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Role of miRNAs in mediating organophosphate compounds induced toxicity

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ABSTRACT

Organophosphate compounds (OPCs) are a diverse class of chemicals utilized in both industrial and agricultural settings. The exact molecular pathways that OPCs-induced toxicity is caused by are still being investigated, despite the fact that studies on this topic have been ongoing for a long time. As a result, it's important to identify innovative strategies to uncover these processes and further the understanding of the pathways involved in OPCs-induced toxicity. In this context, determining the role of microRNAs (miRs) in the toxicity caused by OPCs should be taken into consideration. Recent research on the regulation function of miRs presents key discoveries to identify any gaps in the toxicity mechanisms of OPCs. As diagnostic indicators for toxicity in people exposed to OPCs, various expression miRs can also be used. The results of experimental and human studies into the expression profiles of miRs in OPCs-induced toxicity have been compiled in this article.

1. Introduction

A wide variety of chemicals with the intent to affect living systems, including pesticides, are used to preserve crops, produce food for agriculture, and prevent illness [1]. Widely used pesticides called organophosphates (OPs) cause neurotoxicity and cell death by abruptly inhibiting the acetylcholinesterase enzyme activity [2]. OPs can disrupt mitochondrial function by causing oxidative stress. Several neurological diseases, including Parkinson's disease, seizures, depression, and Alzheimer's disease, are caused by oxidative stress. Observational and experimental research have demonstrated negative impacts on human health from acute acetylcholinesterase inhibition toxicity and probably neurodegeneration from long-term low-level chronic OPs exposure, as found in Alzheimer's disease [3–6]. The molecular pathways relating to OPs and other pesticide-induced long-term toxicity are of tremendous interest for furthering our understanding [7]. Epigenetic modifications resulting from methylation arrays are a recent technology that can assist us in addressing the effects of persistent exposures, which may not cause acute toxicity [8]. The consequences of exposure to disease can then be evaluated, and potentially relevant indicators of chronic low-level exposure are provided by methylation patterns [9]. This is a significant obstacle in the creation of efficient prophylactic, medicines, and/or treatment procedures. The toxicity of OPCs has been studied for a long time, but it has been difficult to identify the precise molecular pathways, and this research is still ongoing [10]. As a result, it is crucial to try new approaches in order to understand these mechanisms and create a comprehensive network of pathways linked to OPCs-induced toxicity [11]. In addition to examining the function of miRs in OPCs-induced toxicity, it's critical to investigate how these molecules function in cellular and animal models of OPCs so that these effects can be investigated in the privacy of the lab for scientific inquiry and the creation of therapies considering that OPCs caused toxicity in human beings, furthermore, miRs, small, single-stranded noncoding RNAs, have important roles in modulating gene expression, specifically via translation repression [12]. The transcription of miRs inside the nucleus into primary miRs occurred and alter into precursor and finally mature miRs [13]. They involve in the regulation of cell progression, proliferation, senescence, inflammation, oxidative stress and apoptosis response, and also tumor genesis [14]. The synthesis and role of miR are shown in Fig. 1 briefly. miRs could also be implicated in the toxicity induced by pesticides and other toxicants, and it is necessary to explore these pathways [13]. miRNAs in Inflammatory Diseases have shown a notable

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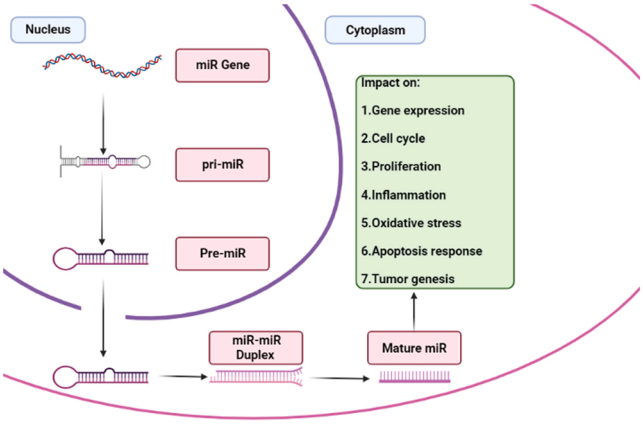

Fig. 1. The synthesis and role of miR in cells. The synthesis of miR begins with the transcription of the miR gene by RNA polymerase II. The resulting primary miR (pri-miR) is processed into pre-miR and moves to the cytoplasm. In the cytoplasm, the pre-miR undergoes further processing and synthesis of the miR: miR duplex. Finally, one strand of the duplex remains as mature miR, while the other strand is degraded. Once primed, mature miRs can repress target mRNA translation or facilitate target mRNA degradation.

overlap in the genetics and clinical manifestations. Among many studies, in Inflammatory DiseasesmiR-155 and miR-146a have received most of the attention. Overexpression of miR-155 in peripheral blood and peripheral blood-derived macrophages induces the production of tumor necrosis factor-alpha (TNF-a) and IL-1b by targeting the suppressor of cytokine signaling 1 (SOCS1). miR-146a acts as an important negative regulator of inflammatory and immune responses[15]. Proinflammatory cytokines play an important role in neurotransmission. By increasing organophosphates, it has increased the inflammatory cytokines TNF-α and IL-6 in the mouse brain[15]. The inflammation caused by organophosphates in the brain increases cytokines (interleukin 1 beta, IL-1β; tumor necrosis factor-alpha, TNFα; interleukin 6, IL-6), and chemokines and remains high for several days[16]. Exposure to organophosphates causes pulmonary damage through oxidative stress and inflammatory responses mediated by the Fkbp5/Nos3/MAPK/NF-κB signal pathway[17]. Recently, numerous studies have been focused on the role of miRs in OPCs toxicity. Therefore, this review study was destined on the role of miRs in the toxicity mediated by OPCs and tried to clarify the involved mechanisms.

2. Role of miRs in OPs-induced toxicity in various biological systems

In the following, the role of miRs in the toxicity caused by organophosphates in the nervous system, kidney, skin, growth and development system, as well as the role of miRs as diagnostic biomarkers of organophosphates have been investigated. Table 1 shows the studies that investigated the effect of organophosphates on the amount of miRs and their effects in different systems of living organisms.

3. Role of miRs in OPs-induced toxicity in nervous systems

The nervous system (NS) is one of the important sophisticated physiological systems, consisting of numerous different sorts of cells and complex synaptic connections as act in concert. Nervous system disorders (NSDs), a common class of disorders affecting the NS, are very complex; although the exact molecular mechanisms underlying most NSDs are not found [18]. Multiple studies have shown that exposure to OP exposure in humans and animals can lead to defects in childhood neurocognition and contribute substantially to neurodegenerative diseases such as Alzheimer's and Motor Neurone Disease. Organophosphates appear to help diseases characterized by axonal degeneration,

Table 1
miRNAs affected OPs toxicity.

Type of OP	miRNA	Pathway implicated	Ref
Chlorpyrifos(CPF)	miR-181	-suppress cell proliferation. -activate cell pyroptosis. -Increase susceptibility to stress-induced toxicity by -upregulating miR-181 through downregulating the SIRT1/PGC-1α/Nrf2 pathway in SH-SY5Y human neuroblastoma cells.	[21]
	miR-19a	-oxidative stress -miR-19a-AMPK axis disorder apoptosis and autophagy in common carp kidney	[29]
	miR-731 and miR-2188–3p	- could lead to damage of head kidney and obvious apoptosis characteristics. - mRNA expression of TLR pathway genes and its downstream genes involved in autophagy and apoptosis pathway including TLR1, TLR2, TLR7, TLR9, MyD88, IRAK1, IRAK4, IRF7, PI3K, AKT, mTOR, Caspase3, Caspase8 and Bax were increased. - ATG13 and Bcl2 decreased.	[30]
	miR-124	-CPF induces pyroptosis by regulating the miR-124–3p/CAPN1 axis. -Pyroptosis in EPC cells -mitochondrial dysfunction -Increasing the level of ROS	[34]
tris (1,3-dichloro-2-propyl) phosphate (TDCIPP)	rno-miR-361–3p, and rno-miR 702–3p	-It plays a role in the regulation of Traf2 gene expression. -It plays a role in regulating the NF-κB signaling pathway and causes apoptosis.	[22]
tri-ortho-cresyl phosphate (ToCP)	miR-966 and miR-281	-The flies treated with the OP compound tri-ortho-cresyl phosphate (ToCP) show behavioral deficits and neurodegeneration. -Flies with overexpression of both miRNAs (miR-966 and miR-281) in glia are also sensitive to ToCP.	[23]
Omethoate	miR-30a	-Cholinesterase (ChE) activity is decreased in workers exposed to emtate and exposed individuals. -Individuals carrying a (--/- T) genotype in miR-30a rs111456995 were more susceptible to damage in their cholinesterase induced by omethoate exposure.	[25]
Dichlorvos (DIC)	Up regulated miRNAs(miR-101, miR-1225, miR-124a-1, miR-155, miR-197, miR-202,miR-21, miR-325, miR-28–3p, miR-323, miR-	-Inhibiting proliferation and increasing apoptosis of PK15 cells	[26]

(*continued on next page*)

Table 1 (*continued*)

Type of OP	miRNA	Pathway implicated	Ref
	34c, miR-454, miR-505, miR-513a-5p, miR-7, miR-325, miR-711) - Down regulated miRNAs (miR-122, miR-138, miR-181, miR-184,miR-196a,miR-199a, miR-206,miR-24, miR-27ab,miR-29a,miR-96)		
	miR-513a-5p	-Overexpression of miR-513a-5p and induced apoptosis in HK-2 cells. -Promoted dichlorvos induced apoptosis in HK-2 cells through the Bcl-2/ Bax-Caspase-3 pathway.	[27]
Malathion	miR-96–5p	-Decreased HK-2 cell viability. -Decreased the expression of miR-96–5p. -MiR-96–5p protects HK-2 cells from malathion-induced ER stress-dependent apoptosis by targeting DDIT3.	[28]
Triphenyl phosphate (TPHP)	miR-137 and miR-141	-It causes developmental delay, phenotypic changes, and embryonic death of zebrafish. -It causes the down regulation of mmp9 and sox9b and the increase of miR-137 and miR-141. -the expression of both igf1b and sox9b decreased in both the presence and absence of the chorion in zebrafish embryos. -mmp9 expression was significantly reduced in dechorionated embryos.	[36, 37]
Chlorantraniliprole	miR-2b-3p and miR-14b-5pb	-overexpression in the transcript levels of potential target genes cytochrome P450 9f2 (CYP9F2) and 307a1 (CYP307a1)	[35]

such as Alzheimer's disease, Parkinson's disease, and motor neuron diseases (MND), including amyotrophic lateral sclerosis (ALS) and progressive bulbar palsy. Similar to humans, animal models have shown that adults are much more susceptible than adolescents[19]. Recently, several studies have focused on finding the mechanisms involved in miRs in NSDs. miRs have the main role in the critical function of NS including gene regulation and expression[20]. Fig. 2 shows the effect of various organophosphates and changes in miRs that cause death and dysfunction in nerve cells. Inappropriate expression of miRs has been involved in a wide range of NSDs. Over-expression of some miRs such as miR-30b-5p, miR-103a-3p, and miR-29a-3p is considered potential biomarkers in numerous PD patients. Glioblastoma (GBM) is the most common and lethal brain tumor [12]. miRs also play critical roles in the glioma process and several neuroimmune and neuroinflammation diseases [12]. Several experimental studies have indicated the involvement of miRs in mediating organophosphate compounds-induced neurotoxicity.

In this context, Zhao et al. investigated the effect of chlorpyrifos (CPF) on the human neuroblastoma cell line (SH-SY5Y cells), to find the

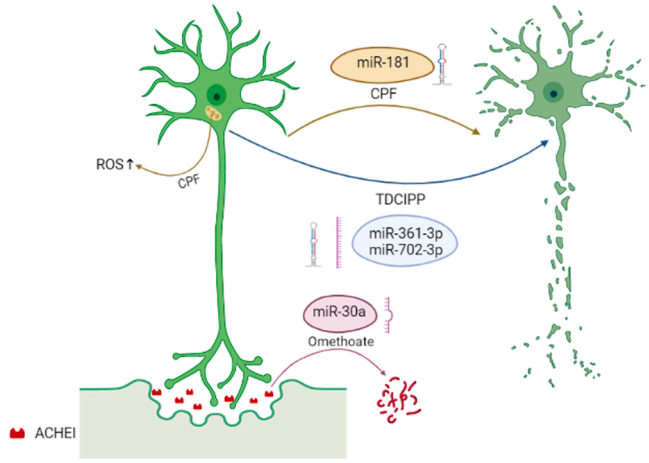

Fig. 2. OPs, including CPF, TDCIPP, affect the expression of miRs and increase ROS, causing the loss of neuron function and finally neuron necrosis. Also, Omethoate organophosphate destroys acetyl-cholinesterase-inhibitor enzyme through miR-30a.

possible roles of oxidative stress and cell pyroptosis in CPF-induced toxicity in SH-SY5Y cells, and also the role of miR-181/SIRT1/PGC 1α/Nrf2 signaling pathway in process of CPF-induced PD. It was found that CPF reduced cell viability in dose-dependent manner. The up-regulation of pyroptosis-related proteins, and ROS levels, as well as the level of caspase-1 was found in CPF-exposed cell lines. In addition, CPF increased miR-181 expression and inhibited SIRT1/PGC-1α/Nrf2 signaling. They also observed that Knockdown of Nrf2 was significantly associated with up-regulation of the expression of pyroptosis-related proteins, caspase-1, and ROS level while inducing Nrf2 expression inhibited this process. The inhibition of SIRT1 was accompanied with the down-regulation of PGC-1α and Nrf2 expressions, while over-expression of SIRT1 increased the levels of PGC-1α and Nrf2. It was found that induction of miR-181 potentiated the CPF-induced oxidative stress and pyroptosis, and also the down-regulated SIRT1/PGC-1α/Nrf2 signaling, while miR-181 inhibition indicated opposite findings. They suggested that CPF inhibited cell proliferation and through elevating miR-181, promoted cell pyroptosis and oxidative stress expression via downregulation of the SIRT1/PGC-1α/Nrf2 signaling in SH-SY5Y cells [21]. Tris (1,3-dichloro-2-propyl) phosphate (TDCIPP), an organophosphorus flame retardant (OPFR), has been indicated to have a neurotoxic effect. Li et al. found that exposure of PC12 to TDCIPP induced the upregulation of 1682 circRNAs and the down-regulation of 1750 of circRNAs. circRNAs are rich in microRNA (miRNA) binding sites, relieving the inhibitory effects of miRNAs on their target genes and increasing their expression levels. Through their interaction with microRNAs related to disease, circRNAs play important roles in the regulation of disease. It was observed that rno-miR-361–3p, rno_circRNA_013845, and rno-miR 702–3p may be implicated in the Traf2 expression, resulting in over-expression of NF-κB signaling and inducing apoptosis[22].

Tri-ortho-cresyl phosphate (ToCP) caused behavioral deficits and neurodegeneration in Drosophila swiss cheese (sws). The Drosophila sws mutants are models of progressive neurodegeneration, glial hypertrophy, and neuronal apoptosis. The findings indicated that the flies with overexpression of the whole sequence of sws and also with a functional knockout in glia are sensitive to organophosphate toxicity. In addition, it was found that flies with miR-966 and miR-281 over-expressions in glia are also sensitive to ToCP similar to sws functional knockout. However, overexpression of miRs at sws expression loci causes OP resistance [23].

Gautam et al. investigated the effect of soman on miR and mRNA expressions in brain regions associated with seizure activity in rats. Preliminary finding from the piriform cortex indicates marked

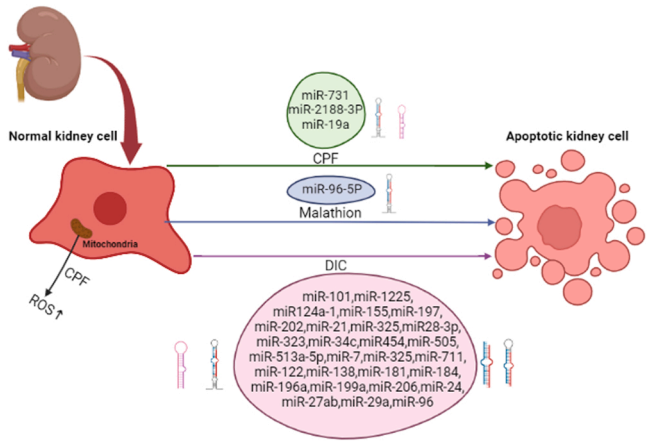

Fig. 3. OPs such as CPF, DIC, and Malathion affect the expression of cell miRs and increase ROS, causing the loss of renal cell function and ultimately renal cell necrosis.

differences in expression patterns of miR between epileptic rat and the control group. The miR expression in hypothalamus and amygdala, the hippocampus, piriform, medial prefrontal cortex, parietal cortex, and thalamus [24].

Zou et al. studied the relation between polymorphisms in miRs and the activity of cholinesterase (ChE) in omethoate-exposed workers and unexposed in Zhengzhou, China. The findings showed a lower activity of ChE in the omethoate-exposed subjects than the non-exposed group. The findings indicated the lower ChE activity of the exposure group in the (- -/- T) genotype in *miR-30a* rs111456995 than in the TT genotype. They suggested that subjects with (- -/- T) genotype in *miR-30a* rs111456995 were more susceptible to omethoate effect in their ChE activity[25].

4. Role of miRs in OPs-induced toxicity in the renal system

miRs can affect both normal and pathological situations in the kidney. Several miRs have been discovered in kidneys, where they have been demonstrated to play an important role in renal development and functions, and also in the pathogenesis of kidney disorders including acute kidney injury, diabetic nephropathy, polycystic kidney disease, lupus nephritis, etc., due to how they affect important genes implicated in these disease processes[26–31]. miRs have also been found as novel biomarkers in these kidney disorders [32]. Fig. 3 shows the miRs that cause dysfunction and death of renal cells.

Li et al. studied miR and mRNA expression profiles in a porcine kidney epithelial cell line (PK15) exposed to dichlorvos (DIC). DIC could inhibit the proliferation and induce apoptosis in PK15 cells. In addition, DIC upregulated 16 miR (miR-101, miR-1225, miR-124a-1, miR-155, miR-197, miR-202,miR-21, miR-325, miR-28–3p, miR-323, miR-34c, miR-454, miR-505, miR-513a-5p, miR-7, miR-325, miR-711) and 339 mRNAs and downregulated 14 miRs (miR-122, miR-138, miR-181,miR-184,miR-196a,miR-199a,miR-206,miR-24,miR-27ab,miR-29a,miR-96) and 282 mRNAs in PK15 cells [26].

Li et al. found that cytotoxicity of DIC in human kidney cell line HK-2 may be related to the up-regulation of miR-513a-5p. Over-expression of miR-513a-5p induced apoptosis and oxidative stress in HK-2 cells with or without exposure to DIC, however, inhibition of miR-513a-5p suppressed apoptosis induced by DIC. miR-513a-5p reduced the Bcl-2 level and potentiated apoptosis induced by DIC in HK-2 cells via the Bcl-2/Bax-Caspase-3 pathway. They suggested that miR-513a-5p potentiated DIC-induced apoptosis by affecting Bcl-2 [27].

Li et al. assessed the role of miR-96–5p in Malathion toxicity in HK-2 cells. Malathion reduced cell viability and the miR-96–5p expression. Transfection with miR-96–5p decreased malathion-induced apoptosis, whereas its inhibitor elevated apoptosis. They found that miR-96–5p decreased malathion-induced apoptosis by targeting the DDIT3/B-cell lymphoma (BCL)−2/caspase-3 signaling pathway in HK-2 cells [28].

Zhang et al. found that CPF increased the expressions of TSC complex subunit 2 (TSC2), light chain 3 (LC3), Dynein, tumor protein 53 (p53), Bcl-2 associated X protein (Bax), caspase-3 and caspase-9 and reduced the expressions of mechanistic target of rapamycin (mTOR), Ras homolog mTORC1 binding (Rheb) and B-cell lymphoma (Bcl-2) via inhibition of miR-19a expression, resulted in autophagy and apoptosis in the kidney of common carp[29]. Liu et al. found that CPF exposure for 30 days could cause through the control of miR-2188–3p and miR-731 by targeting the TLR pathway, apoptosis while inhibiting autophagy in the head kidney of common carp [30].

5. Role of miRs in OPs-induced skin toxicity

For the consistency of signal transduction, transcriptional activity, and the maintenance of homeostasis in numerous organs, including the skin, miR-mRNA interaction is crucial [33]. The interaction between miRs and mRNAs is necessary for the stability of transcriptional and signal transduction processes, and also the homeostasis maintenance in the skin [33]. Miao et al. investigated the role of the miR-124–3p/-CAPN1 axis in the toxic effect of CPF on epithelioma papulosum cyprini (EPC) cell pyroptosis. They found that CPF exposure caused miR-124 overexpression and inhibition EPC cell models. CPF-exposed EPC cells induced pyroptosis followed by a reduction in mitochondrial membrane potential and increase in the level of ROS. It was found that PD150606, CAPN1 inhibitor, potentiated CPF-induced mitochondrial dysfunction, and the elevated NLRP3, CASP1, IL1β and GSDMD expressions. They suggested that CPF caused pyroptosis by modulating the miR-124–3p/CAPN1 axis [34].

6. Role of miRs in OPs-induced developmental toxicity

Numerous studies have suggested that miRs may control post-transcriptional gene regulation by specifically targeting mRNAs important for early embryonic development [21]. Two enzymes are required for miR maturation: Drosha and Dicer [21]. In addition, miR-2b-3p mimics considerably higher mortality in deltamethrin-resistant larvae when added to the diet of P. xylostella. The findings imply that miR-2b-3p may decrease CYP9F2 mRNA levels in P. xylostella and hence prevent the larvae's ability to detoxify [35]. The findings give some insight into how miRs may control how resistant insects are to insecticides metabolically.

Tran et al. evaluated the effect of six major OPC (stributyl phosphate (TBP), tris (2-butoxy ethyl) phosphate (TBOEP), and triphenyl phosphate (TPHP), tris (2-chloroethyl) phosphate (TCEP), tris(1,3-dichloro-2-propyl) phosphate (TDCIPP), and tris (1-chloropropyl) phosphate (TCPP)) in chorinated and dechorionated zebrafish embryos. Chorion removal increased the sensitivity to OPCs, as evidenced by higher mortality and malformation in embryos. The locomotive activity of chorinated and dechorionated zebrafish was significantly decreased by OPCs. TPHP inhibited the expression of miR-137 and miR-141 in chorinated embryos. TPHP decreased the expression of both igf1b and sox9b in both chorinated and dechorionated zebrafish. However, TPHP could not change mmp9 expression in chorionated embryos, but reduced it in dechorionated embryos. They also found that TPHP increased the expression of miR-141 and miR-137 in dechorionated embryos, but could not change their expression in chorionated embryos [36]. Epigenetic deregulation of miRNAs modulates genes involved in phenotypic tail defects in TPHP-triggered developmental toxicity. Over-expressed in TPHP-exposed zebrafish embryos, and the reduced expression of mmp9 and sox9b was compensated after microinjection of miR-137 and miR-141 inhibitors[37]. Src is stimulated by many cytokines and growth factors like TGF-β1 and EGF, resulting in the autophosphorylation of Tyr416. miR-137 has complementarity to the 3′-untranslated region (3′UTR) of Src mRNA targeting Src and inactivating the MAPK signaling

Table 2
miRs useful for therapeutics and diagnostics of OPs toxicity.

Type of OP	miRNA	Diagnostic	Pathway implicated	Ref
Fipronil	miR-199, miR-22b and miR-499)decrease(	-	-	[42]
triazophos	miR-135c, miR-30b, and miR365)decrease(miR-21, miR-31, miR-203b and miR-455)increase(	-miR-30b, miR-21 and miR-31 had been found implicated in tumorgenesis -miR-30b showed overexpressed in polycythemia vera reticulocytes -miR-21 was overexpressed in ovarian cancer	miR-21 had been experimentally tumor suppressors such as caspase-3 and caspase-7 in glioblastoma cells, RECK and TIMP3 genes, phosphatase and tensin homolog tumor suppressor gene in hepatocellular cancer, and tropomyosin	[42]
Fipronil-triazophos) combination(	miR-128 and miR-9)decrease(miR-203b and miR-735)increase(	-	-	[42]
tris(2-butoxyethyl) phosphate)TBOEP (	-miR-125c-3p, miR-133b-3p, miR-133c-3p, miR-1388–3p,−1388 to 5p, miR-1788–3p,−187,−200c-5p, miR-202–5p, miR-222b, miR-458–3p, miR-459–3p, miR-499–5p, miR-736, miR-9–3p)Up regulated(-miR-135a, miR-153a-3p, miR-153c-3p, miR-203a-3p, miR-203b-3p, miR-205–5p, miR-212, miR-216a, miR-216b, miR-2017, miR-375, miR-430b-5p, miR-725–3p, miR-734,−738, miR-7a)Down regulated(	Investigating epigenetic changes in miRNA, a method to evaluate aquatic toxicity	- pyruvate metabolism pathway -propanoat metabolism pathway -glycine serine and threonine metabolism pathway -fatty acid degradation -beta-Alanine metabolism	[43]
tris(1,3-dichloro-2-propyl) phosphate (TDCIPP)	-let-7a,let-7d-5p,let-7e,let-7 f,let-7 g,let-7i,miR-101a, miR-103, miR-107a-5p, miR-107b, miR-10b-5p, miR-10c-5p, miR-10d-5p, miR-125b-3p, miR-129–5p, miR-135b-5p, miR-1388–5p, miR-144–5p, miR-148, miR-152, miR-16a, miR-16b, miR-182–5p, miR-199–3p, miR-19a-3p, miR-19b-3p,− 19d-3p, miR-202–5p, miR-20b-5p,− 222a-5p, miR-25–3p, miR-27a-5p, miR-30a-3p, miR-30e-3p, miR-31, miR-34b, miR-363–5p, miR-375, miR-456, miR-724, miR-9–5p)Up regulated(-miR-100–5p, miR-125b-5p, miR-125c-5p, miR-138–5p, miR-142a-3p, miR-142b-5p, miR-144–3p, miR-153a-3p,- miR153c-3p, miR-1788–3p, miR-193a-3p, miR-194b, miR-19a-5p, miR-203b-3p, miR-205–5p, miR-20a-3p, miR-212, miR-216a, miR-216b, miR-2187–3p, miR-218a, miR-22b-3p, miR-26a-5p, miR-27d, miR-301b-3p, miR-30a-5p, miR-338, miR-365, miR-429a, miR-430b-3p, miR-4603p, miR-460–5p, miR-725–3p, miR-727–3p, miR-731, miR-9–3p, miR-99 Down regulated(	Investigating epigenetic changes in miRNA, a method to evaluate aquatic toxicity	- starch and sucrose metabolism -Renin-angiotensin system -phosphatidylinositol signal system -inositol phosphate metabolism -glycerophospholipid metabolism	[43]
triphenyl phosphate (TPHP)	-miR-10a-3p, miR-10a-5p, miR-10b-3p, miR-10b-5p, miR-10d-5p, miR-125c-3p, miR-181b-5p, miR-193b-3p, miR-221–5p, miR-489)Up regulated(-miR-1788–3 P , miR-184, miR-202–5 P, miR-205–5 P, miR-214, miR-459–5 P, miR-725–3 P, miR-738)Down regulated(	Investigating epigenetic changes in miRNA, a method to evaluate aquatic toxicity	- Steroid biosynthesis - Metabolic pathways -Lysosome -Butanoate metabolism	[43]
Chlorpyrifos (CPF)	214 miRNAs in at least one sample after a thorough study of the expression patterns of control and CPF-treated carp	biomarkers for the detection of CPF contamination in water	- Majority of this miRNA participated in protein biosynthesis, nucleotide binding,and oxidation-reduction activities.	[44]
Pesticide	miR-223–518d-3p, miR-597, miR-517b, & miR-28–5p(positively correlated)	-miRNAs may be novel biomarkers of pesticide exposure	-miR-517b, MiR-133b and MiR-597 are associated with target genes involved in neuronal functions, including receptor binding and neurotransmitter activity -miR-28–5p is associated with the common pathways of acetylcholine binding, acetylcholinesterase activity, and cholinesterase	[45]
Benomyl	miR-17 and miR221 were overexpressed	significant correlation between miR-17 and miR-221 levels and the risk of cancer		[47]
Carbaryl	miR-17 and miR221 were overexpressed	significant correlation between miR-17 and miR-221 levels and the risk of cancer		[47]
Malathion	miR-17 and miR221 were overexpressed	significant correlation between miR-17 and miR-221 levels and the risk of cancer		[47]
Diazinon	miR-17 and miR221 were overexpressed	significant correlation between miR-17 and miR-221 levels and the risk of cancer		[47]

pathway[38,39]. miR-141 overexpression reduces chondrocyte proliferation, apoptosis, and extracellular matrix degradation. And also decreasing the level of miR-141 increases the expression of CUL3, which is a scaffolding protein of the choline family, whose increase is dangerous in late embryogenesis[40].

Tran et al. found that TPHP caused abnormal tail development accompanied with down-regulation of sox9b and mmp9. In addition, they found that TPHP induces the expression of two miRs (i.e., miR-137 and miR-141) in zebrafish embryos. The administration of miR-137 and miR-141 inhibitors compensated for the decreased expression of mmp9 and sox9b following exposure to TPHP. It indicates that TPHP caused tail defects through deregulation of miRs in zebrafish embryos [37].

7. miRs may serve as diagnostic biomarkers for exposure to OPs

miR has an essential role in tumor cell functions, such as cell division, metastasis, differentiation, development and apoptosis. Several discussions indicated the different expression of miRs in cancerous and normal tissues. Considering that miRs are very specific for different tissues and cells in those tissues, several investigations have identified miR patterns in different types of cancer, which have shown the diagnostic and prognostic efficacy of miRs in clinical applications [41]. Table 2 shows cases where miRs were used as biomarkers for organophosphates. In this context, Wang et al. evaluated the effect of triazophos and fipronil and their mixture on the expression of miR in adult zebrafish. After 4 days, these chemicals induced the expression of 21 miRs in the liver. Fipronil, triazophos, and their mixture led to different expression of 14 miRs. Formulations of these chemicals altered the expression level of 5 miRs. The expression of 7 miRs of 14 miRs differs after treatment with triazophos. A reduction in expression levels of miR-135c, miR-30b, and miR365 and an increase in expression of miR-21, miR-31, miR-203b, and miR-455 were observed. Fipronil downregulated the expression of three miRs including miR-199, miR-22b, and miR-499. Treatment with triazophos plus fipronil decreased the expression of miR-128 and miR-9 and increased the expression of miR-203b and miR-735. Triazophos induced the expression of miR-30b, miR-21, and miR-31 in tumorigenesis. The over-expression of miR-30b was observed in polycythemia vera reticulocytes. miR-21, an oncogene miR, which is highly upregulated across a range of tumor cells and tissues and modulates various tumor suppressors including caspase-3 and caspase-7 in cultured glioblastoma cells, RECK and TIMP3 genes in vitro and in a human model of gliomas in nude mice, phosphatase and tensin homolog tumor suppressor gene in hepatocellular cancer, and tropomyosin 1 in breast cancer MCF-7 cells. The over-expression of miR-21 was observed in the gut, ovaries, and testis of adult zebrafish. In addition, the over-expression of miR-21 was found in cancers of the human homolog of the gut. miR-21 was over-expressed in ovarian cancer, cardiocytes, and colon cancer SW480 cells [42].

The effects of sub-acute organophosphorus flame retardants (OPFRs) exposure on the miR and the 3′ isomir expression profiles of the liver of Chinese rare minnows were studied. A total of 84, 32, and 19 different expression of miRs were identified for exposure to tris (1,3–dichloro-2–propyl) phosphate (TDCIPP), tris(2–butoxyethyl) phosphate (TBOEP), and triphenyl phosphate (TPHP), respectively. Target prediction of the differentially expressed miRs and pathway enrichment analysis showed that anticipated changed mRNAs for all three OPFRs were linked to metabolic pathways, whereas base excision repair was only predicted to be affected by the TPHP therapy. Furthermore, 3′ isomiR-Us (e.g., miR-143) were abundantly observed in all groups, and TDCIPP elevated the ratio expression of 3′ isomiR-U. Significant levels of miR-1788 3p were observed in the TBOEP group versus the control groups. The increased expression of miR 202 5p and the decreased expression of miR 205 5p were observed in TBOEP and TDCIPP groups. The decreased expression of miR 725 3p was found in TBOEP and TPHP groups. The existence of differences in the amount of miR expression changes (e.g., miR 205 5p, miR 202 5p, and miR 725 3p) is undeniable. Based on small RNA sequencing, the global expression of miRs indicated the detection of 113 different expression of miRs in the liver following 2 weeks of exposure to OPFR. The decrease in the expression of miR 202 5p, miR 1788 3p, miR 205 5p, miR 205 5p, miR 725 3p, and miR 725 3p was observed in all treated groups [43].

Fu et al. studied the chlorpyrifos effect on gene expression, ribosome biogenesis, and oxidative damage in the liver of common carp (Cyprinus carpio L.). It was found that CPF could change the expression of 1746 from 23,742 genes. These genes were involved in nucleotide binding, protein biosynthesis, and oxidation-reduction activities. The study also found changes in the expression of miR in common carp exposed to CPF exposure [44]. The urinary miRs were considered diagnostic biomarkers of pesticide exposure. Among 384 miRs, 297 miRs were found in one sample. Almost 50% of the samples have 7 miRs, and 96% of the samples have 1 miR. The expression of miR-223–518d-3p, −517b, −597, and −28–5p were detected in the urine of farmworkers in the post-harvest season. From them, the expression of 5 was associated with organophosphate pesticide metabolites in farmworkers. MiR-133b, MiR-517b, and MiR-597 are involved in neurological functions and miR-28–5p is implicated in pathways underlying acetylcholine binding, acetylcholinesterase activity, and cholinesterase activity during Ops exposure [45].

Zhengzhou et al. evaluated the association between polymorphisms of encoding miR genes and telomere length in Chinese workers exposed to omethoate. The result indicated that the miR-145 rs353291 genetic polymorphism and amount of exposure to omethoate were associated with lengthened telomere length of peripheral blood leukocyte cells in the workers exposed to omethoate [46].

The real-time PCR assay on the effect of benomyl, carbaryl, malathion and diazinon on the expression of two oncogenic miRs (miR-17 and miR-221) in male Balb/c mice indicated the over-expression of miR-17 and miR221 in all exposed animals. The study suggested the oncogenic properties of pesticides via dysregulation of two oncogenic miR-17 and miR221 [47].

8. Conclusion

According to the numerous findings from the research, it was suggested that miRs have the main role in OPs-induced toxicity. Several miRs clusters have been found to be related to OPs-induced toxicity within various organ systems. The miR families involved in oxidative stress inflammation, necrosis, proliferation, oncogenesis, and apoptosis have been found in OPs-induced toxicity. Due to the stability of miRs at room temperature, they have been used as diagnostic biomarkers for OPs toxicity. Therefore, epigenetic alterations in miR gene transcription is a suitable method for the evaluation of OPs toxicity. This would aid in developing preventive measures, diagnostic tools, and therapeutic approaches in addition to improving our fundamental understanding of the underlying mechanism of SM-induced toxicity. This will not only help expand our fundamental understanding of the involved mechanism of OPs-induced toxicity, but also help to find preventive, diagnostic, and therapeutic strategies.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

No data was used for the research described in the article.

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