Research advances in the protective effect of sulforaphane against kidney injury and related mechanisms

Ruoxi Chang

Beijing World Youth Academy, Beijing, China.

Abstract: Kidney injury and related diseases have become quite common in recent years, and have attracted more attention. Sulforaphane, a kind of isothiocyanate, is widely distributed in cruciferous plants and it is a common antioxidant. Specifically, sulforaphane can reduce oxidative damage by preventing cells from free-radical damage, preventing cells from degeneration, and acting as an anti-inflammation, etc. This study summarized the investigations of the effects of sulforaphane on kidney injury. This study discussed the mechanisms of sulforaphane on immune, renal ischemia-reperfusion, diabetic nephropathy, age-related, and other factors-induced kidney injury models and discussed the potential and relative mechanisms of sulforaphane for kidney injury protection.

Keywords: Sulforaphane; Kidney injury; Protective effect; Nrf2

1. Preface

The kidney is one of the major organs in our body and contributes to its mechanism of excretion of metabolites and regulation of water, electrolytes, and acid bases, maintaining the homeostasis of the body. When organic damage occurs in the kidney, the kidney will partially or completely lose its normal physiological function. Acute and chronic kidney injury often involves multiple systems in the body and is a common clinical disease that can seriously endanger human health and life. Among them, chronic kidney injury is difficult to treat with a long course and has a high rate of death and disability. According to the WHO, the number of deaths from chronic diseases accounts for approximately 70% of total deaths worldwide . Therefore, this becomes an urgent public health problem to be solved.

Multiple factors can lead to kidney injury. For instance, heavy metal-induced, bacterial-induced, myoglobin-induced, and uric acid-induced kidney injuries are all associated with oxidative damage mechanisms [1, 2]. At physiological concentrations, reactive oxygen species (ROS) and reactive nitrogen species (RNS) play a balancing role, such as cell signaling and the synthesis of some cellular structures, and are used for phagocytic defense against pathogens[3]. However, when there is an imbalance between oxidation and reduction, lipid peroxidation damages cell membranes and lipoproteins, leads to the formation of toxic reactive aldehydes, and promotes further lipid peroxidation, ultimately affecting a large number of lipid molecules. When ROS react with proteins, they may induce conformational changes that partially or completely disable proteins. The reaction of ROS with DNA may lead to mutations that disrupt the cell cycle and cause apoptosis[4].

Recent studies suggest that sulforaphane has a role in alleviating kidney damage. Sulforaphane (SFN), also known as lycopene, is an isothiocyanate produced by the hydrolysis of glucosinolates (Glu) by black mustard enzymes and is widely distributed in cruciferous plants. Considerable studies have shown that sulforaphane can effectively carry out antioxidant damage by activating the nuclear-related factor 2 (Nrf2) pathway and is a detoxification enzyme inducer [5, 6]. Nrf2 is a basic leucine zipper protein that plays an important role in anti-inflammatory antioxidant gene expression caused by antioxidant response elements (AREs). This study reviews the mechanism of sulforaphane on kidney injury protection and provides an outlook on future research approaches.

2. Protective effect of SFN against heavy metal-induced kidney injury

2.1 Cadmium-induced kidney injury

Cadmium (Cd) is an industrial heavy metal with poor degradability. Cadmium is toxic to the human body, and the main target organ is the kidney. The mechanism by which cadmium is thought to cause damage to the kidney in current studies is related to oxidative damage, where cadmium creates oxygen stress by inducing the production of many reactive oxygen radicals in the organism, leading to lipid peroxidation reactions that imbalance the antioxidant body of the organism and thus

produce damage to the organism [7]. Studies on the protective effect of SFN on kidney injury date back to 2015 and were initially applied in the area of cadmium-induced kidney injury.

Li Jinghui et al. constructed a subchronic cadmium-dyed liver injury model by injecting 6 μmol/kg cadmium chloride (CdCl2) into Wistar rats, and the results showed that superoxide dismutase (GSH-px) and superoxide dismutase (SOD) activities in the kidney cortex of the cadmium-dyed group were significantly decreased, indicating impaired kidney function due to cadmium [8]. In contrast, the activities of GSH-px and SOD, antioxidant enzymes that inhibit peroxidation in the kidney cortex, were significantly higher in the SFN intervention group. These two antioxidant enzymes inhibited peroxidation reactions and effectively reduced cadmium-induced damage to the organism by free bodies [9]. This study indicated that SFN antagonized the kidney oxidative damage in cadmium-stained rats to some extent, and its protective effect was achieved by activating Nrf2. The conversion of SFN from glucose isothiocyanate in broccoli leads to its antioxidant effect through the Nrf2 pathway[10]. In the case of cadmium-induced kidney injury, Keap1-Nrf2 protein is disrupted, and Nrf2 enters the nucleus to synthesize antioxidant enzyme genes, leading to the synthesis of large amounts of GSH-px and SOD and other antioxidant enzymes, thus exerting a protective effect against kidney injury [11].

2.2 Mercury-induced kidney injury

SFN also has a protective effect against mercury-induced kidney injury. Mercury (Hg) is a liquid metal that induces the production of free radicals in the body and causes oxidative damage to tissues, which can enter and accumulate in the human kidney. The current study suggests that SFN may have an antagonistic effect on mercury-induced kidney oxidative damage.

Guo Meixin et al. injected Wistar rats with 2.2, 4.4, and 8.8 mg/kg mercuric chloride (HgCl2) and 2.4 mg/kg HgCl2 and 2 mg/kg SFN in the SFN intervention group[12]. The results showed that the urinary protein and blood urea nitrogen (BUN) levels, as well as kidney cortical GSH and malondialdehyde (MDA) levels, were significantly higher in the 8.8 mg/kg HgCl2 group than in the SFN intervention group, and the urinary lactate dehydrogenase (LDH), alkaline phosphatase (ALP), N-acetyl-β-D-aminoglycosides (NAG), and kidney cortical SOD and GSH-Px activities were significantly increased in the SFN intervention group. GSH can help inhibit lipid peroxidation in the body, which can effectively achieve antioxidant effects, and it can act as a free radical scavenger to reduce oxidative damage [13]. The study results suggest that SFN can exert renoprotective effects by increasing GSH activity.

3. Protective effect of SFN against immune kidney injury

Immune kidney injury is based on an immune response that leads to an immune inflammatory response in the kidney through the activation of immune cells by pathogenic factors to infiltrate a large number of inflammatory cells.

3.1 Bacteria-induced kidney injury

Nanobacteria can induce apoptosis by damaging kidney tubular epithelial cells [14]. Pu Daojing et al. constructed a model using nano cells (absorbance 0.035) to induce HK-2 (108/L) damage in renal tubular epithelial cells and showed that SFN significantly reduced the effect of nanobacteria on HK-2 cell proliferation and that the apoptosis rate of HK-2 cells was significantly lower than that of the control group[15]. Meanwhile, BCL2-associated X (Bax) protein expression was upregulated, increased B-cell lymphoma-2 (Bcl-2) protein expression was downregulated, and protein kinase (PTEN induced putative kinase 1, PINK1), parkin protein, and microtubule-associated-protein light-chain-3 (LC-3II) protein expression were significantly reduced. SFN effectively reduced mitochondrial autophagy and inhibited PINK1 and Parkin protein expression, suggesting that SFN effectively inhibited nanobacteria-induced apoptosis in kidney tubular epithelial cells.

3.2 Lipopolysaccharide (LPS)-induced kidney injury

Li Lin et al. constructed a renal kidney epithelial cell injury model by in vitro cultured HK-2 cells injected with 100 ng/mL LPS[16]. The results showed that SFN significantly decreased the proliferative capacity, inflammatory factors and α-SMA, Traf6 and p-TAK1 protein expression and increased E-cadherin protein expression levels in HK-2 cells compared with the LPS intervention group. The results were most pronounced for high doses of SFN. This result suggests that SFN can effectively inhibit kidney tubular epithelial cell fibrosis and suppress the production of inflammatory factors by activating/inhibiting the Traf6 signaling pathway and alleviating kidney injury caused by LPS.

3.3 H_2O_2-induced kidney injury

In the course of kidney lesions, oxidative damage, which is the toxic reaction caused by the accumulation of reactive oxygen species in the body, often occurs. Qin Zhengbi et al. constructed a model of oxidative damage in kidney epithelial cells by culturing Hk-2 cells with DMEM and injected 10 μmol×L-1, 20 μmol×L-1, and 40 μmol×L-1 SFN into the SFN intervention group [17]. The results showed that the higher dose of SFN in the SFN intervention group was associated with a significant decrease in the content of MDA and NO generated by oxidation due to oxygen radicals compared with the H2O2 group, reflecting that SFN could alleviate cellular oxidative response damage in a concentration-dependent manner. At the same time, GSH and SOD activities were also significantly increased in the SFN intervention group, indicating that SFN can promote Nrf2 binding to ARE and resistance to oxidative stress and nucleophilic compounds, thus elevating the activity of the antioxidant gene GSH and alleviating oxidative damage. The results showed that SFN could alleviate H2O2-induced oxidative damage in renal epithelial cells by activating the Nrf2 pathway.

4. Protective effect of SFN on kidney ischaemia–reperfusion injury

Ischaemia–reperfusion will have an impact on structural kidney damage and metabolism and cause a series of related pathologies. The mechanisms are mainly related to oxidative stress injury and apoptosis.

Huang Lin et al. established a renal ischaemia–reperfusion injury (IRI) model in 24 male C57 mice by noninvasive vascular clamping of bilateral kidney tips for 45 min and divided them into the Ctrl, IRI, IRI+SFN, and SFN groups, with the SFN group injected (500 μg/kg) 24 h before surgery [18]. The results showed that the blood creatinine and urea nitrogen levels were reduced in the SFN group compared with the IRI group, suggesting that SFN could restrain phosphorylation and thus initiate downstream expression for the onset of inflammation. Both findings suggest that SFN has an effective role in alleviating renal ischemia-induced kidney injury. In another article, Shokeir et al. also showed that treatment with SFN improved oxidative stress and cell death, reduced the inflammatory cytokines interleukin-1β and interleukin-6 and several proapoptotic factors, and reduced the impairment of kidney function by ischaemia–reperfusion kidney injury [19].

Oxidative stress injury in sepsis can lead to severe kidney injury by a mechanism related to ROS and active RNS levels, and inhibition of ROS and RNS can help reduce the onset of inflammation [20]. Tang Luming et al. used sepsis-associated acute kidney injury (SA-AKI) rats to construct SA-AKI models using cecum ligation perforation, and control rats underwent abdominal wall switch surgery only after anesthesia; SA-AKI models were prepared in the model and treatment groups; the treatment group was pumped with 5 mg/kg SFN 6 h after modelling[21]. The results showed that the expression of granulocyte gelatinase-related lipid transport proteins and messenger RNA (mRNA) was significantly decreased in the SFN group, indicating that SFN balanced the effects of ROS and RNS on the rat kidney and reduced oxidative damage to produce some protective effects on the kidney.

5. Protective effect of SFN on diabetic nephropathy

Recent studies have found that SFN attenuates the symptoms of diabetic nephropathy as well as its complications. Zheng et al. used STZ to induce mice to replicate a diabetic nephropathy model with continuous injection of SFN [22]. The results showed that SFN reduced the symptoms associated with diabetic nephropathy, such as renal hypertrophy, glomerular collagen accumulation, glomerulosclerosis, glomerular basement membrane thickness and urinary albumin excretion. Additionally, SFN attenuated hyperglycemia, polyuria and polydipsia in wild-type mice but not in Nrf2 KO mice. Shang et al., in a study also using STZ-induced mice replicating a diabetic nephropathy model, suggested that SFN provided biochemical and histological protection, as well as protection from oxidative DNA damage [23]. At the same time, transforming growth factor-β (TGF-β) mRNA expression levels of collagen IV and fibronectin were significantly reduced, and transcriptional activation and protein levels of the antioxidant enzymes NQO1 and HO-1 were increased. In a rat model of STZ-induced diabetic nephropathy combined with superimposed contrast injury by Khaleel et al., SFN partially abrogated renal injury treatment, reduced the renal markers of oxidative stress malondialdehyde and 8-hydroxy-2'-deoxyguanosine, and improved renal function [24]. In another article, Wu et al., in a study of the STZ-induced type 2 DM model, showed that SFN alleviated proteinuria and fibrosis in diabetic mice, reducing the profibrotic mediators TGF-β and connective tissue growth factor, the inflammatory mediators hematogen activator inhibitor-1 and vascular cell adhesion molecule-1, as well as the oxidative markers 3-nitrotyrosine and 4-hydroxy-2-ketone-free effects [25]. It is suggested that SFN may reduce renal oxidative damage and act as a nephroprotective agent.

However, it is noteworthy that in another study, Cui et al. significantly increased the expression of Nrf2 pathway activation products such as NQO1 and HO-1 by replicating SFN in a mouse model of STZ-induced diabetes with SFN [26]. The benefits did not persist after three months without further treatment. This suggests that continued intervention with SFN is required to activate the Nrf2 pathway to counteract the oxidative stress damage associated with diabetic nephropathy.

6. Role of SFN in age-related kidney injury

Age is one of the main factors contributing to chronic diseases, including kidney disease. The transcription factor Nrf2 is a major regulator of redox homeostasis, which is altered during aging. Meanwhile, SFN is one of the main activators of the Nrf2 pathway.

Mohammad et al. established a rat model of oxidative stress kidney injury using young (2-4 months) and old (20-24 months) male Fischer 344 rats and treated them with SFN (15 mg/kg) in drinking water for four weeks [27]. It was found that aged Fischer 344 rats had significantly impaired renal cortical mitochondrial function, impaired redox homeostasis, and decreased renal function. Adjuvant treatment with SFN resulted in a significant increase in the expression and activity of the cortical Nrf2 inhibitor Keap1 and a significant decrease in the protein expression of the Nrf2 inhibitor Keap1. Additionally, SFN administration did not affect kidney NRF2 expression or activity or mitochondrial function in young rats. The results showed that SFN significantly improved mitochondrial function and ameliorated renal injury by activating the Nrf2 pathway in aged rats.

7. Role of SFN in kidney injury caused by other factors

7.1 Myoglobin-induced kidney injury

Kidney injury is one of the most serious complications of rhabdomyolysis. Rhabdomyolysis is caused by several factors, mainly due to the entry of myoglobin as well as creatine kinase into the extracellular fluid of the blood circulation [28]. To date, several studies have proposed that SFN can protect the kidney by inhibiting the expression of histone deacetylase 6 (HDAC6) to achieve antitumour effects [29].

Tan Jing et al. used HK-2 human kidney cortical proximal tubule epithelial cells to replicate the myoglobin-induced acute kidney injury model and divided them into a normal control group, model group, SFN group (200 μmol/L), and 23BB group [30]. The results showed that the cell viability was significantly lower in the model group. In contrast, cell viability was significantly increased in the SFN and 23BB groups. HDAC6 is expressed in several tissues, mediates multiple transcription factors, and mediates multiple kidney injuries [31]. These findings suggest that SFN is a potent inhibitor of the HDAC6 enzyme. The effect of SFN is similar to that of 23BB and can be substituted for it to achieve nephroprotective effects.

7.2 Uric acid-induced kidney injury

Tan Jing et al. used 200 mg/L uric acid to induce apoptosis in HK-2 cells and divided them into a control group, uric acid group, low-dose SFN group, medium-dose SFN group, and high-dose SFN group [32]. The results showed that the cell survival in the SFN group was significantly higher and the apoptosis rate was significantly lower than those in the uric acid group. The expression of cleaved caspase-3, cleaved caspase 12, BiP/GRP78, inositol-requiring enzyme 1 (IRE1), and c-Jun N-terminal kinase (JNK) was significantly downregulated. The results suggested that SFN effectively inhibited the activation of the ER stress IRE-1/JNK signaling pathway and reduced kidney tubular epithelial cell apoptosis.

7.3 High glucose-induced kidney injury

Studies have shown that diabetes can trigger nephropathy and that sustained high glucose can lead to apoptosis [33]. SFN can enhance Nrf2 to maintain oxidative damage by activating threonine protein kinase (Akt), while SFN can promote apoptosis in tumor cells through the phosphatidylinositol-3-kinase (PI3K)/Akt signaling pathway . -3-kinase (PI3K)/Akt signaling pathway to promote apoptosis in tumor cells [34].

Zhou Lei et al. used kidney tubular epithelial HK-2 cells inoculated in DMEM and divided into normal, high glucose, irbesartan, and SFN low, medium, and high (10, 20, and 40 μmol/L) groups [35]. The results showed that cell viability was decreased and the apoptosis rate was increased in the high glucose group. In contrast, the SFN group had increased cell viability and a decreased apoptosis rate. SFN effectively inhibited high glucose-induced apoptosis in kidney tubular epithelial cells by inhibiting the PI3K/Akt signaling pathway while upregulating the expression of G1/S-specific cyclin-D1 (Cyclin D1) and Bcl-2 and downregulating the expression of caspase-3 and Bax.

7.4 Calcium oxalate-induced kidney injury

Approximately 90% of kidney stones are calcium-rich, with calcium oxalate stones accounting for approximately 60% of calcium-containing stones. Ruo-Tian Liu et al. used 30 Wistar rats to establish a rat calcium oxalate kidney stone model and used 0.2 mg SFN-injected pharmaceutical control rats [36]. The results showed that the levels of oxalic acid, Ca2+, and MDA in the urine of the rats in the drug intervention group were significantly lower than those in the model group. The results suggest that SFN can effectively activate the Nrf2 signaling pathway and upregulate antioxidant proteins such as HO-1 to act as an antioxidant, thereby inhibiting the formation of calcium oxalate kidney stones.

8. Protective effect of SFN on severe kidney injury

8.1 Protective effect of SFN against kidney fibrosis

Chronic kidney disease (CKD) is the accumulation of excessive fibrotic cells leading to ECM, which alters the kidney structure and eventually leads to kidney failure [37]. Recent studies have shown that inhibition of the TGF-β pathway can lead to effective therapeutic effects [38].

Guo Li et al. divided mice into the Salicylhydroxamic acid (Sham) group, Sham+SFN group, Unilateral Ureteral Obstruction (UUO) group, and UUO+SFN group. A kidney fibrosis model was constructed using UUO surgery[39]. The results showed that the BUN and blood creatinine levels in the UUO group were higher than those in the Sham and SFN groups, and the kidney mass in the UUO group was also lower than that in the Sham and SFN groups. Meanwhile, the kidney tubular injury score and the relative expression of TGF-β, rat phosphorylated cell signaling molecules SMAD, t-Smad, and connective tissue growth factor (CTGF) were higher in the UUO group than in the Sham and SFN groups. The results suggest that SFN is an antioxidant with anticancer properties, can induce phase II enzyme activity to prevent ischemic injury, and can effectively interfere with renal fibrosis by inhibiting TGF-β expression to produce a protective effect on the kidney.

In another article, Sun et al. used in vitro cultured HK2 cells to construct a model of equine uric acid-mediated renal fibrosis[40]. The results showed that the expression of ROS and H2O2 was significantly reduced, and the expression of the antioxidant proteins Nrf2, heme oxygenase HO-1 (HO-1) and quinone NADH dehydrogenase 1 was significantly increased compared to SFN. The results suggest that SFN effectively inhibited the oxidative damage induced by horse uric acid, thus exerting some protective effects on the kidney.

8.2 Protective effects of SFN in nephrotic syndrome

The main symptoms of nephrotic syndrome are glomerular lesions that cause peripheral tissue edema, massive proteinuria, and hyperlipidemia [41].

Du Zonghua et al. divided 32 SPF-grade rats into a blank control group, adriamycin-stimulated group, adriamycin combined with 30 mg/kg SFN group and adriamycin combined with 60 mg/kg SFN group and used a single tail vein injection of adriamycin (5 mg/kg) to construct a model of the adriamycin group[42]. The results showed that the TGF-β stimulation group significantly induced cell proliferation in rat glomerular thylakoid cells and significantly inhibited TGF-β-induced adhesion protein and IV collagen expression compared with SFN alone. Meanwhile, creatinine, urea nitrogen and 24-hour proteinuria levels were significantly lower in the SFN group than in the adriamycin group. The results suggest that SFN can effectively regulate kidney function by inhibiting the activity of the TGF-β signaling pathway induced by adriamycin to reduce glomerular cell proliferation and reduce the extent of glomerular injury in rats.

9. Conclusion

In conclusion, sulforaphane has the potential to treat kidney injury induced by various factors by inhibiting oxidative damage, reducing the inflammatory response, and activating the Nrf2 pathway. However, most of the current studies are limited to animal studies, and clinical trials are relatively rare. Additionally, most of the experiments have limitations, such as not focusing on the possible toxic side effects and the therapeutic impact of the dose. Further research and development related to the application of radicicliclovir are still needed in the future.

References

1. Rapa, S.F., Di Iorio, B.R., Campiglia, P., Heidland, A.&Marzocco, S. Inflammation and Oxidative Stress in Chronic Kidney Disease-Potential Therapeutic Role of Minerals, Vitamins and Plant-Derived Metabolites. Int J Mol Sci 21(1)(2019). https://doi.org/10.3390/ijms21010263
2. Duni, A., Liakopoulos, V., Roumeliotis, S., Peschos, D.&Dounousi, E. Oxidative Stress in the Pathogenesis and Evolution of Chronic Kidney Disease: Untangling Ariadne's Thread. Int J Mol Sci 20(15)(2019). https://doi.org/10.3390/ijms20153711
3. Daenen, K. et al. Oxidative stress in chronic kidney disease. Pediatr Nephrol 34(6): 975-991 (2019). https://doi.org/10.1007/s00467-018-4005-4
4. Pizzino, G. et al. Oxidative Stress: Harms and Benefits for Human Health. Oxid Med Cell Longev 2017: 8416763 (2017). https://doi.org/10.1155/2017/8416763
5. Subedi, L., Cho, K., Park, Y.U., Choi, H.J.&Kim, S.Y. Sulforaphane-Enriched Broccoli Sprouts Pretreated by Pulsed Electric Fields Reduces Neuroinflammation and Ameliorates Scopolamine-Induced Amnesia in Mouse Brain through Its Antioxidant Ability via Nrf2-HO-1 Activation. Oxid Med Cell Longev 2019: 3549274 (2019). https://doi.org/10.1155/2019/3549274
6. Kang, K.W., Lee, S.J.&Kim, S.G. Molecular mechanism of nrf2 activation by oxidative stress. Antioxid Redox Signal 7(11-12): 1664-1673 (2005). https://doi.org/10.1089/ars.2005.7.1664
7. [7] Jomova, K.&Valko, M. Advances in metal-induced oxidative stress and human disease. Toxicology 283(2-3): 65-87 (2011). https://doi.org/10.1016/j.tox.2011.03.001
8. Li.J et al. Protective effect of sulforaphane on renal damage caused by cadmium in rats. Chinese Journal of Industrial Medicine 28(01): 11-13+42 (2015). https://doi.org/10.13631/j.cnki.zggyyx.2015.01.003
9. Genchi, G., Sinicropi, M.S., Lauria, G., Carocci, A.&Catalano, A. The Effects of Cadmium Toxicity. Int J Environ Res Public Health 17(11)(2020). https://doi.org/10.3390/ijerph17113782
10. Uruno, A.&Motohashi, H. The Keap1-Nrf2 system as an in vivo sensor for electrophiles. Nitric Oxide 25(2): 153-160 (2011). https://doi.org/10.1016/j.niox.2011.02.007
11. Wakabayashi, N. et al. Protection against electrophile and oxidant stress by induction of the phase 2 response: fate of cysteines of the Keap1 sensor modified by inducers. Proc Natl Acad Sci U S A 101(7): 2040-2045 (2004). https://doi.org/10.1073/pnas.0307301101
12. Guo, M. et al. Protective effect of sulforaphane on mercury-induced acute renal injury in rats. Practical Preventive Medicine 23(12): 1461-1464 (2016).
13. Zheng S.&Zhou J. Progress in the study of the nephrotoxicity mechanism of inorganic mercury (mercuric chloride). Medicine Abroad (Health Sciences Division) (03): 175-179 (2005).
14. Shen, M. etal. Effects of Tetracycline on the Expression of CaSR and Claudin-14 in Nanobacteria-infected Human Renal Tubular Epithelial Cells HK-2. China Pharmacy 29(19): 2607-2611 (2018).
15. Pu, D. et al. Effects of sulforaphane on mitophagy-related proteins in nanobacteria-induced renal tubular epithelial cell apoptosis. Journal of Clinical Rehabilitative Tissue Engineering Research 23(34): 5503-5507 (2019).
16. Li, L.&Tang J. Regulatory effects of sulforaphane on epithelial to mesenchymal transition in renal tubular epithelial cell through Traf6/TAK1 signaling pathway. International Journal of Urology and Nephrology|Int J Urol Nephrol (02): 305-306-307-308-309 (2020).
17. Qin Z.&Mao W. Effects of Sulforaphane on Oxidative Stress and Nrf2/HO-1 Signaling Pathway in Renal Tubular Epithelial Cells. China Pharmacist 20(05): 809-812 (2017).
18. Huang L. Liao P.&Zhang J. Sulforaphane attenuates renal ischemia reperfusion injury in mice by Nrf-2 against inflammation. Jounal of Xi'an Jiaotong University(Medical Sciences) 40(05): 696-701 (2019).
19. Shokeir, A.A. et al. Activation of Nrf2 by ischemic preconditioning and sulforaphane in renal ischemia/reperfusion injury: a comparative experimental study. Physiol Res 64(3): 313-323 (2015). https://doi.org/10.33549/physiolres.932834
20. Li, J. Pathogenesis and Chinese medicine treatment of acute kidney injury in sepsis. Nei Mongol Journal of Traditional Chinese Medicine. 41(04): 150-153 (2022). https://doi.org/10.16040/j.cnki.cn15-1101. 2022.04.088
21. Tang, L. et al. Protective effect of sulforaphane on oxidative response in rats with sepsis-associated acute

kidney injury. Chinese Journal of Critical Care Medicine （Electronic Edition) 14(03): 187-191 (2021).

22. Zheng, H. et al. Therapeutic potential of Nrf2 activators in streptozotocin-induced diabetic nephropathy. Diabetes 60(11): 3055-3066 (2011). https://doi.org/10.2337/db11-0807
23. Shang, G. et al. Sulforaphane attenuation of experimental diabetic nephropathy involves GSK-3 beta/Fyn/Nrf2 signaling pathway. J Nutr Biochem 26(6): 596-606 (2015). https: //doi. org/10. 1016/j.jnutbio.2014.12.008
24. Khaleel, S.A. et al. Contrast media (meglumine diatrizoate) aggravates renal inflammation, oxidative DNA damage and apoptosis in diabetic rats which is restored by sulforaphane through Nrf2/HO-1 reactivation. Chem Biol Interact 309: 108689 (2019). https://doi.org/10.1016/j.cbi.2019.06.002
25. Wu, H. et al. Metallothionein plays a prominent role in the prevention of diabetic nephropathy by sulforaphane via up-regulation of Nrf2. Free Radic Biol Med 89: 431-442 (2015). https://doi.org/10.1016/j.freeradbiomed.2015.08.009
26. Cui, W. et al. Prevention of diabetic nephropathy by sulforaphane: possible role of Nrf2 upregulation and activation. Oxid Med Cell Longev 2012: 821936 (2012). https://doi.org/10.1155/2012/821936
27. Mohammad, R.S., Lokhandwala, M.F.&Banday, A.A. Age-Related Mitochondrial Impairment and Renal Injury Is Ameliorated by Sulforaphane via Activation of Transcription Factor NRF2. Antioxidants (Basel) 11(1) (2022). https://doi.org/10.3390/antiox11010156
28. Scalco, R.S. et al. Rhabdomyolysis: a genetic perspective. Orphanet J Rare Dis 10: 51 (2015). https://doi.org/10.1186/s13023-015-0264-3
29. Lernoux, M., Schnekenburger, M., Dicato, M.&Diederich, M. Anti-cancer effects of naturally derived compounds targeting histone deacetylase 6-related pathways. Pharmacol Res 129: 337-356 (2018). https://doi.org/10.1016/j.phrs.2017.11.004
30. Tan J.&Yi G. Turnip-sulfur-mediated HDAC6 signaling pathway ameliorates myoglobin-induced apoptosis in renal tubular epithelial cells. Journal of Chinese Medicinal Materials 42(09): 2181-2184 (2019). https://doi.org/10.13863/j.issn1001-4454. 2019.09.042
31. Krukowski, K. et al. HDAC6 inhibition effectively reverses chemotherapy-induced peripheral neuropathy. Pain 158(6): 1126-1137 (2017). https://doi.org/10.1097/j.pain.0000000000000893
32. Tan J.&Yi G. Effect of sulforaphane alleviates uric acid-induced apoptosis in tubular epithelial cells via regulating endoplasmic reticulum stress and its mechanism. International Journal of Urology and Nephrology|Int J Urol Nephrol 40(04): 688-692 (2020).
33. Tang, S.C.&Lai, K.N. The pathogenic role of the renal proximal tubular cell in diabetic nephropathy. Nephrol Dial Transplant 27(8): 3049-3056 (2012). https://doi.org/10.1093/ndt/gfs260
34. Ren J. et al. Sulforaphane and Its Derivative BSFN Induced Apoptosis in SH-SY5Y Cells by Activating the PI3K/Akt Signaling Pathway. Chinese Pharmaceutical Journal | Chin Pharm J 49(20): 1813-1819 (2014).
35. Zhou, L. et al. Effects of Sulforaphane on the Proliferation and Apoptosis of Human Renal Tubular Epithelial Cells Induced by High Glucose and Its Mechanism. Chinese Pharmacy 32(24): 3000-3007 (2021).
36. Liu, R.T.et al. Effect and Mechanism of Sulforaphane on Calcium Oxalate Nephrolithiasis in Rats Through Nrf2 Signaling Pathway. Progress in Modern Biomedicine 22(11): 2028-2033 (2022). https://doi.org/10.13241/j.cnki.pmb.2022.11.005
37. Meng, X.M., Nikolic-Paterson, D.J.&Lan, H.Y. TGF-β: the master regulator of fibrosis. Nat Rev Nephrol 12(6): 325-338 (2016). https: //doi.org/10.1038/nrneph.2016.48
38. Yin, Q. et al. Synthesis and photophysical properties of deuteration of pirfenidone. Spectrochim Acta A Mol Biomol Spectrosc 204: 88-98 (2018). https://doi.org/10.1016/j.saa.2018.06.016
39. Guo,L. et al. Interventional effect and mechanism of sulforaphane on renal fibrosis induced by unilateral ureteral obstruction in mice. Shandong Medical Journal 59(32): 33-36 (2019).
40. Sun, B. et al. Hippuric Acid Promotes Renal Fibrosis by Disrupting Redox Homeostasis via Facilitation of NRF2-KEAP1-CUL3 Interactions in Chronic Kidney Disease. Antioxidants (Basel) 9(9)(2020). https://doi.org/10.3390/antiox9090783
41. Leisti, S. et al. Association of postmedication hypocortisolism with early first relapse of idiopathic nephrotic syndrome. Lancet 2(8042): 795-796 (1977). https://doi.org/10.1016/s0140-6736(77)90726-7
42. Du, Z.H., M, H.H.&Long, Q. Effect of sulforaphane on mesangial cell proliferation in nephrotic syndrome rats through TGF β / Smad3 signaling pathway. Medical Journal of West China 32(01): 43-48 (2020).