**The emerging role of microRNA-based therapeutics in the treatment of preeclampsia**

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**Abstract**

Preeclampsia (PE) is a pregnancy complication that is often diagnosed due to elevated blood pressure and proteinuria. Though current research focuses on the identification of novel biomarkers and therapeutic targets, still, there is a lack of clinical validation for the use of biomarkers and therapeutic targets for early diagnosis and treatment of PE. Several molecules are being studied for their potential role in PE. Among them, microRNAs are studied vastly for their role in the diagnosis, prognosis, and treatment of PE. But only a few studies are focused on the therapeutic efficacy of miRNAs in PE. Thus, the relevant articles were identified and discussed in this review. These studies provide evidence that miRNAs are indeed important molecules in PE that have the role of both therapeutic targets and therapeutic molecules. However, the studies are limited to in vivo an in vitro models, hence further studies are required to validate the complete potential of miRNA therapeutics. Long non-coding RNA (lncRNA) sponges, miRNA mimics, miRNA inhibitors, exosome-associated miRNAs, and several other molecules have been studied as miRNA-based therapeutics in PE. Thus, miRNAs are postulated to be potential therapeutic targets and miRNA-based therapeutics might pave the way for novel therapeutic approaches for PE.

**Keywords:** MicroRNAs, Preeclampsia, Therapeutic targets, microRNA-based therapeutics, Vascular remodeling.

## 1. Introduction

Preeclampsia (PE) is a type of hypertension occurring during pregnancy that is characterized by elevated blood pressure (systolic $\geq$ 140 mmHg and diastolic $\geq$ 90 mmHg) and proteinuria ($\geq$ 300 mg/24 hr). Around 3-5% of pregnancies worldwide are affected by PE, leading to 42,000 deaths annually [1-3]. PE is associated with multiple end-organ dysfunction after 20 weeks of gestation with high blood pressure and proteinuria. Placenta, kidney, liver, lungs, and brain are the main organs affected due to PE. The diagnosis of PE is made based on the criteria established by the International Society for the Study of Hypertension in Pregnancy (ISSHP), which involves maternal age, nulliparity, multifetal pregnancy, diabetes, hypertension, antiphospholipid syndrome, body mass index (BMI), previous stillbirth, and chronic kidney diseases are all risk factors for PE [4,5]. Usually, PE is diagnosed in the $20^{th}$ week of pregnancy, but there are also cases of early-onset preeclampsia (EOPE) and late-onset preeclampsia (LOPE). In general, EOPE occurs prior to the $34^{th}$ week of pregnancy and has a high probability of fetal mortality and LOPE occurs after the $34^{th}$ week of pregnancy and is associated with the maternal disorder [1-5].

The pathogenesis of PE is influenced by the intricate interplay of altered trophoblast invasion, compromised placental function, endothelial dysfunction, and systemic inflammation. Thus, to reduce the impact of trophoblast malfunction and enhance maternal and foetal outcomes in preeclampsia, it is essential to understand these pathways [6-10].

The treatment for PE is limited, since PE often results in fetal uterine growth restriction and placental abruption, leading to early delivery which has a high chance of stillbirth. Though methyldopa and labetalol are used as temporary drugs to control blood pressure, they have undesirable side effects and there are no alternative treatment methods for PE [11]. Hence

limitations in the diagnosis and treatment of PE make the need for research on alternative methods significant.

Interestingly, several biomarkers and therapeutic targets are being studied for their potential role in the diagnosis, prognosis, and treatment of PE. Among them, microRNAs (miRNAs, miRs) are a class of short non-coding RNAs (18 to 25 base pairs) which are capable of manipulating various druggable signaling pathways by targeting the 3′ UTR of the target mRNA [12]. Thus, miRNAs are postulated to be potential therapeutic targets in multiple diseases, including PE [13-15]. Interestingly, miRNAs are easily detectable in bodily fluids such as blood, urine and saliva, which makes them suitable biomarkers for early diagnosis and prognosis of PE [16-18]. Though miRNAs have been extensively studied for their potential role in the disease pathogenesis of PE, only a few studies have explored their role as therapeutic targets. Importantly, long non-coding RNAs (lncRNAs) can serve as competing endogenous RNAs that bind to miRNAs to regulate their function. Notably, exosomes and other small molecules can also influence miRNA function. Hence this review focuses on the role of miRNAs as therapeutic targets in PE, and highlights contributions from lncRNA and small molecules that may also be significant in the context of PE.

## 2. MicroRNAs and their biogenesis

Several miRNAs are being investigated for their potential role in the diagnosis, prognosis, and treatment of PE. These miRNAs emerge in the nucleus and reach the cytoplasm through the biogenesis that follows canonical and non-canonical routes [19-21]. In the canonical pathway, the miRNA gene in the nucleus is transcribed into primary miRNA (pri-miRNA) which is processed into precursor miRNA (pre-miRNA) by the microprocessor enzyme complex consisting of Drosha and DiGeorge syndrome critical region 8 (DGCR8). The pre-miRNA is transported to the cytoplasm by Exportin 5 and RAN GTP. This pre-miRNA forms the miRNA

duplex with the help of Dicer which cleaves the loop of the pre-miRNA to yield the mature miRNA duplex. This mature miRNA is loaded into Argonaute (AGO) proteins, especially AGO2 to form the RNA-inducing silencer complex (RISC). The RISC binds to the target mRNA and hinders expression through mechanisms that span mRNA degradation and translational repression [22,23].

Non-canonical miRNA biogenesis pathways involve Drosha/DGCR8-independent and Dicer-independent pathways. The mirtron pathway was the first non-canonical pathway to be found. The Drosha/DGCR8 complex in the nucleus is not required by this alternative pathway, which uses spliceosomes and debranching enzymes in the nucleus to process intronic miRNAs to create pre-miRNA hairpins. Exportin-5 then exports the pre-miRNA hairpin to the cytoplasm where Dicer will cleave it. As a result, the canonical miRNA pathway and the mirtron pathway merge at the Exportin-5-bound transport stage, bypassing or replacing microprocessor processing [22,23]. In some cases, pre-miRNAs are too short to be dicer substrates and generation of these dicer-independent miRNAs therefore relies on loading of the entire pre-miRNA into AGO2. Initial processing occurs on the 3p strand under the control of AGO2, while their maturation is finished by the 3′–5′ trimming of the 5p strand. Figure 1 represents the biogenesis of miRNAs.

## 3. MicroRNAs in the treatment of Preeclampsia

Though current research focuses on the identification of novel biomarkers and therapeutic targets, still, there is a lack of clinical validation for the use of biomarkers and therapeutic targets for early diagnosis and treatment of PE. Figure 2 represents the potential therapeutic approaches using miRNA-based therapeutics in preeclampsia.

### 3.1. **MicroRNA mimics and microRNA inhibitors in the treatment of PE**

New treatment options for diseases that are currently challenging to treat with conventional methods have been made possible by the development of oligonucleotide therapies such as miRNA mimics and inhibitors. In cases where depletion of endogenous miRNAs contributes to pathogenesis, miRNA mimics can be used to boost the concentration of a particular miRNA in cells, which can then suppress the expression of a target gene. On the other hand, endogenous miRNAs are specifically targeted and inhibited by miRNA inhibitors. They can be used to lower cellular concentrations of particular miRNAs, which can boost the expression of target genes [24,25]. Hence, miRNA inhibitors can be used to reduce the levels of upregulated miRNAs in PE, miRNA mimics can be used to increase the levels of specific miRNAs that are downregulated in this condition. In preclinical studies, miRNA mimics and inhibitors both demonstrated promising outcomes as potential treatment options for PE.

In a study by Han *et al*. in 2020, miR-210 was studied for its potential role in inhibiting apoptosis of cranial nerves *via* TGF-β signaling. Since miR-210 has been proven to be significantly involved in PE, the study focused on using miR-210 mimics to reduce the apoptosis of cranial nerves by targeting the TGF-β axis. The SD rats injected with miR-210 mimics were found to have lower systolic blood pressure and, the apoptosis rate was found to be significantly reduced when compared with the PE group. Thus, the study concluded that miR-210 mimics might be a potential therapeutic molecule for reducing cranial nerve apoptosis in PE [26]. In another study by Liu and colleagues, miR-223 was found to have anti-inflammatory effects in PE by targeting nucleotide-binding domain, leucine-rich–containing family, pyrin domain–containing-3 (NLRP3) [27].

Another study by Xu *et al* (2020) identified a role for let-7d as a therapeutic target in PE. When placental tissues from PE patients and normal pregnant women were processed, let-7d expression was elevated while Lysine demethylase 3A (KDM3A) and enolase 2 (ENO2) expression was decreased. To study how let-7d and ENO2 affect PE, trophoblast cells and PE

rat models were developed. The findings showed that let-7d silencing reduced tissue damage and symptoms associated with PE like urine protein. Overall, let-7d appeared to promote PE progression by suppressing the growth of trophoblasts and inducing apoptosis by down-regulating KDM3A to encourage ENO2 methylation. Hence, the study proved that let-7d inhibitor can be a possible therapeutic molecule for PE [28].

Later in 2021, Lai and Yu explored the effect of miR-183 inhibition in PE and its impact on the Forkhead box protein 1 (FOXP1) and G protein subunit gamma 7 (GNG7) expression. The *in vitro* analysis revealed that the miR-183/FOXP1/GNG7 axis reduced the invasion and angiogenesis of trophoblast cells. Moreover, when the blastocysts were treated with miR-183 inhibitor in combination with rapamycin in PE mice, the protein levels were decreased, and apparently normalized placental structures were seen. Thus, the study concluded miR-183 inhibition is a potential therapeutic strategy for PE [29]. In 2022, Luo and colleagues tested the efficacy of methylation-mediated silencing of miR-155 in the treatment of PE. In the placental tissue of PE patients, miR-155 was noticeably upregulated and inversely correlated with the promoter methylation level. The *in vitro* research showed that miR-155 increased apoptosis in trophoblast cells while decreasing viability, migration, and invasion in trophoblast cells. Notably, miR-155 targeted FOXO3 and miR-155 inhibitor was found to reduce oxidative stress and inflammation and increase trophoblast cell proliferation, migration, and invasion. Treatment with 5-Aza altered the DNA methylation level of miR-155 and the *in vivo* and *in vitro* tests revealed that upregulating FOXO3 by methylation-mediated silencing of miR-155 can prevent trophoblast cells from apoptosis, and inflammation [30]. In another study by Liu *et al* in 2022, miR-222-3p was upregulated in the placentas of PE patients, while Histone deacetylase 6 (HDAC6) mRNA was downregulated. Additionally, in PE patients, miR-222-3p expression was inversely correlated with HDAC6 mRNA expression. Experiments revealed that HDAC6 knockdown inhibited cell proliferation and migration while HDAC6

overexpression promoted trophoblast cell proliferation and migration. Moreover, inhibitory effects of miR-222-3p on trophoblast cell proliferation and migration were reversed by both HDAC6 overexpression. In addition, miR-222-3p inhibitor reduced blood pressure and harmful fetal changes in PE rats. Hence, this study suggested that miR-222-3p may be used as a therapeutic target for PE [31].

In a study by Selvakumar et al., it was identified that anti-miR-510-3p might be a potential therapeutic strategy for PE. The study found that miR-510-3p targeted Vascular endothelial growth factor A (VEGFA) leading to the disease progression in PE. But treatment with miR-510-3p inhibitor improved the disease conditions in both in vitro and in vivo analysis [32]. Other miRNAs studied including miR-183-5p [33], miR-23a [34], miR-219a [35], miR-342-3p [36], miR-141-3p [37], and so on were studied for their potential role as therapeutic targets in PE using miRNA mimics and inhibitor. Table 2 represents the miRNAs studied for their role as mimics and inhibitors in PE.

### 3.2.Long non-coding RNAs (lncRNAs) as competing endogenous RNAs (ceRNAs) in the treatment of PE

The discovery of the competing endogenous RNA (ceRNA) function of lncRNA has opened up fresh perspectives on how genes are controlled and has the potential to completely change miRNA therapeutics. By this ceRNA or “sponge” function arises from the ability of lncRNAs to sequester miRNAs and stop them from binding to their target mRNAs. This may lead to increased expression of the target genes which may have a variety of biological effects [38,39]. LncRNA sponges can have numerous miRNA binding sites, and synthetic lncRNA sponges can be made to specifically target and bind disease-related miRNAs, thereby re-establishing regular gene expression patterns [38-40]. Additionally, by controlling the expression of

important immune-related genes, lncRNA sponges can be used to modify the immune response [40].

In a recent study by Jiang et al in 2024 has identified that NEAT1 targeted miR-217 and regulated PE disease progression. The overall findings of the study was that NEAT1 was a significantly upregulated lncRNA that influenced in the downregulation of miR-217 leading to its effect in Wnt signaling axis. The study provided evidence that silencing NEAT1 and miR-271 mimics could be used in reversing the effects of NEAT1 [41]. According to a study by Liu H *et al*, the lncRNA MEG3 stimulated the growth and invasiveness of trophoblasts and was highly expressed in the placentas of PE patients. MEG3 acted as a sponge for miR-21-5p, which was identified to regulate the levels of bone morphogenetic protein receptor 2 (BMPR2). By interacting with miR-21-5p and blocking it from controlling BMPR2, MEG3 caused BMPR2 levels to rise along with trophoblastic cell growth and invasiveness. These results suggested that MEG3 may be a key player in the emergence of PE and may represent a potential therapeutic target. This research also illuminated the intricate regulatory system that contributes to PE development, which may help in the creation of novel diagnostic and therapeutic approaches [42].

In another study by Li et al, it was found that MALAT1 was inversely correlated to miR-101-3p levels in preeclampsia. Also, the study found that inhibiting miR-101-3p levels and upregulating MALAT1 helped in the increased expression of VEGFA in PE [43]. Yang *et al.* in 2022 investigated the role of lncRNA small nucleolar RNA host gene 5 (SNHG5) in regulating miR-31-5p in PE pathogenesis. The levels of SNHG5 were downregulated in PE leading to increased autophagy and apoptosis. Since SNHG5 was found to be ceRNA for miR-31-5p which regulated autophagy and apoptosis *via* targeting secreted protein acidic and rich in cysteine (SPARC), SNHG5 was overexpressed in PE mice. This revealed that by regulating

SNHG5/miR-31-5p/SPARC axis, the trophoblast proliferation can be increased and apoptosis can be decreased in the PE placenta [44].

Interestingly, Wu *et al* (2022) identified the relationship between LINC00240, miR-155, and nuclear factor erythroid-related factor 2 (Nrf-2) in PE. The study found that the PE patients' and animals' placenta tissues had reduced levels of LINC00240 and Nrf2, increased miR-155 expression levels, and decreased M2 macrophage polarisation. It was also observed that LINC00240 directly inhibited the expression of miR-155 to reduce the oxidative stress-induced pyroptosis. This further enhanced trophoblast proliferation, migration, invasion abilities, and M2 macrophage polarisation. In an in vivo preeclampsia model, overexpression of LINC00240 increased fetal weight and length, induced trophoblast function, and M2 macrophage polarisation while decreasing blood pressure, urine protein, liver, and kidney damage [45]. Thus, LINC00240 sponged miR-155 and reduced the symptoms of PE and could be postulated as a potential therapeutic target for PE.

Zhang and his colleagues investigated the role of GATA3 antisense RNA 1 (GATA3-AS1) and miR-488-3p in PE in 2022. In placental samples with PE, GATA3-AS1 and Rho-associated coiled-coil-containing protein kinase 1 (ROCK1) were overexpressed while miR-488-3p was downregulated. Functionally, trophoblast cell apoptosis was induced by GATA3-AS1 overexpression, and cell proliferation, migration, and invasion were suppressed. Mechanically, miR-488-3p targeted ROCK1 in trophoblast cells while GATA3-AS1 served as a molecular sponge for miR-488-3p. It was observed that ROCK1 overexpression or miR-488-3p downregulation reversed the consequences of GATA3-AS1 silencing on the phenotypes of trophoblast cells. Thus, the study concluded that miR-488-3p/ROCK1 axis promoted PE progression by upregulating GATA3-AS1, which is overexpressed in PE and hence targeting GATA3-AS1 could be a novel therapeutic approach for PE [46]. Studies by Wang *et al*. (2019) showed that the lncRNA pregnancy-specific glycoprotein (PSG10P) regulates miR-19a-

3p/Interleukin 1 receptor accessory protein (IL1RAP) in the disease pathogenesis of PE. Higher expression of PSG10P and IL1RAP, and lower expression of miR-19a-3p were found in the PE placentas. Inhibition of PSG10P was found to regulate miR-19a-3p positively in the treatment of PE. Since IL1RAP is capable of triggering inflammatory signaling, upregulating miR-19a-3p could be a possible treatment strategy for PE. Hence the study conducted *in vivo* and *in vitro* overexpression of miR-19a-3p and identified miR-19a-3p as a potential therapeutic target for PE [47]. In a study by Tang et al. in 2021, it was identified that miR-223-3p and the circular RNA circLRRK1 interaction in PE is crucial in PE. The experiments demonstrated that miR-223-3p inhibitors could restore the circLRRK1 silencing-induced effect on trophoblast cell proliferation, migration, and invasion. Furthermore, it was identified that suppressing circLRRK1 may stimulate the PI3K/AKT signalling pathway by targeting miR-223-3p [48]. Moreover, another study by Hu et al. (2022) also showed the significant role of Circ_0005714/miR-223-3p/ADAM9 in PE treatment. It was identified that circ_0005714 served as a molecular sponge for miR-223-3p, and its effects on trophoblast cells were achieved via sponging miR-223-3p. Furthermore, the study also postulated that miR-223-3p may target ADAM9, and reduction of ADAM9 may reverse the trophoblast function inhibition caused by the miR-223-3p inhibitor [49].

The aforementioned studies concentrate on the function of lncRNAs as miRNA sponges in the pathogenesis of PE. These studies examined how lncRNAs sponging miRNAs control trophoblast cell proliferation, migration, and invasion and how their dysregulation may lead to preeclampsia. Additional studies on other lncRNAs including LINC00534, LINC01347, PVT1, SNHG22, PAXIP-AS1, SNHG7, and XIST were found to modulate the expression of miRNAs like miR-494-3p, miR-101-3p, miR-24-3p, miR-128-3p, miR-210-3p, miR-214-5p, and miR-340-5p which were found to affect trophoblast function and placental development [50-57]. These results demonstrate the potential of lncRNAs and miRNAs as preeclampsia

diagnostic and therapeutic targets. Table 1 represents the lncRNA sponges, miRNAs and their targets in the treatment of PE

### 3.3.**Exosomes or Extracellular vesicles containing microRNAs in the treatment of PE**

Exosomes are small extracellular vesicles that contain a variety of biomolecules, including miRNAs, and are secreted by cells. Exosome-loaded miRNAs have shown promise in the creation of new therapeutics. Exosomes are appealing candidates for drug delivery because they can move their cargo through recipient cell plasma membranes and into their cytoplasm. This makes it possible to deliver miRNAs specifically to certain cell types or tissues, which can help to lessen toxicity and minimise off-target effects [58]. Exosomes are also suitable for use in humans because of their biocompatibility and low immunogenicity. Exosome-loaded miRNAs have been demonstrated in preclinical studies to control signaling pathways, induce cell death, and regulate gene expression in cancer cells. Furthermore, in animal models of heart disease, exosome-loaded miRNAs lowered inflammation and enhance cardiac function. There are currently several exosome-based miRNA therapeutics in clinical trials. Exosome-loaded miRNAs have the potential to change the therapeutics industry by providing precise, secure, and potent therapies for a variety of diseases [58-60].

Cui and colleagues found that miR-101 expression was downregulated in placental tissues from PE patients, whereas Bromodomain 4 (BRD4) and CXC motif chemokine 11 (CXCL11) expression was elevated. The trophoblast cells loaded with EV-encapsulated miR-101 from Human Umbilical cord mesenchymal stem cells (HUCMSCs), showed enhanced migration and proliferation. MicroRNA-101 mechanically targeted and suppressed BRD4 expression. By inhibiting the NF-κB/CXCL11 axis, BRD4 knockdown aided trophoblast migration and proliferation. Notably, EV-encapsulated miR-101 decreased blood pressure and 24-hour urine protein *in vivo* [61]. Another study by Yang *et al* (2020) focused on EV-derived miR-18b in

the treatment of PE. In vivo experiments were carried out to ascertain the effect of EV-derived miR-18b, Notch2, and TIM3/mTORC1 in a rat model of PE, with monitoring of blood pressure and urine proteinuria. Functional roles of EV-derived miR-18b and Notch2 in trophoblasts, were determined using loss- and gain-of-function experiments. By inactivating the T cell immunoglobulin and mucin domain containing 3 (TIM3)/mammalian target of Rapamycin complex 1 (mTORC1) axis *in vivo*, EV-derived miR-18b increased trophoblast proliferation and migration in vitro and decreased blood pressure and 24-hour urinary protein in PE rats via Notch2 down-regulation. Hence, EV-derived miR-18b was identified as a potential therapeutic molecule in the treatment of PE [62].

Moreover, in 2020, the role of exosomal miR-139-5p in PE was analyzed by Liu *et al.* and it was observed that overexpression of exosomal miR-139-5p could aid in the treatment of PE. MicroRNA-139-5p was delivered to trophoblasts via exosomes that were secreted by HUCMSC. It was discovered that miR-139-5p specifically targeted PTEN, a protein tyrosine phosphatase that controls multiple pathways including the ERK/MMP-2 pathway. Exosomes' ability to promote trophoblast growth was significantly diminished by inhibiting the ERK/MMP-2 pathway. *In-vivo* studies revealed that therapy with exosomal miR-139-5p significantly reduced 24-hour proteinuria and blood pressure values in PE rats [63].

In a study by Sha and colleagues identified the effect of EV derived from hypoxic trophoblast in PE. The results highlighted a novel mechanism of hypoxic trophoblasts regulation of endothelial cells and their potential role in PE pathogenesis. In addition, EV encapsuled miR-150-3p derived from hypoxic trophoblasts inhibit endothelial cells proliferation, migration, and angiogenesis by modulating CHPF [64]. Other studies by Xueye *et al* on exosomal encapsulated miR-125a-5p [65], Wu *et al* on exosomal miR-302a [66], Chen *et al* on exosomal miR-342-5p [67], Wang *et al* on exosome encapsulated miR-15a-5p [68], Ma *et al* on exosomal miR-486-5p [69], Jiang *et al* on exosome encapsulated miR-140-5p [70] and so on have

focused on exosomal miRNAs as potential therapeutic targets for PE. However, few articles discuss the ways that exosomal miRNAs influence the development of PE, including by controlling the migration of vascular smooth muscle cells and the expression of vital genes involved in the pathogenesis of this condition. Overall, these studies help to understand the intricate interactions between exosomes, microRNAs, and preeclampsia and pave the way for novel diagnostic and therapeutic approaches for PE. More studies are required, however, to fully comprehend the exosome mediated delivery mechanisms and to improve the creation of exosome loaded miRNAs. Table 3 represents the exosome or extracellular vesicle-associated miRNAs in the treatment of PE

### 3.4.**Other molecules regulating microRNAs in the treatment of PE**

In addition to the above-mentioned molecules, others are also studied for their potential role in miRNA therapeutics. In a study by Yue *et al.* (2022), the effects of the drug Sufentanil (SUF) in the treatment of PE *via* miR-24-3p/11β hydroxysteroid dehydrogenase type 2 (HSD11B2) was investigated. Both in vivo and in vitro analyses were performed to prove the hypothesis. The findings showed that SUF increased cell proliferation and inhibited miR-24-3p to upregulate HSD11B2. In the case of PE, HSD11B2 was lower while miR-24-3p was increased, which specifically targeted HSD11B2. But SUF was found to regulate the miR-24-3p/HSD11B2 axis, which in turn inhibited the progression of PE both in vivo and in vitro. In summary, SUF was identified to increase the levels of HSD11B2 by inhibiting miR-24-3p, which prevented the disease progression of PE. Hence, the study sheds light on the potential for using SUF, which functions by regulating miR-24-3p, a novel therapeutic molecule for PE [71]. Moreover, in a study by He *et al*. (2022), the compound puerarin was explored for its role in regulating miR-20a-5p and its targets vascular endothelial growth factor A (VEGFA) and mitochondrial membrane protein 2 (MMP2). The study identified the potential role of puerarin in inhibiting miR-20a-5p and reducing the cytotoxicity of trophoblast cells in PE [72].

According to the study by Cao *et al* (2021), vitamin D was postulated to have an impact on miR-26b-5p, which in turn may affect the cyclooxygenase-2 (COX-2) expression in the placenta. PE has been linked to COX-2, an enzyme that contributes to inflammation. The study found that by controlling COX-2 expression *via* miR-26b-5p, vitamin D might be helpful in preventing or treating PE [73]. Interestingly, Ligustrazine which is derived from a Chinese medicinal plant was studied for its role in the treatment of PE *via* miR-16-5p [74] and miR-27a-3p [75]. In 2020, Yuan and his colleagues explored the role of miR-16-5p inhibition through ligustrazine or tetramethylpyrazine (TMP) in PE. In trophoblast cells of the placental tissue of PE rats, autophagy-related proteins light chain 3 (LC3)-II/LC3-I, Beclin1 (BECN1), and SQSTM1 were downregulated after TMP treatment. In addition, TMP enhanced the viability and migration of JEG3 placental cells while suppressing autophagy. In PE, miR-16-5p expression was downregulated, and TMP prevented this. In addition, miR-16-5p reduced insulin growth factor-2 (IGF-2) expression, which increased cell autophagy and decreased the ability of JEG3 cells to survive and migrate. Furthermore, in vivo tests confirmed that TMP controlled the miR-16-5p/IGF-2 axis to prevent the progression of PE in rats [74]. Wang and colleagues (2023) further validated the effect of TMP in the treatment of PE by regulating miR-27a-3p. It was shown that miR-27a-3p targeted activating transcription factor-3 (ATF-3) and was involved in the disease progression of PE. Importantly, TMP inhibited apoptosis and promoted the growth, and movement of trophoblast cells. Moreover, the overexpression of miR-27a-3p eliminated the impact of TMP on trophoblast cells. Thus, the study concluded that TMP promoted the proliferation and migration of trophoblast cells by controlling the miR-27a-3p/ATF3 axis, which in turn mediated the Wnt pathway [75]. Hence, TMP regulated the miRNAs and proved to have a potential therapeutic effect on PE. Similarly, other studies on magnesium sulfate targeting miR-218-5p [76], resveratrol targeting miR-363-3p [77], and so

on have been studied proving miRNAs as potential therapeutic targets for PE. Table 4 represents the other molecules regulating miRNAs in the treatment of PE

## 4. Limitations and Future prospects

In recent years, miRNA-based therapeutics have been studied for their potential role in the treatment of various diseases including PE. But few studies have validated the therapeutic role of miRNAs in both *in vivo* and *in vitro* models. Pre-clinical validation through animal models paves the way for the clinical breakthrough of a drug. However, most of the studies on the therapeutic role of miRNAs are limited to *in vitro* cell lines. The above-mentioned studies have provided evidence that miRNAs are potential therapeutic targets in PE. Moreover, altering miRNA expression appears to have therapeutic efficacy in PE. Though the studies showed preliminary evidence on the potential use of miRNA-based therapeutic in PE, still there is a need for proper evaluation of the strategies, detection, quantification, delivery platforms, clinical outcomes, and challenges clinically faced while using miRNA-based therapeutic in PE. Hence, further studies are required clinically and pre-clinically to prove the therapeutic efficacy of miRNA-based therapeutics in PE.

Endothelial dysfunction and vascular remodeling are two of the most common problems associated with PE. These factors are associated with the elevation in the inflammatory markers which results in the release of cytokines leading to tissue damage [78]. Several signaling pathways like STAT3/IL-6 [79], IKK/NF-κB [80], JAK/STAT [81] are involved in inflammation, and PI3K/AKT [82], Notch [83], mTORC [84], ERK/MMP2 [85] are involved in trophoblast cell survival. Thus, targeting these signaling pathways may be efficient in the treatment of PE.

Few other concerns include creating efficient delivery systems that provide stability, specificity, and successful absorption. The small RNA molecules may interfere with

unexpected gene targets, causing results that are not intended [86]. This may have unintended negative effects and jeopardize the treatment's precision and safety. A significant difficulty still exists in achieving high target specificity while minimizing off-target consequences. The immune system can be stimulated and inflammatory reactions can be brought on by certain RNA molecules. The therapeutic efficacy may be limited and responses may result from this immune activation. Moreover, due to their shorter half-life in the body, they must be dosed more frequently or stabilisation mechanisms must be developed.

In addition, to address the demand for wider clinical use, the production processes must be optimised for scalability, cost-effectiveness, and quality control. The approval procedures for miRNA-based therapies can be challenging and time-consuming, and the regulatory paths are still developing. The regulatory system presents a difficulty for these therapies' translation into clinical practise in terms of ensuring their safety, efficacy, and quality.

Importantly, the current lack of agreement between studies regarding PE-associated miRNAs restricts their potential to be of greater, useful clinical value. The definition and categorization of PE type, sampling technique, RNA extraction method, and, most importantly, the methods selected for miRNA studies, are considered to be present challenges. Furthermore, reliable PE animal models will remain crucial for enabling more exact assessments of miRNA functionality across the context of complete biological systems. Continuous research, technology breakthroughs, and interdisciplinary efforts by scientists, doctors, and regulatory authorities are needed to address these limits.

## 5. Conclusion

In conclusion, even though the precise causes of PE are still not completely known, recent findings have highlighted the critical role that microRNAs or miRNAs play in the onset and evolution of this disorder. Thus, understanding the role of miRNAs in PE not only sheds light

on the disease's underlying mechanisms but also on the development of diagnostic markers and potential treatment strategies for PE. Several studies are focusing on deciphering the molecular mechanisms in PE and exploring miRNA-directed therapeutic approaches in PE. Small RNAs and other nucleic acid-based therapies have made huge strides towards the clinic in recent years. We hope the studies of miRNA in PE so far have laid a solid foundation for translational research that will ultimately improve patient outcomes.

**Abbreviations**

Preeclampsia - PE; microRNA – miRNA or miR; International Society for the Study of Hypertension in Pregnancy – ISSHP; Late-onset preeclampsia – LOPE; Early-onset preeclampsia – EOPE; long non-coding RNAs – lncRNAs; interleukin 6 - IL-6; tumor necrosis factor-alpha -TNF-α; soluble fms-like tyrosine kinase 1 – sflt1; Nitric oxide – NO; Intrauterine growth restriction – IUGR; DiGeorge syndrome critical region 8 - DGCR8; primary miRNA – pri-miRNA; precursor miRNA – pre-miRNA; Argonaute2 – Ago2; RNA-inducing silencer complex – RISC; tumor growth factor-beta - TGF-β; Lysine demethylase 3A - KDM3A; enolase 2 - ENO2; Forkhead box protein 1 - FOXP1; G protein subunit gamma 7 - GNG7; Histone deacetylase 6 - HDAC6; competing endogenous RNA – ceRNA; bone morphogenetic protein receptor 2 - BMPR2; small nucleolar RNA host gene 5 - SNHG5; secreted protein acidic and rich in cysteine – SPARC; nuclear factor erythroid-related factor 2 - Nrf-2; GATA3 antisense RNA 1 - GATA3-AS1; Rho-associated coiled-coil-containing protein kinase 1 - ROCK1; pregnancy-specific glycoprotein - PSG10P; Interleukin 1 receptor accessory protein - IL1RAP; Bromodomain 4 - BRD4; CXC motif chemokine 11 - CXCL11; Human Umbilical cord mesenchymal stem cells – HUCMSCs; T-cell immunoglobulin and mucin-domain containing-3 – TIM3; mammalian target for rapamycin complex 1 - mTORC1; Phosphatase and Tensin homologue – PTEN; Extracellular signal-regulated kinase – ERK; Matrix metalloproteinase 2 - MMP-2; 11β hydroxysteroid dehydrogenase type 2 - HSD11B2;

Sufentanil – SUF; vascular endothelial growth factor A – VEGFA; mitochondrial membrane protein 2 - MMP2; cyclooxygenase-2 - COX-2; tetramethylpyrazine – TMP; light chain 3 - LC3; Beclin1 - BECN1; activating transcription factor-3 - ATF-3.

**Conflicts of interest**

The authors declare that there are no potential conflicts of interest

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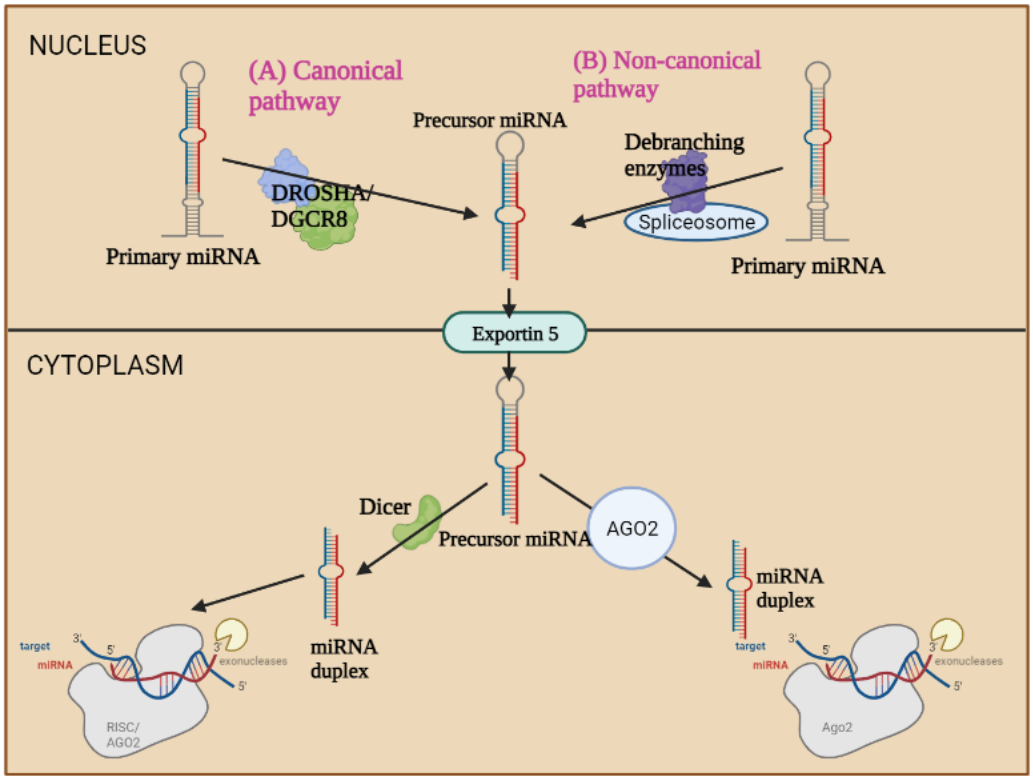


**Figure 1 represents the biogenesis of miRNA**: (A) Canonical pathway: Primary miRNA which is then further converted into precursor miRNA by the enzyme Drosha and DGCR8 which is transported to the cytoplasm by Exportin 5. This pre-miRNA forms the miRNA duplex with the help of dicer which leads to the formation of the mature miRNAs. This mature miRNA with the help of the Argonaute 2 (Ago2) and RNA-inducing silencer complex (RISC) binds to the target mRNA and hinders its expression. (B) Non-canonical pathway: The non-canonical pathway is again divided into Drosha/DGCR8-independent and dicer-independent pathways. Spliceosomes and debranching enzymes in the nucleus process the introns to create miRNA hairpins and exportin-5 then export this hairpin to the cytoplasm where Dicer will cleave it. In the dicer-independent pathway, these pre-miRNAs use AGO2 to finish maturing in the cytoplasm.

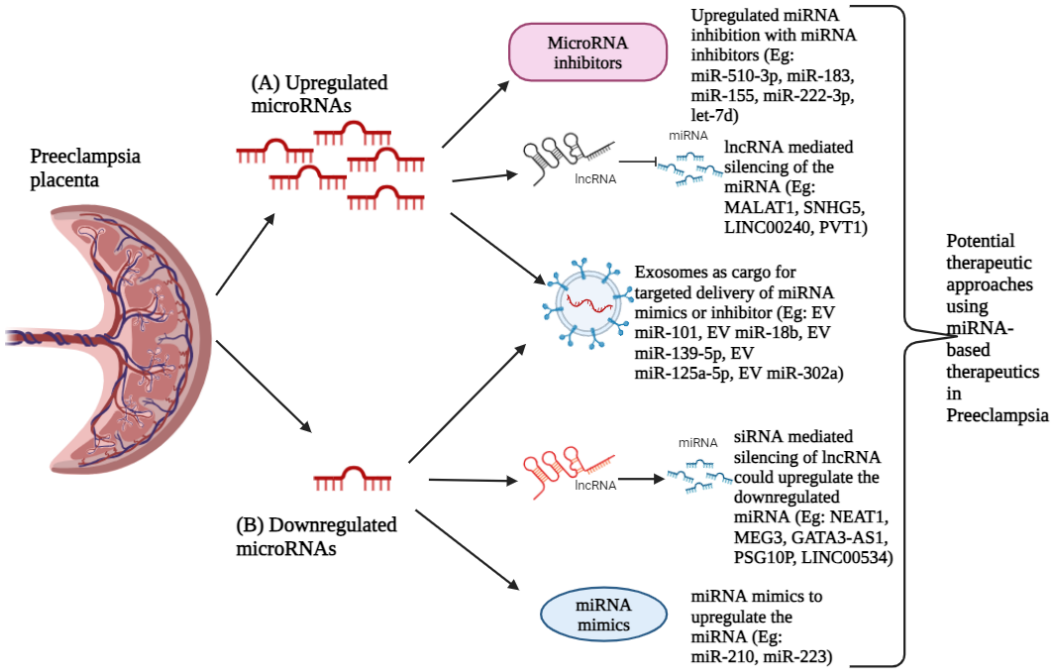


**Figure 2 represents the potential therapeutic approaches using miRNA-based therapeutics in preeclampsia:** (A) In the PE placenta, certain miRNAs are upregulated causing the disease progression in PE. Inhibiting those miRNAs via miRNA inhibitors, lncRNA sponges, or exosome-encapsulated miRNA are postulated to be potential therapeutic strategies for PE. (B) At the same time, few miRNAs are downregulated whose upregulation could be a potential therapeutic strategy for PE. Hence, miRNA mimics, lncRNA silencing, and exosomal miRNAs are hypothesized to be efficient in the treatment of PE.

**Table 1 represents the miRNAs studied for their role as mimics and inhibitors in PE**

| S. No | MicroRNA | Target gene | Mimics / Inhibitor | Sample analyzed | Role of miRNA/gene in PE | References |
|---|---|---|---|---|---|---|
| 1. | miR-210 (Downregulated) | Tumour growth factor-β (TGF-β) | Mimics | Sprague Dawley (SD) rats | Cranial nerve apoptosis | [26] |
| 2 | miR-223 | nucleotide-binding domain, leucine-rich–containing family, pyrin domain–containing-3 (NLRP3). | Mimics | Human placenta, HTR8/SVneo cells | Inflammation | [27] |
| 3 | Let-7d (Upregulated) | Lysine demethylase 3A (KDM3A) | Inhibitor | Human placenta, SD rats, trophoblast cells (BeWo and JEG3) | Trophoblast proliferation and apoptosis | [28] |

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| 4 | miR-183 (Upregulated) | Forkhead box protein 1 (FOXP1) | Inhibitor | Human placenta, HTR8/SVneo cells, HEK293A/17 SF cells, CD1 mice | Angiogenesis and protein levels | [29] |
| 5 | miR-155 (Upregulated) | Forkhead box 3 (FOXO3) | Inhibitor | Human placenta, HTR8/SVneo, JEG3, 293T cells, SD rats | Oxidative stress, Inflammation and trophoblast dysfunction | [30] |
| 6 | miR-222-3p (Upregulated) | Histone deacetylase 6 (HDAC6) | Inhibitor | Human placenta, HTR8/SVneo cells, SD rats | Blood pressure, Trophoblast dysfunction | [31] |
| 7 | miR-510-3p (Upregulated) | Vascular endothelial growth factor A (VEGFA) | Inhibitor | BeWo, HTR8/SVeo cells, Sprague Dawley rats | Trophoblast dysfunction | [32] |

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| 8 | miR-183-5p (Upregulated) | Matrix metalloproteinase 9 (MMP-9) | Inhibitor | Human placenta, HTR8/SVneo cells | Trophoblast cell dysfunction | [33] |
| 9 | miR-23a (Upregulated) | Histone deacetylase 2 (HDAC2) | Inhibitor | Human placenta, HTR8/SVneo cells | Trophoblast cell migration and invasion | [34] |
| 10 | miR-219a (Upregulated) | Vascular endothelial growth factor receptor 2 (VEGFR2) | Inhibitor | HTR8/SVneo cells | Trophoblast cell migration and invasion | [35] |
| 11 | miR-342-3p (Upregulated) | Inhibitor of DNA binding 4 (ID4) | Inhibitor | Human placenta, HTR8/SVneo cells | Trophoblast cell apoptosis and invasion | [36] |
| 12 | miR-141-3p (Upregulated) | Notch 2 | Inhibitor | Human placenta, Human umbilical vein endothelial cells (HUVEC) | Hypoxia, Angiogenesis, Trophoblast cell dysfunction | [37] |

**Table 2 represents the lncRNA sponges, miRNAs and their targets in the treatment of PE**

| S.No | Long non-coding RNA (lncRNA) | MicroRNA (miRNA) | Target Gene | Sample analyzed | Role of lncRNA/miRNA/target gene in PE | Reference |
|---|---|---|---|---|---|---|
| 1. | NEAT1 (Upregulated) | miR-271 (downregulated) | Wingless-related integration site (Wnt) | Human placenta, HTR8/SVneo cells | Trophoblast proliferation and invasion | [41] |
| 2. | MEG3 (Upregulated) | miR-21 (Downregulated) | Bone morphogenetic protein receptor 2 (BMPR2) | Human placenta, JEG3 cells | Trophoblast proliferation and invasion | [42] |
| 3. | MALAT1 (Downregulated) | miR-101-3p (Upregulated) | Vascular endothelial growth factor A (VEGFA) | Human placenta, HTR8/SVneo cells | Trophoblast dysfunction | [43] |
| 4. | SNHG5 (Downregulated) | miR-31-5p (Downregulated) | Secreted protein acidic and rich in | C57BL/6J mice, HTR8/S | Autophagy and apoptosis | [44] |

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|---|---|---|---|---|---|---|
| | | | cysteine (SPARC) | Vneo cells | | |
| 5 | LINC00240 (Downregulated) | miR-155 (Upregulated) | Nuclear factor erythroid 2-related factor 2 (Nrf2) | Human placenta, HTR8/S Vneo cells, SD rats | Trophoblast cell dysfunction, abnormal blood pressure, organ damage | [45] |
| 6. | GATA3-AS1 (Upregulated) | miR-488-3p (Downregulated) | Rho-associated coiled-coil-containing protein kinase 1 (ROCK1) | Human placenta, HTR8/S Vneo cells | Trophoblast cell dysfunction | [46] |
| 7. | PSG10P (Upregulated) | miR-19a-3p (Downregulated) | Interleukin 1 receptor accessory protein (IL1RAP) | Human placenta and blood, HTR8/S Vneo and TEV-1 cells, recombinant mice | Inflammatory signalling | [47] |

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| 8. | LINC00534 (Upregulated) | miR-494-3p (Downregulated) | Phosphatase and Tensin Homologue (PTEN) | Human placenta, HTR8/S Vneo and EVT cells | Trophoblast proliferation and apoptosis | [48] |
| 9. | LINC01347 (Upregulated) | miR-101-3p (Downregulated) | Phosphatase and Tensin Homologue (PTEN) | Human placenta, HTR8/S Vneo cells | Epithelial-Mesenchymal transition | [49] |
| 10. | PVT1 (Downregulated) | miR-24-3p (Upregulated) | Type-2 11β-hydroxysteroid dehydrogenase (HSD11B2) | Human placenta, HTR8/S Vneo cells | Trophoblast cell dysfunction | [50] |
| 11. | SNHG22 (Downregulated) | miR-128-3p (Upregulated) | Protocadherin 11 X-Linked (PCDH11X) | Human placenta, HTR8/S Vneo and JEG-3 cells | Trophoblast migration and invasion | [51] |
| 12. | PAXIP-AS1 (Downregulated) | miR-210-3p (Upregulated) | Brain-derived neurotrophi | Human blood, HTR8/S | Trophoblast cell dysfunction | [52] |

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|---|---|---|---|---|---|---|
| | | | c factor (BDNF) | Vneo cells | | |
| 13. | SHNG7 (Downregulated) | miR-214-5p (Upregulated) | Twist family BHLH transcription factor 1 (TWIST1) | Human placenta, HTR8/S Vneo cells | Trophoblast cell dysfunction | [53] |
| 14. | XIST (Upregulated) | miR-340-5p (Downregulated) | Potassium inwardly rectifying channel subfamily J member 16 (KCNJ16) | Human placenta, HTR8/S Vneo cells | Trophoblast cell invasion | [54] |

**Table 3 represents the exosome or extracellular vesicle-associated miRNAs in the treatment of PE**

| S.No | MicroRNA | MicroRNA Regulation (Up/Down) | Target gene | Samples analyzed | Role of exosome/miRNA/gene in PE | References |
|---|---|---|---|---|---|---|
| 1 | EV encapsulated miR-101 | Downregulated | Bromodomain 4 (BRD4) | Primary culture of HUCMSC, SD rat | Blood pressure, Protein levels, trophoblast cell dysfunction | [61] |
| 2 | EV-derived miR-18b | Downregulated | Notch 2 | Human placenta, HUCMSC, SD rats | Blood pressure, protein levels, trophoblast cell proliferation and migration | [62] |
| 3 | Exosomal miR-139-5p | Downregulated | Phosphatase and Tensin Homologue (PTEN) | HUCMSC, HTR8/SVneo cells, SD rats | Blood pressure, protein levels | [63] |
| 4 | EV miR-150-3p | Upregulated | Chondroitin Polymerizing Factor (CMPH) | Hypoxic HTR8/SVneo cells | Trophoblast dysfunction | [64] |

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| 5 | Exosome encapsulated miR-125a-5p | Upregulated | Vascular endothelial growth factor A (VEGFA) | Human placenta, HUVEC | Angiogenesis, trophoblast cell proliferation and migration | [65] |
| 6 | Exosomal miR-302a | Upregulated | Vascular endothelial growth factor A (VEGFA) | Human placenta, HTR8/SVneo and HUVEC cells | Angiogenesis, trophoblast cell proliferation and migration | [66] |
| 7 | Exosomal miR-342-5p | Downregulated | Programmed cell death 4 (PDCD4) | HUCMSC, SD rats | Blood pressure, protein levels, Inflammatory response, apoptosis | [67] |
| 8 | Exosome encapsulated miR-15a-5p | Upregulated | Cyclin-dependent kinase 1 (CDK1) | Human placenta, HTR8/SVneo cells. SD rats | Trophoblast cell dysfunction | [68] |
| 9 | Exosomal miR-486-5p | Upregulated | Insulin-like growth factor 1 (IGF1) | HPVEC, HTR8/SVneo , TEV1 cells | Trophoblast cell dysfunction | [69] |
| 10 | Exosome encapsulated miR-140-5p | Downregulated | Follistatin-like 3 (FSTL3) | Human placenta, HTR8/SVneo cells | Hypoxia | [70] |

**Table 4 represents the other molecules regulating miRNAs in the treatment of PE**

| S.No | Compound | MicroRNA | Target gene | Samples analyzed | Role of compound/miRNA/target gene in PE | References |
|---|---|---|---|---|---|---|
| 1 | Sufetanil | miR-24b-3p | 11β hydroxysteroid dehydrogenase type 2 (HSD11B2) | Human blood, HTR8/SVneo cells, Wistar rats | Blood pressure | [71] |
| 2 | Puerarin | miR-20a-5p | vascular endothelial growth factor A (VEGFA) and mitochondrial membrane protein 2 (MMP2) | HTR8/SVneo cells | Cytotoxicity | [72] |
| 3 | Vitamin D | miR-26b-5p | Cyclooxygenase-2 (COX-2) | Human placenta, HTR8/SVneo cells | Inflammation | [73] |
| 4 | Ligustrazine | miR-16-5p | Insulin growth factor-2 (IGF-2) | JEG3 cells, SD rats | Autophagy and apoptosis | [74] |

| | | | | | | |
|---|---|---|---|---|---|---|
| 5 | Ligustrazine | miR-27a-3p | Activating transcription factor-3 (ATF-3) | HTR8/SVneo cells | Trophoblast cell dysfunction | [75] |
| 6 | Magnesium sulphate | miR-218-5p | High mobility group box 1 (HMGB1) | SD rats | Apoptosis | [76] |
| 7 | Resveratrol | miR-363-3p | Pigment epithelium-derived factor (PEDF) | SD rats | Trophoblast cell dysfunction | [77] |