment of Melvin [35] evidently confirmed that a mixture of SSRI and SNRI (antidepressant drugs) are capable of altering circadian rhythms (feeding, predation, and competition behaviour) in male mosquitofish (*Gambusia holbrooki*) at concentrations approaching 1g/L. The study of Saaristo *et al*., [31] had shown altered and abnormal behaviour upon the exposure to psychoactive pharmaceutical drugs with other stressors likes temperature and predation in European perch (*Perca fluviatilis*). The 35-day experiment of Martin *et al.*, [36] showed that wild male mosquitofish (*Gambusia holbrooki*) exhibited severe behavioral impacts like boldness, exploration, and mating behaviour upon the exposure of antidepressant fluoxetine at two ecologically relevant concentrations (31 and 374 ng/L). The study of Ziegler *et al.*, [37] have shown that the brown trout (*Salmo trutta* f. *fario*) exposed to an antidepressant drug (citalopram) at two different life stages exhibited severe alterations in behaviour (increased swimming behaviour with reduced anxiety), bioaccumulation, and growth. The study also confirms that behavioral changes were stronger in early life stages, which are linked with the chronic exposure time in larvae compared to juvenile fish.

Based on the above literature, it is evident that various pharmaceuticals and their metabolites can induce behavioural alterations in different species. Nevertheless, both drug- and species-specific effects were also obvious. It is clear from the above literature that antidepressants, psychiatric drugs (benzodiazepines), and antihistamines can induce behavioural changes in fish at environmentally relevant concentrations. However, as such, the data is difficult to forecast the direct effects using solitary species and under static laboratory conditions. More investigations should evaluate the adverse effects of pharmaceuticals and their metabolites in freshwater ecosystems under more complex conditions to achieve an enhanced perception.

Even though the existing literature advocates that the environmental effects of pharmaceuticals may occur in freshwater ecosystems dominated by wastewater effluent, and effects of pharmaceuticals were seen only at higher concentrations but not at ecologically relevant concentrations. Therefore, the scarcity of experiments using behavioral endpoints on wildlife makes it tough to depict any universal conclusions on the subject of the ecological impact of pharmaceuticals found in freshwater ecosystems. Further, the behavioural outcomes produce even more complicated data to understand, synthesize, and extrapolate as fish and another aquatic biota living in polluted environments are exposed to a wide range of pharmaceuticals. For that reason, apart from the regular behavioural endpoints, research on the effects of pharmaceutical mixtures is deeply required to acquire a better perception of the biological effects of exposed wildlife.

Impacts of Residual Pharmaceuticals on the Health of Fish and Wildlife: India is the home for more than 10 percent (9.06 million metric tons) of global fish productivity and ranked in the second position at global level [38]. The huge productivity is achieved by rigorous farming at elevated mass, which has resulted in an increased vulnerability of fish to infections caused by microorganisms [39]. In order to enhance fish productivity, farmers use excessive chemicals and antibiotics to prevent infections and diseases, which enter into the aquatic environment in significant quantities. The introduction of antibiotic drugs in various segments, including aquaculture, threatens the effectiveness of antibiotics [39]. The harmful impacts of left-over pharmaceuticals in the freshwater ecosystem and human health are a big concern. Published literature reveals that species and specific substances mainly influence drug circulation and bioaccumulation in the fish [40]. The laboratory investigations of Triebskorn *et al.*, [41] have confirmed harmful effects of human pharmaceuticals (carbamazepine, clofibric acid, metoprolol, and diclofenac) in liver, gills, and kidney of the in rainbow trout (*Oncorhynchus mykiss*) and common carp (*Cyprinus carpio*) at environmentally relevant concentrations.

The study found severe glomerulonephritis with hyaline droplet degeneration of proximal renal tubule as a major pathological effect. The findings of Gürcü *et al.*, [42] showed that the accumulation of a common antibiotic, Metronidazole (MTZ), in the fish (*Oncorhynchus mykiss*) intestine could affect the histopathological organization of the intestine in dose-dependent and time-dependent manner. The alterations include necrosis, edema, inflammation, and small tears in the villi. For instance, when the juvenile fish rainbow trout (*Oncorhynchus mykiss*) exposed to the common antibiotic oxytetracycline (OTC) had shown the interference of the drug in different biochemical pathways and metabolic processes with increased histological damage like leucocyte infiltrations, hypertrophy, vacuolization, and pyknotic nucleus in the tissues of liver and gills [43]. In another experiment, Rodrigues *et al.*, [44] exposed the fish rainbow trout (*Oncorhynchus mykiss*) with a common antibiotic, Erythromycin (ERY), and are frequently prescribed for humans, and livestock medicine is frequently found in the aquatic environment. In an experiment Rodrigues, S., *et al.*, [43] exposed the juveniles of rainbow trout (*Oncorhynchus mykiss*) exposed to environmentally relevant concentrations of Erythromycin (ERY) exhibited considerable progressive (hypertrophy of mucous cells and hyperplasia) and regressive tissue damage (cytoplasmic vacuolization, pyknotic nucleus and cellular degeneration, hemorrhage, and increase of sinusoidal space) in gills and liver.

The study of Alimba *et al.*, [45] found cytogenotoxic, hematological, and histopathological alterations in *Clarias gariepinus* exposed to pharmaceutical effluents. Pharmaceutical effluent caused a major time-dependent increase in the frequency of micronucleus (MN) and irregular erythrocytes, decline in total erythrocyte counts, hemoglobin and haematocrit values, and increase in total leucocyte number and lymphocytes compared to the control fish. The fish exposed to pharmaceutical effluent also exhibited pathological injuries on gills, liver, and kidneys. Akinpelu *et al.*, [46] found histological alterations like infiltration of secondary lamellae, oedema, congestion of the blood vessels, epithelial thickening and lifting, and necrosis in the gill tissues of *Clarias gariepinus up*on exposure to sub-lethal concentrations of pharmaceutical effluents in dose-dependent manner.

Dos Santos *et al.*, [47] found neurotoxic and respiratory effects in a Neotropical fish species, *Phalloceros harpagos* exposed to two common human used drugs namely paracetamol (analgesic and antipyretic) and propranolol. In a recent study, Santos *et al.*, [48] confirmed that chronic environmental concentrations of methamphetamine could lead to health issues in aquatic organisms. The study found bioaccumulation of methamphetamine (psychostimulant) in various tissues (kidney > liver > brain > muscle > plasma) to induce degenerative symptoms (apoptosis) in liver and heart of the brown trout (*Salmo trutta fario*) exposed to environmentally relevant concentrations for 35 days. The recent study of Hubená *et al.*, [49] showed varied effects of four psychoactive compounds on food intake and brain function in juvenile chub (*Squalius cephalus*) exposed to environmentally relevant concentrations. From the above literature of review, it is clear that pharmaceuticals in wastewater interfered with histopathological changes in the liver, gill, kidney, and gut tissues of various fish species exposed to wastewater with pharmaceuticals. Results reveal that pharmaceuticals and their metabolites, even at ecologically relevant concentrations, can interfere with exerting harmful effects on the histopathology of important organs like the liver, gills, and kidney and obstruct the proper functioning of these organs. Bioaccumulation of pharmaceuticals *via* food webs in fish tissues like plasma, brain and muscle samples are slightest or negligible compared to liver, gills and kidney to induce degenerative symptoms like vacuolization, pyknotic nucleus and cellular degeneration, hemorrhage and infiltration of secondary lamellae and lifting in gills and liver while severe glomerulonephritis with hyaline droplet degeneration of proximal renal tubule as a major pathological effect in the kidney. The gut exhibited necrosis, edema, inflammation, and small tears in villi. Results reveal that the interference of the pharmaceuticals in different biochemical pathways and metabolic processes caused increased histological damages in tissues in a dose-dependent and time-dependent manner. These outcomes of the presented worken lightening a prospective for additional studies on metabolic pathways of pharmaceuticals and its metabolomics in fish exposed under natural conditions.

Impacts of Residual Pharmaceuticals on Fish Reproduction: Reproduction is a biological process, which depends on the synchronizing activities of the neuroendocrine system. Several human and veterinary pharmaceuticals are released into urban wastewater, and upon exposure, such contaminants can induce detrimental effects in aquatic organisms and fish. Runnalls *et al*., [50] found a decline in sperm parameters when adult fathead minnow exposed to clofibric acid (human pharmaceutical). The *in-situ* studies of Sanchez *et al*., [51] confirmed the alterations in the enzyme activities, neurotoxicity, intersex, vitellogenin induction in fish exposed to pharmaceutical effluent downstream of the Dore river (France). The study of Galus *et al.,* [52] confirmed the incidence of developmental abnormalities like decreased embryo production, atretic oocytes, and altered ovarian and kidney histology in adult zebrafish (*Danio rerio*) exposed to a pharmaceutical mixture of acetaminophen, carbamazepine, gemfibrozil, and venlafaxine and to diluted wastewater effluent for 6 weeks.

Based on the results of a laboratory study of Margiotta-Casaluci *et al.,* [21] addressed the mode of action of human pharmaceuticals in fish species. Their study confirmed that the pharmaceutical drug (dutasteride), which is used to cure benign prostatic hyperplasia in humans, may inhibit the activities of both isoforms of 5α-reductase (5αR). This enzyme converts testosterone into dihydrotestosterone and causes detrimental effects in the fish fathead minnow (*Pimephales promelas*).

The study of Prasad *et al.,* [53] proven that certain pharmaceutical contaminants present in the natural environment may influence the fish reproductive process by means of the serotonin system. The *in-vitro* studies of Yokota *et al.,* [54] found severe anti-ovulatory activities of non-steroidal anti-inflammatory medicines in comparison with in vivo reproductive studies in medaka (*Oryzias latipes*). Aguirre-Martínez *et al*., [55] demonstrated significant changes in neurotoxic responses, inflammation, reduced gametogenic activity, and energy status in fish *Corbicula fluminea* exposed to environmentally relevant concentrations of human drugs for 21 days (caffeine, CAF, ibuprofen, IBU, carbamazepine, CBZ, novobiocin, NOV and tamoxifen, TMX). The laboratory experiments of Martin *et al*., [36] and Fursdon *et al.,* [22] confirm that the antidepressant drug (fluoxetine) can alter the reproductive behaviour and sperm traits in fish. Fraz *et al.,* [56] found transgenerational impacts like reduced reproductive function, courtship, aggressive behaviors, sperm speed, and morphology for four generations in zebrafish exposed to a common drug residue (carbamazepine (CBZ).

Constantine *et al.,* [57] found a decline in fecundity and fertility, vitellogenin, and hatching success rate in zebrafish (*Danio rerio*) exposed to ibuprofen at environmentally relevant concentrations. de Lima *et al.,* [58] found that certain diets used to reduce oxidative stress in the human population could interfere with the reproductive process and growth in female Nile tilapia (*Oreochromis niloticus).* Godoi *et al.*, [59] found a significant reduction in reproductive activities by reducing 17β- Estradiol (E_2), and testosterone levels in male fish (*Astyanax altiparanae)* exposed to common drugs (Diclofenac (DCF) and caffeine (CAF) at normal levels. In contrast, the study of Thoré *et al.,* [60] demonstrated increased mating, enhanced fecundity, and alteration in social behaviour in the short-lived kill fish (*Nothobranchius furzeri*) exposed to antidepressants. The results of a recent laboratory study of Liang *et al.,* [61] showed reduced plasma 11-ketotestosterone levels in males, increased reproductive toxicity, decreased spermatogenesis, and anti-androgenicity in Japanese medaka (*Oryzias latipes*) upon the exposure of 3-(4-Methylbenzylidene) camphor (4-MBC) at environmentally relevant concentrations. The above literature survey revealed that pharmaceuticals in the aquatic environment could negatively affect fish reproductive function by affecting sperm parameters, alterations in the enzyme activities, intersex, and vitellogenin induction in fish exposed to pharmaceutical substances. Some reports revealed decreased embryo production, atretic oocytes and altered ovarian histology in exposed fish to even at environmentally relevant concentrations of human drugs. Few studies reported transgenerational impacts like reduced reproductive function, courtship and aggressive behaviors, sperm speed, and morphology in exposed fish species. In contrast, few authors reported better mating, improved fecundity, and alteration in social behaviour in fish exposed to drugs in the laboratory.

Immuno Toxic Effects: The immune system in fish and other organisms possibly affected directly by toxic compounds. The detection of pharmaceutical remains of various drugs in surface waters has provoked concerns about probable adverse effects on freshwater biota. Several ecological pollutants, including pharmaceuticals, are identified as immune modulators in fish and wildlife species 62, making the organism more vulnerable to pathogen infections. The research analysis of Milla *et al.,* [63] had shown the interactions of the immune system with synthetic steroids (estrogenic and androgenic) in fish. The review analysis of Burgos-Aceves *et al.,* [64] demonstrated the immunomodulation functions in fish are regulated by both natural and synthetic estrogens, which act through estrogen receptors and regulate definite target genes, and also through microRNAs (miRNAs). The experimental findings of Ribas *et al.,* [65] revealed significant immunosuppressive effects by declining in RBC, WBC, haemoglobin, and haema-tocrit values in the fish (*Hoplias malabaricus)* exposed to common drugs like diclofenac and dexamethasone. Kleinert *et al.,* [66] observed a significant reduction in the functional activities of the immune system by decreasing lymphocyte transformation and G_0/G_1 phase of the cell cycle in the harbor seal (*Phoca vitulina)* exposed to17α-ethinyl estradiol and 25,000 μg/L naproxen as mixtures. Khoei *et al*., [67] observed reduced aggressions, and IgM levels in fish Siamese fighting fish (*Betta splendens*) exposed to immuno-suppressant drug tacrolimus. The guaranteed immunotoxic effects of pharmaceuticals have been found to be related to the defense mechanism of both host and microbiota [68]. The laboratory findings of Liang *et al.,* [69] demonstrated decreased hatching rate and body length and increased abnormality and mortality in the early life stages of zebrafish *(Danio rerio)* upon exposure of Norfloxacin nicotinate (an antibacterial fluoroquinolone, NOR-N). The results also confirmed increased antioxidant system (MDA, SOD, CAT, and GPx) and expression of TNFα, IFN, IL-1β, IL-8, CXCL-clc, CC-chemokine, Lzy and C3 genes in exposed fish.

Another recent work of Li *et al.,* [70] established immunotoxic effects in association with hepatic damage (hepatic vacuolization and nuclei pyknosis and inflammation) in juvenile zebrafish (*Danio rerio*) exposed to Benzotriazole ultraviolet stabilizers for 28 days. The experimental findings of Bera *et al.,* [71] established that triclosan suppressed both cell-mediated and humoral immune responses with a decrease in respiratory burst activity (RBA), myeloperoxidase activity (MPO), phagocytic activity (PA) in triclosan exposed catfish, *Pangasianodon hypophthalmus*). In an experiment, Rehberger *et al.,* [72] demonstrated that the chronic exposure to low ethinylestradiol (EE2) concentrations combined with parasite infection in juvenile rainbow trout (*Oncorhynchus mykiss*) can induce endocrine disruptive and immunomodulating activities.

In conclusion, it is clear that the majority of pharmaceutical substances and their metabolites mimic hormone structure and interfere in endocrine function to exhibit immunotoxic actions. Accordingly, immunomodulation in affected fish may be a result of such exposure. Several ecological pollutants, including pharmaceuticals are identified as immune modulators in fish and wildlife species. Several authors reported significant immunosuppressive effects like declining in RBC, WBC, haemoglobin, haematocrit values, decreasing lymphocyte transformation and G_0/G_1 phase of the cell cycle in harbor, reduced aggression, and IgM levels in fish exposed to pharmaceutical pollution. Few authors also reported the association of immunotoxic responses with hepatic tissue damage. Therefore, fish immuno-toxicity studies may be used as valuable biomarkers of pharmaceutical contamination. However, to standardize our understanding of these mechanisms, care should be taken when considering the intrinsic and extrinsic factors related to the fish and the contamination model.

CONCLUSION: The presence of persistent drugs in surface waters is a big global concern today. Literature is still scanty regarding how cocktails of pharmaceutical residues in surface water affect the environment or fish health. Until now, the published literature showed bioaccumulation and negative effects on fish and other aquatic organisms. As there is no specific legislation on pharmaceutical waste management, drug contamination in water is increasing globally year by year, effectively forming an epidemiological experiment with the public and freshwater ecosystem. The present study reviewed and analyzed the impacts of pharmaceutical substances on various health aspects of fish. Based on an inclusive assessment of the data and analysis, it is well established that drugs in water can affect fish health by accumulating specific tissues that induce negative effects in histopathology, oxidative stress, haematological indices, reproductive function, gene expression and immunotoxic effects. However, the degree of severity depends on species, sex, and phase of the life cycle, dose, and duration of the substances. The study advocates framing and implementing rigid guidelines for treating and monitoring waste discharged from municipal wastewater and pharmaceutical industries for controlling pharmaceutical pollution in wastewater.

CONFLICTS OF INTEREST: We declare no conflict of interest of any kind with anybody.

Financial Support: None

REFERENCES:

1. Reddy PB: Evaluation of potential biomarkers for effluent induced hepatotoxicity. International Journal on Applied Bioengineering 2012; 6(2).
2. Reddy PB: Histopathogical studies as potential and direct biomarkers of pollution. Trends in Lifesciences 2012; 1(1): 27-31.
3. Reddy PB: Study on the toxic effects of wastewater in catfish (*Heteropneustes fossilis*.Life Sciences International Research 2017; 5(2): 165-74.
4. Kalyva M: Fate of pharmaceuticals in the environment-A review (diva-portal.org). 2017.
5. Grzesiuk M, Spijkerman E, Lachmann SC and Wacker A: Environmental concentrations of pharmaceuticals directly affect phytoplankton and effects propagate through trophic interactions. Ecotoxicology and Environmental Safety 2018; 156: 271-8.
6. Xie Z, Lu G, Yan Z, Liu J, Wang P and Wang Y: Bioaccumulation and trophic transfer of pharmaceuticals in food webs from a large freshwater lake. Environmental Pollution. 2017; 222: 356-66.
7. https://e360.yale.edu/.
8. https://www.iqvia.com/insights.
9. https://www.ibef.org/industry/pharmaceutical-india.aspx.
10. Li ZH and Randak T: Residual pharmaceutically active compounds (PhACs) in aquatic environment–status, toxicity and kinetics: a review. Veterinarni Medicina 2009; 54(7): 295-314.
11. Thomas KV, Dye C, Schlabach M and Langford KH: Source to sink tracking of selected human pharmaceuticals from two Oslo city hospitals and a wastewater treatment works. Journal of Environmental Monitoring 2007; 9(12): 1410-8.
12. WHO: Pharmaceutics in drinking water. (who.int); 2012.
13. EMEA: European Medicines Agency. Committee for Medicinal Products for Human Use. European Medicines Agency. Draft guideline on reporting the results of population pharmacokinetic analyses. EMEA. 2006.
14. Fabbri E and Franzellitti S: Human pharmaceuticals in the marine environment: focus on exposure and biological effects in animal species. Environmental Toxicology and Chemistry 2016; 35(4): 799-812.
15. Corcoran J, Winter MJ and Tyler CR: Pharmaceuticals in the aquatic environment: a critical review of the evidence for health effects in fish. Critical Reviews in Toxicology 2010; 40(4): 287-304.
16. Gunnarsson L, Snape JR, Verbruggen B, Owen SF, Kristiansson E, Margiotta-Casaluci L, Österlund T, Hutchinson K, Leverett D, Marks B and Tyler CR: Pharmacology beyond the patient–The environmental risks of human drugs. Environment Interl 2019; 129: 320-32.
17. Sipes NS, Padilla S and Knudsen TB: Zebrafish-As an integrative model for twenty-first century toxicity testing. Birth Defects Research Part C: Embryo Today: Reviews 2011: 93(3): 256-67.

18. Chakraborty M, RoyK, Sedhain A, Dhakal P and Karunakaran G: Zebrafish an emerging model for Preclinical Drug Discovery. International J of Research in Pharmaceutical Sciences 2020; 11(2): 1638-48.
19. Owen SF, Giltrow E, Huggett DB, Hutchinson TH, Saye J, Winter MJ and Sumpter JP: Comparative physiology, pharmacology and toxicology of β-blockers: mammals versus fish. Aquatic Toxicology 2007; 15; 82(3): 145-62.
20. Örn S, Holbech H and Norrgren L: Sexual disruption in zebrafish (Danio rerio) exposed to mixtures of 17α-ethinylestradiol and 17β-trenbolone. Environmental Toxicology and Pharmacology 2016; 41: 225-31.
21. Margiotta-Casaluci L, Hannah RE and Sumpter JP: Mode of action of human pharmaceuticals in fish: The effects of the 5-alpha-reductase inhibitor, dutasteride, on reproduction as a case study. Aquatic Toxicology 2013; 128: 113-23.
22. Fursdon JB, Martin JM, Bertram MG, Lehtonen TK and Wong BB: The pharmaceutical pollutant fluoxetine alters reproductive behaviour in a fish independent of predation risk. Science of the Total Environment 2019; 650: 642-52.
23. Louis GMB, Lynch CD and Cooney MA: Environmental influences on female fecundity and fertility. In ‘Seminars in Reproductive Medicine 2006: 24 (03): 147-55.
24. Horie Y, Yamagishi T, Shintaku Y, Iguchi T and Tatarazako N: Effects of tributyltin on early life-stage, reproduction, and gonadal sex differentiation in Japanese medaka (*Oryzias latipes*). Chemosphe 2018; 203: 418-25.
25. Madureira TV, Rocha MJ, Cruzeiro C, Rodrigues I, Monteiro RA and Rocha E: The toxicity potential of pharmaceuticals found in the Douro River estuary (Portugal): evaluation of impacts on fish liver, by histopathology, stereology, vitellogenin and CYP1A immunohistochemistry, after sub-acute exposures of the zebrafish model. Environmental Toxicology and Pharmacology 2012; 34(1): 34-45.
26. USFDA: Classification of Products as Drugs and Devices and Additional Product Classification Issues. Guidance document 2017.
27. Legradi JB, Di Paolo C, Kraak MH, Van der Geest HG, Schymanski EL, Williams AJ, Dingemans MM, Massei R, Brack W, Cousin X and Begout ML: An ecotoxicological view on neurotoxicity assessment. Envir Sci Europe 2018; 30(1): 46.
28. Brodin T, Piovano S, Fick J, Klaminder J, Heynen M and Jonsson M: Ecological effects of pharmaceuticals in aquatic systems-impacts through behavioural alterations. Philosophical Transactions of the Royal Society B: Biological Sciences 2014; 369(1656): 20130580.
29. Arnold KE, Brown AR, Ankley GT and Sumpter JP: Medicating the environment: assessing risks of pharmaceuticals to Wildlife and Ecosystems 2014; 1-11.
30. Lagesson A: Fish on drugs: behaviour modifying contaminants in aquatic ecosystems2018; (Doctoral dissertation, Umeå universitet).
31. Saaristo M, Lagesson A, Bertram MG, Fick J, Klaminder J, Johnstone CP, Wong BB and Brodin T: Behavioural effects of psychoactive pharmaceutical exposure on European perch (*Perca fluviatilis*) in a multi-stressor environment. Sci of the Total Env 2019; 655: 1311-20.
32. Bachour RL, Golovko O, Kellner M and Pohl J: Behavioral effects of citalopram, tramadol, and binary mixture in zebrafish (*Danio rerio*) larvae. Chemosphere 2020; 238: 124587.
33. Brandão FP, Rodrigues S, Castro BB, Gonçalves F, Antunes SC and Nunes B: Short-term effects of neuroactive pharmaceutical drugs on a fish species: biochemical and behavioural effects. Aquatic Toxicology 2013; 144: 218-29.
34. McCallum ES, Krutzelmann E, Brodin T, Fick J, Sundelin A and Balshine S: Exposure to wastewater effluent affects fish behaviour and tissue-specific uptake of pharmaceuticals. Science of the Total Environment 2017; 605: 578-88.
35. Melvin SD: Effect of antidepressants on circadian rhythms in fish: Insights and implications regarding the design of behavioural toxicity tests. Aquatic Toxicology 2017; 182: 20-30.
36. Martin JM, Bertram MG, Saaristo M, Ecker TE, Hannington SL, Tanner JL, Michelangeli M, O'Bryan MK and Wong BB: Impact of the widespread pharmaceutical pollutant fluoxetine on behaviour and sperm traits in a freshwater fish. Science of the Total Environment 2019; 650: 1771-8.
37. Ziegler M, Knoll S, Köhler HR, Tisler S, Huhn C, Zwiener C and Triebskorn R: Impact of the antidepressant citalopram on the behaviour of two different life stages of brown trout. Peer J Life & Environment 2020; 8: e8765.
38. FAO: National Aquaculture Sector Overview. India. 2015. http://www.fao.org/fishery/countrysector/naso_india/enhttp://www.fao.org/fishery/countrysector/naso_india/en.
39. Miranda CD, Godoy FA and Lee MR: Current status of the use of antibiotics and the antimicrobial resistance in the Chilean salmon farms. Frontiers in Microb 2018; 9: 1284.
40. Chen H, Liu S, Xu XR, Diao ZH, Sun KF, Hao QW, Liu SS and Ying GG: Tissue distribution, bioaccumulation characteristics and health risk of antibiotics in cultured fish from a typical aquaculture area. Journal of Hazardous Materials 2018; 343: 140-8.
41. Triebskorn R, Casper H, Scheil V and Schwaiger J: Ultrastructural effects of pharmaceuticals (carbamazepine, clofibric acid, metoprolol, diclofenac) in rainbow trout (Oncorhynchus mykiss) and common carp (Cyprinus carpio). Analytical and Bioa Chem 2007; 387(4): 1405-16.
42. Gürcü B, Koca YB, Özkut M and Tuğlu Mİ: Matrix changes due to the toxic effects of metronidazole in intestinal tissue of fish (*Onchorhynchus mykiss*). Chemosphere 2016; 144: 1605-10.
43. Rodrigues S, Antunes SC, Nunes B and Correia AT: Histological alterations in gills and liver of rainbow trout (*Oncorhynchus mykiss*) after exposure to the antibiotic oxytetracycline. Environmental Toxicology and Pharmacology 2017; 53: 164-76.
44. Rodrigues S, Antunes SC, Nunes B and Correia AT: Histopathological effects of the antibiotic erythromycin on the freshwater fish species *Oncorhynchus mykiss*. Ecotoxicology and Environmental Safety 2019; 181: 1-0.
45. Alimba CG Adekoya KO and Soyinka OO: Exposure to effluent from pharmaceutical industry induced cytogenotoxicity, hematological and histopathological alterations in *Clarias gariepinus* (Burchell, 1822). EXCLI Journal 2019; 18: 63.
46. Akinpelu AT, Akinloye OM, Olayinka AS, Olaniyi OA, Stephen OA and Oluwaseun OT: Histological Response of *Clarias gariepinus* to Varying Concentrations of Pharmaceutical Effluents. Annual Research & Review in Biology 2020: 68-75.
47. dos Santos PR, Costa MJ, Dos Santos AC, Silva-Zacarín EC and Nunes B: Neurotoxic and respiratory effects of human use drugs on a Neotropical fish species, *Phalloceros harpagos*. Comparative Biochemistry and Physiology Part C: Toxicology & Pharmacology 2020; 230: 108683.

48. Santos ME, Grabicová K, Steinbach C, Schmidt-Posthaus H, Šálková E, Kolářová J, Staňová AV, Grabic R and Randák T: Environmental concentration of methamphetamine induces pathological changes in brown trout (*Salmo trutta fario*). Chemosphere 2020: 126882.
49. Hubená P, Horký P, Grabic R, Grabicová K, Slavík O and Randák T: Environmentally relevant levels of four psychoactive compounds vary in their effects on freshwater fish condition: a brain concentration evidence approach. Peer J 2020; 8: e9356.
50. Runnalls TJ Hala DN and Sumpter JP: Preliminary studies into the effects of the human pharmaceutical Clofibric acid on sperm parameters in adult Fathead minnow. Aquatic Toxicology 2007; 84(1): 111-18.
51. Sanchez W, Sremski W, Piccini B, Palluel O, Maillot-Marechal E, Betoulle S, Jaffal A, Ait-Aissa S, Brion F, Thybaud E and Hinfray N: Adverse effects in wild fish living downstream from pharmaceutical manufacture discharges Environment International 2011; 37(8): 1342-8.
52. Galus M, Jeyaranjaan J, Smith E, Li H, Metcalfe C and Wilson JY: Chronic effects of exposure to a pharmaceutical mixture and municipal wastewater in zebrafish. Aquatic Toxicology 2013; 132: 212-22.
53. Prasad P Ogawa S and Parhar IS: Role of serotonin in fish reproduction. Frontiers in Neuroscience 2015; 9: 195.
54. Yokota H, Eguchi S, Hasegawa S, Okada K, Yamamoto F, Sunagawa A, Tanaka M, Yamamoto R and Nakano E: Assessment of in vitro antiovulatory activities of nonsteroidal anti-inflammatory drugs and comparison with in vivo reproductive toxicities of medaka (*Oryzias latipes*). Environmental Toxicology 2016; 31(12): 1710-9.
55. Aguirre-Martínez GV, André C, Gagné F, and Martín-Díaz LM: The effects of human drugs in *Corbicula fluminea*. Assessment of neurotoxicity, inflammation, gametogenic activity, and energy status. Ecotoxicology and Environmental Safety 2018; 148: 652-63.
56. Fraz S, Lee AH, Pollard S, Srinivasan K, Vermani A, David E and Wilson JY: Paternal exposure to carbamazepine impacts zebrafish offspring reproduction over multiple generations. Environmental Science & Technology 2019; 53(21): 12734-43.
57. Constantine LA, Green JW and Schneider SZ: Ibuprofen: Fish Short-Term Reproduction Assay with Zebrafish (Danio rerio) based on an Extended OECD 229 Protocol. Environmental Toxicology and Chemistry 2020.
58. de Lima SA, de Oliveira Pedreira AC, de Freitas JM, Dalmaso AC, Chiella RJ, Meurer F, Romão S and Bombardelli RA: Diets containing purified nucleotides reduce oxidative stress, interfere with reproduction, and promote growth in Nile tilapia females. Aquaculture 2020, 528: 735509.
59. Godoi FG, Muñoz-Peñuela M, Gomes AD, Tolussi CE, Brambila-Souza G, Branco GS, Nostro FL and Moreira RG: Endocrine disruptive action of diclofenac and caffeine on Astyanax altiparanae males (Teleostei: Characiformes: Characidae). Comparative Biochemistry and Physiology Part C: Toxicology & Pharmacology 2020; 231: 108720.
60. Thoré ES, Grégoir AF, Adriaenssens B, Philippe C, Stoks R, Brendonck L and Pinceel T: Population-, sex-and individual level divergence in life-history and activity patterns in an annual killifish. Peer J 2019; 7: e7177.
61. Liang X, Wang F, Li K, Nie X and Fang H: Effects of norfloxacin nicotinate on the early life stage of zebrafish (*Danio rerio*): Developmental toxicity, oxidative stress and immunotoxicity. Fish & Shellfish Immunology 2020; 96: 262-9.
62. Segner H, Wenger M, Möller AM, Köllner B and Casanova-Nakayama A: Immunotoxic effects of environmental toxicants in fish—how to assess them? Environmental Science and Pollution Research 2012; 19(7): 2465-76.
63. Milla S, Depiereux S and Kestemont P: The effects of estrogenic and androgenic endocrine disruptors on the immune system of fish: a review. Ecotoxicology 2011; 20(2): 305-19.
64. Burgos-Aceves MA, Cohen A, Smith Y and Faggio C: Estrogen regulation of gene expression in the teleost fish immune system. Fish & Shellfish Immunology 2016; 58: 42-49.
65. Ribas JL, Zampronio AR, and Silva de Assis HC: Effects of trophic exposure to diclofenac and dexamethasone on hematological parameters and immune response in freshwater fish. Environmental Toxicology and Chemistry 2016; 35(4): 975-82.
66. Kleinert C, Lacaze E, Mounier M, De Guise S and Fournier M: Immunotoxic effects of single and combined pharmaceuticals exposure on a harbor seal (*Phoca vitulina*) B lymphoma cell line. Marine pollution bulletin 2017; 118(1-2): 237-47.
67. Khoei AJ, Forsatkar MN and Brown C: Behavioral and immunotoxic effects of Prograf® (tacrolimus) in the male Siamese fighting fish. Ecotoxicology 2019; 28(9):1032-7.
68. Statovci D, Aguilera M, MacSharry J, and Melgar S: The impact of western diet and nutrients on the microbiota and immune response at mucosal interfaces. Frontiers in Immunology 2017; 8: 838.
69. Liang M, Yan S, Chen R, Hong X and Zha J: 3-(4-Methylbenzylidene) camphor induced reproduction toxicity and antiandrogenicity in Japanese medaka (Oryzias latipes). Chemosphere 2020; 249: 126224.
70. Li Z, Liang X, Liu W, Zhao Y, Yang H, Li W, Adamovsky O and Martyniuk CJ: Elucidating mechanisms of immunotoxicity by benzotriazole ultraviolet stabilizers in zebrafish (Danio rerio): Implication of the AHR-IL17/IL22 immune pathway. Env Pollution 2020; 262: 114291.
71. Bera KK, Kumar S, Paul T, Prasad KP, Shukla SP and Kumar K: Triclosan induces immunosuppression and reduces survivability of striped catfish *Pangasianodon hypophthalmus* during the challenge to a fish pathogenic bacterium *Edwardsiella tarda*. Environmental Research 2020; 186: 109575.
72. Rehberger K, von Siebenthal EW, Bailey C, Bregy P, Fasel M, Herzog EL, Neumann S, Schmidt-Posthaus H, and Segner H: Long-term exposure to low 17α-ethinylestradiol (EE2) concentrations disrupts both the reproductive and the immune system of juvenile rainbow trout, *Oncorhynchus mykiss*. Environment International 2020; 142: 105836.

How to cite this article:
Srivastava B and Reddy PB: Impacts of human pharmaceuticals on fish health. Int J Pharm Sci & Res 2021; 12(10): 5185-94. doi: 10.13040/IJPSR.0975-8232.12(10).5185-94.