REVIEW ARTICLE

RECORDS OF PHARMACEUTICAL AND BIOMEDICAL SCIENCES

Pathophysiological mechanisms of diabetic nephropathy: Role of S1R/Nrf2 antioxidant axis

Dalia M. Asal [a*], Alaa S. Wahba [a], Reem M. Hazem [b], Asmaa R. Abdel-Hamed [a], Noha M. Mesbah [a], Dina M. Abo-Elmatty [a]

[a] Department of Biochemistry, Faculty of Pharmacy, Suez Canal University, Ismailia, Egypt; [b] Department of Pharmacology and Toxicology, Faculty of Pharmacy, Suez Canal University, Ismailia, Egypt.

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*Corresponding Author:

E-mail address:

daliaasal_staff@pharm.suez.edu.eg

Abstract

Diabetic nephropathy (DN) stands out as one of the most significant complications of diabetes mellitus, and it is a primary contributor to end-stage kidney disease globally. The progression of DN is complex, involving intricate interplays, including oxidative stress, inflammation, fibrosis, and cellular apoptosis. Recently, scientific investigations have emphasized the significant role of the sigma-1 receptor (S1R) and nuclear factor erythroid 2-related factor 2 (Nrf2) in mitigating these detrimental effects. Scientific evidence indicated that the activation of S1R could effectively diminish cellular oxidative stress, inflammation, and cell death, alleviating renal damage in diabetic nephropathy. Nrf2, a key regulator of antioxidant responses, protects renal cells from oxidative injury and modulates inflammatory responses. Targeting S1R and Nrf2 may provide novel therapeutic approaches for managing diabetic nephropathy. This review offers a detailed overview of the pathophysiological mechanisms underlying DN, focusing on the S1R/Nrf2 axis and its potential as a promising therapeutic target for diabetic nephropathy.

Keywords: Diabetic nephropathy; oxidative stress; inflammation; apoptosis; S1R/Nrf2.

1. Background

Diabetes mellitus (DM) is a severe chronic metabolic condition characterized by impaired carbohydrate metabolism due to either insufficient insulin production or insulin resistance, leading to elevated blood glucose levels. DM is the prevailing cause of mortality globally, ranking within the top 10 causes **(Melonie, 2021; Li et al., 2023)**. Its widespread prevalence has escalated DM to epidemic status. If left without control, this condition can have severe consequences for diabetic patients, leading to both micro- and macro-vascular complications that can lead to significant morbidity and mortality in the long term **(Abouzid et al., 2022)**. Macro-vascular complications result from artery deterioration, which causes accelerated cardiovascular diseases. Microvascular disorders, such as retinopathy, neuropathy, and nephropathy, result from the impairment of small blood vessels **(Nadhiya et al., 2024)**. Diabetic nephropathy (DN) is a prominent kidney-related consequence of type 1 and type 2 DM. Adults worldwide have a 9% incidence of DN **(Liu et al., 2022)**. **Selby and Taal (2020)** stated that DN is the primary cause of end-stage kidney disease (ESKD) worldwide, affecting 20% to 50% of diabetic patients. Understanding the pathophysiology of DN is crucial for developing

effective treatment strategies, as it involves a complex interplay of multiple pathogenic processes, including oxidative stress, inflammation, and fibrosis **(Tanase et al., 2022)**.

2. Diabetic nephropathy risk factors

Diabetic nephropathy risk factors can be categorized into two main groups: modifiable and non-modifiable factors. The former includes managing hypertension, glycemic levels, and dyslipidemia. Furthermore, studies have demonstrated that smoking represents an additional modifiable risk factor. The second group involves non-modifiable factors, such as race, age, gestation, genetic profile, and sex. Researchers have found that individuals who are genetically predisposed to DN are more likely to develop the disorder. Studies on different racial groups, including Mexicans, Africans, and Native American Pima people, have shown higher rates of developing DN. Regarding sex, male diabetic patients have a higher probability of developing DN **(Bornhorst et al., 2020)**.

3. Diabetic nephropathy stages

Renal structure and hemodynamic changes can be monitored for the pathology and clinical advancement of DN. **Table 1** illustrates the stages of DN **(Sagoo and Gnudi, 2020)**.

3.1. Glomerular hyperfiltration (the initial phase)

The initial phase starts with thickening the glomerular basement membrane (GBM). There is no evidence of albuminuria, and the glomerular filtration rate (GFR) is still normal **(Sagoo and Gnudi, 2020; Natesan and Kim, 2021)**.

3.2. The silent stage (the second stage)

This stage involves mild to severe mesangial expansion. The GFR remains normal for two years after the onset of GBM thickness and mesangial proliferation; hypertension frequently lasts five years at this stage. No further clinically significant symptoms were registered **(Natesan and Kim, 2021)**.

3.3. Incipient (early) nephropathy (the third stage)

The third stage is characterized by increased microalbuminuria ranging from 30 to 300 mg/day and glomerular damage. This phase, which begins five to ten years after GBM thickness onset **(Sagoo and Gnudi, 2020; Natesan and Kim, 2021)**.

3.4. Overt nephropathy (the fourth stage)

The fourth stage is advanced diabetic glomerulosclerosis, which involves a substantial reduction in kidney function and an accumulation of tubulointerstitial and vascular lesions **(Sagoo and Gnudi, 2020)**.

3.5. End-stage renal disease

The end stage is characterized by complete renal failure with a GFR below 15 ml/min/1.73 m2. Typically, this stage necessitates dialysis or transplantation **(Sagoo and Gnudi, 2020; Natesan and Kim, 2021)**.

4. Diabetic nephropathy pathogenesis

Several pathways and mediators contribute to the pathophysiology of DN development and progression **(Perez-Morales et al., 2019; Jung and Moon, 2021)**. DN exhibits detrimental structural alterations, including enlargement of the glomerular basement membrane, depletion of podocytes, and thickening of the mesangial matrix **(Lowen et al., 2021)**. Traditionally, it is widely acknowledged that renal hemodynamic changes, oxidative stress, inflammatory response, hypoxia, and the renin-angiotensin-aldosterone system (RAAS) play an integral part in the development of DN **(Sun et al., 2019)**, as demonstrated in **Figure 1**.

Maintaining appropriate glycemic control has been linked to better renal function and a slower rate of DN progression in diabetic patients. It is well established that prolonged elevated glucose levels may lead to extensive negative impacts. These include the formation of advanced glycation end products (AGEs), oxidative damage, reduced oxygen supply, disruptions in metabolism and energy production, and excessive activation of the RAAS. Additionally, sustained hyperglycemia results in the overproduction of inflammatory and fibrotic substances such as transforming growth factor beta (TGF-β), which plays a crucial role in the progression of kidney fibrosis **(Barrera-Chimal and Jaisser, 2020)**. Furthermore, it has

Table 1: Stages of diabetic nephropathy **(Sagoo and Gnudi, 2020)**

Stage of DN		GFR	UAE	BP	Additional comments
Stage 1	**Glomerular hyperfiltration**	Normal >90 mL/ min/1.73 m2 or increased	<30 mg/day	Normotensive	Renal hyperfunction and hypertrophy
Stage 2	**Silent stage**	Normal >90 mL/ min/1.73 m2	<30 mg/day	± Hypertensive	Thickening of basement membrane and mesangial proliferation
Stage 3	**Incipient nephropathy**	<60 mL/min/ 1.73 m2	Microalbuminuria: 30–300 mg/day	± Hypertensive	First clinical signs of kidney disease
Stage 4	**Overt nephropathy**	<30 mL/min/ 1.73 m2	Macroalbuminuria: >300 mg/day	Hypertensive	Significant loss of kidney function
Stage 5	**End-stage renal disease**	<15 mL/min/ 1.73 m2	Macroalbuminuria: >300 mg/day	Hypertensive	Significant loss of kidney function. Usually requires dialysis or transplantation

GFR; glomerular filtration rate, UAE; urinary albumin excretion, BP; blood pressure

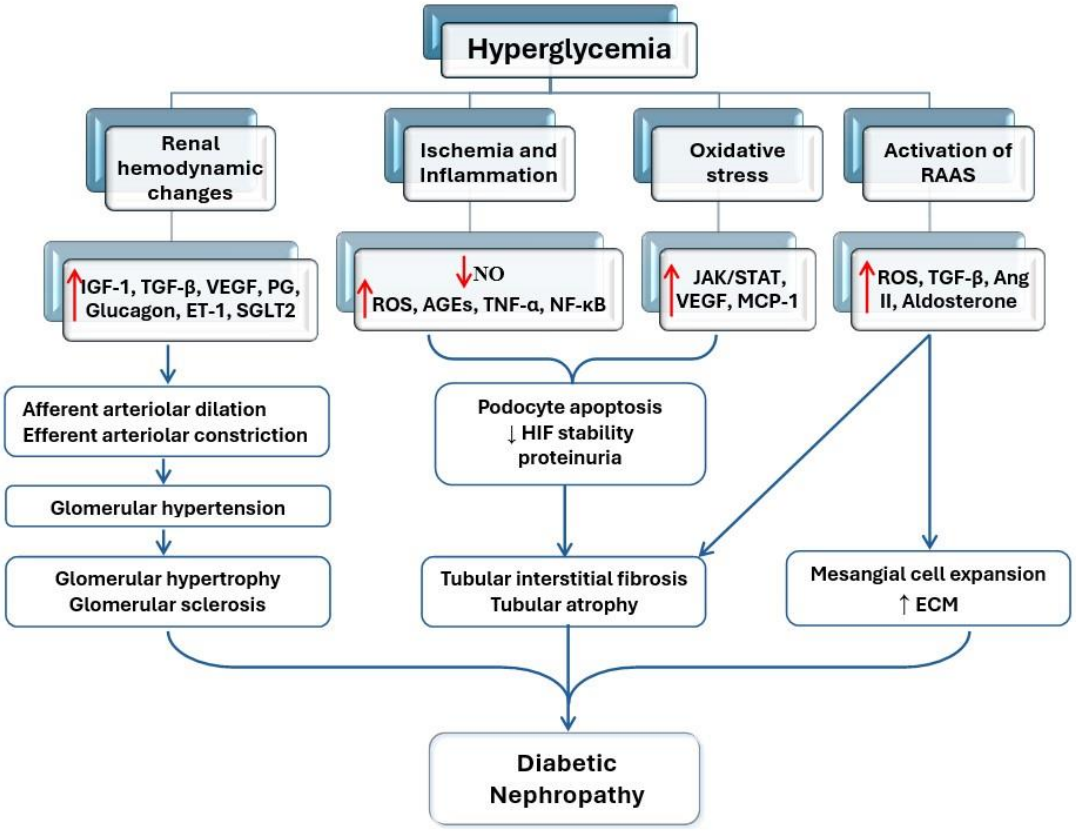

Figure 1: Pathogenesis of diabetic nephropathy. IGF-1, insulin-like growth factor 1; TGF-β1, transforming growth factor β1; VEGF, vascular endothelial growth factor; NO, Nitric oxide; PG, prostaglandin; Ang II, angiotensin II; ET-1, endothelin-1; SGLT2, sodium-glucose co-transporters 2; ROS, reactive oxygen species; AGEs, advanced glycation end products; TNF, tumor necrosis factor; NF-κB, nuclear factor kappa-B; HIF, hypoxia-inducible factor; RAAS, renin-angiotensin-aldosterone system; ECM, extracellular matrix.

been recognized that free radicals and ROS contribute significantly to the emergence and progression of diabetic complications **(Akhigbe and Ajayi, 2021; Tan et al., 2022)**.

4.1. The role of oxidative stress in diabetic nephropathy

Hyperglycemia triggers the release of reactive oxygen species (ROS), which have a significant impact on the development and advancement of diabetic complications **(Akhigbe and Ajayi, 2021; Tan et al., 2022)**. Oxidative stress plays a critical role in the progression of DN. Studies have shown that reducing oxidative stress can significantly improve the main features of streptozotocin-induced diabetic nephropathy, further emphasizing its importance in the disease **(Sagoo and Gnudi, 2018)**.

Oxidative stress-related damage pathways can occur directly or indirectly. Oxidative stress can directly damage mesangial cells, endothelial cells, and podocytes, leading to podocyte death and their subsequent loss, as demonstrated in **Figure 2 (Vodosek Hojs et al., 2020; Erekat, 2022; Jiang et al., 2022)**. Apoptosis provokes glomerular injury in diabetic kidneys, leading to a decrease in podocyte proportion **(Erekat, 2022; Jiang et al., 2022)**. In diabetic nephropathy, a reduced number of podocytes is associated with proteinuria, glomerular structural damage, and tubulointerstitial fibrosis. This can occur because the glomerulus is more susceptible to oxidative stress than other nephron sections **(Piko et al., 2023)**. High glucose levels enhance p53 expression, as displayed in **Figure 2**. This, in turn, activates B-cell lymphoma protein 2 (Bcl-2)-associated X (Bax) and the intrinsic apoptotic pathway, leading to the activation of caspase-3 in podocytes and their subsequent apoptosis **(Wu et al., 2017; Patil and Bihari, 2022)**. On the other hand, decreased expression of P53 inhibits podocyte apoptosis triggered by elevated glucose levels **(Liang et al., 2021)**.

Moreover, oxidative stress can indirectly stimulate other pathogenic pathways, resulting in injury; alternatively, other pathogenic pathways can induce injury through oxidative stress **(Gyuraszova et al., 2020)**. Oxidative stress is accompanied by metabolic and hemodynamic alterations in the kidney, which have detrimental synergistic consequences **(Podkowinska and Formanowicz, 2020)**.

4.2. The role of inflammation in diabetic nephropathy

Studies have demonstrated the critical role that inflammatory and immunological responses play in the development of DN **(Samsu, 2021)**. The development and progression of DN are associated with kidney inflammation. Several studies demonstrate that interleukin-1 (IL-1), IL-6, and IL-18 are involved in the progression of DN **(Donate-Correa et al., 2020; Rayego-Mateos et al., 2020)**. Even so, in experimental DN, researchers concluded that inhibiting the migration of inflammatory cells into the kidney can protect from injury **(Samsu, 2021; Fu et al., 2022)**. The above scenario implies that inflammation may play a significant pathogenic role in the development and progression of DN.

4.3. The interplay between inflammation and oxidative stress in diabetic nephropathy

Figure 3 illustrates the mutually interdependent relationship between inflammation and oxidative stress **(Charlton et al., 2020; Samsu, 2021)**. Inevitably, the interaction between oxidative stress and inflammation plays a significant role in the development and progression of chronic kidney disorders (CKD) **(Podkowinska and Formanowicz, 2020)**. An increase in AGEs can also trigger nuclear factor kappa-B (NF-κB) activation in DN, leading to a surge in ROS generation **(Wu et al., 2021)**. The overproduction of ROS leads to the activation of NF-κB and inflammatory cytokines, playing a vital role in the development of DN **(Samsu, 2021; Jin et al., 2023)**. As a result, inflammation and inflammatory cytokines create an endless cycle of ROS generation, leading to a prolonged state of oxidative stress, inflammation, and apoptosis in DN **(Winiarska et al., 2021; AlTamimi et al., 2023)**.

5. Sigma-1 receptor (S1R)/ Nuclear factor erythroid 2-related factor 2 (Nrf2) axis

Formerly, sigma receptors were proposed to belong to a distinct category of opioid receptors based on behavioral observations **(Martin et al., 1976; Szczepanska et al., 2023)**. Many reports delve into the intricacies of S1R activation and its promising

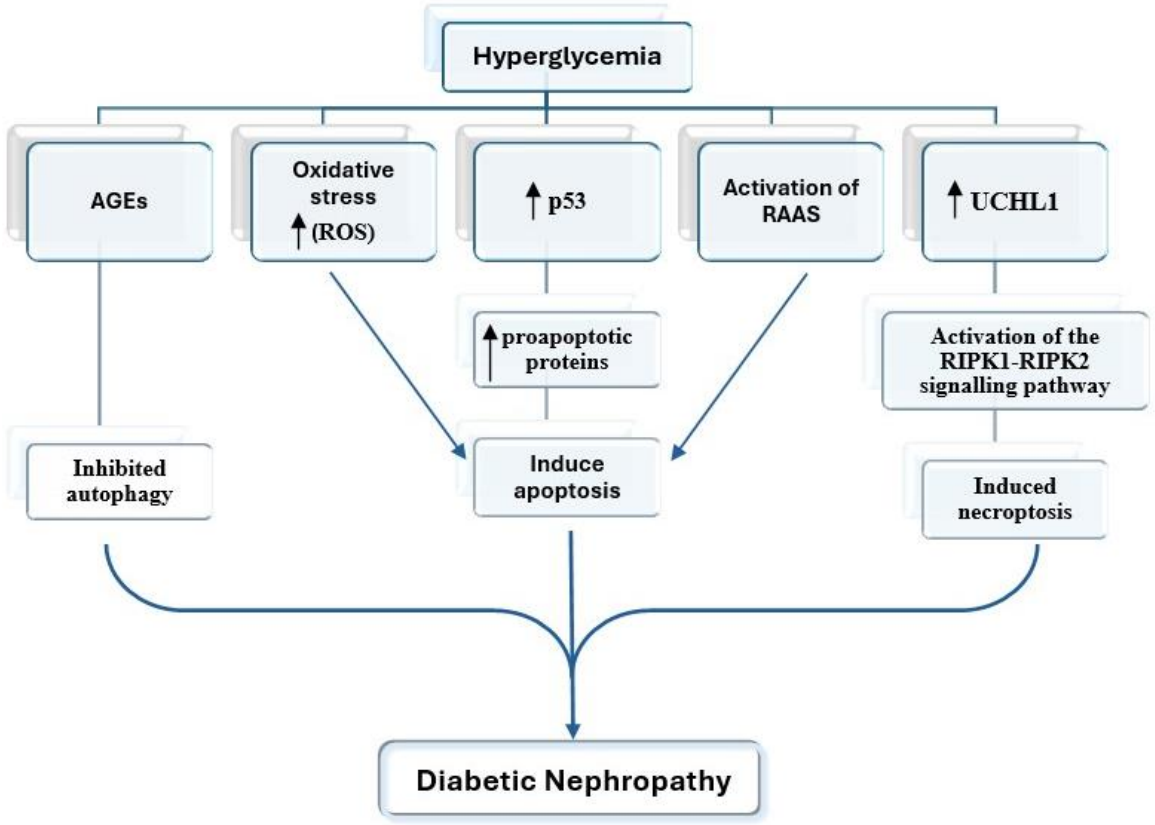

Figure 2: Role of hyperglycemia in induction of apoptosis in diabetic nephropathy. AGEs, advanced glycation end-products; ROS, reactive oxygen species; RAAS, renin angiotensin-aldosterone system; UCHL1, Ubiquitin carboxy-terminal hydrolase L1; RIPK1-RIPK2, serine/threonine protein kinases.

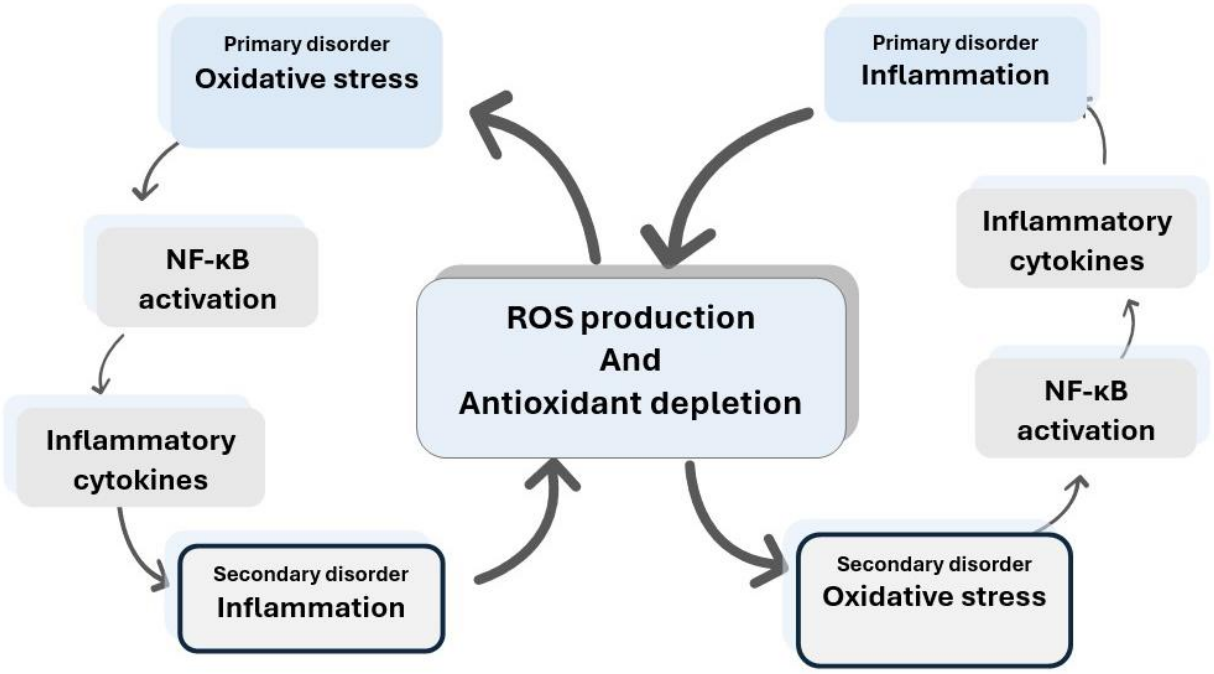

Figure 3: Interdependence between oxidative stress and inflammation. NF-κB, nuclear factor-κB; ROS, reactive oxygen species.

potential as a therapeutic target in various human diseases, particularly neurodegenerative disorders. **(Siddiqui and Bhatt, 2023)**. Researchers have found that S1R protects neuronal cells from ROS damage by suppressing ROS formation, increasing antioxidant levels, and mitigating oxidative stress **(Couly et al., 2020; Shi et al., 2021)**. Similarly, an S1R agonist has been stated to effectively reduce inflammatory and oxidative stress responses by hindering the activity of inducible nitric oxide synthase (iNOS) and tumor necrosis factor-alpha (TNF-α) while simultaneously enhancing reduced glutathione (GSH) **(Wang and Zhao, 2019; Almasi et al., 2020)**. The activation of S1R protected cells from glutamate-induced cell death by modulating intracellular calcium levels, Bax, and caspase-3 activation **(Xu et al., 2022)**. S1R signaling enhances the expression of the apoptosis regulator Bcl-2, providing protection against apoptosis induced by oxygen-glucose deprivation and hydrogen peroxide **(Siddiqui and Bhatt, 2023)**. S1R activation maintains its antioxidant and anti-inflammatory effects, mainly by activating its downstream effector nuclear factor erythroid 2-related factor 2 (Nrf2) and heme oxygenase-1 (HO-1) **(Munguia-Galaviz et al., 2023; Siddiqui and Bhatt, 2023)**.

Nrf2 is essential in regulating the expression of several antioxidant genes, thereby significantly contributing to the prevention of oxidative stress and its adverse consequences **(He et al., 2020)**. In addition to its role in regulating the redox balance, Nrf2 encounters the potential to reduce inflammation by suppressing NF-κB, a key regulator of the inflammatory response **(Ahmed et al., 2017; Jazvinscak Jembrek et al., 2021)**. The activation of the Nrf2/HO-1 pathway can reduce the levels of pro-inflammatory biomarkers such as NF-κB, TNF-α, and IL-6 and also suppress caspase-3 activation and Bax expression while enhancing the expression of the anti-apoptotic protein Bcl-2 **(Ahmed et al., 2017; Abdel-Wahab et al., 2020; Wang and Zhang, 2024)**.

5.1. The role of S1R/Nrf2 axis in diabetic nephropathy

In diabetic nephropathy, the Nrf2 pathway plays a critical role in protecting renal cells from oxidative stress, and emerging research has identified the S1R/Nrf2 axis as a potential therapeutic target to alleviate diabetes-related renal complications. To achieve this, the following mechanisms may be employed:

5.1.1. Synergistic antioxidant effects

S1Rs are recognized for their ability to modulate cellular reactions to stress, especially oxidative stress, which plays a vital role in the progression of DN. S1R activation has the potential to mitigate the inflammatory processes that contribute to renal injury by regulating oxidative stress **(Milardovic et al., 2020)**. S1R activation engages the Nrf2 signaling cascade, which helps to modulate oxidative stress, which lessens the oxidative damage that exacerbates DN **(Wu et al., 2021; Lasbleiz et al., 2022; Li et al., 2024)**. Additionally, activating S1R may alleviate endoplasmic reticulum (ER) stress and improve mitochondrial function, potentially resulting in the upregulation of Nrf2. The upregulation is linked to heightened expression of antioxidant enzymes, thus offering a robust defense mechanism against oxidative stress in diabetic nephropathy **(Lasbleiz et al., 2022; Li et al., 2024)**.

5.1.2. Modulation of inflammatory responses

Nrf2, a significant downstream effector of S1R signaling, plays a crucial role in regulating inflammatory responses by suppressing the production of pro-inflammatory cytokines and counteracting NF-κB signaling, which is strongly implicated in the progression of CKD **(Guerrero-Hue et al., 2020)**. **Figure 4** illustrates the impact of hyperglycemia on the equilibrium between Nrf2 and NF-κB signaling, which is considered to be a crucial factor in the progression of diabetic neuropathy **(Ganesh Yerra et al., 2013)**. This disruption is marked by heightened NF-κB activity in hyperglycemic conditions, resulting in the excessive production of pro-inflammatory mediators, such as IL-6, TNF-α, Cyclooxygenase-2 (COX-2), and iNOS **(Hashim et al., 2024; Zamanian et al., 2024)**. This interplay suggests that modulating the S1R/Nrf2 axis could effectively mitigate the chronic inflammation associated with DN.

5.1.3. Fibrosis prevention

Renal fibrosis is a hallmark of DN, contributing to a progressive decline in kidney function. S1Rs play an integral role in modulating fibrotic pathways, primarily through their impact on TGF-β signaling, a key driver of fibrosis. Recent studies point out that the activation of S1Rs leads to Nrf2 activation, which can subsequently reduce renal fibrosis by inhibiting the TGF-β/Smad signaling pathway

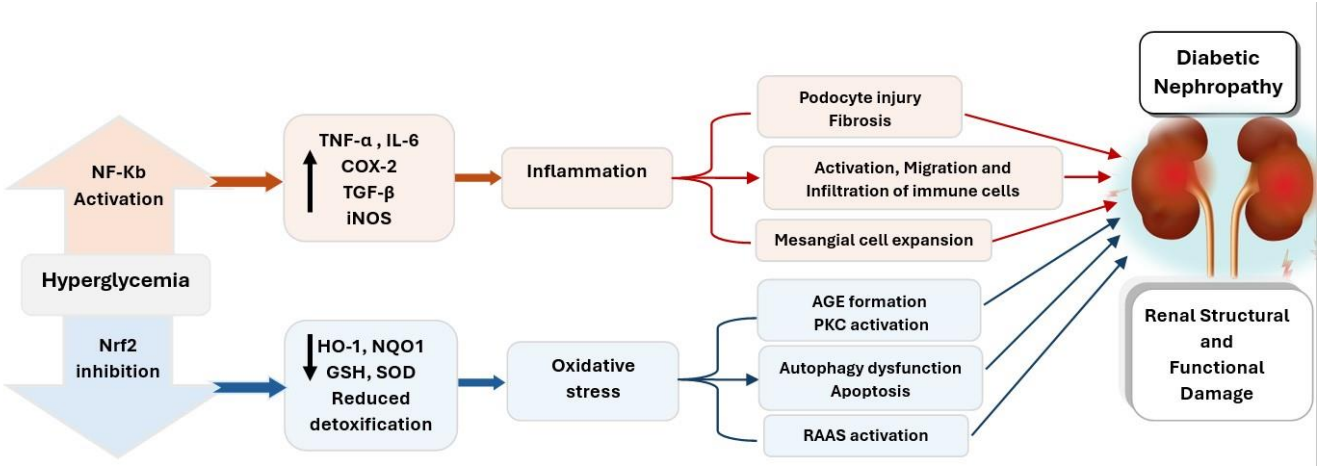

Figure 4: Role of NF-κB and Nrf2 in diabetic nephropathy. NF-κB, nuclear factor kappa B cells; Nrf2, nuclear factor erythroid 2 related factor-2: TNF, tumor necrosis factor; COX-2, Cyclooxygenase-2, iNOS, Inducible nitric oxide synthase; HO-1, haem-oxygenase-1; NQO1, NADPH quinone oxidoreductase; GSH, reduced glutathione; SOD, superoxide dismutase; AGE, advanced glycation end products; PKC, protein kinase C; RAAS, renin-angiotensin-aldosterone system.

(Gupta et al., 2021; Hao et al., 2022; Li et al., 2024). This inhibition may help maintain the kidneys' structure and function, potentially leading to a treatment plan that slows the progression of DN.

5.1.4. Regulation of nitric oxide (NO) signaling

One of the proposed mechanisms by which S1Rs exert their protective effects in DN is through the modulation of NO signaling. NO plays a crucial role in maintaining vascular health, and its dysregulation is a significant contributor to the pathogenesis of diabetic nephropathy. The activation of S1Rs has been shown to restore NO bioavailability, subsequently enhancing renal blood flow and mitigating ischemic injury **(Hosszu et al., 2017)**. This mechanism could emphasize the therapeutic potential of targeting S1Rs to mitigate vascular complications and maintain kidney function in patients with DN.

5.1.5. Inhibition of ER stress and apoptosis

S1R plays a crucial role in protecting renal cells from apoptosis, a key contributor to the loss of functional nephrons in DN **(Hosszu et al., 2017; Samsu, 2021; Jiang et al., 2022)**. S1R agonism has the potential to alleviate ER stress and diminish apoptosis in kidney cells, thus providing a protective effect against the advancement of CKD **(Hosszu et al., 2017; Munguia-Galaviz et al., 2023)**. Recent studies have demonstrated that the activation of S1R results in the upregulation of the anti-apoptotic protein Bcl-2 via the activation of Nrf2. This leads to lower Bax levels, diminished cytochrome c release from mitochondria, suppression of caspase activation, a notable decrease in etoposide-induced apoptotic cell death, and improved cell survival **(Dodson et al., 2019; Jazvinscak Jembrek et al., 2021)**. The potential to modulate these apoptotic pathways underscores the therapeutic implications of the S1R/Nrf2 antioxidant axis in preserving renal function and preventing progressive kidney damage in DN.

5.2. Preclinical evidence supporting the reno-protective impact of S1R activation

5.2.1. Improvement of renal function

Preclinical studies have demonstrated that the administration of S1R agonists in models of renal ischemia-reperfusion injury (IRI) leads to marked improvements in kidney function. The protective effects of S1R activation are evidenced by enhanced renal function, improved cell survival following ischemic events, and reduced kidney structural damage. These benefits are primarily mediated through the activation of protein kinase B (Akt)-dependent NO signaling within renal tissues **(Hosszu et al., 2017)**. Therefore, **Hosszu et al. (2017)** suggested that targeting S1Rs could be a promising therapeutic approach for protecting renal cells from injury.

5.2.2. Reduction of kidney injury and fibrosis

Studies indicate that using S1R agonists in preclinical models of nephrolithiasis enhances renal

function and reduces kidney injury and fibrosis. The observed effects are linked to the suppression of pro-inflammatory and pro-fibrotic signaling pathways alongside the promotion of cell survival mechanisms within the kidney **(Munguia-Galaviz et al., 2023)**.

6. Therapeutic implications and future perspectives

The standard treatment for DN involves strict control of blood glucose levels and managing blood pressure using RAAS inhibitors. While this approach can slow the disease's progression, it cannot stop or reverse kidney damage. As a result, there is an increasing interest in developing new therapeutic strategies targeting DN's underlying mechanisms, particularly oxidative stress and inflammation. These scientific advancements have paved the way for the development of new drugs in the field **(Rayego-Mateos et al., 2020; Wang et al., 2021)**. **Figure 5** provides a concise overview of the emerging therapeutic targets in DN and the associated renal mechanisms through which they may exert protective effects **(Barrera-Chimal and Jaisser, 2020)**.

6.1. Therapeutic potential of targeting the S1R/Nrf2 axis

Recent studies highlight the synergistic interplay between S1R and Nrf2 in optimizing antioxidant defenses and regulating key pathological processes, including inflammation, autophagy, apoptosis, and fibrosis **(Wu et al., 2021; Siddiqui and Bhatt, 2023)**. Extensive clinical trials have validated the efficacy of Nrf2 activators in slowing the progression of DN by reducing oxidative stress **(Chang et al., 2022; Wang and Zhang, 2024)**. Additionally, S1R activation appears to exert its nephroprotective effects partly through the regulation of the Nrf2 antioxidant pathway **(Zheng et al., 2011)**. In the context of diabetic nephropathy, targeting both S1R and Nrf2 in the kidney represents a promising therapeutic strategy, as this dual-target approach could enhance antioxidant defenses and effectively mitigate oxidative stress, a key driver of DN progression **(Hosszu et al., 2017; Chang et al., 2022; Wang and Zhang, 2024)**.

7. Conclusion and future perspectives

This review has highlighted critical findings on the role of the S1R/Nrf2 antioxidant axis in DN. The impairment of the S1R/Nrf2 axis is increasingly recognized as a crucial factor in the onset and progression of kidney disease. Several pathways through which S1R and Nrf2 exert their effects in DN have been explored, revealing that their interaction could offer synergistic protective benefits. These include enhancing antioxidant defenses, reducing inflammation, preventing apoptosis, and limiting fibrosis. This line of research could open new avenues for therapeutic strategies targeting both S1R and Nrf2 in DN treatment. However, these hypotheses need to be validated through experimental studies, including in vitro and in vivo models of chronic kidney diseases.

Conflict of interest

No conflicts of interest exist among any of the authors.

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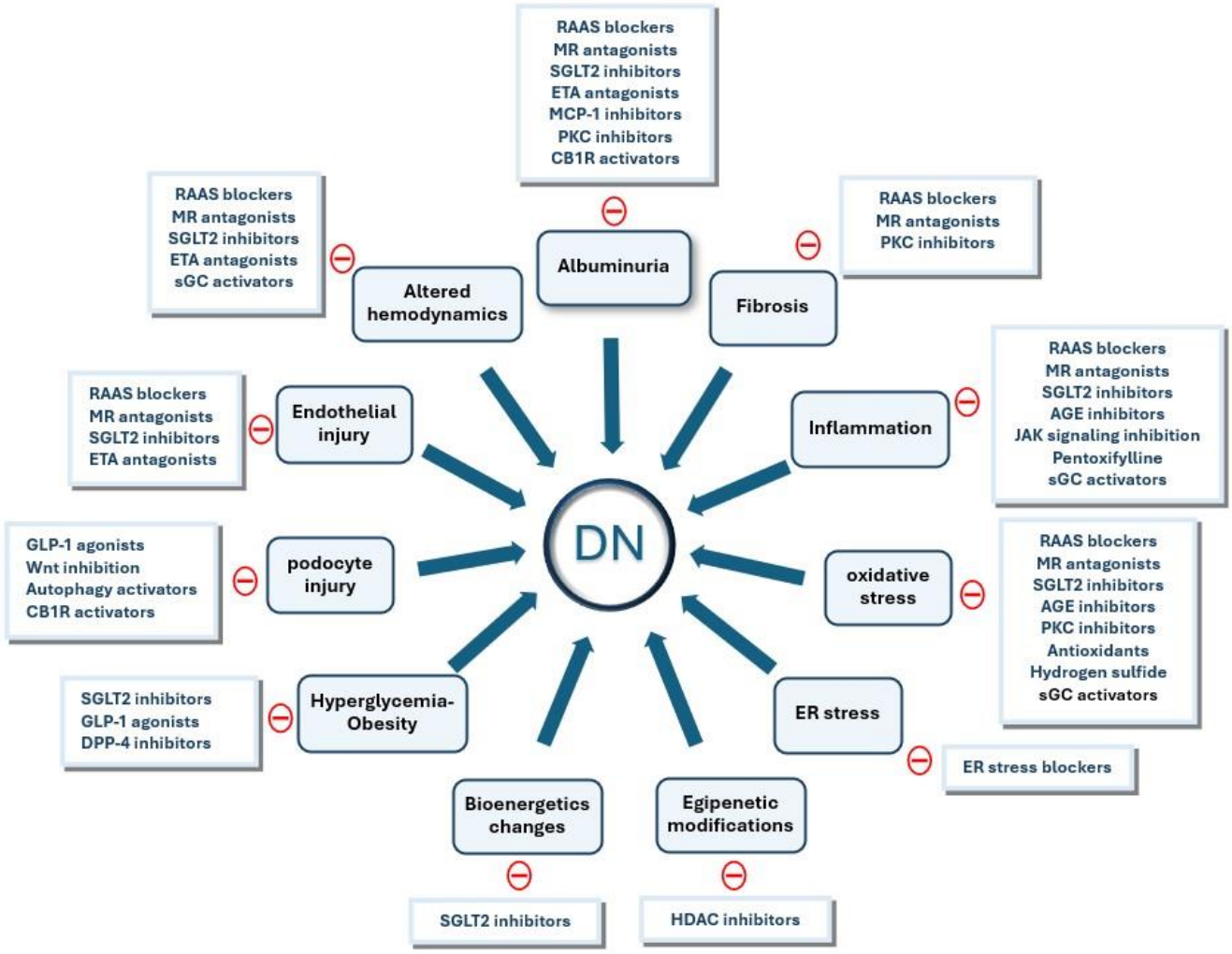

Figure 5: Novel therapeutic agents for DN classified by their target pathological pathways. AGEs, advanced glycation end products; CB1R, cannabinoid-1 receptor; DPP-4, dipeptidyl peptidase-4; ER, endoplasmic reticulum; ETA, endothelin receptor A; GLP-1, glucagon-like peptide-1; HDAC, histone deacetylases; JAK, Janus kinase; MCP-1, monocyte chemoattractant protein-1; MR, mineralocorticoid receptor; PKC, Protein kinase C; RAAS, renin angiotensin aldosterone system; sGC, soluble guanylate cyclase; SGLT2, sodium-glucose cotransporter 2.

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