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Review Article

Biogenesis and implication of miRNAs in the development of diseases and their theranostic inhibitions

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Abstract

MicroRNAs (miRNAs), the naturally derived (canonical or non-canonical biogenesis) small non-coding RNAs linked to many crucial cellular processes and their dysregulations have emerged as the regulators of genes expression, mRNA translation, and proteins synthesis contributing to multiple pathological disease-progression and prognosis. Owing to the un-steadiness of miRNAs and their complex-degradation of mRNAs by nucleases and their dysregulated identifications in biological fluids as biomarkers for the development of diseases, miRNA mimics and anti-miRNAs molecules may be applied to restore miRNA expression or downregulate aberrantly expressed miRNAs as therapeutics loaded with delivery systems. This review denotes mainly the recent advances of the miRNA-based therapeutic delivery systems (such as viral, liposomal, exosomal and polymeric) as well as the novel strategies as emerging delivery systems (such as DNA origami, magnetosomes, micro needles and selenium nanoparticles) to diagnose and treat various diseases.

Keywords: miRNAs; Biogenesis; Biomarkers; Diseases; miRNA-based delivery systems; Novel strategies

Introduction

MicroRNAs, the small, single-stranded non-coding RNA molecules (containing 18-26 nucleotides) coded in various regions of the genome, often in introns or sometimes exons of other genes found in animals, plants, and even some viruses, are involved in RNA silencing and post-transcriptional regulations of expressions of genes [1-4]. Most of the investigations in oncology denote the changeful aspects of RNA molecules and the proteins to code proteins where the coding sequences accounted about 2% of the genome, while the residual 98% of the genome incorporates non-coding RNAs such as miRNAs to play the pivotal roles in various biological actions in the time of normal physiological activities as well as in the creation and development of diverse pathologies/diseases such as inflammation, obesity, type-2 diabetes mellitus, cardiovascular diseases, infectious, respiratory, genetic and neurodegenerative diseases, and cancers owing to their dysregulations/dysfunctions [5-18]. Additionally, miRNAs may play key roles in modulating expressions of enormous genes at transcriptional and post-transcriptional levels exhibiting tissue-specific developmental expression patterns in the biological processes within cells and organisms [19-30], while altered expressions of miRNAs have emerged as various pathogenesis including spanning innate immunity, auto-immunity and auto-immune diseases, acute hepatitis, anxiety, depression and Huntington's disease [31-36].

Generally, primary miRNAs (pri-miRNAs) are deciphered from DNA sequences, and altered to precursor miRNAs (pre-miRNAs) and subsequent mature miRNAs, while miRNAs may interact with the 3' UTR of target mRNAs, or with the other regions including the 5' UTR, gene promoters and coding sequence, and maintain a shuttle between various subcellular compartments to regulate the rate of transcription and translation associated with aberrant expression of miRNAs for the development of diseases [37-43].

A large number of stable miRNAs, secreted into extracellular fluids from different tissues/organs, may be treated as novel diagnostic circulating biomarkers for cancer and other immune-related diseases through expression profiling, such as miRNA-21, localized in microvesicles or anchored to other plasma contents, such as RNA-binding proteins and high-density lipoproteins

(HDLs), may enter/communicate recipient cells to reduce protein levels of target genes [44-48]. Diet-derived exogenous miRNAs may also enter into the circulatory system and tissues to influence gene expression and biological activities [49-54]. The associated/protective elements usually guard miRNAs against gastrointestinal environments to encompass salivary and pancreatic RNases, low pH of the stomach, digestive enzymes, peristaltic activities and microbial enzymes [54]. The other factors such as genetic amplifications/deletions, epigenetic methylations of miRNA genomic loci, and modifications affecting the controlling of pri-miRNA by transcription factors along-with contents involved in the biogenesis of miRNA may result in alterations in miRNA expressions and functions across various types of cancer [55-57]. Moreover, oncogenic drivers like genetic mutations may also have an influence on the miRNA-biogenesis and effector-activities in contributing miRNA-dysregulations [58].

Several developed miRNA-based therapeutics such as antisense miRNA oligonucleotides, small molecular miRNA inhibitors, locked nucleic acid anti-miRNAs and miRNA sponges have exerted great effects for inhibiting miRNA-related disease-processes, while miRNA mimetics have been utilized for miRNA supplementation [59-61]. However, the short circulation time, deficient targeting, immune response of naked miRNA-based components, blood-brain-barrier, drug-resistance, tumor cell non-specificity, nucleic acid un-stability in body fluids and neurotoxicity have set the limitations of miRNA-based therapies for clinical applications. To overcome these obstacles, various biomimetic systems such as bacterial and viral components, and several nanocarriers such as liposomes, solid lipid nanoparticles, polymeric micelles and nanoparticles, aptamers and dendrimers may be utilized for miRNA-based therapies to reduce side effects and get higher therapeutic efficiencies against diseases [62,63]. This review demonstrates mainly the present status of miRNA delivery systems as promising therapeutic approaches to treat diseases.

Biogenesis of miRNAs

In the canonical biogenesis of miRNAs, different combinations of the proteins chiefly Drosha, Dicer, exportin 5, and argonaute-2 (AGO_2) are involved, whereas in the non-canonical biogenesis, Drosha/DiGeorge Syndrome Critical Region-8 (DGCR8)-independent and Dicer-independent pathways are involved [64].

In brief, RNA polymerase II deciphers miRNA genes, resulting in the creation of pri-miRNAs having stem-loop structures composed of hundreds of nucleotides. In the nucleus, pri-miRNAs are processed by ribonuclease Drosha into a 70 to 100 nt hairpin structures named pre miRNAs. The pre miRNAs are then transported into the cytoplasm by the shuttle systems consisted of Exportin 5 and Ran GTP, and cleaved further into the double-stranded miRNA duplexes possessing 22 nt by Dicers, while the mature miRNA strands anchor to the miRNA-inducted silencing complex (miRISC) followed by the subsequent degradation of the antisense miRNAs strands (miRNAs). The miRISC complex possessing the mature miRNA strands may anchor to the 3'-UTR of the target gene mRNA. The specific anchoring between miRNAs and target mRNAs may lead to the repression of protein synthesis followed by the subsequent degradation of the targeted mRNAs [65]. Generally, miRISC may recognize mRNA via complementary base pairing of the miRNAs with the target gene mRNAs. Under a few consequences, the bindings between miRISC and mRNAs do not need perfect pairings [66]. Moreover, miRNAs may also anchor to the 5'-UTR of target genes [67]. The anchoring of miRISC to the mRNA may lead to the either rare promotion or frequent repression of translations [68].

Implications of miRNAs with the drug metabolizing cascades

MiRNAs may participate in the drug-metabolizing processes through affecting the cytochrome P450 family (CYP) enzymes (DMEs) and drug transporters (DTs) [69]. A genetic change may alter drug responses as well as metabolic mechanisms through methylations at the CpG promoter regions, acetylations at the histone regions, and miRNA mutations influencing gene expressions at the post-transcriptional levels [70,71]. In carcinoma cells, miRNAs 27b and 378 restrict the expressions of cytochrome P450 (CYP) cascade enzymes, CYP2E and CYP1B1, while miRNA-27b and mmu-miR-298, miRNAs-122a and 42a, and miRNAs 125 and 126 influence the expressions of CYP3A4, CYP7A1 and CYP24A1, and CYP2A3 respectively [72,73]. MiRNAs also control the activities of drug transporters such as ATP binding cassette (ABC), subfamily B, member 1 (ABCB1/MDR1/P-gp), and solute carrier (SLC) transporters utilized to regulate the absorption, distribution and elimination of drugs [74]. In accordance with investigations, miRNAs-451, 27a and 331-5p target ABCB1 mRNA leading to negative regulations and drug resistances in different cancer cells, while miRNA-31 regulate the expression of ABCB9 transporter, miRNAs-326, 1291 and 134 modulate ABCC1 effect in drug resistance. The interferences of miRNAs- 379, 9 and 128 in different cancer malignancies reduce the expressions of ABCC2, ABCC3 and ABCC6, and also the appearances of ABCC4 and ABCC5 targets. Moreover, drug resistances are monitored in ABCG2 transporter modulations via involvements of a few miRNAs such as miRNAs- 519c, 520h, 328, 212, 181a and 487a in different cancer environments [73,75] (Table 1).

Table 1: The associations of a few miRNAs with the drug metabolizing cascades.

miRNAs	Drug metabolizing cascades	References
miRNA378, miRNA27-b	CYP2E1 and CYP1B1	72
miRNA126, miRNA125	CYP2A3, CYP24A1	76,77
miRNA422a, miRNA122a	CYP7A1	78
miRNA27a, miRNA3315p, miRNA451	ABCB1	79,80
miRNA31	ABCB9	81
miRNA326, miRNA134 and miRNA1291	ABCC1	82,83
miRNA212, miRNA328, miRNA519c, miRNA520h, miRNA181a, miRNA487a	ABCG2	75
miRNA379, miRNA9, miRNA128	ABCC2, ABCC3 and ABCC6, ABCC4, ABCC5	84-86

Implications of miRNAs in the context of metabolic syndromes

It is investigated and established that miRNAs are involved not only in gene regulation but also in a variety of cellular processes and associated diseases. Dys-regulations of miRNAs affect the status and activities of metabolic organs like liver, pancreas, adipose tissue (AT) and muscle with the contribution to the developments of metabolic syndromes (MetS). The investigations on the correlations between MetS and miRNAs may clarify the pathogenesis of MetS to provide the therapeutic targets of miRNAs (Table 2).

Table 2: MicroRNAs associated in metabolic syndrome with metabolic tissues.

Metabolic tissues	miRNAs	Pathways/processes	Targets	Ref
Liver	miR-2, miR-148a-3p, miR-185	Lipid/cholesterol metabolism	SERBP2/LDLR	87,88
	miR-21	Lipid metabolism	Smad7, HMGCR, HOMER1	89-93
	miR-26a	Lipid metabolism	PKC, ACSL3, ACSL4, SREBF2, GSK3β	94
	miR-27a-3p	Lipid/cholesterol metabolism	FAS, FASN, PPARA, SREBF1/LRP6, LDLRAP1	95-98
	miR-27a-3p	De novo lipogenesis/Inflammation	RxRα, scd1/Nrf2, NF-κB	95-98
	miR-27b	Lipid metabolism / Cholesterol efflux	LDLR/ABCA1	95-98
	miR-30c	Lipid/Glucose metabolism	RARB, MTP, LPGAT1/LIN28B, IDH1	99-102
	miR-33a-3p	Cholesterol efflux / Insulin signaling / Lipid metabolism	ABCA1, ABCG1 / IRS2, SIRT6 / SREBP2, SREBF1	103
	miR-33b	Lipid metabolism	SREBF1	104
	miR-34a	Lipid/Fatty acid metabolism	SREBP1/SIRT1	105
	miR-96, miR-183	Lipid metabolism	SREBP	106
	miR-122	Lipid metabolism/Liver functions	SREBF1/HNF4a, HNF6, LETFS	107,108
	miR-128	Cholesterol metabolism / Efflux / Inflammation	LDLR/ABCA1/Nrf2	109
	miR-130b, miR-301b	Cholesterol metabolism / Efflux	LDLR/ABCA1	110-112

	miR-140-5p	Cholesterol metabolism / Inflammation / AMPK/SREBP1pathway	LDLR/Nrf2/NEAT1	113,112 , 1 14
	miR-192-5p	Cholesterol homeostasis / Lipid metabolism / De novo lipogenesis / Inflammation	ABCG4 / EIOVL1, EIOVL5, PPARA, ATF1, FABP3, VLDLR, CRTc2, CAV2, DBT, IGF1 / SREBF1, SCD-1 / FoxO1	115-118
	miR-200	Liver cells growth and proliferation	PI3K	119
	miR-206	Lipid metabolism	LXR-2	120
	miR-223	Cholesterol efflux / Biosynthesis	ABCA1 / HMG-CoA, SC4MOL	103,120
	miR-344	Lipid metabolism (Wnt/β-catenin signaling)	GSK3β	113
	miR-370	Lipid metabolism	MECPT	121
Pancreas	miR-7	Islet cell differentiation	Pax6	122,123
	miR-9	Insulin secretion/release	Stx-1α / Onecut-2, Granuphilin/Slp4	124,125
	miR-15a/b, miR-16, miR-195	Islet functions	Ngn3	126
	miR-29	Insulin secretion	Stx-1α, Mct1	127
	miR-96	Insulin secretion	Stx-1α	124
	miR-103, miR-107	Insulin sensitivity	CaV1	118
	miR-124a	Insulin secretion / release / Islet functions	Stx-1α / SNAP25, Rab3A, Rab27A, Synapin-1A, Noc2 / Foxa2, Pdx1, Creb1	124,128
	miR-195-5p	Islet β-cell functions / Insulin sensitivity	Clock/CaV1	129,115 -117
	miR-375	Islet functions	HNF6, INSM1, Ngn3, PDX1	130,131
Adipose tissue (AT)	Let-7	Cell functions / Glucose metabolism / Adipogenesis	RAS, HMGA2 / INSR, IGF1R / AT-hook2, FABP4, PPARγ	132-134
	miR-8	Adipogenesis / Fat body growth and differentiation	FABP4/PI3K	119,135
	miR-14	Lipid metabolism	P38, MAPK	136
	miR-21	Adipocyte differentiation	AP-1, TGF-β receptor2	137
	miR-22	Adipogenesis	HDAC6	138
	miR-26a	Inflammation / Autophagy	IL-6,17 / BECN1, LC3	139-142
	miR-26b	Adipogenic differentiation	PTEN	143,142
	miR-27a, miR-130a	Adipocyte differentiation	PPARγ	112
	miR-27b, miR-363	Adipocyte differentiation	C/EBPα, PPARγ	144
	miR-30c	Adipocyte differentiation	ACVR1, SERPINE1	99-102
	miR-31	Lipid accumulation	C/EBPα	145
	miR-33b	Lipogenesis	EBF1	104
	miR-93	Adipogenesis	Sirt7, Tbx3	146
	miR-103	Adipogenesis (AKT/mTOR signaling)	MEF2D	147
	miR-125a	Adipogenesis	ERPα	148

	miR-142-5p	Inflammation	Nrf2	112,114,149
	miR-143	Adipocyte differentiation	ERK5 signaling	150
	miR-145	Preadipocyte differentiation	IRS1	151
	miR-146b	Metabolic homeostasis	SIRT1	152
	miR-155	Adipocyte differentiation / Lipid metabolism	PPARγ/C/EBPβ	153,154
	miR-194	Stimulates osteogenesis and inhibits adipogenesis	COUP-TFII	155
	miR-199a	Adipogenesis	Smad1	156
	miR-206	Lipid accumulation	FAS, PPARγ, PTEN, C/EBPα	143
	miR-210	Adipocyte differentiation (PI3K/Akt signaling)	SHIPI	157
	miR-224	Fatty acid metabolism	EGR2	158
	miR-320	Adipogenesis	RUNX2	159
	miR-363	Adipocyte differentiation	C/EBPα, E2F3, PPARγ	144
	miR-369	Adipogenic differentiation	FABP4	160
	miR-370	Metabolic homeostasis	CPTIA	121
	miR-375	Adipocyte differentiation	C/EBPα, PPARγ2	139]
	miR-448	Lipid metabolism	5-HT2AR, 5HT2CR, KLF5	161
	miR-637	Adipogenesis	Sp7	162
	miR-709	Lipid metabolism (Wnt/β-catenin signaling)	GSK3β	163
Muscle	miR-29a	Insulin resistance (IR) / Glucose uptake	PPARδ/7RS-1	164,165
	miR-106b	Mitochondrial dysfunction, IR	Mitofusin-2	166
	miR-199a-3p, miR-590-3p	p/Akt signaling	CLIC5, HOMER1	112,88, 167,156 ,168
	miR-208	Glucose metabolism	MED13	169,170

Usually, the liver (endocrine organ) acts to control blood glucose level and maintain energy homeostasis. A few studies have elucidated that miRNAs play the active roles to regulate liver function as well as the pathogenic processes of MetS like non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) through the expressions of key genes involved in cholesterol homeostasis, fatty acid metabolisms and liver functions including the ATP-binding cassette A1 (ABCA1) and the rate-limiting enzyme 3-hydroxy-3-methylglutaryl-CoA-reductase [171,172]. A few investigators have shown that a dominant hepatocyte-specific miR-122 has the anti-inflammatory activities in the liver, while another group has demonstrated the identification of differentially expressed miRNAs, and the decrement of miRNA-122 level in human subjects with NASH [173,174]. It is investigated that hepatic miR-223 may regulate the biosynthesis of cholesterol by targeting the 3-hydroxy-3-methylglutaryl-CoA synthase 1 and the sterol-C4-methyloxidase-like protein. In addition, miRNA-223 may inhibit the uptake of cholesterol by targeting the scavenger receptor class B member 1 and promote the efflux of cholesterol by controlling the expression of ABCA1 positively.

Insulin and islets β-cells play a significant role in several metabolic diseases such as T2DM manifested by insulin resistance (IR) in peripheral tissues, while reduced insulin level is linked to a decrement in β-cell mass, and the dysfunction of islets in controlling the glucose homeostasis [113]. Numerous miRNAs are involved in insulin secretion and pancreatic development with anchoring to the kinases and the pivotal transcription factors to activate insulin secretion, augment insulin sensitivity or control islets-activities. It is studied that the miR-375 in pancreatic islets targets directly 3-

phosphoinositide dependent kinase-1 (PDK-1) (responsible for the development of pancreatic β-cells) to diminish the blood glucose level [175].

Adipose tissue, the endocrine system to store energy, associated with blood glucose level, insulin sensitivity, and inflammation, take part in pathological processes. Numerous miRNAs in AT contribute to regulate energy balance and metabolic homeostasis correlated with MetS. Several studies have elucidated the identification of various abundant miRNAs during the differentiations of adipocytes. MiR-130, one of them, affects potentially the differentiation of adipocytes, and adipogenesis through repression of the biosynthesis of PPARγ (the regulator of adipogenesis) [176]. It is investigated that miR-143 may also regulate adipocyte differentiation via ERK5 signaling, while its over-expression may restrain the activation of insulin-stimulating AKT and homeostasis of glucose in obese mice.

Glucose and energy are utilized chiefly by skeletal muscle. In strenuous exercise, energy is consumed and muscle glycogen is degraded to produce lactic acid transported to the liver for the amalgamation of liver glycogen and glucose for providing energy. It is reported that a few miRNAs take part in metabolism and proliferation in cardiac and skeletal muscle tissues [177]. A few researchers have shown that miRNA-133a participates to mediate altered gene expressions as well as functional/structural defects in cardiac muscle [178]. A few investigators have exhibited that miRNA-29a upregulated in the skeletal muscle in intra uterine growth retardations inducts MetS characterized by IR, while its over-expression reduces the glucose transporter 4 levels through the partial inductive decrement of uptake of insulin-dependent glucose [179].

Implications of miRNAs as biomarkers as well as therapeutic targets in the development of cardiovascular diseases

MiRNAs involved in downregulations or sometimes upregulations and expressions of their target genes via mRNA degradations or translational repressions as novel regulatory components have been elucidated in the participation of many cellular, physiological, and pathophysiological cell/tissue-specific signaling / processes. MiRNAs have been emerged as significant biomarkers / regulators of cardiovascular physiology / pathophysiology as well as pivotal players in the development of cardiovascular diseases (CVD) such as myocardial infarction (MI), heart failure (HF), atherosclerosis (AS)/coronary artery disease (CAD), atrial fibrillation (AF), other arrhythmias, ischemic stroke (IS), and CVD complications of diabetes/metabolic syndromes (MS) [180] (Table 3).

Table 3: MicroRNAs associated in the pathways/processes as therapeutic targets and biomarkers for the development of cardiovascular diseases (CVD).

Cardiovascular diseases	miRNAs as therapeutic targets	miRNAs as biomarkers	Both as targets and biomarkers	Pathways / Processes	Clinical trials
Myocardial infarction (MI)	miR-1, miR-19a/19b, miR-21, miR-34a-5p, miR-92a, miR-132, miR-144, miR-146a, miR-155, miR-181a/181b, miR-199a, miR-210, miR-212, miR-363, miR—381, miR-449a			PKCδ, AQ9/PI3K/AKT, Fibrosis, Oxidation, Apoptosis, Angiogenesis, Cardiomyocyte proliferation	miR-132
Heart failure (HF)	miR-21, miR-25, miR-34a, miR-99a, miR-132, miR-195-5p, miR-212/132, miRNA-221-3p, miR-222	miR-10a, miR-16p, miR-18a-5p, miR-27a-3p, miR-31, miR-92a, miR-106a-5p, miR-122, miR-155, miR-208a-3p, miR-223-3p, miR-423-3p, miR-423-5p, miR-499-5p, miR-652-3p, let-7i-5p	miR-199a-3p	MAPK, TGF-β/SMAD, Notch, Fibrosis, Inflammation, Angiogenesis, Lipid metabolism, Endothelial dysfunction	miR-132
Atherosclerosis (AS) / coronary artery disease (CAD)	miR-121, miR-126-5p, miR-133, miR-143/145	miR-129a, miR-451a, miR-483-5p,	miR-29a, miR-155, miR216a	PTEN/AKT, Smad3/IκBα, Notch, Inflammation, Angiogenesis, Lipid uptake	

Atrial fibrillation (AF)	miR-26a, miR-155	miR-1, miR-10a, miR-21, miR-24, miR-29a, miR-31, miR-106b-25 cluster, miR-125a, miR-133, miR-150, miR-208a/208b, miR-210, miR-302a, miR-483-5p, miR-499, miR-590	miR-34a-5p, miR-125b-5p, miR-200b-3p, miR-328	Ca^{2+}/CaMKII/HDAC4, Ca^{2+}/Calcineurin/MEF2, Wnt, E2F3, Ica, Ldensity, Fibrosis, Hypertrophy, Apoptosis, Electrical remodeling, Oxidation, Inflammation, Mitochondrial function, Cytokine regulation	
Other arrhythmias	miR-1, miR-34a, miR-208a			Connexin 4, Notch, Cardiac transcription factors	
Ischemic stroke (IS)	miR-126	miR-16, miR-335		Notch	
Diabetes / Metabolic syndrome (MS)		miR-1, miR-1/206, miR-19b, miR-27a / miR-29a, miR-29b, miR-30a, miR-34a, miR-125b, miR-133a, miR-146a, miR-150, miR-155, miR-195, miR-199a, miR-210, miR-212, miR-214, miR-221, miR-320, miR-320b, miR-373, miR-378, miR-423, miR-451, miR-499		PI3K-Akt-mTOR, TGF-β, ErbB, Wnt / MAPK, Calcineurin/NFAT, p27/mTOR, Oxidation, Apoptosis, Fibrosis, Hypertrophy, Autophagy	miR-32

Implications of miRNAs on expressions and involvements in mammalian cells

The tissue specific expressions of miRNAs, their implications as tumor suppressors and oncogenes, and their abnormal expressions during tumorigenesis in mammalian cells have been depicted by several investigators (Table 4).

Table 4: Expressions and involvements of a few microRNAs on mammalian cells.

Expressions and involvements	**Cell/Tissue/Organ specific**	**MicroRNAs**	**References**
Tissue specific	Embryonic stem (ES) cells	miR-296	181
	ES cells, up-regulated on differentiation	miR-21, miR-22	181
	Both ES cells and different adult tissues	miR-15a, miR-16, miR-19,b, miR-92, miR-93, miR-96, miR-130, miR-130b	181
	During mouse brain development	miR-9, miR-19b, miR-103, miR-124a, miR-125b, miR-128, miR-131, miR-178, miR-266	182,183
	Adult brain	miR-7, miR-9, miR-124a, miR-124b, miR-125a, miR-125b, miR-128, miR-132, miR-135, miR-137, miR-149, miR-153, miR-183, miR-190, miR-219	182
	Lung	miR-18, miR-19a, miR-20, miR-24, miR-32, miR-130, miR-141, miR-193, miR-200b, miR-213	182
	Spleen	miR-99a, miR-127, miR-142a, miR-142s, miR-151, miR-189, miR-212	182
	Hematopoietic tissue	miR-142, miR-181, miR-223	182

	Liver	miR-122a, miR-152, miR-194, miR-199, miR-215	182
	Kidney	miR-18, miR-20, miR-24, miR-30b,c, miR-32, miR-141, miR-193, miR-200b	182
	Heart	miR-1b,d, miR-133, miR-206, miR-208, miR-143	182
	Ubiquitously	Let-7a,b, miR-16, miR-21, miR-26a, miR-27a, miR-30b,c, miR-143a	182
Tumor suppressors and oncogenes	Invertebrates and vertebrates	Let-7s	184
	B cell lymphocytes	miR-15a/miR-16-1, miR-15b/miR-16-2	185,186
	Glioblastoma, breast, colon, liver, brain, pancreas, and prostate tumors	miR-21	106,187-192
	Lymphomas, lung, colon, pancreas and prostate cancers	miR-17-92	193-198
Abnormal expressions during tumorigenesis	Down-regulated in chronic lymphocytic leukaemias	miR-15, miR-16	185
	Down-regulated in lung cancer cell lines	miR-26a, miR-99a	184
	Down-regulated in colon cancers	miR-143/miR-145 cluster	199
	Up-regulated in Burkitt lymphoma	miR-155	200

Implications of plant miRNAs in cross-kingdom gene regulations

Several investigations on the implications of plant miRNAs and their effects on cross-species gene regulations have provided their evidences with a number of challenges on their sources, target interests, analysis methods and disease applications (Table 5).

Table 5: Plant miRNAs in gene regulations: The cross-species comparisons.

miRNAs	**Sources**	**Targets of interest**	**Methods of analysis**	**Disease applications**	**References**
miRNAs-168a, 156a, 166a	*Oryza sativa*	Human, mouse, rat, calf, horse, sheep	HTS, qRT-PCR, NB, WB	Low-density lipoprotein receptor adaptor protein-1 (LDLRAP1)	49
miRNAs-1-6-GA-CONTIG1	*Gmelina arborea*	Human genes	Bioinformatics	Signal transduction and apoptosis regulation	201
08 predicted miRNA	*Curcuma longa*	Human genes	Bioinformatics	Diabetes mellitus type-2, cardiovascular disorders, Alzheimer, thalassemia, cancer	202
miRNA-172	*Brassica oleracea*	Mice	qRT-PCR	Not mentioned	203
miRNA-2911	Honeysuckle / *Lonicera japonica*	Mice	qRT-PCR, HTS, NB, fluorescent labeled tracing assay	Not mentioned / Influenza A virus	204/205

miRNA-29b, 200c	Milk derived	Human, mice	qRT-PCR	Not mentioned	206
miRNA-375	Milk derived	Mice	qRT-PCR, NB, HTS	Not mentioned	207
miRNA-168a	*Moringa oleifera*	Human genes	Bioinformatics	Stress signaling, cell survival, cell cycle, cell growth, genome stability	208
miRNA-14	*Curcuma longa*	Human	Bioinformatics	Rheumatoid arthritis	209
miRNA-159	Broccoli / Glycine max / *Arabidopsis thaliana*	Mice	qRT-PCR	Transcription factor-7 / Breast cancer	210
miRNA-159 / miRNA-166a	*Brassica campestris*	Mice	qRT-PCR, HTS	Not mentioned	211
miRNA-160 miRNA-2673	*Brassica oleracea*		qRT-PCR	Not mentioned	212
miRNA-2910	Populous euphratica	Human	Bioinformatics	JAK-STAT signaling	213
14 potential miRNA	*Camptotheca acuminate*	Human genes	Bioinformatics	Focal adhesion, lipolysis regulation, mTOR signaling	214
44 potential miRNA	*Viscum album*	Human genes	Bioinformatics	Cardiovascular and neurological disorders, cancer	215
miRNA-156a	Spinach, cabbage, lattuce	Human	qRT-PCR	Cardiovascular diseases	216
miRNA-414, miRNA-869.1	*Ocimam basilicum*	Human genes	Bioinformatics	Diabetes mellitus, gestational diabetes, rheumatoid arthritis, cataract, Alzheimer's disease, infant death syndrome, infantile achalasia, cantu syndrome	217
Bmn-miRNAs-167h, 168, 396g, 156, 172d, 171d-3p, 399h-3p, 399f, 444b.1, 403e, 159, 857	*Bacapa monnieri*	Human genes	Bioinformatics	Involvements in NF-kB, MAPK signaling	218

Therapeutic applications of antago/mimic miRs against various diseases

The synthetic antagonists to miRNAs (miRs) as miRNA silencing agents are gaining attention for advanced therapeutic applications with promising outcomes [219]. Antago miRs, the part of an anti-miRNA oligonucleotide group, are specific and complementary to their miRNA targets, and active in many tissues to be produced. The complementary substances restrict miRNAs and protect the target mRNAs from suppressions. The usages of antago miRs and also mimic miRs with or without combination elements have been demonstrated with their therapeutic actions against a few major diseases such as asthma, glioblastoma (GBM), chronic obstructive pulmonary disease (COPD), lung adenocarcinoma, lung cancer, non-small cell lung cancer (NSCLC), lung fibrosis, cystic fibrosis (CF), pulmonary hypertension (PH), astrocytoma, and gliosarcoma (Table 6).

Table 6: A few antago/mimic miRs tested as therapies for various diseases.

miRNA elements	Combination elements	Diseases	Actions	References
miR-145 inhibitor / mimic	-	Asthma / Glioblastoma (GBM)	Inhibition of eosinophilic inflammation and TH2 cytokine production, decrement of airway hyper-responsiveness / Inhibition of GBM	220/221
miR-155-5p inhibitor	-	Asthma	Reduction of miR-155-5p expression, poor uptake in lymphocytes	222
miR-21 inhibitor	-/ miR-15a,16,20a,26,222 inhibitors, miR-100 mimic	Asthma / GBM	Increment of PTEN levels, reduction of PI3K activity and restoration of steroid sensitivity / Inhibition of GBM	223/224-235
miR-9 inhibitor	-	Asthma / GBM	Restoration of steroid sensitivity / Inhibition of GBM	236/237
miR-570-3p inhibitor	-	COPD	Restoration of Sirt-1 level and cellular growth, suppression of cellular senescence markers	238
miR-132 inhibitor	-	COPD	Ectopic expression of PKR or miR-132 antago-miR alone incapable of restoring IFN-β	239
miR-125 a& b inhibitors	-	COPD	Inhibition of the activation of inflammatory cytokines, and strengthening of IAV response	240
miR-499a-5p inhibitor	-	Lung adenocarcinoma	Inhibition of miR-499a tumor biomarker as well as tumor development	241,242
miR-519c inhibitor	-	Lung cancer	Enhancement of HIF-1 alpha protein and angiogenic activity	243
miR-135b inhibitor	-	Lung cancer	A potent therapeutic target in NSCLC, inhibition of the invasion of cancer cells, development of lung tumors and metastasis in mice	244
miR-494 inhibitor	-	NSCLC	Inhibition of miR-494 expression, prevention of angiogenesis and mitigation of tumor development	245
miR-34a inhibitor / mimic	-	NSCLC / GBM	Stimulation of tumor production / Inhibition of GBM	246/247,219
miR-1290 inhibitor	-	NSCLC	Inhibition of the proliferation, clonography, invasion and migration as well as tumor volume and weight of CD133+ cells by targeting tyrosine kinase	248
miR-96 inhibitor	-	NSCLC	Induction of tumor suppressor gene (SAMD9) and inhibition of cisplatin chemo-resistance	249
miR-346 inhibitor	-	NSCLC	Inhibition of cellular growth and metastasis	250
miR-214 inhibitor	-	NSCLC	Reversing of gefitinib resistance	251

miR-323a-3p inhibitor	-	Lung fibrosis	Improvement of fibrosis of the murine lungs after bleomycin injury	252
miR-155 inhibitor	-	Cystic fibrosis	Reduction of the expression of miR-155 and IL-8 mRNA levels	253
miR-126 inhibitor	-	Pulmonary hypertension	Mimicking of the pulmonary arterial hypertension and reducing of muscle capillary and exercise tolerance of skeletal muscles	254
miR-17, 21 inhibitors	-	Pulmonary hypertension	Reduction of right ventricular systolic pressure, total pulmonary vascular resistance index and pulmonary arterial muscularization	255
miR-206 inhibitor	-	Pulmonary hypertension	Decrement of right ventricular pressure and hypertrophy index	256
miR-7 mimic	miR-181, 195 mimics	Glioblastoma (GBM)	Inhibition of GBM	257,258,234
miRs-135a, 124a,124-3p, 124,129-3p, 138-5p, 143, 181b-5p, 181d,182,210, 218,302,367 mimics	-	GBM	Inhibition of GBM	259-272
miR-221 inhibitor	miR-222 inhibitor	GBM	Inhibition of GBM	273,274
miR-222 mimic	miR-221 inhibitor	GBM	Inhibition of GBM	274,234
Let-7a,7g miRNA mimics	-	GBM	Inhibition of GBM	275,276
miR-100 mimic	miR-21 inhibitor	GBM	Inhibition of GBM	228
miR-10b inhibitor	miR-137 mimic	GBM	Inhibition of GBM	277
miR-137 inhibitor	miR-10b inhibitor	GBM	Inhibition of GBM	277
miR-148a mimic	miR-269-5p mimic	GBM	Inhibition of GBM	278
miR-15a inhibitor	miR-20a,21 inhibitors	GBM	Inhibition of GBM	234
miR-16 inhibitor	miR-20a,21,222 inhibitors	GBM	Inhibition of GBM	234
miR-181 mimic	miR-7,195 mimics	GBM	Inhibition of GBM	234
miR-195 mimic	miR-7,181 mimics	GBM	Inhibition of GBM	234
miR-20a inhibitor	miR-15a,16,21 inhibitors	GBM	Inhibition of GBM	234
miR-26 inhibitor	miR-21 inhibitor	GBM	Inhibition of GBM	234

miR-296-5p mimic	miR-148a mimic	GBM	Inhibition of GBM	[278]
miR-205 mimic	-	Astrocytoma	Inhibition of astrocytoma	[279]
miR-146b mimic	-	Gliosarcoma	Inhibition of gliosarcoma	[260]
Cel miR-67 mimic	-	Gliosarcoma	Inhibition of gliosarcoma	[260]

Applications of a few miRNAs-based therapeutic delivery systems against various diseases

As the emerging evidences denote the involvements of miRNAs in the onset and progression of diverse pathophysiology, the drastic surge of interests in miRNAs-based therapies has attracted attention [280,281]. As the diminished miRNA expressions may drive the diseases, miRNA mimics may be utilized to restore their expressions and functions, while anti-miRNAs (antago miRs) may be exploited to counteract the activities of up-regulated miRNAs involved in the development of diseases [281-286]. However, the safe and effective delivery of miRNA antago miRs / mimics for targeting tissues possesses several limitations such as non-specificity, susceptibility to degradation by nucleases, rapid clearance from circulatory system, cytotoxicity, and low tissue permeability [287-291]. The chemical modifications and several oligonucleotide carriers have been developed to improve stability, tissue penetration, and therapeutic efficacies against diseases [292-298]. Moreover, a few therapeutic approaches such as lentivirus, exosomes, lipids, micelles, RNA, interfering, protein/peptide nanoparticles, inorganic compounds, and polymers - based delivery systems/vehicles loaded with miRNAs-mimics/antago-miRs have been developed to inhibit or restore the expressions of disease-associated miRNAs to get higher therapeutic efficiencies against various diseases (Table 7).

Table 7: A list of a few vectorized miRNA-based therapeutics.

Delivery systems	**Nucleic acids**	**Target diseases**	**Target actions**	**References**
Lentiviral	let-7	Non-small-cell lung cancer (NSCLC)	CDC25A,CDK6,cyclin-D2, HMGA2, MYC, RAS	[299]
Lentiviral	miR-133b	Spinal cord regeneration	Epha7,P2X,P2RX4,RhoA, Xylt1	[300]
AAV serotype 3	miR-26a, 122	Liver tumor	PIK3C2α/Akt/HIF-1α/VEGFA, Bcl-2,Bcl-w, Bcl-xl,Mcl-1	[301]
AAV serotype 5	miATXN3	Spinocerebellar ataxia type 3	ATXN3	[302]
AAV serotype 9	miR-298	Spinal and bulbar muscular atrophy	Androgen receptor	[303]
Exosomes	siPPARA	Obesity	-	[151]
Exosomes	miR-21 mimic and inhibitor	Myocardial infarction (MI)	-	[148]
Exosomes	Cholesterol-modified miR-210	Cerebral ischemia	Peptide target in ischemic zone	[146]
Exosomes	miR-155 mimic	IR	-	[153]
Exosomes	miR-192-5p inhibitor	Non alcoholic fatty liver disease (NAFLD)	-	[304]
Exosomes (TEVs)	anti-miR-21	Breast cancer	Blocking of miR-21; increment in cell killing; reduction of doxorubicin resistance	[305]
Exosomes	miR-199a-3p	Ovarian cancer	mTOR, c-Met, IKKβ, CD44	[306]

Exosomes-GE11 peptides	Let-7	Breast cancer	HMGA2	307
Exosomes	miR-122	Hepatocellular carcinoma	ADAM10,CCNG1, IGF1R	308
Exosomes	miR-145	Lung cancer	CDH2	309
Liposomes	miR-103,107 antagomiRs	T2DM	-	310
Liposomes	miRs-148b,106b,204 mimics	MI	-	311
Liposomes	anti-miR-712	Atherosclerosis	-/TIMP3,MMPs,ADAMS, ERK5,KRAS,CHEK2	312
Liposomes (antibody-modified)	Anti-miR-1 antisense oligonucleotides	Ischemic myocardium	-	162
Liposomes	miR-182 inhibitor	Cardiac hypertrophy	-	147
Liposomes	siFVII	Liver disease	-/Receptor target liver	159, 313
Liposomes	miR-34a	Lung cancer	Bcl-2,c-Met,KRAS	314
Liposomes	miR-143,145	Colorectal carcinoma	MYCN,FOS,FLI,YES, Cyclin CDK3, D2, MAPK4K4,MAP3K3	312
Liposomes	miR-7,29b	Lung cancer	IRS-1,EGFR,RAF-1, CDK6,DNMT3B,MCL1	315,316
Ionizable liposomes	miR-200c	Lung cancer	GAPB/Nrf2, PRDX2, SESN1	317
Lipid nanoparticle	ds-miR-634	Pancreatic cancer	APIP,BIRC5,LAMP2,NRF2, OPA1,TFAM,XIAP	318
Ionizable lipid nanoparticle	miR-199b-5p	Breast, colon, prostate, glioblastoma, medulloblastoma cancer	Hes-1	319
RNA micelles	anti-miR-21	Cancer cells	Targeted delivery, enhancement of the expression of pro-apoptotic factors, induction of apoptosis, enhancement of permeability	320
RNA nanoparticles	anti-miR-21	Triple negative breast cancer cells	Reduction of tumor growth	321
Interfering nanoparticles	anti-miR-122	Hepatitis	Regulation of gene expression, specific silencing of target genes	322
Mesoporous silica nanoparticles modified with polydopamine and aptamer	anti-miR-155	Colorectal cancer	Enhanced sensitivity, permeability and retention in tumor cells, gene silencing and tumor growth inhibition	323
Polylysine nanoparticles	anti-miR-10b	Breast cancer	Effective delivery and anti-tumor activity	324
Arginine nanoparticles	anti-miR-155	Lymphoma	Down-regulation of the expression of miR-155, modulation of the splicing	325

			to overshadow the expression of MCL-1	
cRGD peptide functionalized LPH nanoparticles	Anti-miR-296	Angiogenesis	Effective delivery; upregulation of HGS expression; inhibition of endothelial cell migration and blood tube formation	[326]
Calcium phosphate nanoparticles	miR-133a	CVD	-	[327]
Carbonate apatite	miR-29b,4689	Colorectal cancers	BCL-2, MCL-1, KRAS, AKT-1	[328,329]
Polymeric nanoparticles	anti-miR-155	Lymphoma	Enhancement of permeability and retention effect	[330]
5-FU-PAMAM dendrimer	antisense miR-21	Glioblastoma	Enhancement of cellular uptake and cytotoxicity of 5-FU	[331]
Polymeric nanoparticles	anti-miR-10b,21	Triple negative breast cancer	Targeted delivery, sustained release and significant reduction in tumor growth	[332]
PEI	miR-145,33a	Colon carcinoma	c-Myc, ERK5	[333]
PEI-PEG	miR-34a	Hepatocellular carcinoma	SNAI-1	[334]
PACE polymer	anti-miR-21	Glioblastoma	PTEN	[335]
Polymer micelle	anti-miR-21	Glioma	PTEN	[233]
Polymers	miR-33 mimic	Atherosclerosis	Inflammation	[336]
Polymers	anti-miR-33	Atherosclerosis	pH-responsive	[337]
Polymers	miR-199a-3p mimic	MI	-	[338]
Polymers	miR-21 mimic	MI	-	[339]
Polymers	sipcsk9	Hypercholesterolemia	-	[340]
Polymers	siapoB	Liver disease	Receptor target liver	[341]

Clinical trials with miRNA therapeutics against various diseases

A few miRNA-based therapeutics are being evaluated in clinical trials against various metabolic, genetic, oncological or other diseased conditions, while a few of them have not entered phase-III or being approved by the FDA and have been terminated owing to their toxicity [342-344] (Table 8).

Table 8: A few miRNA-based drugs (clinical trials) as miRNA therapeutics.

Drugs	**miRNA inhibitions**	**Diseases**	**Clinical trial phases**	**References**
EXONDYS51TM	PMO based	Duchenne muscular dystrophy (DMD)	Approved drug	[345]
MRX34	ASOs (2-O'methyl modifier)	P53/Wnt signaling	I	[346]
Miravirsen (SPC3649)	Phosphorothioate linkage, cholesterol-conjugated AMOs	HCV	I and IIa	[347]

RG-101	miR-122	HCV	II	[348]
RG-012	miR-21	Alport syndrome	I	[348]
Cobomarsen (MRG-106)	LNA-based	Various lymphomas	II	[349]
MRG-107	miR-155	Amyotrophic lateral sclerosis (ALS)	Entering clinical trial	[348]
Formiversen	PNA-based	CMV	III	[342]
Geasense	PNA-based	BCL-2	III	[350,351]
MesomiR-1	miR-16	Malignant pleural mesothelioma or NSCLC	I	[348]
MRG-201	miR-29	Scleroderma	I	[348]
MRG-106	miR-155	Cutaneous T cell lymphoma	I	[348]
RG-125	miR-103/107	Non-alcoholic steatohepatitis	I	[348]
RG-125 (AZD4076)	miR-103/107	Type 2 diabetes	I	[348]
MRG-110	miR-92a	Ischemia	I	[348]
RGLS4326	miR-17	Polycystic kidney disease (PKD)	I	[348]
AMT-130	Artificial miRNA	Huntington disease	I	[352-354]
CDR132L	miR-132	Heart failure	I	[355,356]

Emerging novel delivery systems

Several novel delivery systems have gained attractions regarding their biological suitability and higher therapeutic efficacies against diseases.

Inorganic nanoparticles (NPs)

Calcium phosphate (CaP), the chief inorganic content of hard tissues (teeth and bones), and their synthetic forms are highly biocompatible, and biodegradable for nucleic acid delivery. The bio-inspired and negatively surface-charged CaP-NPs developed are capable to encapsulate and deliver miRNAs to cardiac cells to treat cardiovascular diseases [327].

Selenium (Se), the essential trace element, is used for the synthesis of seleno-protein in the physiological processes with anti-oxidant activities [357]. SiRNAs loaded SeNPs owing to their suitable electrostatic interactions are capable to deliver siRNAs to target cells escaping their degradation from endosomes against drug-resistant tumor cells, palmitic acid-inducted oxidative injury of islet β-cells for their enhanced affinity to cell membranes, and accumulations in the liver, spleen and pancreas against MetS [358,359].

Magnetosomes

Magnetosomes, the emerging magnetic nanocrystals surrounded by phospholipid bilayers, secreted by the magnetosome-generating microorganisms, may be utilized as drug vehicles to the targeted site/s of diseases owing to their suitable features such as single magnetic domain, low toxicity, excellent biocompatibility, easy surface modification, and the capability of controlling through the external magnetic fields [360,361]. Several investigators have shown the excellent anti-tumor activities of purified bacterial magnetosomes loaded with hypoxia-inducible factor-1 (HIF-1) siRNAs [362].

DNA origami

DNA origami, the self-assembled for forming defined arbitrary shapes through the long single DNA scaffolding strands and hundreds of short DNA helper strands has been emerged as novel delivery system with precise nanoscale shape [363]. Several investigations have indicated that the various structures of DNA origami (tube, triangle and square) have been utilized as effective delivery vehicles for siRNAs, and may be targeted to the liver to treat NASH and NAFLD [364].

Microneedles

Microneedles have been emerged as novel delivery systems to administer cargos into the surface-skin. Microneedle patches consisted of several microneedle arrays with 500-800 nm in height, and composed of biodegradable or water-soluble polymers may overcome epidermis-barriers and deliver therapeutic components directly with minimum invasiveness [365]. Several investigations have exhibited that microneedle patches are capable to deliver the anti-obesity drugs to the subcutaneous white adipose tissue (AT), while the rolling microneedle electrode arrays (RoMEA) using parallel circular blades with microneedle arrays on edge as electrodes for allowing low-damage and large-zones

siRNAs-transfection are capable to deliver efficient siRNAs to treat cancer [365-367].

Conclusions and future perspectives

The advancements in understanding the roles of miRNAs in biogenesis, pathophysiology, and diagnosis as biomarkers, the optimizing efficacies and safety of antago-miRs / miRs-mimics -based strategies with their chemical modifications and conjugations with ligands/vectors have forwarded miRNAs research to their translations into clinical practices. However, most of the miRNAs-based therapeutics have not yet succeeded phase III clinical trials or received the approval from FDA for clinical applications owing to their severe toxicity. Therefore, further investigations are required regarding their specificity, sensitivity, bioavailability, selectivity, mechanisms of action, associated off-targeting effects, biodistribution, pharmacokinetics and elimination with optimum dosing, duration of treatment and administration routes associated with identifications of proper disease-specific biomarker/s and new targeting ligands, and large scale uniformed productivity to minimize immunotoxicity and other side effects maximally for availing higher therapeutic efficacies against diseases before clinical translations.

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