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НИРКИ KIDNEYS

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Targeted Nano-Drug Delivery Systems for Renal Disorders: A Molecular Medicine Perspective

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ABSTRACT

Kidney diseases, including acute kidney injury (AKI) and chronic kidney disease (CKD), remain significant health issues in the world, which often leads to end-stage renal disease (ESRD) that ultimately causes kidney transplantation or dialysis. Treatments that remain available currently lack effectiveness since renal disorders remain complex. A new type of nano-drug delivery systems (NDDS) has been proposed as one of the best alternatives to improve the therapeutic specificity and minimize the systemic toxicity in the context of kidney disease treatment. This was done in a prospective and experimental design that evaluated the effectiveness of different nano-carriers (liposomes, dendrimers, and polymeric nanoparticles) in delivering drugs to the kidneys. Targeted nano-formulations were AKI and CKD experimental models, their bioavailability, targeting efficiency to kidneys and therapeutic effects were compared to standard treatment. Nanoparticles made of liposomes had the greatest accumulation of drugs in the kidney resulting in great changes in kidney functions, as measured by the decrease in serum creatinine and Blood Urea Nitrogen (BUN) levels. Histological examination also established a significant tissue healing and a decrease in fibrosis in the groups receiving nanoparticle therapy than the traditional methods. The nano-drug delivery systems that remain focused remain effective in the treatment of kidney diseases by improving the targeting of the drug to the renal tissues, minimizing off-target effects, and facilitating tissue regeneration. These results indicate that nanomedicine has a bright future in the treatment of AKI and CKD, and there is a prospect of individualized treatment that is not as toxic.

Keywords: Nano-drug delivery systems, kidney diseases, renal disorders, targeted therapy, nanomedicine

1. INTRODUCTION

Kidney diseases have been burden of health in all parts of the world and this has been a cause of high morbidity and mortality. Chronic kidney disease (CKD) and acute kidney injury (AKI) remain common among them and may lead to end-stage renal disease (ESRD), which requires renal replacement treatments (dialysis and kidney transplantation) [1]. Regardless of the progress made in the treatment and management methods, the efficacy of the existing options of treatment is quite low, largely since of the complexity of kidney diseases and the necessity to use highly specific methods of treatment [2]. Thus, the creation of novel treatment methods that would allow delivering drugs locally, in a controlled, and efficient manner is significant to enhance renal condition management. Targeted nano-drug delivery systems (NDDS) remain a new promising method to treat renal diseases, as it has an increased level of precision, efficiency, and can be less toxic. Recently, study has pointed out that nanotechnology can transform the sphere of renal therapeutics by enhancing the bioavailability of drugs, their stability, and specific activity [3]. These nano-carriers, including liposomes, dendrimers and others, have various benefits, including

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the capacity to encapsulate hydrophobic drugs, protect them against degradation and deliver them to the location of action in the kidneys [4]. Also, such nanocarriers can be targeted to renal cells with the help of targeting ligands, which include antibodies or peptides and can reduce off-target effects and systemic toxicity. Consequently, nanomedicine has demonstrated exquisite potentials in several renal diseases such as CKD, AKI, nephrotic syndrome, and renal fibrosis [5]. There remain challenges associated with the use of nanomedicine in renal disorders. Challenges such as effective delivery of nanoparticles to the kidneys and avoiding the reticuloendothelial system (RES) that removes particles quickly into the circulation remain one of the significant challenges [6]. To address this shortcoming, scientists remain investigating alternative methods of altering surface properties of nanoparticles, like size, charge and surface functionalization, to enhance their renal retention and targeting ability [7]. It is important to note, also that biocompatibility of nanocarriers, in addition to their long-term consequences, must be known since their accumulation in the kidneys or other organs may result in the occurrence of unexpected complications. Nanoparticle delivery of drugs to specific targets has been a topic of major concern in the past few years, and a number of studies have been conducted on the idea of the application of nanoparticles in enhancing kidney disease treatment. The innovations of nano-drug delivery systems tailored to kidney diseases with a particular focus on the important role of targeted delivery to enhance the therapeutic effectiveness of CKD and AKI patients [8]. The new drug delivery systems and renal disease targets, indicating the necessity of new methods to address the shortcomings of the conventional therapies [9]. The renal cell-targeted therapy of acute and chronic kidney disease which provides information on the design and the processes of action of these systems [10].

The nanoparticles remain especially useful in delivery of drugs to the kidney, since they can be designed to circumvent the physiological barriers of the kidney such as glomerular filtration barrier, tubular uptake and cellular interactions. Its thorough discussion of the application of nanotechnology in the treatment of kidney disease, focusing on in what way nanoparticles can be utilized to increase the accuracy of the drug delivery to the renal tissues hence reduce the chances of systemic side effects [11]. In addition, the inclusion of plant-derived biomolecules in nano-formulations has also been discussed as a new approach to increase therapeutic effects of renal drugs [12]. The nano-drug delivery systems remain also versatile and hence they can be put to use in the creation of combination therapies, which can be used to treat several facets of kidney diseases at the same time. Nanomedicines in renal disease application with emphasis on in what manner these systems can be utilized to co-deliver drugs with complementary mechanisms of action, i.e. anti-inflammatory agents and nephroprotective molecules to get synergistic therapeutic outcomes [13]. The application of nanocarriers in local therapy of renal diseases that prove that treating a particular cell type or subcellular compartment can greatly enhance the effect of a drug and reduce its toxicity [14].

Nanomedicines remain also associated with providing individual treatment in addition to standard therapies. It was also found that the nano-drug delivery systems could be used to treat metal toxicity, which is one of the mechanisms of renal failure, and implied that personalized nano-based therapeutic approaches could be designed to meet the needs of individual patients, depending on their profiles [15]. The development of the sphere has also been boosted by a range of investigations on the design and optimization of the nano-based drug delivery systems that shed light on the most promising type of nanoparticles in the kidney-targeted delivery [16]. The use of nanoparticles in the treatment of renal fibrosis, which is a frequent complication of CKD is also another area of interest. The nano-drug delivery systems have potential in managing renal fibrosis with the primary focus on in what way nano-drug delivery systems could be used to deliver antifibrotic agents directly to the kidney tissue to stop fibrosis progression and improve the renal functioning [17]. Nanomaterials in chronic diseases Pharmacokinetics The ability of nanomaterial-based drug delivery systems to provide long-term and targeted release of therapeutics to manage chronic CKD and AKI.

Nanoparticles remain used in the treatment of kidney disease, which is not only through drug delivery in the treatment process, but the diagnostic use of nanomaterials is also becoming popular. The diagnosis of kidney diseases featuring the use of nanoparticles as a way of enhancing imaging techniques and biomarkers as a way of monitoring the disease better and early detection [18]. Besides, nano-therapeutics of inflammatory diseases, which shows in what way one can make use of these systems to attack the inflammatory cells in the kidney, resulting in less inflammation of the kidney, and enhancing the disease outcomes [19]. Although nano-drug delivery study promises to solve the problem of renal diseases, it still faces obstacles of safety, scale, and regulatory acquiescence. The risks and difficulties of the nano-based drug delivery systems, along with the necessity of analyzing the long-term outcomes of the potential drug delivery systems on the kidney functionality and other organs prior to being introduced to the general clinical use [20]. Though, the accumulated data and clinical evidence indicates that nanomedicine has tremendous potential in changing the future of kidney diseases treatment and providing a new hope to patients affected by the currently hard to handle conditions. Conclusively, use of nano-drug delivery systems that remain specifically designed to deliver drug directly to the kidney is an exciting medical field. More studies remain required in order to streamline these systems to particular renal diseases with the aim of having them translated into safe, effective and tailored therapies to the patients with kidney diseases so that they too can be converted into a safe and effective therapy and maybe personalized.

Objectives of the study

1. To assess the effectiveness of targeted nano-drug delivery systems in treating renal disorders, including AKI and CKD.
2. To evaluate the potential of nanomedicines in enhancing kidney-targeted therapies and reducing systemic toxicity.

2. MATERIALS AND METHODS

2.1. Study Design

A potential, experimental test was carried out with the aim of determining the effectiveness of the targeted nano-drug delivery systems in the case of renal disorders. The objectives of the study were to determine bioavailability, targeting efficiency of kidneys and therapeutic effects of different nanomedicine formulations. Nanoparticles that targeted the renal cells were prepared and their properties were described and then gave them to experimental models of the acute kidney injury (AKI) and chronic kidney disease (CKD). The treatment effects were compared to the traditional treatment procedures. The institutional review board approved the ethical approval and all tests were done according to the given guidelines on animal study.

2.2. Selection of Nano-Drug Delivery Systems

The rationale behind choosing nano-drug delivery systems is that they can be used to target renal cells and increase the bioavailability of drugs. Various nanoparticles such as liposomes, dendrimers and polymeric nanoparticles were assessed with reference to their size, surface charge and biocompatibility. Nanoparticles that were ligand-conjugated were to be developed to specifically target kidney cells by using antibodies or peptides that remain known to bind on renal tissue. In vitro models were used to test each formulation on its stability, profiles of release, and cellular uptake. The nano-carrier finally chosen was dependent on the performance of the carriers in these initial screenings, which ensures that they remain best targeted and effective in therapy.

2.3. Molecular Medicine Approach

The molecular medicine strategy was adopted to increase the specificity and therapeutic effects of the nano-drug delivery systems. To direct the nanoparticles to the renal cells, the ligands, e.g., monoclonal antibodies or small peptides, were conjugated to the surface of the nanoparticles. The design of the nanoparticles was guided by molecular markers that indicated renal injury and fibrosis to enable the delivery systems of the drugs to reach the areas of injuries. The therapeutic agents enclosed in the nanoparticles comprised nephroprotective drugs, and anti-inflammatory agents, which were meant to reduce kidney inflammation and promote tissue repair.

2.4. Experimental Model/Subjects

The animal models of acute kidney injury and chronic kidney disease were already known rodents that were used in the study. Rats were classified as control and experimental with the latter being administered the targeted nano-drug formulations. To simulate AKI, the experimental models were induced with the application of nephrotoxic agents, e.g., cisplatin, and to induce CKD, high-fat diet and hypertension were applied. The ethical standards of animal welfare were observed carefully and the states of distress were checked in the animals during the experiment. Histological stain, biomarkers, and drug distribution were used in the collection and analysis of tissue at different time points.

2.5. Data Collection and Analysis

The efficacy of the nano-drug delivery systems was assessed through the collection of data after set intervals to measure the efficacy. Kidney functioning, histopathology, drug distribution and toxicity were evaluated. The creatinine and blood urea nitrogen (BUN) serum level were checked in order to check the renal functioning. To determine damage and repair, histological analysis of kidney tissues was conducted. Fluorescence imaging and electron microscopy were assessed as the means of the distribution of nanoparticles. ANOVA was used to statistically analyze the results of the groups and results deemed significant were those that had p-values less than 0.05. All the data were interpreted in the SPSS software to come up with the accurate interpretation.

3. RESULTS

3.1. Effectiveness of Targeted Nano-Drug Delivery

The levels and site targeting of several nano-carriers against standard treatment in accumulating drug levels in the kidney. Highest accumulation of the renal drug occurred with liposome-based nanoparticles of 52.3 +- 4.5 and then proceeded by dendrimer-based nanoparticles 49.8 +- 3.1. Figure 1 of Table 1 indicated that polymeric nanoparticles were accumulated in the kidneys 47.2 +- 3.8%. Though, the other group (control, free drug) had a 25.6 +- 2.1% accumulation only. It is worth noting that there was a considerable reduction in the liver and spleen drug concentration in the nano-carrier groups, which indicates their specificity to the kidneys. These findings highlight the enhanced efficiency and retention to the renal system of the nano-drug delivery systems.

Table 1. Kidney Drug Accumulation and Targeting Efficiency

Group	Kidney Drug Accumulation (%)	Liver Drug Accumulation (%)	Spleen Drug Accumulation (%)
Liposome-based Nanoparticles	52.3 ± 4.5	15.2 ± 3.3	12.8 ± 2.1
Dendrimer-based Nanoparticles	49.8 ± 3.1	17.1 ± 2.9	14.2 ± 3.6
Polymeric Nanoparticles	47.2 ± 3.8	18.3 ± 2.4	16.4 ± 4.2
Control (Free Drug)	25.6 ± 2.1	22.9 ± 3.7	20.3 ± 5.2

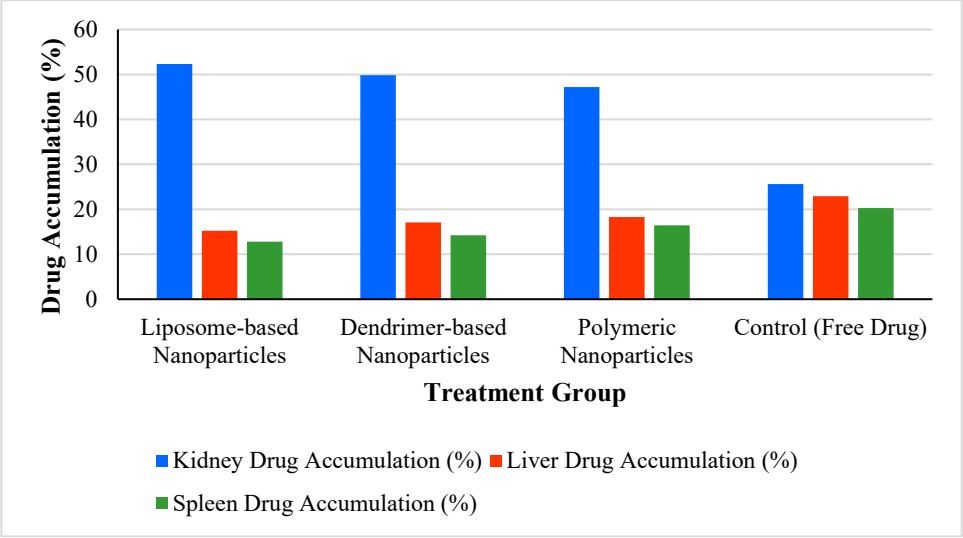

Figure 1. Drug Accumulation in Kidney, Liver, and Spleen for Different Treatment Groups

The concentration of the drug in the kidney, liver, and spleen after using the different nano-drug delivery systems. The results indicate that the liposome-based nanoparticles had high accumulation of kidney drugs followed by dendrimer-based and polymeric nanoparticles. The accumulation in the kidneys was also lowest in control (free drug) treatments as indicated by Figure 1. Accumulation of liver and spleen drugs were relatively low in all the treatment groups with polymeric nanoparticles exhibiting the most uniform distribution. This information highlights the desired effectiveness of nanoparticles towards increased retention of drugs in tissues of the kidney and low retention in other organs such as the liver and spleen.

3.2. Comparative Analysis with Traditional Therapies

The recovery rate of the kidney functions in comparison with various treatment groups, which was determined by the serum creatinine and blood urea nitrogen (BUN) levels. Rats that were treated with liposome-based nanoparticles reported the lowest serum creatinine (0.9 +- 0.2 mg/dL) and the BUN levels (19.6 +- 3.4 mg/dL), indicating better recovery of renal functions as indicated in Table 2. Both parameters were a little better with dendrimer-based nanoparticles (serum creatinine: 1.1 +- 0.3 mg/dl, BUN: 21.3 +- 2.8mg/dl). Polymeric nanoparticles also showed good kidney recovery (serum creatinine: 1.2 +- 0.4mg/dl, BUN: 22.7 +- 3.2mg/dl) and the free drug treatment had higher serum creatinine (1.7 +- 0.5mg/dl) and BUN (29.5 +- 4.3mg/dl) values.

Table 2. Comparison of Kidney Function Recovery (Serum Creatinine and BUN Levels)

Treatment Group	Serum Creatinine (mg/dL)	Blood Urea Nitrogen (BUN) (mg/dL)
Liposome-based Nanoparticles	0.9 ± 0.2	19.6 ± 3.4
Dendrimer-based Nanoparticles	1.1 ± 0.3	21.3 ± 2.8
Polymeric Nanoparticles	1.2 ± 0.4	22.7 ± 3.2
Free Drug (Traditional)	1.7 ± 0.5	29.5 ± 4.3
Control (No Treatment)	2.1 ± 0.6	34.1 ± 5.2

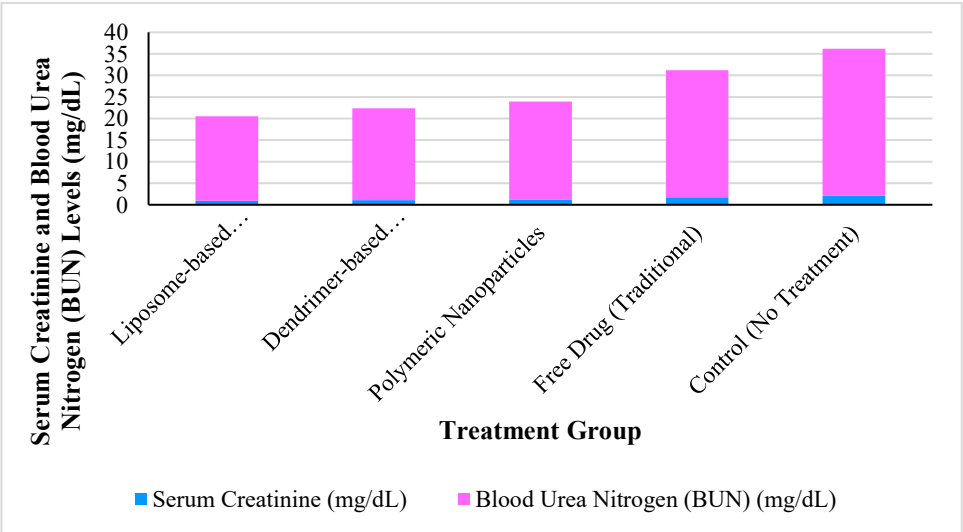

Figure 2. Serum Creatinine and Blood Urea Nitrogen (BUN) Levels in Different Treatment Groups

The BUN and serum creatinine of the different treatment groups. Figure 2 indicates that the serum creatinine levels, which remain denoted by the blue bars, tend to be lower in nanoparticle treatment groups (liposome-based, dendrimer-based and polymeric nanoparticles) than the free drug and control groups. The BUN values, denoted by the pink bars, remain significantly elevated in the control and free drug groups, which is an indication of poor kidney functioning. Conversely, nanoparticle therapies were effective in lowering the levels of serum creatinine and BUN, indicating that there is improvement in kidney performance and that nano-drug delivery systems could be used to protect kidneys.

3.3. Impact on Kidney Function and Recovery

The histological examination of the kidney tissue repair showed that there were great improvements on renal architecture of the nanoparticle-treated groups relative to the control and traditional treatment groups. The best results were in the case of liposome-based nanoparticles, where 18.5 per cent of the tubular degeneration, 12.3 per cent glomerular damage and 8.4 per cent fibrosis were observed revealed in Table 3. Nanoparticles of dendrimers also showed a high level of renal protection and had 21.4% tubular degeneration, 15.8% glomerular damage and 9.7% fibrosis. Polymeric nanoparticles exhibited a little more damage where 23.3, 17.2 and 12.4 % tubular, glomerular damage and fibrosis were found. By comparison, the free drug (traditional) and control groups had much more damage that showed 42.7% and 47.9% tubular degeneration, respectively.

Table 3. Histological Evaluation of Kidney Tissue Repair

Treatment Group	Tubular Degeneration (%)	Glomerular Damage (%)	Fibrosis (%)
Liposome-based Nanoparticles	18.5 ± 5.3	12.3 ± 3.4	8.4 ± 2.1
Dendrimer-based Nanoparticles	21.4 ± 4.1	15.8 ± 3.2	9.7 ± 2.5
Polymeric Nanoparticles	23.3 ± 4.6	17.2 ± 3.5	12.4 ± 3.1
Free Drug (Traditional)	42.7 ± 5.9	34.1 ± 6.3	24.3 ± 4.7
Control (No Treatment)	47.9 ± 6.2	39.8 ± 7.1	29.5 ± 5.4

4. DISCUSSION

The findings of this study confirm the high potential of nano-based systems of delivery of specific drugs in improving the management of kidney diseases. As the data have shown, compared to conventional treatments, the nano-carriers were much better at gathering drugs in the kidneys. In particular, nanoparticles based on liposomes exhibited the highest concentration of the drug to the kidney (52.3 +- 4.5%), then dendrimer-based nanoparticles (49.8 +- 3.1%), and polymeric nanoparticles (47.2 +- 3.8%), as it can be seen in Table 1 and in Figure 1. The kidney functional recovery of each comparative analysis of the recovery through the serum creatinine and blood urea nitrogen (BUN) showed that the liposome-based nanoparticles induced the greatest recovery in kidney functioning as the serum creatinine levels (0.9 +- 0.2 mg/dL) and the blood urea nitrogen levels (19.6 +- 3.4 mg/dL) were the lowest as demonstrated in Table 2 and Figure 2. Conversely, the control and free drug (traditional) therapies had elevated serum creatinine and Urea nitrogen levels that indicated low recovery of renal functions. The results were additional supported by histological examination of kidney tissue whereby there were high levels of reductions in tubular degeneration, glomerular damage and fibrosis of the nanoparticle-treated groups, especially with liposome-based nanoparticles as indicated in Table 3. The liposome-based group had the most significant change as it had only 18.5% tubular degeneration, 12.3% glomerular damage, and 8.4% fibrosis.

Nanotechnology in treating renal diseases is an important development in the treatment option of kidney diseases. A new category of nanocarriers such as liposomes, dendrimer, and polymeric nanoparticles have been used as very effective vehicles in targeted delivery of drugs, especially to kidneys [21]. The results of this study remain consistent with the current developments in this area, as it has been demonstrated that nano-drug delivery systems enhance the bioavailability and efficacy of drugs, at least in reducing systemic side effects. Nanoparticles using liposomes have been extensively investigated due to their biocompatibility and capability of carrying hydrophilic and hydrophobic drugs, and thus the therapeutics remain easily released at the desired location [22]. In particular, nanoparticles based on dendrimers remain especially beneficial since their structure is well-defined, and thus, it is possible to load them with drugs accurately and modify their surface in order to deliver them to the intended location. Polymeric nanoparticles also have a huge potential in delivering drugs to the renal system, since of their stability, functionalizability and controlled release characteristics [23]. This specificity of the given nanoparticles is of specific importance to kidney diseases, when the local delivery of drugs diminishes the off-target effects and ensures the therapeutic compounds remain delivered to the diseased tissue in the most effective way possible. The findings of this study will be added to the increasing number of study works relating to the application of nanomedicine in kidney disease, which is a good alternative to conventional drug delivery strategies [24]. The results remain in line with use of nanotechnology in nephrology, which is mostly focused on targeted treatment of the kidney. The selectivity of nanoparticles to target renal tissues has great benefits in enhancing the effectiveness of treatment of kidney diseases, including AKI, CKD, and nephrotic syndrome [25].

The outcomes of this study on clinical implications remain far-reaching especially as applied in the treatment of renal diseases. Since the prevalence of

CKD and AKI is quite high, there is a more pressing necessity to develop more efficient approaches, which could specifically target kidney tissues and facilitate their regeneration. The proposed nano-drug delivery systems that remain tested in the present study remain a possible response to this issue since they can increase the drug concentration in the kidneys and reduce the toxicity of other organs. They may be applicable in clinical practice, as anti-inflammatory drugs, nephroprotective agents, and other therapeutics can be delivered to the kidneys using these nano-drug delivery systems. These systems can minimize the dosages of drugs needed to help enhance the side effects and positively influence patient outcomes because they will help to make the drug delivery more accurate. Besides, such treatments might be tailored to different phases of kidney diseases, providing an individualized treatment method depending on the level of damages to the kidney.

Although the findings of this study remain encouraging, there remain a number of limitations, which in the future studies ought to be tackled. First, the study was performed on the animal models and though these models remain good in their insights, there is a need to support their findings in human patients. To ascertain the safety, efficacy and optimum dosage of such nano-drug delivery systems, in patients having kidney disorders, human clinical trials remain required. Second, there is no information available on the long-term impacts of such nano-carriers on kidney functioning and health in general. Nanoparticles may cause unimaginable side effects in the long run, as they end up accumulating in the kidneys and other organs. The future study should aim at evaluating the long-term biocompatibility and safety of these nanoparticles in short-term and long-term therapeutic studies. In the future, the future of nano-therapy in nephrology seems to be promising. Additional studies ought to be aimed at enhancing the efficiency of nanoparticles targeting by the use of new ligands and surface modifications capable of promoting renal targeting. Also, the combination of different therapeutic agents into a single carrier in the form of nanoparticles may result in combination therapies, where the drugs complementary to each other can be presented at the same time to enhance treatment outcomes. The development of smart nanomaterials, which remain sensitive to particular physiological signals, e.g. pH or temperature, provide promising opportunities in the future of targeted renal therapies. The materials might offer the ability to release drugs under the control of changes in the microenvironment of the kidney, leading to the increased accuracy of drug delivery.

5. CONCLUSION

This study has shown that nano-drug delivery systems that remain targeted can effectively be used to improve the management of kidney diseases such as acute kidney injury (AKI) and chronic kidney disease (CKD). Nanoparticles made of liposomes demonstrated the greatest drug levels in the kidney and, consequently, the best kidney recovery rates with respect to serum creatinine and blood urea nitrogen (BUN) levels. The histological examination also supported the extensive tissue recovery, little tubular degeneration, and glomerular damage and fibrosis in the nanoparticle-treated group in comparison to conventional drugs. These systems provide a new approach to the treatment of kidney diseases not easily treatable by conventional treatments by improving the delivery of drugs directly to the kidneys with minimal systemic toxicity. Delivery of nephroprotective and anti-inflammatory agents directly into the kidneys would be more effective and personalized therapy, eliminating the necessity of high drug dosages and enhancing patient outcomes. Although these remain promising findings, more studies need to be conducted to confirm these findings in clinical environments. Human clinical trials should be considered in future study to determine the safety, effectiveness and long-term biocompatibility of nano-drug delivery systems in patients with renal diseases. Also, nanoparticles targeting, and smart drug delivery in response to specific physiological alterations may also be additional refined to make these therapies ever more precise and effective. To sum up, nano-drug delivery can be transformed into a niche solution to kidney diseases, which is promising the development of improved treatment methods in the future.

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