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MicroRNAs and Xenobiotic Toxicity: An Overview

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ABSTRACT

The advent of new technologies has paved the rise of various chemicals that are being employed in industrial as well as consumer products. This leads to the accumulation of these xenobiotic compounds in the environment where they pose a serious threat to both target and non-target species. miRNAs are one of the key epigenetic mechanisms that have been associated with toxicity by modulating the gene expression post-transcriptionally. Here, we provide a comprehensive view on miRNA biogenesis, their mechanism of action and, their possible role in xenobiotic toxicity. Further, we review the recent *in vitro* and *in vivo* studies involved in xenobiotic exposure induced miRNA alterations and the mRNA-miRNA interactions. Finally, we address the challenges associated with the miRNAs in toxicological studies.

1. Introduction

Xenobiotics are chemical compounds foreign to the body or ecosystem that are identified persistently in the environment which are accumulated by means of anthropogenic sources. With a stupendous increase in chemicals being synthesized for various sectors, all these compounds end up being dumped into the environment posing a risk for all forms of life from microbes to animals including humans [1]. Once they enter the biological systems, they affect the homeostasis of the body leading to various adverse effects including the alteration in the genes. These alterations in the genes are both stable and transient. One aspect of gene expressions upon exposure to these xenobiotics is controlled by epigenetic mechanisms [2]. Epigenetics in simple terms involves the regulation of genes without altering the nucleotide sequence [3]. They control the gene expression on both transcriptional and translational levels. This includes non-coding RNAs.

miRNAs are short non protein-coding RNAs of ~22 nucleotides in length. They fine-tune the gene expression in response to various external stimuli, including environmental toxicants [4]. Their role in gene regulation was first identified in *Caenorhabditis elegans* in the early 90's.

Abbreviations: ADAMTS9, A disintegrin and metalloproteinase with thrombospondin motifs 9; Ag, Silver; AHR, Aryl Hydrocarbon Receptor; Al_2O_3, Aluminium oxide; AMPK, Adenosine Monophosphate-activated protein kinase; ARRB1, Arrestin beta 1; Au, Gold; Aβ, Amyloid Beta; BaP, Benzo[a]pyrene; BCB, Blood-cerebrospinal fluid barrier; bcl2l11, B-cell lymphoma-2-like protein 11; BNIP3 − 3, BCL2/adenovirus E1B 19 kDa protein-interacting protein 3; CCNB1, Cyclin B1; CDC25A, M-phase inducer phosphatase 1; CDC25C, M-phase inducer phosphatase 3; CDK, Cyclin-dependent Kinase; CDK1, Cyclin-dependent kinase 1; CDK6, Cyclin-dependent kinase 6; CDKN1b, Cyclin-dependent kinase Inhibitor 1B; CEC, Contaminants of Emerging Concern; ceRNA, Competing endogenous RNA; COPD, Chronic obstructive pulmonary disease; COX2, Cyclooxygenase-2; CTGF, Connective Tissue Growth Factor; DGCR8, DiGeorge syndrome chromosomal [or critical] region 8; DNA, Deoxy ribonucleic acid; DON, Deoxynivalenol; ER, Endoplasmic Reticulum; Fadd, Fas-associated protein with death domain; Grp78/BIP, Binding immunoglobulin protein; GTP, Guanosine triphosphate; Hpf, Hours post fertilization; HSPA1A, Heat shock 70 kDa protein 1; IL1R1, Interleukin 1 receptor, type 1; IL-6, Interleukin 6; lncRNAs, Long non-coding RNA; LIN28B, Lin-28 homolog B; LRP-1-, Low density lipoprotein receptor-related protein 1; MAPK, Mitogen Activated Protein Kinase; MC-LR, Microcystin-Leucine Arginine; MC-RR, Microcystin-Arginine Arginine; miRNA, MicroRNA; Mn, Manganese; MRE, MicroRNA Response Elements; mRNA, Messenger RNA; NASH, Non-alcoholic steatohepatitis; NET1, Neuroepithelial Cell Transforming 1; NF- κB, Nuclear Factor kappa-light-chain-enhancer of activated B cells; NFKBAP, NFKB Activating protein-1; NMDAR, N-methyl-d-aspartate receptor; NPs, Nanoparticles; Nrf2, Nuclear factor erythroid 2-related factor 2; PDCD4, Programmed cell death protein 4; PFAS, Poly-fluoroalkyl substances; $PM_{2.5}$, Particulate $Matter_{2.5}$; qRT-PCR, quantitative Real Time-Polymerase Chain Reaction; ripk 1, Receptor-interacting serine/threonine-protein kinase 1; RISC, RNA-induced silencing complex; RNAi, RNA interference; RNA, Ribonucleic acid; RNase III, Ribonuclease III; SEMA6D, Semaphorin-6D; SiO_2, Silicon dioxide; SOLiD, Sequencing by Oligonucleotide Ligation and Detection; SPIONs, Superparamagnetic Iron Oxide Nanoparticles; TCDD, 2,3,7,8-Tetrachlorodibenzodioxin; TNF-α, Tumor necrosis factor – alpha; TP53, Tumor protein 53; TRBP, Transactivation Response RNA Binding Protein; UTR, Untranslated region; WHO, World Health Organization; Wnt, Wingless-related integration site; ZEA, Zearalanone; Zn, Zinc

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There, the first identified miRNA (LIN 4) negatively regulated the gene which is involved in the post-transcriptional development (LIN14) [5,6]. Soon, they have been identified to play a major role in the post transcriptional regulation of genes finding their ways in health and other aspects [7]. Their interactions with environmental toxicants are being explored due to their rising importance as quoted by Lema and Cunningham [8] "Increasing evidence that the expression of microRNAs is affected by several known toxicants as well as oxidative and other forms of cellular stress certainly suggest an important role of microRNAs in toxicology, which could provide a link between environmental influences and gene expression."

2. miRNA biogenesis and their mechanism of action

Extensive research has been carried out to understand the synthesis and function of miRNAs with other epigenetic mechanism also regulating miRNA biogenesis [9]. miRNAs are transcribed by RNA polymerase II/III, either from the intron regions of the protein-coding genes (intragenic) or independently with their own (intergenic) promoters [10,11]. The canonical pathway is the major pathway through which the majority of miRNAs are processed. After transcription, pri-miRNAs are processed into pre-miRNAs by a microprocessor complex. This complex includes RNA binding protein DGCR8 and a ribonuclease III enzyme Drosha, which cleaves the pri-miRNA duplex to form an overhang at 3′ of pre-miRNA of ~70 nt [10]. Once processed, they are exported to the cytoplasm *via* exportin 5 (XPO5)/RanGTP complex [12,13]. After the export, Dicer, RNase III endonuclease along with TRBP, cleaves the pre-miRNA to form a mature miRNA complex which has a guide strand and a passenger strand [14]. The passenger and guide strands are selected based on various factors, including thermodynamic stability. They both are loaded into argonaute proteins where the passenger strand is subsequently degraded [15]. Various canonical pathways have been elucidated. One such pathway is used by mirtrons, miRNAs that are obtained from introns of mRNA during splicing. Others include miRNAs generated from small nucleolar RNA precursors. However, recent research suggests that even in the absence of Dicer, some of the miRNAs can be produced *via* alternative pathways proving the highly complex machinery which is yet to be studied [16].

Studies on miRNA mediated gene regulation are predominantly based on gene silencing *via* translational repression and mRNA degradation (Fig. 1). miRNA induced gene silencing is performed by miRISC which consists of the argonaute protein and the guide strand. They bind to the specific sequence at the 3′ UTR (MRE) of their target mRNA. A full complementary of miR:MRE leads to mRNA slicing while most of the miR:MREs are partially complementary leading to translational inhibition and mRNA decay [17]. miRNA has also been shown to bind to the 5′ UTR and other coding regions leading to gene silencing [18]. However, various research has shown the ability of miRNA to induce transcription as well as translation ([19] [20]). Further studies are needed to understand and validate the functional interaction.

3. Role of miRNAs in xenobiotic toxicity

Aberrant expression of miRNAs has been shown to play a major role in disease pathology, including cancer. The miRNAs are being studied for their non-invasive uses in prognosis, diagnosis and therapeutics [21,22]. Various compounds induce carcinogenicity and other forms of toxicity upon exposure to biological systems. Numerous *in vitro* (Table 1) and *in vivo* (Table 2) studies have been conducted which provide us an overview of miRNAs alteration and their target gene regulation in response to xenobiotic exposure. Most of the studies use a variety of techniques to study miRNAs key aspects. This includes miRNAs identification, *in silico* prediction, expression and functional validation (Fig. 2). These combined studies help us to better understand how miRNAs are regulated during different toxicant exposure. The reviewed chemicals include major toxicants that are grouped on the basis of their characteristic behaviour and their physio-chemical attributes.

3.1. Carcinogens

BaP, a model polyaromatic hydrocarbon is present in coal tar, tobacco products and some foods, in particular smoked foods, which are well-known for their carcinogenicity. Mostly, aromatic hydrocarbon-induced toxicity is mediated by AHR pathway. An early study conducted by Duan et al. [25] on murine bronchial epithelial cells showed that BaP can induce tumorigenesis by inhibiting CDK6, which plays a key role in G1/S transition using miRNAs (miR-320 and miR-494) . However, further studies on human cell lines did not identify any significant change in these miRNAs upon exposure to BaP. This could be due to variable changes, including the fact that the expression of miRNAs and their regulation has been shown to be spatio-temporal. Interestingly, the other studies consistently showed that miRNAs alteration targets cell proliferation and survival pathways upon exposure to BaP [40]. Similarly, some of the miRNAs (miRNA-29b, miRNA-26a-1, and miRNA-122) have been shown to regulate numerous pathways like cell cycle, apoptosis and DNA damage repair concordantly [27].

Dioxins are a group of halogenated aromatic hydrocarbons known to induce various toxicity including cancer. In the mouse model, exposure to dioxin showed alteration in the levels of miR-101a and miR-122. The miR-101a targets the COX2 which catalyses the prostanoid signalling pathway leading to liver damage [66]. Also, miR-122 role in cell proliferation and its alteration upon exposure to xenobiotics has been reported earlier [27]. TCDD in zebrafish embryos disrupted the normal homeostasis development with the deregulation of miRNAs prominently involved in haematopoiesis and cardiovascular development (miR-451, miR-23a, miR-23b, miR-24 and miR-27e). They used a variety of methods to identify the altered miRNAs including microarrays, SOLiD sequencing and qRT-PCR and identified only one miRNA (miR-27e) that was differentially expressed [68]. Bisphenol A is a widely used chemical with endocrine disruption and carcinogenic activity. It alters the miRNA (miR-22) involved in the MAPK pathway by targeting ARRB1, NET1, IL1R1, and HSPA1A in HepG2 cells [16].

An interesting study by Xu et al. (2020) have investigated the miRNA alterations in serum of human subjects who were exposed to increased quantities of PFAS through drinking water. Xu et al. identified that the repression of miR-101 − 3p, miR-144 − 3p and miR-19a-3p is in correlation with the target genes that are involved in carcinogenicity, cardiovascular function, and cell proliferation[130]. Circulating miRNAs is being studied recently with the reports of their involvement in various pathologies. This is one of the studies that include the role of exogenous miRNAs in xenobiotic exposure.

3.2. Metals and metalloids

Metals, especially heavy metals, are a major class of environmental contaminants. Research is being conducted to understand the effect of miRNAs in response to metals, including heavy metals, as metals have been known to impair vasculogenesis [101]. Lead, a potent neurotoxicant has been shown to induce BCB leakage in murine choroidal epithelial cells. The mechanistic study showed that the increase in the expression of miR-203 leads to tricellulin mRNA degradation. Tricellulin, a protein in the epithelial cells, helps in the formation of tight junctions in these barriers [36]. Studies on metal-exposed miRNA alterations in pregnant women are scarce. A study by Sanders et al. [72] showed that pregnant women in Mexico had been exposed to heavy metals such as lead and mercury, as evidenced by the presence of lead in the blood (> 5 μg/dL in 10 % of patients) as well as in the patellar and tibia bones. Increased lead exposure during gestation has been related to premature birth. These patients' cervical cells were collected to identify miRNAs and their correlation with lead concentration. Two notable miRNAs were identified in the blood (miR-297 and miR-188) which target more than 40 genes and 7 miRNAs were found in the

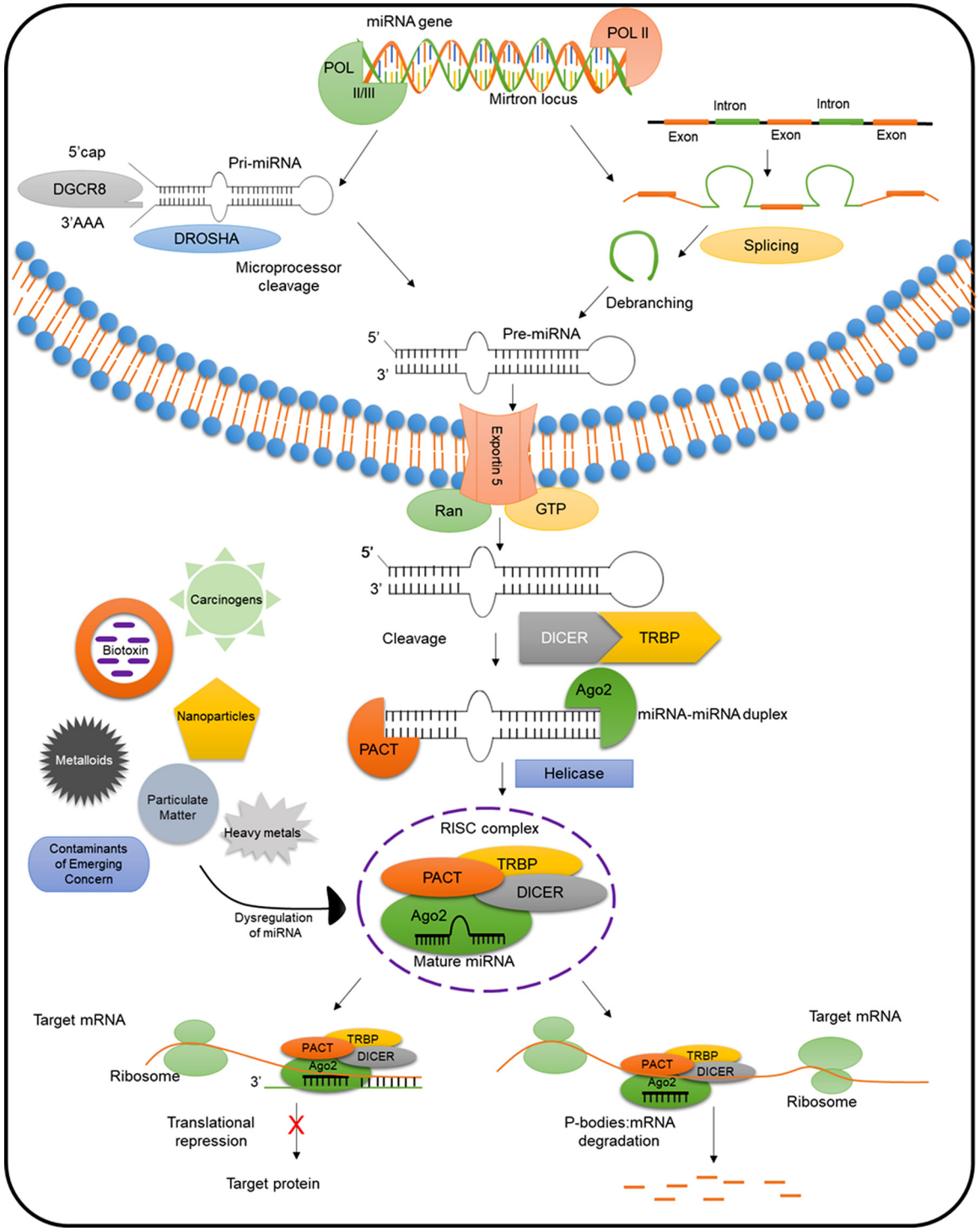

Fig. 1. Overview of the miRNA biogenesis, regulation of gene expression and the possible mechanism of xenobiotics in miRNA alteration. Ago2 – Argonaute2; DGCR8 – DiGeorge syndrome chromosomal [or critical] region 8; DROSHA – Ribonuclease III enzyme; GTP – Guanosine triphosphate; mRNA – Messenger RNA; miRNA – microRNA; PACT – Protein kinase RNA activator; POL II/III – RNA Polymerase II/III; POL II – RNA Polymerase II; Pre-miRNA – Precursor microRNA; Pri-miRNA – Primary microRNA; RAN – Ras-related Nuclear protein; RISC – RNA-induced silencing complex; TRBP - Transactivation Response RNA Binding Protein.

patellar bone of lead exposed patients. In the same patients, the effect on miRNAs and its negative association with toenail mercury were also reported, which showed the miRNAs alterations (miR-205, miR-125b, let-7b and miR-200c).

Cadmium is a heavy metal exhibiting nephrotoxicity and possibly carcinogenicity. miRNAs have been identified to play a major role in nephrotoxicity. It modulates various miRNAs upon exposure in human kidney cells. Altered miRNAs are involved in oxidative stress mediated apoptotic cell death and most cancer pathways leading to renal proximal tubular toxicity. One of the most deregulated miRNAs (miR-27a-3p) in this study has been previously reported to induce malignancy in lung and liver cell lines [59]. Furthermore, a study on hen spleen identified that miR-33 – 5q was repressed by cadmium exposure which bears a negative correlation with the AMPK signalling pathway. AMPK

Table 1
In vitro studies with prominently altered miRNAs upon xenobiotic exposure.

miRNAs	Cell lines	Toxicant	Exposure	Target/s	Effect	Analyses	References
miR-200b	HT-29 and HCT-116	5-fluorouracil	10 μM for 6 days	PTPN12	Alteration in miRNA expression	TaqMan miRNA assay	[23]
miR-205	MCF-7 and HepG2	Nonylphenol	12 μM and 52 μM for 3 and 48 h	TBX21, GRK7, NHLH1, DNAH9, XCR1, ATP1A4 by miR-205	Alterations in metabolism and apoptotic genes	Microarray	[24]
miR-320, miR-494	Primary murine bronchial epithelial cells	BaP	0.01 μM, 0.1 μM and 1 μM for 12, 24 and 48 h	CDK6	Impaired G1 phase cell-cycle arrest	qRT-PCR	[25]
miR-122, miR-143, miR-379	Primary rat hepatocytes	Trichostatin A	25 μM for 2, 4 and 7 days	–	Cell proliferation inhibition.	Microarray	[26]
miR-29b, miR-26a-1, miR-122	HepG2	BaP	2 μM for 6, 12, 24, and 48 h	BaP-responsive pathway	Apoptosis/DNA Damage Response	Microarray	[27]
miR-221	WRL-68	MC-LR	10 μg/L for 5, 10, 15, 20, and 25 passages	Cyclin G1	Tumorigenicity	qRT-PCR and transfection	[28]
miR-21 − 3p	HepG2 and HEK 293 T	Berberine chloride	40 μM for 1, 2, 4 and 8 h	MAT2A and MAT2B	Apoptosis	Microarray	[29]
miR-197 − 3p	A549	Octanal	0.58 mM for 48 h	MAPK signalling pathway	Increased phosphorylation of p38 MAPK	Microarray and qRT-PCR	[30]
miR-31, miR-34a, miR-133	Human Hepatocytes	Rifampicin	10 μM for 48 h	FOXP1, PDAP1	Alterations in metabolism genes	Microarray and qRT-PCR	[31]
miR-2195p, miR-654 − 3p	Jurkat T cell, Jurkat clone E6 − 1	Ag NPs and Ag ions	0.2 mg/L for 24 h	MT1F and TRIB3 by miR-219 − 5p and ENDOGL1 by miR-654 − 3p	Oxidative stress, cell cycle and apoptosis	Microarray and qRT-PCR analysis	[32]
miR-21	GES-1, AGS, BGC-823, HGC-27, MKN-28, and SGC-7901	N-nitroso carcinogen N-methyl-N-nitro-N –nitrosoguanidine	0.1, 0.5, 1.0, 1.5, 2.0, 2.5, or 3.0 μM for 8 h	FASLG and BTG2	Tumorigenesis	qRT–PCR and Transfection	[33]
miR-21	hESC-derived neurons	Research-grade propofol	0, 5, 10, and 20 μg/mL for 6 h either one time or three times (once per day for 3 consecutive days)	Sprouty 2	Cell death	qRT-PCR, miRNA transfection	[34]
miR-210, miR-221	LNCaP	MIB and DHT	MIB − 100 pM DHT − 2 nM for 4, 8, 24 and 120 h	AR receptor	Repression of miR-221 and induction of miR-210	miRNA microarrays and qRT-PCR	[35]
miR-22	HepG2	Bisphenol A	68 μM for 48 h	NET1 and IL1R1	Apoptosis	miRNA microarray and qRT-PCR	[16]
miR-203	Z310	Lead	5, 10 μM for 12 days	TRIC	Pb-induced BCB leakage	qRT-PCR and transfection	[36]
miR-182,miR-185	NIH3T3	$PM_{2.5}$	0.45 mg/mL for 24 h	SLC30A1, SERPINB2, AKR1C1	Carcinogenesis	Microarray analysis, qRT-PCR and transfection	[37]
More than 202 miRNAs	Human dermal fibroblasts	AuNPs (size 21.83 ± 4.79 nm)	200 mM for 1, 4 and 8 h	mRNA processing and MAPK signalling	Alterations in the metabolic process	miRNA sequencing and qRT-PCR	[38]
388 miRNAs were altered	PC-12	SPIONs	214 μg/mL for 24 h	–	Cell death	SOLiD Sequencing	[39]
miR-122	HepaRG	AFB1, AFB2 or BaP	0, 1, 5, 50, 100, or 200 μM for 24, 48, or 72 h	Inhibition of HNF4A/miR-122	Carcinogenicity	miRNA profiling and qRT-PCR	[40]
miR-29b-1, miR-27a	hESC-derived neural cells	Ag NPs	25 μg/mL for 6 and 24 h	Nrf2 Signalling pathway	Oxidative stress and dysfunctional neurogenesis	Microarray analysis and qRT-PCR	[41]
miR-222, miR-877	HepG2	Vildagliptin	100 μM for 24 h	Genes involved in cell proliferation and differentiation	Hepatic dysfunction	qRT-PCR	[42]
43 miRNAs were altered	Rat astrocytes	Ammonia	5 mM for 48 h	HO-1	Astrocyte senescence	Microarray analysis and qRT-PCR	[43]
miR-541	GC-1	MC-LR	500 nM for 24 h	p15, MDM2	Decreased cell viability and increased apoptosis	qRT-PCR, Dual-luciferase reporter assay	[44]

(*continued on next page*)

Table 1 (*continued*)

miRNAs	Cell lines	Toxicant	Exposure	Target/s	Effect	Analyses	References
miR-155	Mouse Neuronal cell line	Manganese NPs	50 μg/mL for 4, 8, 24 and 72 h	TNF-α, IL-6	Cytotoxicity and ROS	Transfection assay, qRT-PCR	[45]
miR-222, miR-494	Lung infiltrating cells	Staphylococcal enterotoxin B	50 μg for 48 h	CDKN1b, p27kIP1, 2l11 and PUMA	Cell cycle arrest and induction of apoptosis	qRT-PCR and Transfection	[46]
miR-222, miR-383, miR-126	Chicken ovarian cells	ZnO NPs (30 nm)	5 μg/mL for 24 h	Genes involved in Wnt, MAPK, mTOR pathway	Adverse effects in the reproductive system	qRT-PCR	[47]
miR-149−3p, miR-4286	HepG2 cells	MC-LR	10 and 50 μM for 24 h	Genes involved in MAPK, Purine and pyrimidine synthesis	Cytotoxicity and hepatitis	qRT-PCR and High throughput sequencing	[48]
miR-29b3p, miR-29a3p, miR-29c3p, miR-1906	Mouse ovarian granulosa cells	MC-LR	5 μM for 48 h	GAB2, FOS, IGF1 and MAN1A	Hormone production and cell growth disruption	Microarray and qRT-PCR	[49]
miR-17−5p	Neuro-2a cells	PQ and MPTP	300 μM for 48 h	Genes involved in cell cycle and endocytosis	Alteration in cell proliferation, and apoptosis	qRT-PCR, and Microarray	[50]
miR-431−5p, miR-1229−5p, miR-3648, miR-6126, miR-6779−5p	A549 cells	Polyhexamethylene guanidine phosphate	0 to 3 μg/mL for 24 or 48 h	ANKRD29, STC2,CYP4V2	Epithelial-mesenchymal transition (EMT), cell cycle changes, and apoptosis	qRT-PCR, and Microarray	[51]
miR-451a, miR-15b-3p and miR-4521	Human liver cell line	MC-LR	1, 2.5,5 or 10 μM for 24 h	mTOR, RAS, RAP 1 and HIF-1	Hepatotoxicity	qRT-PCR	[52]
miR-200b	Primary human hepatocytes and NHPTK cells	Rifampicin	10 μM for 24 h	Genes involved in drug metabolizing	Xenobiotic and endobiotic metabolism	qRT-PCR, ChIP-Seq	[53]
miR-451a	HL7702	MC-LR	5 or 10 μM for 24 h	ERK1/2 and p-ERK1/2	Cytoskeletal damage	qRT-PCR and Transfection	[52]
miR-200b-3p, miR -200c-3p, miR-205−5p	Human primary brain microvascular endothelial cells	Cupric Chloride	0.5 μM for 48 h	Endothelial LRP1	Vascular damage	qRT-PCR	[54]
miR-34a	HepG2 Cells	AgNPs (20 nm), AuNPs and SPIONs	10 μg/mL AgNPs, 10 μg/mL AuNPs, 5 μg/mL SPIONs for 24 h	TNF	Tumorigenesis	qRT-PCR and methylation analysis	[106]
miR-222, miR-210, miR-101miR-34a	A549 cells	$PM_{2.5}$	50 μg/mL for 2 h	NRF2 and NFκB.	Oxidative and inflammation pathway dysfunction	qRT-PCR	[55]
miR-2861	Primary mouse spermatocyte cells	Silica NPs	0 and 5 mg/mL for 30 passages	FADD, CASPASE-8, CASPASE-3, FAS1	Death receptor pathway dysregulation	Transfection	[56]
miR-128−3p, miR-4306	EA. hy926 cell	$PM_{2.5}$	2.5,10 μg/cm^2 for 24 h	Genes involved in the focal adhesion pathway	dysfunction of endothelial cells	Microarray and qRT-PCR	[57]
miR-1303, miR-222−3p,miR-192 −5p	SH-SY5Y	Bortezomib	50 nM for 24 h	DCX, CDK6, ALCAM	Cell proliferation inhibition	Microarray analysis and qRT-PCR	[58]
miR-21−5p, miR-27a-3p, miR-29c-3p, miR-30b-5p, miR-30c-5p	RPTEC/hTERT and human kidney-2 cells	Cadmium Chloride	10 mM	Oxidative stress pathway	Nephrotoxicity	miRNA profiling and qRT-PCR	[59]
miR-689, miR-690, miR-709, miR-1187	Hippocampal neuronal cells from new-born C57BL/6 mice	NMDA	20−30 μM for 10 min	NMDAR signalling	Neural dysfunction	Microarray analysis and qRT-PCR	[60]
miR-1839−5p,miR-126a-5p, miR-15a	Porcine granulosa cells	ZEN	30 μM for 48 h	Cell cycle pathway	Growth inhibition and cell cycle arrest	miRNA sequencing and qRT-PCR	[61]
miR-297	Human bronchial epithelial cells	Aluminium oxide NPs	0, 50 and 100 mg/mL for 24 h	NKAP	Pulmonary inflammation	qRT-PCR, miRNA transfection	[62]

Table 2
Xenobiotics induced miRNA changes in *in vivo* models.

miRNA	Model	Toxicant	Exposure	Target	Effect	Analyses	References
miR-298, miR-370	Male Crl(SD)IGS rats	APAP and CCL4	APAP – 1 g/kg, CCL4 – 0.3 mL/kg for 6 and 24 h	–	Mitochondrial dysfunction	Microarray analysis and qRT- PCR	[63]
miR-26, miR-181, miR-206	Female, virgin B6C3F1 mice	RDX	5 mg/kg for 28 days	Protooncogene, Oncogene homolog 1	Neurotoxicity and carcinogenesis	miRNA Microarray and qRT-PCR	[132]
miR-16, miR-21, miR-146a	Pregnant human females	Cigarette smoking [Nicotine and BaP]	On average, 38 weeks of gestation	BCL2L2, EDA, PLAG1, SATB1, TRAF6	Alteration in cell cycle regulation and development of the placenta	qRT-PCR	[64]
miR-430, miR-125, miR-31	Zebrafish	MC	12 to 48 mM from 0 hpf to 72 hpf	–	Teratogenic effects	miRNA Microarray and qRT-PCR	[65]
miR-101a, miR-122	Male C57BL/6 J strain mice	TCDD	50 μg/kg, 10 mL/kg b.w for 14 days	COX2, EZH2	Liver damage	qRT-PCR	[66]
miR-192, miR-34a, miR-125b, miR-99a – 3p, miR-21 and miR-16	Female BALB/c Mice	MC	20 μg/kg b.w/day for 28 days	–	Liver tumorigenesis	miRNA Microarray, qRT-PCR	[67]
miR-17a, miR-15a, 107, 124, 125b, 203b and 218	Zebrafish embryos	TCDD	5 nM for 1 h, at 30 hpf	–	Abnormal developmental phenotypes	Small RNA sequencing and qRT-PCR	[68]
miR-34c	Crl:CD(SD) rats	DOX	DOX –1 to 3 mg/kg/week for 6 weeks (Intravenous)	SIPA1	Symptoms of Cardiomyopathy, Cardiotoxicity	Affymetrix assay, qRT-PCR	[69]
miR-27b	Zebrafish	Crude microcystins	50, 200, 800 mg/L for 24 h	CYP3A65 and PXR	Hepatotoxicity	qRT-PCR	[70]
miR-146a	Pregnant women	Bisphenol A	40 pregnant women from polluted area	Neural and cardiovascular disease genes	Fetal malformations.	Microarray and qRT-PCR	[71]
miR-575 and miR-4286	Pregnant women	Lead and Mercury	60 Mexican women with known exposure	AHR signalling pathway	Reproductive system development, preeclampsia	NanoString nCounter system	[72]
miR-15a, miR-21, miR-34a, miR-192	Pigs	ZEA and DON	ZEA - 40 μg/kg/day, DON - 12 μg/kg/day, ZEA + DON - 40 + 12 μg/kg/day	PDCD4, IL10	Cell proliferation and survival pathway dysregulation	qRT-PCR	[73]
miR-291a-3p	C57bl/6 mice	Lead acetate	9.6 mM for 1, 2, and 5 weeks	Uc.173	Apoptosis of nerve cells	qRT-PCR	[74]
miR-126−3p	Zebrafish	Atrazine	0.3, 3, or 30 μg/L from 0 hpf to 72 hpf	ANTXR2	Angiogenesis and neurodevelopment	Microarray and qRT-PCR	[75]
miR-541	BALB/c Mice	MC-LR	7.5 μg, 15 μg or 30 μg for 2 weeks	p15, MDM2	Decrease cell viability and increase cell apoptosis	qRT-PCR, Dual-luciferase reporter assay	[44]
miR-222 miR-494	C57BL/6 Mice	Staphylococcal enterotoxin B	50 μg for 48 h	CDKN1b, p27kIP1, BCL2,l11 and PUMA	Cell cycle arrest and induction of apoptosis	qRT-PCR and Transfection	[46]
miR-200a-3p, miR-5132−5p, miR-5130	ICR Mice	*Dioscorea bulbifera*	300 mg/kg, 375 mg/kg and 450 mg/kg for 24 h	MECP2, RNF165, IFFO2	Dnaja1 expression alteration	qRT-PCR	[76]
miR-208, miR-212, miR-18a	Sprague Dawley Rats	Nanosized SiO_2	6.25, 12.5, 25 mg/mL and 25 mg/mL for 7 th, 15 th, 30 th, 60 th and 90 th day	PDCD4,LIN28B and CTGF	Alterations in pulmonary hypoplasia, signal pathways of MAPK and TGF-β	qRT-PCR	[76]
miR-34a, miR-122, miR-370	CD-1 mice	Bisphenol A	25 μg/kg bw/day from gestational day 8 to 4 weeks	NRF2, SREBP-1C	Fat accumulation	qRT-PCR	[121]
miR-122−3p, miR-194−5p,miR-5099	ICR and C57BL/6	*Dioscoreabulbifera* and diosbulbin B	450 mg/kg and 300 mg/kg for 24 h	Genes involved in cellular stress response, cell apoptosis and liver injury	Liver injury	qRT-PCR and Microarray	[] [125]
miR-126 and miR-155	Human	Arsenic (inorganic form)	30.5 ± 25.5 μg/g	Genes involved in vascular homeostasis and inflammatory signalling pathway	Cardiotoxicity	qRT-PCR	[77]
miR-122	Wistar albino Rats	Bisphenol A	0.5 mg/kg, 5 mg/kg and 50 mg/kg for 30 days	JNK, ERK1/2, and MAPKAPK	Oxidative stress and hepatotoxicity	qRT-PCR, Western blotting and Histology	[78]
miR-153b-3p, miR-19a-3p	Zebrafish	$PM_{2.5}$	0, 25, 50, 100, 200, and 400 μg/mL for 6–120 hpf	CYP3A65, MGST2, GSTP1,GSTO2, GSTO1, CYP1A, EHX1, GSTAl and ALDH3B1	Alterations in oxidative stress, response to stimuli and metabolic Processes	qRT-PCR and Microarray	[79]
miR-7147, miR-26a miR-375	Zebrafish	Si-NPs and MeHg (co-exposure)	3 mg/mL of Si-NPs and 0.01 mg/mL of MeHg for 24 h	STXBP1A, CELF4, AHR1B and BAI2	Proinflammatory and cardiovascular toxicity	qRT-PCR and Microarray	[80]

(*continued on next page*)

Table 2 (*continued*)

miRNA	Model	Toxicant	Exposure	Target	Effect	Analyses	References
miR-129−5p, miR-218b, miR-181c	Zebrafish	Si NPs (62 nm) and PbAc (co-exposure)	Si NPs (3 ng/nL) and PbAc (0.5 ng/nL) for 24 h	STXBP1A, NDFIP2, CELF24 and GSK3b	Calcium homeostasis and ER stress	qRT-PCR and Microarray	[80]
miR-122, miR-151a, miR-192, miR-193a, miR-194, miR-21, miR-29c	Male Sprague Dawley rats	Acetaminophen	600 or 1200 mg/kg for 6 or 24 h post-treatment	–	Liver injury	qRT-PCR	[81]
miR-27a	*Mugilogobiusabei*	Diclofenac	0.5, 5, 50, 500 mg/L for 24 and 168 h	P-GP	Dysfunction of detoxification genes	qRT-PCR	[82]
miR-33−5q	Hy-Line Brown Chicken	Cadmium chloride	10 mg/kg for 90 days	NF-kB, p-JNK/JNK, p-AKT/AKT and mTOR	Ion homeostasis disruption	qRT-PCR	[83]
miR-455−3p	Sprague Dawley Rats	Cadmium chloride	0.6 mg/kg for 12 weeks	Genes related to cellular signalling pathways	Renal injury	Microarray and qRT-PCR	[84]
miR-N6, miR-N7, miR-N10	Ciliate *Euplotes vannus*	AgNPs (73.82 nm)	15 mg/L for 1 and 12 h	p34CDC2	Increase ROS production, mitochondrial dysfunction	qRT-PCR	[85]
Let-7b-5p, miR-126−3p, miR16−5p, miR-320b	Humans (coke oven workers)	23 urinary metals and ten other urinary OH-PAHs	0.0004–0.3934 μg/L range and 0.1–0.9 μg/L range	TRIAP1	Genetic damage and oxidative stress	qRT-PCR	[86]
miR-205, miR-184 miR-419	*Cyprinus carpio*	Atrazine	0.428 μg/L for 8 and 24 h	SOX9, GSDF, DMRT, SMAD4	Alterations in reproduction process and developmental process	qRT-PCR	[57]
miR-125b, miR-125b, miR-155, miR-21	Silver Carp	[C8mim] Br	1.095 and 4.380 mg/L for 60 days	Inflammatory pathway	Oxidative stress and inflammation in the fish spleen	qRT-PCR	[87]
miR-503	Porcine	ZEA	0.17 mg/kg, 1.46 mg/kg and 4.58 mg/kg	SPRED1	Dysregulation of the estrogen response, Wnt and TGF-β1/Smad3 signalling pathways in uterus	qRT-PCR, RNA-Sequence and bioinformatic analyses	[117]
miR-184, miR-141	Sprague Dawley rats	Phthalates	20 μg/kg/day: T1; 200 μg/kg/day: T2; 200 mg/kg/day: T3	WNT9b	Delay in prostate development	sncRNAs sequencing	[88]
miR-35, miR-38, miR-76, miR-354	*C.elegans*	100 nm nanopolystyrene	1 μg/L from L1-larvae to adult day-3	–	Alteration in reproduction, development, metabolism, and rhythmic process	SOLiD sequencing, qRT-PCR and RNAi assay	[89]
miR-34a-5p, miR-497−5p, miR-34a-5p, miR-34a-5p	Pigs	Ochratoxin A	50 μg/kg and 200 μg/kg feed for 28 days	CCND1, BCL2, MAP2K1, TNF-α	TP53 signalling network dysregulation	Microarray and qRT-PCR	[90]
miR-451a	Sprague-Dawley rats	Si NPs	1.8 mg/kg b.w, 5.4 mg/kg b.w and 16.2 mg/kg b.w for 30 days	IL6R, STAT3, ACSL4l, FOS, TXNDC5	Alterations in signalling cascades	Immunohistoche-mistry, Western blotting and qRT-PCR	[91]
miR-367−3p	C57BL/6 mice	*Melia toosendan Sieb. et Zucc*	10 mg/kg for 6 and 12 h	–	Liver injury	ChIP analysis, qRT-PCR and Microarray	[92]
miR-181a-5p	Zebrafish	Triclosan	0, 62.5, 125 and 250 mg/L	PAX2Aand VASH2	Fatty acid biosynthesis and phosphatidylinositol signalling systems	qRT-PCR, Whole-mount *in situ* hybridisation	[87]
miR-24, miR-29a, miR-34a, miR-375	Wistar Albino rats	Zinc oxide NPs	5 mg/kg for 15 consecutive days	–	Diabetes development	qRT-PCR	[93]
miR-223, miR-503, miR-10a, miR-200c	Mouse lungs	Ricin	7 μg /kg for 24 h	BDP1, CREB5, CCL9, JUN	Changes in inflammatory pathway	qRT-PCR	[94]
miR-222	Male BALB/c mice	*Melia toosendan Sieb. et Zucc*	40 g/kg for 9 days intraperitoneally	Autophagy pathway	Hepatocyte cell death	Microarray analysis and qRT-PCR	[95]
miR-16, miR-181a-3p, miR-223, miR-451	Silver Carp	MC-LR	0, 50 μg/kg, 200 μg/kg for 1, 3, 6, 12, 24, and 48 h	Genes involved in cellular, metabolic and single organism process	Multiorgan toxicity	Small RNA sequencing and qRT-PCR	[96]
miR-155, miR-338, miR-210	Humans	Arsenic (form not specified)	0.5−4600 μg/L of arsenic in drinking water	DAPK1, EGR2, APP	Notch signalling pathway impairment	RNA sequencing	[97]
miR-199a-3, miR-152, miR-7b	Carp fish	Cadmium dichloride hemipentahydrate	0.25 mg/L for 30 days	–	Oxidative stress	RNA sequencing	[98]
miR-181, miR-291a-3p, miR-493−5p	Sprague Dawley Rats	2,5-hexanedione	400 mg/kg/day for 5 weeks	GSK3β, BDNF, MAP1B	Neurotoxicity	Microarray, qRT-PCR and Western blotting	[99]
miR-181a	(SPF) C57bl/6 Mice	MC-LR	0, 3 or 15 mg/kg from gestation day 6−19	GRP78	Endoplasmic reticulum stress and neuronal apoptosis	Microarray, qRT-PCR and Dual luciferase reporter assay	[100]

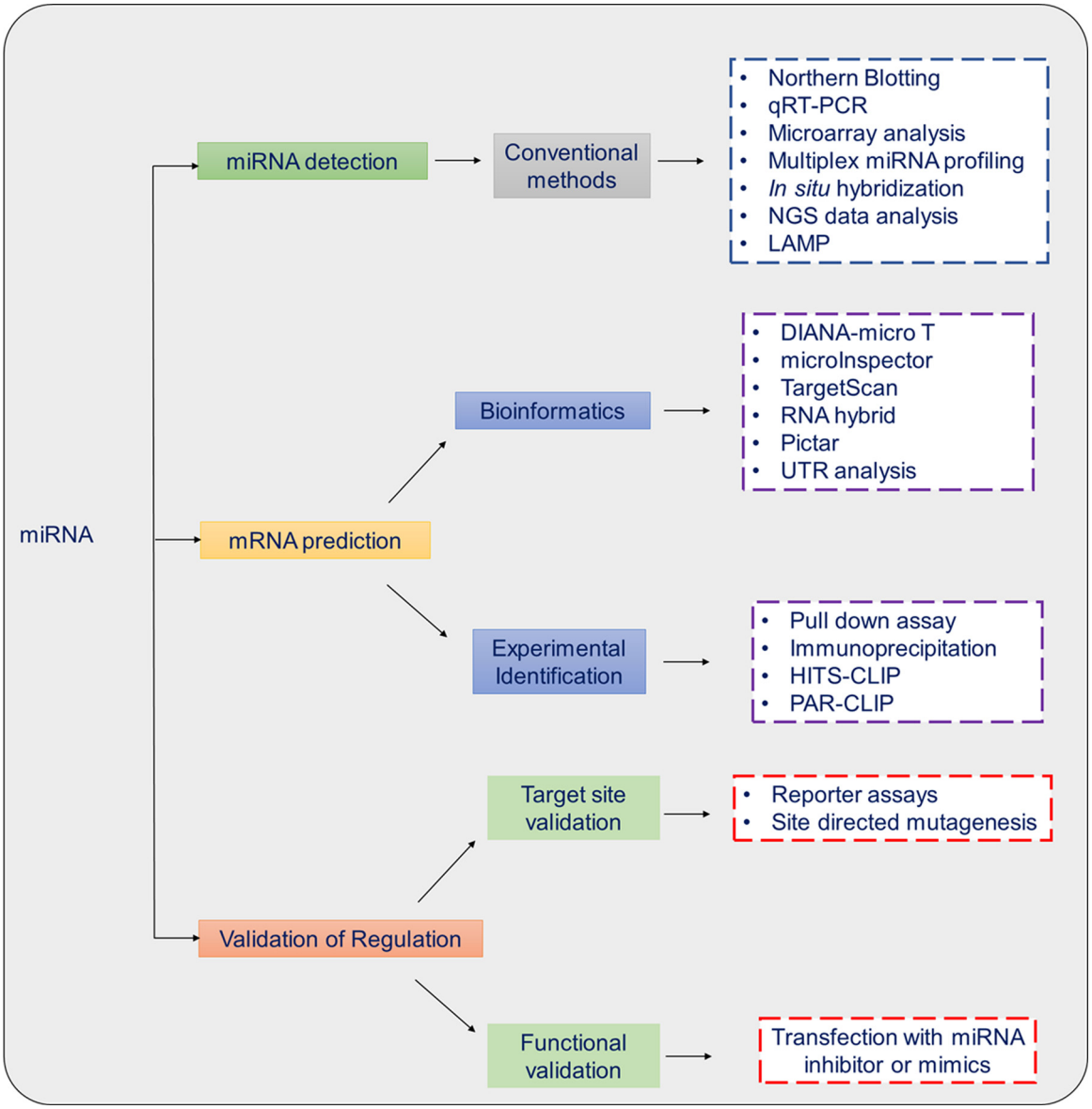

Fig. 2. Techniques involved in the study of miRNAs. qRT-PCR - quantitative Real Time-Polymerase Chain Reaction; NGS – Next Generation Sequencing; LAMP - loop-mediated isothermal amplification; UTR – Untranslated region; HITS-CLIP – High-throughput sequencing of RNA isolated by crosslinking immunoprecipitation; PAR-CLIP – Photoactivatable ribonucleoside-enhanced crosslinking and immunoprecipitation.

in turn, regulates BNIP3 – 3 dependent autophagy [83]. In rats, the nephrotoxicity induced by cadmium was found to be regulated by miRNA alteration with 44 miRNAs identified to be dysregulated [84]. In one particular study, where carp was exposed to cadmium, around 15 miRNAs were differentially altered which were identified to be players in cell growth and oxidative stress [98].

Copper, another neurotoxicant, has been shown to induce upregulation of miRNAs (miR-200b-3p, miR-200c-3p, miR-205 – 5p) in human primary microvascular endothelial cells, where the miRNAs target the suppression of LRP1 protein. The latter plays a significant role in brain Aβ clearances [54].

Arsenic, a metalloid, is one of the major groundwater contaminants which induces numerous health hazards including cardiotoxicity and affects the health of millions of people globally [102]. The mechanism of arsenic toxicity has been well established in both *in vitro* and *in vivo*. The epigenetic intervention of miRNAs in arsenic exposure is being explored with very few studies providing us a comprehensive understanding ([103] [116]. Humans are the most affected organisms by arsenic. Two studies focus on the miRNAs perturbations in humans exposed to arsenic. A study conducted by Pérez-Vázquez et al. [77] reported the negative association between arsenic toxicity and plasma miR-126 levels in children. However, the sample size was limited and had too many variables to provide any conclusive proofs. Chen et al. [97] instigated the relation between arsenic and miRNAs in adult females of Bangladesh origin. Bangladesh is one of the leading countries with high levels of arsenic contamination in groundwater. They found major miRNAs that might play a role in various cancer induction genes (miR-155, miR-338, miR-210).

3.3. Nanoparticles

Due to their advantageous physiochemical properties, nanoparticles (NPs) are elaborately used in various sectors including health and personal care products [104]. These NPs ultimately end up in the environment *via* various routes including air, water and soil leading to various ill-effects to biological systems. NPs enter cells *via* endocytosis or in ionic form inducing toxicity mainly by generating oxidative stress leading to apoptosis and inflammation [105]. miRNAs have been

identified to modulate the pathways involved in oxidative stress. Pulmonary inflammation induced by Al_2O_3 NPs was identified to be regulated by miR-297 in human bronchial epithelial cells by repression of NF- κB-activating protein which activates the notch signalling pathway [62]. Mn NPs have also been identified to induce an inflammatory response by targeting TNF-α and IL-6 through miR-155 in neuronal cells. The decrease in the miR-155 level in Mn NPs exposed cells led to an increase in mRNA levels of TNF-α and IL-6, which was validated by the transfection of miR mimics [45]. Nano polystyrene, a type of plastic widely used in personal care products, is one of the contaminants of emerging concern. Upon exposure to *C.elegans*, five altered major miRNAs were validated (miR-35, miR-38, miR-76, miR-354, and miR-794) using RNAi assay and were identified to be involved in various signalling pathways including the Wnt pathway [89]. Granulosa cells of hens, when exposed to Zn NPs, differential expression of miRNAs was found and they were predicted to play a major role in the normal development than the usual signalling cascades involved in NPs toxicity [47].

Nanosized SiO_2 induced lung damage in rats is due to the disturbance in the inflammatory signalling pathway. This was controlled by miRNAs as evinced by a decreased expression of PDCD4, an anti-inflammatory marker at the protein level, but with little significance in mRNA levels along with the increased expression. Moreover, the raised protein levels of LIN28B, CTGF promote fibrosis formation which is associated with miR-212 and miR-18a [76]. SiO_2 NPs have been shown to induce apoptosis *via* the death receptor pathway in murine spermatocyte cells. In this study, miR-2861 was shown to be repressed, which in turn upregulates the mRNA levels of fas/fasl/ripk1/fadd [56]. Combinatorial effects of SiO_2 NPs along with methylmercury and lead acetate in zebrafish provides a pandect on the effects on miRNAs. Along with methylmercury, SiO_2 NPs have been demonstrated to reshape the miRNAs threshold (miR-7147, miR-26a and miR-375) in zebrafish embryos (48 hpf) leading to cardiovascular toxicity (*i.e.,* cardiac muscle contraction) *via* inflammatory pathways [80]. Furthermore, in conjunction with lead acetate, SiO_2 NPs cause cardiac muscular contraction leading to cardiovascular toxicity. However, the impaired miRNAs were different and they were found to modulate alternate mechanisms including ER stress and disrupt calcium homeostasis [80].

Silver, iron and gold NPs are some of the most widely used NPs in medicine. All these NPs have been shown to induce toxicity and control gene expression *via* epigenetic mechanisms, especially by controlling miRNAs. Ag NPs exposure to human jurkat T cells has been shown to induce DNA damage and apoptosis. The miRNAs altered in a study carried out by Eom et al. underwent *in silico* prediction of miRNA-mRNA network analysis to identify putative pairs [32]. However, unless the prediction of miRNA targets is validated, it is difficult to obtain a conclusive evidence. A similar study was done by Oh et al. [41] in human embryonic stem cell-derived neural stem/progenitor cells showed that exposure to citrate-coated Ag NPs alters miRNAs involved in oxidative stress (especially Nrf2 mediated) and inflammatory pathways. Moreover, miR-297, which was previously shown to target NFKBAP in exposure to Al_2O_3 NPs, here was predicted to target ADAMTS9, and SEMA6D. When ciliates *Euplotes vannus* was exposed to Ag NPs, they showed similar ill effects including alteration in the cell cycle regulation, induced oxidative stress and antioxidant response modulation with over 15 miRNAs detected to play a possible action in the toxicity [85]. Research done by Huang et al. [38] in Au NPs upon exposure to human dermal fibroblasts showed the alteration of miRNAs prominently in the mRNA processing pathway, and MAPK signalling pathway. A key aspect of the finding is that Au NPs showed no cytotoxic effects even though they altered the levels of numerous miRNAs (*i.e.,* miR-205, miR-21, miR-129−5p, miR-20a, miR-30b, miR-181a, miR-190, miR-16, miR-195, miR-30d, and miR-9) and affected the cell cycle pathway. SPIONs have been shown to induce cell death by targeting the NMDAR-Caspase pathway in PC12 cells leading to neurotoxicity. NMDAR, a receptor which regulates neuronal plasticity, was downregulated in SPIONs exposed cells and miRNAs has been shown to be varied [39]. A recent study compared the effect of three major NPs (*i.e.,* Ag, Au, and SPIONs) in HepG2 cells where the similarity of miRNAs between treated NPs was very low. However, miRNAs altered in these NPs have been previously reported to play a role in cell proliferation and tumorigenesis [106]. An *in-silico* prediction by Hu et al. [107] identified six major miRNAs that have been found in response to various NPs exposure in zebrafish. These miRNAs include miR-124, miR-144, miR-148, miR-155, miR-19a, and miR-223. It is noteworthy that these miRNAs have been validated earlier in mammalian and zebrafish miRNAs Profiling studies and their predicted targets were found to be interacting with various signalling pathways (as reviewed by [107]). There is no regulation for the accumulation of NPs in the environment, which is of growing concern.

3.4. Biotoxins

Biotoxins are toxins produced by various organisms that have become a threat to human health and the environment. This includes but is not limited to mycotoxins, bacterial toxins, aflatoxins and plant toxins. MCs that are released by cyanobacteria and other algae are one of the major environmental toxins. MC-RR, one of the common and abundant MCs, has been shown to disrupt miRNAs expression in zebrafish embryos leading to cardiotoxicity. The loss of vascular integrity was predicted to be due to miR-31 and miR-126. Apart from these two miRNAs, numerous other miRNAs with known functions in multiple signalling pathways, were identified [65],

Upon exposure to mouse granulosa cells, MC−LR - a form of microcystin–has been shown to alter numerous miRNAs involved in MAPK signalling pathway [48,49]. In human liver cells, differential expression of miRNAs (*i.e.,* miR-451a, miR-4521 and miR-15b-3p) leading to MC−LR induced hepatotoxicity was observed [76]. The same group further validated the role of miR-451a by using miR mimics and observed that the decreased expression of miR-451a by MC−LR is irreversible [52]. This miR-451a plays a role in numerous signalling cascades and has also been shown to be functioning as circulatory miRNAs. In mice, the exposure to MC-LR– even at low dosages– induced non-alcoholic steatohepatitis (NASH), a common form of non-alcoholic fatty acid liver disease. Deregulation of miRNAs (*i.e.,* miR-12, miR-21, miR-24 and miR-34a) has been identified as oncomirs which leads to hepatocarcinogenesis in NASH [108]. The possible role of miR-541 in MC−LR –induced cell death was studied by Meng et al. [44] using miRNA mimics and inhibitors. They validated the downstream target of miR-541 (p15) in Mouse GC-1 cells by using a dual-luciferase-reporter assay which confirms the interaction between miR-541 and the 3′ UTR region of p15. p15, a CDK inhibitor, is one of the key players involved in cell cycle regulation. Inhibition of p15 by miR-541 leads to the cell death mechanism as evidenced by the findings of the study. Similarly, prenatal exposure to MC−LR in mice leads to ER stress and neuronal apoptosis in the hippocampi region of offspring leading to cognitive impairment. One of the key signalling regulators involved in ER stress is Grp78/BIP, which acts as a chaperone, and was significantly upregulated in treated mice. This was due to the inhibition of miR-181a-5p upon MC−LR exposure, which was supported by the reporter assay [100]. MC−LR has been shown to induce liver toxicity in juvenile silver carp where the unbalanced miRNA levels play a crucial function. Furthermore, systemic toxicity in the carp was predicted due to the upregulation of four miRNAs (*i.e.,* miR-16, miR-181a-3p, miR-223, miR-451) which are the key components of multiple signalling cascades [96].

Mycotoxins are secondary metabolites produced by the fungi and most of them have been found as contaminants in animal feed. These–when fed to animals –easily enter the human systems. They have been shown to have varied toxic potency such as mutagenicity, teratogenicity, neurotoxicity as well as carcinogenicity [129].

ZEA is a mycotoxin from *Fusarium* genera that is one of the widely

prevalent toxins. Li et al. [61] investigated the regulatory mechanism of miRNA-ceRNA networks. It is one of the very few studies exploring miRNA-ceRNA networks upon xenobiotic exposure. They studied the effect of ZEA on porcine granulosa cells. Upon exposure to porcine granulosa cells, ZEA arrests the cell cycle at the G2/M phase by targeting the genes involved in the cell cycle including CDK1, CCNB1, CDC25A, and CDC25C. These genes are modulated by various miRNAs (*i.e.,* miR-1839 − 5p, miR-126a-5p, miR-15a, miR-152, miR-29b, miR-143 − 3p, and miR-7857 − 3p) which in turn are being controlled by various lncRNAs. These lncRNAs compete with miRNAs for binding towards these mRNAs, and fine tunes the miRNAs expression. However, the ceRNA hypothesis –which states that ceRNAs can compete with miRNAs for mRNA binding– is controversial and has to be validated further [109]. DON is another toxin of the same category, but more hazardous than ZEA [110]. The combinatorial effect of ZEA and DON on the ascending colon of porcine showed an alteration of miRNAs (*i.e.,* miR-15a, miR-21, miR-34a, and miR-192) involved in the cell cycle, signal transduction and apoptosis. However, the alteration of miRNAs was tissue-specific. The other tissues including liver did not showed any significant changes [73].

Ochratoxin A, is a type of mycotoxin obtained from *Aspergillus* and *Penicillium* genera. It is considered as a potential carcinogen exhibiting severe toxicity. Marin et al. [90] reported that ochratoxin A alters miRNA levels in the kidneys of pigs with the identified miRNAs playing a major role in renal damage. The elevated miRNAs (*i.e.,* miR-497, miR-133a-3p, miR-423 − 3p, miR-34a, miR-542 − 3p) and repressed miRNAs (*i.e.,* miR-421 − 3p; miR-490; miR-9840 − 3p) were predicted for the pathways involved in the TP53 signalling cascade, a prominent pathway in tumorigenesis.

Apart from these mycotoxins, bacterial and plant toxins have also been reported to alter miRNAs. Staphylococcal Enterotoxin B produced by S*taphylococcus aureus* induces lung damage, and shown to be regulated by two major miRNAs (*i.e.,* miR-222 and miR-494) which target CDKN1b, P27KIP1, and BCL2L11, some of the major genes involved in cell cycle [46]. Ricin, a highly potent toxin classified as a bioterror agent, is isolated from *Ricinus communis*. Mice, when intoxicated with ricin, show severe damage in the lungs. Transmuted miRNAs were identified in the lungs. These modified miRNA levels were found to have targets in various immune response and immune regulation pathways [94].

3.5. Particulate matter

Particulate matter (PM) is one of the major toxicants in air affecting more than 91 % of the people globally (as reported by WHO) [111]. They can cause various respiratory illnesses including lung cancer, COPD and even cardiovascular diseases. These toxicants are altering the epigenetic landscape [112]. $PM_{2.5}$ has been shown to dysregulate the miRNAs involved in oxidative stress and inflammatory pathways [55]. Furthermore, it has been shown that it induces cardiotoxicity by altering miRNAs (*i.e.,* miR-128 − 3p and miR-4306) in which miR-128 − 3p targets MAPK activity [57]. In zebrafish, $PM_{2.5}$ has been shown to disrupt homeostasis of miRNA levels, upregulate the miRNAs involved in the inhibition of immune responses and DNA damage repair (*i.e.,* let-7b, miR-153b-3p, miR-122 and miR-24) as well as to downregulate miRNAs that control autophagy (*i.e.,* let-7i, miR-19a-3p, miR-19b-3p and miR-7a) [79]

Cigarette smoking generates a large amount of particulate matter of various sizes which affects both first hand as well as second hand smokers [113]. A study conducted by Xi et al. [114] showed that in human respiratory epithelial cells, cigarette smoke condensate induces the expression of miR-31, one of the key oncomir. Moreover, environmental cigarette smoke has been shown to dysregulate miRNA expression in both liver and lungs of mice with significant alterations in the lungs [115]. Maternal cigarette smoking is a major concern which affects the unborn child. It has been shown to affect the placenta by inhibiting the cell cycle regulation leading to improper placenta development. This is due to the suppression of miR-16, miR-21 and miR-146a in the placenta [64]. However, further studies are needed to address the environmental cigarette smoke (passive or second hand) and their role in miRNA regulation in human subjects.

3.6. Contaminants of emerging concern

Contaminants of emerging concern (CEC) are chemical compounds that are widely present in the environment with recent identification. While no common definition for this term exists, the present review focuses on major chemical compounds that can cause severe health effects in biological systems. Phthalates, is a family of phthalic acid diesters which exhibits endocrine disruption ability. Phthalates are being widely used along with plastics and pose a risk to human health. Scarano et al. [88] reported the effect of a mixture of phthalates from the environment in miRNA levels of pregnant rats. The altered miRNAome and the target prediction indicated that the majority of altered genes involved in inflammation and androgenic toxicity were modulated by miR-143-p and miR-184.

Pesticides are another major CEC with an increased usage in agriculture. Atrazine is one of the more common herbicides used to prevent the growth of broadleaf and grassy weeds. In zebrafish, atrazine exposure altered miRNA levels that participate in various functions including angiogenesis. Wirbisky et al. have identified one key miRNA, namely miR-126 − 3p that was altered in various dosages [75]. The miR-126 family has been predicted to be involved in various toxicant exposures. The endocrine disrupting ability was further supported by a study done by Wang et al. [50]. In common carp, atrazine exposure at different developmental stages modulated the miRNAs involved in reproductive toxicity. Triclosan, one of the prevalent bactericides, affects the vascular development of zebrafish by upregulating miR-181a-5p levels involved in the phospholipid signalling pathway [87].

4. Challenges

There have been numerous studies on the interaction of miRNAs in various xenobiotics in both *in vitro* and *in vivo* of various model systems, including human subjects. However, they pose various challenges as well as limitations for the possible interpretation of data to environmental relevance. Most of the studies have focused on the identification of miRNAs altered through sequencing and predicted their targets *in silico*. Only very few of them have validated the interaction between miRNA and mRNAs and their role in gene regulation. Quantification of miRNA levels and *in silico* target prediction alone does not confirm their functional validation. Moreover, one of the interesting observations in xenobiotics-based studies is that though some of the miRNAs share the same pathways leading to toxicity, almost all of the altered miRNAs in various toxicants are different from each other, showing an increased specificity of these miRNAs. Even the similar miRNAs in different toxicant exposures have differed targets interacting with varied signalling pathways. The generalization of these results is very difficult at this stage due to their variability. The variables include dose, time, model systems, tissue specificity, toxicant characteristics and the method of analysis.

Most of the *in vitro* studies were done using cancer cell lines which might distort miRNAs alteration in normal functioning cells. Human studies have been very limited, and even in the few human studies that have been conducted, sample sizes were on the lower side and focused on a specific set of people. This does not contribute to a deeper understanding of the miRNAs effect on xenobiotic exposure. Furthermore, there are very limited studies that yield a conclusive evidence on the stability of miRNA alteration, whether it is transient or stable over generations.

5. Future directions

Future work should focus on the validation of predicted targets with high specificity and robust methods of identification that will help us in elucidating the exact mechanism of miRNA-xenobiotic perturbations. Meta-analysis of these studies will provide us an in-depth interpretation and comparison for generalization. Another interesting area of research includes miRNA-induced transcription activation and their possible mechanisms. Moreover, circulatory miRNAs and their role in xenobiotic exposure is very limited at this stage. It is one of the unexplored areas which promises an exciting future due to their applications as biomarkers useful in the identification of environmental toxicity. Furthermore, the controversy behind ceRNAs and miRNAs in gene regulation has to be ratified conclusively. Ligorio et al. (2011) predicted the Dicer to play a major role in xenobiotic targets, however there have not been many studies on the effect of toxicants in regulating miRNAs and their biogenesis[131]. These studies possess great potential in explaining xenobiotic toxicity and the possible role of miRNAs as biomarkers.

6. Conclusion

In conclusion, this review summarizes the effect of xenobiotics on gene expression *via* epigenetic regulation of miRNAs both *in vitro* and *in vivo*. Most xenobiotic toxicity is induced by the generation of oxidative stress, which leads to the dysregulation in antioxidant response, inflammation and other cell death mechanisms. These alterations are regulated by epigenetic modulation of miRNAs, which targets mRNAs and cause translational repression or degradation. Even with an increased amount of research going on, a lot of complex mechanisms behind miRNA regulation and its role in toxicity still remains largely unexplored.

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.

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