

Review

Promising Therapeutic Strategies Targeting Mitochondria in Kidney Diseases: From Small Molecules to Whole Mitochondria

Alexis Paulina Jiménez-Uribe  and José Pedraza-Chaverri * 

Departamento de Biología, Facultad de Química, Universidad Nacional Autónoma de México, Mexico City 04510, Mexico; jimenez.uribe.ap@comunidad.unam.mx

* Correspondence: pedraza@unam.mx

Abstract: Kidney function highly depends on mitochondria, organelles that regulate different metabolic pathways. Mitochondria-altered function and structure are present during acute kidney injury (AKI) and chronic kidney disease (CKD). Targeting mitochondria using several strategies has been shown to improve kidney function. Here, we review some experimental mitochondria targeting strategies with clinical potential in kidney diseases encompassing cationic/lipophilic small molecules, peptides, nanocarriers, and even the entire organelle.

Keywords: mitochondrial alterations; kidney diseases; mitochondria targeting therapy



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1. Introduction

Kidneys are among the most energy-demanding organs due to their filtration and reabsorption functions. In particular, the proximal tubular segment of the nephron consumes large amounts of energy in the form of adenosine triphosphate (ATP) provided by oxidative phosphorylation, a metabolic process performed in the mitochondria [1].

In addition to their energy-producing function, mitochondria also exert other metabolic processes such as glutaminolysis, the catabolism of branched-chain amino acids, fatty acid beta-oxidation, nucleotide biosynthesis, heme metabolism, redox balance, the management of metabolic by-products, cellular death regulation, calcium homeostasis, etc. [2,3].

Acute kidney injury (AKI) is characterized by an abrupt reduction in kidney function due to pre-renal, renal, and post-renal causes such as the reduction of blood supply, nephrotoxins, and obstruction, respectively [4]. On the other hand, chronic kidney disease (CKD) is characterized by the progressive and irreversible loss of kidney function and structure for more than three months and may be a consequence of other conditions such as diabetes, hypertension, or aging [5].

AKI and CKD are related to each other since the presence of one could predispose the development of the other [6–8]. In addition to their complicated pathophysiology, several mitochondrial alterations have been reported in both pathologies, contributing to their progression.

In different experimental AKI models, mitochondrial morphological alterations are prevalent in tubular segments, showing fragmentation, swelling, and the loss of cristae; moreover, functionality is also compromised, with reduced electron transport chain (ETC) activity, a loss of membrane potential, and increased reactive oxygen species (ROS) production as a consequence [9–15]. Interestingly, these alterations also persist during AKI to CKD progression [16–18]. Similarly, in established CKD, mitochondrial alterations are present, showing low membrane potential and consequently reduced ETC activity and overproduction of ROS [19–21]; on the other hand, morphological alterations such as mitochondrial fragmentation have been noticed, especially in podocytes [21–24].

ROS overproduction is present in AKI and CKD, representing a therapeutic target since their abrogation reduces tissue damage and improves kidney function [25–34]. ROS are

well-known inducers of the inflammatory response through the activation of the transcription factor nuclear factor kappa B (NF- κ B) [35]; moreover, mitochondria-derived ROS are activators of the NLR family pyrin domain containing 3 (NLRP3) inflammasome/interleukin (IL)-1 β axis [36,37], which has been reported to promote kidney injury [38]. The specific blocking of mitochondria-derived ROS also reduces kidney damage and improves kidney function [15,23].

Hence, specific mitochondrial targeting in order to block excessive ROS production and restore some mitochondrial functions could be a suitable complementary therapeutic strategy for kidney diseases.

Here, we review some of the most promising strategies to improve mitochondrial function in kidney diseases. Many of these strategies have been proven in the treatment of other diseases; for this reason, drug repositioning may be advantageous in the context of regulatory procedures [39] for its implementation in kidney diseases.

Mitochondria targeting strategies include the use of small molecules, peptides, nanocarriers, and mitochondria transplantation (Figure 1).

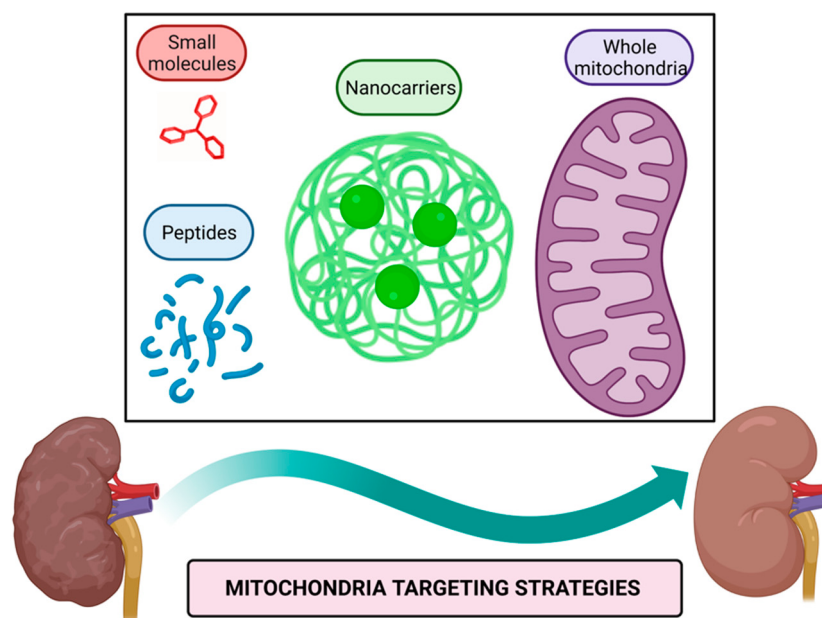


Figure 1. Mitochondria targeting strategies. Small molecules, peptides, nanocarriers, and whole mitochondria transplantation represent therapeutic strategies targeted to mitochondria to alleviate their dysfunction in kidney diseases. Figure created with [BioRender.com](https://www.biorender.com/).

Mitochondria targeting compounds include lipophilic cationic small molecules and peptides that can be used alone or conjugated with other bioactive molecules [40,41]; additionally, nanocarriers of drugs harboring signals that direct them to mitochondria or even whole mitochondria transferred to target tissue could be used to alleviate mitochondrial dysfunction [42,43].

2. Lipophilic and Cationic Small Molecules

These molecules possess lipophilic characteristics which allow them to pass through membranes and positive charges that confer their affinity to mitochondrial membrane potential. They usually do not exert a biological activity by themselves; hence, they are used as carriers of other compounds.

2.1. Triphenylphosphonium (TPP) Conjugates

TPP is one of the small molecules that target mitochondria because it contains a central positively charged phosphorus atom linked to three phenyl rings [44]. This

molecule has been extensively used in the famous molecular probe MitoSOXTM that detects mitochondrial-derived ROS since it contains a TPP moiety bound to hydroethidine [45]. TPP has also been extensively conjugated with other molecules to direct them to and act in mitochondria, such as antioxidants and chemotherapeutics that have been used in different disease models [46,47].

As mentioned above, TPP has been conjugated with a broad range of antioxidants such as ubiquinone, vitamin E, vitamin C, curcumin, and quercetin, among others [46]; here, we review some of the TPP–antioxidant conjugates with potential use in kidney diseases.

MitoQ is a TPP–ubiquinone conjugate that is already marketed as a nutritional supplement; in addition, clinical trials in healthy young and older adults using mitoQ are demonstrated to be safe and reduce oxidative stress markers in plasma and leukocytes [48–50]. Although this compound is not prescribed as a treatment for any diseases, it has been tested in clinical trials for chronic and degenerative diseases. In phase II clinical trials in patients with chronic liver damage due to hepatitis C viral (HCV) infection who cannot receive the standard treatment, the oral intake of mitoQ after 28 days reduces alanine aminotransferase (ALT) and aspartate aminotransferase (AST) serum levels, indicating a reduction in liver damage [51]. On the other hand, in patients with Parkinson's disease, the oral intake of mitoQ for several months seems not to affect disease outcomes [52]. Moreover, antioxidant protective effects of mitoQ have been tested in a broad range of disease models, including AKI and CKD.

Regarding AKI, in a model of ischemia/reperfusion (I/R) in mice, a single intravenous (IV) administration of mitoQ preserves mitochondrial desoxyribonucleic acid (mtDNA) content and reduces functional kidney alterations [53]. More profound findings were reported in a cisplatin-AKI model in which mitoQ intraperitoneally (IP) administrated one hour before cisplatin administration results in kidney function improvement, less oxidative stress, less inflammation, and reduced mitochondrial structural alterations [54].

In terms of CKD, in a model of galactose-induced aging that leads to renal damage, the IP administration of mitoQ for two weeks IP reduces fibrotic markers in the kidney [55]; moreover, in a CKD model by angiotensin II infusion, the co-administration of mitoQ for four weeks ameliorates glomerular and podocyte injury by decreasing mitochondrial fission and ROS production [23].

Diabetic nephropathy are one of many complications of diabetes mellitus physiopathology and are one of the leading causes of CKD and end-stage renal disease (ESRD) [56]. In different diabetic nephropathy (DN) models, the use of mitoQ seems to ameliorate kidney damage and reduce fibrotic and inflammatory markers. In diabetic mice models, conversely to other CKD models, ATP and ADP levels are increased; interestingly, the oral administration of mitoQ for twelve weeks reduces their levels similar to control mice and mitigates structural and functional damage in kidneys without affecting glycemic levels [57,58]. Additionally, the IP administration of this compound for twelve weeks seems to have more in-depth effects, decreasing oxidative stress, diminishing NLRP3-derived IL-1 β production and tubular damage, and slightly reducing glucose levels; at the mitochondrial level, mitoQ treatment preserves membrane potential and mtDNA content, reduces mitochondrial fragmentation and restores mitophagy [37,59].

Although mitoQ seems to have promising results in kidney diseases models, some *in vitro* findings are relevant to take into account, in which direct administration of mitoQ to proximal tubules causes mitochondrial swelling and depolarization due to TPP–ubiquinone linker, the alkyl chain [60]; hence, a modification of the linker could improve the effects of mitoQ.

SkQ1 is a TPP–plastoquinone conjugate that has been tested as an ophthalmic solution in clinical trials for dry eye syndrome reducing corneal damage and discomfort symptoms [61,62]; in fact, SkQ1 is already marketed in Russia as Visomitin drops (Mitotech LLC, Moscow, Russian Federation). Although it functions similarly to mitoQ and even has more potent antioxidant effects [63], this has not been tested in kidney diseases yet. However, its protective effects could be possible since, in an aging model in mice with mtDNA defects, SkQ1 treatment reduces oxidative damage in several organs, including kidneys, when

administrated in drinking water for 150 days [64], suggesting that its use is suitable in AKI or CKD.

MitoTEMPO is a TPP-2,2,6,6-tetramethylpiperidine-N-oxyl (TEMPO) conjugate that acts as a mimetic of the antioxidant enzyme superoxide dismutase (SOD) [65]. Although this compound has not been tested in clinical trials yet, this has been used in hepatic, cardiovascular, nervous system, infectious, and kidney disease models.

In different AKI models in rodents, the pre-treatment and treatment with mitoTEMPO reduce kidney and mitochondrial damage, as has been demonstrated in cisplatin-induced AKI in which seven days pre-treatment with mitoTEMPO administrated IP reduces oxidative and tubular damage in kidneys [66]; or in I/R-induced AKI, in which mitoTEMPO administration directly to the kidney during the ischemic induction and followed by four days of IP administration preserves mtDNA and ATP content, avoids mitochondrial swelling, and reduces oxidative damage [15]. Additionally, in septic shock-associated AKI, in which mitoTEMPO administration IP or IV after sepsis induction partially restores ETC function and ATP content in kidney mitochondria, whereas in whole tissue reduces oxidative damage and decreases IL-1 β levels resulting in improved kidney function [67–69].

In CKD models, mitoTEMPO shows similar results improving mitochondrial function and reducing kidney damage. In 5/6 nephrectomy-induced CKD models in rodents, with or without aldosterone administration, the IP mitoTEMPO administration for four to twelve weeks maintains mitochondrial function and morphology; moreover, it reduces fibrotic, inflammatory, and oxidative markers in the kidney, preserving podocyte's structure [70–72]. Interestingly, mitoTEMPO also impacts the skeletal muscle, promoting its regeneration and recovering ATP production [73]. In a model of kidney fibrosis by unilateral ureteral obstruction (UUO) in mice, the IP administration of mitoTEMPO for seven days reduced ROS levels and the fibrotic area in kidneys, as well as decreased gene expression of alpha-smooth muscle actin (α -SMA), collagen, transforming growth factor-beta (TGF- β), and fibronectin [74].

On the other hand, during DN using the db/db mice model, the oxidative stress induces an increase in apoptotic cell death and impaired mitophagy in the kidney, which could be partially reversed by antioxidant treatment, including IP administration of mitoTEMPO for four weeks, thus resulting in improved renal function [75]. Similar results in other models of diabetes using streptozotocin and Ins2^{+/–Akita} mice have been reported, in which subcutaneous administration of mitoTEMPO for three weeks improves kidney function, reduces glomerular injury, and partially avoids the loss of endothelial cells and podocytes [76].

Many antioxidants have been demonstrated to have beneficial effects on mitochondrial function during AKI and CKD models [25–34]; among these, curcumin and lipoic acid represent two molecules to potentially be conjugated with TPP to reach mitochondria and to explore in kidney diseases. A TPP–curcumin conjugate has been developed and tested in rotenone-induced liver damage in mice, reducing the lipid peroxidation and partially preserving the activity of the antioxidant enzymes superoxide dismutase and catalase [77]. On the other hand, a TPP–lipoic acid conjugate has also been developed; however, the conjugation with TPP seems to compromise the antioxidant effect [78].

Despite the great potential of TPP conjugates, there are some shortcomings, such as transportability, as TPP can only transport electroneutral and small molecules. Furthermore, some adverse effects on mitochondrial function of TPP conjugates have been reported, such as decreased ETC activity and reduced membrane potential [79]. For this reason, more research is needed to improve transportability and reduce the toxicity of TPP. For example, it has been proposed that phenyl rings of TPP could be modified by trifluoromethyl groups that function as electron withdrawers to abrogate adverse effects [44].

2.2. Rhodamine Conjugates

Rhodamines, such as fluorescein, are xanthene derivatives that have been extensively used as fluorescent probes. Depending on the chemical modifications, there are several

rhodamine types, such as rhodamine B, 6G, 19, 101, 110, 116, 123, and tetramethyl rhodamine [80]. Among these, rhodamine 123, tetramethylrhodamine methyl ester (TMRM), and tetramethylrhodamine ethyl ester (TMRE) possess mitochondrial affinity and has been used as mitochondrial membrane potential probes [81,82].

Rhodamine 19 has also been demonstrated to target mitochondria, acting as a mild uncoupler, and has been used as a carrier of the antioxidant molecule plastoquinone, a compound named SkQR1 [83,84].

SkQR1 Has Been Proven in Neurological Disease, Kidney Disease, and Aging Models. In AKI models, the renoprotective effects of SkQR1 have been demonstrated in rhabdomyolysis and I/R-induced AKI in rats, in which its IP administration previous and after damage induction decreases oxidative stress markers, lowers tubular epithelial necrotic areas, and reduces tubular dilatation, thus resulting in improved renal function and increased animal survival rate [85,86]. Similarly, in a model of gentamicin nephrotoxicity-induced AKI in rats, SkQR1 administrated IP improves kidney function and increases animal survival rate; moreover, the hearing loss associated in this model is also abrogated by SkQR1 treatment [87]. In addition, in the sepsis-associated AKI model in rats, the pre-treatment with SkQR1 IP reduces the damage markers kidney injury molecule-1 (Kim-1) and neutrophil gelatinase-associated lipocalin 2 (NGAL) levels, improves kidney function, and reduces mortality [88].

Although pyelonephritis is not considered a cause of AKI, its presence is a risk factor for AKI development [89]. In an acute pyelonephritis model in rats, the IP administration of SkQR1 after bacterial inoculation and followed by four IP administrations every 12 h reduces neutrophil infiltration and oxidative damage in the kidney; moreover, it impacts systemic inflammatory status by reducing tumor necrosis factor-alpha (TNF- α) in serum, reducing neutrophil numbers in blood and increasing animal survival rate [90].

SkQR1 has not been tested in CKD and DN models, opening a new field to explore.

Rhodamine B also targets mitochondria and has been conjugated with the antioxidant enzymes superoxide dismutase (SOD) and catalase (CAT) [91] which have been proved in vitro, suggesting the potential use in kidney disease models.

A summary of proven and not proven mitochondria targeting small molecules in kidney disease models is shown in Figure 2.

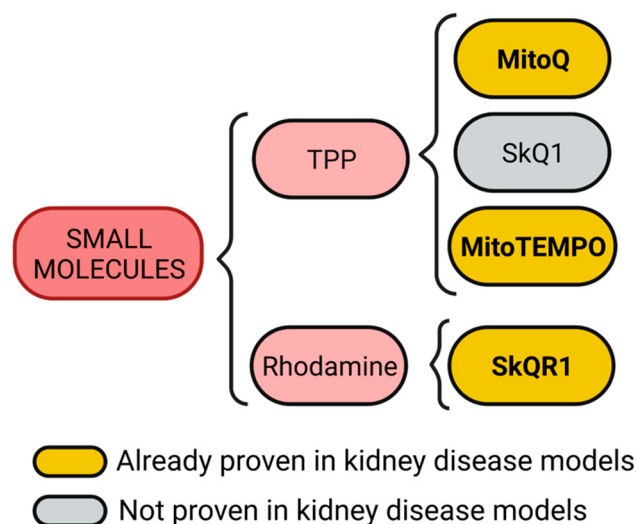


Figure 2. Mitochondria targeting small molecules. Triphenylphosphonium (TPP) and rhodamine are small molecules with cationic and lipophilic characteristics. TPP can be conjugated with quinone, plastoquinone, or 2,2,6,6-tetramethylpiperidine-N-oxyl (TEMPO) to generate mitoQ, SkQ1, and mitoTEMPO molecules, respectively. On the other hand, rhodamine conjugated with plastoquinone generates the SkQR1 molecule. Figure created with [BioRender.com](https://www.biorender.com/).

3. Mitochondria Targeting Peptides

Peptides as therapeutics have emerged recently and show several advantages over other molecules, such as their chemical synthesis, selectivity, and minimal side effects. These could be used alone or conjugated with another bioactive compound [92,93].

Nowadays, the peptide peginesatide, an antagonist of the erythropoietin receptor, is used to treat CKD-associated anemia in humans [94]. Hence, other experimental approaches focused on mitochondria have been explored; for example, using a peptide to block the interaction of nucleophosmin with Bcl-2-associated X protein (Bax) inhibits apoptotic cell death; thus, resulting in decreased renal damage caused by ischemia [95] and suggesting that mitochondria targeting peptides could also be a potential therapy for kidney diseases.

Therapeutic peptides are classified as cell-targeting peptides (CTP) if they are directed specifically to a receptor or as cell-penetrating peptides (CPP) if they pass the plasma membrane to reach the cytoplasm [92,93]. Mitochondria targeting peptides require CPP characteristics to enter cells, and to reach mitochondria requires CTP characteristics harboring a mitochondria targeting sequence (MTS) or possessing cationic charges.

Although only one kind of cationic mitochondrial penetrating peptides named Szeto-Schiller (SS) peptides has been proven in kidney diseases, here we review some MTS-containing peptides and other cationic mitochondrial penetrating peptides with potential use.

3.1. MTS-Containing Peptides

Mitochondrial proteome mainly is constituted by nuclear-encoded proteins that once synthesized possess an MTS to reach mitochondria through the recognition by the mitochondrial TOM complex eliciting the integration to mitochondrial membranes. The conserved pattern residues on MTS are $\varphi\chi\chi\varphi\varphi$, where φ represents an aromatic or hydrophobic residue, whereas χ represents any kind of residue, for example, the pattern LSRL; additionally, MTS acquires an alpha-helix conformation that facilitates the insertion to the mitochondrial outer membrane. Once inside, MTS is degraded by mitochondrial processing proteinases (MPP) [3,96,97]. Considering those mentioned above, synthetic MTS-containing peptides have been developed and used as carriers of other compounds to facilitate their delivery into mitochondria to exert biological functions. The construct of a CPP with an MTS improves cellular and mitochondrial uptake [98], as has been demonstrated in vitro with peptides conjugated with DNase, human metallothionein 1A (hMT1A), and manganese-porphyrin [99–101]. Moreover, the cell-penetrating artificial mitochondria targeting peptide (CAMP)-hMT1A conjugate has been tested in a Parkinson's disease model in rats and demonstrated to restore tyrosine hydroxylase levels in striatum and substantia nigra resulting in improved motor coordination when it is administered intracerebrally [100]; similarly, using a recombinant MTS-containing mitochondrial transcription factor A (TFAM) IV injected in mice also improves motor coordination, although it could be by the increase in complex I of the ETC [102]. MTS-containing TFAM has also been proven in a septic shock model, increasing animal survival and, in healthy mice, increasing the brain and muscle complex I level of the ETC [102,103].

Although for kidney diseases, there are no reports of the use of MTS-containing peptides, the conjugation of these with antioxidant molecules such as the mentioned metallothionein and manganese-porphyrin could have promising results, since both molecules have been reported to reduce renal damage in aristocholic acid-induced CKD and I/R-induced AKI, respectively [104,105]. Moreover, recombinant MTS-containing TFAM could also help maintain mitochondrial DNA and increase complex I levels in kidney tubular epithelial cells.

One advantage of MTS-containing peptides over other molecules that target mitochondria is that cationic charges are expendable to enter mitochondria; hence, their insertion mechanism is independent of mitochondrial membrane potential.

3.2. Cationic Mitochondrial Penetrating Peptides

Positive charges and alpha-helix structures are basal characteristics of these peptides, and they differ from each other due to other structural features. Among this category, we found the cationic amphiphilic polyproline helix (CAPH) peptides, the cationic cysteine-rich peptides, the hexapeptides, the structurally modified peptoids, and the SS peptides.

CAPH peptides possess the ability to enter the cell through endocytosis and reach mitochondria due to enriched proline residues in their structures, such as P11LRR and P14LRR peptides [106,107]; moreover, the addition of a dimethyl tyrosine (Dmt) residue to P11LRR structure exert antioxidant functions demonstrated in vitro [106,107].

As mentioned above, oxidative stress is a hallmark of kidney diseases, in which mitochondria are the primary sources of ROS [108]. Ergo, the use CAPH-Dmt has excellent potential to explore in AKI and CKD models.

The plant derivate rosel tide rT1 is a cationic cysteine-rich peptide recognized by the TOM complex in an MTS-independent way; interestingly, rosel tide rT1 by itself can bind ATP synthase and enhance ATP production in different cell lines [109]. During AKI and CKD, ATP production is compromised, as demonstrated in experimental models [11,16–18,26,31,110,111], and for this reason, rosel tide rT1 by itself without conjugation with another bioactive compound could be helpful in the treatment of kidney disease.

Hexapeptides with delocalized lipophilic cations contain the modified residue cyclohexyl alanine in their structure to bring hydrophobicity and facilitate cellular uptake; positive charge residues such as lysine and arginine also are incorporated. In addition to these characteristics, cationic moieties of pyridyl salts in alanine residues bring mitochondrial selectivity [112]. Although these peptides are not proven in any disease model, it seems to have great potential as a drug delivery system to mitochondria. As described above, non-peptidic cationic molecules are a comprehensive system to target mitochondria due to the charge affinity.

Peptoids resemble backbone peptide structures but are resistant to proteolysis due to structural modifications, in which side chains are attached to the nitrogen atom instead of the alpha carbon [113]. These peptoids also require the lipophilic, cationic, and alpha-helix structure characteristics to enter the cell and mitochondria [114]. Although peptoids conjugated with any kind of drugs are not assessed in any disease models in animals, they represent a vast field to explore in kidney diseases, in which the conjugation with molecules that require more stability, such as transcription factors, bioactive lipids, or proteins involved in mitochondrial dynamics.

SS peptides are aromatic and cationic tetrapeptides able to enter mitochondria and, if they possess a tyrosine or Dmt residue in their structure, also function as antioxidants themselves. SS-01 and SS-20 that lack tyrosine or Dmt residues can enter mitochondria but lack antioxidant activity, whereas SS-02 and SS-31, which possess any of those two residues, enter mitochondria and are potent antioxidants.

Among SS peptides, SS-31 (also known as MTP-131, Bendavia, and elamipretide) has gained great attention for the potent antioxidant activity and safety demonstrated in experimental models; in fact, SS-31 has been proved in clinical trials for human mitochondrial myopathies, Barth syndrome, cardiovascular diseases, and renal arterial stenosis [115–119].

In AKI, SS-31 IP administration reduces structural and functional damage induced by cisplatin in mice; moreover, it decreases oxidative damage and NLPR3-derived IL-1 β synthesis [120]. Similarly, in I/R-induced AKI in rats, SS-31 subcutaneous administration reaches a high concentration in kidneys and reduces epithelial and endothelial damage; at the subcellular level, it avoids mitochondrial swelling, maintains cristae structure by its binding with cardiolipin, and recover ATP levels [121–123]. SS-31 peptide has been modified with CPP characteristics or encapsulated in nanopolyplexes to increase its cellular uptake and mitochondrial accumulation, thus resulting in enhanced antioxidant capacity demonstrated in vitro [124,125]. Moreover, the efficiency of SS-31 encapsulated in nanopolyplexes has been demonstrated in lipopolysaccharide (LPS)-induced AKI model in mice, showing better results than SS-31 alone [125]. Although cisplatin, I/R, and LPS-induced

AKI SS-31 have demonstrated promising results, for other models such as aristocholic acid (AA) and adriamycin-induced AKI, there are controversial results [126] that could be explained by the specific physiopathology induced by these compounds or even by their chemical interaction with SS-31. It is known that AKI predisposes to CKD development; as has been reported in CKD development induced I/R, in which the treatment with SS-31 for six weeks and started four weeks after ischemic injury reduces the structural damage of kidneys, fibrotic damage, and mitochondrial swelling; surprisingly, this protective effect persists even nine months after I/R induction [127].

On the other hand, during diabetic nephropathy, the IP or subcutaneous administration of SS-31 for at least four weeks of SS-31 does not affect glycemic levels; however, it improves kidney function, preserves podocyte structure, diminishes inflammatory and fibrotic markers, and reduces oxidative stress [128–133].

SS-02 and SS-20 peptides in conjugation with deferoxamine have also been demonstrated to possess mitochondrial antioxidant properties in vitro [134], suggesting their potential use.

A summary of proven and not proven mitochondria targeting peptides in kidney disease models is shown in Figure 3.

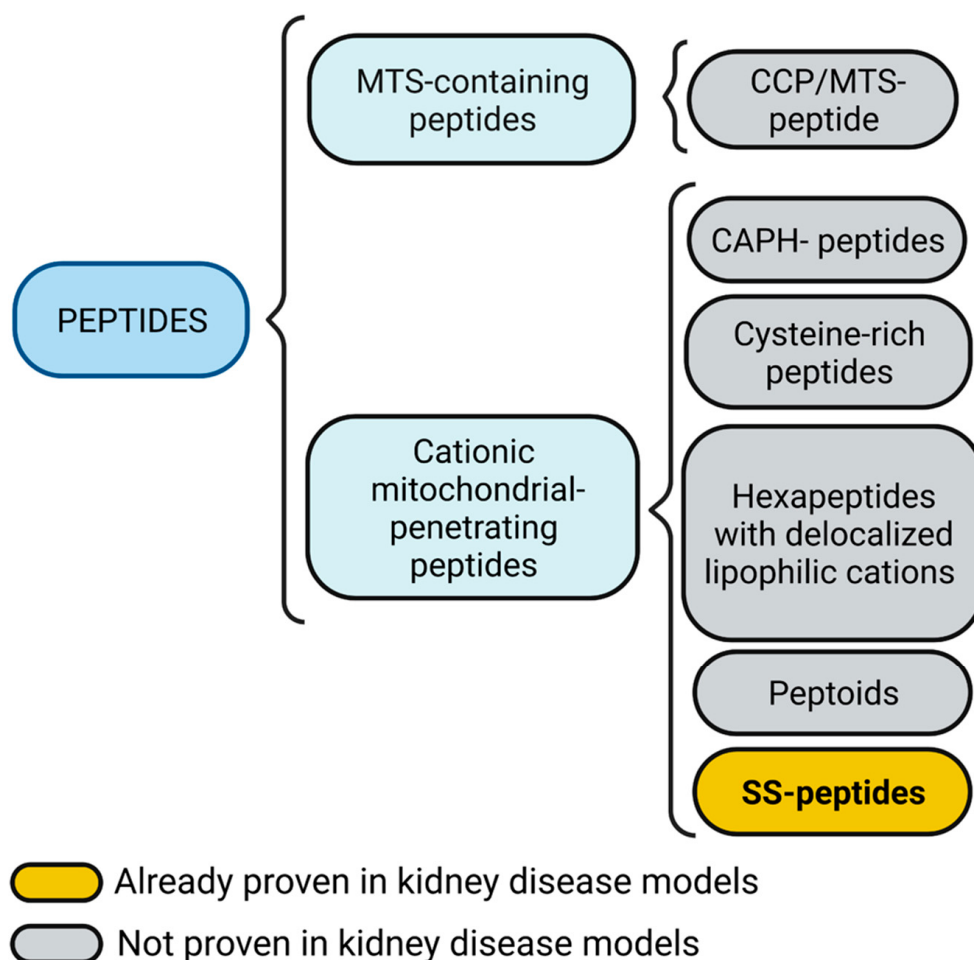


Figure 3. Mitochondria targeting peptides. Mitochondria targeting sequence (MTS)-containing peptides also could include a cell-penetrating peptide (CPP) feature. Cationic mitochondrial penetrating peptides could be subdivided into cationic amphiphilic polyproline helix (CAPH) peptides, cysteine-rich peptides, and hexapeptides with delocalized lipophilic cations, peptoids, and Szeto-Schiller (SS) peptides. Figure created with [BioRender.com](https://www.biorender.com).

4. Nanocarriers

Nanocarriers serve as a platform to deliver different compounds to the target tissue. Several nanocarrier systems targeting mitochondria have been developed and proven in disease models other than kidney diseases; among the most known are mitoPorter, DQAsomes, and PEG-based nanoparticles.

MitoPorter is a liposome-based system composed of 1,2-dioleoyl-sn-glycerol-3-phosphatidyl ethanolamine, phosphatidic acid, and sphingomyelin; its surface also contains octarginine moieties to facilitate its cellular uptake [135]. MitoPorter has been used for nucleic acids delivery [136–139] with potential use in mitochondrial diseases; however, has recently been used to deliver ubiquinone in an I/R model in the liver, showing protective effects even compared to ubiquinone treatment alone [140], suggesting that this delivery system of antioxidants also could be helpful in kidney diseases.

DQAsomes are made from dequalinium chloride molecules, which form a liposome-like structure in an aqueous solution [141], serving as a delivery system for anti-cancerogenic compounds [142–144]; DQAsomes have also been proven to deliver curcumin without toxic effects [145], a natural antioxidant that ameliorates damage in kidney diseases.

Polyethylene glycol (PEG)-based nanoparticles are molecules coated with PEG to improve their biodisponibility, a process called PEGylation [146]. Some strategies to use PEGylation and target mitochondria include the combination of PEG by itself with TPP moieties to improve doxorubicin delivery [147]; in addition; other strategies such as the using PEGylated nanoparticles of poly (lactic-co-glycolide acid) (PLGA) with TPP moieties has been proven as nanocarrier systems for curcumin, lodinamine, α -tocopheryl succinate, and dinitrophenol [148].

Some mitochondria targeting nanocarriers based on PEGylation including nanoceria, PEG-polycaprolactone (PCL) nanoparticles; and the encapsulation of SS peptides in hyaluronic Acid (HA)-Chitosan nanoparticles have been proven in kidney disease models.

4.1. Nanoceria

Cerium oxide nanoparticles, also known as nanoceria, are metal-based nanoparticles sized from 5 to 36 nm with antioxidant capacity by themselves [149]; in addition, the formulation of nanoceria with vitamin C has been demonstrating renoprotective effects in rhabdomyolysis-induced AKI model in mice [150]. In LPS-induced AKI in mice, nanoceria has been modified by adding a TPP moiety to target mitochondria, loaded with atorvastatin, a drug that improves kidney function, and covered with methoxy PEG-thioetal-PLGA as stabilizers, showing that its IV administration reduces oxidative damage and inflammation; moreover, preserves mitochondrial structure [151].

4.2. PEG-PCL Nanoparticles

PEG-PCL nanoparticles with TPP moieties and carrying ubiquinone molecules have been proven in I/R-induced AKI, demonstrating a marked reduction of tubular damage and inflammation compared to ubiquinone alone [152].

4.3. Hyaluronic Acid (HA)-Chitosan Nanoparticles

As mentioned above, SS-31 is a mitochondria targeting peptide with renoprotective functions; to increase its biodisponibility, this was encapsulated in nanoparticles made of HA and chitosan, demonstrating better results than SS-31 alone in an LPS-induced AKI model in mice [125].

A summary of proven and not proven mitochondria targeting nanocarriers in kidney disease models is shown in Figure 4.

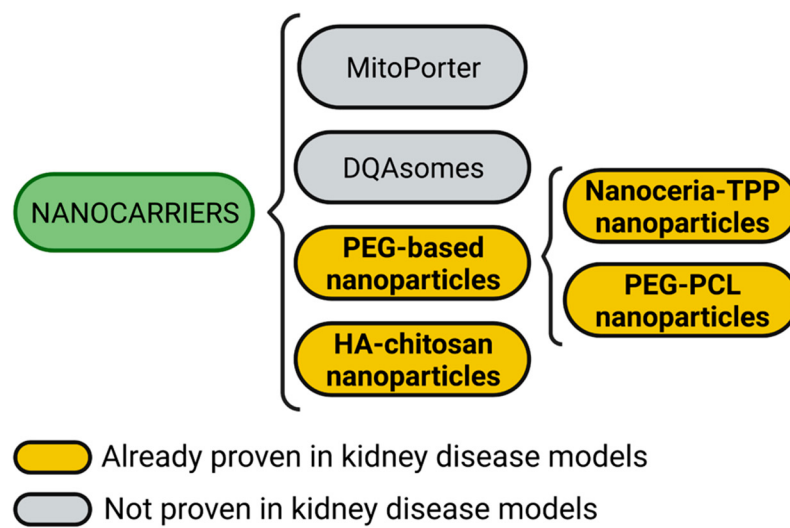


Figure 4. Mitochondria targeting nanocarriers. Nanocarrier systems targeting mitochondria include mitoPorter, DQAsomes, hyaluronic acid (HA)-chitosan nanoparticles, and polyethylene glycol (PEG)-based nanoparticles. PEG-based nanoparticles could also be subdivided into cerium oxide nanoparticles (nanoceria) harboring triphenylphosphonium (TPP) moieties and PEG-polycaprolactone (PCL) nanoparticles. Figure created with [BioRender.com](https://www.biorender.com).

5. Mitochondrial Replacement

Mitochondrial replacement, also known as mitochondrial transplantation, is a novel experimental therapeutic strategy to transfer healthy mitochondria to the target tissue to recover mitochondrial function (Figure 5). This strategy has already been used in pediatric patients after cardiogenic shock, in which mitochondria isolated from their muscles are directly injected into the myocardium, demonstrating that patients with mitochondrial transplantation do not suffer short adverse effects and show fewer cardiovascular events several months after the intervention [153,154].

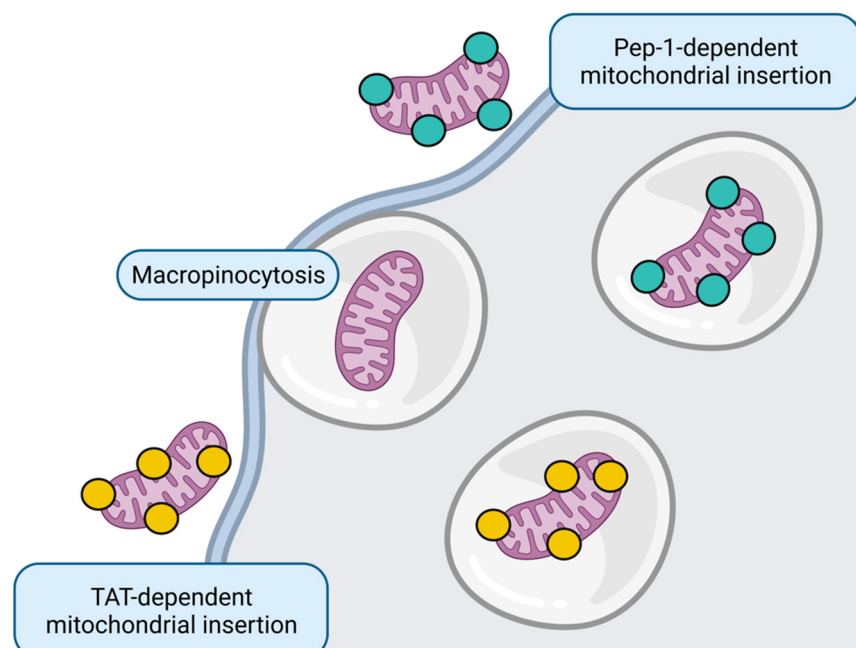


Figure 5. Mitochondrial replacement. Whole healthy mitochondria insertion to target cell could occur through micropinocytosis or directed through Pep-1 and transactivator of transcription (TAT) peptides. Figure created with [BioRender.com](https://www.biorender.com).

Only AKI models have explored the effect of mitochondrial replacement. In the doxorubicin-induced AKI model, the transplantation of mesenchymal stem cell (MSC)-derived mitochondria to the renal subcapsular region results in improved kidney function and increased antioxidant enzyme levels; however, although tubular regeneration was increased, tubular dilation persists [155]. Similarly, in I/R-induced AKI in rats and pigs, the intra-arterial administration of muscle-derived mitochondria improves renal function in the first 24 to 48 h [156,157] and even promotes proliferation of renal cells [156] and reduces inflammation [157]. However, for CKD, mitochondrial replacement remains unexplored.

Although the primary mechanism described for internalization of transferred mitochondria to the tissue is micropinocytosis [158], some strategies that improve the uptake in vitro include mitochondria harboring CPP, such as Pep-1 [159–161] and transactivators of transcription (TAT) peptides [162].

6. Concluding Remarks

Mitochondria targeting strategies have been explored in different diseases and represent a suitable additional therapeutic option for AKI and CKD. Taking advantage of some clinical trials that have tested some of these strategies, drug repositioning facilitates their scaling to be used in other diseases [39], including kidney diseases, based on the experimental result with the same molecules. In this context, mitoQ, SkQ1, SS-31, and mitochondrial replacement are the most suitable therapeutic strategies already proven in clinical trials (Table 1) with potential use in kidney diseases.

Table 1. Mitochondrial targeting strategies have already been tested in clinical trials.

Mitochondrial Targeting Strategy	Clinical Trial	Administration Route	Duration	Ref.
MitoQ	Patients with chronic hepatitis C	Oral intake	28 days	[51]
	Aging healthy volunteers	Oral intake	28 days	[48]
	Healthy volunteers	Oral intake	28 days	[49]
	Healthy volunteers under high-intensity exercise	Oral intake	21 days	[50]
SkQ1	Dry eye syndrome	Ophthalmic solution	4–6 weeks	[61,62]
SS-31	Barth syndrome	Subcutaneous administration	36 weeks	[116]
	Mitochondrial myopathy	Intravenous	5 days	[115]
	Heart failure	Intravenous/subcutaneous	3/28 days	[117,118]
	Renal artery stenosis	Intravenous	3 days	[119]
Mitochondrial replacement	Cardiogenic shock	Intracardiac	During surgical intervention	[153,154]

On the other hand, here, we present some other mitochondria targeting strategies already proven in kidney disease models with great potential to be used in clinics (Table 2), such as the case of mitoTEMPO and SkQR1. Additionally, some other mitochondrial targeting strategies not explored already in kidney disease models, such as peptides (other than SS peptides) and the nanocarriers mitoPorter and DQAsomes, have been tested in vitro or other disease models, opening a field to explore them in kidney diseases models.

Table 2. Mitochondria targeting strategies tested in kidney disease models.

Mitochondria Targeting Strategy			Kidney Disease	Model	Ref.
Small molecules	TPP-based	MitoQ (TPP-ubiquinone)	AKI	I/R in mice	[53]
				Cisplatin in mice	[54]
			CKD	Aging in mice	[55]
				Angiotensin II infusion in mice	[23]
				DN in db/db and Ins2+/-AkitaJ mice	[37,57–59]
		SkQ1 (TPP-plastoquinone)	Aging-associated CKD	Aging in mice	
	Rhodamine-based	MitoTEMPO (TPP-2,2,6,6-tetramethylpiperidine-N-oxyl)	AKI	I/R in mice	[15]
				Cisplatin in mice	[66]
				Sepsis in rats and mice	[67–69]
			CKD	5/6 nephrectomy in mice	[70–72]
				UUO in mice	[74]
				DN in mice	[75,76]
Peptides	Cationic lipophilic	SS-31	AKI	I/R and rhabdomyolysis in rats	[85,86]
				Gentamicin in rats	[87]
				Sepsis in rats	[88]
				Pyelonephritis in rats	[90]
	Cationic lipophilic	SS-31	AKI	I/R in rats	[121–123]
				Cisplatin in mice	[120]
			CKD	Sepsis in mice	[125]
				I/R in rats	[127]
				DN in mice	[128–133]
Nanocarriers	PEG-based	NanoCeria	AKI	Rhabdomyolysis in mice	[150]
				Sepsis in mice	[151]
		PEG-PCL		I/R in mice	[152]
		HA-chitosan		Sepsis in mice	[125]
Mitochondrial replacement			AKI	I/R in rats and pigs	[156,157]
				Doxorubicin in rats	[155]

Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease; DN diabetic nephropathy; HA, hyaluronic acid; I/R, ischemia/reperfusion; PCL, polycaprolactone; PEG, polyethylene glycol; TPP, triphenylphosphonium; UUO, unilateral ureteral obstruction.

Most of the mitochondria targeting strategies used in AKI and CKD models rely on antioxidant function by the conjugation with scavengers; however, most of the described mitochondria targeting molecules possess the ability to carry more complex compounds such as enzymes or transcription factors, as the mentioned metallothionein and TFAM [100,102]; hence, we open the possibility that mitochondria targeting molecules could exert other functions, such as promoting the mitochondrial biogenesis, stimulating ETC components transcription, and enhancing enzymatic reactions, among others.

Despite all the beneficial effects described above, some points must be considered. For example, the efficiency of many of these molecules depends on mitochondrial membrane potentials, such as small molecules, cationic peptides, and some nanocarriers; in this

context, only MTS-containing peptides, some nanocarriers, and whole mitochondria could be helpful in the loss of membrane potential during kidney diseases.

For the case of safety in terms of immunogenicity, small molecules and peptides represent the strategies with lower risk; conversely, nanocarriers have immunogenicity potential [163] to take into consideration; similarly, if the whole mitochondrial for transplantation is damaged this could induce a proinflammatory response due to the exposure of danger-associated molecular patterns (DAMPs) [164].

In terms of obtention, small molecules, peptides, and whole mitochondria isolation seem to be the more suitable options, followed by nanocarrier systems.

Additionally, for each one, pharmacokinetic and pharmacodynamic studies are necessary; in this context, SS-31 is the most advanced option for AKI and CKD treatment.

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