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Review

Potential of Small-Molecule Natural Products Against Autophagy Dysfunction in Kidney Diseases

Tanvir Zaman Shoyshob [1,†], Nusrat Afrin [1,2,†], Md Minhajul Islam [1], Mithila Farjana [1], Md. Tarek Ahmed Roni [1], Mithila Sen [1], Mohammad Shafiul Azam [1], Ajahar Islam Hridoy [1,3], Akhi Moni [1] and Md Jamal Uddin [1,*]

[1] ABEx Bio-Research Center, East Azampur, Dhaka 1230, Bangladesh; tanvirzaman749@gmail.com (T.Z.S.); afrinanamikanusrat@gmail.com (N.A.); minhaj.bge@gmail.com (M.M.I.); mithilafarjanabge@gmail.com (M.F.); tarekroni287@gmail.com (M.T.A.R.); mithila.1906025@student.bau.edu.bd (M.S.); shafiulazam786@gmail.com (M.S.A.); hridoy2307271008@diu.edu.bd (A.I.H.); akhimoni840818@gmail.com (A.M.)
[2] Department of Pharmacy, University of Chittagong, Chattogram 4331, Bangladesh
[3] Department of Public Health, Faculty of Health and Life Sciences, Daffodil International University, Savar, Dhaka 1216, Bangladesh
* Correspondence: hasan800920@gmail.com; Tel.: +88-01761928396
† These authors also contributed equally to this work.

Abstract

Kidney disease is an alarming universal health concern and a leading cause of morbidity and mortality. About 861 million individuals around the world suffer from kidney complications. However, current treatment alternatives are limited. These limitations underscore the urgent need for new therapeutic approaches. Autophagy is a dynamic and cellular housekeeping mechanism. The use of conditional autophagy-related gene knockouts in kidney cells has led to a better understanding of autophagy's significance. Basal autophagy in the kidney serves as a quality control mechanism, vital for cellular metabolism and organelle homeostasis. Under stressful conditions, kidney cells adapt their autophagic activity. This process is intricately controlled by signaling pathways that control autophagic flux, with sirtuins, AMP-activated protein kinase (AMPK), and mammalian target of rapamycin (mTOR) acting as key regulators. Additionally, autophagy plays a role in the natural aging process of renal tissue. Small-molecule natural products have demonstrated efficacy in regulating autophagy and mitigating kidney damage in several experimental studies. However, specific mechanisms by which small molecules regulate autophagy across different renal disorders have yet to be fully understood. This study shows that the recent advancements in using small molecules in autophagy research have reignited interest in the related signaling pathways and their role in the pathophysiology of renal diseases. Further research on autophagy and its regulatory signaling networks could provide new therapeutic targets for small-molecule intervention in renal disorders.

Keywords: autophagy; autophagy dysfunction; herbal medicine; kidney diseases; small-molecule natural products

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1. Introduction

According to projections, 700 million individuals worldwide currently have chronic kidney disease (CKD) [1]. The prevalence of kidney disease increases to around 850 million people worldwide when acute kidney injury (AKI) and kidney failure, including dialysis patients and kidney transplant recipients, are considered [2,3]. Current treatment

alternatives, including dialysis and kidney transplantation, are inadequate, inaccessible, and often accompanied by major complications like cardiovascular disease, stroke, and immunosuppression. Thus, it is essential to investigate the effective therapeutic approaches to cure and avert the progression of kidney diseases.

Autophagy is a dynamic, strictly controlled self-degradative process that breaks down cytosolic components through lysosomal enzymes. It is a pro-survival mechanism that has been conserved through evolution and is found in all eukaryotic organisms, such as yeast, plants, and mammals. It serves constitutively as a cellular housekeeping mechanism during relaxation, facilitating the removal of long-lived macromolecules and damaged organelles to restore homeostasis and cellular integrity [4]. Dr. Yoshinori Ohsumi was granted the 2016 Nobel Prize in Physiology or Medicine for his pioneering research on the regulation and functional importance of autophagy, which opened the door for an extensive amount of research on the role of autophagy in human disorders [5,6]. Studies have demonstrated a strong link between autophagy and the underlying cause of various diseases, including kidney diseases [7].

Plants are considered to be a source of medicines for various kidney diseases [8]. Several phytochemicals, such as Ferulic acid, dioscin, resveratrol, celastrol, hispidulin, catalpol, curcumin, berberine, Asiatic acid, astilbin, wogonin, and trigonelline, etc., showed promising activities in terms of autophagic function modulation [9]; thus, they were used to control diabetic kidney disease (DKD) in different in vivo and in vitro models [10–12]. The recent reviews show the beneficial effects of small-molecule natural products in the protection against CKD [13,14]. These findings demonstrate that autophagy is a promising target for therapeutic intervention in kidney disease, while highlighting the potential of traditionally used phytoconstituents. In this review, we explore the mechanisms of action of small-molecule natural products in the context of kidney disease pathogenesis and treatment, highlighting their prospective roles in maintaining autophagic balance.

2. Materials and Methods

A comprehensive literature search was conducted to identify original research articles published in English that focus on therapeutic compounds for kidney diseases and their underlying mechanisms of action. Google Scholar, Web of Science, Scopus, and PubMed are the four main scientific databases that we explored. Natural compounds, kidney disease, phytochemicals, drug delivery approaches, targeted signaling pathways, renal diseases, autophagy, apoptosis, and therapeutic possibilities in kidney treatment were among the relevant keywords and search terms. The retrieval of appropriate information was improved by using binary operators and combinations of these phrases. All of the figures in this manuscript were drawn using Adobe Illustrator version 2020 (Adobe Inc., San Jose, CA, USA) for clarity and visual consistency.

3. Role of Autophagy Dysfunction in the Pathophysiology of Kidney Diseases

Autophagy has been recognized as a key mechanism in various biological processes and diseases [7]. The protective role of autophagy activation and inhibition in CKD has been previously reviewed [15]. Autophagy is frequently impaired in CKD, which leads to cellular malfunction and the progression of the disease. The management of autophagy activation and inhibition is important since too much autophagy can result in cell death, while too little autophagy causes the accumulation of damaged proteins and organelles [16].

Table 1 shows renal cell types, disease stage, regulators of autophagy, signaling pathways, and biomarkers to clarify the contexts in which autophagy activation or inhibition contributes to protective or detrimental outcomes in CKD and related disorders.

Table 1. Cell-type- and disease stage-specific roles of autophagy in kidney diseases.

Kidney Cell Type	Disease Stage/Models	Activator/ Inactivator	Mechanisms/Pathway Involved	Markers	Role of Autophagy	Ref.
Podocytes	CKD	mTOR inhibition (rapamycin, starvation)	mTOR	↑ LC3, Lysotracker	Protective, ↓ Podocytes apoptosis	[17]
Podocytes	ESRD	*mTOR* deletion	mTOR–autophagy signaling pathway	LC3, autophagosomes, damaged mitochondria	Harmful, ↑ Proteinuria and ESRD	[18]
Tubular epithelial cells	ADPKD	Mutation of *pkd1* and *pkd2*	mTOR signaling pathway, cAMP signaling pathway, growth factor signaling	↑ LC3-II, Beclin-1, autophagosomes	Harmful, ↑ cyst formation and enlargement	[19,20]
Primary mouse mesangial cells	Renal Fibrosis model	TGF-β1, TFP, CO (low dose)	TAK1-MKK3-p38 signaling	↑ Beclin-1, ↑ LC3, LAMP-1 colocalization	Protective, ↓ Col-I protein and collagen accumulation	[21]
Mesangial cells	DN	AGEs	RAGE-PI3K—AKT-mTOR signaling	↑ LC3-II/LC3-I, Atg5 ↓ p62	Protective, ↓ AGEs-induced injury and apoptosis	[22]
Mesangial cells	Toxic kidney injury	Cadmium exposure	ROS, GSK-3β activation; Ca^{2+} signaling, mitochondrial depolarization	↑ ROS, LC3	Dual role, ↑ cell death but also acts as protective housekeeping and toxicity biomarker	[23]
Mesangial cells	Stress condition	Stress		↑ LC3, Atg	Dual role, ↑ Type II programmed cell death, TGF-β1	[7]
Podocytes	Aging-associated CKD	*Atg5* gene knockout (autophagy inhibition)	Atg5-dependent autophagy and proteasome pathway dysfunction	Ubiquitinated proteins, oxidative proteins	Harmful, ↑ Damaged proteins, podocyte loss, proteinuria, and glomerulosclerosis	[24]
Distal tubular epithelial cells	Renal fibrosis (UUO model)	*Atg7* gene deletion	TGF-β/Smad4 signaling, NLRP3 inflammasome activation, EMT	LC3-II/LC3-I, PAI-1, E-cadherin, α-SMA, vimentin, FSP-1	Protective, ↓ NLRP3 activation, apoptosis, EMT, and tubulointerstitial fibrosis	[25]
Tubular epithelial cells	AKI	ER Stress/XBP1	XBP1 activation, ULK1, PI3K-Beclin1 initiation	Angiogenin, CRELD2, LC3-II	Protective, ↑ Homeostasis ↓ Misfolded proteins.	[26]
Proximal tubular cells	DKD	High Glucose	Lysosomal dyshomeostasis; mTOR overactivation	LC3, p62 accumulation	Harmful, ↑ Cellular damage and end-stage failure.	[27]
Mesangial cells	DKD	High Glucose	SIRT1 deacetylation, NF-κB inhibition	p65 acetylation	Protective, ↑ Renal function ↓ Fibrosis	[28]

ADPKD: Autosomal Dominant Polycystic Kidney Disease; AGEs: Advanced Glycation End-products; AKI: acute kidney injury; AKT: protein kinase B; ATG5: autophagy-related gene 5; Atg7: autophagy-related gene 7; CKD: chronic kidney disease; CO: Carbon Monoxide; Col I: Type I Collagen; CRELD2: cysteine-rich with EGF-like domains 2; DKD: diabetic kidney disease; DN: diabetic nephropathy; EMT: epithelial–mesenchymal transition; ESRD: end-stage renal disease; FSP-1: Ferroptosis Suppressor Protein 1; GSK-3β: Glycogen Synthase Kinase-3β; LAMP1: Lysosome-Associated Membrane Protein 1; LC3: Microtubule-Associated Protein 1A/1B-Light Chain 3; MKK3: Mitogen-Activated Protein Kinase Kinase 3; mTOR: Mechanistic Target of Rapamycin; NF-κB: Nuclear

Factor Kappa B; NLRP3: NOD-like Receptor Family Pyrin Domain Containing 3; PAI-1: Plasminogen Activator Inhibitor-1; p62: Sequestosome 1; PI3K: Phosphatidylinositol 3-Kinase; pkd1: Polycystin-1; pkd2: Polycystin-2; RAGE: Receptor for Advanced Glycation End-products; SIRT1: Sirtuin 1; Smad4: SMAD Family Member 4; TAK1: Transforming Growth Factor-β-Activated Kinase 1; TGF-β1: Transforming Growth Factor Beta-1; TFP: Trifluoperazine; ULK1: Unc-51-like Kinase 1; XBP1: X-box Binding Protein 1. Activator: mTOR inhibition (rapamycin, starvation), TGF-β1, TFP, CO (low dose), AGEs, cadmium exposure, cellular stress conditions, ER stress/XBP1 activation, high glucose (context-dependent). Inhibitor: mTOR overactivation, Atg5 gene knockout, Atg7 gene deletion, mutation of PKD1 and PKD2, and lysosomal dyshomeostasis. ↑ indicates activation or increase, and ↓ indicates downregulation or decrease.

3.1. Autophagy and Oxidative Stress

Oxidative stress mediates kidney injury by promoting inflammation and cellular damage through excessive reactive oxygen species (ROS) production [29]. It activates signaling pathways that stimulate autophagy, creating a feedback loop that can either protect or harm renal cells, depending on the context [29].

Autophagy is typically activated in response to cellular stressors such as glucose or amino acid scarcity, oxidative stress, hypoxic conditions, and xenobiotic compounds [30]. It has gained recognition as a key regulator of pathological processes, closely linked to ROS, that influences both cellular signaling pathways and oxidative damage [31]. Autophagy serves as a cellular recycling mechanism that mitigates oxidative damage by degrading dysfunctional organelles and proteins, while oxidative stress arises from an imbalance in ROS and antioxidant defenses [32,33]. This interplay is essential for maintaining renal homeostasis and offers potential therapeutic targets for kidney disorders.

Autophagy and oxidative stress are critical factors in the pathogenesis of kidney diseases, influencing both acute and chronic conditions. Autophagy plays a vital renoprotective role in acute kidney injury (AKI), particularly in proximal tubular cells, by maintaining cellular homeostasis through the removal of damaged proteins and organelles [34,35]. Numerous studies have shown that autophagy disruption greatly exacerbates kidney damage. For instance, tubular cells are more susceptible to hypoxemia and reactive oxygen species (ROS) when the autophagy-related gene *Atg5* is deleted globally in mice [36]. Similar to this, *Atg5* deletion specific to the proximal tubule leads to the buildup of damaged cellular components and ultimately culminates in irreversible kidney damage [37,38]. In addition, the discovery that proximal tubule-specific *Atg7* mutant animals also show greater renal damage further supports the significance of autophagy [39]. In several experimental models of AKI, such as kidney injury caused by cisplatin and sepsis, autophagy has been demonstrated to have a protective role [23].

CKD is associated with impaired autophagy, which exacerbates renal damage and dysfunction. Apart from having impaired body homeostasis, protein aggregation, and inflammation, CKD patients exhibit enhanced oxidative stress and increased ROS generation in mitochondria [40]. Targeting the balance between autophagy and oxidative stress enables novel therapeutic strategies for kidney diseases, including the modulation of autophagy to enhance renal recovery [4,41]. Research indicates that interventions aimed at reducing oxidative stress and enhancing autophagy could improve outcomes in patients with kidney diseases [23,42].

3.2. Autophagy and Inflammation

As inflammation is widely acknowledged as the core of most kidney-related diseases, the inflammation pathway can act as a breathing room for treatment [43]. Inflammation is a major component in kidney dysfunction, distinguishable in AKI [44]. Another condition, CKD, arises due to low-grade systemic inflammation, which eventually triggers terminal illness. A few physical states, for instance, metabolic syndrome, diabetes, and heart disease, correlate with low-grade inflammation [45]. In CKD, the elongated inflammation process occurs when an injury leads to the production of proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-1 (IL-1), which later enhances blood circulation, fluctuations in chemical mediators, and the apparent infiltration of leukocytes [46].

The kidney requires the impeccable function of autophagy to preserve an integral endogenous atmosphere; however, dysregulations in autophagy can hinder the process. Disruptive autophagy can be a consequence of inflammation, along with ischemia and virulent injury, which can lead to renal cell cancer [47]. There are some crucial observations suggesting the combined role of inflammasome NOD-like Receptor Family Pyrin Domain Containing 3 (NLRP) and NOD-like Receptors (NLRs) eventually triggers caspase-1 to express IL-1β and IL-18. This phenomenon is instigated by the inflammasome NLRP3, ambiguously related to autophagy dysregulations, leading to several diseases accompanied by kidney disease [48].

The in vitro model, which consists of transwell co-culture endothelial cells along with kidney organoids and an Atg-7-lacking mouse model, precise to the level of endothelial cells in the role of in vivo representation, demonstrated that autophagy disruption in endothelial cells leads to impaired endothelial barrier. This indicated enhanced NLRP3 inflammasome function, resulting in kidney degradation [25].

A clinical study conducted on 60 DKD patients showed a disproportionate rise in inflammatory factors such as AIF-1, miR-34a, NLRP3, IL-1β, and IL-18 in DKD patients' blood and urine samples. Conversely, the presence of autophagy-related gene ATG4B declined in the sample, hence establishing the impact of extreme inflammation on autophagy dysregulation in kidney disease [49].

3.3. Autophagy and Fibrosis

The characteristic symptoms of fibrosis include the loss of capillary networks and the buildup of inflammatory cells, fibrillary collagens, and activated myofibroblasts [50,51]. This fibrogenic response, which is closely linked to inflammation and occurs after various forms of tissue injury, is the initial attempt at tissue repair in the dynamic wound healing process. Fibroblasts and myofibroblasts deposit extracellular matrix (ECM) components, such as fibrillar collagen, elastin, and fibronectin [52]. Renal fibrosis occurs due to injury to the kidney that triggers local pericytes and fibroblasts to proliferate and transform into myofibroblasts, which exhibit greater motility and ECM deposition [53,54]. After severe or repeated AKI, incomplete or maladaptive tubular repair results in persistent inflammation and renal interstitial fibrosis, which links AKI to the advancement of CKD [55–57]. Progressive CKD often results in tubulointerstitial fibrosis. The latest study demonstrates that renal fibrosis is accelerated by persistent autophagy dysfunction or deficiency [58].

After three days of unilateral ureteral obstruction (UUO) in an in vivo rat model, autophagy and interstitial fibrosis peaked in the rat kidneys that had been obstructed. A clinical study explains that in chronic renal graft dysfunction, decreased levels of ATG16L expression hinder autophagy, which elevates inflammation (IL-1β, IL-6, and TNF-α) and induces EndMT and renal interstitial fibrosis [59]. The 3-methyladenine (MA)-induced autophagy suppression consequently decreased Akt/mTOR signaling, exacerbated tubular

cell death, and interstitial fibrosis [60]. Another study exhibited that autophagy has a protective function in diabetic nephropathy, as demonstrated by diabetic mice with impaired autophagy and exacerbated renal hypertrophy, tubular damage, inflammation, fibrosis, and albuminuria after Atg7 was ablated from the proximal tubules [61]. Again, pharmacologically inhibiting autophagy in UUO mice significantly decreased the accumulation of lipids in kidney tubules, which resulted in a decrease in tubular cell degeneration and apoptosis, as well as the suppression of kidney interstitial fibrosis [62].

In an in vitro experiment, autophagy inhibitors inhibited the accumulation of fibrotic proteins and the secretion of pro-fibrotic growth factors in renal proximal tubular cells, which were activated by repeated low-dose cisplatin treatment. After cisplatin nephrotoxicity, results demonstrated the crucial role autophagy plays in maladaptive kidney repair and interstitial fibrosis, improving the generation and release of pro-fibrotic cytokines [63]. Another study showed that TGFβ1 caused primary proximal tubular cells to undergo autophagy, death, and FN1 accumulation in vitro. While autophagy promotion boosted TGFβ1-induced cell death, autophagy suppression decreased both FN1 accumulation and apoptosis. According to these results, renal interstitial fibrosis during UUO may be facilitated by persistent autophagy activation in kidney proximal tubules, regulating tubular cell death, interstitial inflammation, and the synthesis of profibrotic factors [64].

3.4. Autophagy and ER Stress

The endoplasmic reticulum (ER) plays a numerous function, which includes the transportation of proteins to the cell surface or various organelles, as well as being associated with the processing, synthesis, and folding of proteins [65]. When excess misfolded proteins accumulate in the ER, ER stress occurs, and the unfolded protein response (UPR) is activated to restore homeostasis [66]. However, if ER stress becomes severe or ongoing, the adaptive UPR pathway may be interfered with, and UPR-related apoptosis may be triggered [67].

Recent studies have shown that ER stress affects kidney function and that increased markers of ER stress are found in renal biopsies of AKI patients [14,68]. In numerous murine models, the genetic silencing of RTN1A reduces kidney damage, apoptotic signaling, and ER stress [69,70]. Mechanistic investigations further show that RTN1A interacts with PERK (PKR-like ER kinase) to promote the activation of ER stress pathways mediated by CHOP (C/EBP homologous protein) [69]. Urinary angiogenin was produced by renal tubular cells as a result of the activation of the transcription factor XBP1 during ER stress, indicating the incidence of ER stress in this clinical situation [26]. Cysteine-rich with EGF-like domains 2 (CRELD2) is a newly identified urinary biomarker that sensitively detects ER stress and is significantly increased in uromodulin (UMOD)-associated kidney diseases, such as ischemic AKI [71]. Autophagy is the degradation of misfolded proteins and damaged organelles by lysosomes, resulting in the release of essential components for cellular metabolism [72]. Generally, during prolonged oxidative stress, AMPK is suppressed [41]. The ATG genes, *AMPK*, and the mechanistic target of rapamycin (*mTOR*) all control it. The autophagy process can be triggered by AMPK activation or mTOR inhibition [73,74]. The PI3K–Beclin1 (Phosphoinositide 3 kinase) complex is activated by ULK1 (Serine/Threonine Kinase Unc-51-like Kinase-1) to commence autophagy. This results in the formation of autophagosomes, which mature through Atg12 and LC3 before being transported to lysosomes for destruction, with LC3-II serving as a key autophagy marker [75]. This correlation is especially important in AKI, where autophagy is activated as a protective mechanism [76,77].

Abnormal regulation of autophagy associated with pathogenic ER stress causes podocyte injury and tubular cell apoptosis, which accelerates CKD progression [67]. Similarly, in podocyte models, Inositol-requiring enzyme 1 deletion causes microvilli alterations

and foot process shrinkage, which increases albuminuria due to reduced autophagy [78]. ER stress does not always promote autophagy. In certain pathological conditions, such as neurodegenerative diseases, ER stress can disrupt the autophagy process [79]. Studies have shown that the deletion of the Atg5 gene in podocyte cells of aged mice (20–24 months) results in glomerulosclerosis and podocyte degeneration, ER stress, decreased proteasome activity, accumulation of ubiquitinated proteins, and albuminuria [80]. In contrast, young mice showed no significant problems and only low levels of albuminuria; multiple unspecified mechanisms may be at work behind protein accumulation when autophagy is disrupted [81].

3.5. Molecular Mechanisms Involved in Autophagy Dysfunction in Kidney Disease

Autophagy, a crucial cellular housekeeping mechanism (Figure 1), plays an essential role in maintaining kidney cell health, particularly under stress [82]. In healthy kidneys, autophagy removes damaged proteins and organelles, sustaining cellular function and homeostasis. However, impaired or dysregulated autophagy is increasingly recognized as a central contributor to various kidney diseases, including DKD, CKD, and uric acid nephropathy [83,84]. In DKD, which is a major cause of end-stage renal failure, high-glucose environments disrupt autophagic processes, exacerbating cellular damage [27]. Podocytes and proximal tubular cells are especially vulnerable, with impaired autophagy accelerating their dysfunction [83]. Similarly, lysosomal dyshomeostasis—critical for autophagic flux—has emerged as another layer of dysfunction in DKD, suggesting that strategies to enhance lysosomal function may hold therapeutic promise [85]. Hyperuricemia-induced kidney injury also involves autophagy dysregulation. In urate oxidase knockout rat models, elevated serum urate levels triggered kidney inflammation and fibrosis through autophagy-related pathways, including AMPK, p38 Mitogen-Activated Protein Kinase (p38 MAPK), Extracellular Signal-Related Kinase (ERK), and c-Jun N-terminal Kinase (JNK) [84]. Notably, inhibiting autophagy via the PI3K pathway mitigated these effects, underscoring the complex, sometimes detrimental, role of autophagy in kidney pathology [84]. In CKD, the scenario is equally nuanced. Impaired autophagy contributes to progressive damage and renal fibrosis, often influenced by cytokines like TGF-β1, which has dual roles—promoting both fibrosis and autophagy depending on the disease context. Protective autophagy activation in proximal tubular cells has been shown to counteract stressors such as proteinuria and ischemia [83]. However, these effects are tightly modulated by multiple intersecting signaling pathways [86,87].

A network of signaling pathways controls autophagy, including the PI3K/Akt/mTOR system, which inhibits autophagy [87,88], the AMPK/ULK1 [89] and SIRT1/LC3 pathways, which promote autophagy activation in response to cellular and metabolic stress [90,91]. Additionally, the ERK, STING1, and PKC pathways demonstrate context-dependent roles in either promoting or inhibiting autophagy, influencing outcomes in inflammation, fibrosis, and toxic injuries [92,93]. Autophagy also intersects with regulated cell death pathways, including apoptosis, necroptosis, and ferroptosis, adding further complexity to kidney disease mechanisms [94]. These processes contribute to inflammation and fibrosis, highlighting autophagy as a potential modulator of broader cell fate decisions in the kidney. Despite significant advances, the dual nature of autophagy—as both protective and potentially harmful—underscores the need for precise, context-specific modulation [27,85].

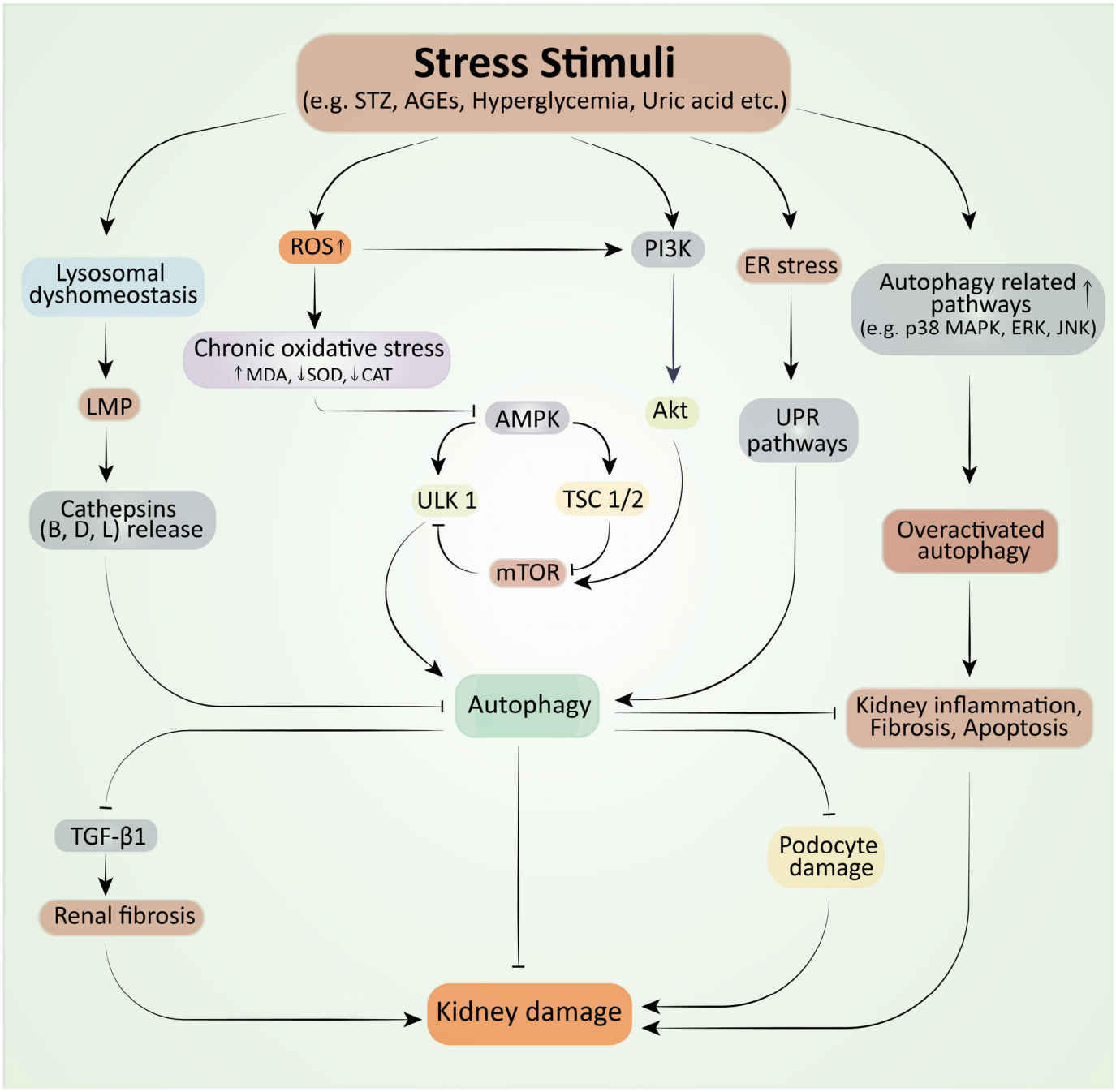


Figure 1. Autophagy dysfunction in kidney disease. Stress stimuli STZ, AGEs, hyperglycemia, and uric acid raise ROS production, which lowers antioxidant enzyme (SOD, CAT) activity and causes oxidative stress. As a result, chronic oxidative stress disrupts autophagy by inhibiting the AMPK pathway. Elevated ROS also suppresses autophagy through the activation of the PI3K pathway. The hyperglycemia condition triggers the PI3K pathway, which in turn triggers the mTOR pathway through the activation of the Akt pathway, finally resulting in a reduction in autophagy. The lysosomal dyshomeostasis causes LMP, which releases cathepsins and suppresses autophagy. ER stress also activates autophagy through the activation of the unfolded protein response (UPR) pathway. Both autophagy disruption and overactivation by several pathways (p38 MAPK, ERK, JNK) cause inflammation, fibrosis, apoptosis, and injury in podocytes. Collectively, these pathological mechanisms lead to kidney damage. ↑ indicates activation or increase, and ↓ indicates downregulation or decrease.

4. Therapeutic Effects of Phytochemicals Against Autophagy Dysfunction in Kidney Diseases

Table 2 and Figure 2 show the pharmacological potential of various phytochemicals against several pathophysiological mechanisms (i.e., oxidative stress, inflammation, fibrosis, and other pathologies) in autophagy dysfunction in kidney diseases.

Table 2. Effects of phytochemicals on autophagy dysfunction in kidney diseases.

Disease Models (Animals and Cells)	Phytochemicals	Doses and Times	Alterations in Autophagy and Renal Outcome	Alterations in Mechanism/Pathway Involved	Ref.
Sepsis-induced AKI in rats	Resveratrol	30 mg/kg; i. p. for 5 days	↓ Renal tubular damage	↑ p53 deacetylation, deacetylase Sirt1	[91]
DKD in experimental rats	Ferulic acid	50 mg/kg, orally, daily for 8 weeks	↓ Kidney injury, apoptosis, inflammation, and defective autophagy	↑ AGEs, MAPKs, NF-κB, modulation Autophagy, ↓ mTOR	[10]
STZ-induced diabetic rats	Icariin	20, 40, and 80 mg/kg orally, daily for 12 weeks	↑ Autophagy ↓ Tubulointerstitial fibrosis	↑ GLP-1R ↓ mTOR phosphorylation	[95]
STZ/HFD-induced T2DM rats	Isorhamnetin	50 mg/kg, orally and daily for 4 or 8 weeks	↑ Renal function, glucose/lipid metabolism, autophagy	↑ FYCO1, ULK-1, TECPR1, WIPI	[96]
STZ-treated Male Sprague Dawley rats	*Cyclocarya paliurus* triterpenic acids	40 and 160 mg/kg CPT intragastric, daily for 10 weeks	↑ Autophagy; ↓ kidney injury and apoptosis	↑ p-AMPK; ↓ p-mTOR	[97]
Arsenic-induced nephrotoxicity in rats	Zingerone	50 mg/kg, orally for 14 days	↓ Oxidative stress, inflammation, apoptosis, and kidney damage; excessive autophagy	↑ AKT2 and FOXO1, ↓ NF-κB and IL-1β, TNF, IL-6, iNOS, COX-2, MAPK14, MAPK15, JNK	[98]
Sprague-Dawley rats with puromycin aminonucleoside	*Plantago asiatica*/major (Hispidulin)	200 mg/kg oral gavage, daily for 7 days	↑Autophagy; ↓ Podocyte apoptosis, Proteinuria	↑ MAPK pathway (animal models)	[99]
Male C57BL/6 UUO mice model	Sulforaphane	25–75 mg/kg; i. p. daily for 7 days	↓ Renal fibrosis	↑ mTOR pathway	[100]
High-glucose-induced podocyte injury	Ursolic acid	In vitro: 5 μmol/L for 24 h (in vitro)	↑ Autophagy, ↓ Podocyte injury	↓ miR-21, ↑ PTEN, ↓PI3K/Akt/mTOR pathway	[101]
Serum of DKD mice	Tripterygium glycoside	In vitro: 1.25 μg/mL, 72 h	↑ Autophagy; ↓ EMT and podocyte apoptosis	↓mTOR/Twist1 pathway	[102]
High-glucose-induced podocyte	Isorhapontigenin (polyphenol)	In vitro: 10 μM and 20 μM for 10 to 14 days	↑ Autophagy, ↓ Oxidative stress, podocyte/endothelial cell damage	↑ AMPK/Nrf2 pathway, Beclin-1, Atg5, ↓ P62	[103]

DKD: diabetic kidney disease; CKD: chronic kidney disease; AKI: acute kidney injury; MAPKs: Mitogen-Activated Protein Kinases; STZ: Streptozotocin; HFD: high-fat diet; T2DM: type 2 diabetes mellitus; SD: Sprague Dawley; and UNx: Uninephrectomy. ↑ indicates activation or increase, and ↓ indicates downregulation or decrease.

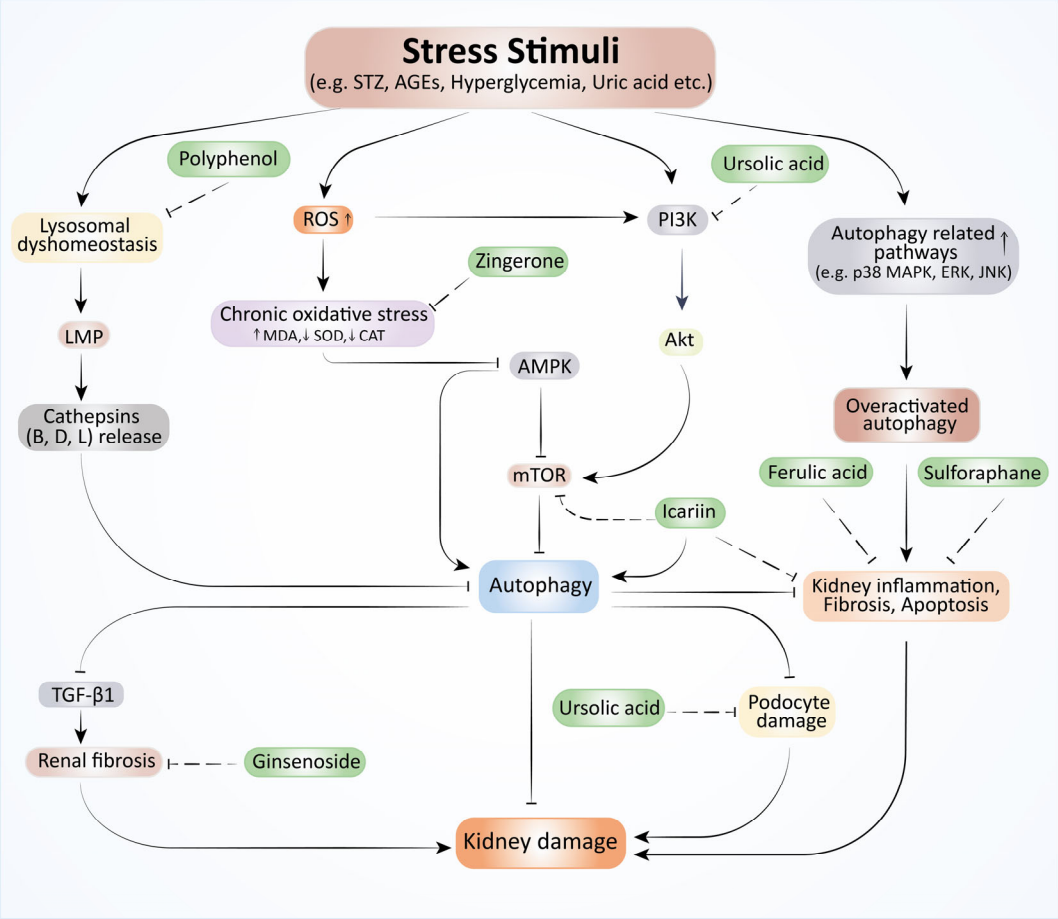


Figure 2. Schematic representation of stress-induced pathways leading to kidney damage and the modulatory effects of natural compounds. Stress stimuli such as STZ, AGEs, hyperglycemia, and uric acid trigger lysosomal dyshomeostasis, ROS accumulation, PI3K/Akt signaling, and autophagy-related pathways (e.g., p38 MAPK, ERK, JNK), contributing to chronic oxidative stress, overactivated autophagy, renal fibrosis, podocyte damage, and ultimately kidney injury. Key molecular players include LMP (lysosomal membrane permeabilization), cathepsins, AMPK, mTOR, and TGF-β1. Natural compounds, including polyphenols, zingerone, ursolic acid, icariin, ginsenoside, ferulic acid, and sulforaphane, can modulate these pathways, reducing oxidative stress, autophagy dysregulation, inflammation, fibrosis, and apoptosis, thereby mitigating kidney damage. ↑ indicates activation or increase, and ↓ indicates downregulation or decrease.

4.1. Acute Kidney Injury

AKI is a condition where kidney function abruptly diminishes to maintain its basic function, which may further lead to CKD with a significant fatality rate. AKI is identified through the increased serum creatinine level and the low volume of urine production [104].

Autophagy initiation in proximal tubules illustrated its nephrotoxic utility in AKI; however, dysregulated autophagy eventually leads to decreased cell activity [105]. A study demonstrated the promising impacts of fibroblast growth factor 10 in alleviating IRI-AKI by hindering disproportionate autophagy, which is thus perceptible as a significant therapeutic objective for AKI [106]. Several studies demonstrated the crucial impact of omitted autophagy protein-related consequences, which ultimately had a detrimental effect on renal function, as well as rising P62 levels and oxidative stress. Moreover, autophagy dysregulation is associated with impaired tubules, indicating that dysregulated autophagy pathways possess potential therapeutic sites [107].

Rapamycin is regarded as an autophagy inducer and is used in AKI therapeutic strategies along with some autophagy inhibitors, such as 3-MA and Chloroquine [108].

Nevertheless, these interventions are unable to ensure a reduced mortality rate in AKI-related cases. At present, despite some interventional therapeutic strategies, renal replacement therapy remains the only effective approach in the minimization of AKI [109]. Since AKI has come to be regarded as a global health concern, an approach based on applying traditional Chinese medicine (TCM), which is enriched in phytochemicals, has shown some splendid clinical outcomes [110]. Phytochemicals present in TCM demonstrated their efficacy via their effect on different pathways of AKI, e.g., reducing oxidative stress, modifying autophagy, and lessening impairment in mitochondria [111]. Berberine (BBR), an active organic compound originating from rhizomacoptidis, exhibits widespread pharmacological impact in mitophagy. By inhibiting NLRP3 inflammasome instigation, BBR initiates mitophagy in contrast-induced AKI (CI-AKI) mice [112]. Another bioactive compound, Tetramethylpyrazine (TMP), exhibited its potential in modulating mitochondrial autophagy in renal tubular cells by overwhelming the CCL2/CCR2 pathway [113]. A recent study revealed the role of Paeoniflorin (PF), derived from *Paeonia lactiflora* Pal, in attenuating the damage of autophagy flux due to intestinal I/R through LKB1/AMPK trail initiation [114]. Furthermore, Neferine (Nef), a bisbenzylisoquinoline alkaloid and a bioactive compound, possesses diverse pharmacological potentials, including autophagy stimulation in CIS-induced AKI [115]. An earlier study of Quercetin's impact on prompted the initiation of SIRT1, eventually leading to p53 deacetylation. These phenomena endorsed autophagy in renal TECs, ultimately decreasing sepsis-induced AKI [91]. In both in vivo and in vitro studies, an investigation concentrated on proteins and genes concomitant with kidney injury, apoptosis, and autophagy. BBR evidently displayed a substantial defensive approach against CI-AKI. BBR initiated autophagy, as per the deviations that occurred in autophagy-related proteins and autophagic flux [116].

4.2. Chronic Kidney Disease

CKD involves progressive loss of kidney function due to structural and functional changes [117]. It is characterized by nephron loss, inflammation, myofibroblast activation, and ECM deposition. Lipotoxicity, oxidative stress, inflammation, and fibrosis lead to the exacerbation of CKD, which is a global health concern affecting 10% of the population [86,118].

Ultimately, the primary cause of CKD progression to end-stage renal disease (ESRD) is renal fibrosis. Autophagy can be activated as an endogenous defense mechanism in podocytes and renal tubular epithelial cells, and CKD progresses when the autophagic process is compromised [119]. In kidney cells, oxidative stress, inflammation, and mitochondrial dysfunction alter autophagy activation and inhibition, which results in dysfunctional cellular recycling [23]. Since autophagy may either protect or damage cells depending on the experimental setup, targeting autophagy malfunction in CKD patients with phytochemicals is a possible therapeutic approach [120].

A recent computational study reported that potential plant flavonoids may have potential against kidney fibrosis targeting TGFβR-1 [13]. Curcumin could potentially treat CKD by improving renal autophagy in rats with experimental membrane nephropathy via controlling the Nrf2/HO-1 and PI3K/AKT/mTOR signaling pathways [121]. Similarly, in renal tubular epithelial cells, ginsenoside Rb1 (G-Rb1) improves autophagy through the AMPK/mTOR pathway both in vitro and in vivo [122]. In addition, Astragaloside IV boosted autophagy activation and markedly suppressed PI3K/AKT/AS160 pathway activity in both in vitro and in vivo conditions [123]. Likewise, Isovitexin (IV) alleviated renal injury and inflammation by promoting protective autophagy primarily through its anti-ROS production, anti-inflammation, and anti-pyroptosis in mice [124]. Notably, Phytosterols (PS), especially stigmasterol and β-sitosterol, alleviate CKD-related renal damage by stimulating PINK1/Parkin-mediated mitophagy and reducing inflammation,

highlighting the role of PS and autophagy in CKD therapy [125]. Furthermore, Danggui Shaoyao San (DSS) reduces TGF-β1-induced apoptosis and fibrosis in NRK-52E renal cells by promoting autophagy, highlighting the potential of phytochemicals targeting autophagy to slow CKD progression [126]. Moreover, Pterostilbene (PT) induces autophagy, which may help prevent renal fibrosis by attenuating NLRP3 inflammasome activation and epithelial–mesenchymal transition, indicating its potential clinical application for better CKD management [127]. Meanwhile, sulforaphane (SFN) reduces renal fibrosis in UUO mice by dual-regulating mTOR-mediated autophagy, increasing autophagy in renal fibroblasts and decreasing it in tubular epithelial cells, emphasizing SFN's potential in CKD treatment through autophagy modulation [100].

By contrast, Rhein suppresses autophagy in rat renal tubular cells by modulating AMPK/mTOR, p38/Erk MAPK, and Akt-independent pathways, suggesting its potential therapeutic role in treating CKD patients in the clinic [128]. Finally, Rhubarb–Astragalus may improve CKD, possibly by inhibiting autophagy via the p38-MAPK/TGF-β1 and p38-MAPK/smad2/3 pathways [129].

4.3. Obesity-Related Nephropathy

Obesity-related nephropathy (ORN) is a growing health concern due to its rising incidence and progressive impact on kidney function. Obesity acts as a potent risk factor for CKD, primarily through the interplay of lipotoxicity, insulin resistance, systemic inflammation, and adipocyte dysfunction; these features ultimately impair renal structure and function [130]. Histopathological features such as obesity-related glomerulopathy (ORG) emerge as specific manifestations, characterized by glomerular hypertrophy, focal segmental glomerulosclerosis, and altered renal hemodynamics [131]. Additionally, the adipose–renal axis—involving proinflammatory adipokines and metabolic disturbances—contributes significantly to ORN progression [132].

Despite current treatment strategies—including renin–angiotensin–aldosterone system (RAAS) inhibitors, sodium–glucose co-transporter 2 (SGLT2) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, and bariatric surgery—many patients continue to experience progressive renal decline, as these therapies do not specifically target the underlying mechanisms of obesity-induced kidney injury [132,133]. Given this limitation, phytochemicals have attracted considerable attention for their potential to modulate oxidative stress, inflammation, and autophagy dysfunction—key processes in obesity-related kidney damage. This therapeutic gap has spurred interest in phytochemicals for their ability to influence key pathological pathways such as oxidative stress, inflammation, and autophagy dysfunction, all of which contribute to obesity-related nephropathy. Among these, Wedelolactone (WDL)—a bioactive compound isolated from *Eclipta prostrata*—has demonstrated anti-obesity effects in preclinical models, primarily through the activation of the SIRT1, AMPK, and peroxisome proliferator-activated receptor alpha (PPARα) signaling axis. This activation not only improves energy metabolism and glucose tolerance but may also support kidney health indirectly by alleviating obesity-induced metabolic strain [134]. Similarly, sulforaphane, found in broccoli sprouts, enhances nuclear factor erythroid 2 (NRF2) activity, thereby reducing hepatic gluconeogenesis and systemic oxidative stress. In diabetic and obese models, sulforaphane supplementation lowered fasting glucose and improved HbA1c, pointing to its relevance in managing obesity-related metabolic and renal dysfunctions [135]. NRF2 is a key transcription factor involved in regulating the cellular antioxidant response and protecting renal tissues from oxidative stress and inflammation. Natural bioactive compounds such as resveratrol, curcumin, and quercetin have been found to stimulate NRF2 activation and promote its translocation to the nucleus. This activation leads to the upregulation of detoxifying and antioxidant enzymes, includ-

ing heme oxygenase-1 (HO-1) and glutathione S-transferase (GST). Additionally, these phytochemicals can suppress the expression of proinflammatory cytokines like IL-6 and TNF-α. Through these mechanisms, NRF2 activation may play a crucial role in mitigating autophagy dysfunction associated with obesity-related kidney damage [136,137]. Furthermore, bilberries and blueberries, rich in anthocyanins and polyphenols, demonstrate the ability to reduce inflammation, improve cytokine profiles, and ameliorate glucose and lipid metabolism in obese models. In high-fat-diet-fed mice, blueberry polyphenols embedded in defatted soybean flour (BB-DSF) reduced weight gain, improved glucose tolerance, and lowered fasting glucose and serum cholesterol levels. In vitro studies further revealed their ability to suppress hepatic glucose production—highlighting the potential of polyphenol-enriched foods in mitigating metabolic dysfunctions underlying ORN [138]. Betaine, a naturally derived osmoprotective compound present in dietary sources such as beets, spinach, wheat, and certain seafood, supports cellular homeostasis and overall metabolic function. Endogenously, it is produced via the oxidation of choline. Studies using high-fat-diet-induced models have shown that betaine supplementation can enhance metabolic performance and reduce insulin resistance [139]. Moreover, individuals with CKD often exhibit reduced circulating betaine levels, which are associated with metabolic syndrome and unfavorable clinical outcomes, indicating its relevance as a potential therapeutic or diagnostic marker in CKD management [140]. Dietary patterns rich in phytochemicals—fruits, vegetables, legumes, and whole grains—have been inversely associated with the risk of diabetic nephropathy, a condition that shares overlapping mechanisms with obesity-related kidney disease. The protective effects are attributed to improved glucose tolerance, reduced inflammation, and blood pressure control [141]. Cinnamon, widely used in traditional medicine, contains active compounds that reduce oxidative stress, modulate gut microbiota, and improve metabolic profiles—traits that make it a potential complementary therapy for obesity-related CKD [142].

Despite their promise, the therapeutic efficacy of phytochemicals is influenced by their metabolism, bioavailability, and interaction with gut microbiota. Processes like glucuronidation, methylation, and hepatic transformation determine their systemic availability and renal protective effects. Understanding this area of pharmacokinetics is essential for optimizing dosing and delivery systems, potentially paving the way for personalized phytochemical-based therapies in metabolic and renal disorders [143]. These findings suggest that phytochemicals, through the modulation of autophagy, metabolic signaling pathways, and antioxidant defense, offer a promising adjunct or preventive approach against obesity-related nephropathy. However, further clinical validation and mechanistic studies are warranted to clarify their bioavailability, dosage, and long-term effects in human subjects.

4.4. Diabetic Nephropathy

Diabetic nephropathy (DN) is a long-term complication of diabetes, and its clinical and pathological characteristics take many years to develop in the human body [144]. DN occurs in patients with both type I and type II diabetes, and its main clinical features are proteinuria and the progressive deterioration of the glomerular filtration rate [145]. Mortality in patients with DN is about 30 times higher than that in patients with diabetes but without DN [146]. In primary DN, there is glomerular enlargement, mesangial expansion, and basement membrane thickening. Advanced DN exhibits nodular glomerulosclerosis, mesangiolysis, and tubulointerstitial fibrosis [147]. Nutrient-sensing signaling pathways regulate autophagy activity and are disrupted by metabolic stress in diabetes [148,149]. Reduced autophagy activity contributes to DN pathogenesis, and an auspicious therapeutic target for DN may be the restoration of autophagy activity [150,151]. Re-

cently, phytochemicals have been increasingly measured against autophagy dysfunction in kidney diseases.

BBR, derived from *Rhizoma Coptidis* and *Phellodendron amurense Rupr.*, can stimulate autophagy by activating the AMPK signaling pathway, and can reduce podocyte cell death (apoptosis) caused by a high-glucose environment [152]. Similarly, curcumin reduces cell death (apoptosis) and increases protective autophagy by phosphorylating the PI3K/Akt signaling pathway in tubular epithelial cells of AGE-induced rats [153]. Also, the phenolic-rich fraction of Golden berry (*P. peruviana* L.) may help prevent diabetic nephropathy by increasing autophagy and reducing cell death through the AMPK/mTOR signaling pathway [154]. In vivo studies have found that the Keluoxin Capsule regulates autophagy in podocytes and that it works by increasing the expression of LC3-II and p62 proteins [155]. Furthermore, the Dendrobium mixture is effective in protecting the kidney in the streptozotocin (STZ)-induced rat model, which suppresses PI3K/Akt/mTOR signaling pathway and increases autophagy in the kidney [156]. In addition, the Yishen Capsule increases the expression of Beclin-1, SIRT1, and LC3-II proteins and simultaneously reduces the expression of NF-κB p65 [157]. Researchers have shown that flavonoids are effective in preventing the development of STZ-induced experimental diabetic nephropathy, inhibiting disease progression by reducing the expression of AGEs, collagen IV, laminin, as well as TGF-β1, p-Smad 2/3, and CTGF proteins in mice [158]. In vitro experiments have shown consistent results in podocytes in a high-glucose environment [159]. Celastrol has been reported to protect podocytes from inflammatory responses and restore podocyte viability by activating heme oxygenase-1-mediated autophagy [160]. Astragaloside IV has been reported to play a critical role in reducing the overproduction of ECM proteins and stimulating autophagy through the regulation of Sirt1/NF-κB signaling in KK-ay mice [28]. In addition, resveratrol also reduces kidney cell death by stimulating autophagy in podocytes of db/db mice in vitro, and reduces damage in DKD by suppressing miR-383-5p and increasing miR-18a-5p [161,162]. Leaf extract from *Cassia auriculata* ameliorates kidney damage by reducing autophagy-related necroptosis through RIP-1/RIP-3-p-p38MAPK signaling in glomerular endothelial cells of STZ-induced rats [163]. A recent study showed that *Radix astragali* delayed the development of DKD by increasing podocyte autophagy and possibly suppressing the PI3K/Akt/mTOR pathway [164]. In vivo experiments showed that Tongluo Digui decoction protected podocytes and reduced proteinuria by inhibiting mTOR phosphorylation and increasing autophagy in STZ-induced mice [165].

4.5. Hypertensive Nephropathy

Hypertensive nephropathy (HN) is a main cause of CKD and ESRD, which has a vital role in morbidity, mortality, and rising healthcare costs. Long-term high blood pressure can be responsible for HN, which primarily damages the kidneys. It can lead to glomerulosclerosis, glomerular hypertrophy, tubular atrophy, interstitial fibrosis, and inflammation [166]. The NLRP3 inflammasome, which is a predominant source of activated IL-1β, has been found responsible for the development of hypertensive kidney injury [167]. Essential hypertension can damage renal structure and function, leading to renal inflammation [168]. At this stage, the renin–angiotensin–aldosterone system (RAAS) becomes activated, which upregulates the expression of angiotensin II (AngII). It promotes dysfunction of renal endothelial cells that release different inflammatory factors and promote renal inflammation. AngII is an important mediator of HN [169]. Different studies have shown that hydrogen sulfide donors can relieve renal damage by regulating autophagy and oxidative stress through different signaling pathways [170]. On the other hand, many studies show that hydrogen sulfide also regulates miRNAs to improve cardiac and renal dysfunction [171,172]. Studies are being conducted to find out which miRNAs and mRNAs control autophagy

in hypertensive kidney disease; research is also assessing the effect of hydrogen sulfide donors to elucidate molecular-level treatment [173].

The phytochemical YGYSG is a herbal medicine that works on kidney damage caused by hypertension during a specific cellular process in the PI3K/AKT/mTOR signaling pathway. Network pharmacology identified autophagy targets and ten core components in the YGYSG treatment of Hypertensive Renal Disease. Here, YGYSG is involved with the PI3K/AKT/mTOR signaling pathway, as well as with the autophagy process. The treatment was introduced to kidney cells with AngII, where it effectively reversed the AngII function and protected the cells. As it normalizes autophagy in a cell line, it may also work in vivo [174].

4.6. Obstructive Nephropathy

Obstructive nephropathy is a common disease in all ages, from children to older people. It is a renal disease mainly caused by the impaired flow of urine or tubular fluid [175]. Many studies have shown that AngII has a vital role in the initiation and development of obstructive nephropathy, which directly or indirectly promotes the production of molecules that can contribute to renal injury [176]. Inhibition of angiotensin production can cause renal injury, which is responsible for obstructive nephropathy [177]. The pathophysiology of obstructive nephropathy is multifactorial and has multiple interactions with hemodynamic, inflammatory, and fibrotic pathways. Primary response to acute, full ureteral obstruction is a temporary rise in renal blood flow, followed by profound vasoconstriction [178]. This is mediated by several vasoactive compounds, such as AngII, thromboxane A2, and antidiuretic hormone [175].

Most of the studies in the case of autophagy in renal interstitials have been conducted using the UUO model [179]. For renal interstitial fibrosis, UUO is a perfect model of renal interstitial fibrosis, which can respond to inflammation, ECM deposition, and tubular atrophy [60,180]. Some studies have shown that autophagy has antifibrotic effects in UUO-associated renal fibrosis. It can reduce the extent of renal fibrosis by decreasing ECM deposition and renal tubular atrophy [60]. Autophagy also has an effect on renal fibrosis by regulating the TGF-β1 and NLRP3 inflammatory vesicle signaling pathways. Autophagy can slow down renal interstitial fibrosis through negative regulation of TGF-β1 by promoting mature TGF-β1 degradation in the UUO kidney [150]. A study found that treatment with rapamycin, a drug known to increase autophagy, successfully increased autophagy in the kidney of a rat model with obstructive kidney disease, and this led to a significant reduction in kidney fibrosis and also decreased disease progression [181].

Researchers found that curcumin can effectively reduce interstitial fibrosis in mice with obstructive nephropathy. They found two mechanisms, one of which involves suppressing the inflammatory response, which remarkably reduces key inflammatory proteins (IL-6, IL-1β, and TNF-α). Another involves inhibiting the epithelial–mesenchymal transition that drives fibrosis by reducing vimentin expression. Here, curcumin mainly blocked the LR4/NF-κβ and PI3K/AKT signaling pathways in mice, which are the main drivers of inflammation and fibrosis [182].

5. Combination Therapy of Natural Molecules with Drugs Used in CKD Treatment

Combination therapy employing natural molecules with conventional drugs would be a great option in CKD treatment. Though a limited study was conducted, the treatment showed a promising effect. For instance, *Abelmoschus manihot* was reported to improve autophagy, and combined therapy with irbesartan significantly reduced proteinuria in DKD patients [145,183]. Similarly, another study reported that the combination of nano-

liposomal BBR with vildagliptin activates the autophagy process and reduces kidney fibrosis in diabetic nephropathy in rats [184]. In addition, the combination of curcumin with PP242 activates autophagy-induced cell death by inhibiting mTORC1/2 and Akt protein in renal cancer cells [32]. Collectively, these findings suggest that combining natural molecules with conventional drugs may improve therapeutic outcomes in CKD.

6. Clinical Trials of Natural Products Against Autophagy Dysfunction in CKD

Patients with CKD have modified autophagy responses as shown by clinical data [40]. A clinical study showed the effect of extreme inflammation on autophagy dysregulation in kidney disease [49]. Resveratrol was proven to support angiotensin receptor blockers in lowering proteinuria for DKD patients in a randomized double-blind placebo-controlled clinical trial [185]. Additionally, curcumin has been demonstrated to reduce urinary microalbumin excretion and inflammation in type 2 DKD patients [186]. Several small-molecule compounds, including hydroxychloroquine, rapamycin, and metformin, induce autophagy to improve podocyte injury in kidney diseases [187–189]. However, the substantial adverse effects of these small-molecule medicines limit their clinical application in the treatment of kidney injury. Also, there are some limitations in terms of replicating the beneficial effects of these polyphenols in clinical settings, such as polyphenol absorption and bioavailability. To fully utilize the therapeutic potential of focusing on the autophagy pathway in kidney diseases, further investigation is required.

7. Recent Updates on Bioactive Compounds for Autophagy in Kidney Diseases

Several phytochemicals, including alkaloids, flavonoids, polyphenols, phytosterols, etc., ameliorate autophagy dysfunction in kidney disease. In a mouse model of AKI, BBR, an alkaloid, had therapeutic potential. Nevertheless, BBR has extremely limited solubility and bioavailability. Because of this, substantial doses of BBR are needed to achieve a therapeutic impact, which may have negative effects on the digestive system [190,191]. An advanced drug delivery system would be a viable option to address this problem. A study showed that the BBR carried by Janus nanoparticles consisting of Fe_3O_4 head was effective in treating hepatocellular carcinoma [192]. Another study reported that Linaxiang microemulsion of BBR chloride increased bioavailability [193]. Another phytochemical, TMP—possessing lower bioavailability, permeability, and solubility—is very effective in treating AKI [194,195]. According to a study, the encapsulation rate of TMP delivered by liposome carriers was higher both in vitro and ex vivo [196]. Another investigation on rats with spinal cord injuries revealed that TMP nanoparticles containing HIV-1 transcription factor increased the drug's half-life and, as a result, prolonged its activity [197]. The bioactivity of Nef, an alkaloid, is limited because of its low bioavailability. A study on $NaNO_2$-induced anoxia in mice showed that Nef nanoliposomes were effective in protecting against cerebral embolism [198]. Similarly, due to quercetin's poorer solubility and bioavailability, a study recommended delivery via nanoparticles to treat kidney disease [199].

8. Prospects and Limitations

In renal pathophysiology, autophagy plays an important role in treating kidney disease. Numerous phytochemicals such as BBR, TMP, PF, Nef, Quercetin, Curcumin, G-Rb1, Astragaloside IV, Isovitexin, stigmasterol and β-sitosterol, PT, and SFN improve autophagic pathways in AKI, DKD, CKD, and DN. Despite their promising therapeutic potentials, some limitations should be addressed. First, some phytochemicals are associated with

low toxicity and adverse effects. PF showed low toxicity [200]. The LD50 with rats was 14.55 g/kg, suggesting a safety margin [102]. BBR can interact with other drugs and increase the nephrotoxicity. For instance, in combinatorial therapy with vancomycin, the immune system can cause nephrotoxicity [201]. Second, the human body metabolizes SFN very quickly. In order to achieve a therapeutic effect, a dose determination study is necessary [202]. Third, despite numerous studies on animal models, clinical research is very limited. Clinical trials are needed for evaluating safety, optimal dosing, and pharmacokinetics. By resolving these issues, it will become possible to harness the autophagy-modulating potential of these bioactive phytochemicals to treat kidney diseases.

9. Conclusions

Autophagy function must be maintained to improve many illnesses, including kidney disease. This review highlighted the pathophysiology of autophagy dysregulation in kidney disease and explored the potential of small bioactive natural molecules to maintain the autophagic process. Collectively, this study suggests that small-molecule natural products could be a potential option for therapeutic intervention for renal disease. The autophagy-targeted treatment might be promising for advanced drug delivery techniques, such as a nano-guided system. Further studies on the mode of action and therapeutic effects of phytochemicals are required to establish them as alternative therapeutic agents for combating kidney disease.

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