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Review article

Targeted therapy of kidney disease with nanoparticle drug delivery materials

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ABSTRACT

With the development of nanomedicine, nanomaterials have been widely used, offering specific drug delivery to target sites, minimal side effects, and significant therapeutic effects. The kidneys have filtration and reabsorption functions, with various potential target cell types and a complex structural environment, making the strategies for kidney function protection and recovery after injury complex. This also lays the foundation for the application of nanomedicine in kidney diseases. Currently, evidence in preclinical and clinical settings supports the feasibility of targeted therapy for kidney diseases using drug delivery based on nanomaterials. The prerequisite for nanomedicine in treating kidney diseases is the use of carriers with good biocompatibility, including nanoparticles, hydrogels, liposomes, micelles, dendrimer polymers, adenoviruses, lysozymes, and elastin-like polypeptides. These carriers have precise renal uptake, longer half-life, and targeted organ distribution, protecting and improving the efficacy of the drugs they carry. Additionally, attention should also be paid to the toxicity and solubility of the carriers. While the carriers mentioned above have been used in preclinical studies for targeted therapy of kidney diseases both in vivo and in vitro, extensive clinical trials are still needed to ensure the short-term and long-term effects of nano drugs in the human body. This review will discuss the advantages and limitations of nanoscale drug carrier materials in treating kidney diseases, provide a more comprehensive catalog of nanocarrier materials, and offer prospects for their drug-loading efficacy and clinical applications.

1. Introduction

Nanomedicine is an emerging field that utilizes nanomaterials to diagnose and treat diseases. For example, applications include non-invasive examinations based on nanomaterials, in nerve injury, and targeted nano-drug therapy for kidney disease [1–4]. In recent years, combining nanoscience and pharmaceutical science has shown promising prospects and rapid development. Various organic, inorganic, and polymer nanomaterial structures, including nanoparticles, hydrogels, liposomes, micelles, dendrimer polymers, mesoporous materials, adenoviruses, lysozymes, elastin-like polypeptides, chitosan [4–27], are used as drug carriers, providing drugs with targeting and controllable

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release properties. Nano-drug delivery overcomes the shortcomings of traditional pharmaceuticals, particularly for drugs with poor absorption, low solubility, and low accumulation in target organs, enabling drug targeting and sustained release. The application potential of carriers depends on their size, shape, hydrophobicity, surface parameters, and other characteristics [28]. Ideally, nanomaterials with high biocompatibility and biodegradability are considered the best choice for biomedical applications [29,30]. When particle size reaches the nanometer scale, the total surface area increases by several orders of magnitude compared to micrometer-scale materials traditionally used in diagnosis and treatment, thereby increasing the potential for drug interaction with the system [31]. However, extensive research on their toxicity is also required to ensure safety in clinical use [32].

The pathophysiological mechanisms of kidney injury during acute kidney injury (AKI) include ATP depletion, oxidative stress, mitochondrial dysfunction, inflammatory cell infiltration, and production of inflammatory cytokines. Severe or prolonged injury can lead to endothelial damage and acute tubular necrosis. Acute tubular necrosis is characterized by damaged renal tubular epithelium, tubular obstruction, and eventual cell necrosis. Therefore, renal tubular epithelial cells and renal vascular endothelial cells may be appropriate targets for drug delivery, as they may be damaged during the early stages of AKI under sustained or severe ischemia or exposure to nephrotoxins [33]. AKI is a significant risk factor for the development of chronic kidney disease (CKD). CKD can also experience worsening of kidney function due to the occurrence of AKI. Endothelial dysfunction, microcirculatory changes, tubular injury, and renal inflammation characterize AKI. AKI causes approximately 13 million cases and 2 million deaths worldwide each year, which may exceed the burden of heart failure or diabetes [34]. CKD is a complex disease, and recent statistics show that its prevalence is still increasing, affecting 14% of the general adult population and up to 38% of those over 65 years old [35]. Human understanding of kidney disease development mechanisms has significantly increased, but there are still limited, targeted organ or cell therapies available for clinical use. Immunosuppressive therapy is commonly used for immune-mediated kidney disease, which may lead to a general decrease in patient immunity; CKD and AKI are primarily treated with supportive therapy, and there are no specific treatment plans.

2. The structural basis of the kidney as a multi-potential target organ for treatment

The kidney consists of approximately one million nephrons, including glomeruli with filtration function and renal tubules with reabsorption function, with a complex structure and various cell types (see Fig. 1), pathological features of CKD or AKI (see Fig. 2). It regulates aspects such as the body's water and electrolyte balance, excretion of metabolic waste, and the regulation of acid-base and blood pressure, all of which can serve as potential targets for treatment. Nanocarrier materials for drug delivery mainly include active targeting, passive targeting, and other mechanisms for targeting the kidneys.

2.1. Passive targeting of nanomedicine-based drug to the kidneys

After blood passes through the filtration barrier within the capillaries, the filtrate enters the renal tubule system. The filtration barrier is composed of endothelial cells, the basement membrane, and podocytes. Passive targeting of nanomedicine-based drug requires them to pass through the filtration barrier with urine production to reach the target cells. This places high demands on the characteristics of the nanoparticles, including the following points (see Fig. 3): First, particle size. Studies have shown that in the glomerular filtration barrier, the fenestrations of the glomerular capillaries (diameter 60–80 nm) and the slit diaphragms formed at the foot processes of the podocytes (diameter 12–22 nm) create a physical barrier for blood filtration, and particle size significantly affects drug delivery [36,37]. Typically, particles with a diameter <10 nm can freely enter the renal tubules through glomerular filtration without obstruction [38]. Particles with a particle size range of >10 and < 200 nm may face obstruction at the foot processes of podocytes or the fenestrations of the glomerular basement membrane (GBM). However, in diseased kidneys, the gaps in the filtration barrier increase, thereby reducing the obstruction of particles [39,40]. Second, surface charge. Since the filtration barrier has a strong negative charge, it exerts a strong repulsion force on particles with a negative charge,

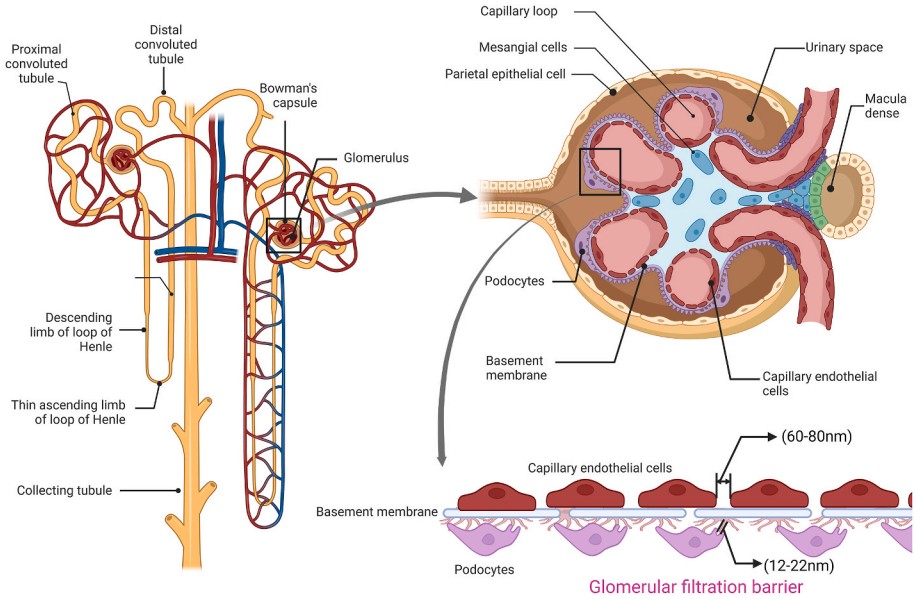

Fig. 1. The complex structure and multiple cell types of the kidney. The renal unit is the fundamental unit of kidney structure and function. Each renal unit consists of the renal corpuscle and renal tubules. The renal corpuscle is composed of the glomerulus and the urinary space. The glomerulus consists of capillaries, while the urinary space is a double-layered capsule surrounding the glomerulus, with the outer layer being the parietal layer and the inner layer being the visceral layer. The parietal layer contains parietal epithelial cells, the visceral layer has podocytes, and endothelial cells are on the capillary lumen's side. A basement membrane separates the endothelial cells and podocytes, and mesangial cells and mesangial matrix connect adjacent capillaries. These three layers form the filtration barrier. The glomerular vessel pole has a macula dense.

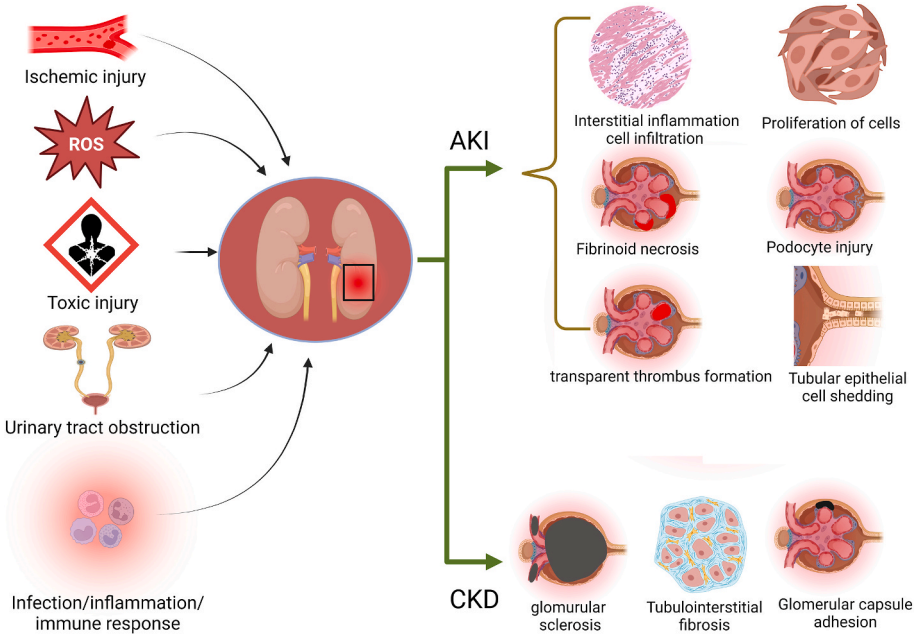

Fig. 2. An overview picture about the pathological characteristics of CKD or AKI.

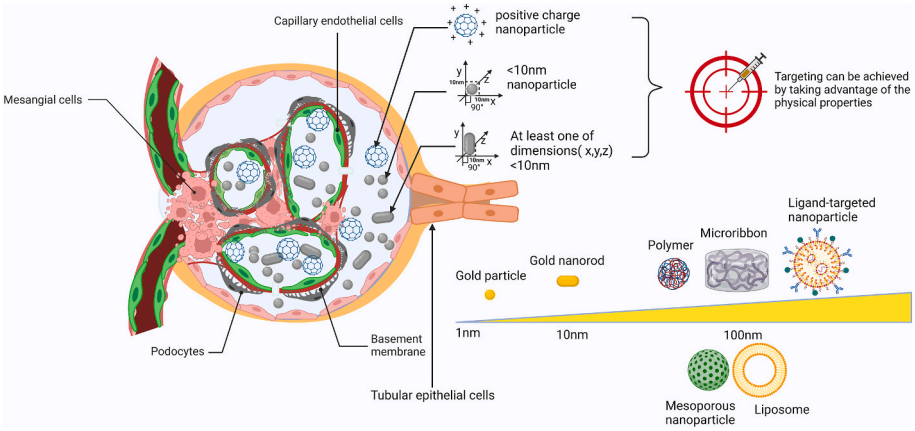

Fig. 3. Passive targeting of nanodrug materials to the kidneys. Nano drugs pass through the filtration barrier, enter the urinary cavity, and reach the target cells.

preventing their passage. Compounds with a positive charge are easily filtered, and compared to a negative charge, a higher presence of positively charged compounds has been found in urine. The difference in charge leads to differences in drug deposition and biodegradation in the kidneys, allowing drugs to have better effects and longer half-lives [41, 42]. Third, particle shape [43]. Studies have shown that spherical nanoparticles may be cleared faster than rod-shaped nanoparticles (possibly related to their ability to follow blood flow), while the circulation time and tissue residence time of oblate and rod-shaped carriers are prolonged [44]. After injecting nanoparticles with at least one dimension smaller than 10 nm, their ability to pass through the filtration barrier can be observed, indicating that rod-shaped or cylindrical nanoparticles with lengths close to micrometers can serve as therapeutic carriers. Additionally, non-spherical nanoparticles can make it difficult for macrophages to engulf them. In addition to the characteristics of the nanoparticles themselves, the state of the glomerulus under different diseases also affects the filtration of particles. For example, in Alport syndrome, the collagen structure of the basement membrane is disrupted, leading to an increase in porosity and allowing nanoparticles with a larger diameter to pass through.

2.2. *Active targeting of nanomedicine-based drug to the kidneys*

By introducing specific functional groups or bioactive molecules on the surface of nanomaterials, such as receptor ligands for renal tubular cells and particular proteins for glomeruli, the nanoparticles exhibit stronger affinity and targeting ability, allowing for more effective interaction with kidney tissues (see Fig. 4). These specific functional groups or bioactive molecules mainly include peptides and antibodies, with the most widely used antibodies. Nanoparticles can accurately reach target cells by binding to cell membrane surface antigens. However, attaching antibodies to particles significantly increases their diameter, which hinders their filtration capacity. Compared to antibodies, peptide chains demonstrate significant advantages as they retain specificity without substantially increasing the particle's volume. Active targeting of the kidneys with nanomaterials holds the promise of achieving more precise drug delivery and treatment, enhancing drug efficacy, reducing adverse effects on other tissues, and potentially bringing breakthroughs and innovations to treating kidney diseases.

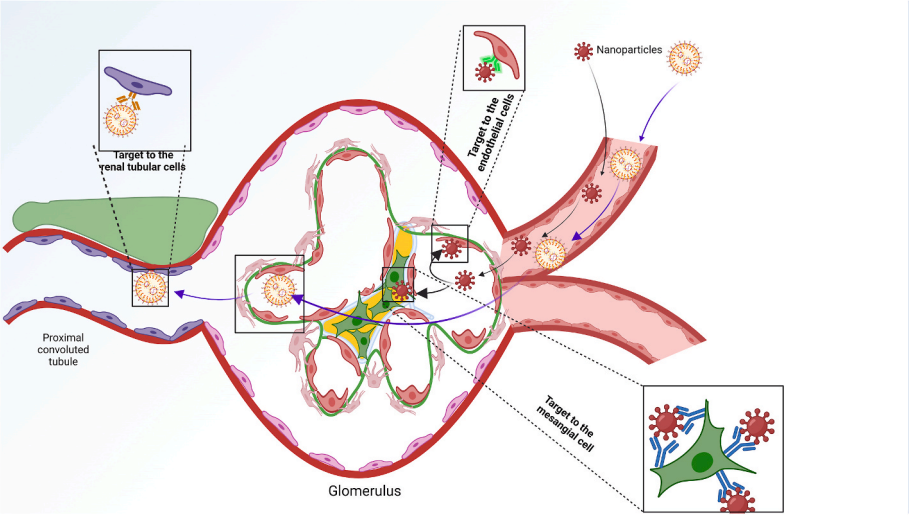

Fig. 4. Active targeting of nanomaterials to the kidneys. Introducing specific functional groups or bioactive molecules, such as receptor ligands for renal tubular cells and particular proteins for glomeruli, makes it possible to interact more effectively with renal tissues and reach target cells.

2.3. The complexity of renal cells provides targets for nanoparticle drug delivery to the kidneys

The glomerulus also includes mesangial cells, which provide structural support to the glomerular capillaries, act as sources of secreted signaling factors, and exhibit contractile activity, aiding in the control of glomerular capillary blood flow and participating in the regulation of the surface area of the glomerular filtration barrier. Mesangial cell disease is an essential factor in many glomerular diseases, and increased proliferation of mesangial cells occurs in a wide range of kidney diseases, making mesangial cells another potential target for drug therapy [45]. Additionally, nanoparticles with a diameter of 80–100 nm have a longer retention time in the kidneys and circulation, making them less likely to be filtered and, therefore, suitable for targeting the glomerular structure [46], at the same time, easily captured by the RES/MPS system and accumulated in organs such as kidney or spleen. When some renal diseases occur, such as AKI, the permeability and the structural integrity of GFB may change significantly, leading to particles larger than the renal filtration threshold being allowed to pass through GFB. Therefore, Nanoparticles with a diameter of 80–100 nm can also target renal tubules. Some large-sized nanoparticles (up to 400 nm) were observed in proximal tubular cells, apparently delivered through endocytosis, as their size is larger than fenestrations [47]. When AKI occurs, renal tubular epithelial cells [48] can serve as the main target cells for the action of nanodrugs, while in CKD, cells within the renal glomerulus serve as target cells, such as mesangial cells [49], podocytes [50], etc. Due to the different etiologies of AKI and CKD, the selection of target cells may also differ.

2.4. Imaging Nanomedicine-Based Drug Delivery

Nanomedicine imaging plays a crucial role in the preclinical evaluation of drug delivery systems, providing valuable information on pharmacokinetics, biodistribution, and target site accumulation. These imaging technologies enable us to select the best candidate drugs by answering important questions such as their distribution in vivo, residence time, clearance mechanisms, ability to reach the target site, and release profile. In the clinical setting, the heterogeneity of different individuals and diseases can impact the efficacy of drugs, particularly nanomedicines [51–53]. The approval of nanomedicines is based on their higher safety relative to traditional drugs [54]. Imaging methods play a critical role in overcoming this issue, allowing us to predict drug delivery systems and efficacy at the patient's physiological level [52]. In the clinical application of drug delivery systems and imaging technologies, nuclear medicine imaging techniques are advantageous, principally planar gamma scintigraphy, with only a minority using single-photon emission computed tomography (SPECT) or PET. A few studies also use ultrasound and magnetic resonance imaging. Readers can find an overview and comparison of various imaging technologies in James and Gambhir's Introduction to Imaging [55]. "Imaging Nanomedicine-Based Drug Delivery" primarily focuses on tumor-related research, with limited research related to the kidneys, often conducted in animal experiments [56] or cell experiments [57], as shown in Table 1.

Although kidney drug delivery technology is still preclinical, the efficacy of various therapeutic agents delivered by different drug delivery platforms has been demonstrated through in vitro and in vivo animal model tests. We will provide an overview of various nanomaterials and discuss their potential therapeutic value in treating kidney diseases.

3. Overview of different nanomaterials and their current applications in the kidney disease

Compared to non-targeted systemic drug delivery, targeted therapy releases drugs to specific sites of interest, enhancing efficacy, adjusting dosage, and minimizing toxicity. Targeted drug therapy for kidney diseases relies on excellent carriers, the drugs being carried, target tissues, and specific and appropriate kidney structures. Although most kidney drug delivery technologies are still in the preclinical stage, in vitro studies and in vivo tests using animal models have demonstrated the efficacy of various drug nanocarriers, including nanoparticles, hydrogels, liposomes, micelles, dendrimer polymers, adenoviruses, lysozymes, and elastin-like polypeptides. Next, we will provide an overview of nanomaterials for targeting the kidneys and their targeting mechanisms.

3.1. Nanoparticles

Nanoparticle drug delivery is an efficient drug delivery system that has garnered widespread attention in the field of drug delivery due to its various characteristics. Nanoparticles are small, allowing them to pass through cell membranes and blood vessel walls, increasing drug concentrations in target cells or tissues. Nanoparticles can be designed as controlled release systems, achieving slow and continuous drug release by regulating the properties and structure of the particles, enhancing efficacy, and reducing side effects. Many nanoparticle are made from

Table 1
Studies of image-guided approaches to nanomedicine drug delivery.

Reference	Nanomedicine type	Drug	Imaging modality	Tracer	Disease	subject
Koukourakis et al. [58]	Liposome	Doxorubicin	Scintigraphy + SPECT	99mTc	Lung cancer and head and neck cancer	Homo
Murray et al. [59]	Liposome	Muramyl tripeptide phosphatidylethanolamine	Scintigraphy	99mTc	Metastatic cancer	Homo
Giovinazzo et al. [60]	Liposome	Doxorubicin	SPECT	99mTc sulfur colloid	Ovarian cancer	Homo
Weers et al. [61]	Liposome	Amikacin	Scintigraphy	99mTc	Infection	Homo
Bhavna et al. [62]	Nanoparticle	Salbutamol	Scintigraphy	99mTc	Respiratory diseases	Homo
Lee et al. [63]	Liposome	Doxorubicin	PET	64Cu	Breast Cancer	Homo
Ramanathan et al. [64]	Liposome	Irinotecan	MRI	Iron oxide nanoparticles	Metastatic solid tumors	Homo
Lyon et al. [65]	Liposome	Doxorubicin	Ultrasound	–	Liver cancer	Homo
Chen et al. [56]	Nanoparticle	thrombin inhibitor	MRI	Perfluoro-15-crown-5-ether-core NP	AKI	Rat
Lin et al. [57]	Glucosamine	prednisolone	NMR/MS	–	–	Cell lines

biocompatible and biodegradable materials, meaning they can be safely used in the body and eventually broken down by biological processes. The encapsulation of drugs in nanoparticle carriers can protect them from external environmental damage, such as enzymatic degradation and pH changes, enhancing drug stability. The surface of nanoparticles can be modified to avoid recognition and clearance by the immune system, thereby extending the circulation time of drugs in the body. Through targeted delivery and controlled release, nanoparticles can reduce the impact of drugs on non-target tissues, thereby minimizing side effects.

3.1.1. *Polymer nanoparticles and inorganic nanoparticles*

The role of nanoparticles as drug carriers has been widely studied. Polymer nanoparticles comprise different hydrophilic and hydrophobic parts with varying structures, lengths, and charges, allowing them to encapsulate hydrophilic and hydrophobic drugs [66] (see Fig. 5). Polymer nanoparticles (PNP) have shown satisfactory results over the past few decades and have a wide range of potential applications in the medical field. Polymer nanoparticles are particles or particle materials with at least one dimension in the range of 10–100 nm, possessing a high specific surface area, tunable pore structure, excellent biocompatibility, and low toxicity, making them highly promising for drug delivery, bioimaging, diagnostics, and therapies. In drug delivery, polymer nanoparticles can be used as drug carriers, including prodrugs, stimulus-responsive systems, and combinations and entanglements of imaging and treatment. Biodegradable polymer nanoparticle structures (BPN) have shown extraordinary potential in therapeutic applications such as analysis, imaging, drug delivery, cosmetic repair, organ implantation, and tissue engineering. Additionally, polymer nanoparticles can overcome the limitations of conventional polymers and address many critical clinical issues. With the latest advances in the explicit functional balance of polymer nanoparticle structures, the prospects for applying polymer nanoparticles in the medical field are even broader. They are expected to be crucial in drug delivery, bioimaging, therapy, and diagnosis [67]. Inorganic nanoparticles have also been widely studied for their biomedical applications. There are various methods for preparing inorganic nanoparticles, such as hydrothermal, precipitation, sol-gel, redox, and template methods [68]. Adding metal precursors to organic solvents with stabilizers, inorganic nanoparticles are used for the large-scale production of stable inorganic nanoparticles. Various inorganic nanoparticles (such as silver, gold, platinum, zinc oxide, iron oxide, and cerium oxide) have been successfully prepared, as shown in

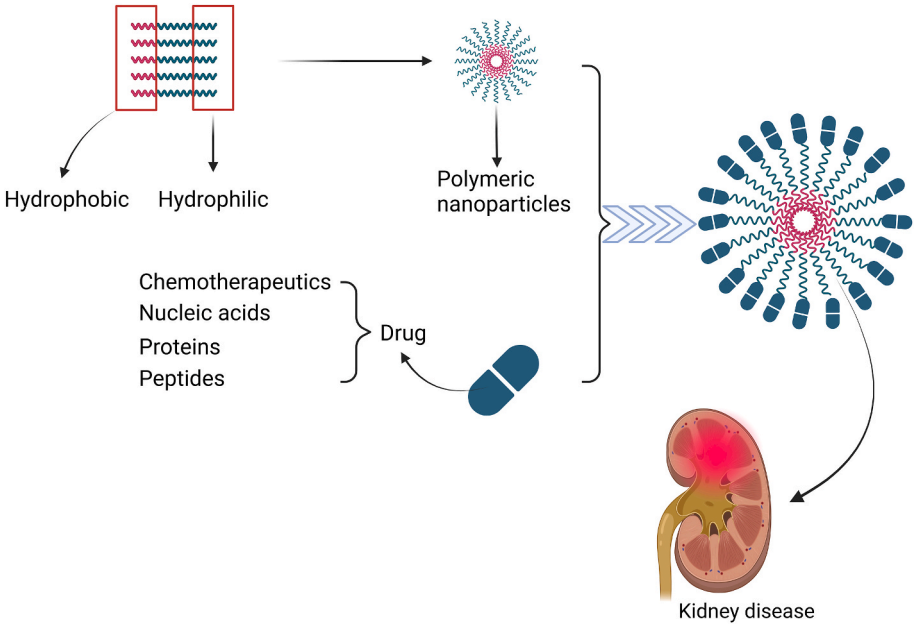

Fig. 5. Polymer nanoparticles targeting damaged renal tissues for precise treatment of kidney diseases.

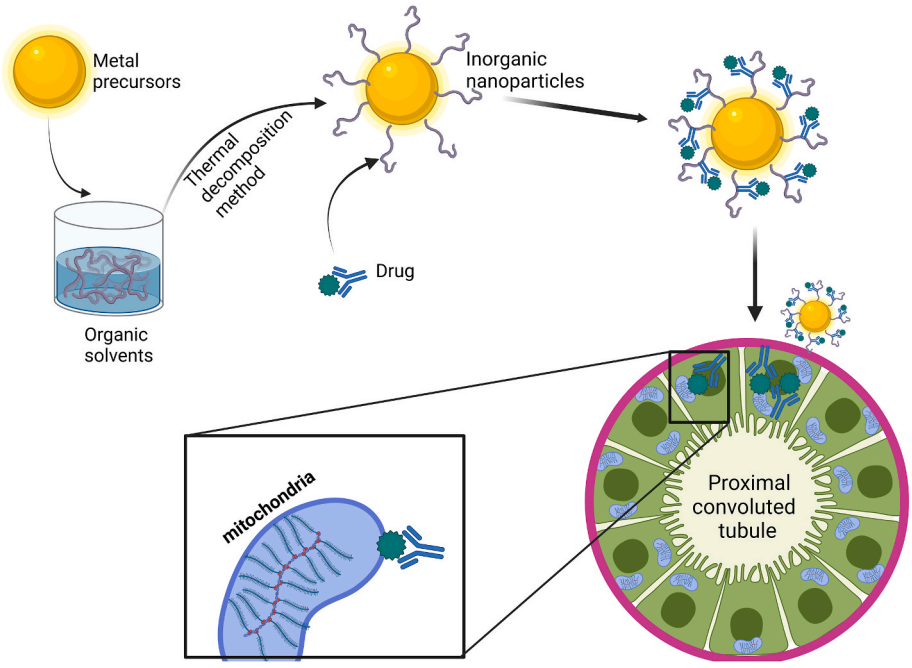

Fig. 6. Process of inorganic nanoparticles targeting the mitochondria of renal tubular epithelial cells.

Fig. 6. Using mesoporous materials can achieve efficient drug loading and ideal site-specific release, where pore size, surface functionalization, and specific surface area are the main factors affecting drug loading and release [69]. The synthesis methods for mesoporous materials include sol-gel, hydrothermal, microwave, and template methods [70]. Acute kidney injury is related to inadequate peritubular capillary perfusion, the generation of reactive oxygen species (ROS), and the infiltration of inflammatory cells. Endogenous carbon monoxide (CO) can protect cells or organs by vasodilation, anti-inflammatory effects, and reducing oxidative stress damage. However, direct supplementation of exogenous carbon monoxide is difficult to control in precise doses, and excessive carbon monoxide is significantly toxic, making it challenging to use in clinical treatment. Research has shown that by loading carbonyl manganese (MnCO) onto hollow mesoporous silica nanoparticles (MSN) and inserting phosphatidylserine (PS) into the membrane surface, a nanomedicine for AKI carbon monoxide therapy has been developed. It has shown sound therapeutic effects on oxidative damage in tubular cells and glycerol-induced AKI [18]. However, due to the high biocompatibility, biodegradability, and reduced systemic toxicity of polymer nanoparticles, they are preferred over inorganic nanoparticles [71]. Additionally, surface-modified polymer nanoparticles as drug delivery systems have various advantages, such as targeted delivery, reduced side effects, decreased dosage, and improved efficacy. Furthermore, they can help enhance drugs' physical and biochemical properties, pharmacokinetics, and pharmacodynamic characteristics [72].

Small polymer nanoparticles with a polyethylene glycol shell diameter of 5–30 nm can be excreted through glomerular filtration in urine, with excretion inversely proportional to particle size [5]. Ultra-small nanoparticles are typically constructed by modifying a metal core, using glutathione-modified gold nanoparticles to release pH-dependent Co2+. The glutathione coating imparts a negative charge to the particles, allowing them to interact with transition metals through pH-sensitive coordination bonds [6]. Since Co2+ can activate hypoxia-inducible factors, it has a protective effect on interstitial tubular injury, maintaining capillary stability and thus improving the potential for fibrosis. The modified nanoparticles with a diameter of 2.9 nm co-localize with aquaporins in the tubules and accumulate significantly in other organs such as the liver. When transporting Co2+, the nanoparticles are expected to reduce fibrosis and renal tubular damage in a unilateral ureteral obstruction (UUO) model. Another type of tiny nanoparticles that act on the renal system is cerium-based nanoparticles, modified with triphenylphosphine and polymer coatings and then used to encapsulate atorvastatin. The particle size is 43 nm, with a slight negative charge. During AKI injury, these nanoparticles can accumulate in the kidneys and target mitochondria to eliminate excess ROS. In vitro experiments have shown that these nanoparticles have potent antioxidant and anti-apoptotic activity. In vivo experiments have demonstrated that these particles can effectively reduce oxidative stress and inflammation, protect mitochondrial structure, and reduce tubular cell apoptosis and necrosis in a sepsis-induced AKI mouse model [4]. Another nanoparticle targeting tubules is a nano-composite made of hydrocaffeic acid and chitosan, which can form ternary complexes with metals and drugs, carrying a positive charge. When the particle size is around 70 nm, these nano-composites can pass through the renal filtration barrier and act on tubular epithelial cells by interacting with chitosamine with megalin receptors. These nanoparticles transport the traditional Chinese medicine rhein, which can be used to maintain the body weight of a unilateral ureteral obstruction (UUO) model and alleviate renal fibrosis [7]. Chitosan, a polysaccharide, transports drugs to the renal tubules through renal filtration and tubular reabsorption. Wang et al. used glucosamine (the basic unit of chitosan) to deliver ferulic acid to the kidneys [26]. Increasing the size of nanoparticles to a diameter more significant than the glomerular filtration threshold is an effective method for targeting the glomeruli. Studies have shown that nanoparticles with a diameter of 95 nm have the highest renal deposition rate and co-localize with mesangial cells. These particles deliver celastrol, and in vivo, experiments have shown anti-inflammatory, anti-fibrotic, and reduced cell death effects in a thy1.1 rat nephritis model while reducing the drug's toxicity [8]. A polymer nanoparticle of about 80 nm with a positive charge introduced on the surface of polyethyleneimine is used to deliver the natural compound rhein (4, 5-dihydroxyanthraquinone-2-carboxylic acid), which has been shown to reduce blood sugar and promote kidney function. In streptozotocin-induced diabetic mice, compared to healthy kidneys, these particles showed enhanced deposition in the kidneys, improving blood glucose levels, alleviating weight loss, improving creatinine clearance rate, and reducing renal fibrosis. However, it was also found

that these particles can lead to off-target accumulation [9]. The Heller laboratory studied nanoparticles made of poly(lactic-co-glycolic acid) (PLGA) and polyethylene glycol (PEG), which have both positive and negative charges, allowing them to target the kidneys while having minimal effects on the heart and lungs [10]. A polymer-based medium-sized nanoparticle, after intravenous injection, localized to the renal tubules. In mice subjected to renal ischemia-reperfusion injury, these nanoparticles selectively delivered a Toll-like receptor 9 (TLR9) antagonist to the kidneys, reducing tubular necrosis, inflammation, reduced proinflammatory cytokine synthesis, neutrophil and macrophage infiltration and apoptosis, DNA fragmentation, and reduced caspase 8/9 activation compared to mice treated with negative control nanoparticles [11]. Nanoparticle drugs can benefit CKD (such as diabetic nephropathy) and AKI (such as ischemic kidney injury). Colombo et al. synthesized biocompatible polymer nanoparticles with specific surface properties and controllable sizes for local delivery of glucocorticoids to treat injured podocytes. They copolymerized with aggregating methyl acrylate surfactants to produce negatively charged, positively charged, and neutral polycaprolactone NPs with a 30–120 nm particle size range. The size and surface charge of the nanoparticles can affect their cytotoxicity and absorption. As dexamethasone can effectively repair damaged podocytes, it exhibits a sustained therapeutic effect when encapsulated in the podocyte culture medium [50].

3.2. Nanogels

Nanogels, also known as hydrogel nanoparticles, possess the properties and functions of both nanomaterials and hydrogels. Hydrogels are polymer systems with a three-dimensional network structure formed by a simple reaction of one or more monomers containing a large amount of water. The diameter of these nanoparticles ranges from 20 to 10,000 nm and can be artificially produced using various techniques. We focus on nanogels. The water-absorbing capacity of nanogels materials comes from the hydrophilic functional groups on the polymer skeleton, while their water insolubility comes from the cross-linking of the network chains. Compared to traditional nanogels drug carriers, nanogels nanoparticles have higher drug loading capacity, sustained release properties, higher permeability, and a larger specific surface area available for modification. Nanogels are physically or chemically cross-linked network polymers that exhibit swelling capacity in the presence of water or organic solvents. The hydrophilic groups have water absorption capacity and solvent resistance [73]. Nanogels can be synthesized in various ways, including bulk polymerization, solution copolymerization, suspension polymerization, and radiation polymerization [74].

3.2.1. Characteristics of nanogels

Firstly, biocompatibility and biodegradability. In studies using injectable nanogels for treating bone and joint injuries, no inflammatory reactions were observed, confirming the excellent biocompatibility of nanogels [75]. Nanogels can be modified or compounded to create high-performance nanogels with biodegradability, showing great potential in applications for implants and drug delivery [76]. Secondly, swelling and water absorption properties. Nanogels can absorb large amounts of water due to the presence of hydrophilic groups in the main chain or end chains of the polymer material, with a water content of up to 99%. When used as medical dressings, nanogels can absorb wound exudate while maintaining a moist environment, adhering closely to the wound without causing adhesion, reducing bacterial contact, and preventing secondary trauma [77]. Additionally, they exhibit stimulus responsiveness. Nanogels, with high water content, high sensitivity, and controllable structure and physicochemical properties, can respond rapidly to external environmental stimuli through swelling, contraction, or sol-gel phase transition. Based on the different stimuli that trigger the response, the stimulus responsiveness of nanogels can be classified as a physical response and a chemical response. Physical response refers to the nanogels's response to changes in the physical environment, such as thermal response, light response, magnetic field response, and mechanical response [78]. Chemical response refers to the nanogels's response to changes in the chemical environment, such as pH and ionic strength [79].

3.2.2. Types and preparation methods of polymer nanogels

Polymer nanogels can be classified into chemical and physical nanogels based on cross-linking mechanisms. Polymer chains covalently cross-link chemical nanogels and are permanent, while physically cross-linked nanogels are not permanent because they are formed through hydrogen bonds, entanglement of chains, hydrophobic interactions, crystal interactions, host-guest mechanisms, etc. Another type is double network nanogels, where the "first network" is usually rigid, closely cross-linked by covalent bonds, and the "second network" is typically soft, loosely cross-linked by supramolecular interactions (such as hydrogen bonds, ionic interactions, coordination interactions, etc.), and the combination of these chemical and physical cross-links ultimately forms the double network nanogels [80]. Yukun Wang et al. prepared a gelatin/hydrophobically modified polyacrylamide (HPAAm) double network (DN) nanogels, where the "first network" is formed by hydrogen bonds instead of covalent bonds, providing a new approach for the preparation of nanogel drug carriers with good stability [81]. Additionally, a type of peptide nanogels forms a 3D fibrous network model through supramolecular non-covalent interactions of peptides, encapsulating gelators to form nanogels, also showing good biocompatibility and low toxicity. The number of peptide chains can be increased to include dipeptides, tripeptides, and polypeptides, and factors such as temperature, pH, and the hydrophilicity and hydrophobicity of amino acids can affect the physicochemical properties of peptide nanogels [82,83]. The principle of synthesizing nanogels by radiation involves free radical polymerization, which triggers the intramolecular complexation of polymer radicals through ionizing radiation.

3.2.3. Trends in polymer nanogels as drug carriers

Applying polymer nanogels as drug carriers is becoming an essential trend in drug delivery. These nanogels have highly controllable structures and adjustable drug release characteristics, making them an effective drug delivery system. The future development trends of polymer nanogels as drug carriers focus on several aspects: efficient drug delivery, targeted delivery, controlled release characteristics, and biocompatibility, providing innovative solutions for the field of drug delivery and offering more effective and safer approaches for disease treatment.

3.2.3.1. Supramolecular hydrogels. Supramolecular hydrogel systems are composed of interactions between non-covalent molecules involving stacking two or more monomer molecules. This non-covalent cross-linking is a beautiful feature that allows the hydrogel to have a broader range of drug encapsulation [84]. Research has reported the preparation and biological evaluation of a hydroxypropyl-β-cyclodextrin-g-poly (acrylic acid)/gelatin (HP-β-CD-g-PAA/gelatin) semi-interpenetrating network (semi-IPN) for the colonic delivery of dexamethasone sodium phosphate (DSP). The prepared hydrogel showed pH-dependent swelling and mucosal adhesion properties. The adhesive strength of the hydrogel increased with the concentration of gelatin. Based on swelling and mucosal adhesion, AG-1 was selected as the optimized formulation (gelatin content of 0.33%, acrylic acid (AA) content of 16.66%) for further analysis. Fourier-transform infrared spectroscopy (FTIR) revealed the successful development of a polymer network without interacting with DSP. Electron microscopy images showed a slightly rough surface after drug loading. In vitro, drug release tests showed pH-dependent release, with rapid release of loaded DSP at pH 1.2, and over 72 h required for 90.58% drug release at pH 7.4. The optimized formulation showed no toxicity to rabbits' major organs and

exhibited blood compatibility, confirming the biocompatibility of the hydrogel [85]. Notably, the targeted anti-inflammatory properties for the intestine provide potential therapeutic value for the "quadruple hit" theory of IgA nephropathy.

3.2.3.2. DNA-hydrogels. In terms of composition, DNA hydrogels can mainly be divided into two categories, namely hybrid DNA hydrogels and pure DNA hydrogels. For hybrid DNA hydrogels, DNA primarily serves as a cross-linking agent during the gelation process, and the synthetic polymer still dominates the gel scaffold, which is in sharp contrast to pure DNA hydrogels. Highly structured network structures can be obtained through cross-linked complementary DNA molecules, and the resulting hydrogel structure can swell and expand upon contact with water. These materials can load other types of nucleic acid molecules (such as siRNA and miRNA) and drugs that can bind to DNA. These hydrogels exhibit high solubility, biocompatibility, functionality, and responsiveness [86].

3.2.3.3. Bio-inspired hydrogels. Bio-inspired hydrogels are a relatively novel type of hydrogel. For example, post-traumatic bleeding and wound healing are common health issues. Research has developed a biomimetic hydrogel by covalently cross-linking natural platelets and alginate to promote wound healing, demonstrating excellent biocompatibility and blood compatibility. By changing the ratio of platelets to alginate, the mechanical properties of the resulting hydrogel can be varied to adapt to different wound environments. Additionally, silver nanoparticles can be loaded into the interstices of the hydrogel, imparting excellent anti-infective properties to the composite material [87].

3.2.3.4. Multifunctional and stimuli-responsive hydrogels. Hydrogels can also achieve a variety of functions through different modifications, enabling effective drug delivery of drugs. For example, there are thermoresponsive hydrogels, photo-controlled release hydrogels (light and NIR), magnetic gels, ultrasound-responsive hydrogels, pH-responsive hydrogels, and ATP-responsive hydrogels, among others [88–90].

3.2.4. Application of polymer nanogels in kidney disease

Hydrogels, as a delivery system for biomedical materials, are typically used to deliver drugs smaller than 15 nm, such as small molecule drugs or small proteins. Generally, drug-loaded hydrogels primarily release through diffusion, and controlled drug release can be achieved by controlling the hydrogel network's degradation, swelling, and mechanical deformation [91]. Hydrogels can serve as carriers to transport growth factors, anti-inflammatory drugs safely, and even stem cell therapy for acute kidney injury (AKI) [12,92]. Substantial research evidence supports hydrogel carriers' direct targeted drug delivery capability, such as the significant effectiveness and biocompatibility of counteracting oxidative stress-driven mechanisms (such as inflammatory signals and mitochondrial damage). These studies provide encouraging evidence for the potential therapeutic value of hydrogel drug delivery [12]. These studies are derived from preclinical small animal experiments. See Table 2.

Table 2
Applications of hydrogels in kidney diseases.

Hydrogel Carrier Types	Loaded Cargo	*AR	Target Location	**KDT
Collagen Hydrogel	Polyethylene glycol 2 [93]	Injection	Renal parenchyma and interstitium	AKI
	Extracellular vesicles [94]	Injection	Renal parenchyma and interstitium	AKI
Chitosan Hydrogel	NO donor enzyme-prodrug system [95]	Injection	Renal parenchyma and interstitium	AKI
Self-Assembling Peptide Hydrogel	Extracellular vesicles [96]	Injection	Renal parenchyma and interstitium	AKI
	Anti-TNF-α and hepatocyte growth factor [12]	Injection	Renal tubules	AKI
	Mitochondrial antioxidant [97]	Injection	Renal parenchyma and interstitium	AKI
Polyethylene Glycol Gel	Growth factors [92]	Injection	Renal tubules	AKI
Biotin/ Chitosan Gel	Mesenchymal stem cell-secreted extracellular vesicles [98]	Injection	Renal ischemia/ reperfusion site	AKI
Hyaluronic Acid Hydrogel	Anti-TGFβ antibody [99]	Injection	Renal interstitium	CKD
Hydrogel	Mesenchymal stem cells [100]	Cell sheet transplantation	Subcapsular renal	***DN

Note: *AR, Administration Route; **KDT, Kidney Disease Type; ***DN, Diabetic nephropathy.

3.3. Liposomes

Liposomes are tiny hollow spherical structures composed of phospholipids and are a commonly used nanocarrier system, typically ranging from 100 to 200 nm. They consist of a bilayer membrane of one or more phospholipid molecules surrounding an internal aqueous compartment. This structure gives liposomes hydrophilic and hydrophobic properties, allowing them to form an interface between water and oil, effectively encapsulating and delivering water-soluble and lipid-soluble drugs. Liposomes (mainly composed of phospholipids) have received more attention due to their drug-carrying properties, and their advantages and disadvantages are summarized in Table 3.

3.3.1. Methods of liposome preparation

There are several methods for preparing liposomes, and almost all techniques involve dissolving phospholipids in organic solvents and then removing the organic solvents in the later stages of the process, which is crucial to the formation of liposomes. The components of liposomes are phospholipids and/or cholesterol, and the phospholipid concentration used for liposome manufacturing is well above the critical micelle concentration. To ensure uniform dispersion of liposomes, it is essential to create thin lipid films before exposing them to the aqueous phase or to introduce an organic phospholipid solution into the water environment in a controlled manner to form liposomes. Therefore, liposome manufacturing techniques, such as solvent evaporation, solvent dispersion/antisolvent addition, or detergent removal, will focus

Table 3
Advantages and disadvantages of liposomal drug delivery materials.

Advantages [101]	Disadvantages [102]
High biocompatibility	Cationic liposomes may produce high toxicity
Low toxicity and immunogenicity	Lack of targeting when administered intravenously
Biodegradability	
Relatively high drug concentration in the body	
Easy modification with various ligands and functional molecules	
Simultaneous loading of two types of drugs	

on first breaking down the phospholipids into individual phospholipid molecules and then exposing them to the water environment to form different types of liposomes, including small unilamellar vesicles (SUV) with particle diameters of 20–100 nm, large unilamellar vesicles (LUV) more prominent than 100 nm, multilamellar vesicles (MLV) larger than 500 nm, and oligolamellar vesicles (OLVs) with diameters ranging from 100 to 1000 nm.

3.3.1.1. Solvent evaporation. This technique dissolves phospholipids in organic solvents (commonly an equimolar mixture of chloroform and methanol, with other possible solvents being ether, ethanol, or dichloromethane) [103]. If the drug is lipophilic, it is added to the organic solvent to form a single-phase solution. Subsequently, the organic solvent is slowly removed under vacuum to form a thin lipid film, with the drug evenly dispersed. The lipid film is hydrated with an aqueous buffer above the glass transition phase of the lipids. If the drug is hydrophilic, it should be dissolved in the buffered aqueous solution. The resulting dispersion produces multilamellar vesicles (MLVs) with particle sizes in the micrometer range. This technique is more suitable for lipophilic drugs, allowing for high encapsulation efficiency. For hydrophilic drugs, the capture efficiency of this passive process is lower based on the physicochemical properties [104].

3.3.1.2. Solvent dispersion. In this technique, phospholipids are often dissolved in organic solvents containing water-soluble substances, with ethanol being the preferred solvent [105]. Lipophilic drugs are dissolved together with phospholipids in the ethanol solution, and the ethanol-phospholipid/drug solution is added to an aqueous buffer solution, causing the ethanol to dilute into the water, thus spontaneously forming multilamellar vesicles (MLVs). The particle size of MLVs is in the micrometer range. This technique is most suitable for lipophilic drugs and can achieve high encapsulation efficiency.

3.3.1.3. Reverse phase evaporation. This technique is the optimal method for loading hydrophilic drugs into liposomes. For hydrophilic drugs, the internal aqueous core is the only region where the drug can be loaded. Therefore, a technique that can capture many water cores during liposome formation will result in high encapsulation efficiency and drug loading. In the reverse phase evaporation method, a water-in-oil (w/o) emulsion is prepared by dissolving the hydrophilic drug in water and dissolving the phospholipids in a solvent that is immiscible with water (usually chloroform). The organic solvent is slowly removed under a vacuum to form a gel phase. Further evaporation of the organic solvent produces dispersed liposomes, with the water cores highly captured in the inner core of the liposomes. This technique can passively capture hydrophilic drugs up to 30%–50% [106].

3.3.1.4. Control of particle size. Both solvent evaporation and solvent dispersion produce micrometer-sized MLVs. For drug delivery applications, it is essential to further reduce the particle size of these liposomes to submicron levels, specifically in the range of 50–200 nm, as the particle size of liposomes has a significant impact on the pharmacokinetic and pharmacodynamic properties in the body, thus affecting the therapeutic efficacy of the final formulation [107]. There are many techniques to reduce the particle size of liposomes, including ultrasonication [108], freeze-thawing [109], and others. All techniques have their advantages and disadvantages. Ultrasonication is a relatively fast technique that reduces particle size by dissipating a large amount of energy in a small volume. However, ultrasonication generates heat during the process, which may lead to phospholipid degradation and drug thermal instability. Freeze-thawing can also be used to convert MLVs into smaller vesicles such as SUVs or LUVs; however, in many cases, it can only reduce the particle size to a certain extent and has a relatively high particle size distribution, i.e., a high polydispersity index.

3.3.2. Methods of liposome drug loading

After the formation of liposomes, drugs can be loaded into them through two methods: active and passive. The principle of active drug loading is based on ion gradients. Passive drug loading techniques involve dissolving lipophilic drugs together with phospholipids in organic solvents and water-soluble drugs in aqueous media during the preparation of liposomes, directly obtaining drug-containing liposomes, as shown in Fig. 7. The preparation of liposomes mainly relies on the spontaneous arrangement of amphiphilic phospholipids in solvents. The particle size, membrane layers, and particle size distribution of liposomes are influenced by the preparation method, lipid type, lipid composition, surfactants, organic solvents, and the ionic strength of the dispersing medium [110–112].

3.3.3. Application of liposomal nanocarriers in kidney disease

Compared to microparticle carriers, nanoliposomes have many advantages: they can avoid phagocyte recognition, thus circulating in the bloodstream for a longer time; they can penetrate tissues through capillaries and biological membranes. Additionally, they are easily absorbed by cells, enhancing the therapeutic effect at the target site, prolonging the duration of drug action in the desired area, and even lasting several weeks. This dramatically improves controlled drug release and achieves precise targeting. Liposomes usually do not have renal targeting properties and active targeting ligands must be attached to the particle surface for renal targeting drug delivery. Mesangial cell abnormality is a significant cause of chronic kidney disease (CKD). There is no basement membrane interval between mesangial and endothelial cells, so it is favorable for drug transport. Mesangial cells express the Thy1.1 antigen specifically, and Fab fragments targeting Thy1.1 combined with liposomes form OX7-coupled immunoliposomes (OX7-IL). Compared to non-targeted liposomes, drug deposition in the kidneys significantly increases with Thy1.1-targeted liposomes, with drug deposition occurring in the glomeruli and co-localizing with mesangial cell markers [113]. Different from antibody conjugation, adding 3,5-dipentadecyloxybenzamidine hydrochloride (TRX-20) to the liposome surface imparts a positive charge. It has an affinity for chondroitin sulfate proteoglycans, forming liposomal drug carriers with targeting functions for endothelial and mesangial cells. This drug carrier can transport a large amount of drugs to the damaged tissue area. TRX-20 targeted liposomes with a size of approximately 100 nm significantly increased drug deposition in the kidneys' glomeruli and spleens of healthy rats [114]. A study used TRX-20 targeted liposomes to deliver Triptolide, which has excellent anti-inflammatory properties and can improve proteinuria and abnormal serum albumin levels in a rat model of membranous nephropathy [115]. In conclusion, nanoliposomes can exert anti-inflammatory effects and protect glomeruli by acting on mesangial and endothelial cells.

3.4. Micelles

Micelles are thermodynamically stable colloidal aggregates formed by the self-assembly of molecules when the surfactant reaches a particular concentration in an aqueous solution. The mechanism of micelle formation involves surfactants with adsorption capacity dispersing in the aqueous solution after reaching saturation. Due to the presence of hydrophobic groups, the repulsion force between water molecules and surfactants is stronger than the attraction force, causing the hydrophobic groups to aggregate into the core of the micelle under van der Waals forces, while the hydrophilic groups form the outer layer of the micelle, stabilizing its dispersion in the aqueous solution. The particle size of micelles is generally in the range of 10–100 nm. The nanocore's small size and the micelle's hydrophilic outer shell minimize micelles' clearance from the body, extending the drug's bioavailability. Polymer micelles, due to the high drug-carrying capacity of the core, are advantageous for targeted therapy and sustained drug delivery.

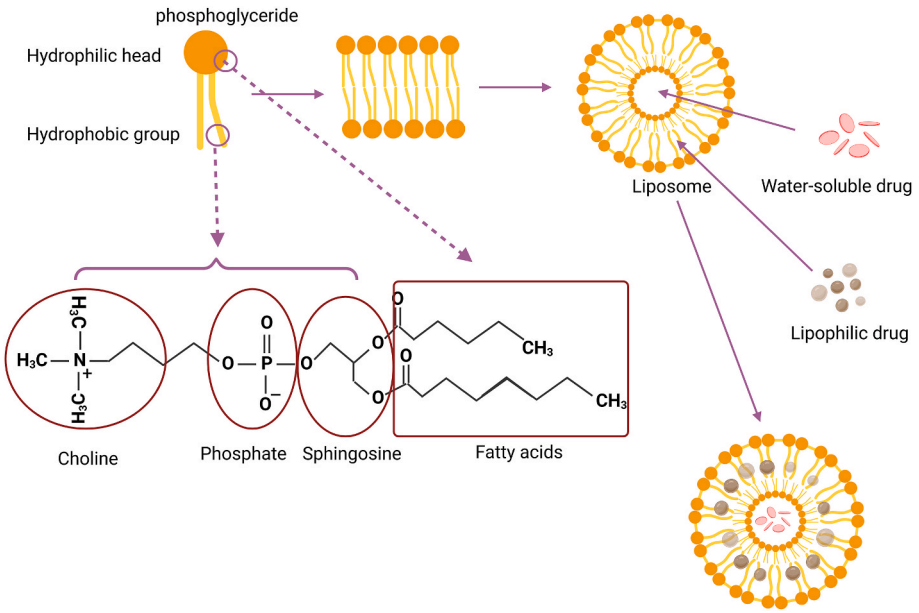

Fig. 7. Passive drug loading process of liposomes.

3.4.1. Unique structure and function of micellar nanocarriers

First, micelles can encapsulate hydrophobic drug molecules, increasing their solubility and stability, thereby enhancing the drug's bioavailability. Secondly, nanocarriers can achieve sustained release and targeted delivery of drugs by regulating the properties and structure of the drug-carrying material. This targeting capability enables precise delivery of drugs to the disease site, reducing damage to healthy tissues and improving treatment efficacy. The selection of an appropriate surfactant is necessary for such drug carriers. When the surfactant reaches a specific concentration, it can form micelles. Micelles are formed by the dispersion of hydrophilic and hydrophobic molecules in a solution. Factors determining micelle formation include amphiphilic molecule concentration, the hydrophilic/hydrophobic regions in amphiphilic molecules, temperature, and solvent type [116]. Micelles are formed through self-assembly, which only begins when a specific minimum concentration, the critical micelle concentration, is reached. The temperature at which amphiphilic molecules exist in an aggregated form is known as the critical micellization temperature. Micelles will decompose when the temperature is below this threshold [117]. Micelles have gained attention due to their high stability, low cytotoxicity, and ability for controlled and sustained drug delivery. By adjusting the ratio of copolymer monomers, suitable micelles can be obtained, and most hydrophobic drugs can be easily incorporated into the core of the micelles. Micelles need to exhibit good stability to avoid sudden drug release. Micellar stability includes thermodynamic stability, which characterizes the process of polymer micelle formation and reaching thermodynamic equilibrium, and kinetic stability, which describes the microscopic changes in the entire polymer micelle system over time.

3.4.2. Drug loading characteristics of micellar nanomaterials

Polymer micelles comprise a hydrophobic core and a hydrophilic shell, giving the micelles multiple functions crucial in the delivery system. Highly functionalized structures are suitable for drug delivery systems. The hydrophilic shell can interact with biological components such as proteins and cells, affecting the pharmacokinetic behavior and drug distribution, thereby controlling the drug delivery behavior in the body. The hydrophobic core is used for drug encapsulation and release. Due to different assembly principles, polymer micelles are divided into block copolymer micelles, polyelectrolyte copolymer micelles, non-covalent bond micelles, and graft copolymer micelles, among others [118]. See Table 4.

Table 4
Drug loading characteristics of different types of micellar nanomaterials.

Micelle Type	Structural Composition	Drug Loading Capacity
Block Copolymer Micelles [119]	Diblock copolymers, Triblock copolymers	Weak
Polyelectrolyte Copolymer Micelles [120]	Polyelectrolyte complexes as the core	Good sustained release and controlled release capability
Non-covalent Bond Micelles [119]	Hydrogen bonds or metal coordination to form non-covalent bonds	Weak
Grafted Copolymer Micelles [121]	Hydrophobic graft copolymers form micelle cores, sometimes cannot self-assemble completely	Fair

3.4.3. Drug loading methods of micellar nanomaterials

The drug-loading methods of micelles mainly include physical encapsulation, chemical conjugation, and electrostatic interactions. Physical encapsulation and chemical conjugation are primarily used to load small molecule drugs, while electrostatic interactions are mainly used to load charged nucleic acid and protein drugs. Physical encapsulation of drugs involves physically incorporating the drug into the core of the micelle without the need for specific functional groups for chemical bonding. It utilizes the hydrophobicity of the micelle core and the hydrophobic interaction and hydrogen bonding between poorly soluble drugs to solubilize the drug in the polymer micelle and is suitable for most hydrophobic drugs [122]. See Fig. 8. With the development of various amphiphilic copolymers, micelle-based drug delivery systems have become a potential nanotechnology for drug delivery.

3.4.4. Application of micellar nanocarriers in kidney disease

Chrysophanol-loaded micelles (CLM) have been shown to delay chronic renal failure and improve bioavailability by targeting the kidneys. The particle diameter is 29.64 ± 0.71 nm, and apart from kidney enrichment, these micelles have also been accumulated in the brain and liver. Both in vivo and in vitro experiments have shown that the cumulative release rate of chrysophanol (CH) in the CLM micelle system is significantly higher than that of free CH (86% m/m vs. 15% m/m, $p < 0.01$), providing better protection to podocytes [13]. Cyclosporine is a commonly used drug for treating nephrotic syndrome. A polymeric

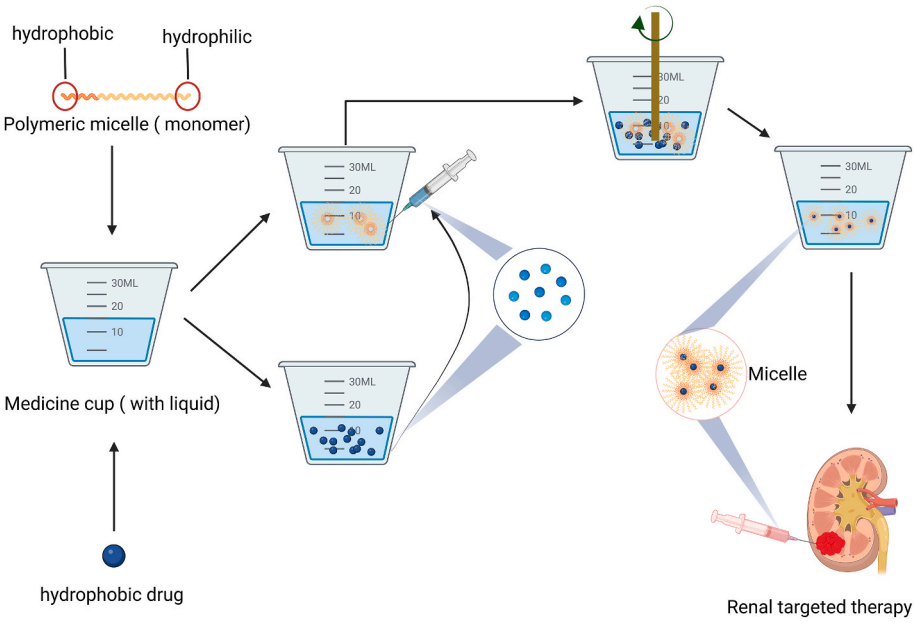

Fig. 8. Process of micelles targeting renal lesions through physical encapsulation of drugs.

micellar formulation of Cyclosporine A (CyA) based on poly(ethylene oxide)-block-poly(ε-caprolactone) (PEO5K-b-PCL13K) has been developed. Unfortunately, in vivo experiments have shown that this formulation accumulates more in the liver than in the kidneys [14]. Celastrol, a pentacyclic triterpenoid compound isolated from the root of Tripterygium wilfordii, has been selected for treating interstitial fibrosis in the kidneys due to its potent anti-inflammatory and anti-proliferative activities. Without an appropriate carrier system, intravenous administration of Celastrol can lead to dose-related systemic toxicity due to its interaction with multiple organs. Pluronic is an amphiphilic non-ionic triblock copolymer consisting of a hydrophobic poly(propylene oxide) (PPO) core and hydrophilic poly(ethylene oxide) (PEO) chains on both sides. Utilizing a hyaluronic acid-derived hydrogel crosslinked with Pluronic micelles, localized and prolonged release of Celastrol in the kidneys can be achieved. In vivo experiments have shown that this micellar drug delivery system has therapeutic significance in kidney fibrosis in a unilateral ureteral obstruction (UUO) mouse model [15].

3.5. Dendrimers

Dendrimers are large molecules with a dendritic structure composed of low-molecular-weight polymers that are repetitively branched and linearly connected. They typically consist of a core, a polymer main chain, and side chains of dendritic units and are a type of highly branched, monodisperse polymer. Dendrimers contain internal cavities and are rich in surface-active functional groups with controllable physicochemical properties, making them a novel drug delivery technology widely used in the pharmaceutical industry [123]. The size of dendrimers is typically 1–100 nm. The toxicity of dendrimers is the major obstacle limiting their clinical application, primarily arising from surface charges. As the generation of the polymer increases, the densely packed cationic surface of dendrimers leads to increased toxicity. Therefore, mature techniques are needed to modify dendrimers, reduce toxicity, and expand their applications [124]. Dendrimers are mirror-symmetrical, spherical, and nanoscale densely structured molecules with dendritic branches or arms. The dendrimer structure consists of a core composed of an atom or group of atoms, with branches of other atoms derived through chemical reactions [125]. See Supplementary Fig. 1. Dendrimers are mainly synthesized through divergent or convergent methods. In the divergent method, the synthesis starts from the core and gradually extends towards the periphery. When a multifunctional core molecule reacts with a monomer molecule composed of one reactive group and two dormant groups, the first generation of dendrimers is synthesized. Subsequently, more monomers participate in the cascade reaction to form the new peripheral arrangement. In the convergent method, the synthesis starts from the periphery, and the endpoint becomes the outermost layer of the final dendrimer. Some modifications are made to the peripheral groups of the dendrimer to enable them to play a role in a wide range of biomedical applications [126].

3.5.1. Characteristics of dendrimers

Dendrimers, as drug carriers, have the characteristics of high drug loading, controlled release, targeted delivery, and good biocompatibility. However, they also have certain drawbacks, such as potential toxicity. Compared to some traditional drug carriers, research and application of dendrimers are relatively new, and more experiments and clinical validation are needed to prove their safety and effectiveness.

3.5.1.1. Physical properties of dendrimers. The polymerization monomers are controllable, which means that precise control of the molecular weight, structural shape, molecular size, and functional groups of dendrimers can be achieved. The biological size of the molecules increases with the generation, and the precise control of the synthesis generation further controls their fluid dynamics and viscosity. At the same time, dendrimers have a broad internal cavity structure. Dendrimers have a core, with branching units outside the core. When the generation of branching units is low, an open amorphous configuration is formed. When the generation reaches the fourth generation, the molecular structure gradually changes from an open and loose state to a three-dimensional spherical or quasi-spherical structure with a tight exterior and loose interior. This structure provides dendrimers with broad cavities that can be used for drug encapsulation. With the formation of the three-dimensional spherical structure, the surface of the entire molecule exposes the functional groups of the branching units. By selecting highly active branching units or introducing special functional groups at the center and end of the molecule, it is possible to ensure that the molecule's surface has densely packed active groups. Through surface modification, it can be used for drug delivery [127]. In addition, many amino and amide groups in conventional dendrimers give them good

water solubility.

3.5.1.2. Toxicity of dendrimers and solutions. First is the cell membrane toxicity. Existing literature reports that nanostructured cationic dendrimers form complexes with negatively charged phosphate groups on the cell membrane's lipid bilayer through electrostatic interactions, creating nano-sized pores on the membrane. This reduces the stability of the cell membrane while increasing its permeability, and at high concentrations, it can lead to cell membrane rupture. Therefore, within a specific concentration range, dendrimers can more efficiently deliver drugs by increasing the permeability of the cell membrane. However, exceeding this concentration range increases the risk of membrane rupture and cell leakage. Additionally, whether the mechanism of cation-induced increase in cell membrane permeability is reversible requires further study to ensure that the protective mechanism of the cell membrane can rapidly recover after the dendrimers are cleared. The second is hemolytic toxicity. The terminal cationic groups on the surface of dendrimers interact with red blood cells, causing hemolysis. For example, the hemolysis rates of G4 and G5 PPI dendrimers with free amine groups on the surface are 35.7% and 49.2%, respectively. When G4 and G5 PPI dendrimers are surface-wrapped with lactose, the hemolysis rates decrease to 10% and 7.1%, respectively. Anionic dendrimers do not exhibit hemolytic toxicity. Additionally, dendrimer macromolecules have cytokine toxicity. They typically regulate the release of reactive oxygen species (ROS), which governs cytokine release. This can be a useful therapeutic approach, but it can also lead to significant toxic reactions. For example, as the generation of polyamidoamine (PAMAM) dendrimers increases, the densely packed terminal amino groups on the surface generate a large amount of reactive oxygen and cytokines within the cells. Excessive cytokines induce cell toxicity, and at high concentrations, they can even cause cell apoptosis. The strategies for addressing the toxicity issues mainly include two approaches: first, the use of biocompatible or biodegradable materials, such as polyesters, polyacetal, peptides, polyethers, polyetherimide, phosphates, melamine, and triazines; second, the surface modification of dendrimers, such as pegylation, acetylation, glycosylation, peptide conjugation, antibody conjugation, tuftsin (a substance that promotes phagocytosis of bacteria by polymorphonuclear leukocytes) conjugation, folate conjugation, semi-dendrimerization, and drug conjugation. Additionally, dendrimers may have weak immunogenicity depending on the end groups and particle size. Current research indicates that dendrimers may exhibit weak immunogenic reactions or no immune response. Similarly, studies on G5 polypropyleneimine dendrimers have shown no detectable humoral immune response. This suggests that dendrimers, as a nanodrug delivery technology, may not be recognized by the host immune cells as "invaders" and cleared, which helps transport drugs to the site of lesions [128].

3.5.2. Application of dendrimers in the diagnosis and treatment of kidney diseases

The lack of nitric oxide (NO) plays a role in renal ischemia/reperfusion injury and kidney-targeted NO donors are expected to prevent renal ischemia/reperfusion injury. Research has developed a polyamidoamine dendrimer modified with S-nitrosated L-serine (SNO-Ser-PAMAM), in which multiple S-nitrosothiols (NO donors) are covalently bound to L-serine-modified dendrimers, serving as a kidney-targeted NO donor. In a mouse model of renal ischemia/reperfusion injury, intravenous injection of SNO-Ser-PAMAM effectively inhibits the elevation of plasma creatinine, renal injury markers, and histological changes [16]. In addition to therapeutic applications, dendrimer drug delivery also plays a role in diagnosing diseases. The second-generation polypropyleneimine diaminobutyl (DAB) dendrimer (DAB-G2), with a molecular weight of approximately 14 kDa, can be rapidly excreted from the body and has significant advantages in detecting early-stage renal tubular damage [17].

3.6. Other nanodrug materials

RNA self-assembling nano-delivery carriers have shown great potential in the biomedical field, to some extent addressing the urgent need for improvement in drug delivery. Due to its high biocompatibility and in vivo selectivity and the rapid development of RNAi therapy technology, RNA nano-assemblies have received widespread attention in drug delivery, especially in gene-drug delivery in recent years. Rolling circle transcription (RCT) technology can transcribe reproducible long RNA single strands in vitro. Various functional units can be included in the assembly by designing specific templates. Additionally, by controlling the transcription conditions, the morphology and size of RCT self-assembling nanostructures can be controlled, efficiently synthesizing structurally dense and stable RNA nano-carriers within a certain period. Furthermore, RNA can form densely structured, programmable, and relatively stable polymer aggregates through chemical conjugation or hybridization self-assembly. Strategies such as thiol modification have been widely applied in RNA conjugation self-assembly research. Interactions between RNA single strands can achieve self-assembly by forming cleavable disulfide bonds. This strategy increases the density of RNA nanostructures, prolongs their circulation time in the bloodstream, and provides opportunities for stimulus-responsive drug release, thereby improving therapeutic effects. RNA has made initial progress in a mouse polycystic kidney model, where knocking out AC5 with siRNA reduced the cAMP level in Pkd2-deficient kidney epithelial cells, lowering the cyst index and demonstrating breakthrough therapeutic value [129]. Extracellular vesicles (EVs) belong to cell-derived vesicles, mainly secreted into the extracellular matrix by the fusion of specific intracellular organelles known as multivesicular bodies with the plasma membrane. They are endogenous vesicles (30–200 nm) that regulate intercellular communication, exhibiting good biocompatibility and targeting ability. Surface modification can hold their in vivo targeted delivery. Currently, surface modification strategies mainly include chemical modification and genetic engineering. Chemical modification especially involves coupling functional components to lipids or membrane-bound proteins through chemical reactions. For instance, extracellular vesicles modified with PSMA peptide ligands can deliver siRNA to xenografts in vivo and induce tumour regression. Genetic engineering modification is another method of extracellular vesicle modification. Researchers fuse the gene sequence encoding the target protein or peptide with the gene sequence of a specific extracellular vesicle membrane protein using genetic engineering technology to achieve the delivery of the target protein with the help of the extracellular vesicle membrane protein. This method requires specific structural and size considerations for the target protein/peptide and the extracellular vesicle membrane protein, which must be carefully considered in practical applications. Shang et al. found that exosomes derived from mesenchymal stem cells (MSC-Exos) exhibit beneficial effects on wound healing through anti-inflammatory and angiogenic properties, providing a potential strategy for using exosomes to improve inflammatory responses and ischemic kidney injury in kidney diseases [130]. Adeno-associated virus (AAV) is a commonly used vector in gene therapy. AAV is a vector for gene therapy targeting other organs and has been particularly successful in monogenic diseases, such as genetic kidney disease syndrome [19]. Low molecular weight proteins are used as carriers to target the kidneys. Lysozyme (14 kDa) is a common choice and has been used to target many small-molecule drugs in the kidneys, including naproxen [20], methylprednisolone [21], various kinase inhibitors [22], and traditional Chinese medicine [23]. Peptide structures can also serve as drug carriers. Elastin-like polypeptides (ELPs) are non-toxic, minimally immunogenic nanoscale drug carriers made from a simple pentapeptide repeat sequence. They can be designed with acid-labile or protease-cleavable linkers for drug release under specific cellular conditions (e.g., in the acidic environment of lysosomes or through intracellular proteases after endocytic uptake) [24]. Unmodified ELPs are reabsorbed in the proximal tubules after kidney

filtration, with the accumulation in the cortex or medulla determined by the size of the ELP. Unmodified ELPs are an ideal method for targeting drugs to the proximal tubules. The accumulation levels of all ELPs in the kidneys are much higher than in other organs, with intermediate-sized ELPs having the highest total levels (37–74 kDa) [25]. Yuan et al. tested several chitosan molecular weights and found that plasma clearance rates slowed with increasing molecular weight, with the optimal size for kidney targeting being 19 kDa [27].

4. Challenges and prospects of targeted therapy for kidney disease with nanodrug materials

The most ideal delivery system is to transport drugs to the lesion site, where the drug carrier is then degraded and metabolized in the normal physiological environment without accumulation. Currently, most targeted drugs are still in the preclinical stage, and the administration route often involves invasive injection, indicating that there are still limitations in kidney-targeted drug delivery carriers. When treating kidney diseases, and pharmaceutical experts face the daunting task of designing an ideal platform to deliver therapeutic drugs to kidney tissues, as the kidneys tend to excrete drugs from the body. Many nanoparticle drugs are already in clinical trials, indicating that nanoparticle drugs are expected to become an important treatment modality. As for most current research, AKI is the most beneficial kidney disease for nanoparticle therapy, due to the ischemic and hypoxic conditions caused by acute injury. This implies that kidney damage caused by factors such as inadequate effective circulating volume, ischemia-reperfusion, drug toxicity, etc., may benefit from these nanoparticle drugs. Further preclinical or clinical experiments are still needed to verify whether these nanoparticle drugs are more beneficial as preventive treatments or therapeutic measures. CKD also benefits from nanoparticle therapy, including anti-fibrotic effects and podocyte and mesangial cell function protection. This implies that CKD resulting from podocyte and mesangial cell damage, such as diabetic nephropathy [131], may also benefit. At the same time, the use of natural or endogenous substances to create nano-drug materials brings the advantage of good biocompatibility. Still, it may also lead to the body being exposed to iatrogenic pathological conditions. For example, hyaluronic acid exists in both low molecular weight form (<120 kDa) [132] and high molecular weight form (>900 kDa) [133] in healthy tissues. Recently, Kaul et al. found that high molecular weight hyaluronic acid is beneficial in mediating kidney diseases, while low molecular weight hyaluronic acid is associated with harmful effects [134]. Liposomes are a relatively mature drug delivery technology, but they are still primarily administered through injection. According to the principle of safety, oral administration is preferred over injection. Overcoming the first-pass effect of liposomes and avoiding drug degradation in the gastrointestinal tract are challenges that need to be addressed in liposomal nanodrug delivery. The physicochemical properties of dendrimers have been proven to be a promising drug delivery system. However, their development is less mature than liposomes, microspheres, emulsions, and other technologies. This is because dendrimers are mainly chemically synthesized for drug delivery, which is costly. In contrast, drug formulations mostly use physical methods for drug encapsulation and delivery, leading to a lack of theoretical basis and production equipment in many formulation development organizations. Additionally, the toxicity of dendrimer materials is an essential factor affecting their development. The focus of reducing material toxicity lies in modification, such as glycosylation, acetylation, polyethylene glycol (PEG)ylation, or peptide modification, to neutralize cationic cytotoxicity or make dendrimers biodegradable [135]. A current research hotspot is using nanoparticles, liposomes, and hydrogels as nanodrug carriers. As shown in Supplementary Fig. 2 (searching the PubMed database using keywords “nanomaterial,” “Nanoparticle,” “Hydrogel,” “Liposome,” “Micelle,” “Dendrimer,” or “Mesoporous material,” and “Drug Delivery” to create a trend chart based on the number of achievements), there is still significant innovation space for nano drug materials in the future.

When selecting nanodrug materials, minimizing potential hazards is crucial for successfully translating biotechnology to clinical applications. As the main organs for clearing foreign substances, the kidneys filter approximately one-quarter of the blood output by the heart. Therefore, reducing the renal toxicity induced by nanomaterials is an essential goal in developing nanomedical drugs. The biocompatibility and safety of nanomaterials can be improved by adjusting the material size, charge, and surface chemical composition to reduce harmful interactions with the glomerular basement membrane (GBM) and the cells of the renal filtration barrier [136]. In various preclinical applications, the concentration of nanomaterials has been optimized to achieve the expected therapeutic effects. However, the extent of biological accumulation resulting from repeated doses in long-term use remains unknown. The impact of organ cross-talk, liver-kidney coupled metabolic degradation pathways, and the intraorgan transport of nano drugs with different physicochemical properties is still largely unexplored. For example, it is widely accepted that the surface charge of biomaterials determines their interaction with the GBM of the glomerulus. Still, the effect of charge on the liver’s metabolic degradation of biomaterials remains unknown. Nano drugs can accelerate the effective clearance rate of the liver and kidneys to reduce systemic exposure and toxicity, but this contradicts the desire to avoid liver uptake and accumulation in kidney cells to prolong therapeutic effects. Current research strategies may focus on using natural, biocompatible, and readily biodegradable materials to minimize the risks of toxicity and biological accumulation while promoting the effective and safe clearance of biodegradation products from nanomaterials [137,138].

In conclusion, nanomedicine is gradually gaining attention, and developing drug delivery systems based on nanotechnology is crucial. Finding suitable drug carriers is essential for controlling drug release and improving pharmacokinetics and pharmacodynamics. New evidence supports the feasibility of nanodrug technology, but most research is still in the preclinical stage. Preclinical data supports the potential of kidney-targeted therapy for restoring kidney function and reducing kidney damage. Still, there are also reports indicating that the cytotoxic characteristics of nanodrugs may lead to macrophage destruction and potential immune suppression. In summary, nano drug technology offers promising prospects for kidney disease, and we should pay attention to the selection of nanomaterials.

CRediT authorship contribution statement

Shunlai Shang: Visualization, Validation, Supervision, Resources, Project administration, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Xiangmeng Li:** Writing – original draft, Visualization, Validation, Resources, Formal analysis, Data curation, Conceptualization. **Haoran Wang:** Writing – original draft, Visualization, Software, Project administration, Investigation, Formal analysis, Conceptualization. **Yena Zhou:** Visualization, Validation, Software, Methodology, Data curation. **Keying Pang:** Visualization, Software, Methodology, Investigation, Conceptualization. **Ping Li:** Visualization, Resources, Project administration, Investigation, Funding acquisition. **Xiaomin Liu:** Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization. **Min Zhang:** Visualization, Resources, Project administration, Investigation, Funding acquisition, Data curation, Conceptualization. **Wenge Li:** Validation, Supervision, Software, Resources, Investigation, Formal analysis, Data curation. **Qinggang Li:** Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Formal analysis, Data curation, Conceptualization. **Xiangmei Chen:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declared that they have no conflicts of interest to this paper. Figures were created with BioRender software (https://app.biorender.com/).

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Appendix ASupplementary data

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