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Environmental risk of clinical selective serotonin reuptake inhibitors (SSRIs): Toxic effects of sertraline and fluoxetine on the freshwater fish

Vishal Rajput[1]* | Khusi Saraswat[1] | Pooja Sajwan[1] | Kanak Verma[1] | Manish Tenguria[2] | Avnish Chauhan[3] | Vivek Kumar[1]

Selective serotonin reuptake inhibitors (SSRIs), in particular, are antidepressants that are among the most often prescribed medications in the world. Sertraline and fluoxetine are the most often used for treating anxiety disorders, depression, and other mental health issues. In aquatic settings, Sertraline and fluoxetine are noticeably emerging as pollutants. Particularly to non - target creatures like fish, which are extremely sensitive to neuroactive substances, these pharmaceutical leftovers provide new ecological hazards. This study evaluated the effects of Sertraline and fluoxetine on the freshwater catfish species *Clarias batrachus*. Following a week of dosage, the fish's behavioral reactions and metabolic characteristics were closely examined. The fish displayed irregular and agitated swimming, cornering behavior, and a total lack of splashing or surface behavior. Additionally, opercula movement, decreased dramatically. Significant physiological abnormalities were also noted, as shown by fluctuation in the concentration of total protein in several important organs, in addition to behavioral alterations. Protein depletion is frequently linked to decreased development, compromised organ function, and general physiological discomfort.

Keywords: Serotonin reuptake inhibitors, Freshwater fish, Toxicity, Protein alteration

INTRODUCTION

Ecological balance, biodiversity, and the sustainability of water supplies all depend on aquatic ecosystems. Fish, macro - invertebrates, phytoplankton, and zooplankton are among the many aquatic species that call these ecosystems - lakes, rivers, marshes, and streams[1,2]. Climate change, water flow management, deforestation, pollution, and the development of hydropower are examples of artificial forces that affect the health of these habitats in addition to natural dynamics. Such pressures have led to a decline in water quality and a deterioration of aquatic biodiversity during the last several decades, which has raised significant ecological concerns[3].

Furthermore, river systems are increasingly being found to include new contaminants such endocrine - disrupting chemicals, pharmaceutical residues (such as antibiotics and antidepressants), and designed nanoparticles. According to[4,5], these compounds have an impact on fish behavior, growth, immunological function, and reproduction. They may also have long - term ecological effects that are not fully known. The decrease in fish biomass and diversity is clear indication of the effects of pollution on aquatic life. Pollution and climate - induced stressors have been found to reduce fish biomass by 22 - 30 % and fish diversity by 10 - 25 % in the Ganga and Alaknanda River systems. Important species like *Schizothorax* species and

[1] School of Biosciences, Swami Rama Himalayan University, Dehradun, Uttarakhand, India
[2] Department of Biotechnology, Graphic Era (Deemed to Be University), Dehradun, Uttarakhand, India
[3] Department of Environmental Sciences, Graphic Era Hill University, Dehradun, Uttarakhand, India

***Corresponding Author** Vishal Rajput (vishalrajput@srhu.edu.in)

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Clarias batrachus are especially at risk, as seen by their rapid population decreases brought on by habitat loss, heightened competition between species, and deteriorating water quality[6,7,8,9].

According to Rajput (2012), neurological disorders, metabolic dysfunctions, and infertility have all been connected to heavy metal buildup in fish tissues. According to experimental research, in waterways tainted with lead and cadmium *Clarias batrachus* exhibits reduced immunological responses and increased mortality rates[10,11] (Fig. 1).

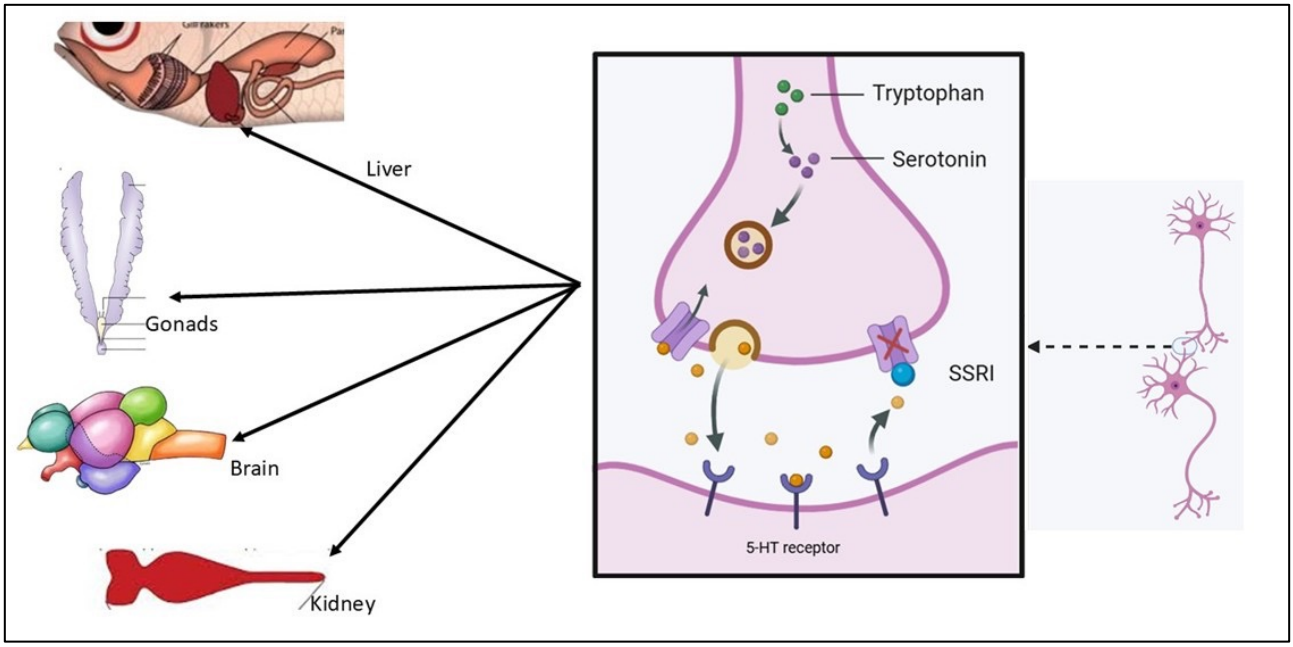
Since medications are used more often worldwide and their residues are frequently found in water bodies, pharmaceutical pollution has grown to be a serious issue for aquatic ecosystems. There is a growing presence of active pharmaceutical ingredients (APIs) and their metabolites in sediments, lakes, rivers, and even sources of drinking water. Agricultural runoff, human and animal excretion, wastewater discharge from hospitals and pharmaceutical companies, and inappropriate disposal of leftover drugs are some of the ways that these substances get into aquatic habitats[12].

Numerous pharmaceutical chemicals are frequently ineffectively removed by wastewater treatment (WWTPs) in urban and industrialized areas, because of this, surface waters are often found to include antibiotics, antidepressants, anti - inflammatory medications and hormone therapy. Designed to be biologically active, these compounds can concentrate in sediments and survive in aquatic systems, hence influencing biodiversity and water quality. Manure runoff and the usage of bio solids (treated sewage sludge) on agricultural areas, which can spread to nearby water bodies, are two further ways that livestock operations, which frequently utilize veterinary antibiotics and hormone therapies, contribute to pharmaceutical pollution[13].

Significant amounts of medicines are also introduced into sewage systems by inappropriate medication disposal, such as dumping unwanted prescriptions down sinks or toilets. When wastewater is not sufficiently cleaned, this can lead to the contamination of rivers and lakes. These compounds pose ecological and physiological hazards because they bioaccumulate in aquatic species after being discharged into the environment[14].

While antidepressants like fluoxetine and sertraline can alter fish behavior, swimming patterns, and predator avoidance, non - steroidal anti - inflammatory medicines (NSAIDs) like diclofenac have been linked to gill and liver damage in fish, according to several studies. The presence of pharmaceutical residues in fish tissues has been seen to be up to 1000 times greater than those in the surrounding water, suggesting a high potential for bioaccumulation.

The appearance of antibiotic - resistant bacteria (ARB) in aquatic habitats is one of the most concerning effects of pharmaceutical pollution. The selection and growth of resistance strains are encouraged by ongoing exposure to



Brain: Alteration in neurogenesis, Transcript level changes related to stress **Kidney:** Cortisol synthesis hampered	**Gonad:** Changes in egg formation, Sex steroid level reduction **Liver:** Reduction in somatic index

Figure 1. Effect of antidepressant on various organs

low concentrations of antibiotics. These resistant bacteria frequently have antibiotic resistance genes (ARGs), which can be passed on to human pathogens and pose a serious risk to world health while making the management of infectious illnesses more difficult[15].

Aquatic food webs and environmental processes are also disturbed by pharmaceuticals. Antidepressants may have an impact on sedimentary microbial populations, changing the cycling of nutrients and impairing the general health of ecosystems. Fish behavior changes brought on by psychoactive chemicals also disrupts eating, breeding, and predator - prey relationships, which can have a domino effect on the food chain[16].

Pharmaceutical residues eventually endanger human health through trophic transmission in aquatic food webs, especially for populations that depend on fish and shellfish from contaminated waterways. The necessity for improved management and control of pharmaceutical pollutants in the environment is highlighted by the increased probability of human exposure to harmful quantities caused by the biomagnification of medicines in higher trophic levels.

Material and Methods

A total of 32 healthy specimens of *Clarias batrachus* (average weight: 234 g; average length: 20.12 cm) were collected from a local freshwater source and transferred to the laboratory for experimental studies. The fish were acclimatized to laboratory conditions for a period of three weeks in aerated aquaria. During this acclimatization phase, the fish were fed daily with flour balls prepared from a standard formulation to ensure uniform nutritional status[17].

After acclimatization, the fish were randomly divided into groups: 2 sets of control (8 specimens in one set) and 2 sets each drug for sertraline and fluoxetine with 8 specimens in one set. The experimental groups were subjected to ascending sublethal doses of sertraline and fluoxetine, administered at predetermined intervals to stimulate chronic environmental exposure[18].

Sertraline (0.1-6.5 µg/L) and Fluoxetine (5-88 ng/L)[18] in ascending 5 doses and each dose was followed by a complete water change to maintain optimal water quality and to avoid accumulation of drug residues. Behavioural observations were conducted immediately after each exposure to assess changes such as cornering behaviour, opercula movements, surfacing activity, and swimming patterns. At the end of the exposure period, fish were neutralized, and samples of liver, gill, intestine, and muscle tissues were carefully dissected for biochemical analysis. Total protein content in each tissue was determined using standard method[19].

Results

During the investigation behavioural as well as physiological aspects were analysed and compared under the sertraline and fluoxetine exposure.

Behavioural observations

Prior to treatment, the fish did not exhibit cornering behaviour; however, post - treatment, compact assemblage at corners was observed under sertraline exposure whereas specimen given fluoxetine exhibited cluster assemblage (Table 1, Fig. 2). Splashing on the water surface is the symptom of natural movement of fish and before treatment, specimens were showing 4-5 surfacing in a minute whereas no such activity was recorded under the exposure of both drugs. Irritable or erratic swimming was absent before treatment thereafter the dose of sertraline, aggressive pattern was reported whereas under the exposure of fluoxetine moderate pattern of irritable swimming was observed. Opercula movement of any fish is considered as the most significant visible symbol of health or stress, similarly, operculum movement rate ranged Between 38 to 45 movements per minute before treatment, which markedly declined to 15 to 16 movements per minute after treatment of sertraline, on other hand under the exposure of fluoxetine 21 to 26 movements per minute reported.

Physiological observations

Physiological effects of sertraline on protein content in selected organs

In the present study, significant alterations in protein content were observed in various tissues of fish exposed to the LC_{50} concentration of sertraline. The results are summarized in the table below:

A marked decrease (−40.31%) in liver protein content was recorded following sertraline exposure, whereas, substantial increase (+217.46%) in intestinal protein content was observed after treatment. Protein levels in gill tissues increased significantly (+168.48%) after exposure. On other hand, a notable increase (+139.54%) in muscle protein content was recorded after sertraline treatment (Table 2; Fig. 3a-d). These changes suggest tissue-specific metabolic and physiological responses to pharmaceutical-induced stress in fish.

Physiological effects of fluoxetine on selected organs observations

A moderate increase (+18.22%) in liver protein content was observed following fluoxetine treatment. Noticeable increase (+425.47%) in intestinal protein content was observed post fluoxetine exposure. While examining gill proteins, increase of (+95.86%) was recorded. Muscle tissue exhibited increase of (+50.48%) in protein content in response to fluoxetine treatment (Table 3; Fig. 4a-d). Fluoxetine generally increased protein levels across all tissues, with the highest rise seen in the intestine. Tissue-specific responses to antidepressant exposure and highlight

Table 1. Behavioural and opercula response of Clarias batrachus before and after sertraline and fluoxetine exposure

	Control	Sertraline	Fluoxetine
Cornering	No	Compact assemblage	Cluster assemblage
Splashing on surface	4-5	0	0
Irritable swimming	No	Aggressive pattern	Moderate pattern
Opercula movement per minute	38 - 45	15 - 16	21-26
Surfacing/minute	5 - 6	0	1-2

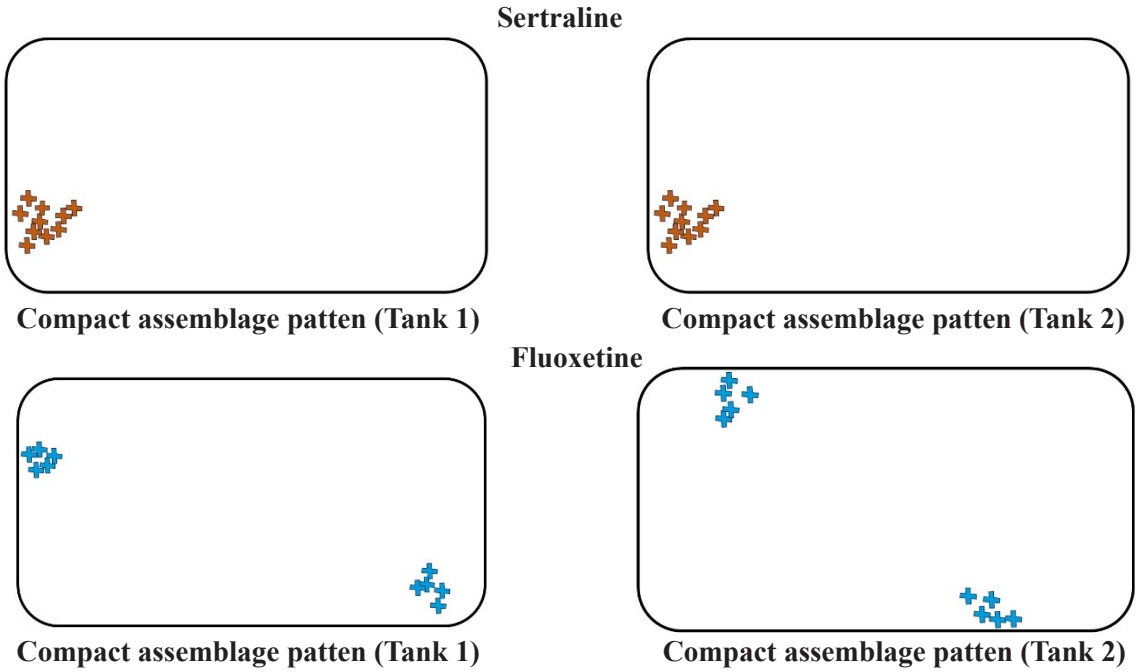


Figure 2. Cornering patten under the exposure of SSRI

Table 2. Changes in total protein content (%) in fish organs after the exposure of sertraline

Organs	Control (Average ± SD)	Treatment (Average ± SD)	% Change
Liver	0.965 ± 0.015	0.593 ± 0.113	- 40.31
Intestine	0.252 ± 0.011	0.797 ± 0.214	+217.46
Tissue	0.925 ± 0.022	2.229 ± 0.102	+139.54
Gills	0.443 ± 0.015	1.192 ± 0.254	+168.48

"+" shows gain of total protein content; "-" shows reduction in total protein content

the potential physiological impact of SSRIs on aquatic organisms.

Discussion

The current study evaluates the toxicological effects of the selective serotonin reuptake inhibitor (SSRI) on the levels of total proteins in different *Clarias batrachus* tissues. In particular, the study looks at changes in protein levels in the liver, gut, gills, and entire body tissues when exposed to increasing dosages of sertraline and fluoxetine, in comparison to a control group[20].

These findings indicate complicated physiological interactions between pharmaceutical pollutants and aquatic fauna, highlighting a tissue - specific and dose - dependent biochemical response to sertraline and fluoxetine exposure. After being exposed to drugs, the liver showed a significant fluctuation in total protein levels[21]. This indicates that hepatic metabolism of *Clarias batrachus* was negatively impacted, most likely as a result of increased catabolic enzyme activity, hepatocellular degeneration, and reduced protein synthesis. The liver's vulnerability to pharmacological toxicity is well - established, given that it is primary organ for detoxification and xenobiotic processing[22].

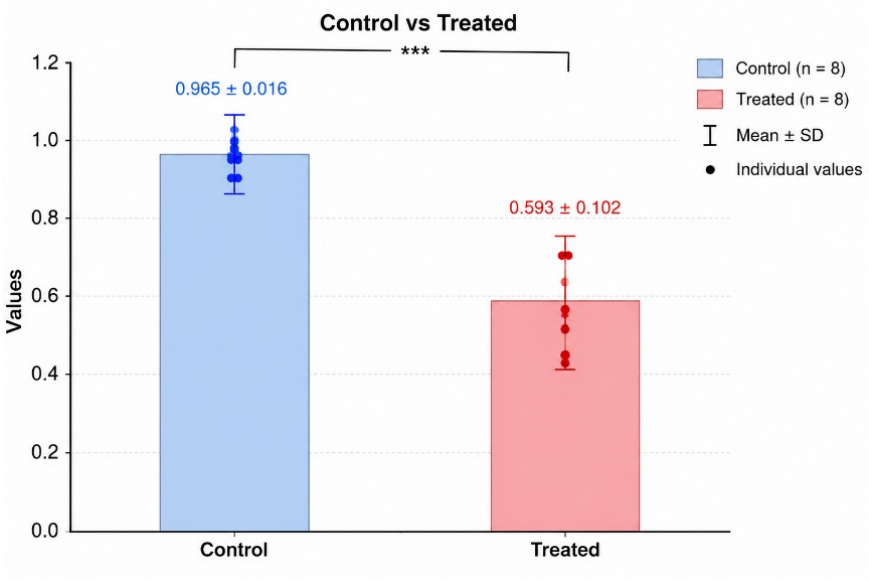


Fig. 3a. Liver

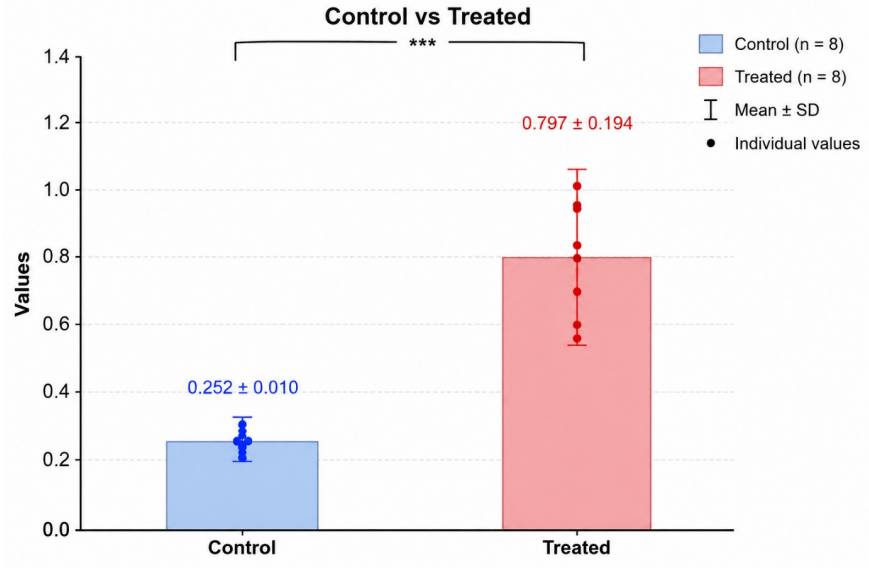


Fig. 3b. Intestine

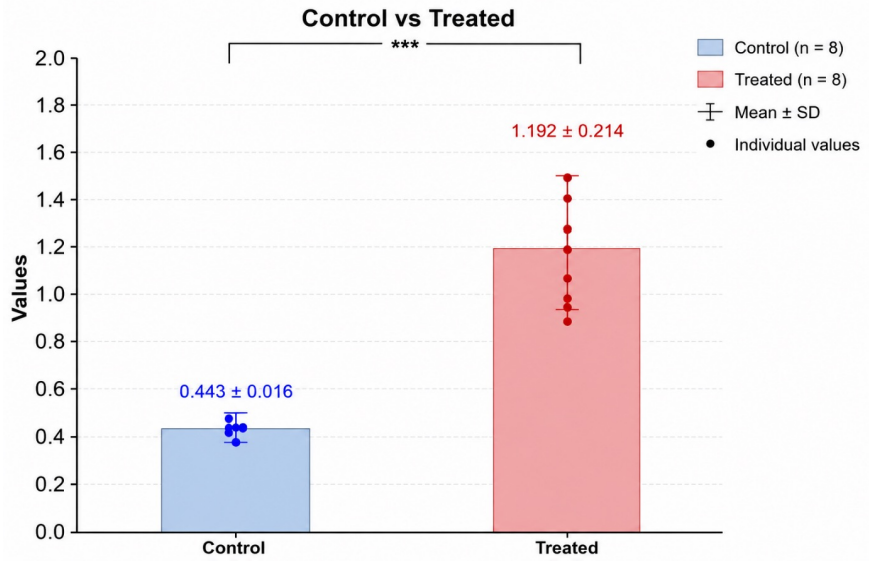


Fig. 3c. Gills

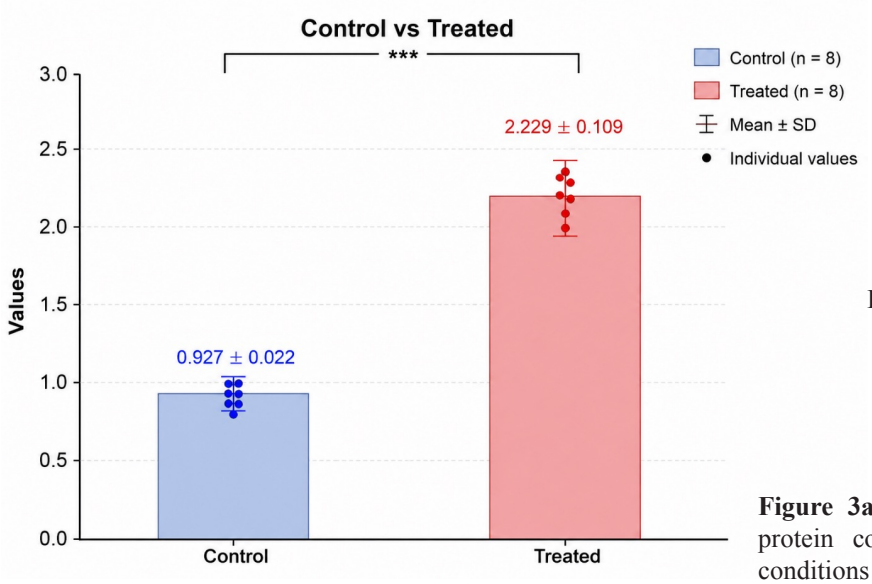


Fig. 3d. Tissue

Figure 3a-d. Organ specific variation in total protein content across control and treatment conditions of sertraline

Table 3. Changes in total protein content (%) in fish organs after the exposure of fluoxetine

Organs	Control (Average ± SD)	Treatment (Average ± SD)	% Change
Liver	0.968 ± 0.056	1.190 ± 0.239	+ 18.22
Intestine	0.256 ± 0.037	1.353 ± 0.228	+ 425.47
Gills	0.459 ± 0.077	0.903 ± 0.151	+ 95.86
Tissue	0.937 ± 0.156	1.460 ± 0.486	+ 50.48

"+" shows gain of total protein content

On the other hand, the amount of protein in the gut also exhibited noticeable changes. This surprising outcome might be explained as a physiological response that involves the overexpression of digestive enzymes, protective proteins, and mucosal components to preserve gut integrity in the face of toxic stress[23]. Sertraline and fluoxetine induced enteric remodeling and higher epithelium turnover may potentially be the cause of the elevated protein levels. Similar results were found in additional teleost species that SSRI exposure changed the dynamics of food absorption and enterocyte proliferation[24].

Sertraline and fluoxetine exposure also caused a notable change in the overall protein content of the gills. The gills are sensitive bioindicators of waterborne pollutants because they are in close proximity to the aquatic environment. Increased enzymatic defense mechanisms, mucoprotein overproduction, and epithelial cell hyperplasia can all be causes of elevated protein levels. Similar results were found, SSRI exposure to changes in the respiratory epithelium and protein upregulation brought on by osmotic stress[25].

The widespread alterations observed in a variety of organs points to sertraline and fluoxetine's role as a systemic disturbance of metabolic balance and these results are consistent[8], reported about the fish exposed to sub lethal pharmaceuticals had broad biochemical disruptions. Various studies summarized about the oxidative, behavioral, and reproductive abnormalities in Zebrafish after exposure to sertraline, similarly, changes in *Clarias batrachus* neuroendocrine pathways were found, indicating that SSRIs could disrupt hormone control[3,26].

Sertraline has more significant biochemical effects and a larger bioaccumulation factor than older SSRIs like citalopram and fluoxetine. SSRIs change metabolic and enzymatic profiles, especially when exposed to them over an extended period of time[27]. The increased protein responses in metabolically active and absorptive tissues such as the liver and gut may be explained by sertraline's enhanced tissue penetration due to its lipophilic nature[28].

Surface waters contain bioavailable residues as a result of conventional wastewater treatment plants' inability to completely remove these micropollutants, according to studies[3,29]. More significantly, the compounding effects of toxicity may occur when chemical pollutants are combined with additional stressors like as habitat fragmentation, eutrophication, and climate change. Synergistic and cumulative interactions should thus be taken into account in integrated risk assessment systems[24].

The potential for sertraline and fluoxetine to interfere with metabolic and physiological processes in *Clarias batrachus* is highlighted by the tissue - specific changes in

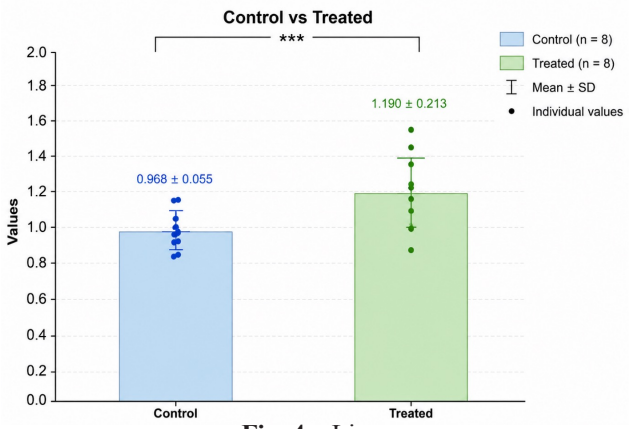


Fig. 4a. Liver

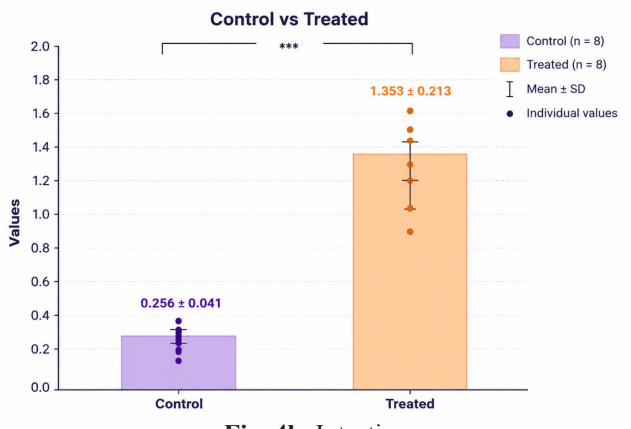


Fig. 4b. Intestine

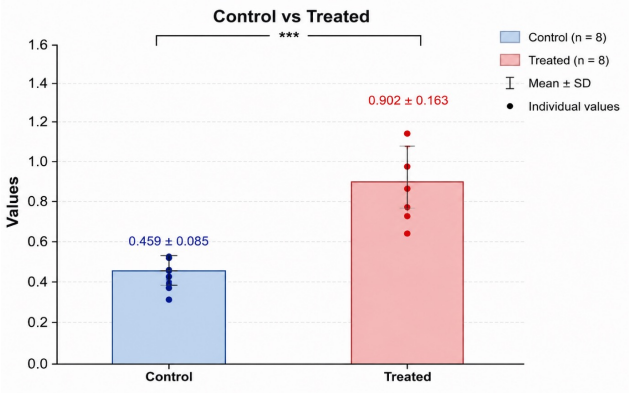


Fig. 4c. Gills

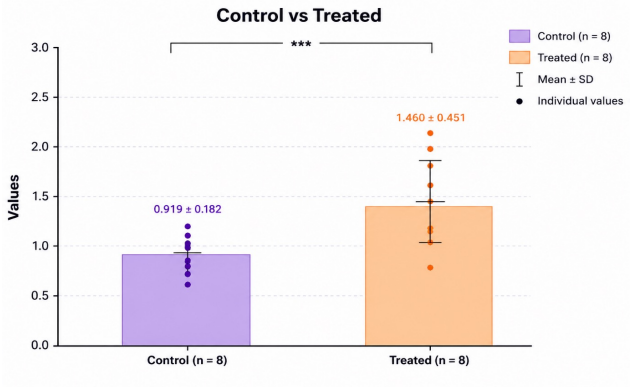


Fig. 4d. Tissue

Figure 4a-d. Organ specific variation in total protein content across control and treatment conditions of fluoxetine

protein composition that have been reported. Hepatotoxic suppression is seen in the liver, but compensatory overproduction of proteins, perhaps related to stress adaptation, is shown in the gut and gills. These results support increased environmental monitoring, regulatory actions, and the creation of cutting - edge wastewater treatment technology to lessen the ecological effect of pharmaceutical pollutants in aquatic systems, which is a developing problem.

Conclusions

The present study underscores the significant ecotoxicological risks posed by selective serotonin reuptake inhibitors (SSRIs), particularly sertraline and fluoxetine, on freshwater fish species such as *Clarias batrachus*. Behavioral disturbances, including erratic swimming patterns, loss of natural surface activity, and altered opercula movements, clearly indicate acute neurological stress induced by these pharmaceuticals. Furthermore, the tissue - specific alterations in protein content reveal profound physiological and metabolic disruptions, with sertraline generally exerting a stronger impact compared to fluoxetine. These results highlight those pharmaceutical pollutants, even at sublethal concentrations, may compromise fish health by interfering with viral biochemical processes and inducing systemic stress response. This study recommends the inclusion of antidepressants in ecotoxicological risk assessments.

Author's Contribution

Vishal Rajput: Conceptualization, Experimental supervision, Resources, Writing, Khusi Saraswat: Experimentations, Writing; Pooja Sajwan: Experimentations, Writing; Manish Tenguria: Writing; Avnish Chauhan: Editing; Vivek Kumar: Editing.

Conflict of Interest

The author has not reported any conflicts of interest that may influence the research findings.

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Data availability

No datasets were generated or analysed during the current study

Ethical approvals

Fish sampling and handling was carried out following standard ethical practices to minimize the stress to test animal.

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