Role of Cytochrome P450 in Xenobiotic Metabolism in Fishes (Review)

Saima Andleeb, Muddasir Sharief Banday, Sumaira Rashid, Irfan Ahmad, Mehak Hafeez, Oyas Asimi, Mohd Ashraf Rather, Sajad H. Baba, Azra Shah, Nakeer Razak, Anees Fatima, and Ishraq Hussain

Abbreviations

ATR	Atrazine
CPF	Chlorpyrifos
CYP	Cytochrome P450
FAD	Flavin adenine dinucleotide reductase

S. Andleeb · S. Rashid · M. Hafeez · A. Shah · N. Razak
Division of Fish Genetics and Biotechnology, Faculty of Fisheries, Sher-e-Kashmir University of Agricultural Sciences and Technology, Kashmir, Rangil, Ganderbal, Jammu and Kashmir, India

M. S. Banday
Department of Clinical Pharmacology, Sher-e-Kashmir Institute of Medical Sciences, Soura, Srinagar, Jammu and Kashmir, India

I. Ahmad (✉) · M. A. Rather
Division of Fish Genetics and Biotechnology, Sher-e-Kashmir University of Agricultural Sciences and Technology, Kashmir, Rangil, Ganderbal, Jammu and Kashmir, India
e-mail: ahmadirfan@skuastkashmir.ac.in

O. Asimi
Division of Fish Nutrition and Biochemistry, Faculty of Fisheries, Sher-e-Kashmir University of Agricultural Sciences and Technology, Kashmir, Rangil, Ganderbal, Jammu and Kashmir, India

S. H. Baba
Division of Agri Economics and Hotibusiness Management, Sher-e-Kashmir University of Agricultural Sciences and Technology, Kashmir, Shalimar, Jammu and Kashmir, India

A. Fatima
Department of Botany, Govt College for Women, Cluster University-Kashmir, Srinagar, Jammu and Kashmir, India

I. Hussain
Division of Vety Biochemistry, FVSc & AH, Sher-e-Kashmir University of Agricultural Sciences and Technology, Kashmir, Shuhama, Jammu and Kashmir, India

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FMN	Flavin mononucleotide
NADH	Nicotinamide adenine dinucleotide
NADPH	Nicotinamide adenine dinucleotide phosphate

1 Introduction

Due to human interventions, huge loads of pollutants enter into aquatic environment through various sources like dumping and disposal, increased industrialization, and direct discharge. Various studies on cytochrome P450 (CYP) have revealed its use as a biomarker for aquatic contamination (Lee et al. 2005). Molecular biomarkers such as CYP have been shown to be very useful for the detection of fatal disturbances in fish (Bucheli and Fent 1995). They respond to a wide variety of xenobiotics and therefore detect the presence of both known and unknown pollutants relevant for organisms (Lemaire et al. 2010). CYP enzymes help in the transformation of environmental contaminants like harmful drugs and carcinogens and in the disintegration of endogenous substrates like prostanoids, steroids, vitamins, and fatty acids (Havelkova et al. 2007).

Cytochrome P450 was first explained by Klingenberg in 1948, and since then, this enzyme system has been studied intensively. In fishes, the first CYP gene was first isolated from rainbow trout followed by some other fishes in the late 1980s (Stegeman 1989; Winston et al. 1988; Uno et al. 2012). Cytochromes are generally most prevalent in the endoplasmic reticulum or mitochondria of the liver which accounts for 1 to 2% mass of hepatocytes (Kilemade et al. 2009). However, cytochromes are also present in other organs like the olfactory system, heart, gonads, kidney, gills, brain, alimentary canal, and placenta (Arukwe 2002; Arellano et al. 2009; Siroka and Dratichova 2004). Cytochrome was discovered as a pigment with maximum absorption at 450 nm, thus got its name as cytochrome P450; however, the inactive form of CYP has maximum absorption at 420 nm, same as other hemoproteins (Schenkman and Jansson 1998).

Based on the transfer of NADPH electrons to the catalytic site, P450 enzymes are classified into four classes (Table 1) (Werck-Reichhart and Feyereisen 2000).

The cytochrome P450 Standardized Nomenclature Committee suggested categorization based on the degree of similarity between amino acid sequences and has classified P450 genes as isoforms, families, and subfamilies (Nelson 1999). A CYP gene is granted in a subfamily when the homology percentage is greater than 55% and in a family when it is greater than 40% (Nelson 1999). But this type of classification has been argued due to the new sequences that are being described. At the VII P450 International Symposium, a different classification based on biological P450 functions was recommended (Kelly et al. 2006). So far, 18 CYP families are identified in fishes, viz., CYP1, CYP2, CYP3, CYP4, CYP5, CYP7, CYP8, CYP11, CYP17, CYP19, CYP20, CYP21, CYP24, CYP26, CYP27, CYP39,

Table 1 Classification of CYP

Class I	Flavin adenine dinucleotide reductase (FAD) and ferric redoxin sulfur are required Commonly found in eukaryotes Helps in detoxification
Class II	Need flavin mononucleotide (FMN) Commonly found in eukaryotes Helps in detoxification
Class III	There is no requirement for any electron donors
Class IV	Accepts electrons from NADPH (nicotinamide adenine dinucleotide phosphate)

CYP46, and CYP51, out of which only 8 families are studied in detail, i.e., CYP1, CYP2, CYP3, CYP4, CYP11, CYP17, CYP19, and CYP26.

The main functions of different CYP families along with the respective species in which they are found are summarized in Table 2.

CYP has been identified from fresh, marine, and brackish-water fish. Some freshwater fish include Atlantic salmon, rainbow trout, catfish, zebrafish, carp, Chinook salmon, crucian carp, pufferfish, rohu, catla, mrigal carp, medaka, Japanese medaka, common whitefish, toad fish, tilapia, killifish, stripey sea perch, winter flounder, mummichog, fathead minnow, bluegill, blue gourami, and guppy. Some marine water fish include Atlantic croaker, mangrove killifish, European sea bass, marine flatfish, southern stingray, and dogfish shark, while Japanese pufferfish and rita are some examples of brackish-water fish.

All CYP families are found in the liver of respective fish species except CYP11. The sites of induction of different CYP families and subfamilies are summarized in Table 3.

NADPH (nicotinamide adenine dinucleotide phosphate)-cytochrome P450 reductase and the phospholipid membrane fraction are the two key factors influencing CYP activity. The general monooxygenase reaction mediated by CYP manifests as:

$$RH + O_2 + NADPH + H^+ \xrightarrow{\text{Cytochrome P450}} ROH + H_2O + NADP^+$$

In the above monooxygenase reaction, due to the insertion of an oxygen atom, one molecule becomes more polar than the other. In actual, the entire reaction is much more complicated because the cytochrome may utilize oxygen from peroxides in addition to molecular oxygen and NADH may also supply electrons (Shalan et al. 2018).

As depicted in the above reaction, NADPH reductase and membrane phospholipids are also required. The function of NADPH reductase is to transfer electrons on cytochrome P450 with the help of FAD (flavin adenine dinucleotide) and FMN (flavin mononucleotide) prosthetic groups. The detailed schematic representation of this reaction is illustrated in Fig. 1.

Table 2 Functions of CYP families in the respective fish species

Family	Functions	Species	References
CYP 1	Hydroxylation of pregnenolone, metabolism of xenobiotics, probable regulator of gas and fluids in gills Helps in embryogenesis, detoxification, and excretion	Atlantic salmon (*Salmo salar*), Atlantic croaker (*Micropogonias undulatus*), Japanese pufferfish (*Takifugu rubripes*), rainbow trout (*Oncorhynchus mykiss*), catfish (*Ancistrus multispinis*), zebrafish (*Danio rerio*), carp (*Cyprinus carpio*), pufferfish (*Takifugu obscures*), Chinook salmon (*Oncorhynchus tshawytscha*), Rita (*Rita rita*), crucian carp (hybridized *Prussian* carp), mangrove killifish (*Rivulus marmoratus*), European sea bass (*Dicentrarchus labrax*)	Lee et al. (2005), Klemz et al. (2010), Tuan et al. (2014), Rahman and Thomas (2012), Sakamoto et al. (2003), Zanette et al. (2009), Meyer et al. (2002), Brammell et al. (2010), Jung et al. (2011), Stien et al. (1998), Arukwe (2002) and Kim et al. (2004, 2008)
CYP 2	Metabolism of nitrosodialkylamines Metabolism of xenobiotic Hydroxylation of lauric acid Epoxylation of arachidonic acid	Rainbow trout (*Oncorhynchus mykiss*), Japanese pufferfish (*Takifugu rubripes*), striped sea perch (*Lutjanus carponotatus*), threadfin butterfly (*Chaetodon auriga*), atoll butterfly (*Chaetodon mertensii*), zebrafish (*Danio rerio*), graysby sea bass (*Cephalopholis cruentata*), tomtate grunt (*Haemulon aurolineatum*), channel catfish (*Ictalurus punctatus*), rohu (*Labeo rohita*), *Catla catla*, mrigal carp (*Cirrhinus mrigala*)	Ruus et al. (2002), Kaplan et al. (1999), Yang et al. (2000), Wang-Buhler et al. (2005), Haasch (2002), Oleksiak et al. (2000, 2003), Schlenk et al. (2002), Buhler et al. (1994) and Yang et al. (1998)
CYP 3	Metabolism of xenobiotics Hydroxylation of testosterone	Japanese pufferfish (*Takifugu rubripes*), toad fish (*Opsanus tau*), zebrafish (*Danio rerio*), rohu (*Labeo rohita*), *Catla catla*, mrigal carp (*Cirrhinus mrigala*), rainbow trout (*Oncorhynchus mykiss*), European sea bass (*Dicentrarchus labrax*), medaka (*Oryzias latipes*),	Lee et al. (2001), Lee and Buhler (2003), Nelson (2003), Barber et al. (2007), Christen et al. (2010), Kullman and Hinton (2001) and Kashiwada et al. (2005)

(continued)

Table 2 (continued)

Family	Functions	Species	References
		fathead minnow (*Pimephales promelas*)	
CYP 4	Metabolism of free fatty acids Hydroxylation of lauric acid	Toad fish (*Opsanus tau*), zebrafish (*Danio rerio*), rare minnow (*Gobiocypris rarus*) Rainbow trout (*Oncorhynchus mykiss*) Japanese pufferfish (*Takifugu rubripes*) European sea bass (*Dicentrarchus labrax*) Bluegill (*Lepomis macrochirus*)	Simpson (1997), Ibabe et al. (2002) and Falckh et al. (1997)
CYP 5	Biosynthesis of thromboxane	Japanese pufferfish (*Takifugu rubripes*) Zebrafish (*Danio rerio*)	Arellano et al. (2009), Siroka and Dratichova (2004) and Uno et al. (2012)
CYP 7	Steroid metabolism	Japanese pufferfish (*Takifugu rubripes*) Zebrafish (*Danio rerio*)	Arellano et al. (2009), Siroka and Dratichova (2004) and Uno et al. (2012)
CYP 8	Biosynthesis of prostacycline	Japanese pufferfish (*Takifugu rubripes*) Zebrafish (*Danio rerio*)	Arellano et al. (2009), Siroka and Dratichova (2004) and Uno et al. (2012)
CYP 11	Steroid biosynthesis and cholesterol hydroxylation	Rainbow trout (*Oncorhynchus mykiss*), Japanese eel (*Anguilla japonica*), European sea bass (*Dicentrarchus labrax*), Nile tilapia (*Oreochromis niloticus*), Japanese pufferfish (*Takifugu rubripes*), zebrafish (*Danio rerio*), southern stingray (*Dasyatis americana*), Black porgy fish (*Acanthopagrus schlegelii*), Atlantic salmon (*Salmo salar*), Medaka (*Oryzias latipes*)	Nunez and Trant (1997), Hsu et al. (2002), Nelson (2003) and Socorro et al. (2007)
CYP 17	Steroid biosynthesis Hydroxylation of pregnenolone, progesterone, and corticosteroids	Rainbow trout (*Oncorhynchus mykiss*), Japanese pufferfish (*Takifugu rubripes*), zebrafish (*Danio rerio*), fathead minnow (*Pimephales promelas*)	Filby et al. (2007), Wang and Ge (2004), Wang-Buhler et al. (2005) and Yu et al. (2003)

(continued)

Table 2 (continued)

Family	Functions	Species	References
		Dogfish shark (*Squalus acanthias*), European perch (*Perca fluviatilis*)	
CYP 19	Steroid biosynthesis Aromatization of androgens and testosterone	Rare minnow (*Gobiocypris rar*us), rainbow trout (*Oncorhynchus mykiss*), carp (*Cyprinus carpio*), channel catfish (*Ictalurus punctatus*), zebrafish (*Danio rerio*), catfish (*Clarias gariepinus*), Nile tilapia (*Oreochromis niloticus*), guppy (*Poecilia reticulate*), rice field eel (*Monopterus albus*)	Simpson et al. (1994), Chang et al. (1997) and Barney et al. (2008)
CYP 20	Unknown	Zebrafish (*Danio rerio*), Japanese pufferfish (*Takifugu rubripes*)	Arellano et al. (2009), Siroka and Dratichova (2004) and Uno et al. (2012)
CYP 21	Steroid biosynthesis	Zebrafish (*Danio rerio*), Japanese pufferfish (*Takifugu rubripes*)	Arellano et al. (2009), Siroka and Dratichova (2004) and Uno et al. (2012)
CYP 24	Vitamin D metabolism	Zebrafish (*Danio rerio*), Japanese pufferfish (*Takifugu rubripes*)	Arellano et al. (2009), Siroka and Dratichova (2004) and Uno et al. (2012)
CYP 26	Retinoid metabolism Hydroxylation of retinoic acid	Japanese pufferfish (*Takifugu rubripes*), zebrafish (*Danio rerio*)	Gu et al. (2005), Zhao et al. (2005), Nelson (2003) and Kudoh et al. (2002)
CYP 27	Bile acid biosynthesis	Zebrafish (*Danio rerio*), Japanese pufferfish (*Takifugu rubripes*)	Arellano et al. (2009), Siroka and Dratichova (2004) and Uno et al. (2012)
CYP 39	Steroid biosynthesis	Zebrafish (*Danio rerio*)	Arellano et al. (2009), Siroka and Dratichova (2004) and Uno et al. (2012)
CYP 46	Steroid biosynthesis	Zebrafish (*Danio rerio*), Japanese pufferfish (*Takifugu rubripes*)	Arellano et al. (2009), Siroka and Dratichova (2004) and Uno et al. (2012)
CYP 51	Fungal isoforms	Zebrafish (*Danio rerio*), Japanese pufferfish (*Takifugu rubripes*)	Arellano et al. (2009), Siroka and Dratichova (2004) and Uno et al. (2012)

Table 3 Induction sites of cytochrome P450 enzymes in fish

CYP family	Subfamily	Liver	Kidney	Gills	Brain	Heart	Gut	Ovaries	Testis	Blood
CYP 1	1A1	I	I	I		I	I+	I		
	1B1	I	I	I+			I			I
	1B2	I		I+			I			
	1C1	I+	I	I		I				
	1C2	I	I	I						
CYP2	2E1	I								
	2 K1	I	I+		I		I			I
	2 K6	I						I		
	2 M1	I+	I		I		I			I
	2 N1	I	ND	ND	I	I	I	ND	ND	
	2 N2	I	I	I	I	I	I			
	2P1	I	ND	ND		ND	I	ND	ND	
	2P2	I					I			
	2P3	I					I			
	2X	I								
CYP3	3A27	I			I		I+			I
	3A38	I								
	3A40	I								
	3A45	I					I+			
	3A56	I+	I	I	I		I+	I		
	3A30	I+	I	I	I		I+	I		
	3A65	I		I	I	I	I			
	3C1	I				I	I	I		
CYP4	4 T1	I								
CYP11	11A1		I					I	I	

(continued)

Table 3 (continued)

CYP family	Subfamily	Liver	Kidney	Gills	Brain	Heart	Gut	Ovaries	Testis	Blood
CYP17	17A1							I	I+	
	17A2							I	I	
	17B							I	I	
	17C	I	I	I	I		I	I	I+	
CYP19	19A1	I			I			I		
	19A2	I			I			ND		
CYP26	26A1									
	26B1	I			I					
	26D1	I			I					

ND nondetected, *I* induction, *I+* high induction

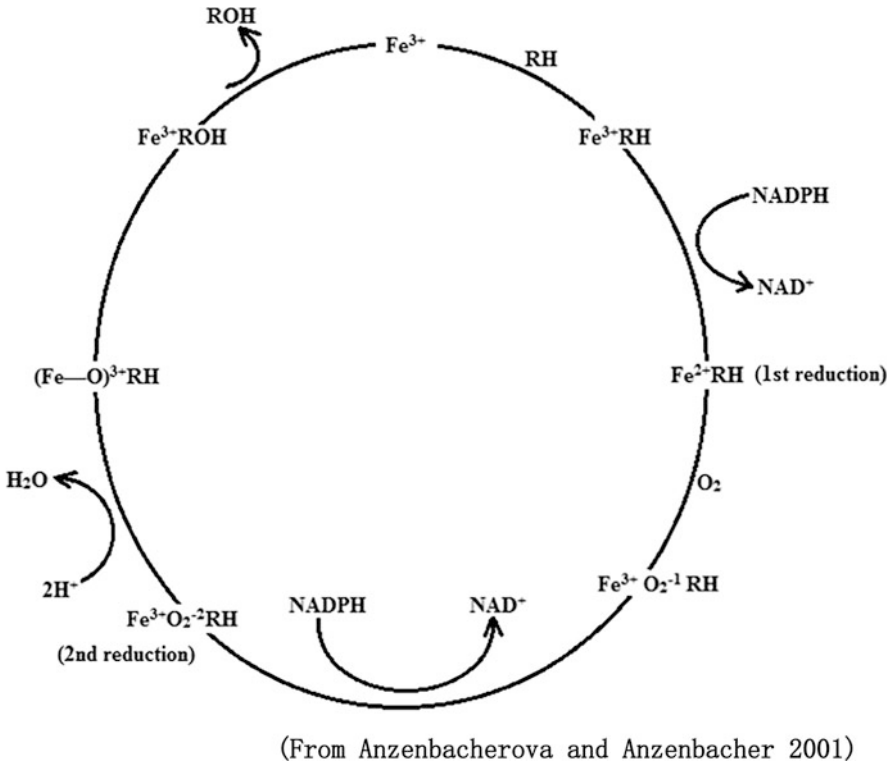

Fig. 1 Metabolic pathway of cytochrome P450. (*Fe* iron atom in P450 heme, *RH* substrate, *ROH* oxidized product)

2 Cytochrome P450 Metabolism

Cytochrome P450 (CYP 450) is recognized to perform a substantial role in the oxidative metabolism/biotransformation of an enormous arraying together the endogenous and exogenous compounds and is thought to be one of the most significant phase I biotransformation enzymes (Siroka and Dratichova 2004). CYP1 to CYP3 are regarded as the most important families of CYP that are accountable for the xenobiotic metabolism and to lesser extent CYP4, while cytochrome P450 enzymes metabolize endogenous substrates (Ioannides and Lewis 2004). Quantifiable reactions to an organism being exposed to xenobiotics are known as biochemical markers. They can react to a set of either similar or extremely diverse xenobiotics because they react to the mechanism of toxic activity rather than the presence of a specific xenobiotic. Biochemical indicators indicate the type of toxicity; for some of them, the strength of the reaction is correlated with the pollution level (Siroka and Dratichova 2004).

P450 enzymes are found mostly in the endoplasmic reticulum of hepatocytes, but their production can also be triggered in organs such as the lungs, colon, kidney, heart, skin, gonads, brain, and placental tissue (Van der Oost et al. 2003). During phase I metabolism, these enzymes regulate oxidation, reduction, and hydrolysis processes, and their function is to biosynthesize substances such as steroids, fatty acids, and prostaglandins (Groves 2005). In fish, CYP1A subfamily plays a significant role in the metabolism and activation of carcinogenesis and is used as a biomarker to estimate contamination of the aquatic environment (Brammell et al. 2010; Jung et al. 2011). Various authors (Rabergh et al. 2000; Morrison et al. 1998; Arukwe 2002; Kim et al. 2004, 2008; Fu et al. 2011) isolated cDNAs encoding CYP1A enzymes from several fish species [rainbow trout (*Oncorhynchus mykiss*), mummichog (*Fundulus heteroclitus*), Atlantic salmon (*Salmo salar*), medaka (*Oryzias latipes*), yellow catfish (*Pelteobagrus fulvidraco*), yellow catfish (*Pelteobagrus fulvidraco*)], respectively, and also from hermaphroditic fish, mangrove killifish (*Rivulus marmoratus*) (Lee et al. 2005). 7-ethoxyresorufin, estradiol, and benzopyrene are all metabolized by CYP1A expressed from zebrafish (*Danio rerio*) cDNA (Scornaienchi et al. 2010). *E. coli* transformed with CYP1A9 cDNA from Japanese eel (*Anguilla japonica*) bioconverts estradiol and flavanone (Uno et al. 2008). Each isoform is involved in the metabolism of a wide variety of substances, and many cytochrome isoforms can metabolize the same substrate. But nearly every isoform has a unique substrate that may be utilized to recognize it (Lewis 2001). However, P450 isoforms are highly substrate-specific in bacterial and mitochondrial cytochrome (Lewis 2001).

3 Effects of Environmental Pollutants on Cytochrome P450 (CYP1A)

Fish CYP1A is induced by a variety of environmental pollutants, and CYP1A has been recognized as a biomarker for the assessment of aquatic pollution. Furthermore, induction of CYP1A has been associated with detrimental outcomes in exposed fish, such as embryonic death and programmed cell death (apoptosis) (Dong et al. 2002). As a result, pharmaceutical substance interactions with the CYP1A enzyme are considered to be toxicologically substantial in fish. By measuring CYP1A mRNA levels, it is possible to track the transcriptional response to the CYP1A induction response caused by pollutants (Rees and Li 2004). There is limited documentation on the toxicity of ATR (atrazine) and CPF (chlorpyrifos) in freshwater fish. It is unclear how CYP1A affects the biotransformation of CPF (chlorpyrifos) and ATR (atrazine) in fish. According to Chang et al. (2005), common carp exposure to 7-ppb ATR (atrazine) could induce CYP1A1 mRNA level after 4 days. According to Xing et al. (2014), CYP1A, which is essential for fish liver antidotal function, was induced in the mRNA expression patterns and EROD activity in carp liver by ATR, CPF, and ATR/CPF combination. Salaberria et al. (2009) revealed a dose-dependent rise in

vitellogenin (Vtg) as well as a decrease in CYP1A. Additionally, CYP1A varied in a hormetic manner with testosterone (T) concentrations and was negatively correlated with liver CAT (catalase activity) and 17 beta-estradiol (E2). These results showed the potential for ATR to alter hepatic metabolism, produce estrogenic effects, and induce oxidative stress in vivo, as well as the relationship between these effects. In a previous investigation, a significant alteration in glutathione S-transferase and antioxidant enzymes was found in the liver of the same carp (Xing et al. 2012a, b). These studies (CYP1A, glutathione S-transferase, and antioxidant enzymes) revealed that ATR and CPF, both alone and together, affect the liver of carp. Liver microsomal EROD activity is often used to assess fish CYP1A induction. According to Torre et al. (2011), the effects of musk xylene on EROD activity and CYP1A mRNA levels in PLHC-1 and RTG-2 fish cell lines were distinct. The highest concentration of pesticides used increased EROD activity by about twofold. At the same time, the amount of CYP1A mRNA rose sixfold to sevenfold, as we are all aware that protein is what gives enzymes their chemical makeup. The process of transforming RNA into protein is known as translation, and it can be hampered by a number of reasons. As a result, fluctuations in mRNA levels and enzyme activity are often inconsistent. The results show that pesticides (ATR and CPF) can boost CYP1A expression. However, more research is needed to see if the CYP1A induction has a direct effect on the overall CYP rise.

Cytochrome P450s (CYPs) and heat-shock proteins (HSPs) are key predictors for determining contamination levels in the aquatic system (Yamashita et al. 2004; Alak et al. 2017). Planar constituents of numerous polycyclic aromatic hydrocarbons (PAH), polychlorinated naphthalenes, polychlorinated dibenzodioxins and dibenzofurans (PCDD, PCDF), polychlorinated biphenyls (PCB), and others induce CYP-1A in organisms exposed to a wide spectrum of environmental contaminants (Fent 2001). When a foreign substance binds to a cellular receptor, CYP-1A may be induced (Perdew and Poland 1988). This binding stimulates the CYP-1A gene to express, which enhances RNA transcription (Okey et al. 1994), and thus boost CYP-1A synthesis (Hassanain et al. 2007). As a result, CYP-1A induction is used as a biomarker in fish and fish cell systems to indicate exposure to such contaminants. CYP-1A induction has also been utilized as a biomarker of exposure to different contaminants in a range of vertebrate species, including mammals, in various studies (White et al. 1994), fish (Woodin et al. 1997), reptiles (Rie et al. 2000), and birds (Sanderson et al. 1994). According to previous research, deltamethrin inhibits antioxidant enzymes, increases the expression of heat-shock protein 70, and has negative effects on the expression of IGF-I, IGF-II, and GH (Ceyhun et al. 2010; Aksakal et al. 2010). In fish, cytochrome P450 is essential for the metabolization of a variety of contaminants. In rainbow trout, deltamethrin exposure dramatically increased CYP1A gene expression in a time-dependent way. When a sublethal dose of deltamethrin was used, the pesticide's toxic metabolism was shown to be rapid than in the other groups (Guardiola et al. 2014). The proportion of pesticide or its brain-accumulated metabolites was found to be related to the potential for CYP1A induction to signify neurological toxicity (Johri et al.

2006). Several pyrethroids, particularly DLM, have previously been demonstrated to boost CYP1A activity (Johri et al. 2006; Alak et al. 2017).

It is presently well-established that the activation of xenobiotic metabolism in fish by CYPs is a viable technique for ecotoxicology investigations and environmental pollution biomonitoring (Dong et al. 2009). In recent years, ATR (atrazine) has been related to the induction of CYP isozyme activity in *Chironomus tentans* larvae (Miota et al. 2000). In zebra fish, 3,3,4,4,5-pentachlorobiphenyl can stimulate the expression of cytochrome P4501A, 1B, and 1C genes (Jonsson et al. 2007). Fish have proven to be reliable experimental paradigms for determining how well aquatic ecosystems are doing after being exposed to pollution and biochemical changes. Several research demonstrating the detrimental effects of ATR (atrazine) and CPF (chlorpyrifos) on fish have just recently been published (Wiegand et al. 2001; Kavitha and Venkateswara Rao 2008; De Silva and Samayawardhena 2005). Experiments have demonstrated that exposure to ATR (atrazine), CPF (chlorpyrifos), and mixtures can affect a number of organs, including the liver, kidney, brain, gills, and muscle (Xing et al. 2012a, b; Wang et al. 2011). Because CYPs are the essential enzymes that catalyze the oxidative metabolism of toxicants, including crucial environmental substances, their activity or content is typically altered when the tissues of organisms are damaged by an exogenous toxicant. The gills are involved in gas exchange and come into direct contact with external aquatic chemicals. Furthermore, preliminary studies have shown that benzo(a)pyrene (Bap), indigo, and polyaromatic hydrocarbon (PAH) induction in the gills is more sensitive than that in the liver (Jonsson et al. 2006; Abrahamson et al. 2007).

4 Conclusion

Cytochrome P450 is a biomarker which aids in detoxification in fishes. The maximum expression of this enzyme has been found in the liver. Cytochrome P450 has been identified from many fish families like Salmonidae, Sciaenidae, Tetraodontidae, Siluridae, Cyprinidae, Bagridae, Rivulidae, Moronidae, Fundulidae, Sparidae, Pleuronectidae, Gasterosteidae, Adrianichthyidae, Poeciliidae, Cichlidae, Chaetodontidae, Serranidae, Haemulidae, Centrarchidae, Dasyatidae, Adrianichthyidae, and Squalidae. Several environmental chemicals can inhibit the P450 activity in fish. The list of chemicals comprises chlorinated aromatics (PCB 77, PCB 169), heterocyclic compounds (e.g., piperonyl butoxide), metals (Cd), aromatic hydrocarbons (e.g., benzo[a]pyrene, naphthalene, benzene), and alkylmetals (tributyltin). This system either undergoes direct reduction of molecular dioxygen through peroxide pathway or utilizes electrons from NADPH in order to activate the CYP catalytic pathway.

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Conflict of Interest The authors affirm that they do not have any competing interests.

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