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The Role of Cytochrome P450 in Fish Health and Metabolism: A Vital Enzyme System

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ABSTRACT

Cytochrome P450 (CYP450) enzymes are vital enzymes in the metabolic processes of fish, playing a crucial role in the detoxification of xenobiotics and the regulation of endogenous compounds. The biotransformation of pollutants, including pesticides, medicines, and polycyclic aromatic hydrocarbons (PAHs), which build up in aquatic environments, is facilitated by these enzymes, especially those in the CYP1A, CYP2, and CYP3A families. Immunity of fish and their health, can be negatively impacted by metabolic byproducts, which can occasionally be more toxic than the original compounds even though CYP450 activity helps with detoxification. Exposure to pollutants and other environmental stressors can alter the expression and activity of CYP enzymes, which can cause physiological disruptions in fish species. This review explores the key roles of CYP450 enzymes in fish metabolism and health, emphasizing their importance as biomarkers for environmental toxicity and their potential impact on aquatic ecosystems. Assessing the effects of environmental contaminants and creating plans for environmental preservation and fish health management require an understanding of CYP450 mediated metabolic pathways in fish.

INTRODUCTION

The diverse family of heme-containing enzymes known as cytochrome P450 (CYP) enzymes is essential to the metabolism of a broad range of substances, including toxins, drugs, and endogenous compounds. Numerous biotransformation processes, such as the synthesis, breakdown, and detoxification of molecules, depend on the CYP enzymes. According to Stegeman & Hahn (1994), fish need CYP enzymes in order to metabolize pollutants, maintain homeostasis, and respond to environmental changes. Their primary role is to take part in the constantly evolving process of oxidative metabolism, which occurs to a wide range of

substances, both produced and naturally occurring. The CYP superfamily normally catalyses the primary phase I reaction, which is an enzymatic oxidation in the presence of NADPH as a co-factor. The CYP content of fish varies greatly depending on the species, and it is lower than that of mammals (Uno et al., 2012). Flavin containing monooxygenases (FMO) is an additional highly significant oxidase that aids in the oxidation of nucleophilic atoms such as sulfur and catalyzes the conversion of fenthion and aldicarb to sulfoxides (Schlenk, 2005). Though cytochrome P450 enzymes are present in all body cells, the majority of them are found in liver cells. Cytochrome P450 enzymes are found in the endoplasmic reticulum, a structure involved in the processing and transport of proteins, and the mitochondria. While enzymes located in the mitochondria are usually involved in the synthesis and metabolism of internal substances, those found in the endoplasmic reticulum usually metabolize external substances, primarily medications and environmental pollutants (Guengerich, 2007).

CYP enzymes are necessary for detoxification as well as the synthesis of active metabolites, even though they metabolize most bioactive compounds (Zhang et al., 2016; Giang et al., 2018). The fact that cytochrome P450 enzymes are involved in the control of physiological processes like growth, reproduction, and immune response emphasizes the significance of these enzymes in fish (Uno et al., 2012). Studies indicate a strong correlation between water quality parameters, such as organic pollution, and the outbreak of diseases in fish with CYP enzymes (El-Matbouli & Hoffmann, 2002). The presence of contaminants can lead to altered CYP450 activity, which may exacerbate disease susceptibility in aquatic organisms (Kloepper-Sams & Stegeman,1992). Pollutants and other xenobiotics are broken down into less dangerous substances by CYP450 enzymes. But instead of neutralizing the substances, CYP enzymes in rare cases may produce toxic metabolites if the detoxification process is improperly executed or overburdened by pollutants. The fish may become overexposed to these toxic byproducts, which could lead to tissue damage, oxidative stress, and abnormal metabolic processes. This can therefore cause imbalances in the parameters that determine the quality of the water, such as elevated ammonia, nitrite, and pH levels, further taxing the aquatic ecosystem. Because of the toxic metabolites and declining water quality, the compromised fish's immune system becomes weaker, making them more susceptible to diseases.

The study of fish CYP450 genes is becoming more and more popular, with a focus on the toxicological mechanisms of pollutants and how harmful they are to aquatic species. Given the increasing use of fish as model organisms for pesticide, pharmaceutical, and emerging contaminant exposure, it is imperative to comprehend the expression and activity of CYP in diverse tissues. Thus, it is crucial to comprehend how CYP enzymes affect fish health and disease in order to monitor the environment and implement aquaculture techniques. To accurately predict the bioavailability of xenobiotic compounds, however, requires a general understanding of the precise distribution of CYP in the various tissues. The primary focus of this article is on the roles of cytochrome P450 (CYP) enzymes and how they contribute to a good habitat, which is essential for the growth of a healthy fish culture.

METHODS

This study employed a narrative literature review approach to synthesize and analyze the roles and mechanisms of cytochrome P450 (CYP450) enzymes in fish health and metabolism. A comprehensive collection of peer-reviewed scientific literature, reports, and

databases was examined to gather relevant information. The methodology encompassed the following steps:

1. Literature Collection and Selection

Peer-reviewed articles, reviews, and experimental studies were sourced from reputable scientific databases including PubMed, Scopus, Web of Science, and Google Scholar. Keywords used in the search included: "Cytochrome P450," "CYP450 in fish," "xenobiotic metabolism in aquatic species," "CYP enzymes in aquaculture," and "CYP biomarkers." Literature was selected based on its relevance to the function, regulation, and biological importance of CYP enzymes in fish.

2. Inclusion Criteria

The inclusion criteria were as follows:

- Studies focusing on fish species commonly used in toxicology and aquaculture research (e.g., zebrafish, rainbow trout, tilapia).
- Articles examining CYP gene expression, enzymatic activity, response to pollutants or drugs, and related physiological effects.
- Reports on CYP evolution, classification, and tissue-specific expression in fish.

3. Data Extraction and Synthesis

Relevant data were extracted concerning:

- The role of CYP450 enzymes in detoxification, metabolism of drugs and endogenous compounds.
- Expression patterns of CYP genes under exposure to environmental contaminants.
- Enzyme activity assays such as EROD (ethoxyresorufin-O-deethylase).
- Regulatory pathways involving receptors such as AhR, PXR, and Nrf2.

The extracted information was then categorized under specific themes: CYP system in fish, metabolism of exogenous and endogenous compounds, effects of pollutants and pharmaceuticals, and CYP as a biomarker in ecotoxicology and aquaculture.

4. Comparative Analysis

Findings were compared across multiple fish species to identify conserved and divergent patterns in CYP enzyme functions and responses. Phylogenetic studies and genomic comparisons were also discussed to highlight evolutionary insights into CYP gene diversification in fish.

5. Critical Evaluation

The review critically examined limitations and knowledge gaps in current studies, particularly the need for tissue-specific expression analysis and the mechanisms underlying differential CYP regulation under chronic exposure scenarios.

RESULTS AND DISCUSSION

1. Intensive Aquaculture and Use of Drugs

Intensive aquaculture has become increasingly prevalent to meet growing global demand for seafood. However, this high-density farming approach often relies heavily on the use of drugs, particularly antibiotics, to prevent and treat diseases that can spread rapidly in crowded conditions. While these practices have boosted production, they raise significant concerns about environmental impacts and human health risks. Overuse of antibiotics in aquaculture can lead to the development of antibiotic-resistant bacteria, potentially compromising the effectiveness of these drugs in treating human infections. Additionally, residual antibiotics and other chemicals used in fish farms can contaminate surrounding water

bodies, affecting wild aquatic ecosystems. As the aquaculture industry continues to expand, there is a pressing need for more sustainable practices that reduce reliance on drug while maintaining fish health and productivity. Antibiotics, disinfectants, and other chemicals have become necessary to prevent and control disease outbreaks in intensive fish farming practices. However, the negative impacts of the use of synthetic chemical drugs on environmental health have sparked discussions, making research into alternative treatments inevitable. Antimicrobial substances are compounds used in livestock production with the objectives of inhibiting the growth of microorganisms and treatment or prevention of diseases. It is well recognized that the issues of antimicrobial use in food animals are of global concern about its impact on food safety (Banerjee et al., 2014). Many drugs have traditionally been used for the treatment and prevention of diseases in farmed fish, but they are not recommended, because the continued overuse of antibiotics can lead to the development of antibiotic-resistant bacteria, environmental pollution and the accumulation of toxic residues in fish (Hossain et al., 2022).

Amoxicillin and oxytetracycline (OTC) are poorly absorbed from fish intestines. These antimicrobials are often administered at doses two to five times higher than those required to achieve therapeutic systemic concentrations in mammals (Burka et al., 1997). The medications Pondkleen, M H Aqua powder, Aqua photo (soil probiotic), Mega Zeo Plus, ACME's Zeolite, and Super Fish Carp (Hasan et al., 2020) are used for intensive aquaculture in the Patuakhali district of Bangladesh and have been shown to be extremely harmful. According to Faruk et al. (2008), medications such as Bio Aqua, Mega Zeo, JV Zeolite, and Geotox are used to improve the quality of water. In this region, eleven marketed antibiotics with active components like oxytetracyclin, amoxicillin, sulphadiazine, and sulphamethaoxazole were widely utilized.

Lulijwa et al. (2020) found that 73% of the major aquaculture-producing countries utilized oxytetracycline, florfenicol, and sulfadiazine, whereas 55% used erythromycin, amoxicillin, sulfadimethoxine, and enrofloxacin. According to Reantaso et al. (2023), 75% of antibiotics administered to fish are excreted into the water, which causes resistant bacteria to evolve in sediments where leftover medical feed may build up. Quinolones (27%) Tetracyclines (20%) Amphenicols (18%) and Sulfonamides (14%) are the most commonly utilized antibiotic classes worldwide (Schar et al., 2020). With an estimated 10,259 tons consumed in 2017, the Asia-Pacific region—particularly China (57.9%), India (11.3%), Indonesia (8.6%), and Vietnam (5%), accounts for the highest portion of the world's aquaculture antimicrobial consumption (Schar et al., 2020).

Similarly, pesticides utilized to control parasites, algae, and other pests in aquaculture environments can enhance crop yields and protect the health of cultivated species. These compounds are particularly important in managing ectoparasites, such as gill fluke, sea lice, in various fish farming, which can cause substantial economic losses if left uncontrolled. Of the 293 registered pesticides, 104 are now produced in India (Nayak & Solanki, 2021). Neonicotinoids, pyrethroids, organophosphates, bifenthrin, λ-cyhalothrin, and permethrin are among the pesticides now in use. Acephate, chlorpyrifos, dimethoate, dimethion, malathion, profenophos, quinalphos, diazinon, dichlorvos, ethion, fenitrothion, fenthion, methyl parathion, monocrotophos, phosphamidon, pirimiphos methyl, temephos, trichlorofon, kitazine, and anilophos are among the organophosphate pesticides that are frequently used in India (GoI, 2020). Pesticides also play a role in controlling algae blooms that can deplete oxygen levels in water and harm aquatic organisms. However, the use of pesticides in aquaculture settings may also have unintended consequences on non-target organisms and

surrounding Many pesticides are not species-specific and can affect a wide range of aquatic life, including beneficial organisms that play crucial roles in maintaining ecosystem balance.

2. Evolution of CYP

CYPs are in fact present in all eukaryotic organisms and even in prokaryotes (Brown et al., 2008). Rat cytochromes P450s were among the first to be identified and isolated. Rat form P450d is actually among the earliest known CYP enzymes, and studies have indicated that it resembles human counterparts. The enzyme, which is currently known by its new name, CYP1A2, is conserved in all species and is typically supported by aromatic structures (Guengerich, 2002). Aquatic environments, where fish are frequently exposed to a wide range of pollutants, have significant selective pressures that have shaped the evolution of CYP enzymes. Understanding the evolutionary relationships and diversification of CYP genes among various freshwater fish families was made possible by the phylogenetic analysis. According to Whyte et al. (2000), the CYP1 family, in particular CYP1A, has evolved to metabolize a range of environmental pollutants, making it a crucial part of fish detoxification processes. This evolutionary adaptation has assisted fish in surviving and successfully occupying a range of ecological niches, in addition to enhancing their ability to detoxify toxic substances (Schlenk et al., 2008).

The family CYP2 exhibits the highest level of divergence (Nelson, 2013). In order to better understand CYP2 diversity, Kirischian et al. (2011) proposed a phylogenetic analysis of 196 CYP2 protein sequences from 16 species using a maximum likelihood method and Bayesian inference. These findings demonstrate that there is only one ancestral vertebrate CYP2 gene and that all CYP2 subfamilies are monophyletic. Two subfamilies (CYP2R and CYP2U) predate vertebrate diversification, allowing for direct comparison across vertebrate classes. All other subfamilies originated during vertebrate diversification, frequently within specific vertebrate lineages. Immunochemical identification has demonstrated that fish possess P450 forms homologous to mammalian CYP2B (Gurumurthy & Mannering, 1985). The ability of fish liver microsomes to dealkalyze the fish carcinogen dienthylnitrosamine suggests a cytochrome P450 form associated with CYP2E (Kaplan et al., 1991). The rare minnow's CYP 1B1 and 1C1 as well as CYP2Aa, 2Y3, and 2K showed a high amino acid sequence identity when compared to their zebrafish orthologs in the study done by Yuan et al. (2013). In all eight tissues examined (liver, gill, intestine, kidney, spleen, brain, skin, and muscle), basal expression revealed CYP1C1 and CYP 2Aa expression. All tissues, with the exception of muscle and skin, expressed CYP 1A and 1B1. Nevertheless, CYP 2Y3 was expressed in the liver, spleen, intestine, and muscle, whereas CYP 2K was detected in the kidney, liver, and intestine.

In a comparison study between fugu and humans CYPs one nearly intact pseudogene (CYP3A50P) and 54 P450 genes were found in fugu. While CYP1A lacks a significant portion of its N-terminal half, 45 P450 genes are fully assembled, and the only information available about CYP2X4 is from an EST. Apart from 2X4, sixteen other pseudogene fragments, or truncated portions of P450 genes exist (Nelson, 2013). The only CYP2 subfamilies that are preserved across species are CYP2R1 and CYP2U1. The Nile tilapia CYP3A40 gene has four polymorphic sites, two of which alter the amino acid sequence, according to research by Rashed et al. (2017). The Cichlidae (Nile tilapia) and Poecilidae families were clearly distinguished from one another by the phylogenetic analysis, which also revealed both shared and fixed mutations in these families. There are multiple lines of evidence indicating that fish contain CYP3A forms. Mammal CYP3A is responsible for catalysing the 6beta-hydroxylation attributed to P450LMC5 in trout and P450 in scup (Miranda et al., 1991).

Based on sequence similarity, five groups of 58 CYP genes were identified in Amur

stickleback (*Pungitius sinensis*). There were conserved motifs in every group, indicating functional similarity. Through whole genome analysis, the CYP genes of Japanese pufferfish and zebrafish were discovered to have 61 and 94 CYPs, respectively, and 61 CYPs have also been reported in channel catfish (Zhang et al., 2014). The presence of distinct isoforms of the CYP protein is suggested by the observed polymorphisms and structural alterations in the protein, which may have consequences for the fish metabolism of diverse substances. Ensuring accurate assembly of protein sequences from new genomes is crucial for constructing phylogenetic trees and naming P450 genes, which are determined by their evolutionary relationships (Nelson, 2013). Genes that coexisted close to CYP genes in the animal ancestor were identified using both macrosynteny and microsynteny. According to Nelson et al. (2013), 11 CYP (Clans 2, 3, 4, 7, 19, 20, 26, 46, 51, and 74) clans shared a common gene environment at birth in mammals. Research indicates that there is a single locus, known as the "cytochrome P450 genesis locus" where a single progenitor CYP gene duplicated to create a tandem pair of genes that were the progenitors of the 11 mitochondrial animal CYP clans. Mammal's CYP1A1 and CYP1A2 may have descended from CYP1A.

The evolution of CYP450 enzymes is also influenced by ambient temperature. Sexuality also affects CYP enzyme activity, as demonstrated in the study, where male fish were shown to have higher levels of P450 enzymes than females (Forlin & Haux, 1990). Phospholipids surrounding P450 in the endoplasmic reticulum have been suggested to have an impact on the formation of CYPs in fish, given that variations in ambient temperature can alter the composition of membranes (Kloepper & Stageman, 1992). The complexity of CYP gene's evolutionary history is demonstrated by the detection of recombination events in numerous of them (Cao & Cheng, 2019).

3. CYP System in Fish

Research on CYPs in mammals still makes up most of the literature, but there is a growing recognition of the biological significance of CYPs in fish. Studies conducted in the late 1960s by Buhler & Rasmusson (1968) revealed that these enzymes were present in the livers of rainbow trout and other fish, despite the initial belief that fish lacked CYP linked mono-oxygenases. Fish liver microsomes display the characteristic reduced carbon monoxide (CO) absorption spectra with a peak at about 450 nm and the low-spin g values near 2.41, 2.25, and 1.91 that are typical for CYPs in electron paramagnetic resonance. Fish hepatic microsome's specific CYP contents are grouped between 0.2 and 0.5 nmol mg^{-1}. Microsomal protein levels vary from less than 0.1 nmol mg^{-1} to almost 2.0 nmol mg^{-1}. Different activities may be exhibited by CYP forms that share structural homology with teleosts and mammals (Stegeman, 1989). The constitutive levels of aryl hydrocarbon hydroxylase (AHH) in certain fish species are significantly higher than in their mammalian counterparts, which is one of the main distinctions between CYPs found in mammals and fish (Lee et al., 1993). Variations in activity are linked to fish species, strains, seasons, water temperatures, and gonadal status (Husoy et al., 1994). It has been reported that 54 CYP isoforms from aquatic species have been cloned, partially purified, or completely purified (Uno et al., 2012).

CYP 1 holds CYP1A, CYP1B, CYP1D and CYP1C. All these subfamilies, aside from CYP1D, are activated by AhR and upregulated in response to various compounds, including benzo(a) pyrenes (BaP) and polychlorinated biphenyls (PCB) (Goldstone et al., 2010). Furthermore, exposure to ultraviolet (UV) radiation and oxidative stress induces the majority of CYP enzymes (Behrendt et al., 2010). As the primary hydrocarbon-inducible CYP, CYP1A has drawn the greatest attention. Fish subfamily CYP1A proteins metabolize benzo ring bound benzopyrene (BP); they are strongly inhibited by a-naphthoflavone, are inducible by polycyclic

aromatic hydrocarbon (PAHs), and exhibit reciprocal cross-reactivity with antibodies and mammalian 1A1. They also have reduced CO maxima at 447 nm and are the primary catalysts for 7-ethoxyresorufin O-deethylase (EROD), ethoxycoumarin O-deethylase, and AHH (Stegeman, 1993). According to Lester et al. (1993), CYP1A1 is found in sinusoidal endothelium, kidney, hepatocytes, endothelial cells of the heart, and biliary epithelial cells of fish. During embryonic development, the cardiovascular system is the primary site of expression for CYP1A, with the abdominal cavity and heart having the highest levels of mRNA expression (Jonsson et al., 2007; Otte et al., 2010). In zebrafish, CYP1B is the sole subfamily that is expressed in the heart and eyes (Jonsson et al., 2007). The CYP1BI present in eye and brain show an AhR2 independent pathway prior to hatching, while the heart and branchial arches show an AhR2 dependent pathway following hatching (Yin et al., 2008). The ovaries express CYP1C1 and CYP1C2 at the lowest levels, whereas the heart and eyes express them at the highest levels (Jonsson et al., 2007).

Different fish species have produced the CYP2 family of enzymes, which includes CYP2K, CYP2M, CYP2N, CYP2P, and CYP2X. The genes encoding members (enzymes) of CYP2K, CYP2N, CYP2P, CYP2R, CYP2U, CYP2X, CYP2Y, and CYP2Z have been identified in Japanese pufferfish. Endogenous and exogenous compounds are metabolized by CYP2E1, a member of the cytochrome P450 mixed-function oxidase system. Inducers of this enzyme include certain medications, industrial chemicals, procarcinogens/carcinogens, and other exogenous substrates (Mueller et al., 2018). PXR and AhR appear to be involved in the regulation of CYP2 in fish (Mosadeghi et al., 2007; Yuan et al., 2013). Certain CYP1 and CYP3 enzymes in humans and zebrafish have orthologous relationships. Zebrafish have 47 CYP2 genes; in contrast, humans only have 16. Of these, only two (CYP2R1 and CYP2U1) are known to be orthologous based on sequence (Goldstone et al., 2010). On the other hand, a number of substrates typically cause mammals, including humans, to produce CYP2s through the nuclear receptor CAR (Handschin & Meyer, 2003). According to Szabo (2018), CY2E1 was initially discovered in rabbits and later in rats, where it is primarily found in the liver. It is simple to induce CYP2E1 expression, and it can happen when one of its substrates like ethanol, toluene, benzene, acetone, and isoniazid containing compounds are present. CYP2K1 and CYP2K6 have same orthological relationship but their metabolic characters are not completely the same (Saad et al., 2015). The localisation of 11 genes (CYP2AD 2,3,6, CYP2N13, CYP2P6-10, CYP2J20, CYP2V) have a synteny with the CYP2J2 in humans (Goldstone et al., 2010). In most of the vertebrate and invertebrate species, CYP2R and CYP2U exists (Kirischian et al., 2011; Nelson et al., 2013). Most of the ray finned species has only one gene for CYP2X, whereas zebrafish has six genes, namely CYP2X6-9 and CYP2X10 (Goldstone et al., 2010). CYP2X has a broad spectrum of distribution in channel catfish but low biotransformation activities and induction responses (Zhang et al., 2014).

The CYP3A, CYP3B, and CYP3C subfamilies, which are primarily present in the liver, comprise the CYP3 family in fish (Yan & Cai, 2010). Whereas in the intestinal ceca of rainbow trout, CYP3A27 is highly expressed. Additionally, in medaka fish genes encoding CYP3A38 and CYP3A40 have been identified. Zebrafish have been found to harbor the fish-specific CYP3C1 gene (Corley-Smith et al., 2006). The Japanese pufferfish genome has revealed the presence of CYP 4T1, CYP4T2, CYP4T5 and CYP4F28, which are yet to be characterized (Uno et al., 2012).

Localizing to the inner membrane of the mitochondria, CYP11A (also known as P450scc, or P450 side-chain cleavage enzyme) catalyses the rate-limiting first step in the biosynthesis of steroids, which is the conversion of cholesterol to pregnenolone. Although CYP11B, also known as P45011beta, is involved in the adrenal cortex's conversion of progesterone to

cortisol, it also localizes to the mitochondrial membrane. Zebrafish CYP11A mRNA expression in ovarian follicles decreases with follicular development (Ings & Van Der Kraak, 2006). Fish CYP11 gene expression is changed by a variety of xenobiotics and steroids. The subsequent 17alpha-hydroxylase and C17,20-lyase processes are controlled by the steroidogenic enzyme CYP17, also referred to as P450c17 (Zuber et al., 1986). The steroid 17α-hydroxylation and 17α,20-lyase reactions are catalyzed by fish and human cytochrome P450 (P450) 17A1. P450 17A2 in fish exclusively catalyzes 17α-hydroxylation. The two enzymes are integral membrane proteins of the microsomal-type P450s, which attach to the membrane via the signal anchor sequence, which is their N-terminal hydrophobic segment (Lei & Egli, 2016).

CYP19, also referred to as P450arom or aromatase, is the final steroidogenic enzyme in the pathway leading to the biosynthesis of estrogen. It catalyzes the conversion of C19 androgen into aromatic C18 estrogen (Simpson et al., 1994). As per Tchoudakova & Callard (1998); Melo & Ramsdell (2001); Goto-Kazeto et al. (2004), CYP19 mRNA is predominantly expressed in the brain, pituitary, and gonads. CYP19A1 (also called CYP19a) and CYP19A2 (also called CYP19b) are two CYP19 genes that encode different isoforms in fish that vary in structure and function. As CYP19 catalyses the last stage of the androgen to estrogen conversion, it contributes to the temperature-dependent determination of sex. According to Fujii et al. (1997) and White et al. (1997), retinoic acid (RA) is metabolized by enzymes of the CYP26 family into its hydroxylated polar derivatives. Zebrafish have produced three CYP26 genes (CYP26A1, CYP26B1, and CYP26C1) that have been isolated (Gu et al., 2005; White et al., 1997; Zhao et al., 2005). Japanese pufferfish have also produced three CYP26 genes (Nelson, 2013).

3.1 Mechanism of Action of CYP

Fish also have CYP enzymes with a conserved structure. In CYP-catalyzed reactions, the reduction of the ferric enzyme to a ferrous state via one electron from cytochrome P450 reductase, which contains Flavin mononucleotide (FMN), Flavin adenine dinucleotide (FAD), and an iron-sulfur center, is the initial and rate-determining step. Oxidation of substrates and oxygen molecules is catalyzed by CYP enzymes' active sites (Schlenk et al. 2008). The terminal oxidase of an electron transfer system found in the microsomal fraction of the cell, the cytochrome P450 haem protein, is in charge of the metabolism of numerous xenobiotics. The reaction's specificity is determined by cytochrome P450, which is the substrate binding component (Andersson et al., 1993). The heme group's iron atom is required for the catalytic process and for binding oxygen, which supports the idea that it serves as a reducing agent (Pompella et al., 2003). Additionally, the heme group's substrate-binding pocket, which regulates enzyme specificity (Williams & Buhler, 1983), further demonstrates the complex organization of this class of molecules. CYP enzymes are also an essential component of endoplasmic reticular microsomes, indicating cisternae-bound sites where metabolic pathways take place. Cytochrome P450 (P450, CYP) enzymes catalyze the majority of chemical oxidations employing pyridine nucleotides as electron donors and typically using mixed-function oxidase stoichiometry.

$$NAD(P)H + O_2 + R \rightarrow NAD(P)^+ + RO + H_2O$$

(where R is a carbon substrate and RO is an oxidized product).

NADPH and molecular oxygen help to reduce Fe (III) within the heme group of an enzyme when an enzyme-substrate complex forms, which starts the catalytic cycle of CYP enzymes. This process produces further reduction and protonation by allowing oxygen to bind, which

results in the formation of a hydroperoxide Fe (III) complex. CYP induction sites are frequently identified and characterized using catalytic activity assays, immunodetection assays, or mRNA quantification techniques (Sarasquete & Segner, 2000).

3.2 Biological Functions

CYP450: Metabolism and Detoxification

Current information indicates that fish health risks can vary based on the type and concentration of medications administered, as well as the specific fish species involved. A lack of knowledge about how these medications are metabolized in aquatic species makes it difficult to assess the risks connected to their presence in water (Burkina et al., 2015). Almost every pharmaceutical compound ends up being discharged into sewage treatment plants (STPs), which are designed to remove such substances and often to the open water sources. However, in reality, many organic compounds persist due to the inefficiency of STPs in completely eliminating them, leading to their accumulation as a distinct class of pollutants in aquatic environments. Aiding in the metabolism of substances that are foreign to the body, such as medications and environmental pollutants, is one of the main roles of CYP enzymes. CYP enzymes facilitate the excretion of these substances from the body by converting them into more water-soluble forms, thereby shielding the organism from potentially harmful effects. The liver, which is where most drug metabolism takes place, is where this detoxification process is especially crucial. Serious health issues could arise from the buildup of toxic substances if CYP enzymes were not active.

The concept of chemical defensome was developed by Goldstone et al. (2007). It was described as a collection of genes from various families working together as a network to help organisms maintain chemical homeostasis and respond to chemical stress. Eide et al. (2021) and Goldstone et al. (2007) have delineated genes associated with oxidative biotransformation, including cytochrome P450s (CYPs), aldehyde dehydrogenases, and flavoprotein monooxygenases. In pollution research, those affecting exogenous compounds have received special attention. In fact, it has been suggested that the CYP family 1 subfamily A (CYP1A) gene and the enzyme it encodes serve as a biomarker for pollution (Lee & Yang, 2008). Thus, the expression patterns of CYP1A have been studied in detail. When tilapia (*Oreochromis mossambicus*) was exposed to coastal sediments, Wong et al. (2001) examined the CYP1A1 expression levels in various tissues. They found that the liver and intestines had higher expression levels than the other tissues. According to Yuan et al. (2013), basal CYP gene expression levels varied between tissues in the rare Chinese minnow fish *Gobiocypris rarus* following exposure to benzo[a]pyrene (BaP). The fish exhibited substantial overexpression of CYP1A, CYP family 1 subfamily B member 1 (CYP1B1), and CYP family 1 subfamily C member 1 (CYP1C1) in the liver, gills, and gut.

The metabolism of endogenous substances, such as steroids, and xenobiotics is largely regulated by members of the CYP2 and CYP3A families in fish (Thibaut et al., 2002). CYP3A68 and CYP2P11 expression peaked throughout the reproductive phase in largemouth bass exposed to dieldrin, with both males and females displaying two-fold higher expression (Barber et al., 2006). Dieldrin feed premix at a dose of 0.8 ppm for 30 days had no discernible impact on CYP expression. Nevertheless, dieldrin exposure for four months caused both sexes to express CYP3A68 and 3A69. The pregnane X receptor (PXR) and the target genes cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (Pgp) can interact negatively with drugs in humans. Fish have these genes as well, but we know little about their purposes. BaP metabolites were found in the bile and CYP1A, UDP-glucuronosyltransferase (UGT), and glutathione S-transferase (GST) enzymatic activity of sunfish and chub that were injected with

BaP at doses of 0, 25, and 50 mg/kg after three days. Following BaP dosing, CYP1A activity considerably increased in both the chub and sunfish groups; however, chub levels were significantly lower than those of the sunfish. In both species group, the UGT activity in the unexposed animals was similar, and the dosage of BaP caused a significant increase in both groups. Lastly, exposure to BaP resulted in a significant increase in GST activity in chubs but not in either species group (Van et al., 2017). In rare minnows, benzo[a]pyrene (BaP)-induced patterns revealed a significant up-regulation of CYP 1A, 1B1, and 1C1 expression in the intestine, gills, and liver. Moreover, BaP treatments significantly increased the induction of CYP 2Y3 in the liver (Yuan et al., 2013). Red mullet (*Mullus barbatus*) and flounder (*Platichthys flesus*) showed a progressive inhibition of their ethoxyresorufin O-deethylase (CYP1A) and BaP hydroxylase (BPH) activities upon increasing concentrations of Tributyltin (TBT). The effects were more prominent for EROD than for BPH (Martínez et al., 2012).

The stickleback fish genes CYP1A, CYP1B1, CYP1C1, and CYP1C2 transcripts were induced by the aryl hydrocarbon receptor (AhR) agonists polychlorinated biphenyl 126 (PCB126), suggesting that the AhR pathway is responsible for their regulation (Gao et al., 2014). In medaka fish (*Oryzias latipes*), triadimefon and myclobutanil both increased hepatic CYP3A activity, but only triadimefon increased CYP1A activity. Triadimefon was found to increase the expression of the genes for cyp3a38, cyp3a40, p53, retinoid acid receptor γ1 (rarγ1), cyp26b, and pregnane x receptor (PXR) compared to myclobutanil (Liao et al., 2014). Fascinatingly, though, recent research suggests that CYP1A induction might also be mediated by processes other than the traditional binding of AhR agonists (Beijer et al., 2013). CYP2X expression increased when goldfish was exposed to environmental pollutions (Wang et al., 2007). Low concentration of 7-benzyloxy-4-trifluoromethyl coumarin (BFC, 0.06 µM or 20 µg/L) were found to significantly induce CYP3A activity in Gulf killifish (*Fundulus grandis*) embryos and zebrafish (*Danio rerio*) larvae in response to exposures to benzo[a]pyrene (BaP) and fluoranthene (FL) in the study by Oziolor et al. (2017). The activity of ethoxyresorrufin-O-deethylase (EROD) was measured in Nile tilapia that had been exposed to benzo[a]pyrene (BaP) and 17β-estradiol (E2). The findings demonstrated that after three days of exposure, EROD activity in the E2-treated group dropped, but by the fifth day, it had returned to normal levels. EROD activity in the BaP-treated group also declined at days three and five of exposure, reaching normal by day ten. All throughout the exposure period, the combined effect of BaP and E2 significantly decreased EROD activity. The study conducted on air-breathing catfish that received 50 mg/kg of β-naphthoflavone (β-NF) intraperitoneally (IP) showed that β-NF treatment increased total CYP450 content and CYP1A-mediated EROD (ethoxyresorufin-O-deethylase) activity significantly (Bhutia & Pal, 2022). It has also been demonstrated that giving fish oil can increase CYP enzyme activity. In a study on grass carp (*Ctenopharyngodon idella*), Shi et al. (2018) provided evidence of this by showing that fish oil increased the expression of CYP2AA in adipose tissue but showed little induction in the liver.

Fish are commonly employed as sentinel species in aquatic monitoring initiatives because of their vulnerability to contaminants and their role as a source of protein at different food web levels (Henczova et al., 2006). Zebrafish (*Danio rerio*), rainbow trout (*Oncorhynchus mykiss*), channel catfish (*Ictalurus punctatus*), Japanese medaka (*Oryzias latipes*), mummichog (*Fundulus heteroclitus*), Atlantic salmon (*Salmo salar*), scup (*Stenotomus chrysops*), and nile tilapia (*Oreochromis niloticus*) are significant species utilized in toxicology research and monitoring initiatives. CYP monooxygenases are important biomarkers for exposure in these investigations because of their ability to respond to a wide range of contaminants, including pesticides, heavy metals, benzo[a]pyrene (BaP), polycyclic aromatic hydrocarbons (PAHs),

polychlorinated biphenyls (PCBs), dioxins, and steroidogenic compounds (Whyte et al., 2000). In certain circumstances, this metabolism can activate reactive intermediates that have harmful and cancer-causing properties, or it can result in detoxification. The transcriptional regulation of fish CYP450 enzyme expression is triggered by xenobiotic sensing receptors, such as nuclear factor-E2 related factor 2 (Nrf2), aryl hydrocarbon receptor (AhR), pregnane-X receptor (PXR), peroxisome proliferator-activated receptor alpha (PPARα), and aryl hydrocarbon receptor (AhR) (Ibabe et al., 2002; Ibabe et al., 2004; Wassmur et al., 2010; Giuliani & Regoli, 2014; Liu et al., 2014). The functions of cytochrome P450 enzymes present in various fishes are given in the Table 1.

Table 1. The Functions of CYP Enzymes Commonly Seen in Fishes

CYP Enzyme	Functions	Reference
CYP1A1	Hydroxylation of pregnenolone	Petkam et al. (2003)
CYP1B	Probable regulator of gas and fluids in gills	Leaver & George (2000)
CYP1C	Probable participation during embryogenesis	Godard et al. (2005)
CYP2K1	Benzphetamine N-demethylase and steroid hydroxylase activities	Wang-Buhler et al. (2005)
CYP2K1 and CYP2K6	Oxidation of lauric acid	Yang et al. (2008)
CYP2M1	Lauric acid hydroxylation activity	Yang et al. (1998)
CYP2P3	Catalyze benzphetamine N-demethylase and arachidonic acid oxidation	Oleksiak et al. (2003)
CYP2N1 and CYP2N2	Metabolize arachidonic acid to epoxyeicosatrienoic acid	Oleksiak et al. (2000)
P4502X1	Catalyzes aminopyrine and benzphetamine demethylase activity	Mosadeghi et al. (2007)
CYP3A27	Catalyzes testosterone and progesterone 6beta-hydroxylation	Lee & Buhler (2003)
CYP3A45	Exhibits testosterone 6beta-hydroxylation activity	Lee & Buhler (2003)
CYP3A38 whereas	Testosterone 6beta- and 16beta-hydroxylase activity,	Kashiwada et al. (2005)
CYP3A40	Catalyzes 2alpha- and 6beta-hydroxylation	Kashiwada et al. (2005)
CYP4T1	Function unknown	Uno et al. (2012)
CYP4T2	Function unknown	Uno et al. (2012)
CYP11A	Conversion of cholesterol to pregnenolone	Kazeto et al. (2006)
CYP11B1	Conversion of 11-deoxycortisol to cortisol	Beijer et al. (2010); Hermansson et al. (2007)
CYP11B2	Conversion of 11-deoxycorticosterone to aldosterone	Beijer et al. (2010); Hermansson et al. (2007)

CYP Enzyme	Functions	Reference
CYP17	Conversion of pregnenolone and progesterone to their 17-alpha-hydroxylated products	Wang & Ge (2004)
CYP19	Aromatization of androgens to oestrogens	Tchoudakova & Callard (1998); Kazeto et al. (2005)
CYP21	Conversion of progesterone to 11-deoxycorticosterone, mineralocorticoid pathway; 17-alpha-hydroxyprogesterone to 11-deoxycortisol, glucocorticoid pathway	Uno et al. (2012)
CYP 26A1	Hydroxylation of retinoic acid	White et al. (1997)
CYP 26B1	Probable participation in metabolism of retinoic	Nelson (2004)
CYP26D1	Probable participation in metabolism of retinoic acid	Gu et al. (2006)
CYP51	14-demethylation of sterol precursors	Uno et al. (2012)

Table 2. Effect of Pharmaceutical Drugs on Various Fish CYP's

Drug	Inhibition	Species	Reference
Diclofenac	Inhibition of CYP2M	Carp	Thibaut et al. (2006)
Ibuprofen	Inhibition of CYP2M	Carp	Thibaut et al. (2006)
Naproxen	Inhibition of CYP2M	Carp	Thibaut et al. (2006)
Ketoprofen	Inhibition of CYP2M	Carp	Thibaut et al. (2006)
Ketoconazole	Increased levels of CYP17 and CYP11A	Fathead minnow	Ankley et al. (2006)
Clofibrate	Inhibition of EROD activity (CYP1a)	Rainbow trout	Laville et al. (2004)
Fenofibrate	Inhibition of EROD activity (CYP1a)	Rainbow trout	Laville et al. (2004)
Gemfibrozil	Inhibition of CYP2M	Carp	Thibaut et al. (2006)
Oxytetracycline	Increase expression of CYP17,19	Hybrid striped bass, channel catfish, nile tilapia	Popovic et al. (2012)
Oxolinic acid	CYP1A inducer	Carp	Ishida. (1992)
Difloxacin	CYP1A inducer	Carp	Fu et al. (2011)
Enrofloxacin	Inhibition of CYP1A	Atlantic tomcod	Williams et al. (1997)
Enrofloxacin	Inhibition of CYP3A	Seabass	Vaccaro et al. (2003)
Enrofloxacin	Inhibition of CYP1A	Carp	Hu et al. (2012)
Flumequine	Inhibition of CYP1A	Rainbow trout	Moutou et al. (1998)
Oxolinic acid	Inhibition of CYP1A	Rainbow trout	Moutou et al. (1998)
Sulfamethoxazole	Inhibition of CYP1A	Three-spined sticklebacks	Beijer et al. (2010)
Berberine	Inhibition of CYP1A, CYP3A	Carp	Zhou et al. (2011)

Drug	Inhibition	Species	Reference
Chloramphenicol	Inhibition of CYP1A	Rainbow trout	Snegaroff et al. (1989)

3.3 Metabolism of Exogenous Drug Compounds

CYP enzymes play a crucial role in the biosynthesis and metabolism of vital endogenous molecules, in addition to their role in detoxification. They have a major role in the synthesis of steroid hormones, such as estrogen, testosterone, and cortisol, which control many physiological functions like metabolism, stress response, and reproduction. In addition, CYP enzymes support the production of bile acids and the metabolism of fatty acids, both of which are essential for proper digestion and nutrient absorption. Therefore, CYP450 activity plays a critical role in determining an organism's capacity for detoxification. Since CYP enzymes are in control of the metabolism of a sizable fraction of pharmaceutical drugs, they play a crucial role in pharmacology. Individual differences in CYP enzyme activity can have a major impact on the safety and effectiveness of medications. Comprehending CYP enzymes facilitates improved drug formulation, dosage, and potential interaction prediction.

Fish undergo biotransformations when they are exposed to harmful substances. The process of biotransformation has two stages. In order to facilitate the Phase II reaction, Phase I reactions typically add one or more functional polar groups (-OH, -NH_2, -SH, or -COOH) to a foreign molecule. The oxidation reactions in phase I include those involving the CYP450 family of drug-metabolizing enzymes, flavin-containing monooxygenases (FMOs), monoamine oxidases, alcohol and aldehyde dehydrogenases, peroxidases, and aldehyde oxidase, reduction reactions involving DT diaphorase, azo- and nitroreductases, etc., and hydrolysis reactions involving epoxide hydrolase, carboxylesterases, and others. The CYP450 group of enzymes and other enzymes connected to the smooth endoplasmic reticulum (oxygenases, reduced oxygen-scavenging enzymes, hydrolytic enzymes, and others) catalyze phase I. The Phase I reactions' metabolites can be easily eliminated at this stage if they are sufficiently soluble in water. The Phase II products are generally free of pharmacological activity and organism toxicity, and they are easily excretable and water soluble. Biochemical conjugation, which attaches small chemical moieties like glucuronic acid, sulphate, glycine, and other amino acids to biological activity, is a common step in phase II detoxification. Glutathione (GSH) conjugation, on the other hand, shields the body from chemically reactive compounds or metabolites. While glutathione (GSH) conjugation shields the body from chemically reactive substances or metabolites, phase II pathways like methylation and acetylation stop or reduce biological activity. Various drug classes may have an impact on fish health at relatively low concentrations and through relatively specific modes of action. Fish livers are the primary sites of xenobiotic metabolism and CYP450 expression. The kidney is the second organ that is crucial for the metabolism of xenobiotics (Hahn & Stegeman, 1994). Furthermore, according to Bartram et al. (2012), the gills are the organs of first-pass metabolism, where receptor-mediated processes through the CYP450 system occur. Many other tissues also express CYP450. CYP1A was discovered in the brains of teleost fish, *Sparus aurata*, and seabream (Ortiz-Delgado et al., 2002). But the gut, bile, and blood plasma are also crucial locations for xenobiotic metabolism. Sensitive biomarker of exposure to organic contaminants, CYP1A mRNA expression is induced by trace amounts of various aromatic compounds.

The physico-chemical characteristics (particularly, Kow of the aquatic environment, removal rates in the STPs, stream/river dilution factors, and other factors, all affect the concentrations of pharmaceutically active compounds. The fate of pharmaceuticals in watery settings is a worrying matter. Pharmacies are predominantly metabolized by cytochrome P450

enzymes (CYP450) in fish and mammals. Research by Beijer et al. (2013) found that the wastewater from about 90 bulk drug manufacturers is treated at a factory near Hyderabad, India, and contains extremely high amounts of pharmaceuticals. Hermansson et al. (2007) and Beijer et al. (2010) demonstrated that, in the three-spined stickleback (*Gasterosteus aculeatus*), wastewater exposure at concentrations of 0.8%, 1.6%, and 3.2% significantly induced mRNA expression of CYP1B1 and CYP1C1 in the gills, while having minimal or no effect on these genes in the liver and brain. They also showed that ketoconazole, an antifungal medication known to inhibit CYP17 (androgen synthesis) and CYP11B1 (glucocorticoid synthesis) in mammals and CYP51 in fungi, serves as a potent inhibitor of gill EROD activity in this species.The administration of ketoconazole, nonylphenol, and their combination in an in vitro study on Atlantic cod produced a 60% increase in CYP1A-mediated ethoxyresorrufin-O-deethylase (EROD) activity for ketoconazole, and a 40% reduction in CYP1A activity for nonylphenol. When nonylphenol and ketoconazole were exposed together, CYP1A protein levels increased by 93% and CYP1A activities were induced by 70%. On the other hand, using ketoconazole and nonylphenol alone decreased the CYP3A-mediated benzyloxy-4-[trifluoromethyl]-coumarin-O-debenzyloxylase (BFCOD) activity by 54% and 35%, respectively. The combined administration of nonylphenol and ketoconazole led to a 98% reduction in CYP3A activity (Hasselberg et al., 2005).

The combination of ethinylestradiol exposure with the broad-spectrum CYP inhibitor ketoconazole enhanced the sensitivity of juvenile rainbow trout to ethinylestradiol exposure. The inhibition of CYP1A and CYP3A enzyme activities in rainbow trout liver was the cause of this drug interaction (Wassmur., 2012). By assessing the mRNA expression of GST, P-glycoprotein (P-gp), cytochrome P450 1A (CYP1A), and cytochrome P450 3A (CYP3A), along with their corresponding enzyme activities, the sub-chronic toxic effects of norfloxacin (NOR) in swordtail fish (*Xiphophorus helleri*) were investigated. The results indicated that NOR significantly affected the expression of GST, CYP1A, and P-gp genes in swordtail fish (Liang et al., 2015). The interactions of fibrates (clofibrate, fenofibrate, bezafibrate, gemfibrozil), anti-inflammatory medications (ibuprofen, diclofenac, naproxen, ketoprofen), and antidepressants (fluoxetine, fluvoxamine, paroxetine) with CYP-catalyzed pathways (CYP1A, CYP3A-like, CYP2K-like, and CYP2M-like) and Phase II activities (UDP-glucuronosyltransferases and sulfotransferases) were examined in a study conducted on carps by Thibaut et al. (2006). In fish, these enzymes are involved in endogenous and xenobiotic metabolism. The study was conducted in vitro by incubating carp liver subcellular fractions with the substrate and the selected drugs. Antidepressants were found to be potent inhibitors of CYP2M-like activity (32−74% inhibition), while anti-inflammatory drugs were strong inhibitors of CYP1A (92−94%), CYP3A-like (69−80% inhibition), and CYP2K-like (36−69% inhibition) catalyzed activities. Corcoran et al. (2012) studied the effects of exposing carp (*Cyprinus carpio*) primary hepatocytes to the human Pregnane X Receptor (PXR) agonist rifampicin (RIF) on target gene expression related to phase I (cyp2k, cyp3a) and phase II (gstα, gstπ) drug metabolism as well as drug transporters mdr1 and mrp2. All target genes measured showed increased expression in response to RIF, and responses of cyp2k and cyp3a were inhibited by the PXR antagonist ketoconazole. Exposure to erythromycin both acutely and chronically resulted in marked increases in *O. mykiss* liver EROD (7-ethoxyresorufin O-deethylase) activity; after a prolonged period of exposure, gill GST (glutathione S-transferases) activity was also increased. After the prolonged exposure, there was a marked decrease in UGT (uridine-diphosphate-glucuronosyltransferases) branchial activity. According to Rodrigues et al. (2019), EROD, GST, and UGT enzymatic forms appear to be involved in the biotransformation of erythromycin. In

comparison to the control, the synthetic pyrethroid cypermethrin significantly enhanced the activity of CYP1A, CYP2B, and CYP2E1 enzymes and inhibited the activity of CYP3A4 enzymes. *Heteropneustes fossilis* (Bloch) groups showed a notable induction of total CYP450 content in response to both intraperitoneal (IP) and oral treatments (Bhutia et al., 2013). In order to investigate the effects of imidazole and triazole fungicides on cytochrome P4501A (CYP1A) and cytochrome P4503A (CYP3A) expression, the fungicides were given to adult killifish and juvenile rainbow trout. These compounds have been found in the aquatic environment and have been demonstrated to bioaccumulate in fish. Rainbow trout showed only a small variation in CYP1A, indicating that imidazole inhibits CYP1A activity (Hegelund et al., 2004). The effect of pharmaceutical drugs on various fishes are given in Table 2.

3.4 Metabolism of Endogenous Compounds

Glucocorticoids, estrogens, progestogens, androgens, and neurosteroids are the six main classes of steroid hormones. The three main sterols that contribute to estrogenic activity in the aquatic environment are synthetic 17αethynilestradiol (EE2), natural estrone (E1), and natural 17β-estradiol (E2). Estrogenic compounds are known to cause a variety of reactions, including decreased sex steroid circulation, decreased gonad size and fecundity, marked changes in the reproductive system, and intersex characteristics (Parrott & Blunt, 2005; Saaristo et al., 2010; Vosges et al., 2012). The gonadosomatic index, gonad histology, protein levels (i.e., zona radiata proteins), vitellogenin, plasma steroid hormones, CYP450 activity, and other endpoints were measured in order to determine these effects (Teng et al., 2018). Enzyme activities such as CYP450 are influenced by compounds that have the imidazole ring system. The class of antifungals known as demethylation inhibitors includes miconazole, ketoconazole, clotrimazole, and others, which work by inhibiting the enzyme lanosterol 14α-demethylase, disrupting the synthesis of ergosterol, an essential component of fungal cell membranes. By either activating or inhibiting CYP450, these chemicals affect aquatic organisms' endocrine systems, resulting in a cascade of molecular and cellular processes (Burkina, 2015). It has been suggested that the NSAIDs mefenamic acid and ibuprofen have endocrine disruptive qualities since they increased 17βestradiol, testosterone, and CYP19A gene transcription in zebrafish (Ji et al., 2013). Initial steps in the detoxification process include the transcriptional activation of individual CYP450 genes in the liver. This in turn causes an increase in enzyme activity and protein synthesis frequently, though not always. AhR (through which agonists cause altered gene expression and toxicity) regulates the expression of CYP1A (Bradshaw et al., 2002). PXR is primarily linked to CYP3A expression (Wassmur et al., 2010). Nevertheless, Kubota et al. (2014) proposed that PXR and AhR regulate the zebrafish CYP1, CYP2, and CYP3 genes. Pharmacological-induced alterations in PPAR expression are expected to impact xenobiotic metabolism, as PPARs, particularly PPARα, may regulate the expression of Phase II enzymes and some CYP450 isoforms in humans (Cizkova et al., 2012). Pharmaceuticals in aquatic environments may have direct effects on enzymatic reactions in addition to their effects on nuclear receptors. Substances that prevent substrates from attaching to CYP450 isoforms may have unfavorable or dangerous consequences. Aquatic environments that are contaminated expose the fish CYP450 system to a variety of pollutants. Thus, CYP450 activity, whether induced or insufficient, may interfere with detoxification processes. A number of variables, including age, sex, type of feed, and fish species, can influence the catalytic activity of CYP450-mediated reactions and lead to discrepancies in the findings of various studies. Other pathways may play a major role in the metabolism of at least some pharmaceuticals, even though the CYP450 system is the primary pathway for xenobiotic metabolism in fish. Changes in these enzymes' activities are used in aquatic toxicology as early

warning indicators of xenobiotic toxicity. CYP450 genes did not, however, react to every contaminant. CYP450-mediated reactions were not impacted by verapamil exposure in a study done with rainbow trout (Burkina et al., 2012). Two of the eleven CYP450-mediated reactions that measured in another study (Smith & Wilson, 2010) showed responses to exposure of fish to the glucocorticoid drug dexamethasone.

To the best of our knowledge, however, the expression patterns of the endogenous and exogenous CYP family categories in various tissues have not been investigated. In a biomonitoring program, they might be crucial for comprehending how an organism has adapted to pollution. The Mediterranean-style Maipo River Basin in Central Chile is one instance of freshwater pollution. Due to the large population, nearly 40% of all Chileans, living in this basin, pollution from domestic and agricultural activities has primarily affected this catchment (Instituto Nacional de Estadística (INE), 2017). Cortés-Miranda et al. (2024) found that only a small portion of the seven CYP genes found in both the liver and the gills displayed differential expression, with those associated with endogenous compounds exhibiting different expression in the liver and those associated with exogenous compounds exhibiting different expression in the gills. The majority of CYP genes were not dysregulated in the study, but those that were were primarily downregulated at polluted sites.

A popular biomarker for identifying environmental estrogens and fish reproductive disruption is vitellogenin (VTG). Using mummichogs (*Fundulus heteroclitus*) from two reference locations and a creosote-contaminated site in lower Chesapeake Bay, USA, Mirabilio et al. (2001) examined the expression of plasma VTG. Reference fish exposed to the sediment contaminated with creosote after seven days showed significant mortality (roughly 25%), but no VTG expression was seen. Other than an increase in HSI and the induction of the biotransformation enzyme cytochrome P4501A (CYP1A), no other indices changed. This implies that, unlike what VTG indicates, there was no direct disruption of reproduction in the physiological reaction to the contaminant.

CYP enzymes are often employed as biomarkers for determining fish exposure to environmental contaminants because of their function in xenobiotic metabolism. Particularly, the induction of CYP1A is a recognized marker of exposure to dioxin-like compounds and PAHs. Increased CYP1A activity is a useful tool for environmental monitoring because it has been linked to higher pollutant levels in a variety of aquatic environments. CYP enzymes are used in ecotoxicology and are being researched as possible fish health biomarkers in aquaculture. Fish health can be managed in aquaculture operations by monitoring the expression levels of particular CYP enzymes, which can serve as useful indicators of fish health and stress tolerance. Many fish diseases have been linked to changes in CYP enzyme activity. Normal metabolic processes can be disrupted by modulating the expression of CYP enzymes, which can be caused by infections, inflammatory conditions, and exposure to toxins. For instance, alterations in CYP enzyme activity are frequently observed in fish with liver diseases such as steatosis or hepatocellular carcinoma, which is indicative of the liver's compromised ability to metabolize both endogenous and exogenous substances. CYP enzymes can also affect the immune response in fish. According to some research, specific CYP enzymes may be involved in immune system modulation through the metabolism of immunomodulatory substances or the production of reactive metabolites that have an impact on immune cells. Comprehending these interplays is essential for formulating tactics to augment fish resistance against illness, specifically in aquaculture environments.

CONCLUSION

CYP enzymes are biomarkers that offer important information about the environmental and health conditions of fish populations. Water quality parameters play a critical role in fish health, as pollutants can weaken fish immunity and increase susceptibility to diseases. Furthermore, sometimes the metabolic byproducts generated by cytochrome P450 (CYP) enzymes may pose more significant threats to fish health than the xenobiotics typically found in their environment. This highlights the importance of maintaining optimal water quality and understanding the biochemical processes involved in fish metabolism to safeguard aquatic ecosystems and the health of fish populations. As such, they are useful tools for managing aquaculture and ecological assessment. To improve aquaculture and environmental conservation methods as well as our knowledge of fish health, more research into the regulation, roles, and consequences of CYP enzymes is needed.

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