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Interactions of Environmental Chemicals and Natural Products With ABC and SLC Transporters in the Digestive System of Aquatic Organisms

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An organism's diet is a major route of exposure to both beneficial nutrients and toxic environmental chemicals and natural products. The uptake of dietary xenobiotics in the intestine is prevented by transporters of the Solute Carrier (SLC) and ATP Binding Cassette (ABC) family. Several environmental chemicals and natural toxins have been identified to induce expression of these defense transporters in fish and aquatic invertebrates, indicating that they are substrates and can be eliminated. However, certain environmental chemicals, termed Transporter-Interfering Chemicals or TICs, have recently been shown to bind to and inhibit fish and mammalian P-glycoprotein (ABCB1), thereby sensitizing cells to toxic chemical accumulation. If and to what extent other xenobiotic defense or nutrient uptake transporters can also be inhibited by dietary TICs is still unknown. To date, most chemical-transporter interaction studies in aquatic organisms have focused on ABC-type transporters, while molecular interactions of xenobiotics with SLC-type transporters are poorly understood. In this perspective, we summarize current advances in the identification, localization, and functional analysis of protective MXR transporters and nutrient uptake systems in the digestive system of fish and aquatic invertebrates. We collate the existing literature data on chemically induced transporter gene expression and summarize the molecular interactions of xenobiotics with these transport systems. Our review emphasizes the need for standardized assays in a broader panel of commercially important fish and seafood species to better evaluate the effects of TIC and other xenobiotic interactions with physiological substrates and MXR transporters across the aquatic ecosystem and predict possible transfer to humans through consumption.

Keywords: *multixenobiotic resistance, intestine, ABC transporters, aquatic, transporter-interfering chemicals (TICs), induction, SLC transporters*

INTRODUCTION

Fish and other aquatic animals can be exposed to water-soluble environmental chemicals via uptake through the gills and hydrophobic xenobiotics through ingestion of contaminated food. Gills are commonly considered a part of the respiratory system of aquatic animals (Collinder et al., 2009; Carvalho, 2011; Ray and Ringø, 2014). In addition to respiration, fish gills are critical for excretion

of nitrous waste, pH regulation, hormone production, and osmoregulation (Foyle et al., 2020; Zhang et al., 2021). In most bivalves, gills have undergone a secondary adaptation to mainly serve as feeding structures while their function in osmoregulation and ion transport have been less studied (Riisgård et al., 2011, 2015; Moreira et al., 2015). Due to their permanent contact with the aquatic environment, the gills of fish and mollusks represent a crucial interface between the aquatic organism and the environment. As such, gills are typically equipped with selective (membrane) barriers that control nutrient uptake and toxic xenobiotic or metabolite elimination (Maetz and García Romeu, 1964; Erickson et al., 2006; Luckenbach and Epel, 2008; Hwang et al., 2011; Armitage et al., 2013; Wang and Wang, 2015). In fish, these barriers are present along the whole digestive system to provide precise control over small molecule uptake. While the digestive anatomy across terrestrial and aquatic vertebrates is highly similar, including a digestive tract with a basic segmentation into esophagus, stomach, midgut, and hindgut, the relative lengths and volumes of each section can differ according to diet and means of nutrient extraction and uptake (Chapman, 1997; Collinder et al., 2009; Karasov and Douglas, 2013; Furness et al., 2015).

In fish and mammals, most nutrients as well as water and ions in the diet are typically absorbed through the epithelial cells of the small and large intestines (Sundell and Rønnestad, 2011; Kiela and Ghishan, 2016). Thereby, macro- and micronutrient uptake is often mediated by simple diffusion, facilitated diffusion, or secondary active transport coupled to an electrochemical gradient (Sundell and Rønnestad, 2011). Conversely, the uptake of dietary toxins, toxicants and other harmful xenobiotics is prevented by a combination of primary active ATP-binding Cassette (ABC) and secondary active solute carrier (SLC) proteins lining the apical and basolateral membrane of the enterocytes (Dietrich et al., 2003; Müller et al., 2017; Nicklisch and Hamdoun, 2020). These membrane proteins effectively regulate xenobiotic bioavailability and often act in concert to either pump compounds into the blood stream for metabolic processing in the liver (primarily SLCs) or to efflux them back into the gut lumen (primarily ABCs) for immediate excretion.

Yet, despite the similarities in intestinal macro- and micro-anatomy between terrestrial and aquatic organisms, little is known about the molecular composition and levels of both nutrient uptake and xenobiotic defense systems along the digestive tract of fish and other aquatic organisms. In addition, there is limited data available on the molecular interactions of aqueous and food-borne contaminants with these transport systems and how these interactions could affect nutrient homeostasis and toxic contaminant bioaccumulation.

1. EPITHELIAL TRANSPORT IN THE DIGESTIVE SYSTEM OF AQUATIC ORGANISMS

One of the key functions of the digestive system is to absorb nutrients from the diet that can be metabolized to provide energy for growth and development. At the same time, the intestinal

tract serves as a major environmental barrier to prevent toxic xenobiotic uptake and accumulation. In the gills and intestine of fish and other aquatic organisms, several members of both the solute carrier (SLC) and ATP-Binding Cassette (ABC) family of transporters have been identified to participate in essential physiological functions such as nutrient uptake, ion flux, cell signaling processes, and toxic metabolite and xenobiotic efflux.

1.1 Nutrient and Endogenous Substrate Transporters

Transepithelial transport of nutrients in the gastrointestinal tract is typically mediated by secondary active transporters of the solute carrier (SLC) family. In humans, SLCs represent the largest group of secondary active membrane transporters (Hediger et al., 2004, 2013; Almén et al., 2009; Höglund et al., 2011). SLCs are capable of facilitating bidirectional transport (Kottra and Daniel, 2001; Kottra et al., 2002; Winter et al., 2011), though are primarily implicated in cellular uptake of nutrients and ions (Planchamp et al., 2007; Colas et al., 2016; Zhang et al., 2018; Felmlee et al., 2020; Song et al., 2020). Despite their important role in nutrient uptake and metabolic homeostasis, SLC transporters are notoriously understudied in humans and aquatic organisms (Verri et al., 2012; Schlessinger et al., 2013; César-Razquin et al., 2015; Barat et al., 2016).

In fish, SLCs play an important role in organismal development and transport of endogenous compounds to allow for proper development of swim bladders (Kim et al., 2020), inner ears (Liu et al., 2015), kidneys (Schoels et al., 2021), and normal development of embryos (Takesono et al., 2012). In addition, SLCs play a crucial role in intestinal absorption and transport of amino acids and other physiological compounds, including thyroid hormones (Arjona et al., 2011; Muzzio et al., 2014), iron (Cooper et al., 2007), zinc (Yan et al., 2012; Jiang et al., 2014), coenzyme-A (Kim et al., 2020), and amino acids and peptides (Romano et al., 2006, 2014; Verri et al., 2010, 2017; Margheritis et al., 2013; Rimoldi et al., 2015; Song et al., 2017; To et al., 2019; Vacca et al., 2019). Several SLC transporters have been shown to be involved in intestinal methionine absorption as well as iron transport and acid-base regulation in the gills (Cooper et al., 2007; Ivanis et al., 2008; To et al., 2019). For instance, in the intestine of rainbow trout, 8 SLC transporters (SLC1A5, SLC6A19, SLC6A15, SLC7A7, SLC43A1, SLC43A2, SLC3A1, and SLC3A2), which represent both high and low affinity methionine transporters, were found to have differential expression both along the length of the intestine and between the apical and basolateral membranes of the intestine (To et al., 2019). In the gills, sodium/hydrogen exchanging proteins SLC9A2 and SLC9A3, which are highly expressed in the gills and kidney, were found to localize to mitochondria rich cells that were also enriched with sodium/potassium ATPase, indirectly suggesting their involvement in acid-base regulation in rainbow trout (*Oncorhynchus mykiss*) gills (Ivanis et al., 2008). Furthermore, peptide transporting proteins of the SLC15 protein family are highly expressed in zebrafish (*Danio rerio*) intestines (Romano et al., 2006; Vacca et al., 2019). High intestinal expression was also shown for SLC15 proteins in tilapia

(*Oreochromis niloticus*) (Huang et al., 2015). In Zebrafish, the expression of SLC22 proteins is low in the intestine, gills and heart while high in the liver and kidney (Mihaljevic et al., 2016). However, Organic Anion Transporting Proteins (OATPs), a subfamily of SLC22 proteins, are highly expressed in the gills and intestine (Popovic et al., 2010a). Intestinal SLC type transporters have also been described to transport vitamins, including vitamin E (alpha-tocopherol), vitamin B1 (thiamine), vitamin C (ascorbic acid), vitamin B7 (biotin), vitamin B9 (folate), and vitamin B2 (riboflavin) (Said and Nexo, 2018). Deficiencies in some of those vitamins have been shown to cause severe organ damage, oxidative stress, and developmental toxicity in fish (Wang et al., 2016; Pan et al., 2017; Harder et al., 2018).

1.2 Multidrug/Multixenobiotic Resistance Transporters

Members of both the ABC and SLC-type families have been shown to be part of a highly conserved defense mechanism against chemical insults, often referred to as multidrug-resistance (MDR) transporters (Ling, 1997; Gottesman et al., 2002; Glavinas et al., 2004; Leslie et al., 2005; Sharom, 2008; Giacomini et al., 2010; Hillgren et al., 2013; Nigam, 2015). The mammalian homologs of these transporter superfamilies have been extensively studied in the past, unraveling their precise molecular interactions with drugs and environmental chemicals (Juliano and Ling, 1976; Beck, 1987; Horio et al., 1988; Hediger et al., 2004; Oosterhuis et al., 2008; Staud et al., 2013; Nicklisch et al., 2016; Chedik et al., 2019; Guéniche et al., 2020; Nicklisch and Hamdoun, 2020).

In the early 90s, a mechanism similar to MDR was reported in aquatic organisms and since then referred to as multixenobiotic-resistance or MXR (Kurelec, 1992, 1997; Bard, 2000; Epel et al., 2008; Luckenbach and Epel, 2008; Ferreira et al., 2014). The MXR phenotype and its inducibility by environmental chemicals was first demonstrated in invertebrate species in the 1990s (Cornwall et al., 1995; Kurelec et al., 1995; Smital and Kurelec, 1998). Thereby, baseline levels of MXR inducibility and activity between different species have been correlated with the amount of pollution present in their habitat (Kurelec et al., 1995; Smital et al., 2000). Over the past three decades, fish and other aquatic invertebrates, such as sea urchins and mussels, have been instrumental in understanding MXR transporter interactions with xenobiotics and the chemosensitization effects of so called Transporter-Interfering Chemicals or TICs (Eufemia et al., 2002; Hamdoun et al., 2004; Luckenbach and Epel, 2005, 2008; Kwong et al., 2006; Stevenson et al., 2006; Faria et al., 2011; Martins et al., 2020; Nicklisch and Hamdoun, 2020; Protopopova et al., 2020; Nicklisch et al., 2021).

1.2.1 ABC-Type MDR/MXR Transporters

The ABC-type transporter P-glycoprotein (aka MDR1 or ABCB1) is one the best characterized mammalian MDR/MXR transporters that shows high expression in biological barriers such as the liver, brain, kidney and the intestine (Juliano and Ling, 1976; Beck, 1987; Horio et al., 1988). The

identification of two P-glycoprotein genes in the winter flounder *Pleuronectes americanus* using Southern blot techniques represented the first set of P-glycoprotein orthologs reported in lower vertebrates (Chan et al., 1992; Luckenbach et al., 2014; Gordon et al., 2019). Since then, numerous ABC transporter proteins, which mediate the MXR phenotype, have been identified, characterized, and cloned in other fish species including Emerald rockcod (Zucchi et al., 2010), carp (Smital and Sauerborn, 2002), catfish (Liu et al., 2013), killifish (Christine Paetzold et al., 2009), mullet (Diaz de Cerio et al., 2012), Nile tilapia (Costa et al., 2012, 2013), rainbow trout (Lončar et al., 2010; Kropf et al., 2016; Love et al., 2021), zebrafish (Popovic et al., 2010b; Long et al., 2011; Fischer et al., 2013), and more recently yellowfin tuna (Nicklisch et al., 2021).

The mammalian MDR/MXR transporters include the ABCB, ABCC and ABCG subfamilies. Each of these subfamilies is comprised of members with physiological efflux function, xenobiotic efflux function, or both (Dean et al., 2001; Giacomini et al., 2010; König et al., 2013; Nicklisch and Hamdoun, 2020). For instance, in the human ABCB subfamily, ABCB1 has been characterized as a key drug efflux transporter in multiple barrier tissues while ABCB4 mainly serves as phosphatidylcholine transporter in the liver (Borst and Elferink, 2002; Dean and Annilo, 2005; Jonker et al., 2009). The human *abcb5* gene has been suggested to confer drug resistance in malignant melanoma cells (Chen et al., 2005; Frank et al., 2005). Based on synteny analysis, the human *abb1* and *abcb4* genes are co-orthologs of zebrafish *abcb4* (Ferreira et al., 2014; Luckenbach et al., 2014). Notably, several teleost fish, including zebrafish, lack the *abcb1* ortholog but possess the two P-glycoproteins ABCB4 and ABCB5 (Fischer et al., 2013; Luckenbach et al., 2014). Thereby, the Zebrafish ABCB4 transporter has been described as major multixenobiotic efflux transporter while ABCB5 might be implicated in xenobiotic efflux in gill and skin ionocytes (Dymowska et al., 2012; Gordon et al., 2019). Yet, other fish species have been shown to possess *abcb1* and *abcb4* but lack the *abcb5* ortholog (Liu et al., 2013). The confusion in annotating human versus fish MDR/MXR transporter genes mainly arises from lineage-specific genes, i.e., genes that have no detectable homologs in the other species (Dean and Annilo, 2005; Annilo et al., 2006; Gabaldón and Koonin, 2013). For the sake of clarity, in this perspective, we will refer to the aquatic species' transporter genes as they have been annotated by the cited authors. Future combined synteny and phylogenetic analysis will likely revise those annotations and provide means to reduce the difficulty of inferring transporter function and nomenclature.

Studies on localization and expression levels of fish ABC-type MDR/MXR transporters have mostly focused on two model organisms, rainbow trout and zebrafish. For instance, the qPCR analysis of eight different ABC transporters (*abcb1*, *abcb11*, *abcc1*, *abcc2*, *abcc3*, *abcc4*, *abcc5*, and *abcg2*) in the liver, brain, gonads, kidney, gills, and intestine of rainbow trout revealed similar expression patterns to mammalian tissues (Lončar et al., 2010). Thereby, relative expression was higher in digestive and excretory tissues such as the liver, kidneys, and intestine compared to

the brain or gills. Interestingly, the expression of the key efflux pump *abcb1* was highest in brain but not detected in the gills (Lončar et al., 2010). The bile salt pump *Abcb11* had very low expression across the tested tissues except for the liver.

The mRNA levels of *abcb1a*, *abcb1b*, *abcc1*, *abcc2*, *abcc3*, *abcc4*, *abcc5*, and *abcg2* were also examined in earlier stages of rainbow trout embryo development and increased from 1 to 20 days post hatch. The predominant increases in *abcb1a* and *abcb1b* gene expression occurred in abdominal viscera (intestine, liver, kidney) and head (gills) of early larvae (Kropf et al., 2016). Gills of early larvae were also high in *abcb5*, *abcc3*, and *abcg2* mRNA (Kropf et al., 2020). The ABC proteins *abcb4*, *abcb5*, *abcc2* and *abcb1* have also been characterized in zebrafish and have been shown to confer the MXR phenotype (Popovic et al., 2010b; Long et al., 2011; Fischer et al., 2013). Cellular ABC transporter efflux activities have been detected in zebrafish embryos within 48 h of development (Long et al., 2011; Fischer et al., 2013). The *abcb1* transporter gene is unique to vertebrate fish and showed higher expression in tissues such as the gills and brain than in the intestine or liver (Popovic et al., 2010b). Expression of the *abcc2* gene was highest in the intestine, followed by the kidney and liver (Long et al., 2011).

1.2.2 SLC-Type MDR/MXR Transporters

The SLC proteins are responsible for transporting a wide range of substrates including both organic and metal ions, endogenous

metabolites, and xenobiotics such as pharmaceuticals and toxicants (Hediger et al., 2004; König et al., 2013; Lin et al., 2015; Bruyere et al., 2017; Chedik et al., 2019; Nicklisch and Hamdoun, 2020; Pizzagalli et al., 2021). In clinical research, there has been particular focus on members of the SLC22 family, which encompasses many organic ion transporters, and the SLC47 family, the multidrug and toxicant extrusion (MATE) proteins (Nigam, 2015, 2018). Yet, similar to nutrient uptake transporters, there have been very few studies on the tissue expression levels and localization of MDR/MXR-type SLC transporters in aquatic organisms. In the earlier stages of rainbow trout embryo development, the multidrug and toxin extrusion protein 1 (*mate1*) and organic anion transporting polypeptide 2 (*oatp2*) genes were detected in yolk sac epithelium, while the mRNA levels of the organic anion transporting polypeptide 1d gene (*oatp1d*) were high in abdominal viscera (Kropf et al., 2016). During the development of zebrafish embryos, *mate6* and *mate7* genes are highly expressed after 6 hpf (Lončar et al., 2016). Interestingly, tissue-specific *mate* gene expression in kidney, liver, intestine, and brain was generally higher in male than in female zebrafish, indicating gender differences in these important detoxification systems. The lowest gene expression of *mate3*, 4, 5, 6, 7, and 8 was found in the gills, irrespective of sex.

TABLE 1 | List of tissue specific MXR transporter gene induction or repression by environmental chemicals, heavy metals, and natural toxins.

Compounds	Transporter(s)	Genetic effects	Organism	Tissue	References
Cadmium chloride (CdCl ₂)	ABCB1, ABCC2	Induction	Emerald rockcod (<i>Trematomus bernacchii</i>)	Liver	Zucchi et al., 2010
Mercury (Hg) Lead (Pb)	ABCC2	Induction	Zebrafish (<i>Danio rerio</i>)	Liver, kidney, intestine	Long et al., 2011
Mercury chloride (HgCl ₂)	ABCG2b	Induction	Zebrafish (<i>Danio rerio</i>)	Intestine	Zhang et al., 2020
Gossypol	SLC6A6, SLC1A2a, SLC1A3, SLC7A7, SLC7A6, SLC7A1, SLC6A19b, SLC7A5, SLC7A8, SLC1A5, SLC38A2, PepT1	Repression	Grass carp (<i>Ctenopharyngodon idella</i>)	Intestine	Wang et al., 2018
Clotrimazole (CTZ)	ABCB1b	Induction	Rainbow trout (<i>Oncorhynchus mykiss</i>)	Optic lobe, distal intestine	Love et al., 2021
Copper (Cu ²⁺) Mercury (Hg ²⁺)	SLC15a1b	Induction	Nile tilapia (<i>Oreochromis niloticus</i>)	Proximal intestine	Huang et al., 2015
Cadmium telluride quantum dots (CdTe-QDs) Cadmium (Cd ²⁺) Silver (Ag ⁺)	MRP1, MRP2, P-glycoprotein	Induction	Zebrafish (<i>Danio rerio</i>)	Whole embryo	Tian et al., 2019; Hu et al., 2019
Pentachlorophenol (PCP)	ABCB1	Induction	Water flea (<i>Daphnia magna</i>)	Whole organism	Campos et al., 2014
Mercury chloride (HgCl ₂)	ABCC4	Induction			
Okadaic acid (OA) Dinophysistoxin-1 (DTX1)	P-glycoprotein (ABCB1), SLC6A7, SFXN1, MDR1, MRP2	Induction	Mediterranean mussel (<i>Mytilus galloprovincialis</i>)	Digestive glands, gills	Martins et al., 2020; Martínez-Escarriaza et al., 2021
Benzo(α)pyrene (BaP)	ABCB1, ABCC	Induction	Korean mussel (<i>Mytilus coruscus</i>)	Gills	Guo et al., 2020

2. REGULATION OF NUTRIENT AND MDR/MXR TRANSPORTER EXPRESSION

2.1 Diet and Adaptive Regulation of Intestinal Uptake

The quantity and quality of diet have been shown to influence transporter expression levels in the intestine of fish. For instance, fasting of Nile tilapia (*Oreochromis niloticus*) was shown to significantly decrease mRNA levels of the SLC15 peptide transporter gene family, but mRNA levels recovered upon refeeding (Huang et al., 2015). Similar results were seen in the Mummichog (*Fundulus heteroclitus*), where short-term fasting increased, long-term fasting decreased, and re-feeding restored SLC15 mRNA levels (Bucking and Schulte, 2012). Further, short-term starvation of rainbow trout induced an increase of P-glycoprotein concentration in the intestinal epithelia (Baumgarner et al., 2013).

Diet quality has also been shown to have a pronounced effect on fish transporters, and is particularly relevant in the field of aquaculture, where farmers have direct control over the primary source of nutrition as well as any form of dietary supplementation. Replacement of traditional fishmeal with meat and bone meal in the diet of juvenile turbot (*Scophthalmus maximus*) was shown to increase intestinal peptide transporter 1 (PepT1/SLC15A1) (Song et al., 2017). Similarly, large reductions in fishmeal content and replacement with vegetable meal in European sea bass (*Dicentrarchus labrax*) diet was shown to increase PepT1 gene expression but not affect the expression of the monocarboxylate transporter SLC6A19 (Rimoldi et al., 2015). Atlantic salmon (*Salmo salar*) fed diets supplemented with saponins and pea protein were shown to have several metabolic systems greatly altered, including differential expression of several SLC proteins (Kortner et al., 2012). Studies on dietary restrictions and feed supplementation that may decrease fitness of farmed fish are still in the early stages, but could serve as guideline to help elucidate mechanisms leading to various forms of intestinal pathology (Kortner et al., 2012).

2.2 Environmental Stressors

As a result of climate change and associated alterations in salinity, pH, and temperature of aquatic environments, the bioavailability and toxicity of environmental chemicals can increase (Noyes et al., 2009; Hasenbein et al., 2018; Ross and Behringer, 2019; Paul et al., 2020; Derby et al., 2021; Fulton et al., 2021). Recent studies have shown that these environmental stressor can also affect gene regulation, expression, and overall fitness of fish populations both within and between species (Jeffries et al., 2018, 2019; DeCourten et al., 2019; Romney et al., 2019; Mundy et al., 2020; Komoroske et al., 2021; Segarra et al., 2021). Most of these investigations have been conducted in fish and focused on SLC-type transporters and the effect of pH and temperature on substrate affinity and transport rate.

For instance, increased pH (pH > 7.4) was shown to cause a decrease in copper absorption in rainbow trout gut sacs as well as a decrease in iron absorption by SLC11 proteins isolated from rainbow trout gills and expressed in *Xenopus laevis* oocytes (Cooper et al., 2007; Nadella et al., 2007). The pH dependence of PepT1 in teleost fish has been thoroughly examined. In Zebrafish and other teleost fish, PepT1 tends to exhibit a higher substrate affinity with decreasing pH (Romano et al., 2014; Verri et al., 2017). Zebrafish PepT1 also exhibited an increase in maximal transport rate when extracellular pH transitioned from acidic (pH = 6.5) to alkaline (pH = 8.5), while other teleost fish PepT1 proteins exhibit little or no change in maximal transport rate in response to similar pH shifts (Romano et al., 2014; Verri et al., 2017).

The transport rate of SLC transporters at different temperatures has been shown to vary by species (Romano et al., 2014; Verri et al., 2017). Interestingly, teleost fish PepT1 proteins have higher transport rates at lower temperatures (22°C) than the mammalian PepT1 orthologs, which function better at temperatures around 30°C and higher. This possibly demonstrates an adaptive evolution between terrestrial and aquatic species living in different temperature regimens (Romano et al., 2014; Verri et al., 2017). The Antarctic icefish (*Chionodraco hamatus*) represents an extreme example, with structural changes to its PEPT1 protein facilitating in part its ability to function at very cold (−1.9°C) temperatures (Romano et al., 2014; Verri et al., 2017). In Delta smelt (*Hypomesus transpacificus*), the expression of the ion exchange transporter SLC8B1 was shown to have non-linear responses to increasing temperature, with decreased expression at 20°C and 25°C compared to the control (14°C) and re-elevated expression at 27°C (Jeffries et al., 2018). This u-shaped response was attributed to sublethal thermal threshold with partial downregulation of non-essential cellular processes during the period of stress.

If and to what extent ABC-type MDR/MXR transporters can be regulated by changes in salinity, temperature or pH is not well understood. For mammalian P-glycoprotein (ABCB1), a linear increase in transport rate with increasing temperature has been demonstrated (Litman et al., 1997; Lu et al., 2001; Clay and Sharom, 2013). The authors suggested that the increase in drug transport rate at higher temperatures can be attributed to several factors, including the increased partitioning of the drug/xenobiotic into the membrane and the structural changes in the protein that increase substrate affinity. Effects of other environmental stressors on the affinity and/or transport rate of ABC transporters are still elusive.

2.3 Chemical Inducers and Repressors

Multixenobiotic Resistance transporters represent a critical line of defense in preventing xenobiotic chemicals from accumulating and harming an aquatic organism. Initial investigations identifying MXR transporters as molecular targets of xenobiotics focused on chemical exposure experiments and subsequent evaluation of transporter mRNA and/or protein expression levels (Table 1). Thereby, transporter downregulation

suggested a mechanism of direct inhibition or that upstream or downstream regulatory pathways might be targeted by the compound. Whereas upregulation of transporters indicated that they could be involved in the elimination of those compounds.

In rainbow trout, the expression of two P-glycoprotein isoforms, *abcb1a* and *abcb1b*, was significantly increased upon exposure to the antifungal agent clotrimazole (Love et al., 2021). In addition, several heavy metals were shown to induce the expression of ABC proteins and act as their substrates in fish. For instance, both cadmium and silver ions have been shown to induce *pgp* (ABCB4) and *abcc2* expression in zebrafish embryos (Hu et al., 2019). Mercury and lead induced *abcc2* expression in both larval and adult zebrafish, and the overexpression of *abcc2* alleviated the accumulation of these metals along with cadmium (Long et al., 2011). In the Antarctic fish species Emerald rockcod (*Trematomus bernacchii*), the *abcb1* and *abcc2* genes are induced in the liver upon exposure to cadmium ions (Zucchi et al., 2010). Cadmium telluride quantum dots (CdTe-QDs) are nanoparticles that are often released into environmental water bodies and accumulate in aquatic biota. Zebrafish embryos exposed to CdTe quantum dots show delayed hatching and induce the expression of *abcc1* and *abcc2*, indicating that quantum dots could be possible substrates for these ABCC-type transporters (Tian et al., 2019).

There has been limited studies on the inducing or repressing effects of xenobiotics on SLC transporter expression. In Nile tilapia (*Oreochromis niloticus*) the expression levels of peptide uptake transporters SLC15a1a, SLC15a1b, SLC15a2, and SLC15a5 decreased after fasting (Huang et al., 2015). Subsequent exposure to waterborne copper, but not mercury, prevented the restoration of the expression levels. In young grass carp (*Ctenopharyngodon idella*), the cotton derived phenol gossypol was shown to down-regulate several peptide and amino acid SLC transporters in the intestine, leading to intestinal damage and reduced growth (Wang et al., 2018). This is particularly important for aquaculture species where commercially available plant protein sources like rapeseed and cottonseed meal are used as cost effective feed (Deng et al., 2014). Unintentional exposure to gossypol in cottonseed meal could ultimately reduce feeding efficiency and overall percent weight gain.

3. MOLECULAR INTERACTIONS OF XENOBIOTICS WITH MXR TRANSPORTERS

To date, the number of identified MXR transporter substrates and inhibitors among xenobiotics is low and assay protocols have yet to be standardized (Table 2; Nicklisch and Hamdoun, 2020). Still, several environmental chemicals, including pharmaceuticals, pesticides, herbicides, industrial chemicals, and polycyclic aromatic hydrocarbons (PAHs) have been shown to interact with and inhibit the function of MXR transporters in fish, bivalves, and crustaceans.

For instance, in PLHC-1 (*Poeciliopsis lucida hepatoma cells*) the ABCB1 homolog P-gp1 was shown to be inhibited by a series of pharmaceuticals, with sildenafil and simvastatin

showing highest inhibition potency (Caminada et al., 2008). In zebrafish, ABCB4 efflux function was inhibited by different environmental chemicals, including insecticides, fragrances, and pharmaceuticals (Fischer et al., 2013; Bieczynski et al., 2021). Divalent metals (Cd, Mn, Zn, Pb, and Co) have been shown to cause (competitive) inhibition of rainbow trout SLC11 iron uptake in *Xenopus* oocytes (Cooper et al., 2007). Using HEK293 cells, heterologously expressing zebrafish MATE7/SLC47a7 protein, interactions with 89 different environmental chemicals were investigated with the majority of compounds being inhibitors (Lončar and Smital, 2018). Similarly, the model substrate transport of zebrafish organic anion transporting polypeptide 1d1 (OATP1d1) and organic cation transporter 1 (OCT1) expressed in HEK293 cells was shown to be (competitively) inhibited by nearly all tested endo- and xenobiotics (Popovic et al., 2014; Mihaljević et al., 2017).

In bivalves, exposures to organic pesticides, pharmaceuticals, industrial chemicals, cadmium, and benzo(a)pyrene led to increased deformities, impaired growth, and increased toxicant accumulation. For instance, in the Californian mussel (*Mytilus californianus*), moderately hydrophobic pesticides and PFAS compounds have been shown to inhibit gill tissue efflux of Rhodamine B, a known P-glycoprotein substrate (Cornwall et al., 1995; McFadzen et al., 2000; Stevenson et al., 2006). In the thick shell mussel (*Mytilus coruscus*), gill tissue pre-exposure to benzo(α)pyrene (BaP) reduced the inhibitory effect of ABCB1- and ABCC1-specific inhibitors reversin 205 and MK572 on Calcein-AM efflux (Guo et al., 2020). This indicated that BaP could bind to both transporters and possibly alter their detoxification function in these mussels.

Using mussels, sea urchin larvae, and the water flea *Daphnia magna*, it was shown that MXR transporter inhibition may also facilitate toxic synergism in environmental chemical mixtures (Faria et al., 2011; Anselmo et al., 2012; Campos et al., 2014). For instance, when early life stages of the green sea urchin (*Psammechinus miliaris*) were exposed to combinations of the toxic MXR transporter substrates vinblastine and triclosan (TCS) or P-85 nanoparticles, the toxicity increased by a factor of 2-8 (Anselmo et al., 2012). Similarly, when early life stages of the zebra mussel (*Dreissena polymorpha*) were exposed to a combination of vinblastine and model ABC transporter inhibitors, the toxicity increased super-additively (Faria et al., 2011).

Further, marine biotoxins and other naturally occurring marine products have been shown to upregulate ABC and SLC protein expression and function as substrates in various mussel species (Eufemia et al., 2002; Martins et al., 2020). *In vitro* and *ex vivo* experiments in rainbow trout and the Patagonian silverside (*Odontesthes hatcheri*) suggest that microcystin-LR may act as a substrate and competitive inhibitor of ABCC-like proteins in intestinal tissues (Bieczynski et al., 2014, 2016). Additional *ex vivo* and *in vitro* experiments in rainbow trout intestines demonstrated that paralytic shellfish toxin (PST) is capable of inhibiting ABCC-like transporters when absorbed by intestinal epithelial cells (Painefilú et al., 2020). The activity of ABC proteins can also be regulated by endogenous compounds.

TABLE 2 | Summary of known xenobiotic interactions with MXR transporters in fish and aquatic invertebrates.

Compounds	T.a. Abcb1	D.r. MATE/Sic47					D.r. Oct1/Sic22a1	D.r. Oatp1d1/Sic1d1	D.r. Abcb4	D.r. Abcb4	D.r. Abcc2	D.r. Sic16a2/Mct8	O.m. Abcc	O.m. Abcc2	O.m. Abcg2a	O.m. Sic11	O.h. Abcc	Pl. P-gp1 (Abcb1)	Pl. P-gp1 (Abcb1)	D.p. gills	M.c. gills	P.m. larvae
	(ATPase activity, purified protein)	(HEK293 cells + DAPI)					(HEK293T cells)	(HEK293 cells)	(ZF embryos + RhB)	(LLC-PK1 cells + embryos)	(ZF embryos & ZF4 cells)	(COS-1 cells)	(intestine & enterocytes)	(intestine + calcin)	(S9 insect cells)	(X. laevis oocytes)	(intestine + calcin)	(PLHC-1 cells + CAM)	(ATPase activity, PLHC-1 membrane vesicles)	(whole gills + RhB)	(whole gills + RhB)	(larvae + CAM)
	Nickisch et al., 2021	Lončar et al., 2016 ^a Lončar and Smital, 2018 ^b					Mihaljević et al., 2017	Popović et al., 2013 ^a , 2014 ^b Marić et al., 2021 ^c	Fischer et al., 2013 ^a Bieczynski et al., 2021 ^b	Lu et al., 2015	Long et al., 2011	Arjona et al., 2011	Paineflu et al., 2020	Bieczynski et al., 2014	Zaja et al., 2016	Cooper et al., 2007	Bieczynski et al., 2016	Caminada et al., 2008 ^a Zaja et al., 2011 ^b	Zaja et al., 2011	Smital et al., 2004	Cornwall et al., 1995 ^a Luckenbach and Epel, 2005 ^b Stevenson et al., 2006 ^c	Anselmo et al., 2012
		Mate3	Mate4	Mate6	Mate7	Mate8																
5-Fluorouracil	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	WP	I	-	-	-	
Acebutolol	-	-	-	-	S ^b	-	-	-	-	-	-	-	-	-	-	-	P	-	-	-	-	
Amprenavir	-	-	-	-	-	-	-	WP	-	-	-	-	-	-	-	-	-	-	-	-	-	
Atorvastatin	-	-	-	-	P	-	-	-	-	-	-	-	-	I	-	-	P/P	I	-	-	-	
Azithromycin	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	WP	WI	-	-	-	
Bezafibrate	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P	-	-	-	-	
Caffeine	-	-	-	-	-	-	-	S ^b	-	-	-	-	-	-	-	-	-	-	-	-	-	
Cimetidine	-	P	P	P	P	P	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Cisplatin	-	-	-	-	-	-	I	-	-	-	-	-	-	I	-	-	WP	WI	-	-	-	
Clofibrate	-	-	-	-	-	-	-	P	-	-	-	-	-	-	-	-	-	-	-	-	-	
Colchicine	-	-	-	-	-	-	-	WP	-	-	-	-	-	I	-	-	WP	S	-	-	-	
Curcumin	-	-	-	-	-	-	-	-	-	-	-	-	-	S	-	-	-	-	-	-	-	
Cyclosporin A	I	-	-	-	-	-	-	P	-	-	-	-	-	I	-	-	P/P	I	-	-	-	
Dasatinib	-	-	-	-	-	-	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Dexamethasone	-	-	-	-	-	-	-	WP	-	-	-	-	-	-	-	-	WP	WI	-	-	-	
Diclofenac	-	-	-	-	-	-	-	S ^b	-	-	-	-	-	-	-	-	P	-	-	-	-	
Diltiazem	-	-	-	-	P	-	I	-	-	-	-	-	-	-	-	-	P	S	-	-	-	
Dipyridamole	-	-	-	-	-	-	-	P	-	-	-	-	-	-	-	-	-	-	-	-	-	
Doxorubicin	-	-	-	-	S ^b	-	-	-	-	-	-	-	-	S	-	-	P/WP	WI	-	-	-	
Diphenhydramine	-	-	-	-	S	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Emetine	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P	
Erythromycin	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	WP	I	-	-	-	
Etoposide	-	-	-	-	-	-	-	WP	-	-	-	-	-	-	-	-	WP	WI	-	-	-	
Fenofibrate	-	-	-	-	-	-	-	-	-	-	-	-	-	S	-	-	P	-	-	-	-	
Fluoxetine	-	-	-	-	P	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Forskolin	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P	
Furosemide	-	-	-	-	-	-	-	-	-	-	-	-	-	S	-	-	P/WP	I	-	-	-	
Gemfibrozil	-	-	-	-	-	-	-	S ^b	-	-	-	-	-	-	-	-	P/WP	I	-	-	-	
Hoechst 3334	-	-	-	-	-	-	-	S ^b	-	-	-	-	-	I	-	-	P	I	-	-	-	
Ibuprofen	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Imipramine	-	-	-	-	S	-	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Ivermectin	-	-	-	-	-	-	-	P	-	-	-	-	-	-	-	-	-	-	-	-	-	
Ko143	-	-	-	-	-	-	-	-	-	-	-	-	-	I	-	-	P	WI	-	-	-	
Methotrexate	-	-	-	-	P	-	-	-	-	-	-	-	-	-	-	-	WP	WI	-	-	-	
Mitoxantrone	-	-	-	-	P	-	I	-	-	-	-	-	-	-	-	-	WP	I	-	-	-	
MK-571	-	-	-	-	-	-	-	P	-	-	-	-	-	-	-	-	P/P	I	-	-	-	
NEM-SG	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P	WI	-	-	-	
Nicardipine	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P	S	-	-	-	
Novobiocin	-	-	-	-	-	-	-	-	-	-	-	-	-	I	-	-	-	-	-	-	-	
Oxaliplatin	-	-	-	-	-	-	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Phenytoin	-	-	-	-	-	-	-	WP	-	-	-	-	-	-	-	-	-	-	-	-	-	
Pheophorbide	-	-	-	-	-	-	-	-	-	-	-	-	-	S	-	-	-	-	-	-	-	
Pramipexole	-	-	-	-	P	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Pravastatin	-	-	-	-	-	-	-	-	-	-	-	-	-	S	-	-	P/WP	I	-	-	-	
Prazosin	-	-	-	-	-	-	I	-	-	-	-	-	-	S	-	-	P	S	-	-	-	
Procainamide	-	-	-	-	S	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Propranolol	-	-	-	-	S	-	I	-	-	-	-	-	-	S	-	-	P/P	S	-	-	-	
Pyrimethamine	-	-	-	-	S	-	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Quinidine	-	P	P	P	P/P	P	I	-	-	-	-	-	-	-	-	-	P	S	I	P/P	-	
Ranitidine	-	-	-	-	S	-	-	-	-	-	-	-	-	-	-	-	P	-	-	-	-	
Reserpine	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P	I	-	-	-	
Reversin 205	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P	S	-	-	-	

(Continued)

TABLE 2 | (Continued)

Compounds	T.a. Abcb1	D.r. MATE/Slc47					D.r. Oct1/Slc22a1	D.r. Oatp1d1/Slc1d1	D.r. Abcb4	D.r. Abcb4	D.r. Abcc2	D.r. Slc16a2/Mct8	O.m. Abcc	O.m. Abcc2	O.m. Abcg2a	O.m. Slc11	O.h. Abcc	P.l. P-gp1 (Abcb1)	P.l. P-gp1 (Abcb1)	D.p. gills	M.c. gills	P.m. larvae
	(ATPase activity, purified protein)	(HEK293 cells + DAPI)					(HEK293T cells)	(HEK293 cells)	ZF embryos + RhB)	(LLC-PK1 cells & embryos)	ZF embryos & ZF4 cells)	(COS-1 cells)	(intestine & enterocytes)	(intestine + calcein)	(S9 insect cells)	(X. laevis oocytes)	(intestine + calcein)	(PLHC-1 cells + CAM)	(ATPase activity, PLHC-1 membrane vesicles)	(whole gills + RhB)	(whole gills + RhB)	(larvae + CAM)
	Nicklisch et al., 2021	Lončar et al., 2016 ^a Lončar and Smital, 2016 ^b					Mihaljević et al., 2017	Popovic et al., 2013 ^a , 2014 ^b Marić et al., 2021 ^c	Fischer et al., 2013 ^a	Lu et al., 2015	Long et al., 2011	Arjona et al., 2011	Painefiló et al., 2020	Bieczynski et al., 2014	Zaja et al., 2016	Cooper et al., 2007	Bieczynski et al., 2016	Caminada et al., 2006 ^b Zaja et al., 2011 ^b	Zaja et al., 2011	Smital et al., 2004	Cornwall et al., 1995 ^a Luckenbach and Epel, 2005 ^b Stevenson et al., 2006 ^c	Anselmo et al., 2012
		Mate3	Mate4	Mate6	Mate7	Mate8																
Rofecoxib	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P ^a	-	-	-	-	
Sildenafil	-	-	-	-	-	P ^b	-	-	-	-	-	-	-	S	-	-	P ^a /P ^b	I	-	-	-	
Simvastatin	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P ^a	-	-	-	-	
Sulfasalazine	-	-	-	-	-	-	-	-	-	-	-	-	-	S	-	-	WP ^b	I	-	-	-	
Tamoxifen	-	-	-	-	-	-	I	-	-	-	-	-	-	I	-	-	P ^a /P ^b	I	-	-	-	
Tetracycline	-	-	-	-	-	P ^b	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Trifluoperazine	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P ^a	I	-	P ^a	-	
Trospium chloride	-	-	-	-	-	-	-	-	-	WP ^b	-	-	-	-	-	-	-	-	-	-	-	
Valsopodar (PSC833)	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P ^a	I	-	-	-	
Vandetanib	-	-	-	-	-	-	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Verapamil hydrochloride	I	P ^a	P ^a	P ^a	P ^a /P ^b	P ^a	I	-	-	-	-	-	-	I	-	-	P ^a	I	I	P ^a /P ^b	I	
Vinblastine sulfate	-	-	-	-	-	-	-	-	-	P ^a /WP ^b	-	-	-	I	-	-	WP ^b	WI	-	P ^a	-	
2,4-D	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	I	-	-	
2-Acetylaminofluorene	-	-	-	-	-	-	-	-	-	-	-	-	-	S	-	-	WP ^b	WI	-	-	-	
2-CDEC	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P ^a	-	
AHTN	-	-	-	-	-	-	-	-	-	P ^b	P ^a /P ^b	-	-	-	-	-	-	-	-	P ^a	-	
Aldrin	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Aroclor 1254	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	WP ^a	
Arsenic Trioxide (As ₂ O ₃)	-	-	-	-	-	-	-	-	-	-	-	-	-	S	-	-	WP ^b	S	-	-	-	
Atrazine	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Azinphos-methyl	-	-	-	-	-	-	-	-	-	P ^b	-	-	-	-	-	-	-	-	-	-	-	
Benzo[a]pyrene (BaP)	-	-	-	-	-	-	-	-	-	-	-	-	-	S	-	-	WP ^b	WI	-	-	-	
BDE-3	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
BDE-47*	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
BDE-47-3-OH	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
BDE-49	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
BDE-100*	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
BDE-209	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Bisphenol A	-	-	-	-	-	P ^b	-	-	-	-	-	-	-	-	-	-	-	-	-	-	I	
Cadmium (Cd ²⁺)	-	-	-	-	-	-	-	-	-	S	-	-	-	-	I	-	WP ^b	WI	-	-	-	
Carbamazepine	-	-	-	-	-	-	-	-	-	P ^b	-	-	-	-	-	-	-	-	-	-	-	
Carbaryl	-	-	-	-	-	-	-	-	-	S ^b	-	-	-	-	-	-	-	-	-	-	-	
Celestrolide (ADB)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P ^a	-	
Chlorbenside sulfone	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P ^a	-	
Chlorpyrifos-methyl	-	-	-	-	-	-	-	-	-	-	-	-	-	I	-	-	WP ^b	S	I	-	-	
Cobalt (Co ²⁺)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	I	-	-	-	-	-	-	
DCPA	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P ^a	-	
Diazinon	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Diclorvos	-	-	-	-	-	S ^b	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Dieldrin*	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
-Dibutyltin chloride	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Diethyl phthalate (DEP)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Dimethoate	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Diuron	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Endrin*	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Endosulfan	-	-	-	-	-	-	-	-	-	-	-	-	-	I	-	-	P ^a	I	I	-	-	
Fenoxycarb	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P ^a	WI	I	-	-	
Fosalon	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P ^a	S	-	-	-	
Furathiocarb	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Galaxolide (HHC8)	-	-	-	-	-	-	-	-	-	P ^a	-	-	-	-	-	-	-	-	-	I	-	
Galaxolide (HHC8)	-	-	-	-	-	-	-	-	-	P ^a	-	-	-	-	-	-	-	-	-	I	P ^a	
Glyphosate	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Hexabromocyclododecane	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	WI	
Hexachlorobenzene	WI	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	

(Continued)

TABLE 2 | (Continued)

Compounds	Ta. Abcb1	D.r. MATE/Sic47					D.r. Oct1/Sic22a1	D.r. Oatp1d1/Sico1d1	D.r. Abcb4	D.r. Abcb4	D.r. Abcc2	D.r. Sic16a2/Mct8	O.m. Abcc	O.m. Abcc2	O.m. Abcg2a	O.m. Sic11	O.h. Abcc	Pl. P-gp1 (Abcb1)	Pl. P-gp1 (Abcb1)	D.p. gills	M.c. gills	P.m. larvae
	(ATPase activity, purified protein)	(HEK293 cells + DAPI)					(HEK293T cells)	(HEK293 cells)	(ZF embryos + RhB)	(LLC-PK1 cells & embryos)	(ZF embryos & ZF4 cells)	(COS-1 cells)	(intestine & enterocytes)	(intestine + calcein)	(Sf9 insect cells)	(X. laevis oocytes)	(intestine + calcein)	(PLHC-1 cells + CAM)	(ATPase activity, PLHC-1 membrane vesicles)	(whole gills + RhB)	(whole gills + RhB)	(larvae + CAM)
	Nickisch et al., 2021	Lončar et al., 2016 ^a Lončar and Smital, 2018 ^b					Mihaljević et al., 2017	Popović et al., 2013 ^a , 2014 ^b Marčić et al., 2021 ^c	Fischer et al., 2013 ^a Bieczyński et al., 2021 ^b	Lu et al., 2015	Long et al., 2011	Arjona et al., 2011	Painefilú et al., 2020	Bieczyński et al., 2014	Zaja et al., 2016	Cooper et al., 2007	Bieczyński et al., 2016	Caminada et al., 2008 ^a Zaja et al., 2011 ^b	Zaja et al., 2011	Smital et al., 2004	Cornwall et al., 1995 ^a Luckenbach and Epel, 2005 ^b Stevenson et al., 2006 ^c	Anselmo et al., 2012
		Mate3	Mate4	Mate6	Mate7	Mate8																
Iron (Fe ²⁺)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	S	-	-	-	-	-	-	
Lead (Pb ²⁺)	-	-	-	-	-	-	-	-	-	S	-	-	-	-	-	I	-	-	-	-	-	
Malathion	-	-	-	-	-	-	-	S ^b	-	-	-	-	-	S	-	-	I ^b	WI	I	-	-	
Malic Hydrazide	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	I	-	-	
Manganese (Mn2+)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	I	-	-	-	-	-	-	
Mercury (Hg)	-	-	-	-	-	-	-	-	-	S	-	-	-	-	-	-	W ^b	WI	-	-	-	
Metazachlor	-	-	-	-	-	-	-	I ^b	-	-	-	-	-	-	-	-	-	-	-	-	-	
Metolachlor	-	-	-	-	-	-	-	S ^b	-	-	-	-	-	-	-	-	-	-	-	-	-	
Methomil	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	I	-	-	
MPP+	-	I ^a	I ^a	I ^a	I ^a /S ^b	I ^a	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Mirex	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Musk ketone (MK)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	I ^b	-	
Musk xylene (MX)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	I	I ^b	-	
Nanoparticles P-85	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	I	
Nonylphenol	-	-	-	-	-	-	-	S ^b	-	-	-	-	-	-	-	-	-	-	-	-	-	
o,p'-DDT	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	I	
Paraquat	-	W ^b	I ^a	I ^a	W ^a	I ^a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
p,p'-DDD*	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	W ^a	
p,p'-DDE*	I	-	-	-	-	-	-	-	-	-	-	-	-	I	-	-	I ^b	I	-	-	W ^a	
p,p'-DDT*	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	W ^a	
PCB-118	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
PCB-134	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
PCB-142	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
PCB-145	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
PCB-146*	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
PCB-147	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
PCB-152	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
PCB-153	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
PCB-154	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
PCB-161	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
PCB-168	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
PCB-169	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
PCB-170*	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
PCB-186	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
PCB-187*	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Pentachlorophenol (PCP)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	I ^a	I	
PFDA	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	I ^c	-	
PFHxS	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	I ^c	-	
PFNA	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	I ^c	-	
PFOA	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
PFOS	-	-	-	-	-	-	-	S ^b	-	-	-	-	-	-	-	-	-	-	-	-	I	
Phenanthrene	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Phosalone	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	I	-	-	
Primicarb	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	I	-	-	
Propiconazole	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	I	-	-	
Tetrabutylammonium (TBA)	-	-	-	-	S ^b	-	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Tri-n-butyltin (TBT) chloride	-	-	-	-	I ^b	-	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Terbutylazine	-	-	-	-	-	-	-	I ^b	-	-	-	-	-	-	-	-	-	-	-	-	-	
Triethyltin chloride	-	-	-	-	I ^b	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Tetraethylammonium (TEA)	-	W ^b	I ^a	W ^a	I ^a	W ^a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	

(Continued)

TABLE 2 | (Continued)

Compounds	T.a. Abcb1 (ATPase activity, purified protein)	D.r. MATE/Slc47					D.r. Oct1/Slc22a1 (HEK293T cells)	D.r. Oatp1d1/Slc1d1 (HEK293 cells)	D.r. Abcb4 (ZF embryos + RhB)	D.r. Abcb4 (LLC-FK1 cells & embryos)	D.r. Abcc2 (ZF embryos & ZF4 cells)	D.r. Slc16a2/Mct8 (COS-1 cells)	O.m. Abcc (intestine & enterocytes)	O.m. Abcc2 (intestine + calcein)	O.m. Abcg2a (S9 insect cells)	O.m. Slc11 (X. laevis oocytes)	O.h. Abcc (intestine + calcein)	P.l. P-gp1 (Abcb1) (FLHC-1 cells + CAM)	P.l. P-gp1 (Abcb1) (ATPase activity, FLHC-1 membrane vesicles)	D.p. gills (whole gills + RhB)	M.c. gills (whole gills + RhB)	P.m. larvae (larvae + CAM)
		Mate3	Mate4	Mate6	Mate7	Mate8																
Thiacloprid	-	-	-	-	-	-	-	-	WP ^b	-	-	-	-	-	-	-	-	-	-	-	-	
Tetrapentylammonium chloride	-	-	-	-	I ^b	-	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Triphenyltin chloride	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Tetrapropylammonium chloride	-	-	-	-	S ^b	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Tri-n-propyltin chloride	-	-	-	-	I ^b	-	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Trasolide (ATI)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Triclosan (TCS)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	I ^b	-	
Zinc (Zn ²⁺)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	I	-	-	-	-	-	-	
17 α -Ethinylestradiol (EE2)	-	-	-	-	-	-	-	S ^b	-	-	-	-	-	-	-	-	-	-	-	-	-	
17 β -Estradiol (E2)	-	-	-	-	I ^b	-	I	PI/P ^b	-	-	-	-	-	-	-	-	WP ^b	WI	-	-	-	
19-Methyltestosterone	-	-	-	-	-	-	I	-	-	-	-	-	-	-	-	-	WP ^b	S	-	-	-	
Acetylcholine	-	-	-	-	-	-	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Androstenedione	-	WP ^b	I ^b	I ^b	I ^b	I ^b	I	I ^b	-	-	-	-	-	-	-	-	-	-	-	-	-	
Androstenediol	-	-	-	-	-	-	-	S ^a	-	-	-	-	-	-	-	-	-	-	-	-	-	
Bilirubin	-	-	-	-	-	-	-	I ^b	-	-	-	-	-	-	-	-	-	-	-	-	-	
Corticosterone	-	WP ^b	I ^b	I ^b	I ^b	I ^b	I	I ^b	-	-	-	-	-	-	-	-	-	-	-	-	-	
Cortisol	-	-	-	-	-	-	-	S ^a	-	-	-	-	-	-	-	-	-	-	-	-	-	
Cholate	-	-	-	-	-	-	-	I ^b	-	-	-	-	-	-	-	-	-	-	-	-	-	
Deoxycholate	-	WP ^b	WP ^b	WP ^b	I ^b	I ^b	-	I ^b	-	-	-	-	-	-	-	-	-	-	-	-	-	
DHEAS	-	WP ^b	I ^b	I ^b	I ^b	I ^b	-	I ^b	-	-	-	-	-	-	-	-	-	-	-	-	-	
Dihydrotestosterone	-	-	-	-	-	-	I	I ^b	-	-	-	-	-	-	-	-	-	-	-	-	-	
Estradiol 17 β -glucuronide	-	-	-	-	-	-	-	S ^a	-	-	-	-	-	-	-	-	-	-	-	-	-	
Estrone	-	-	-	-	-	-	-	I ^b	-	-	-	-	-	-	-	-	-	-	-	-	-	
Estrone 3-sulfate	-	-	-	-	-	-	-	S ^a	-	-	-	-	-	-	-	-	-	-	-	-	-	
Progesterone	-	-	-	-	-	-	I	I ^b	-	-	-	-	-	-	-	-	-	-	-	-	-	
Taurocholate	-	-	-	-	-	-	-	I ^b	-	-	-	-	-	-	-	-	-	-	-	-	-	
Taurochenodeoxycholate	-	-	-	-	-	-	-	I ^b	-	-	-	-	-	-	-	-	-	-	-	-	-	
Testosterone	-	I ^b	I ^b	I ^b	I ^b	I ^b	I	I ^b	-	-	-	-	-	-	S	-	-	-	-	-	-	
Thyroxine (T4)	-	-	-	-	-	-	-	-	-	-	S	-	-	-	-	-	-	-	-	-	-	
Thiamine	-	I ^b	I ^b	I ^b	I ^b	I ^b	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Triiodothyronine (T3)	-	-	-	-	-	-	-	I ^b	-	-	-	-	-	-	-	-	-	-	-	-	-	
Tyramine	-	-	-	-	-	-	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Microcystin-LA (MCLA)	-	-	-	-	-	-	-	I ^b	-	-	-	-	-	-	-	-	-	-	-	-	-	
Microcystin-LR (MCLR)	-	-	-	-	-	-	-	-	S	-	-	-	-	-	-	-	-	-	-	-	-	
Microcystin-LF (MCLF)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Microcystin-LW (MCLW)	-	-	-	-	-	-	-	I ^b	-	-	-	-	-	-	-	-	-	-	-	-	-	
Microcystin-YR (MCYR)	-	-	-	-	-	-	-	I ^b	-	-	-	-	-	-	-	-	-	-	-	-	-	
Paralytic shellfish toxins (PST)	-	-	-	-	-	-	-	-	-	-	-	I	-	-	-	-	-	-	-	-	-	

Compounds marked with an asterisk (*) have been previously identified as Transporter-Interfering Chemicals or TICs (Nicklisch et al., 2016, 2021; Nicklisch and Hamdoun, 2020). T.a., *Thunnus albacares*; D.r., *Danio rerio*; O.m., *Oncorhynchus mykiss*; O.h., *Odontesthes hatcheri*; P.l., *Poeciliopsis lucida*; D.p., *Dreissena polymorpha*; M.c., *Mytilus californianus*; P.m., *Psammecinus miliaris*; S, substrate; I, inhibitor; WI, weak interactor (i.e., compounds that are not recognized or weakly interact with MXR transporters and do not alter transporter activity or function (Nicklisch and Hamdoun, 2020)); BTs, biotoxins; NEM-SG, N-ethylmaleimide S-glutathione; CDEC, chloroallyl diethylthiocarbamate; AHTN, Acetyl-hexamethyltetrahydro-naphthalene; DCPA, Dimethyl tetrachloroterephthalate; MPP+, 1-methyl-4-phenylpyridinium; 2,4-D, 2,4-dichlorophenoxyacetic acid; DHEAS, dehydroepiandrosterone sulfate; PFDA, Perfluorodecanoic acid; PFHxS, Perfluorohexanesulfonate; PFNA, Perfluorononanoic acid; PFOS, Perfluorooctanesulfonic acid; PFOA, Perfluorooctanoic acid.

For instance, in the rectal salt glands of dogfish sharks (*Squalus acanthias*), ABCC2 activity was shown to be inhibited by the vasoconstrictor endothelin-1 via the ET_B receptor and protein kinase C signaling (Miller et al., 2002).

4. IMPLICATIONS OF TRANSPORTER INHIBITION FOR CHEMICAL BIOACCUMULATION AND NUTRIENT DEFICIENCIES

Many of the environmental chemicals that have been tested with MDR/MXR and nutrient uptake transporters were shown to be competitive substrates or inhibitors of the transporters in aquatic organisms. These so-called Transporter-Interfering Chemicals or TICs had been previously identified and shown to bind and inhibit mammalian and fish defense transporters, such as ABCB1 (Nicklisch et al., 2016, 2021; Nicklisch and Hamdoun, 2020). It has been hypothesized that the exact type of transporters also serve endogenous roles during development and for maintaining cellular and organismal homeostasis (Ahn and Nigam, 2009; Wu et al., 2011; Nigam, 2015, 2018). In addition, the known substrate overlaps and structural similarities between several nutrient and MDR/MXR transporter subfamilies would likely make nutrient uptake systems another target for TICs (Kaler et al., 2007; Truong et al., 2008; Ahn and Nigam, 2009). This is critical since the inhibition of both xenobiotic defense systems and nutrient uptake transporters can potentiate detrimental effects on a developing aquatic organism. Nutrient deficient animals, specifically with vitamin deficiencies, have been shown to grow slower and suffer from other conditions such as hypoxia, neurological disorders, immunosuppression, and lower reproductive viability (Deng et al., 2014; Wang et al., 2016; Pan et al., 2017; Harder et al., 2018; Talukder Shefat, 2018). Likewise, the inhibition of xenobiotic efflux transporters will further promote the accumulation of toxic substrates that are otherwise eliminated.

Hence, contaminant-laden diets can represent a critical exposure pathway for fish to toxic environmental chemicals and natural compounds (Streit, 1998; Mackay and Fraser, 2000; Macdonald et al., 2002; Armitage et al., 2013; Mackay et al., 2018). This is particularly relevant in aquaculture, as it has been demonstrated that farmed fish can carry higher pollutant loads than wild caught fish (Hites et al., 2004a,b). Feed contamination is a prevalent issue and includes persistent organic pollutants, such as polybrominated diphenyl ethers (PBDEs) and polychlorinated biphenyls (PCBs), and heavy metals such as mercury, arsenic, cadmium, iron, and lead (Choi and Cech, 1998; Dórea, 2006; Kundu et al., 2017; Biancarosa et al., 2019; Li et al., 2019). While individual levels of

these contaminants in fish feed or aquatic environments might be low, local tissue concentration in the digestive tract of these mostly hydrophobic compounds and the synergistic action of their mixtures can effectively act in concert to inhibit the protective efflux function of intestinal transport systems.

As such, it is important to both expand the panel of tested environmental chemicals and to include physiological transporters to evaluate the impacts on nutrient uptake, metabolism, and homeostasis. Furthermore, the transporter/chemical interaction assays need to be standardized and include co-exposures to chemical mixtures, representing environmental levels found in fish feed and/or the aquatic environment. Finally, given the differences in MDR/MXR transporter sequences between model and commercial fish species (Nicklisch et al., 2021), it is important to include MXR and nutrient transporters from commercial fish species to better predict and mitigate toxic chemical and heavy metal bioaccumulation fish and seafood species (Nicklisch et al., 2017a,b). Together, such studies will inform fish and shellfish advisories on guidelines for the selection of TIC-free aquaculture feed to develop safe eating guidelines.

CONCLUSION AND FUTURE DIRECTIONS

To date only a handful of MDR/MXR transporters have been cloned and functionally characterized in fish and aquatic invertebrates. Among those, the least characterized MXR transporter superfamily are the solute carriers (SLCs). Transporter localization, gene expression levels and endogenous and xenobiotic substrate/inhibitor identification has mainly focused on two model organisms: zebrafish and rainbow trout. Furthermore, there have been only a few studies conducted on fish feed and dietary levels of contaminants and transporter-mediated uptake and bioaccumulation in commercial fish and other human-relevant aquaculture species. Finally, the extent to which other mutable environmental factors, such as salinity, temperature, and pH, may impair the levels and function of MXR and other nutrient transporters remains elusive. This perspective further highlights the urgent need to identify novel TICs, to determine their environmental levels in the natural diets and feeds of fish and other aquatic invertebrates, and to specify the transporter targets that regulate their uptake and disposition in aquatic organisms. Special emphasis should be placed on determining the interactions of TICs with protective MXR efflux transporters and essential nutrient uptake transporters lining the gills and intestinal epithelia to better predict toxic chemical accumulation and/or nutrient deprivation. The key strategies to mitigate toxicant and toxin accumulation in aquatic organisms include targeted chemical analysis of fish feed in aquaculture operations, a continuous biomonitoring of TIC levels in lower trophic level organisms that serve as prey or feed for commercial

fish species and the development of regulatory guidelines that inform industrial chemical and agricultural pesticide management strategies to reduce or eliminate the use of environmentally persistent TIC compounds.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

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AUTHOR CONTRIBUTIONS

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