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Mitochondrial Homeostasis as a potential therapeutic target to combat chronic kidney disease

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Abstract

The prevalence of chronic kidney disease (CKD) is rapidly rising worldwide and will become the fifth leading cause of death by 2040. CKD is a complex condition characterized by mitochondrial dysfunction, oxidative stress and inflammation. This review explores the central role of mitochondrial homeostasis in the etiology of CKD, highlighting the complicated relationships between mitochondrial dynamics, biogenesis, cell death, mitophagy and epigenetic changes. We will discuss how mitochondrial dysfunction contributes to renal damage and the advancement of CKD, review existing treatments, examine the capability of natural compounds and neuroendocrine and maintain a healthy lifestyle as an interventional strategy to target mitochondrial dysfunction. Furthermore, we outline future directions for research, emphasizing the need to unravel the molecular pathways driving mitochondrial decline in CKD. By targeting mitochondrial homeostasis, we may uncover novel therapeutic strategies to combat aging and CKD, improving affected individuals' lifespan and quality of life.

Keywords: Chronic kidney disease (CKD), epigenetic, mitochondrial dynamics, mitophagy, natural compounds.

Introduction

Mitochondrial dysfunction is identified as a key biological hallmark of the aging process (Liu *et al*. 2020), characterized by changes in the mitochondrial network, accumulation of genetic mutations, mitochondrial depolarization and enhanced ROS reactive oxygen species (ROS) generation. These changes can impair energy metabolism, cellular senescence and kidney aging (Choi *et al*. 2024). Mitochondria are pivotal organelles that perform multiple critical functions within cells. These include orchestrating the oxidative phosphorylation pathway

and modulating carbon metabolism, generating adenosine triphosphate (ATP) to fuel cellular activities, and regulating key signaling molecules such as calcium ions (Ca^{2+}) and ROS. These processes are integral to maintaining cellular homeostasis and influencing cell fate decisions (Boyman *et al*. 2020; Choi *et al*. 2024). Researchers have consistently demonstrated that maintaining optimal mitochondrial dynamics is essential for promoting longevity across various contexts, including conditions mediated by the target of rapamycin complex 1 (TORC1) and adenosine monophosphate-activated protein kinase (AMPK) signaling pathways and caloric restriction (Weir *et al*. 2017; Zhang *et al*. 2019). Studies in mice and *Caenorhabditis elegans* have shown that inhibiting the insulin/IGF-1 Insulin-like growth factor -1 (IIS) signaling pathway can significantly extend lifespan, indicating an evolutionarily conserved mechanism. Furthermore, manipulating IIS pathways has been linked to improved mitochondrial function, increased respiratory capacity and enhanced membrane potential (Akbari *et al*. 2019; Rostamian *et al*. 2021).

As a metabolically active organ, the kidney's energy requirements rely heavily on the efficient functioning of its mitochondria, specifically the process of oxidative phosphorylation, to generate the necessary energy to support its metabolic activities (Guo et al. 2024). Chronic kidney disease (CKD) poses a significant and growing threat to worldwide health, with projections indicating it will become the fifth leading cause of mortality worldwide by 2040. Furthermore, in countries with high life expectancy, CKD is predicted to rank as the second highest cause of mortality by the end of the century (Foreman *et al*. 2018; Ortiz *et al.* 2019). Consequently, mitochondrial stability is essential for maintaining healthy kidney function and preventing premature aging of the kidney. Additionally, research has shown that impaired mitochondrial function and elevated levels of oxidative stress play a significant role in the promotion and progression of numerous prevalent diseases, including metabolic disorders, and neurodegenerative conditions (Alqahtani *et al.* 2023).

Studies have demonstrated that aging is associated with a multi-layered remodeling of the kidney and other organs, leading to changes in their architecture and functional capacity (Miwa *et al.* 2022). Kidney aging is associated with a multifaceted pattern of histological alterations, spanning microscopic and macroscopic changes, which in turn contribute to a steady decline in kidney function, manifesting as a loss of cortical mass, glomerular filtration capacity, arteriosclerosis, tubular integrity and interstitial fibrosis (Hommos *et al.* 2017). Investigations and data have revealed that older adults are at a higher risk of developing renal fibrosis and chronic kidney disease compared to their younger counterparts (Denic *et al.* 2016; Yang *et al.* 2023). A deeper insight into the complex molecular mechanisms underlying

mitochondrial homeostatic control in the kidney can facilitate the discovery of novel therapeutic approaches to delay kidney aging and prevent chronic kidney disease.

Mitochondrial homeostasis in CKD

Maintaining mitochondrial homeostasis is essential for cellular energy metabolism, redox balance and signaling pathways (Bhargava and Schnellmann 2017). However, in CKD, mitochondrial homeostasis is disrupted, leading to impaired mitochondrial dynamics, increased oxidative stress and altered biogenesis (Forbes 2016; Srivastava *et al*. 2023). Furthermore, CKD is associated with increased cell death, impaired mitophagy and epigenetic changes that affect mitochondrial function (Aranda-Rivera *et al.* 2024). We undertake a comprehensive review of the research on the complex interplay between mitochondrial dysfunction and CKD, exploring the key mechanisms underlying mitochondrial dynamics, oxidative stress, biogenesis, cell death, mitophagy, and epigenetic changes. By elucidating these mechanisms, we hope to identify potential therapeutic targets for the prevention and treatment of CKD.

Mitochondrial dynamics

The kidneys are highly energy-demanding organs, utilize 7% of daily ATP and contain numerous mitochondria. These organelles generate ATP via oxidative phosphorylation, varying densities across nephron segments based on energy requirements. Proximal tubular cells, critical for reabsorption and secretion, heavily rely on ATP from mitochondrial oxidative phosphorylation (Blagov *et al*. 2024). Unlike other kidney cells, they primarily use fatty acids, metabolized through β-oxidation in mitochondria (Takemura *et al*. 2020). Effective mitochondrial function is vital for kidney function, especially in proximal tubules where filtration occurs. Mitochondrial dysfunction can severely impair kidney function and contribute to CKD.

Mitochondria change shape via fusion and fission, a balance essential for their health. Too much fission causes fragmentation, while too much fusion causes hypertubulation. Maintaining this balance is crucial for preventing mitochondrial dysfunction and cell damage (Galvan *et al*. 2017). Mitochondrial fission and fusion are controlled by molecular machinery, first found in yeast and later in mammals. Dynamin-related protein 1 (Drp1), a guanosine triphosphatase (GTPase), drives fission by forming rings around mitochondria and constricting them until they divide, with receptors like Mitochondrial fission 1 (FIS1), Mitochondrial dynamics protein of 49 kDa and 51kDa (MiD49/51), and mitochondrial fission

factor (MFF) helping Drp1 bind (Galvan *et al*. 2017). Post-translational modifications regulate Drp1 activity. In contrast, mitofusin 1 and mitofusin 2 (Mfn1 and Mfn2) mediate outer membrane fusion (Tubbs and Rieusset 2017), while while Optic atrophy 1 (Opa1) mediates inner membrane fusion (Morigi *et al*. 2015) (**Fig. 1**).

Problems with these processes are linked to diseases like cancer, cardiovascular issues, neurodegeneration and diabetes. Specifically, increased fission is tied to kidney injury (Galvan *et al*. 2017). Studies show that deleting or inhibiting Drp1 in kidney cells protects against diabetic kidney disease (Ayanga *et al*. 2016). Drp1's activity is regulated by phosphorylation, and different kinases have varying effects depending on the cell type and stimulus (Galvan *et al*. 2017). Targeting mitochondrial dynamics could be a therapeutic approach for kidney disease and other conditions involving mitochondrial dysfunction, but further research is needed.

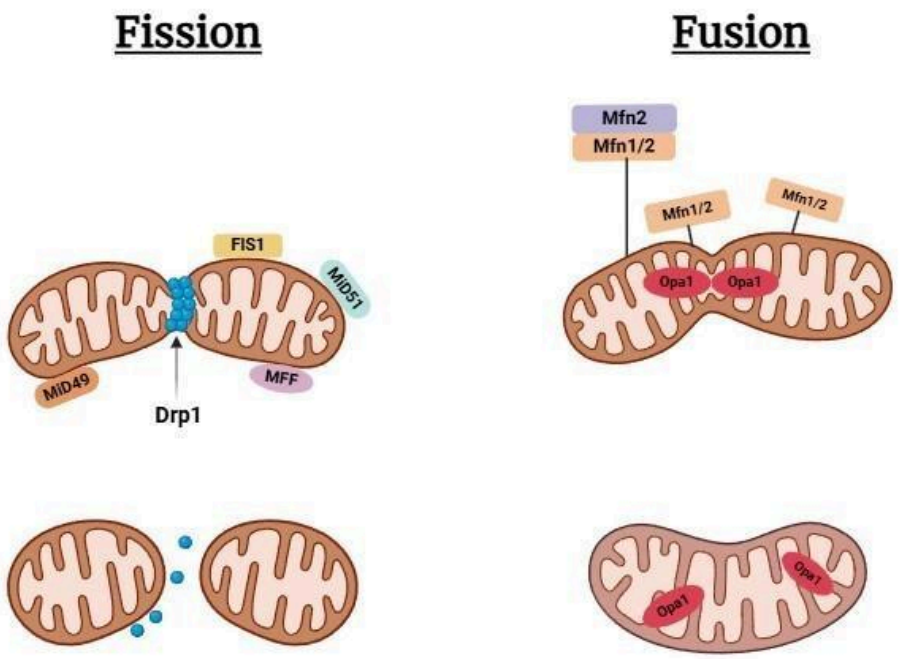

Fig. 1. Mitochondrial fission involves Drp1, which uses GTPase activity to oligomerize, form a ring, constrict, and divide the mitochondrion. Mitochondrial fusion requires MFN1 and MFN2, located on the outer membrane, to interact as homo- or heterodimers, while Opa1 mediates the fusion of the inner membrane. *Abbreviations: Drp1, dynamin-related protein 1: FSI1, mitochondrial fission protein 1: MFF, mitochondrial fission factor: MiD49 and MiD51, mitochondrial dynamics proteins of 49 and 51 kDa: Mfn 1/2, mitofusion proteins 1 or 2: Opa1, optic atrophy 1.* Adopted from Galvan *et al*. 2017.

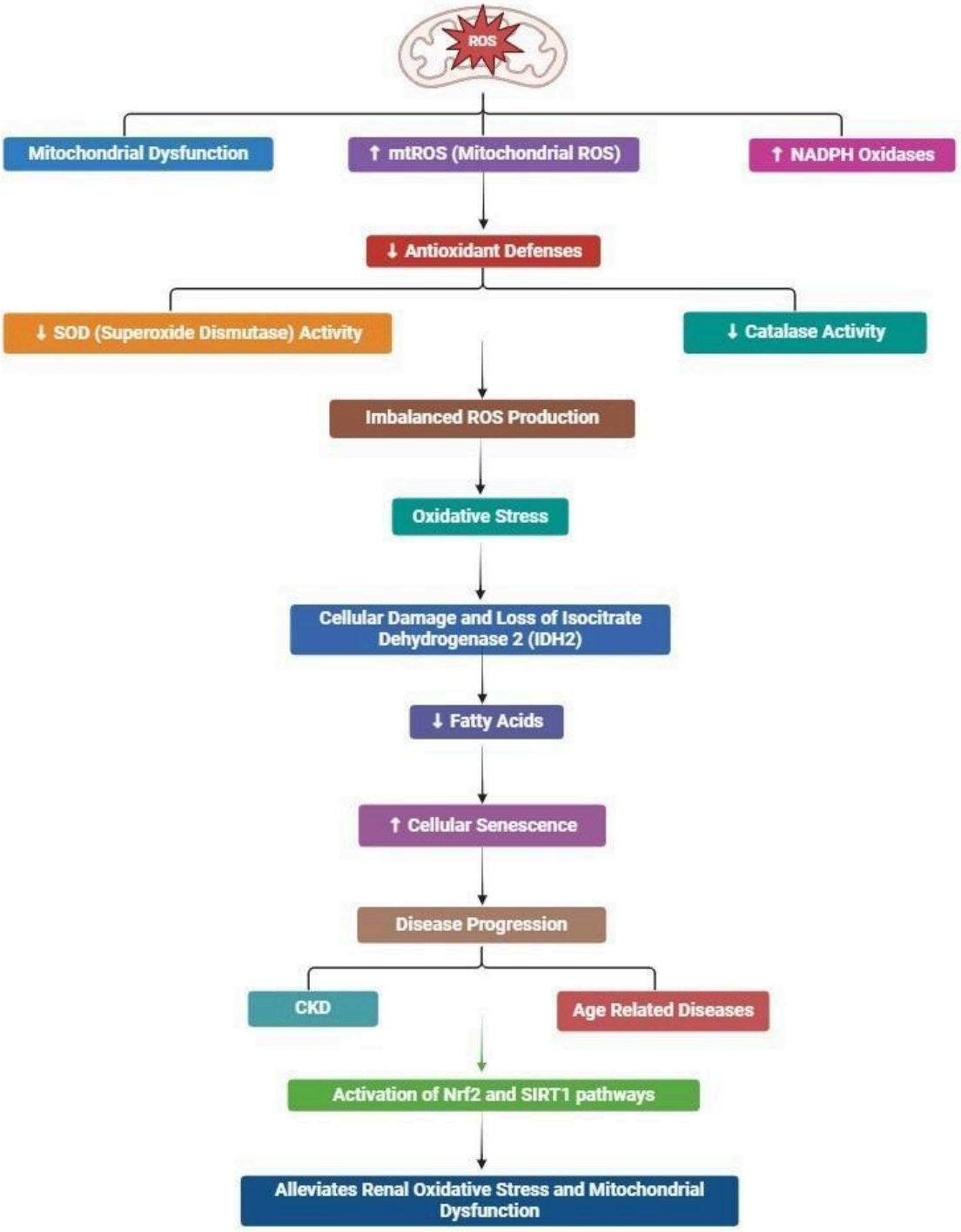

Fig. 2. Sources of ROS and oxidative stress in CKD and Aging. This flow chart shows how increased ROS in aging kidneys leads to oxidative stress, damaging cell membranes, and accelerating senescence. Loss of antioxidants and IDH2 worsen this process while activating Nrf2/Sirt1 pathways can offer protection. *Abbreviations: ROS, reactive oxygen species; CKD, chronic kidney disease; Nrf2, Nuclear factor erythroid 2-related factor 2; Sirt1, sirtuins 1; IDH2, isocitrate dehydrogenase 2.*

Mitochondrial oxidative stress

ROS are molecules capable of independent existence, containing at least one oxygen atom and one or more unpaired electrons. Different compartments generate ROS in cells, with mitochondria being the primary source, generating about 90% of cellular ROS (Tirichen *et al.* 2021). Studies show that ROS levels increase in aged mammalian kidneys (Davalli *et al*. 2016). The depletion of mitochondrial superoxide dismutase (SOD) and catalase (CAT) elevates oxidative stress (Hajam *et al*. 2022), while increased mitochondrial reactive oxygen species (mtROS) disrupts cell membranes and reduces fatty acids, accelerating cellular senescence (Giorgi *et al*. 2018).

Nicotinamide adenine dinucleotide phosphate (NADPH) oxidases also generate ROS, and elevated NADPH oxidase activity can predict oxidative stress in aging kidneys (Zhang *et al*. 2024). Loss of isocitrate dehydrogenase 2 (IDH2) accelerates kidney aging (Lee *et al*. 2017), while activating Nrf2 and Sirt1 pathways alleviates renal mitochondrial damage and oxidative injury (Naghibi *et al*. 2023) (**Fig. 2**). Mitochondrial oxidative stress is higher in CKD kidneys compared to healthy ones. CKD patients show elevated oxidative stress, linked to mitochondrial respiratory dysfunction (Ho and Shirakawa 2022). A biosensor confirmed increased mitochondrial ROS in CKD kidneys (Zhang *et al*. 2021). Thus, treating mitochondrial-targeted antioxidants like mitochondrially targeted 2,2,6,6-Tetramethylpiperidine-oxyl (mitoTEMPO) alleviate podocyte injury in diabetic nephropathy as reported (Qi *et al*. 2017).

Mitochondrial biogenesis

Mitochondrial biogenesis refers to the cellular mechanism responsible for synthesizing new mitochondria and modulating mitochondrial abundance as required. This intricate process involves the harmonized expression of proteins encoded by nuclear and mitochondrial genomes (Selfridge *et al*. 2013). Peroxisome proliferator-activated receptor γ co-activator - 1α (PGC-1α) serves as a key orchestrator of mitochondrial biogenesis, directing the transcriptional apparatus to elevate mitochondrial content and enable tissues to adapt to heightened energy requirements (Sun *et al*. 2021). PGC-1α can be activated through post-translational modifications. Various stressors, including starvation, glucose deprivation and exercise, trigger the activation of PGC-1α via AMP-activated protein kinase (AMPK) mediated phosphorylation and increased nicotinamide adenine dinucleotide (NAD) levels. Elevated NAD levels activate Sirtuin-1 (SIRT1), a NAD-dependent deacetylase that deacetylates and activates PGC-1α (Guan *et al.* 2017; Poyan *et al*. 2018). Activated PGC-1α

translocates to the nucleus, where it stimulates the expression of Nrf1 and Nrf2, leading to the transcriptional activation of nuclear-encoded mitochondrial genes, mitochondrial transcription factor A (Tfam), and the promotion of mitochondrial biogenesis, protein synthesis, and mitochondrial deoxyribonucleic acid (mtDNA) replication (Uittenbogaard and Chiaramello 2014).

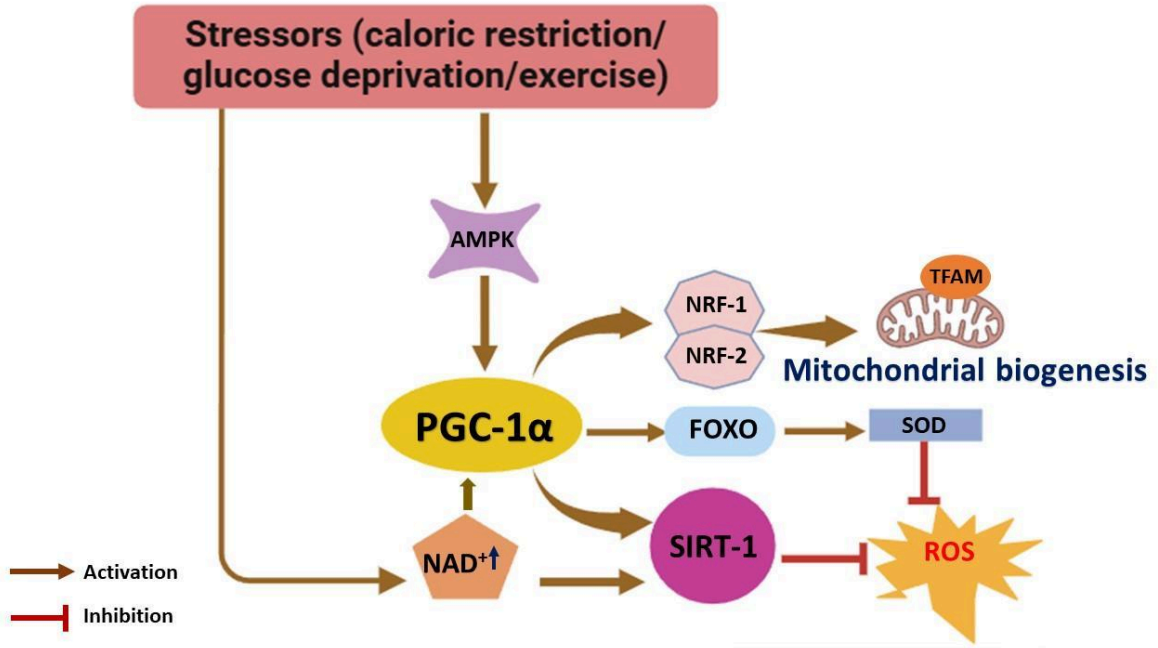

Fig. 3. PGC-1α role in regulating mitochondrial biogenesis and mitigating ROS. The activation of PGC-1α is mediated by AMPK-dependent phosphorylation. Once activated, PGC-1α triggers a cascade of events, including the activation of Nrf1 and Nrf2, which upregulate the transcription of Tfam, promoting de novo mitochondrial biogenesis. Furthermore, PGC-1α activation leads to increased NAD^+ levels, resulting in the activation of SIRT1 and subsequent inhibition of ROS in CKD. Additionally, PGC-1α stimulates the activation of FOXOs, leading to the enhanced expression of antioxidant genes, such as superoxide dismutase (SOD), which counteract ROS and alleviate renal damage. *Abbreviations: Peroxisome proliferator-activated receptor γ co-activator - 1α (PGC-1α), superoxide dismutase (SOD), sirtuins-1 (SIRT1), nuclear respiratory factors 1 and 2 (Nrf1 and Nrf2), forkhead box O1 (FOXO1), Superoxide dismutase (SOD), AMP-activated protein kinase (AMPK), Nicotinamide adenine dinucleotide (NAD+), Chronic kidney disease (CKD), Reactive oxygen species (ROS).*

Furthermore, PGC-1α interacts with various transcriptional partners, including peroxisome proliferator-activated receptor alpha (PPARα), peroxisome proliferator-activated

receptor beta (PPARβ), retinoid receptors (RXR), myocyte enhancer factor-2 (MEF-2), forkhead box O1 (FOXO1) and estrogen-related receptors (ERRs), to regulate multiple energy metabolic pathways within and outside mitochondria (Yuan *et al*. 2023). These pathways are crucial for tissues with high energy demands, such as skeletal muscle, heart, kidney and brain. PGC-1α's transcriptional regulatory network influences genes involved in lipogenesis, mitochondrial fatty acid oxidation, thermogenesis and glucose metabolism, ultimately impacting energy homeostasis and mitochondrial function in metabolically active tissues (Fontecha-Barriuso *et al.* 2020). It has been revealed that PGC-1α acts as a crucial guardian against CKD progression by modulating mitochondrial biogenesis. Studies have demonstrated that decreased PGC-1α expression in CKD patients and animal models is associated with mitochondrial dysfunction, increased oxidative stress and kidney damage (Tran *et al.* 2016). Conversely, enhancing PGC-1α levels in the kidney may offer protective benefits against kidney injury, reducing fibrosis and inflammation (Chambers and Wingert 2020) (**Fig. 3**).

Mitochondria and cell death

Cell death refers to the irreversible loss of cellular function and viability. Cell death occurs in two primary forms. One form, necrosis, involves the catastrophic rupture of the cell membrane, releasing cellular contents into the surrounding environment. The second form is apoptosis, a tightly regulated process where cells undergo orderly self-destruction, with neighboring cells rapidly clearing away the dying cells before membrane rupture and content release occur in response to specific signals (**Fig. 4**). Apoptosis can be activated through intrinsic mechanisms, responding to internal cellular stress, or extrinsic mechanisms, triggered by the engagement of death receptors (Medina *et al.* 2020; Sanz *et al*. 2023). B-cell lymphoma 2 protein (Bcl-2) and Bcl-2-associated protein (Bax) play critical roles in regulating cell fate, with their relative expression levels serving as a molecular switch that determines cellular survival or demise (Yang *et al.* 2001).

During kidney development, apoptosis occurs at an exceptionally high rate. Immature kidneys exhibit widespread apoptotic activity, accompanied by elevated expression of genes involved in programmed cell death. In contrast, adult kidneys respond to injury through cell death mechanisms that affect various renal compartments, including tubular and glomerular structures, as well as distinct cell types such as distal tubular, and proximal cells, glomerular, and endothelial cells (Bard 2002). Renal cell death plays a pivotal role in the pathogenesis of kidney diseases including AKI, and CKD (Havasi and Borka 2011; Priante *et al.* 2019). As CKD advances, the gradual loss of renal tubular cells by apoptosis accelerates, leading to the

deterioration of tubular structure and the accumulation of scar tissue. This process ultimately contributes to the progression of CKD, characterized by the relentless deterioration of kidney function (Choi *et al.* 2000).

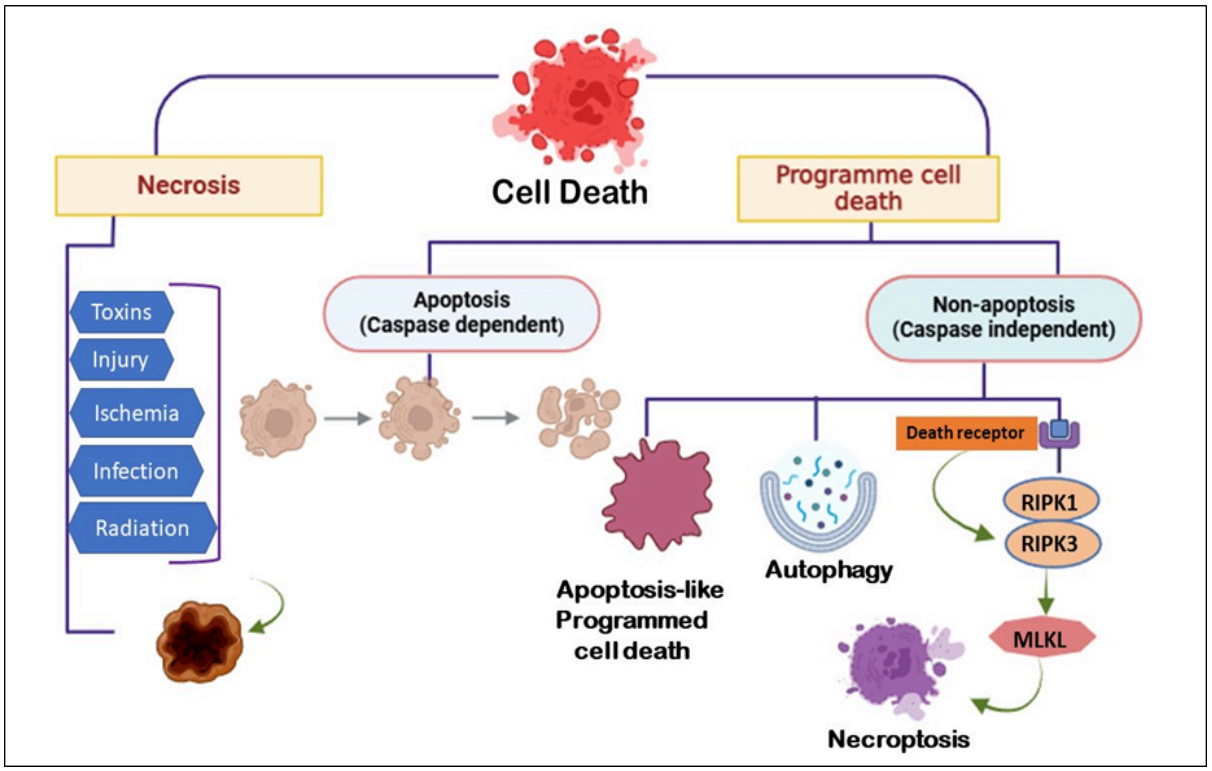

Fig. 4. Cell death is broadly classified into two distinct categories: programmed cell death and necrosis. Programmed cell death is a highly regulated process that encompasses various mechanisms, including apoptosis, which is characterized by cellular shrinkage and DNA fragmentation. In addition to apoptosis, programmed cell death also includes non-apoptotic forms, such as autophagy, a process involving cellular self-digestion; necroptosis, a form of programmed necrosis; and apoptosis-like programmed cell death, which shares similarities with apoptosis but lacks certain characteristic features. *Abbreviations: Deoxyribonucleic acid (DNA), receptor-interacting serine threonine kinase 1/3 (RIPK 1), Mixed lineage kinase domain-like (MLKL).* Adopted from Mustafa *et al.* 2024.

Regulated necrosis encompasses multiple forms, each distinguished by unique molecular signatures and responsiveness to inhibitors. Necroptosis, a kinase-driven process, involves the oligomerization and phosphorylation of receptor-interacting serine threonine kinase 1/3 (RIPK 1) and mixed lineage kinase domain-like (MLKL). In contrast, pyroptosis is a pro-inflammatory form characterized by gasdermin-mediated pore formation. Ferroptosis,

meanwhile, is marked by iron-dependent lipid peroxidation, leading to plasma membrane disruption (Cao and Kagan 2022; Vandenabeele *et al.* 2023). Research from interventional studies suggests that necroptosis, mitochondrial permeability transition-regulated necrosis (MPT-RN) and ferroptosis may play a role in the development of ischemia-reperfusion injury-associated acute kidney injury (IRI-AKI). Studies using mouse models of IRI-AKI have demonstrated that inhibiting necroptosis, either through pharmacological inhibition with Nec1 or genetic deletion of RIPK3, provides partial protection against tubular damage and reduces serum urea and creatinine levels. Although these findings suggest that necroptosis, MPT-RN, ferroptosis and possibly pyroptosis contribute to the development of IRI-AKI, the precise mechanisms by which these pathways interact with specific cell types, and the upstream factors that trigger their activation, remain to be elucidated (Linkermann *et al*. 2012; Xia *et al*. 2021).

Mitochondrial mitophagy

CKD is marked by a gradual decline in renal function and the emergence of kidney scarring (Zhan *et al*. 2015). Studies have shown CKD is accompanied by increased mitochondrial fragmentation and elevated mROS production. Efficient and timely removal of excess or damaged mitochondria in the kidney is essential for preserving cellular homeostasis. Conversely, failure to remove the accumulation of dysfunctional mitochondria exacerbates oxidative stress, leading to tubular apoptosis and kidney damage in CKD (Gamboa *et al*. 2016; Bhatia and Choi 2019). Mitophagy is vital for ensuring mitochondrial function and quality, which facilitates the removal of damaged mitochondria or dysfunctional mitochondria thereby, maintaining mitochondrial balance and ensuring the optimal quality and quantity of these vital organelles (Meng *et al*. 2025). In response to cellular stress, mitophagy is triggered as a protective response to maintain mitochondrial homeostasis. This process can be initiated through two primary mechanisms: the classical ubiquitin-mediated pathway, exemplified by the Phosphatase and TENsin homolog-induced putative kinase 1 PINK1/Parkin Parkinson protein 2, E3 ubiquitin-protein ligase axis, and the receptor-mediated pathway, which encompasses the Bcl2 interacting protein 3, BNIP3/Nix, FUN 14 domain-containing protein 1 (FUNDC1), and cardiolipin pathways (Ashrafi and Schwartz. 2013; Tang *et al*. 2020).

Emerging evidence advocates that mitophagy has a crucial impact on chronic kidney disease mechanisms. Excessive mitophagy may have a self-regulatory effect, suppressing the expression of PINK1 and Parkin, which in turn downregulates these critical genes.

Conversely, a deficiency in PINK1 triggers a compensatory increase in Parkin expression, which significantly inhibits the upregulation of Drp1. This suppression of Drp1, a key regulator of mitochondrial fission and apoptosis, ultimately mitigates excessive mitophagy and renal damage (Zhou *et al.* 2019) (**Fig. 5**). Recent studies propose that augmenting mitophagy could represent a novel therapeutic strategy for CKD (Yang *et al*. 2024).

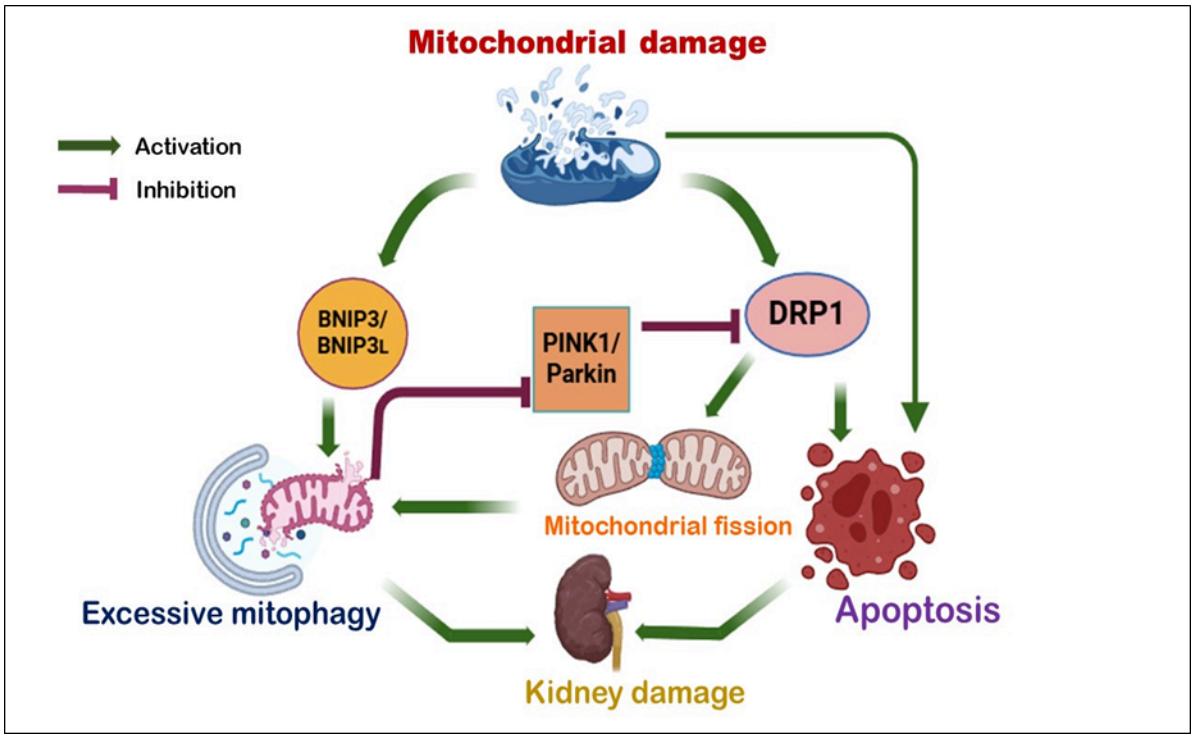

Fig. 5. Damage to the mitochondria of renal tubular epithelial cells triggers a cascade of cellular responses, including mitophagy mediated by BNIP3/BNIP3L, mitochondrial fission regulated by DRP1, and programmed cell death, ultimately leading to kidney damage. *Abbreviations: Phosphatase and Tensin homolog-induced putative kinase 1 (PINK1), Parkinson protein 2 (Parkin2), Bcl2 interacting protein 3 (BNIP3/Nix), Dynamic-related protein 1 (DRP1).*

Mitochondrial epigenetic changes

Mitochondrial epigenetic modifications contribute significantly to CKD pathophysiology by regulating mitochondrial gene expression, which can lead to impaired mitochondrial function, elevated oxidative stress and accelerated kidney damage. Specifically, alterations in mitochondrial DNA methylation patterns can have far-reaching consequences, disrupt mitochondrial function, affect kidney cell viability and contribute to CKD progression (Galvan *et al.* 2017). Research has revealed that epigenetic modifications within

mitochondria can trigger the upregulation of genes involved in fibrogenesis, thereby contributing to the progression of renal fibrosis, a characteristic feature of advanced CKD (Feng *et al.* 2022). This epigenetic reprogramming can lead to the excessive accumulation of extracellular matrix proteins, ultimately disrupting normal kidney architecture and function (Ding *et al.* 2021).

To elucidate the epigenetic alterations that contribute to CKD, researchers are conducting comprehensive analyses of mtDNA methylation patterns in kidney tissue samples from CKD patients (Feng *et al.* 2022; Rysz *et al.* 2022). Studies have also shown that unfavorable conditions during fetal development, including maternal malnutrition or high blood sugar, can predispose individuals to hypertension and kidney disease in adulthood (Lelièvre-Pégorier and Merlet-Bénichou 2000; Ruggenenti *et al*. 2022). By examining how environmental stressors influence mitochondrial epigenetic marks, researchers seek to understand the molecular mechanisms underlying CKD progression better and identify potential therapeutic targets (Yan *et al*. 2024).

Interventional strategies to target mitochondrial dysfunction in CKD

The development of novel mitochondria-targeted therapies is a rapidly evolving field, with several promising strategies underway, including certain antidiabetic medications, sodium-glucose linked transporter 2 (SGLT)- inhibitors and glucagon-like peptide 1 (GLP-1) receptor agonists (Tanriover *et al.* 2023), the use of small molecules, nanocarriers (Yu *et al*. 2020), peptides, mitochondrial transplantation and the design of mitochondria-specific compounds and the development of agents that enhance mitochondrial biogenesis, function and overall bioenergetic capacity (Declèves and Sharma 2014; Huang *et al.* 2023). This review endeavors to summarize the key findings and implications of interventional strategies that target mitochondrial dysfunction, including the use of natural compounds, neuroendocrine modulators (melatonin, serotonin, estrogen), healthy lifestyle and dietary interventions. We will explore the current evidence supporting these interventions, their potential mechanisms of action, and their therapeutic potential for improving mitochondrial function and slowing disease progression in aging and CKD.

Natural compounds

Bioactive compounds derived from natural sources, including plants, animals, and microorganisms, offer a wealth of opportunities for the unearthing and development of new medications. These natural products, composed of single molecules or complex mixtures,

have evolved to produce a wide range of biologically active ingredients (Mu *et al*. 2020; Liang *et al*. 2021; Aranda-Rivera *et al.* 2024). Research has demonstrated that Berberine, a compound extracted from *Coptidis rhizoma* and *Phellodendri Cortex (*Fujii *et al.* 2017) shown to mitigate mitochondrial dysfunction in palmitic acid-induced podocyte, and DKD (diabetic kidney disease) models damaged by the activation of AMPK (Joshi *et al*. 2019), and PGC-1α pathways (Qin *et al.* 2020; Li *et al.* 2021). Furthermore, the salidroside found in *Rhodiola rosea* (Liu *et al.* 2022b; Liang *et al*. 2021), displays a broad spectrum of pharmacological activities, including anti-apoptotic, anti-inflammatory, and mitochondria-protective effects, which contribute to its renal protective properties (Huang *et al.* 2019; Wang *et al.* 2022; Fan *et al.* 2023). Resveratrol, a polyphenol found in Vaccinium species berries (Rimando et. al. 2004), has been found to safely improve renal function and enhance peritoneal ultrafiltration in individuals with kidney disease (Lin *et al*. 2016; Dai *et al.* 2018; Singh *et al*. 2019). Formononetin, a key phytochemical component of *Astragalus membranaceus* (Zhang *et al.* 2018), has also been identified as a potential therapeutic agent, capable of upregulating and activating Sirtuin-1 and mitigating nephrotoxicity in various models of kidney injury (Aladaileh *et al.* 2019; Hao *et al*. 2021; Althunibat *et al.* 2022; Tovar-Palacio *et al.* 2022).

Puerarin, a bioactive compound derived from the root of *Pureraria lobota* (Zhou *et al*. 2014; Tovar-Palacio *et al.* 2022), has been shown to protect mitochondrial damage and inhibit cadmium-induced apoptosis in renal tubular epithelial cells (TECs) (Song *et al.* 2016). Additionally, capsaicin, the most active constituent found in red chili peppers (Lu et al. 2020), has demonstrated therapeutic effects in kidney disease of various animal models including unilateral ureteral obstruction (UUO), DKD (Liu *et al.* 2022a), and nephrotoxicity (Jung *et al.* 2014). Furthermore, sulforaphane, a compound extracted from *Brassica oleracea var. italica* (González *et al*. 2021) has been found to activate the Nrf2 signaling pathway, protecting against mitochondrial oxidative stress and alleviating age-related mitochondrial dysfunction and kidney injury (Briones-Herrera *et al.* 2018; Mohammad *et al.* 2022).

Many studies have verified the therapeutic potential of thymoquinone, a compound derived *Nigella sativa* seeds (Warinhomhoun *et al.* 2023), in enhancing renal mitochondrial function. Thymoquinone enhanced cellular antioxidant defense by increasing the expression of key antioxidant enzymes, notably SOD, catalase, glutathione peroxidase (GPX), and glutathione (GSH), which helps mitigate mitochondrial oxidative stress and restore renal mitochondrial viability through Nrf2 activation (Hannan *et al.* 2021; Hashem *et al.* 2021).

Endocrine modulators

Targeting mitochondrial dysfunction with pharmacological endocrine secretions such as melatonin (Agil *et al.* 2013), serotonin (Hurtado *et al*. 2024), and estrogen-related receptors (ERRs) (Wang *et al*. 2023) has become a viable therapeutic strategy to modulate mitochondrial dynamics, bioenergetic deterioration, oxidative stress and improve kidney functions. Melatonin is a neurohormone primarily produced by the pineal gland (Ganguly *et al*. 2002). Recent investigations have confirmed that melatonin indeed protects against kidney damage caused by diabetes and obesity (Stacchiotti *et al.* 2014; Winiarska *et al.* 2016). Melatonin was found to have a dual beneficial effect on mitochondrial dynamics, suppressing Drp1 expression, a protein associated with the fission of mitochondria, while concurrently upregulating the expression of optic atrophy 1 (Opa1) and Mfn2 proteins involved in mitochondrial fusion (Chang *et al.* 2019). This finding is corroborated by a study demonstrating that melatonin increases Mfn2 expression in the renal convoluted tubules of obese mice (Ding *et al.* 2018; Agil *et al*. 2020).

Serotonin or 5-hydroxytryptamine (5 -HT) is best known as a neurotransmitter with a key function in the central nervous system. Still, it exerts widespread influence through its synthesis and activity in organs like the liver, gut, and kidneys (Hurtado *et al.* 2024). The 5-HT receptor family comprises seven established subtypes, ranging from 5-HT1 to 5-HT7. Research has demonstrated that stimulation of 5-HT1F and 5-HT2 receptors confer renoprotective effects in animal models of AKI, including the induction of mitochondrial biogenesis, attenuation of renal injury, and preservation of vascular integrity (Gibbs *et al*. 2018). In contrast, mice deficient in the 5-HT1F receptor exhibited increased renal vascular leakiness (Dupre *et al*. 2019), impaired renal recovery and decreased mitochondrial biogenesis following bilateral I/R injury (Hurtado *et al.* 2023), highlighting the receptor's role in maintaining renal vascular integrity and function.

Beyond its well-known role in reproductive biology, estrogen and estrogen-related receptors (ERRs) exert significant effects on various physiological processes, including kidney function, in mammalian species (El-Gendy *et al.* 2019). Estrogen receptors in the kidney comprise three main subtypes: ERα, ERβ, and G-protein-couple estrogen receptor (GPER) (Chen *et al.* 2004). These receptors are primarily nuclear but also exhibit cytoplasmic and mitochondrial localization (Lee *et al.* 2013). Animal models of kidney disease have revealed a sex-specific difference in disease progression, with females showing slower progression than males (Neugarten 2002). Estrogen therapy or surgical removal of the testes in male rats has been found to slow disease progression. Moreover, estrogen treatment

has been shown to reduce proteinuria and glomerular fibrosis and decrease markers of glomerular damage in rats with hypertension or puromycin-induced nephrosis (Wen *et al*. 2009; Lee *et al.* 2013). Although the impact of ERRs on age-related mitochondrial decline and chronic kidney disease is not yet fully understood, a recent study demonstrated that the pan-ERR agonist SLU-PP-332 enhanced mitochondrial function and mitigated inflammation in the kidneys of aging mice (Wang *et al.* 2023), highlighting a potential therapeutic avenue worthy of further investigation.

Healthy lifestyle and dietary interventions

Aging is marked by declining tissue and organ function, often paired with chronic inflammation, which can shorten health span and lifespan. Nevertheless, research has identified calorie restriction (CR) as a promising non-genetic intervention capable of preventing age-related diseases and promoting increased longevity, as evidenced by numerous studies conducted in various animal models (Mercken *et al.* 2012; Redman *et al.* 2018). The implementation of CR has been found to profoundly impact various physiological processes. One of the primary benefits of CR is its ability to modulate mitochondrial activity, thereby reducing oxidative damage. This is achieved through the induction of endogenous antioxidant systems, which serve to neutralize harmful reactive oxygen species. Furthermore, CR has decreased metabolic rate, alleviated oxidative stress, and enhanced insulin sensitivity. Additional benefits of CR include improved function of the neuroendocrine and parasympathetic systems, as well as the induction of autophagy and suppression of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB). These adaptations ultimately contribute to improved molecular and metabolic function (Kim *et al*. 2017; Di Francesco *et al*. 2018; Hwangbo *et al.* 2020). Recent research has demonstrated that CR can significantly mitigate ischemia/reperfusion (I/R) injury in aged mice, as evidenced by reduced infarct size. Additionally, CR has been shown to enhance glycolytic processes, independent of I/R injury, and restore myocardial glucose uptake in older mice. This is achieved through the upregulation of key proteins, including p-AMPK, p-PGC1α, SIRT1, and SOD2, and the downregulation of PPAR (Guo *et al.* 2023).

Numerous studies have underscored the significance of regular physical activity in preventing muscle atrophy, enhancing exercise capacity and improving quality of life in patients with CKD. Exercise has also been shown to restore mitochondrial turnover and promote a healthy mitochondrial pool, thereby supporting muscle preservation (Roshanravan *et al*. 2013; Tamaki *et al*. 2014; Isoyama *et al*. 2014) Conversely, a sedentary lifestyle and

reduced skeletal muscle mass in CKD patients is associated with an increased risk of sarcopenia and premature mortality (Joseph *et al*. 2016). Animal studies have demonstrated that exercise protocols, such as swimming or wheel running, can mitigate the decline in mitochondrial density in rodents with renal failure. Specifically, citrate synthase activity, a proxy for mitochondrial density, was maintained in exercising rodents despite disease progression. This preservation of mitochondrial density appeared to prevent the anticipated deconditioning of skeletal muscle, highlighting the importance of maintaining skeletal muscle health for overall well-being (Davis *et al*. 1983; Adams *et al.* 2005).

Chronic alcohol consumption can lead to kidney damage by disrupting mitochondrial function and antioxidant defenses (Harris *et al.* 2015). Additionally, nicotine, found in tobacco, has been shown to mediate the relationship between smoking and renal damage by inducing oxidative stress, characterized by elevated mitochondrial-derived ROS levels in renal proximal tubular cells (Nguyen *et al.* 2015). Maternal smoking can even increase the risk of kidney disease in offspring (Stangenberg *et al*. 2015). Fortunately, adopting a healthy lifestyle, including dietary restrictions, avoidance of harmful habits, and regular physical exercise, can improve overall health by reducing oxidant production and enhancing antioxidant defenses.

Future directions for targeting mitochondrial homeostasis in CKD

Targeting mitochondria may hold significant promise for innovative therapeutic interventions in patients with kidney impairment. By combining mitochondria-targeted interventions with established treatments and lifestyle modifications, it may be possible to prevent or delay the development of CKD and minimize the incidence of severe systemic hitches associated with mitochondrial dysfunction (Granata *et al*. 2015; Jiménez-Uribe and Pedraza-Chaverri 2022). Despite extensive research that has explored various aspects of kidney disease, including mitochondrial metabolism and ROS production, the precise role of mitophagy in CKD remains poorly understood. The mechanisms by which mitophagy modulation influences renal fibrosis, CKD progression, and prognosis require systematic investigation (Yang *et al.* 2024) Elucidating the molecular mechanisms and regulatory pathways of mitophagy in kidney diseases is crucial for developing effective therapeutic interventions.

A new therapeutic strategy, mitochondrial transplantation, has emerged as a potential treatment for kidney disease. However, large-scale clinical trials are necessary to assess the therapeutic potential of mitochondrial transplantation in kidney disease (Tanriover *et al*. 2023). Furthermore, the development of effective therapeutic strategies targeting

mitochondrial homeostasis in CKD is hindered by a lack of understanding of the optimal timing, dosage, and duration of treatment. Natural compounds possess unique properties that make them attractive candidates for developing novel therapeutics that regulate energy metabolism. While their therapeutic potential is well recognized, the specific mechanisms by which natural compounds target mitochondrial dysfunction in kidney diseases remain understudied (Aranda-Rivera *et al.* 2024). By addressing these knowledge gaps and exploring these future directions, researchers can develop effective therapeutic strategies targeting mitochondrial homeostasis in aging and CKD, ultimately improving affected individuals' health span and quality of life.

Conclusion

This comprehensive review highlights the intricate relationships between mitochondrial dynamics, oxidative stress, mitophagy, biogenesis, and epigenetic changes in the context of aging and chronic kidney disease. The evidence underscores the life-threatening role of mitochondrial dysfunction in the pathogenesis of these conditions, emphasizing the need for effective therapeutic strategies. Natural compounds, such as polyphenols and flavonoids, have emerged as promising agents for targeting mitochondrial dysfunction, offering a potential adjunct to conventional therapies. However, further research is necessary to elucidate the molecular mechanisms underlying mitochondrial dysfunction in aging and CKD, and to develop targeted interventions that can be translated into clinical practice. Future investigations should prioritize exploring novel therapeutic targets, developing biomarkers for mitochondrial function and optimizing treatment strategies to improve outcomes for individuals with aging-related CKD. By advancing our understanding of the complex interplay between mitochondrial homeostasis, aging and CKD, we can unlock new avenues for preventing and treating these debilitating conditions.

Disclosure

All the authors declared no competing interests and have consented to the manuscript for submission.

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