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REVIEW

Nano-Enabled Therapeutics: Novel Strategies for Preeclampsia Treatment

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Abstract: Preeclampsia (PE), a pregnancy-specific disorder characterized by hypertension and placental dysfunction, remains a leading cause of maternal and fetal morbidities worldwide. Recent advances in nanomedicine offer promising therapeutic strategies by targeting placental pathologies. Studies have demonstrated that in PE mouse models, the regulation of key disease-related genes (such as sFlt1 and VEGF) using siRNA- or mRNA-loaded carriers (eg, lipid nanoparticles, exosomes, or elastin-like polypeptides) can effectively alleviate PE symptoms. This review summarizes the progress in nanoparticle-based therapies for PE, discusses challenges such as scalability and clinical translation, and highlights the potential of nanomedicine to revolutionize PE management.

Keywords: preeclampsia, nanocarrier, placenta, sFlt1

Introduction

Preeclampsia (PE), a pregnancy-specific multisystem disorder characterized by new-onset hypertension and proteinuria occurring after 20 weeks of gestation, affects 3–8% of pregnancies globally. It remains a leading cause of maternal and fetal morbidity and mortality, particularly in low-resource settings.[1,2] The pathogenesis of PE is broadly categorized into two sequential stages: first, defective placental development, is characterized by insufficient invasion of extravillous trophoblasts (EVTs) and impaired remodeling of the uterine spiral arteries, which leads to reduced placental perfusion, hypoxia, and the induction of oxidative stress and endoplasmic reticulum stress.[3] This pathological state triggers the second stage: the systemic release of antiangiogenic factors (eg, soluble fms-like tyrosine kinase-1, sFlt1) and pro-inflammatory mediators from the placenta into the maternal circulation.[4]

The excessive release of sFlt-1 is a pivotal event in this cascade, which disrupts vascular endothelial growth factor (VEGF) signaling and placental growth factor (PIGF), inducing widespread endothelial dysfunction and proteinuria. Beyond the sFlt-1/VEGF axis, other vascular regulators are implicated. For instance, angiopoietin-like protein 4 (ANGPTL4) has been closely associated with hypertensive disorders of pregnancy, with serum levels significantly elevated in PE patients, suggesting a role in disease progression potentially through effects on lipid metabolism and vascular permeability.[5] Furthermore, local placental microenvironment regulators, such as growth differentiation factor-11 (GDF-11), have been shown to promote EVT invasion by upregulating ANGPTL4 expression, implicating the dysregulation of this pathway in the pathogenesis of PE.[6] Current clinical management of PE is limited to symptomatic relief (eg, antihypertensives agent for blood pressure control, magnesium sulfate for seizure prophylaxis) and definitive treatment via placenta delivery, often necessitating preterm birth with associated risks.[7–9] Despite advances in understanding the underlying molecular mechanisms of PE, no therapies have been developed to reverse placental dysfunction or delay disease progression, thereby highlighting a critical unmet need in obstetric care.[10]

Nanoparticle-based drug delivery systems offer transformative potential to address these challenges in PE management. Their tunable physicochemical properties enable targeted delivery, reduced off-target effects, and enhanced

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stability of therapeutic payloads-including nucleic acids, proteins, or small molecules.[11,12] For instance, lipid nanoparticles (LNPs) have emerged as a versatile platform, leveraging ionizable lipids to encapsulate and deliver mRNA or siRNA with high efficiency, a capability validated by FDA-approved applications: mRNA vaccines (eg, COVID-19 vaccines) and gene silencing therapies (eg, patisiran for hereditary transthyretin amyloidosis).[13,14] The success of LNPs in drug delivery hinges on their ability to overcome biological barriers through endogenous targeting mechanisms-specifically, apolipoprotein E (ApoE)-mediated hepatic uptake and β2-glycoprotein I (β2-GPI)-driven splenic and placental tropism.[15] These features make LNPs particularly suited for treating placental disorders like PE, where selective placental targeting is essential to mitigate fetal toxicity and maternal complications (eg, HELLP syndrome).[16]

Recent preclinical studies have explored nanotechnology-driven strategies to modulate key pathogenic pathways in PE. For example, siRNA-loaded LNPs targeting placental sFlt1 have demonstrated efficacy in reducing hypertension and proteinuria in rodent PE models,[17] while VEGF mRNA delivery via LNPs restored angiogenic balance and improved fetal outcomes. Notably, high-throughput screening of LNP libraries identified formulations with >100-fold greater placental tropism than clinical benchmarks (eg, DLin-MC3-DMA LNPs), achieved through β2-GPI adsorption and optimized excipient compositions.[15] Poly-amidoamine (PAMAM) dendrimers have also been employed to deliver sFlt1 siRNA, demonstrating reduced circulating sFlt1 levels and alleviated symptoms in preeclamptic rats.[18] Elastin-like polypeptide (ELP) has shown promise by achieving maternal–fetal barrier sequestration while effectively delivering therapeutic peptides (eg, VEGF) to ameliorate PE symptoms in rodent model.[19] Similarly, exosomes derived from human umbilical cord mesenchymal stem cells (HUCMSCs) have exhibited therapeutic potential through their innate ability to modulate placental angiogenesis and immune responses, as evidenced by improved fetal outcomes in sFlt-1 overexpressing PE mice.[20] However, challenges remain in balancing efficacy with safety, ensuring minimal fetal exposure, and scaling production for clinical translation. Innovations such as reduced graphene oxide (RGO) hybrids, which mitigate oxidative stress and enhance nitric oxide bioavailability, further exemplify the diversity of nanotherapeutic approaches under investigation.[21] Together, these advances underscore the potential of nanotechnology to revolutionize PE treatment by addressing its root causes rather than merely managing symptoms. The following sections will synthesize the development of these four strategies (Figure 1), evaluating the design, efficacy, and translational prospects of nanotherapeutics for PE, with a focus on mechanistic insights and unmet challenges in the field.

Nanocarriers for PE Treatments

Lipid-Based Nanocarriers for PE Treatments

Lipid-based nanocarriers, primarily encompassing LNPs and liposomes, represent a highly versatile and advanced class of drug delivery systems. Their notable advantages include excellent biocompatibility, biodegradability, and a demonstrated capacity for efficient encapsulation and delivery of a diverse range of therapeutic cargo, from small molecule drugs to nucleic acids like mRNA and siRNA.[22–25] The clinical translation of this platform has been profoundly validated by the widespread success of LNP-based COVID-19 mRNA vaccines and the FDA-approved siRNA therapeutic, Onpattro, heralding a new era for RNA therapeutics.[13] However, the application of these sophisticated nanocarriers for treating obstetric conditions, such as PE, remains a nascent yet immensely promising frontier in maternal–fetal medicine. Recently, Dr Michael J. Mitchell's group engineered a placenta-tropic LNP platform for mRNA therapy to treat PE. Utilizing a high-throughput in vivo screening approach, the researchers evaluated a library of 98 LNP formulations and identified LNP 55 as the lead candidate, which comprises the ionizable lipid C14-494, phospholipid DOPE, cholesterol, and C14-PEG2000. The platform's efficacy stems from a novel endogenous targeting mechanism, where adsorption of β2-GPI onto LNP 55 promotes preferential delivery to the placenta by bypassing traditional ApoE-mediated liver uptake. Therapeutic validation in two murine models—inflammation-induced via lipopolysaccharide and hypoxia-induced by sFlt1 overexpression—demonstrated that a single intravenous dose of VEGF mRNA-loaded LNP 55 resolved maternal hypertension, improved placental vasculature, and restored fetal health.[15]

Before conducting the research on the treatment model of PE, the study on which kind of formulation could target the placenta was also extremely crucial. This same research group employed orthogonal design of experiments to optimize excipient molar ratios, identifying LNP C5 with enhanced placental tropism and reduced hepatic accumulation. Subsequently, they advanced this by developing epidermal growth factor receptor (EGFR)-targeted LNPs via strain-

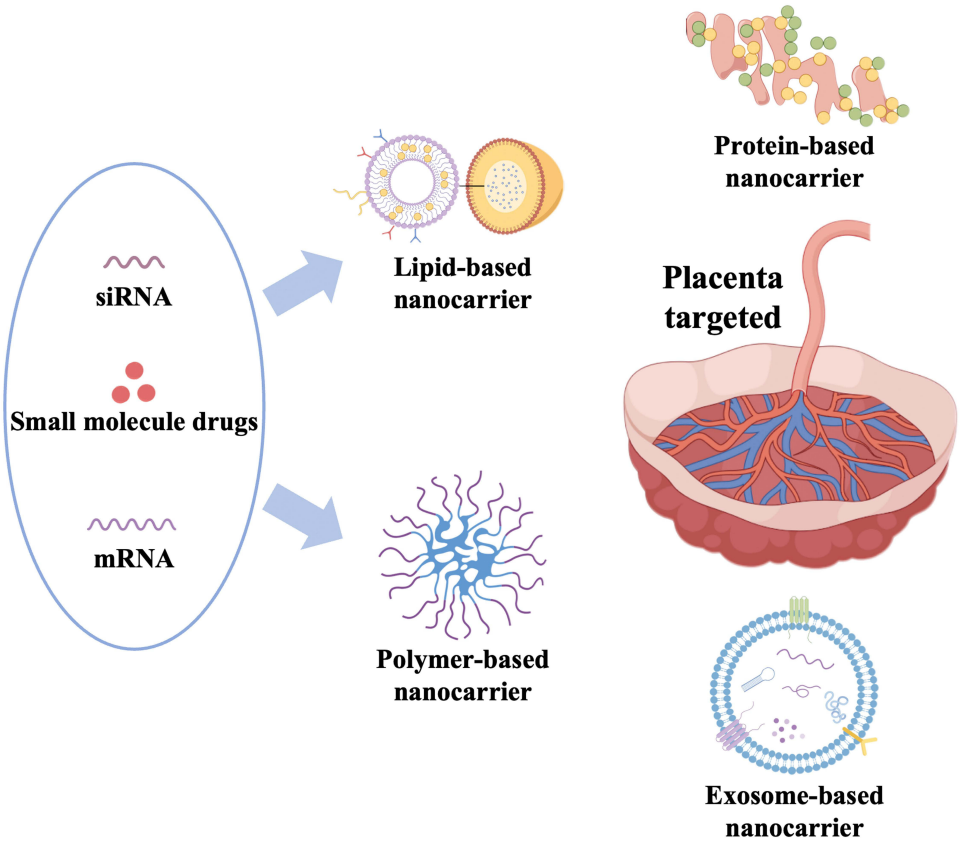

Figure 1 Schematic diagram of four placenta targeted nanostrategies for preeclampsia therapy.

promoted azide-alkyne cycloaddition, which demonstrated superior specificity and uptake in placental trophoblasts, offering a refined strategy for PE therapy.[26] In 2024, Young et al employed a systematic Design of Experiments (DOE) approach to optimize ionizable LNP formulations for enhanced mRNA delivery to the placenta, identifying C12-200 and DOPE as critical components for maximizing transfection efficiency in trophoblasts (Figure 2). Their comprehensive screening revealed that reducing poly (ethylene) glycol (PEG) molar ratios increased the apparent pKa of LNPs, correlating with improved placental tropism and minimal off-target accumulation in maternal organs such as the liver and spleen. This study demonstrated successful in vivo delivery of PIGF mRNA, resulting in significant protein secretion and restoration of angiogenic balance in pregnant mice, without inducing fetal toxicity or systemic inflammation. By rigorously defining lipid composition parameters that govern placental delivery, this work provides a scalable framework for designing LNPs tailored to obstetric applications, complementing prior strategies involving antibody conjugation or immunomodulatory cytokine delivery.[27] Together, these advances underscore the versatility of LNPs as a platform for precise nucleic acid therapeutics in pregnancy disorders.

Building upon previous investigations into placenta-targeted LNP therapies, Zhu et al developed a novel folic acid (FA)-modified LNP platform encapsulating siRNA against pyruvate kinase M (FA-LNP@si-PKM) to precisely target dysregulated glycolytic metabolism and aberrant histone lactylation in PE. Integrated multi-omics analyses identified PKM as a key upstream regulator, driving lactate overproduction and subsequent histone H3 lysine 18 (H3K18l) lactylation via the histone acetyltransferase KAT7. The FA-LNP@si-PKM system demonstrated enhanced placental tropism and uptake in trophoblasts through folate receptor-alpha (FRα)-mediated endocytosis, effectively silencing PKM expression and suppressing the KAT7-H3K18la axis. In L-arginine methyl ester (L-NAME)-induced PE mice, treatment with FA-LNP@si-PKM significantly ameliorated maternal hypertension and proteinuria, reduced placental inflammation, restored trophoblast invasion capacity, and improved fetal outcomes.[28] This study highlights the therapeutic potential of epigenetically targeted nanotherapeutics for resolving placental dysfunction in PE.

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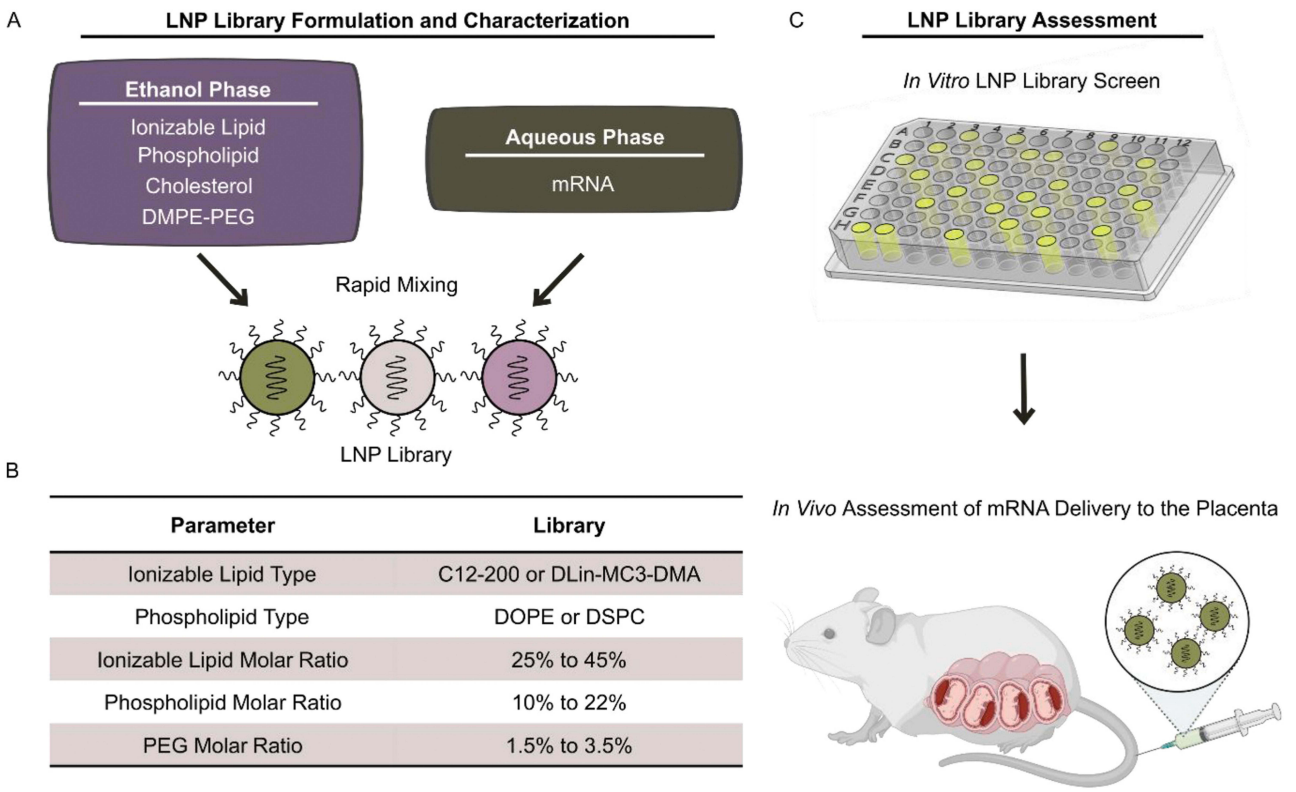

B

Parameter	Library
Ionizable Lipid Type	C12-200 or DLin-MC3-DMA
Phospholipid Type	DOPE or DSPC
Ionizable Lipid Molar Ratio	25% to 45%
Phospholipid Molar Ratio	10% to 22%
PEG Molar Ratio	1.5% to 3.5%

Figure 2 (**A**) LNPs are formulated by rapidly mixing lipid components in an ethanol phase and mRNA in an aqueous phase consisting of pH 3 citrate buffer. (**B**) Ranges of parameters used in the DSD to make the library (A1–A18). (**C**) The library was assessed in vitro with encapsulated luciferase mRNA and in vivo with encapsulated luciferase or PlGF mRNA.

Hofbauer et al engineered a novel LNP platform encapsulating IL-4 and IL-13 mRNA to specifically modulate placental immunity. This FRα-targeted system facilitated efficient trophoblast uptake and subsequent local cytokine secretion, which polarized macrophages toward an anti-inflammatory M2 phenotype, characterized by enhanced CD206/CD209 expression and IL-10 production. Crucially, their work identified an inverse relationship between mRNA dose and polarization efficacy, informing optimized dosing strategies. Successful in vivo application in pregnant mice demonstrated targeted placental delivery and immunomodulation with minimal systemic inflammatory exposure, establishing a promising strategy to resolve immune dysregulation in pregnancy disorders.[29]

Based on the exploration of epigenetic and immunomodulatory mechanisms, more established active targeting strategies, particularly antibody-mediated approaches continue to be refined for enhanced precision. Geisler et al designed targeted ionizable LNPs surface-conjugated with varying densities of EGFR antibodies (aEGFR-LNPs) to enhance mRNA delivery to the placenta. In vitro cultured placental trophoblasts and in vivo pregnant mouse models, an intermediate density of antibody (1:5 aEGFR-LNP) yielded optimal performance by specifically binding to overexpressed EGFR on trophoblasts and undergoing efficient cellular uptake via receptor-mediated endocytosis, thereby facilitating therapeutic mRNA delivery to placental tissues. Moreover, this optimized formulation achieved an approximate two-fold increase in mRNA delivery to the murine placenta and enhanced uptake in EGFR-expressing trophoblasts compared to non-targeted counterparts.[30] This work underscores the critical role of optimizing ligand presentation for efficient receptor-mediated tropism; however, its therapeutic advantages have not been validated in PE disease models. Complementing this, Dong et al directly translated an antibody-targeting strategy into a therapeutic intervention by developing anti-EGFR antibodies-modified liposome (E-Lip-siRNA-sFlt1) for the delivery of sFlt1 siRNA. In a rat model of PE, this targeted system utilized the overexpression of EGFR on trophoblast cells to achieve placental-specific accumulation through an antibody-mediated active targeting mechanism. Following receptor-mediated endocytosis into cells, the sFlt1 siRNA payload effectively silenced the targeted gene, resulted in significant reduction in maternal circulating sFlt1 levels, blood pressure, and proteinuria, while significantly improving key

pregnancy outcomes.[31] These studies collectively validate the potential of antibody-directed nanocarriers for PE therapy, though considerations regarding potential immunogenicity and further validation in diverse disease model remain important for clinical translation.

In contrast to antibodies, small-molecule ligands offer distinct advantages in targeted delivery due to their smaller size and ease of synthesis and modification, enabling versatile application for both nucleic acids and small-molecule drugs.[11,22] For instance, an FA-modified PEGylated lipid hybrid micelle was designed for the encapsulation of sFlt1 siRNA, leveraging the overexpression of FA receptors on placental trophoblasts for active targeting. Their comprehensive characterization demonstrated successful nanoparticle fabrication, efficient in vitro gene silencing, and preliminary evidence of placental targeting in vivo.[32] Similarly, Li et al constructed CRNPs by employing a CGKPK to functionalize LNPs loaded with rosiglitazone (RGZ). In an L-NAME induced PE mice model, CRNPs facilitated targeted RGZ delivery to the placenta, subsequently releasing RGZ to active peroxisome proliferator-activated receptor γ (PPARγ), further regulated the downstream PGC1α and UCP2, thereby effectively ameliorating placental oxidative stress and improving placental development and fetal growth without observed maternal or fetal toxicity.[33] Beyond these molecularly targeted strategies, an alternative physically oriented therapeutic paradigm using nano-scale size artificial oxygen carriers was proposed. In a rat PE model, these artificial oxygen carriers directly alleviated placental hypoxia, subsequently downregulating sFlt1 levels and mitigating fetal growth restriction.[34] This innovative approach highlights the potential of addressing placental ischemia, however, the biological safety and clinical feasibility warrant further extensive investigation.

Polymer-Based Nanocarriers for PE Treatments

Polymer-based nanocarriers constitute another major pillar in the field of drug delivery, distinguished by their exceptional material diversity and functional programmability. These systems benefit from precise control over key physicochemical properties (such as size, surface charge, and degradation kinetics) and possess easily functionalizable surfaces, enabling controlled release and targeted delivery of diverse therapeutic agents, including siRNA and small molecule drugs.[11,35,36] Ranging from natural polymers with inherent biocompatibility to synthetic variants offering structural robustness, these carriers demonstrate immense potential for PE intervention through multiple mechanisms, such as silencing pathogenic genes, reprogramming the immune balance, and mitigating inflammatory responses.[37–39] Yu et al employed PAMAM as non-viral vectors to complex and deliver sFlt1 siRNA. In a tumor necrosis factor-α (TNF-α) induced rat model of PE, the siRNA-sFlt1-PAMAM complex effectively delivered sFlt1 siRNA into cells, utilizing the RNAi to specifically silence the overexpressed sFlt1 gene in the placenta. The results demonstrated that this nanocomplex treatment significantly reduced circulating sFlt1 levels, mean arterial pressure, and proteinuria, while improving fetal and placental weights.[18] This work provided crucial initial validation for the use of polymer-based nanocarriers in PE therapy.

Subsequent research incorporated active targeting strategies to enhance the placental specificity and silencing efficiency of polymer-based nanocarriers. Li et al engineered PEG-PLA nanoparticles surface-functionalized with a placental chondroitin sulfate A (CSA)-binding peptide to enable the targeted delivery of sFlt1 siRNA (T-NPsisFlt1). This targeted system revealed significant trophoblast accumulation both in vitro and in vivo, effectively reducing placental sFlt1 mRNA and maternal serum sFlt1 protein levels without observable toxicity to the mother or fetus, making a significant optimization towards a placenta-specific siRNA delivery platform.[40] Following the success of targeted single gene silencing, they further designed CSA-binding peptide-targeted lipid-polymer hybrid nanoparticles for the co-delivery of siRNAs against both sFlt1 and nuclear factor-erythroid 2-like 2 (Nrf2). This combination therapy achieved simultaneous downregulation of placental oxidative stress and anti-angiogenic pathway in a PE mouse model, indicating superior therapeutic efficacy in ameliorating maternal hypertension and fetal growth restriction compared to single gene targeting.[37]

Beside gene silencing, the versatility of polymer-based nanocarriers extends to modulating more complex, systems-level pathophysiological disturbances in PE, encompassing both the immune microenvironment and intracellular organellar function. A chitosan-low molecular weight heparin sodium nanoparticle (CHsN) was developed, which ameliorated PE by upregulating Heparin-binding epidermal growth factor (HB-EGF), further reprogrammed the maternal–fetal interface by shifting the Treg/Th17 immune balance toward tolerance and suppressing inflammation, effectively mitigating disease symptoms in an L-NAME-induced rat model.[41] Concurrently, the application of polymer-based nanocarriers have been

pushed to the subcellular level to address oxidative stress. A placenta-targeted strategy (nMitoQ) was constructed by encapsulating mitochondrial antioxidant (MitoQ) into polymer nanoparticles. In a model of prenatal hypoxia, nMitoQ rescued placental mitochondrial function in a sexually dimorphic manner, restoring Complex IV activity in male placentas while enhancing mitochondrial fusion in females, highlighting the potential of organelle-specific interventions for PE.[3] These studies underscore the capability of polymer-based nanocarriers to intervene in sophisticated disease mechanisms, which is beyond the reach of traditional therapy strategies.

Protein-Based Nanocarriers for PE Treatments

Protein-based nanocarriers exploit their intrinsic bio-origins and precise molecular recognition capabilities to offer a unique pathway for PE therapy characterized by high biosafety.[42] Among these, engineered ELP systems are particularly notable. ELPs can be efficiently purified through a simple thermal cycling process and serve as stable carriers for therapeutic proteins via genetic fusion technology.[43] Which not only significantly extends the drug's half-life in the maternal circulation but, crucially, its large hydrodynamic radius effectively prevents placental transfer. This mechanism enables an innovative maternal sequestration strategy, establishing a new standard for ensuring fetal safety during pregnancy. Bidwell et al systematically developed an ELP-based maternal sequestration therapeutic platform, achieving a breakthrough from multi-pathway targeting strategies to precise treatment of specific inflammatory pathways. In 2014, they first proposed utilize ELP as a universal platform to develop a series of peptide therapies targeting multiple pathogenic pathways in PE. This study revealed that ELP could be synthesized in different sequences and sizes to stabilize therapeutic peptides and effectively prevent crossing the placental interface, avoiding fetal exposure.[38] Building on this, they further focused on precise intervention in the inflammatory pathway, developing a nuclear factor-κB (NF-κB) inhibitory peptide (SynB1-ELP-p50i), which effectively blocked NF-κB activation in vitro and inhibited TNF-α induced endothelin production. In a pregnant rat model, SynB1-ELP-p50i exhibited slowed plasma clearance and effective placental barrier blocking, resulting in its specific deposition in maternal kidney, liver, and placenta. Moreover, partially improved hypertensive symptoms and reduced placenta TNF-α levels with no signs of toxicity in a rat model of placental ischemia.[44] This study established a complete ELP platform technology and achieved target therapy for the NF-κB inflammatory pathway for the first time. However, the antihypertensive effect was only partially alleviated, and its efficacy requires further optimization.

The ELP platform also demonstrated significant efficacy in the anti-angiogenic pathway of PE, Logue et al constructed a fusion protein combining VEGF with ELP (ELP-VEGF), which exhibited a prolonged half-life in the maternal circulation and accumulated in maternal organs and the placenta in a rat model of placental ischemia, but was undetectable in fetal tissues. ELP-VEGF dose-dependently ameliorated maternal hypertension by neutralizing excess sFlt1 and restoring nitric oxide signaling, providing critical proof-of-concept for a safe and effective protein therapy.[19] Besides, natural protein materials also show great potential as PE therapeutic carriers. Wang et al developed nanoparticles based on Zein protein, functionalized with hydroxypropyl-β-cyclodextrin and co-loaded with curcumin and eugenol (Cu/Eu@H-β-CD-ZNPs). This formulation exerts its therapeutic effect by inhibiting the TLR4/NF-κB signaling pathway, effectively reducing pro-inflammatory cytokine levels in serum and placental tissue, while promoting the proliferation, migration, and invasion of trophoblasts under hypoxic conditions in an LPS-induced rat model of pregnancy-related hypertension.[45] Whereas, the synergistic mechanism of the complex multi-component system has not been fully elucidated.

Exosome-Based Nanocarriers for PE Treatments

Exosomes, as naturally secreted nanoscale vesicles, have emerged as highly promising natural nanocarriers for PE therapy due to their inherent low immunogenicity, excellent biocompatibility, and remarkable biological barrier penetration capability.[46,47] These vesicles serve as carriers for complex biological information molecules (such as proteins and miRNAs), participating in and precisely regulating various pathophysiological processes at the maternal–fetal interface, including immune microenvironment reprogramming, placental angiogenesis, and trophoblast function restoration.[48] Research on the therapeutic functions of exosomes has revealed their potential in regulating the function of the maternal–fetal interface. Chang et al evaluated the therapeutic effects of HUCMSC-derived exosomes (HUCMSC-exos). In a PE mouse model induced by sFlt1 overexpression, treatment with HUCMSC-exos reduced maternal blood pressure, increased fetal weight, and promoted the reconstruction of the placental vascular network. Proteomic analysis showed that these exosomes were rich in functional proteins such as

Versican, which are associated with angiogenesis and cell migration, potentially forming the molecular basis for their protective effects.[20]

Following the validation of natural exosome functionality, researchers have further enhanced therapeutic efficacy through exosome engineering. HUCMSC-EVs-TFCP2, exosome derived from HUCMSCs overexpressing TFCP2 was developed. In an in vitro model of hypoxia/reoxygenation-treated extravillous trophoblasts and an in vivo PE mouse model induced by RUPP surgery, the engineered exosomes effectively promoted the proliferation, migration, and invasion of trophoblasts by activating the Wnt/β-catenin signaling pathway, thereby alleviating PE-like symptoms.[49] However, the in vivo efficacy is relatively weak, and the dose–effect relationship needs further clarification.

Beyond therapeutic applications, understanding the pathological role of exosomes provides crucial insights into PE pathogenesis. Ma et al found that exosomes secreted by human placental microvascular endothelial cells (HPVEC) under hypoxia/reoxygenation conditions exhibited significantly elevated levels of miR-486-5p. These exosomes could be taken up by trophoblasts and negatively regulate their proliferation, migration, and invasion by targeting and inhibiting the expression of insulin-like growth factor 1 (IGF1).[50] It revealed the intercellular communication mechanism by which endothelial cells regulate trophoblast function via exosomal miRNAs under pathological conditions.

Comprehensive Analysis of Nanocarriers for PE Treatments

The rapid evolution of nanotechnology in PE therapy has led to the emergence of diverse nanocarriers, including lipid-, polymer-, protein-, and exosome-based nanocarriers, which provide rich strategies for the precise intervention of placental pathologies.[11] However, these nanocarriers differ significantly in their material properties, targeting capability, delivery efficiency, and safety profiles. Thus, a systematic comparison of their core characteristics is crucial for understanding the overall landscape and selecting appropriate nanocarrier.[51] This section synthesizing the advantages, limitations, targeting strategies, payloads, and key preclinical outcomes of the four major nanocarriers discussed above, with the aim of offering a clear guidance for future research.

As summarized in Table 1, the four nanocarriers exhibit distinct and complementary features. Lipid-based nanocarriers, particularly LNPs, have become one of the most promising platforms for clinical translation, primarily due to their exceptional efficiency in delivering nucleic acids (eg, mRNA, siRNA) and established industrial-scale production pathways.[15,27] Furthermore, they possess the ability to achieve placental targeting by engineering lipid composition and surface modifications (eg, with CGKRK peptide, EGFR antibodies), which has been shown to significantly ameliorate maternal hypertension and improve fetal growth in various PE animal models.[30,31,33] Nonetheless, challenges persist, including their inherent tendency for hepatic and splenic sequestration and potential immunotoxicity at higher doses, which require careful optimization.[15,21] For example, cationic lipid components can activate the immune system via pathways such as TLR4, provoking inflammatory responses.[52]

In contrast, polymer-based nanocarriers stand out for their design flexibility, enabling precise control over properties like degradation kinetics, charge, and functional groups through tailored chemical synthesis.[18,54] This versatility makes them suitable not only for nucleic acid delivery[18,40,62] but also for the efficient encapsulation of small-molecule drugs.[3] However, their application in clinic is often hampered by complex manufacturing processes and the potential cytotoxicity associated with some cationic polymers.[18,53] Additionally, the formation of a dynamic protein corona in vivo can profoundly alter their surface identity and biological fate, making their targeting specificity and biodistribution difficult to predict accurately.[55]

Protein-based nanocarriers offer a unique set of advantages centered on biocompatibility and safety. Macromolecular constructs such as ELP, employ an innovative maternal sequestration strategy. This approach effectively alleviates maternal symptoms like hypertension while minimizing the risk of fetal exposure, establishing a new paradigm for high-safety therapeutics during pregnancy.[19,38,44] Natural protein nanocarrier like Zein, provide an alternative route for delivering bioactive natural compounds, which demonstrated efficacy in improving trophoblast function and pregnancy outcomes by modulating inflammatory pathways such as TLR4/NF-κB.[45] However, this class of nanocarriers also faces challenges, including the potential immunogenicity risk of exogenous or engineered proteins[56] and limitations in drug-loading capacity and efficiency for certain payloads.[57]

Exosomes, as endogenous biological nanovesicles, possess unparalleled attributes such as low immunogenicity, an innate ability to traverse biological barriers, and a natural role in intercellular communication.[20,49,58] They sever as delivery vehicles

Table 1 A Comparative Overview of Nanocarriers for Preeclampsia Treatment

Nanocarrier	Advantages	Limitations	Targeting Ligands/ Strategies	Payloads	Key Preclinical Outcomes
Lipid-based nanocarriers	1. Easy to be functionalized, which facile surface modification with targeting ligands like peptides and antibodies.[30,33] 2. High delivery efficiency, especially for nucleic acids such as mRNA, siRNA.[27] 3. Tunable biocompatibility, such as reduced non-specific uptake via screening lipid components and PEGylation.[26] 4. Strong clinical transformation potential, as multiple lipid nanoparticles have been approved for other diseases.[15]	1. Liver tropism: systemic administration tends to accumulate in the liver, which limits placental targeting.[15,30] 2. Dose-dependent side effects: maternal inflammation or fetal risks may be induced at high doses.[21] 3. Potential immunogenicity: some ionizable lipids may trigger inflammatory.[52]	β2-glycoprotein I adsorption strategy,[15] folic acid,[28,32] CGKRK peptide,[33] EGFR antibody.[30]	mRNA,[15,29] siRNA,[19,28,53] chemical drugs,[33] artificial oxygen carriers.[34]	Significantly reduced maternal blood pressure, proteinuria, and placental inflammation, improved placental vasculature and fetal health, decreased circulating sFlt-1 levels.
Polymer-based nanocarriers	1. High adjustability structure and properties, precise design of the molecular weight, charge, degradation rate.[18,54] 2. Excellent stability, effectively protecting nucleic acid payloads from degradation.[41] 3. Polymer materials such as PLA and chitosan are biodegradable, which offer favorable safety profiles.[40,41]	1. Synthesis and purification of some polymers are complex, the fabrication process is quite intricate.[53] 2. Potential cytotoxicity, such as cationic polymers may cause membrane damage at high concentrations.[18] 3. Complex in vivo behavior, the formation of a protein corona may alter targeting.[55]	Chitosan,[41] CSA-binding peptide,[37,40] PAMAM dendrimer.[18]	Proteins,[41] siRNA,[18,37,40] antioxidant.[3]	Specific accumulation in placenta, effective target gene silencing like sFlt-1, improved maternal symptoms and fetal weight, modulation of placental immune microenvironment.
Protein-based nanocarriers	1. Derived from natural or biomimetic design, which exhibit excellent biocompatibility and safety.[38,44,45] 2. Maternal sequestration, large carriers like elastin-like polypeptide avoid placental transfer, which protect the fetus.[19,38,44] 3. Capability to load natural active molecules, such as Zein can efficiently encapsulate hydrophobic compounds like curcumin and eugenol.[45]	1. Facing the challenge of large-scale production, like costly recombinant expression and purification or standardized fabrication of natural protein nanoparticles.[45] 2. Exogenous or modified proteins may trigger immune responses.[56] 3. The loading capacity of certain drugs may be inefficient.[57]	Functional peptides,[44] endogenous carrier properties.[38]	Inhibitory peptides,[44] therapeutic proteins,[19] natural bioactive compounds.[45]	Long-lasting retention in maternal circulation, significant attenuation of hypertension with no fetal exposure. Moreover, downregulated maternal blood pressure and placental pro-inflammatory factors such as IL-6, TNF-α, inhibited the TLR4/NF-κB pathway, and improved trophoblast function.

(*Continued*)

Table 1 (Continued).

Nanocarrier	Advantages	Limitations	Targeting Ligands/ Strategies	Payloads	Key Preclinical Outcomes
Exosome-based nanocarriers	1. As endogenous nanovesicles, exosomes exhibit excellent biocompatibility and minimal immune activation.[49,58] 2. Inherent ability to mediate intercellular signaling and traverse biological barriers.[20,49] 3. Carrying and protecting a wide range of endogenous bioactive molecules like proteins, nucleic acids, and lipids.[50,59]	1. Challenges in isolation, standardization, and scalability, making it difficult to obtain high purity exosomes with consistent properties at a large scale.[58,59] 2. The efficiency of active loading of exogenous therapeutic cargos is limit and often disrupts vesicle integrity.[60] 3. Biodistribution, clearance mechanisms, and precise targeting principles of exosomes remain unclear.[61]	Innate homing capability[20,49]	Endogenous biological molecules like proteins and miRNAs.[49,50]	Modulated trophoblast function, alleviated placental inflammation and endothelial dysfunction, and improved fetal outcomes in preeclampsia models.

for endogenous therapeutic molecules (eg, miRNAs, protein) to modulate the placental microenvironment.[20,49] Despite these advantages, exosomes face considerable translational hurdles. Compared to mature synthetic carriers like liposomes, the efficient and controllable loading of exogenous therapeutic cargo remains a major technical challenge.[60] Furthermore, their biodistribution, clearance mechanisms, and precise targeting principles remain unclear.[61] Coupled with the difficulties in achieving large-scale,[59] standardized production has impeded their clinical development. In summary, the selection of an optimal nanocarrier depends on a triad of factors, including the specific therapeutic goal, the nature of the payload, and the paramount consideration of safety, requiring a careful balance of maternal and fetal risks.

The Influence of Physicochemical Properties of Nanocarrier on PE Treatments

The therapeutic efficacy of nanocarriers is fundamentally governed by their intrinsic physicochemical properties, including size, surface charge, surface modifications, and core composition. These properties precisely regulate their fate in the maternal circulation, enrichment in placental tissue, uptake by trophoblast cells, and ultimate intracellular bioactivity.[11] This section discusses the impact of this physicochemical properties on the therapeutic effect of PE, aiming to provide guidance for the development of efficient targeted treatments for PE.

Size

The size of nanocarrier is the primary determinant of their pharmacokinetics and biodistribution. In nanomedicine, a widely recognized optimal size range (approximately 50–200 nm) is considered beneficial for balancing long circulation with tissue penetration capacity, a principle that also applies to placental targeting.[51] For instance, LNP C5, identified through high-throughput screening, demonstrates superior placental mRNA delivery efficiency in vivo. Its suitable size is believed to facilitate retention in the placental sinusoids and sufficient contact with target cells.[26] Furthermore, size significantly influences the cellular uptake mechanism. Smaller particles (<100 nm) tend to enter cells more readily via clathrin-dependent endocytosis, a pathway particularly prominent in metabolically active trophoblast cells.[63] Therefore, optimizing size of nanocarrier to match the dominant endocytic pathway of target cells is key to maximizing intracellular delivery efficiency.

Surface Charge and PEGylation

Surface charge (Zeta potential) and hydrophilic modifications jointly determine the interaction of nanocarriers with the biological environment. Nanocarriers with positive charges (eg, PAMAM-siRNA complexes) can strongly promote cell membrane adsorption and endocytosis through electrostatic interactions, but this is often accompanied by higher cytotoxicity and the risk of rapid clearance by the mononuclear phagocyte system.[18] Consequently, recent designs often aim for a neutral or slightly negative charge under physiological conditions. PEGylation plays a central role here, where its density and chain length are critical levers for modulating properties and targeting ability.[35] The PEG layer reduces non-specific adsorption of serum proteins through steric hindrance, thereby extending circulation half-life.[11] More importantly, Young et al revealed that adjusting the molar ratio of PEG-lipid in LNPs can alter their apparent pKa, which is directly linked to a switch in tropism between the placenta and the liver, providing a principled strategy for selective organ targeting.[27] However, excessive PEGylation may hinder the function of targeting ligands or induce immune responses, necessitating the search for an optimal balance.

Density

For active targeting nanocarriers modified with antibodies or peptides, the density of surface ligands is a key determinant of their efficacy. Geisler et al discovered an optimal modification density for anti-EGFR antibodies on the LNP surface (a 1:5 antibody-to-LNP molar ratio). At this density, aEGFR-LNPs achieved optimal placental mRNA delivery and trophoblast cell uptake both in vitro and in vivo.[30] Insufficient density leads to inadequate targeting, while excessive density may reduce internalization efficiency due to steric hindrance or receptor over-crosslinking, and can even alter the overall physicochemical properties of the particle.

Core Composition

The core lipids or polymers of nanocarriers form the chemical basis for their cargo protection, membrane fusion, endosomal escape, and even endogenous targeting capabilities. In lipid-based nanocarriers, the design of ionizable lipids (eg, C12-200) allows them to remain neutral at neutral blood pH for prolonged circulation and to become protonated in the acidic endosomal environment, promoting membrane fusion and nucleic acid release, which is crucial for successful mRNA or siRNA delivery.[27] Swingle et al showed that their selected LNP 55 specifically adsorbs β2-GPI, a protein that mediates the efficient homing of LNPs to the placenta, revealing a new paradigm for precise targeting through material-protein corona-biological interface interactions.[15] Furthermore, different material platforms confer unique functionalities, for example, ELP serve as ideal carriers for the maternal sequestration strategy due to their thermal responsiveness and large molecular weight,[19] whereas exosomes inherently possess low immunogenicity and membrane fusion capability, with their own membrane proteome constituting the intrinsic component of their targeting ability.[20] Thus, a holistic and rational design strategy that integrates the precise control of these physicochemical parameters is essential to unlock the full therapeutic potential of nanocarriers for targeted PE therapy.

Conclusion and Outlook

In recent years, significant progress has been made in the application of nanocarriers for PE therapy. Through precise targeting design and functional modifications, various nanosystems can specifically deliver therapeutic agents (such as siRNA, mRNA, and small molecule drugs) to placental tissues, thereby enhancing efficacy while minimizing potential risks to the mater and fetus.[64–66] In brief, liposome-based nanocarriers have emerged as the most promising platform due to their efficient nucleic acid delivery capabilities and established clinical translation foundation.[67] Polymer-based nanocarriers enable precise drug release regulation through material diversity.[68] Protein-based nanocarriers have set a new standard for fetal safety with their innovative maternal sequestration strategy.[69] Meanwhile, exosomes, as natural nanoscale messengers, demonstrate exceptional biocompatibility and intercellular communication capabilities.[50] However, these nanocarriers still face some challenges. First, insufficient targeting efficiency and specificity, including non-specific accumulation of lipid-based nanocarriers in the liver and spleen, limited targeting capability of polymer-based nanocarriers, and incompletely elucidated targeting mechanisms of exosome-based nanocarriers.[11,70,71] Second,

safety and toxicity concerns, such as immunogenicity risks of lipid-based nanocarriers, potential cytotoxicity of polymer-based nanocarriers, and adverse reactions at high doses of protein-based nanocarriers.[11,72,73] Furthermore, limitations in therapeutic efficacy, where most nanocarriers only partially alleviate symptoms, with insufficient gene silencing efficiency and weal in vivo performance.[23,74] Finally, challenges in manufacturing processes and standardization, involving quality control in large-scale production of lipid-based nanocarriers, high production costs of protein-based nanocarriers, and difficulties in exosome isolation and purification.[75–77]

In the future, the development of nanocarriers in PE therapy should focus on the following crucial directions:

1. Developing placental-responsive intelligent targeting systems that leverage unique characteristics of the placental microenvironment (eg, hypoxia, acidic pH) to enhance treatment precision. These nanocarriers would enable triggered drug release, thereby confining therapeutic activity precisely to the disease site;
2. Constructing multi-mechanism synergistic therapeutic platforms, leveraging the inherent co-delivery and spatio-temporal control capabilities of nanotechnology, future platforms should aim to precisely load and sequentially release therapeutic agents targeting different pathological pathways (eg, angiogenesis, excessive inflammatory responses, and heightened oxidative stress) from a single nanocarrier. This strategy seeks to generate synergistic effects with the potential to reverse the disease process;
3. Strengthening the establishment of standardized manufacturing processes, it is crucial to advance standardized, continuous nano-manufacturing, for instance, through microfluidic technologies. Concurrently, innovative safety assessment paradigms must be developed. These include utilizing advanced models like placenta-on-a-chip organoids and sophisticated imaging techniques to comprehensively evaluate maternal–fetal safety during the preclinical stage;
4. Promoting the development of diagnostic-therapeutic integrated strategies, integrating diagnostic functions (eg, imaging probes) with therapeutic capabilities within a single nanocarrier would allow for visualization of placental pathology, real-time monitoring of treatment response, and individualized therapeutic adjustment to achieve precision medicine.

Through interdisciplinary collaboration and continuous technological innovation, nanocarriers are expected to overcome current translational limitations. This advancement will position them as a key breakthrough in PE therapy, ultimately achieving the fundamental goal of improving maternal and fetal health outcomes.

Abbreviations

PE, preeclampsia; EVTs, extravillous trophoblasts; sFlt1, soluble fms-like tyrosine kinase-1; VEGF, vascular endothelial growth factor; PIGF, placental growth factor; ANGPTL4, angiopoietin-like protein 4; GDF-11, growth differentiation factor-11; LNPs, lipid nanoparticles; ApoE, apolipoprotein E; β2-GPI, β2-glycoprotein I; PAMAM, poly-amidoamine; ELP, elastin-like polypeptide; HUCMSCs, human umbilical cord mesenchymal stem cells; RGO, reduced graphene oxide; EGFR, epidermal growth factor receptor; DOE, Design of Experiments; PEG, poly ethylene glycol; FA, folic acid; H3K18l, histone H3 lysine 18; FRα, folate receptor-alpha; L-NAME, L-arginine methyl ester; aEGFR-LNPs, EGFR antibody-conjugated LNPs; RGZ, rosiglitazone; PPARγ, peroxisome proliferator-activated receptor γ; TNF-α, tumor necrosis factor-α; CSA, chondroitin sulfate A; Nrf2, nuclear factor-erythroid 2-like 2; HB-EGF, Heparin-binding epidermal growth factor; NF-κB, nuclear factor-κB; HUCMSC-exos, human umbilical cord mesenchymal stem cell-derived exosomes; HPVEC, human placental microvascular endothelial cells; IGF1, insulin-like growth factor 1.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest.

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