Free Radical Biology and Medicine 141 (2019) 141–149

Contents lists available at ScienceDirect

Free Radical Biology and Medicine

journal homepage: www.elsevier.com/locate/freeradbiomed

Redox signaling in aging kidney and opportunity for therapeutic intervention through natural products

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ARTICLE INFO

Keywords:
Redox signaling
Aging kidney
Renal disease
Oxidative stress
Natural product
Therapy target

ABSTRACT

Kidney diseases are serious public problems with high morbidity and mortality in the general population and heavily retard renal function with aging regardless of the cause. Although myriad strategies have been assigned to prevent or harness disease progression, unfortunately, thus far, there is a paucity of effective therapies partly due to an insufficient knowledge of underlying pathological mechanisms, indicating deeper studies are urgently needed. Additionally, natural products are increasingly recognized as an alternative source for disease intervention owing to the potent safety and efficacy, which might be exploited for novel drug discovery. In this review, we primarily expatiate the new advances on mediators that might be amenable to targeting aging kidney and kidney diseases, including nicotinamide adenine dinucleotide phosphate oxidase (NOX), transforming growth factor-β (TGF-β), renin-angiotensin system (RAS), nuclear factor-erythroid 2 related factor 2 (Nrf2), peroxisome proliferator-activated γ receptor (PPARγ), advanced glycation endproducts (AGEs) as well as microRNAs and vitagenes. Of note, we conclude by highlighting some natural products which have the potential to facilitate the development of novel treatment for patients with myriad renal diseases.

1. Introduction

Kidney diseases remain major health problems with a high prevalence around the world and a variety of pathophysiological processes are implicated in the progression [1–3]. Oxidative stress is a pathological condition that reactive oxygen species (ROS) generation far exceeds the scavenging capacity of anti-oxidant defense systems, which plays a particularly pivotal role in the pathogenesis of myriad renal disorders [4–6]. Given the few and limited efficacy of current therapies for renal diseases, normalization of ROS utilizing mechanism-based intervention represents a promising alternative towards arresting kidney disease progression [7–11].

Mounting evidence revealed that a series of physiological processes that devoted much to ROS production were previously published in detail, such as hexosamine pathway activation, protein kinase C upregulation, polyol pathway alteration and autonomic nervous system hyperactivation [4,12,13]. Here we only briefly emphasize the recent advances in mediators of ROS generation that were closely associated with the regulation of kidney with aging and pathological conditions for the sake of brevity, including nicotinamide adenine dinucleotide phosphate oxidase (NOX), transforming growth factor-β (TGF-β), renin-angiotensin system (RAS), nuclear factor-erythroid 2 related factor 2 (Nrf2), peroxisome proliferator-activated γ receptor (PPARγ), advanced glycation endproducts (AGEs) as well as microRNAs and vitagenes (Fig. 1). ROS is of paramount significance to disease progression and a thorough understanding of these mediators will pave the way to the booming development of therapies against kidney diseases since they play vital roles in redox signaling.

Abbreviations: PPARγ, peroxisome proliferator-activated γ receptor; RAGE, receptor for AGEs; AGEs, advanced glycation endproducts; RAS, renin-angiotensin system; Keap1, Kelch-like ECH-associated protein 1; ROS, reactive oxygen species; NF-κB, nuclear factor-κB; Smad, small mother against decapentaplegic; NOX, nicotinamide adenine dinucleotide phosphate oxidase; TGF-β, transforming growth factor-β; Nrf2, nuclear factor-erythroid 2 related factor 2

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https://doi.org/10.1016/j.freeradbiomed.2019.06.012
Received 14 May 2019; Received in revised form 4 June 2019; Accepted 10 June 2019
Available online 11 June 2019
0891-5849/

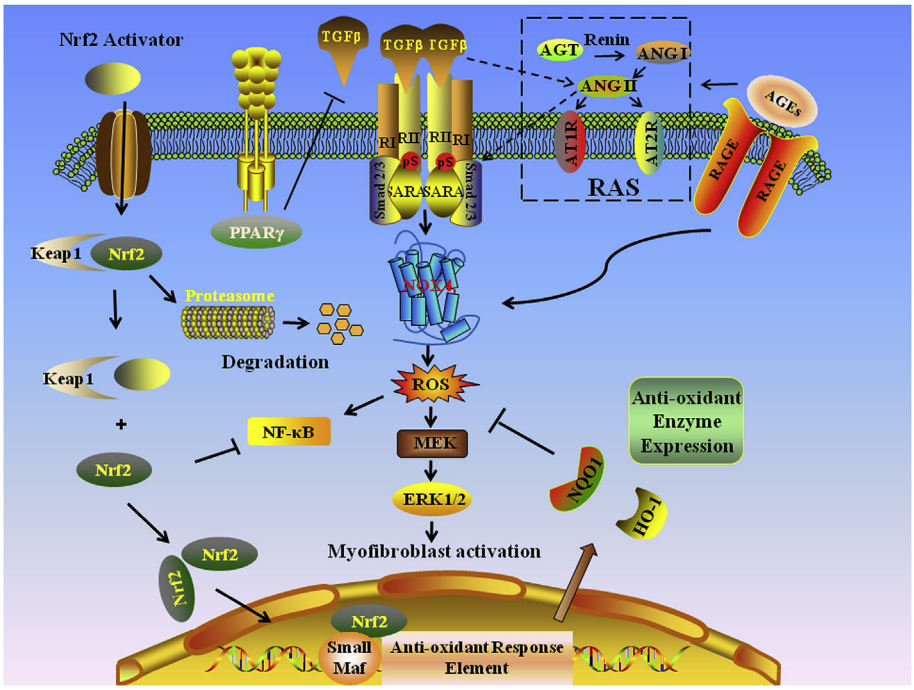

Fig. 1. The mainly molecular mechanisms and their cross-talk of redox signaling in aging kidney and kidney disease. Myriad enzymes contribute to ROS generation, of which NOX family is dedicated generators of intracellular superoxide and hydrogen that strongly involve in redox signaling. RAS elements are of paramount importance to TGF-β/Smad signaling activation, which play pivotal roles in ROS generation through NOX4 regulation. Additionally, AGE-RAGE signaling pathway is also implicated in oxidative stress progression by mediating NOX4. Of note, PPARγ and Nrf2 show protective potential against oxidative stress via inhibiting TGF-β/Smad and promoting anti-oxidant responses, respectively. AGT, angiotensinogen; ANG I, angiotensin I; ANG II, angiotensin II; AT1, angiotensin II type 1 receptor; AT2, angiotensin II type 2 receptor; ERK, extracellular signal-related kinase; HO, haem oxygenase; MEK, mitogen-activated protein kinase/extracellular signal-related kinase; NQO1, NAD(P)H dehydrogenase (Quinone) 1; SARA, smad anchor for receptor activation.

In addition, some commercial drugs approved by FDA were reported to show serious side effects, which severely impeded their clinical use, hinting new drugs and strategies are urgently needed [14–16]. In this review, we highlight a number of natural products that could target the above-mentioned mediators as exemplified by 25-*O*-methylalisol F [17], poricoic acid ZA [18] and salvianolic acid A [19], which might provide novel therapeutic strategy for the treatment of renal diseases.

2. Oxidative stress associated novel mediators in aging kidney and renal diseases

2.1. NOX signaling

Myriad enzymes contribute to ROS generation, of which NOX family is dedicated generators of intracellular superoxide and hydrogen that strongly involve in redox signaling under healthy and pathological conditions [20–22]. NOX family consists of five isoforms including NOX1, NOX2, NOX3, NOX4 and NOX5, which accelerate ROS production in the vasculature [23–27]. In this scenario, we shift the concept to NOX4 as a critical driver for various renal disorders since NOX4 is most plentiful in kidney [28–30].

In the kidney, fibrosis is the pathologic extension of wound healing process response to chronic or repeated injuries, which represents a common pathway of nearly all progressive renal diseases regardless of the etiology, and may ultimately lead to architecture disruption and function loss [31,32]. Wound healing generally proceeds through three periods that are provisional overlapping but functionally distinct, including the initial inflammatory phase as well as proliferative phase and maturation phase [31,33]. The provisional extracellular matrix exacerbated by fibrogenic cytokine undergoes degradation and facilitates tissue remodeling, the dysregulation of which or persistent chronic injury permits adequate opportunity for the formation of fibrotic lesion [34–36]. Although fibrosis was previously recognized as an irreversible progress [37], emerging evidence demonstrated that certain circumstances allowed fibrosis resolution when the underlying preventable causes of fibrogenesis were eradicated [38–40]. NOX-derived ROS were intimately involved in numerous organ fibrosis such as heart, liver, lung and kidney [41–43], particularly for NOX4 in the nephropathic milieu, which was recognized as the most abundant isoforms in renal proximal tubular epithelial cells [29]. A reduction of NOX4 expression by carnosic acid treatment has been proved to protect against unilateral ureteral obstruction-induced renal fibrosis, fueling considerable enthusiasm for NOX4 blockade as an attractive therapy [44]. However, sustained controversy about the role of NOX4 suppression on alleviating fibrogenesis existed as NOX4 deletion was associated with fibrosis acceleration as well [45]. In addition, ROS elevation may act as a potent signal for accelerated senescence [46] and NOX4 was strongly associated with advanced age since it facilitated wound healing and myofibroblast differentiation in young animal models whereas exacerbated substantial fibrosis in aged mice. Moreover, the consensus that NOX4 acted as a key mediator of glomerular dysfunction in hyperglycemic milieu through modulating fumarate hydratase is increasingly recognized as an emerging mechanism of diabetic kidney disease [47], highlighting the importance of NOX4 inhibition in the treatment of diabetic nephropathy [29].

NOX also played a decisive role in the initiation and progression of tumorigenesis [48,49] via mediating redox homeostasis. NOX4 promoted renal tumorigenesis through the expression and accumulation of hypoxia inducible factor expression, which was triggered by transcriptional and post-translational mechanisms [50]. Of note, angiogenesis accelerated tumor growth and NOX4 contributed to renal tumorigenesis by modulating angiogenesis as well, indicating NOX4 is a potential target for therapeutic exploitation [51]. Nevertheless, owing to the corresponding studies of NOX4 in cancer are still in the infancy, deeper mechanistic understand of NOX4 in renal tumor remains to be determined.

2.2. TGF-β/Smad signaling

As we reflect on relevant investigations as well as summarize the accumulating findings, it is generally acknowledged that oxidative stress had a pivotal role in myriad kidney diseases besides inflammatory milieu, underscoring the potential of ROS eradication in the development of novel therapeutic strategies [52–54]. TGF-β and its receptor-small mother against decapentaplegic (Smad) are of critical importance to kidney fibrosis through myofibroblast differentiation and inflammatory cytokine accumulation [55]. Additionally, a growing body of evidence revealed that TGF-β was implicated in oxidative stress and

NOX4 was most accountable for TGF-β-induced ROS generation through a TGF-β/Smad/ROS signaling cascade [56,57]. The most compelling evidence of fibrogenesis resolution associated with TGF-β/NOX4 in human beings was observed in the lung. Mounting studies highlighted that NOX4 was upregulated in response to TGF-β among patients with idiopathic pulmonary fibrosis [58] and therapeutic treatment with NOX4 inhibition mediated by the enhancement of proteasomal degradation [59] or small interfering RNA [60] could attenuate the progression of fibrogenesis. Unfortunately, thus far, the underlying mechanism of TGF-β and NOX4 in humans and animal models of renal fibrosis remains elusive and a deeper elucidation is essential to preventing or harnessing kidney complications.

2.3. RAS

Another severe consequence of excessive ROS in intrarenal cells is the activation of RAS and its related elements [61], a better understanding of which may facilitate the exploitation of effective therapeutic strategies for patients with renal disease. RAS has the potential to trigger renal fibrosis and RAS activation is induced by ROS directly or mediated via AGEs generation. All of RAS components exist in renal tissues, including renin, angiotensinogen, angiotensin converting enzyme, angiotensin II, angiotensin II type 1 receptors and angiotensin II type 2 receptors, and fibrosis can evidently seize control of angiotensin II to deteriorate fibrogenesis via stimulating TGF-β expression or phosphorylating Smad2 and Smad3 [55]. Of note, RAS blockade by angiotensin receptor blockers or angiotensin converting enzyme inhibitors was the first effective anti-fibrotic drug that proved efficient to alleviate the progression of renal fibrogenesis [62].

In addition, oxidative stress is also implicated in the pathogenesis of renal damage [63] and TGF-β-induced RAS activation displays huge potency in disease progression [64]. The resolution of angiotensin II-induced kidney damage and fibrosis in animal models provides additional evidence to the fact that restraining RAS signaling cascade has made survival possible for patients with kidney diseases [65].

Oxidative stress/RAS axis also contributes to diabetic nephropathy [4], underscoring the importance of oxidative stress/RAS axis blockade in the treatment of patients with diabetic nephropathy. Notably, a careful understanding of the underlying mechanisms about oxidative stress modulation is prerequisite before reaching clinical application as oxidant species are dynamically altered. Moreover, RAS, especially for angiotensin II/angiotensin II type 1 receptor axis, accelerated renal damage with aging via ROS generation [66], providing new insight into disease prevention.

2.4. Nrf2 signaling

Nrf2, an inducible transcription activator, is generally recognized as a master mediator of variant detoxification responses as well as redox homeostasis and provides cytoprotection from oxidative stresses or xenobiotic [67,68]. Anti-oxidant responses are modulated by Nrf2 signaling pathway in combination with Kelch-like ECH-associted protein 1 (Keap1), resulting in the elevated expression of a series of anti-oxidant factors to counterbalance oxidative stress, such as haem oxygenase 1, glutathione S-transferase and c-glutamylcysteine synthetase etc [69]. Under basal conditions, Nrf2 predominantly exists in the cytoplasm as a temporarily inactive complex via bounding to Keap1, a repressor molecule that positively associated with Nrf2 ubiquitination [70], while Keap1 alkylation facilitates the accumulation of Nrf2 synthesis as well as its translocation to nucleus in oxidative milieu [70–73]. Within the nucleus, Nrf2 combines with the regulatory sequences of the genes in charge of anti-oxidant and detoxifying molecules, which were known as electrophile response elements or anti-oxidant response elements.

Given the role of Nrf2 impairment in CKD-induced inflammation and oxidative stress [74], there are numerous studies demonstrated that pharmacological development aimed at enhancing Nrf2 expression might be exploited for preventing not only renal diseases but also myriad other pathology obstacles in which oxidative stress played a particularly paramount role in pathogenesis [4,75]. Additionally, Xiao et al. highlighted that Nrf2 restoration and Keap1 inhibition dramatically ameliorated tubular injury induced by mitophagy in animal models of diabetes, underscoring Nrf2 may be a potential therapeutic target for kidney damage [76]. Keap1-null mouse is an ideal model to investigate Nrf2 activity since Keap1 tightly represses Nrf2 signaling pathway in normal conditions, while Keap1-null mice frequently die of oesophageal hyperkeratosis due to Nrf2 hyperactivation, which severely restricts Nrf2 investigation. Fortunately, the emerging mouse model, oesophageal Nrf2-defective and systemic Keap1-null mice, exhibits high Nrf2 expression due to Keap1 deficiency but without juvenile lethality or oesophageal hyperkeratosis, fueling considerable enthusiasm for a better understand of cytoprotective defense systems [77].

In addition, there are numerous studies highlighted that persistent fibrosis in aging might be associated with the redox imbalance between Nox4 and Nrf2 [78,79]. The prevalence of pathological fibrosis was increased with advanced age through the loss of Nox4-Nrf2 redox homeostasis and aged mice showed an impaired potential for fibrosis reversal, underscoring the importance of Nox4-Nrf2 restoration in therapeutic intervention [80,81]. Nonetheless, although Nrf2 preservation might be plausible in impeding persistent fibrosis, there is a severe paucity of relevant studies on renal fibrosis and their clinical use remains a tremendous challenge.

2.5. PPARγ signaling

PPARγ is a ligand-dependent transcription factor that plays critical roles in various metabolic processes besides significant anti-inflammatory effect [82]. Emerging evidence suggested that PPARγ was involved in redox equilibrium [83] and PPARγ agonist showed protective potential against oxidative stress [84]. PPARγ was of paramount importance to the maintenance of renal metabolic homeostasis, the defectiveness of which exacerbated nephropathy/renal fibrosis, indicating PPARγ preservation might be pursued for pharmaceutical exploitation. Additionally, PPARγ interacted with TGF-β1 as well. TGF-β1 could downregulate PPARγ via miR-130a/301b in vascular smooth muscle cells, whereas PPARγ inhibited glucose metabolism through mediating TGF-β1/Smad3, hinting PPARγ was a promising target with particular promise to terminate fibrogenesis [62].

Except for above-mentioned factors, Klotho, an anti-aging protein primarily expressed in the kidney, is a target gene of PPARγ that intimately associated with the development and the progression of renal diseases [85], which makes advanced age more preventable than inevitable. The aging kidney is susceptible to variant kidney damage [86] and PPARs has been instrumental for myriad age-related inflammatory responses including renal diseases [87]. The probability of harbouring kidney injury is higher in animal models or patients with Klotho loss and Klotho preservation could protect kidney against various pathological milieu [85], highlighting the importance of Klotho intervention in therapeutic strategy development. Nevertheless, although PPARγ agonists have been shown to reverse or prevent kidney damage, there is still a paucity of randomized clinical trials to further elucidate the safety and efficacy of these molecules, which severely retards their use.

2.6. AGEs

AGEs and the receptor for AGEs (RAGE) are inseparably involved in renal inflammation and oxidative stress [88]. Chronic or sustained hyperglycaemia led to the non-enzymatic covalent bonding of a series of carbohydrates as exemplified by glucose, to lipids and proteins in a physiological process known as glycation [89]. Glycation products that formed in the short term could combine to generate cross-linked structures recognized as AGEs. These modified lipids and proteins were

closely associated with RAGE and triggered a signaling cascade through which ROS generation and nuclear factor-κB (NF-κB) activation. Additionally, there is a vicious cycle since NF-κB could upregulate RAGE expression as well, accelerating further cytokine and ROS synthesis [90].

Myriad studies highlighted that oxidative stress was a major etiology of diabetic nephropathy [4], and AGE-RAGE signaling pathway played crucial roles in the pathogenesis via exacerbating ROS generation [91], which had been recognized as one of the five cellular and molecular mechanisms of redox signaling in diabetic complications [4]. In addition, AGE inhibition or RAGE knockout could dramatically attenuate renal damage caused by redox molecular mechanisms as well as the production of numerous pro-inflammatory cytokines [92], hinting AGE-RAGE-ROS axis intervention might be investigated for preventing or harnessing diabetic nephropathy through alleviating oxidative stress. Unfortunately, thus far, the precise process of AGE/RAGE on ROS generation remained elusive due to the severely limited investigations, but there is a growing body of evidence suggested that AGE-RAGE signaling contributed much to NOX activation [19].

Apart from above-mentioned factors, AGE overexpression was associated with nondiabetic progression of renal disorders as well, such as obesity [93] and advanced age [94]. RAGE knockout could facilitate damage recovery, underscoring the importance of RAGE blockade as a potential therapeutic approach [94,95]. Of note, although the fact that a reduction of RAGE has been instrumental to protect against obese and aging in mice is plausible, deeper studies remain to be determined since available animal models often cannot fully recapitulate relevant human diseases, and thus promising therapies that lead to damnification regression may not directly translate into strategy in humans.

2.7. MicroRNAs

Functional studies have shown that microRNA dysregulation is causal in myriad diseases, with microRNAs acting as activators or suppressors, and insight into the roles of microRNAs in disease progression has made microRNAs attractive targets of therapeutic modalities [96–99]. Here, we only highlight microRNA-21, -205 and -153 that play pivotal roles in renal disorders.

Numerous studies indicated that microRNA-21 contributed to the pathogenesis of fibrosis in multiple organs as exemplified by the kidney via mediating metabolic pathways that were of prominent significance to ROS production as well as ATP generation and inflammatory signaling [100], while microRNA-21 inhibition or knockout could protect against fibrogenesis in response to renal injury [101]. Moreover, fibrosis-associated microRNA-21 was the most upregulated microRNAs in animal models of allogenic kidney transplantation, the antagonism of which had beneficial effects on chronic renal allograft dysregulation, highlighting microRNA silencing might be a promising therapeutic option in patients following kidney transplantation via halting the progression of chronic renal allograft dysfunction [102]. Nonetheless, the emerging consensus that both overexpression and suppression of microRNA-21 could accelerate basal as well as maximal mitochondrial respiration is increasingly recognized [103], which is quite distinct from that of previous investigations. Collectively, thus far, there is a paucity of relevant studies about the optimal level of microRNA-21 in clinical use, and the therapeutic efficacy of microRNA-21 silencing in human beings remains a tremendous challenge due to the severely limited investigations.

A reduction of microRNA-205 in cells was susceptible to oxidative stress, the supplementation of which alleviated renal damage, suggesting microRNA-205 may be a novel therapeutic target for acute kidney injury and chronic kidney disease [104]. Astonishingly, this is the only time that microRNA-205 has been studied in renal tubular cells under oxidative stress, and the efficacy of microRNA-205 in reversing kidney damage remains to be determined. Liu et al. uncovered Pb-induced redox signaling in rat kidney was attenuated by grape seed procyanidin extract treatment through Nrf2 signaling pathway activation and microRNA-153 suppression for the first time [105], providing new insight into the prevention and regression of Pb-induced nephrotoxicity. Unfortunately, although the anti-oxidation of grape seed procyanidin in lessening kidney injury has been further validated in a series of studies, the potential of microRNA-153 inhibition was rarely covered, which severely impeded their clinical use [106].

2.8. Vitagenes

Oxidative stress may contribute to aging kidney and renal diseases via modulating vitagene system. Vitagene system is responsible for the generation of cytoprotective heat shock proteins and protects against oxidative stress by acting as a paramount intracellular redox system [107]. Redox signaling devotes much to cognitive impairment [108,109] and targeted therapeutics aiming at restricting age-related changes could facilitate clinical outcomes as well as survival benefit [110,111]. Mounting evidence has shed light on the unexpected role of vitagenes in mediating aging and neurodegenerative diseases imparted by heat shock proteins [112], which dramatically expands our armaments beyond traditional strategies to win more battles against advanced age.

Considering the prominent relationship of vitagene restoration and long-term survival in neurodegenerative diseases by mitigating free radical-induced cellular damage [112–114], it is highly reasonable to postulate that therapeutically targeting vitagenes portend a novel paradiagm in anti-oxidant modalities, which may aid our understanding between redox signaling and aging kidney. Unfortunately, thus far, there is a paucity of sufficient knowledge of vitagenes on renal diseases since the dominant view of the anti-oxidative effects of vitagenes weighs heavily towards neurodegenerative diseases. Therefore, deeper investigations are expected to progress toward therapeutic development for the intervention of kidney disorders.

3. Therapeutic opportunities for natural products in aging kidney and kidney disease

Natural products and their relevant secondary metabolites have been proven to be the fertile ground for drug discovery and pharmaceutical exploitation [31,62,115]. Moreover, recent advances of powerful analytical platforms based on genomics, proteomics and metabolomics as well as bioinformatics have been ubiquitously employed to reveal the bioactivities of myriad natural products [116–119]. A growing body of studies supported that natural products should be revisited since the side effects of available commercial drugs brought risks and severely restricted their use. Actually, about half of drugs that approved by FDA from 1981 to 2014 were recognized to be natural products and their derivatives [120]. In this scenario, we demonstrate a series of compounds that were isolated from natural products with therapeutic potentials in patients with aging kidney and kidney disease by interfering with above-mentioned mediators (Table 1).

Diabetic nephropathy is deeply implicated in the etiology of end-stage renal disease, and therapeutic strategies for restraining its progression remain limited [16,121]. Although molecular signaling mechanisms that contributed to the progression of diabetic nephropathy had been elucidated, various nephroprotective agents with promising future were failed in clinical trials, underscoring an insufficient understanding of pathological pathways [122]. In addition, oxidative stress played pivotal roles in the pathogenesis of diabetic nephropathy and a thorough comprehension of oxidative stress may pave the way for the advancement of therapeutic agents against diabetic nephropathy [4]. The important findings of natural products against diabetic nephropathy were described [123,124]. Scutellarin [125] as well as Schisandrin B [126] and *myrciaria cauliflora* extracts [127] could alleviate diabetic nephropathy by activating Nrf2 or inhibiting RAS signaling pathway. Moutan Cortex had therapeutic effects against kidney

Table 1
Summary of primary natural products in aging kidney and kidney disease.

Natural products	Resources	Model	Therapeutic target	Refs
Diabetic nephropathy				
Scutellarin	*Erigeron breviscapus*	Mice	AGEs inhibition and Nrf2 promotion	[125]
Schisandrin B	*Schisandra chinensis*	Mice	Nrf2 activation	[126]
Myrciaria cauliflora extracts	*Myrciaria cauliflora*	Mice	RAS regulation	[127]
Moutan Cortex	*Paeonia suffruticosa*	Rats	TGF-β inhibition	[128]
Salvianolic acid A	*Salvia miltiorrhiza*	Rats	AGE/RAGE/NOX4 inhibition	[19]
Diphlorethohydroxycarmalol	Ishige okamurae	HEK cells	AGE inhibition and Nrf2 activation	[129]
Resveratrol	Plants	Rats	RAGE inhibition	[131]
	Grapevines; berries	Rats	Nrf2-Keap1 regulation	[132]
Kaempferitrin	Plants	Rats	AGE/RAGE and TGF-β inhibition	[133]
Chrysin	Passion flowers; honey; mushroom	Mice	AGE/RAGE and TGF-β inhibition	[134]
Aging kidney				
Resveratrol	Plants	Mice	Angiotensin II inhibition	[66]
Renal fibrosis				
Schisandrin B	*Schisandra chinensis*	Mice	TGF-β inhibition	[126]
Resveratrol		Mice	NOX4/ROS regulation	[135]
Curcumin	*Turmeric*	Rats	Nrf2-Keap1 regulation	[139]
Poricoic acid ZA	*Poria cocos*	HK-2 cells	RAS and TGF-β/Smad pathway inhibition	[18]
Poricoic acid ZF, ZG and ZH	*Poria cocos*	HK-2 cells	RAS and TGF-β/Smad3 inhibition	[150]
Poricoic acid ZC and ZD	*Poria cocos*	HK-2 cells	RAS inhibition	[151]
Poricoic acid ZE	*Poria cocos*	HK-2 cells	Renin inhibition	[151]
25-O-methylalisol F	*Alisma orientale*	Rats	RAS and TGF-β/Smad3 inhibition	[17]
Renal damage				
Resveratrol	Grapes; berries; red wines; peanut skins	NRK-52E cells	Nrf2 activation	[136]
Salvia miltiorrhiza extract	*Salvia miltiorrhiza*	Rats/HK-2 cells	NOX/ROS and TGF-β/Smad regulation	[157]
Poricoic acid A	*Poria cocos*	Rats	Nrf2 regulation	[158,159]
Ergone	*Polyporus umbellatus*	Rats	TGF-β regulation	[160]
Nephrotoxicity				
Procyanidin extract	Grape seed	Rats	Nrf2 activation and microRNA153 inhibition	[105]

dysregulation via TGF-β in rats with diabetic nephropathy [128]. Moreover, AGE-RAGE was also intimately involved in the progresion of diabetic nephropathy, and diphlorethohydroxycarmalol, a polyphenol isolated from Ishige okamurae, alleviated renal damage through preventing AGE generation in HEK cells, which might be pursued for potential therapeutic agent in patients with diabetic nephropathy [129]. Hou et al. demonstrated that Salvianolic acid A prevented from diabetic nephropathy by restraining AGE-RAGE-NOX4 with validated safety for the first time [19], which dramatically accelerated the advances of drug discovery since myriad compounds concerning AGE-RAGE inhibition and diabetic nephropathy regression had been withdrawn from clinical trials due to its unsatisfactory safety [130]. Resveratrol [131,132], kaempferitrin [133] and chrysin [134] could reduce renal damage through AGE/RAGE or Nrf2-Keap1 in animal models of diabetic nephropathy. Additionally, resveratrol also played paramount roles in protecting against diabetic renal fibrosis [135], aging kidney [66] and kidney damage [136,137] in animal models. Nevertheless, the clinical application of resveratrol remains a tremendous challenge due to the unfavorable pharmacokinetic and biochemical properties, while resveratrol conjugates may portend a novel paradigm in the development of pharmaceutical exploitation, which has been proved to be more efficacious than resveratrol in human neuroblastoma SH-SY5Y cells [138].

Fibrosis is a chronic process in response to excessive inflammation and epithelial injury, and represents the common process of nearly all progressive nephropathies [34]. Nrf2-Keap1 is of great significance to fibrosis resolution and curcumin aimed at restoring Nrf2 activity could effectively attenuate fibrogenesis in animal models with 5/6 nephrectomy [139]. TGF-β and RAS also play vital roles in the pathogenesis of fibrosis [32]. Mou et al. demonstrated that Schisandrin B could retard renal fibrosis via inhibiting TGF-β signaling for the first time [126], providing additional evidence to previous studies. Our previous studies uncovered that some diuretic traditional Chinese medicines, such as *Alisma orientale* (Sam.) Juzep. [140–142] and *Poria cocos* (Schw.) Wolf (Polyporaceae) [143–149], showed good therapeutic effects on fibrosis. Poricoic acid ZG and ZH exhibited strong inhibitory effects against renal fibrosis compared with poricoic acid ZF via modulating TGF-β/Smad3 and angiotensin II, which might be caused by their diverse chemical structures in carboxyl groups and the first six-membered ring [150]. Additionally, given the incomplete efficacy of traditional RAS blockader in renal diseases, it is of paramount significance to develop novel therapies that simultaneously target multiple RAS components. Poricoic acid ZA significantly mitigated tubulointerstitial fibrosis through inhibiting the upregulation of renin, angiotensinogen, angiotensin converting enzyme, angiotensin II type 1 receptor and TGF-β/Smad pathway [18]. The secolanostane tetracyclic triterpenoids poricoic acid ZC and ZD effectively protected against renal fibrosis by simultaneously targeting all RAS components than lanostane tetracyclic triterpenoid poricoic acid ZE, indicating compounds with secolanostance skeletons might perform better against fibrogenesis than those with lanostance skeletons, which may be exploited for novel RAS inhibitors [151]. Moreover, 25-O-Methylalisol F, isolated from *Alisma orientale*, could attenuate tubulointerstitial fibrosis by targeting multiple RAS components without remarkable proliferative or cytotoxic effect on NRK-52E cells, providing new insight into the development of novel therapeutic intervention against fibrosis and RAS blockade [17].

Natural products also retarded chronic kidney disease [152], renal failure [153,154] and nephrotoxicity [155]. *Salvia miltiorrhiza* Bunge is a natural product with a thousand years of clinical application [156]. *Salvia miltiorrhiza* extract could significantly alleviate adenine-induced chronic renal failure through NOX/ROS and TGF-β/Smad signaling pathways [157], which offers additional evidence for the incorporation of natural products into the future study against chronic renal failure. Poricoic acid A, isolated from *Poria cocos*, lessened chronic kidney disease [158] and the transition of acute kidney injury to chronic kidney disease by regulating Nrf2 signaling cascade [159]. Ergone, a major compound of *Polyporus umbellatus*, halted tubular damage and further prevented tubulointerstitial fibrosis through blocking TGF-β signal transducer [160]. Furthermore, the burden of myriad diseases attributable to heavy metal pollution is becoming a global health problem [161]. Studies aimed at investigating the relationship of natural products as well as oxidative stress and metal-induced kidney diseases

may aid the development of pharmaceutical exploitation. Liu et al. demonstrated that grape seed procyanidin extract had the potential to mitigate Pb-induced oxidative stress via suppressing microRNA-153 and activating Nrf2 signaling pathway for the first time, providing new therapeutic targets for Pb-induced nephrotoxicity [105]. Unfortunately, although the extracts of *Salvia miltiorrhiza* and grape seed procyanidin have made survival possible for patients with chronic renal failure and nephrotoxicity, there is a paucity of sufficient knowledge on active ingredients and their potential adverse effects, which severely restricts the clinical use.

4. Concluding remarks

Kidney disease is a global burden that severely impedes renal function with aging regardless of the etiology, and a thorough understanding of pathological mechanisms may permit the disease resolution. Oxidative stress plays a pivotal role in the pathogenesis of myriad renal disorders, while the clarification of underlying mechanisms remains elusive, indicating deeper studies are urgently needed. In this review, we expatiated some important advances in mediators of aging kidney and kidney disease that might be amenable to the development of therapeutic targeting, including NOX, TGF-β, RAS, Nrf2, PPARγ, AGEs as well as microRNAs and vitagenes.

Of note, given the serious side effects of existing commercial drugs, natural products are increasingly recognized as an emerging alternative source for drug discovery. We highlight a number of natural products with prominent therapeutic effects in aging kidney and kidney diseases by interfering above-mentioned factors. A series of poricoic acids, isolated from *Poria cocos*, and *Salvia miltiorrhiza* extract have been studied in human kidney proximal epithelial cells. In addition, the therapeutic effect of diphlorethohydroxycarmalol was investigated in human embryonic kidney cell lines as well. Notably, poricoic acids showed no remarkable cytotoxic effect on HK-2 cells at the therapeutic dosage, fueling considerable enthusiasm for natural products as promising treasure trove of drug discovery, particularly within the arena of antifibrotic studies. Moreover, recent success in technical advances, illustrated by metabolomics-guided fractionation tools, has brought renewed enthusiasm that the bioactive structure of natural products may be screened at the fractionation with the help of databases [162], which predominantly reduces the cost of drug development. Additionally, it is generally accepted that reverse pharmacokinetics helps clarificate key questions in drug discovery from various natural products with proven clinical benefits [163], dramatically facilitating the pace of active ingredient in clinical practice since a substantial portion of natural products are used as extracts. Nonetheless, given the fact that available animal models cannot adequately recapitulate human diseases, current effective treatment of other natural products in animal models might not directly translate into therapies in humans and relevant studies remains to be determined, which is prerequisite before clinical application.

Undoubtedly, natural product is a precious treasure trove for new drug discovery, while some issues severely restrict their development. The most difficult obstacle is the paucity of well-designed, randomized, placebo-controlled trials in humans, which make it hard to reach clinical application. Additionally, the safety of natural products is another crucial issue since natural products are primarily used as extracts or prescription, while the active ingredients are rarely covered. Considering the fact that natural product cannot be utilized in humans until proper clinical evidence, there is intense impetus to combine pharmacological exploitation with the identification of bioactive components. Once these impediments are eradicated, utilizing natural products as an alternative source to exploit new drug will be at hand.

Declaration of conflicting interests

The authors declare that there is no conflict of interest.

Acknowledgments

This study was supported by the National Natural Science Foundation of China (Nos. 81673578, 81872985, 81603271).

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