

Pharmacological Modulation of the Nrf2–Keap1 Pathway in Diabetes: Mechanisms, Therapeutic Advances, and Future Directions

Amar Saxena¹, Shrestha Saxena², Yash Saxena³, Ashita Jain⁴, Rama Chaudhary⁵, Pooja Bharti⁶, Shivdeep Mishra⁷, Chandrabhan Singh⁸, Abhishek Kumar⁹, Ankit Kumar¹⁰ and Sanjeev Kumar¹¹

¹Department of Pharmacy, Institute of Pharmaceutical Research, GLA University, Mathura, Uttar Pradesh, INDIA

²Department of Arts, Lalit Kala Sansthan, Agra, Uttar Pradesh, INDIA

³Department of Pharmacy, Anand College of Pharmacy, Agra, Uttar Pradesh, INDIA

⁴Department of Pharmacy, Sharda School of Pharmacy, Agra, Uttar Pradesh, INDIA

⁵Faculty of Pharmacy, Agrawan Heritage University, Agra, Uttar Pradesh, INDIA

⁶Faculty of Pharmacy, Agrawan Heritage University, Agra, Uttar Pradesh, INDIA

⁷Department of Pharmacy, College of Pharmacy, Agra, Uttar Pradesh, INDIA

⁸Department of Pharmacy, ABESIT College of Pharmacy, Ghaziabad, Uttar Pradesh, INDIA

⁹Department of Pharmacy, College of Pharmacy, Agra, Uttar Pradesh, INDIA

¹⁰Faculty of Pharmacy, Agrawan Heritage University, Agra, Uttar Pradesh, INDIA

¹¹Faculty of Pharmacy, Agrawan Heritage University, Agra, Uttar Pradesh, INDIA

*Corresponding Author: amarsaxenapharmacy@gmail.com

ORCID

<https://orcid.org/0009-0006-3593-6927>



www.jrasb.com || Vol. 4 No. 5 (2025): October Issue

Received: 29-09-2025

Revised: 03-10-2025

Accepted: 15-10-2025

ABSTRACT

Diabetes mellitus remains a major global challenge driven by oxidative stress, inflammation, and metabolic imbalance. The nuclear factor erythroid 2–related factor 2 (Nrf2)–Kelch-like ECH-associated protein 1 (Keap1) pathway acts as a pivotal intracellular Défense axis against redox and inflammatory insults. This review comprehensively explores the pharmacological modulation of the Nrf2–Keap1 system in diabetic complications, including nephropathy, retinopathy, neuropathy, and cardiomyopathy. Natural compounds such as sulforaphane, curcumin, and resveratrol, alongside synthetic activators like bardoxolone methyl and dimethyl fumarate, demonstrate multi-organ protection through the restoration of antioxidant, mitochondrial, and anti-fibrotic functions. However, translation to clinical success remains constrained by poor bioavailability, tissue-selectivity issues, and safety concerns. Advanced drug-delivery platforms, such as redox-responsive nanocarriers and prodrug formulations, offer promising precision in targeting oxidative microenvironments. Future therapeutic paradigms should integrate controlled Nrf2 activation with metabolic modulators, including SGLT2 inhibitors and GLP-1 receptor agonists, to achieve synergistic efficacy without exceeding toxicity thresholds. Ultimately, the convergence of pharmacogenomic profiling, biomarker discovery, and nanotechnological innovation is expected to transform Nrf2-based interventions from experimental insights into clinically viable therapies for diabetes management.

Keywords- Nrf2–Keap1 pathway, Oxidative stress, Diabetes mellitus, Diabetic complications, Mitochondrial dysfunction, Antioxidant defense, Inflammation and redox signalling, Pharmacological modulation of Nrf2, Natural Nrf2 activators, Bardoxolone methyl, Metabolic regulation in diabetes, SGLT2 inhibitors and GLP-1 receptor agonists

I. INTRODUCTION

Diabetes mellitus is a common metabolic syndrome that is characterised by a persistent rise in the level of glucose in the blood and is assumed to be a result of dysfunctions in insulin synthesis, insulin responsiveness, or both[1]. There is an increasing rate of childhood diabetic disease worldwide which is accompanied by subsequent increasing rates of prevalence of associated minor comorbidities including nephropathy, neuropathy, and retinopathy[2]. Oxidative stress represents a key pathological feature in the acute development of these complications and owes its genesis to an imbalance between the formation of reactive oxygen species (ROS) and natural endogenous antioxidant defence mechanisms of a host[3]. The Nrf2 pathway functions as a critical cellular defence mechanism against oxidative damage through its control of antioxidant response elements. The protein Keap1 maintains Nrf2 at low levels through their interaction which leads to its degradation under normal conditions[4]. The oxidative stress conditions trigger Keap1 to experience particular structural and chemical changes which prevent it from marking Nrf2 for degradation. The stabilization of Nrf2 in the cytoplasm enables its nuclear translocation. The nuclear presence of Nrf2 enables it to bind to antioxidant response elements (AREs) in DNA which activates the transcription of multiple protective genes. The genes that Nrf2 regulates through ARE binding control antioxidant defences and detoxification systems and cellular repair functions. The adaptive response functions as a vital mechanism which defends cells against oxidative damage while it works to restore redox equilibrium and sustain cellular equilibrium[5]. The Nrf2–Keap1 pathway dysfunction in diabetes causes the body to lose its antioxidant defence which and worsening of diabetic complications including neuropathy and nephropathy and retinopathy. The pathway needs results in uncontrolled oxidative stress. The resulting cellular and tissue damage from this imbalance leads to the development proper regulation to stop diabetes-related cellular destruction and protect metabolic health[6]. The Nrf2–Keap1 pathway dysfunction in diabetes leads to impaired antioxidant defines which results in oxidative stress that causes cellular damage and creates diabetic complications including neuropathy and nephropathy and retinopathy. Medical researchers now focus on developing drugs that target this pathway because they aim to restore redox equilibrium and defend tissues while halting or stopping diabetes-related complications from advancing[7].

1.1 Epidemiology And Clinical Significance Of Diabetes

The chronic metabolic condition known as diabetes mellitus (DM) leads to long-term high blood sugar levels because of problems with insulin production and insulin function. The worldwide occurrence of diabetes has experienced a major increase throughout the past few decades. The number of adults aged 20–79 years

with diabetes reached 536.6 million in 2021 and scientists predict this number will increase to 783.2 million by 2045 which represents a 46% growth[8]. The majority of diabetes cases amount to 90% of all diabetes cases because of Type 2 diabetes mellitus (T2DM) which develops from poor diet and physical inactivity and obesity. Type 1 diabetes mellitus (T1DM) represents a less common condition which mainly affects children and teenagers through pancreatic β -cell destruction by autoimmune processes.

The medical effects of diabetes reach further than the simple elevation of blood glucose levels. The long-term presence of high blood sugar creates major risks for developing microvascular complications which include diabetic retinopathy and nephropathy and neuropathy. The 2021 global prevalence of diabetic retinopathy among diabetic patients reached 22.27% while projections show that 160.5 million people will develop the condition by 2045[9]. Furthermore, diabetes significantly increases the risks of macrovascular complications, such as coronary artery disease, cerebral strokes, and peripheral arterial disease, which leads to increased mortality and morbidity rates among diabetic patients.

The prevention of diabetes complications depends on early detection and proper diabetes management. The prevention of diabetes complications requires patients to make lifestyle changes and take medication while maintaining constant blood sugar level checks. The implementation of these measures leads to better patient results while decreasing the high expenses linked to diabetes-related medical care. The 2021 global health costs for diabetes management reached 966 billion USD and experts predict these expenses will increase to 1,054 billion USD by 2045[10].

1.2 Oxidative Stress as a Central Pathogenic Mechanism

The development and worsening of diabetes mellitus type 2 (T2D) heavily depends on oxidative stress. The imbalance between reactive oxygen species (ROS) production and the body's antioxidant defence mechanisms results in cellular damage and dysfunction. The combination of high blood sugar levels and dysfunctional mitochondria in diabetes causes elevated ROS production which intensifies oxidative stress. The oxidative stress burden causes damage to beta-cell function and insulin resistance which results in poor glucose control. The combination of blood vessel damage from oxidative stress and impaired endothelial function leads to the development of diabetic vascular complications including retinopathy and nephropathy and cardiovascular diseases[11]. Moreover, malfunctioning mitochondria due to oxidative stress contributes significantly during the pathogenesis of diabetic complications. Essentially, elevated glucose levels actually disrupt mitochondria, thereby affecting metabolism and energy synthesis, as well as augmentation of ROS generation. Mitochondrial dysfunction has a role

in the development of diabetic complications of the microvascular system through its facilitation of the effects of endothelial cell apoptosis and inflammation[12]. The combination of oxidative stress and mitochondrial dysfunction leads to beta-cell dysfunction in diabetes. The high levels of reactive oxygen species (ROS) decrease insulin release while triggering beta-cell death which results in the destruction of insulin-producing cells. The combination of oxidative stress with epigenetic changes leads to beta-cell identity and functional changes that disrupt glucose regulation and speed up diabetes progression which negatively affects metabolic control[13]. The connection between oxidative stress and inflammation plays a vital role in creating diabetic complications. The activation of inflammatory pathways through oxidative stress results in the production of pro-inflammatory cytokines which attract immune cells to

damaged areas. The persistent mild inflammation causes insulin resistance and leads to the formation of diabetic nephropathy and cardiovascular diseases[14]. Since oxidative stress sits at the core of diabetes pathology, there is hope for therapy toward oxidative damages. Antioxidant therapies act to restore the balance between ROS production and antioxidant defense so that it prevents the damage to cells. Nonetheless, all of the clinical-based evidence regarding the effectiveness of antioxidant supplementation in the management of diabetes is inconclusive. Lifestyle interventions, including changes in diet and exercise, reduce oxidative stress and improve insulin resistance. Moreover, metformin and GLP-1 receptor agonists exhibit antioxidant activity, further indicating their use in diabetes management[15].

Table 1. Recent Advance in the Epidemiology, Clinical Impact, and Oxidative Stress Pathogenesis of Type 2 Diabetes Mellitus: A Curated Evidence-Based Summary

Year	Study Title	Key Findings	DOI
2021	Global diabetes prevalence and projections	Demonstrated significant rise in global diabetes prevalence with projections exceeding 780 million cases by 2045, highlighting urgent need for preventive strategies.	[16]
2022	Oxidative stress in type 2 diabetes mellitus	Confirmed oxidative stress as a central mechanism driving β -cell dysfunction and vascular complications in T2DM; emphasized potential of antioxidant-based therapies.	[17]
2023	Epidemiology of diabetic complications	Reported that diabetic retinopathy affects ~22% of diabetic patients globally with rising prevalence; emphasized early screening and management.	[18]
2024	Antioxidant interventions in diabetes	Reviewed clinical trials on antioxidant supplementation, concluding benefits remain inconclusive, but lifestyle interventions remain highly effective.	[19]
2025	Oxidative stress and diabetic cardiovascular disease	Highlighted the mechanistic link between oxidative stress and cardiovascular complications in T2DM, reinforcing oxidative stress as a therapeutic target.	[20]

II. RELEVANCE OF NRF2–KEAP1 PATHWAY IN REDOX HOMEOSTASIS

Nrf2/Keap1/ARE is one of the major antioxidant defence mechanisms, and its impairment in hyperglycaemic conditions significantly increases the degree of dysfunction in the pancreatic β -cells, endothelia, and progression of diabetic-related complications[21]. The hyperglycaemia state chronic attenuates the nuclear translocation of Nrf2 due to sustained sequestration by Keap1 as a result of progressively increasing tissue injuries that reduces the activity of antioxidant genes transcription and leads to the large concentration of reactive oxygen species hence impairs tissue regeneration in diabetic wounds[22]. In the context of diabetes, oxidative stress interferes with Keap1's redox-sensing function, which in turn disrupts Nrf2 signalling. However, studies have demonstrated that forcing Nrf2 activation, such as through Keap1 repression, can help bring back redox balance and

improve the resilience of cells[23]. A number of small, molecule Nrf2 activators (e.g., sulforaphane, curcumin, resveratrol) have been explored in preclinical as well as early, stage clinical studies for their potential to reduce oxidative damage and postpone the development of diabetic complications via elevated expression of Nrf2 target genes[24]. The Nrf2, Keap1 system is directly involved in the regulation of enzymes for detoxification, antioxidants of phase II, and genes that ensure the balance of redox (for instance, HO, 1, NQO1, GCLC). Hence, the prolonged disturbance of its function in a situation of chronic oxidative stress turns out to be the main mechanism cause of nephropathy, retinopathy, and the impairment of the cardiovascular system in diabetes[21]. Treatment procedures which focus on the suppression of Keap1 (whether genetic or pharmacologic) for the purpose of increasing Nrf2 activity, appear to be beneficial not only in the revival of antioxidant gene expression, but also in the alleviation of insulin resistance, the decrease of liver gluconeogenesis and the improvement of metabolic disorder in mice with Type 2 diabetes, have been demonstrated by these therapeutic

approaches[21]. The ongoing research brings to light that the recall of metabolic changes in endothelial cells of diabetics may be changed to the opposite through the intervention of Nrf2 signalling, hence reopening the affected epigenetic sites and restoring antioxidant defences despite the glucose levels having been normalized for some time[25].

III. MOLECULAR BIOLOGY OF THE NRF2-KEAP1 SIGNALLING PATHWAY

Keap1 keeps Nrf2 in the cytosol under normal basal physiological conditions and through the E3 ligase complex which is ubiquitin ligase based on Cullin, 3, it promotes Nrf2 ubiquitination, thereby leading to a rapid proteasomal degradation; however, oxidative stress or an electrophilic modification of the essential cysteine residues in Keap1 (such as Cys151, Cys273, Cys288) changing the binding state of Nrf2 allowing Nrf2 stabilization, translocation to the nucleus, and ARE, mediated transcription of antioxidant and cytoprotective genes[26]. Removal of genes or a reduction in Keap1 levels in β cells result in a significant activation of Nrf2, which subsequently elevates β -cell division and volume, positively affects glucose tolerance in both standard and high-fat dietary conditions, and inhibits the occurrence of oxidative injury caused by hyperglycaemia[27]. Epigenetic factors are responsible for many changes in mutual relationships.

These include: suppression of the Nfe2l2 gene by methylation of DNA in the promoter region, changing of the chromatin structure by histone deacetylase (HDAC) and influence of certain microRNA (e.g., miR-200a, miR-24-3p) on the regulation of Nrf2 expression in the tissues of diabetes patients, which causes the redox imbalance to be extended, and as a result, vascular and cardiac complications have been observed[28]. Either by using a drug like CDDO-Im (an oleanolic acid derivative) or by gene therapy (reduction of Keap1 expression), the deliberately induced Nrf2 signalling has been found to have mitigating effects on insulin resistance in mouse models of diabetes. Besides, the two treatments were also observed to lower hepatic gluconeogenesis and systemic inflammation in these animals[29]. Diabetic skin and wound healing models show that targeted inhibition of Keap1 with siRNA leads to the recovery of Nrf2-driven gene transcription activity, which in turn regulates the redox balance, gives the growth of new vessels and speeds up tissue renewal[25]. The molecular biology of the Nrf2-Keap1 pathway in diabetic retinopathy involves changes in the expression of Keap1 that are abnormal, a relocation of a part of Nrf2 to the cell nucleus which is hindered and a decrease of antioxidant enzymes that depend on ARE to be activated by Nrf2, all of these changes being the main factors of oxidative stress, inflammation and retinal vascular leakage aggravation[30].

IV. STRUCTURAL AND FUNCTIONAL CHARACTERISTICS OF NRF2 AND KEAP1

"Dysregulation of the Nrf2/Keap1 redox pathway in diabetes affects the multipotency of stromal cells" (Rabbani et al., 2019) indicates that the bone marrow stromal cells from diabetic mice (dBMSCs) carry high levels of ROS and have changed metabolism; even though Nrf2 is normally active, it is reported that chronic oxidative stress leads to its irregular repression by Keap1 and the loss of multipotency. The forced Keap1 knockdown not only turns on Nrf2 nuclear localization thereby giving back redox homeostasis but also Sox2 expression is rescued thus wound healing ability in diabetic mice is reactivated[23]. Many studies demonstrate that Nrf2 pathway activation has a protective effect against renal damage, in different models of diabetic nephropathy: as a case, sinapic acid (SA) administration to streptozotocin (STZ)-induced diabetic rats strongly elevates Nrf2, HO-1, I κ B α , Bcl-2 expression and decreases NF- κ B, which is followed by a reduction in inflammation, apoptosis, lipid peroxidation and an increase in renal function markers[31]. In the setting of diabetic nephropathy stem cell exosomes isolated from adipose tissue (ADSCs-Exos) change the Nrf2/Keap1 signalling pathway. In podocytes and renal tissue, high glucose levels were found to elevate Keap1 expression and decrease Nrf2 nuclear localization. Moreover, injection of ADSCs-Exos not only changed these indicators to the opposite but also decreased ROS/MDA levels, while the protective effect was partly lost when HO-1 was knocked out[32]. Nrf2 is a modular transcription factor with seven conserved Neh domains (Neh1Neh7); the Neh2 domain is equipped with both a high-affinity ETGE and a low-affinity DLG motif that interact with Keap1 and hence determine Keap1-Cul3-dependent ubiquitination under basal conditions. The Neh1 domain gives a CNC-bZIP DNA-binding motif that interacts with small Maf proteins which leads to the recognition of AREs (antioxidant response elements), whereas Neh3Neh5 serve as transactivation modules facilitating the binding of co-activators such as CBP/p300[33]. Keap1 is a multi-domain sensor protein (BTB, IVR and Kelch/DGR domains) that morphs structurally as a homodimer via the BTB domain, associates with Cul3 for E3 ligase recruitment, and functionally employs several reactive cysteines (most prominently Cys151, Cys273, Cys288) in the IVR as electrophile/redox sensors, thus modulating Nrf2 degradation[34]. Upon exposure to oxidative or electrophilic stress, the covalent modification of Keap1 cysteines results in a conformational change that breaks the interaction between Keap1 and Nrf2 (DLG/ETGE binding), thus a Nrf2 stabilization is achieved, allowing its nuclear translocation and transcription of the ARE

genes[33]. Keap1 employs a 'hinge-and-latch' two-site binding method: ETGE acts as the high-affinity hinge and DLG as a lower-affinity latch breaking this bi-partite interaction is the cellular switch for quick Nrf2 activation[35]. Diabetes leads to chronic high blood sugar and continuous reactive oxygen species (ROS) production that interfere with Keap1 sensing and Nrf2 post-translational regulation (for example, modification by GSK-3 and other kinases), thereby resulting in insufficient nuclear translocation of catalytically active Nrf2 even with ongoing oxidative stress[21]. The Neh6 domain grants a degradation pathway that is not dependent on Keap1 by way of -TrCP binding areas (DSGIS/DSAPGS); the latter degradative mechanism is of particular importance when the usual Keap1 control is impaired in pathological conditions like diabetes[36]. Disease-linked changes to the Keap1-Nrf2 complex in diabetic tissue often result from epigenetic changes (such as promoter methylation and histone modifications) and microRNA-mediated regulation that both control the transcriptional response of Nrf2 and evoke the metabolic memory of oxidative injury[28]. Detailed images of Kelch domain attached to ETGE/DLG peptides have been the basis for designing small-molecule PPI (protein protein interaction) inhibitors and non-covalent modulators by backtracking the synthetic path. Such molecules are capable of either halting the Keap1 binding or imitating the changes in structure caused by stress to treat Nrf2 therapeutically[35]. When considering Nrf2 and Keap1 (Neh motifs, PTM sites, cysteine sensors, BTBKelch architecture) in combination, their individual structural features combine to generate a redox sensor effector system that can be adjusted very precisely. As a result, their derangement in diabetes is at the basis of decreased antioxidant Défense and enhanced vulnerability to micro- and macrovascular complications[21].

V. REGULATORY MECHANISMS AND PATHWAY ACTIVATION

Keap1 detects electrophiles and oxidants through reactive cysteines (especially Cys151, Cys273, and Cys288); a covalent modification to these residues generates a conformational change that inhibits Keap1-dependent ubiquitination of Nrf2 by Cullin-3, thus allowing Nrf2 stabilization and transcriptional activation of ARE to occur quickly[33]. Keap1Nrf2 binding is a "hinge-and-latch" two-site type of interaction where the high-affinity ETGE motif has the role of a hinge and the lower-affinity DLG motif acts as a latch; the removal of the latch being the molecular point at which an acute Nrf2 activation is triggered[35]. A model of diabetes is such that long-term high blood glucose and continuous overload with reactive oxygen species (ROS) may result to a paradox where the accumulation of Nrf2 in the nucleus is decreased due to the combined effects of changed Keap1 structure, increased degradation

dependent on GSK-3 and reduced nuclear import a failure at multiple levels that aggravates oxidative damage to - cells and blood vessels[37]. p62/SQSTM1, an autophagy adaptor protein, offers a feeder circuit to the Nrf2 hub by binding Keap1 (through an STGE motif) in a way that is competitive, encouraging both Keap1 sequestration and autophagic degradation, thus allowing prolonged Nrf2 activation in some stress situations[21]. Such modifications as phosphorylation (PKC, MAPKs), acetylation, and ubiquitination that are post-translational in nature not only adjust the Nrf2 function, its localization, and stability, but also if their changes are detected in diabetic tissues, they result in insufficient antioxidant induction in the situation when oxidative stress continues[33]. "MicroRNAs (such as miR-200a, miR-153, and miR-144) and lncRNAs change the Keap1-Nrf2 system in diabetes operable by silencing Nrf2 expression or enzymatic degradation of Keap1 mRNA resulting in changes in the tissues specificity for redox responsiveness impacting the number of affected tissues like diabetic cardiomyopathy and nephropathy[28]. One of the ways in which diabetes induces oxidative stress is through epigenetic repression of Nfe2l2 (the Nrf2 gene) which hampers the restoration of cellular antioxidant capacity after normalization of blood sugar levels. The principal mechanisms causing epigenetic suppression of the Nrf2 gene, which consequently lead to a delay in the re-establishment of antioxidant capacity, are promoter methylation, repressive histone marks, and changed chromatin occupancy[28]. There are two main ways to activate the therapeutic Nrf2: one is through electrophilic covalent modifiers that break the most important Keap1 cysteine bonds, and the other is through non-electrophilic small molecules or peptides that prevent the Keap1Nrf2 protein protein interaction. Each group of substances also differs in terms of specificity, reversibility, and the risk/benefit profiles of translational research[38]. "The reason is that chronic, systemic Nrf2 hyperactivation over a long period can lead to negative effects depending on the situation (such as changed metabolism, pro-survival signalling in cancer cells), so that the treatment of diabetes focuses on the regulated, organ-specific or on/off activation to bring the original redox balance, not to cause a response of the body harmful to it[37]. There are interactions between metabolic sensors (AMPK, PI3K/Akt), inflammatory kinases (IKK, JNK) and the Keap1-Nrf2 module, which allow the immune system to recognize the nutrient status and insulin signalling as well as to merge these pathways that activation both indicates and affects the pathophysiology of diabetes[21]. Recent mechanistic studies have uncovered that GSK-3 overactivity is a common mechanism associated with diabetes, which leads to Keap1-independent Nrf2 degradation and continuous antioxidant failure. This indicates that to achieve a complete recovery of Nrf2 function in diabetic tissues, co-targeting GSK-3 (or - TrCP) together with Keap modulation might be required[39].

VI. DOWNSTREAM GENE TARGETS AND ANTIOXIDANT DEFENCE

Nuclear factor erythroid 2-related factor 2 (Nrf2) coordinates the expression of a multitude of genes that provide resistance to the cell, among which are the ones coding for heme oxygenase-1 (HO-1), NAD(P)H quinone dehydrogenase 1 (NQO1), and glutamate-cysteine ligase (GCL), thus alleviating oxidative stress and maintaining cellular equilibrium in tissues affected by diabetes[33]. When oxidative stress is a diabetic nephropathy trigger, Nrf2 activation leads to elevated expression of antioxidant enzymes such as superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPx) that together eliminate the oxidative damage and inflammation that are the main cause of renal dysfunction, thus improving renal function[40]. In diabetes animal models it was demonstrated that the medicinal activation of Nrf2 results to an increase in the synthesis of phase II detoxifying enzymes such as NQO1 and GCLM, which in turn by restoration of redox balance, are able to relieve the different organs from oxidative stress[21]. "One of the mechanisms by which diabetic complications are alleviated is the increased expression of Nrf2-dependent genes like HO-1 and NQO1, that provide the cell with antioxidant and anti-inflammatory protection[33]. The activation of Nrf2 as a result of exercise eventually causes a rise in the levels of antioxidant enzymes such as SOD and GPx, which means that the body's protective system against oxidative stress has been strengthened and metabolic conditions have improved in type 2 diabetes[33].

6.1. Pathophysiological Role of the Nrf2–Keap1 Pathway in Diabetes

Nrf2–Keap1 is an important signalling system, which is a fundamental redox-regulating pathway that keeps parameters of oxidative balance and ensures the cellular defense mechanisms. Disruptions of its regulation lead to a crucial role in the etiology of diabetes mellitus and the associated complications. In normal physiological conditions, Kelch-like ECH-associated protein 1 (Keap1) ligates the nuclear factor erythroid 2–related factor 2 (Nrf2) in the cytoplasm, which makes the Nrf2 undergo ubiquitination and subsequent proteasomal degradation. But during the oxidative stress—e.g. chronic hyperglycaemia-induced—reactive oxygen species (ROS) alter the cysteine sites of Keap1, thus liberating Nrf2 that moves to the nucleus and attaches to the antioxidant response elements (AREs). This action results in the transcription of many cytoprotective genes i.e., heme oxygenase-1 (HO-1), NAD(P)H quinone oxidoreductase 1 (NQO1), glutamate-cysteine ligase catalytic subunit (GCLC), superoxide dismutase (SOD), and glutathione peroxidase (GPx), which by themselves are a great combination of the antioxidant defense system and simultaneously help in the reduction of oxidative overload[33]. Research on diabetic macrovascular tissues has also shown that the Nrf2 response is initially activated

after acute hyperglycaemia as a compensatory reaction, however, a sustained oxidative insult results in a reduction or lack of this compensatory response, hence endothelial damage and atherogenesis progression (Protective role of NRF2 in macrovascular complications of diabetes[41]. Moreover, in stromal cells originating from the bone marrow of diabetic experimental models, elevated levels of Keap1 and inhibited nuclear Nrf2 were reported, which linked with lowered expression of NQO1 and MnSOD as well as diminished regenerative potential (Nrf2/Keap1 pathway dysregulation in diabetes impairs stemness, Diabetes[23]. Epigenetic changes and microRNAs that keep Nrf2 suppressed have recently been implicated by new evidence: for example, in organs affected by diabetes, Nfe2l2 promoter methylation and overexpression of miRNAs that focus Nrf2 have been recognised as causes of prolonged oxidative injury even after glycaemic control has been ameliorated (Exploring links between polyphenols, Nrf2 and diabetes[42].

6.2. Mechanisms of Oxidative Stress in Diabetes

Diabetes mellitus, and more specifically, the non-insulin-dependent diabetes Type 2, chronic high blood sugar and abnormal blood lipid levels lead the body to generate excessive amounts of reactive oxygen species (ROS) over several overlapping pathways, at the same time that antioxidant defences are weakened, thus producing a sort of vicious circle that results in oxidative stress forming the background to both insulin resistance and β -cell malfunction. To be more detailed the energy from the breakdown of high glucose, that is transported through the mitochondria greatly exceeds the capacity of the mitochondria leading the electron transport chain to overproduce superoxide. Thus the scientists have found that expression of NADPH oxidases (NOX) especially in blood vessels and the fat tissue have the most significant role in activation of the ROS originating from the cytosol[43]. Multiple metabolic pathways, which are parallel to each other, for example, the polyol pathway, hexosamine branch, protein kinase C (PKC) activation, and advanced glycation end products (AGEs) accumulation, not only increase intracellular ROS and reactive carbonyl stress but also trigger a cascade of events that eventually lead to the impairment of lipids, proteins, and DNA[43]. Normally, the levels of catalase, glutathione peroxidase, and superoxide dismutase are very low in the pancreatic β -cells. In these cells, mitochondrial dysfunction and increased intracellular calcium cause oxidative damage that also inhibits insulin gene expression (through transcription factors such as Pdx1 and MafA) and finally, the cells undergo apoptosis[43]. In tissues that are sensitive to insulin on the periphery, reactive oxygen species (ROS) disrupt insulin receptor substrate (IRS) signalling, bring on the activity of stress kinases like JNK and p38 MAPK, and cause the serine phosphorylation of IRS-1, thus changing the downstream Akt activation and GLUT4 translocation to be impaired. Moreover, the main factors giving rise to these changes may be the endoplasmic reticulum (ER)

stress, an increase in free fatty acid oxidation and mitochondrial-derived reactive oxygen species (ROS) in obesity situation, which, together, have a higher potential for triggering inflammation and causing oxidative injuries[43]. Besides that, high blood sugar also causes "metabolic memory" due to epigenetic changes and ongoing oxidative damage, that is, long after glycaemic control has been restored, resulting in the sustained occurrence of NF- κ B signalling and proinflammatory cytokine generation[44]. When combined, these cross-talk pathways have a major effect on the development of vascular complications, neuropathy, nephropathy, and other diabetic comorbidities. The implication that such a mechanistic basis of disease involving oxidative stress and its upstream regulators be therapeutically targeted is clearly underscored by these findings[44]. Diabetes mellitus is a condition in which, due to hyperglycaemia, a number of molecular pathways intertwine, resulting in the increased production of reactive oxygen species (ROS) and oxidative stress, which not only overwhelm the antioxidant Défense systems but also contribute to the dysfunction of β -cells and to insulin resistance to a great extent. In short, the process of mitochondrial oxidative phosphorylation is malfunctioning under high glucose load, hence more electrons are escaping at complexes I and III, and consequently more superoxide is formed; at the same time NADPH oxidase (NOX) enzymes are activated in the ailing vascular endothelial and renal cells, thus ROS production is further sustained[43]. The polyol (aldose reductase/sorbitol dehydrogenase) pathway utilizes NADPH, which limits the amount of NADPH available for the regeneration of reduced glutathione (GSH), at the same time elevated generation of advanced glycation end products (AGEs) and the protein kinase C (PKC) pathway activation exacerbate oxidative injury of lipids, proteins, and DNA[43]. The prolonged high blood sugar levels (hyperglycaemia) and abnormal blood lipid levels (dyslipidaemia) in diabetes have multiple overlapping molecular mechanisms which in turn create a pro-oxidant state that goes beyond the body's antioxidant systems that are made to restore the redox balance, hence the continuous redox imbalance. One of the major contributors to the production of reactive oxygen species (ROS) is the failure of mitochondria, where the electron transport chain is so overloaded with electron donors that the electrons escape and at the same time in both complexes I and III reach with oxygen and therefore produce superoxide. Simultaneously, the enzymes NADPH oxidase (NOX), particularly NOX4 in kidney and blood vessel tissues, become more activated due to the presence of oxygen and thus contribute to the increased ROS load in the cytosol[42].

6.3. Dysregulation of Nrf2-Keap1 Signalling in Diabetic Complications

Stromal cells, that are derived from bone marrow of diabetics, show a very strong upregulation of Keap1 which is in the cytoplasm while Nrf2 in the nucleus is drastically lowered resulting in a decrease the expression

of Nrf2 target genes such as NQO1 and MnSOD and reduction of multipotency, hence proving that the malfunction of Nrf2-Keap1 interaction has a direct effect on the ability of tissue regeneration in diabetes[23]. In the tissues that have suffered the most from diabetic complications, sustained elevated glucose not only increases reactive oxygen species (ROS) production but also diminishes Nrf2 nuclear translocation and transcriptional activity, thus lowering the expression of typical ARE-driven genes and disrupting the loop that usually re-establishes the redox equilibrium[45]. The decrease in Nrf2 sensitivity is by far not a mere change of appearance - it leads in a major way to the deterioration of different body structures (kidney, heart, retina, nerve and vasculature) due to the increased oxidative damage, inflammation and profibrotic signalling that extend four major processes: one quite obvious – oxidative stress, and three less known but intricately interwoven with it – inflammation, profibrotic signalling, and the conversion of early, reversible stress into irreversible tissue remodelling[46]. From a mechanistic point of view, diabetes changes the factors that control Nrf2 from the top (post-translational modifications, Keap1 oxidation, and non-canonical regulators, such as microRNAs and epigenetic marks), hence the pathway function is influenced by both metabolic signals and complex regulatory circuits without the presence of one sole on/off switch[47]. Pharmacologic and natural Nrf2 activators (from bardoxolone to sulforaphane and polyphenols) put on a consistent performance regarding organ- protective effects in various preclinical models of diabetes. However, human translation has revealed safety concerns linked with timing and dosage as illustrated by the clinical outcomes of bardoxolone- a case of both positive and negative effects that has led to the recognition of the need for careful modulation (rather than complete permanent activation) as a prerequisite for safety[48]. Multi-modal tactics that utilize targeted Nrf2 activation along with inflammation management, glycaemic stabilization, and organ-specific delivery (nanoparticles, tissue scaffolds) are important in that they are currently coming up as the most effective means of bringing back redox homeostasis while avoiding off-target effects[6]. Re-engaging the Nrf2-Keap1 system in diabetes can have a ripple effect on cellular health as it is the intersection of mitochondrial health, detoxification enzymes (HO-1, NQO1, GCL), and immune signalling. Through such an action, mitochondrial ROS can be reduced, the amplification of the AGE-RAGE cycle can be limited, and the cytokine cascades driven by NF- κ B can be blunted. However, the condition for this to happen is that the physiological dynamics must be restored, and not that the activation of the system be forced[49]. When we look at all the evidence, the model which explains that diabetes gradually worsens Nrf2-mediated Défense is supported by all kinds of changes in metabolism, epigenetics and proteostasis; this pathway is still a valuable target to delay or even reverse the diabetic complications, if the

interventions are appropriate in terms of context, organ and safety[30].

6.4. Impact on Vascular, Renal, Neural, And Retinal Health

Continual hyperglycaemia in diabetes is the main cause of endothelial oxidative stress, mitochondrial dysfunction as well as impaired nitric-oxide signalling which, when combined, cause endothelial senescence, lowered reparative endothelial-progenitor cell function and a pro-atherogenic change in the vessel wall - these changes are very close to the malfunction of the Nrf2-Keap1 antioxidant sentinel and thus led to the progression of macrovascular disease[50]. In detail, Nrf2 deficiency in blood vessels cells has the effect of reducing gene transcription of antioxidant genes driven by ARE (for example HO-1, NQO1, and GCL), which allows the constant presence of ROS to raise the endothelial permeability, stimulate the expression of adhesion molecules that amplify vascular inflammation - these alterations which represent a molecular bridge between the metabolic stress and clinically visible atherosclerosis and vasoreactivity impairment in diabetes[51]. In the kidney, prolonged high blood sugar levels and local hemodynamic stress lead to oxidative injury of the glomerular and tubular structures that exceed the antioxidant responses; if Nrf2 signalling is impaired the glomerular filtration barrier (endothelium, GBM, and podocytes) is exposed to oxidative stress and fibrosis by AGE-RAGE and TGF- β that slowly cause unregulated albuminuria and decrease in GFR typical of diabetic kidney disease[45]. Studies before clinical trials and at a mechanistic level provide evidence that the recovery of Nrf2 function in the kidneys of diabetics promotes the induction of enzymes with cell protective functions, lowers the level of inflammatory cytokines and decreases the accumulation of extracellular matrix. However, the transformation of clinical practice has been difficult due to safety and timing problems specific to the agents used, thus highlighting that the key to a renal advantage is the return of normal Nrf2 dynamics (rather than an unregulated activation)[52]. While these events are taking place in the dorsal root ganglion, excess blood sugar in the peripheral nerves is causing the generation of mitochondrial reactive oxygen species (ROS), overactivation of poly-ADP ribose polymerase (PARP), and local microvascular insufficiency in the vasa nervorum that feed the nerves. When Nrf2 is downregulated, oxidative and inflammatory cascades that injure axons and Schwann cells - the pathophysiological substrate of sensory loss and painful neuropathy - continue to proliferate. (Kumar A & Mittal R., *Inflammopharmacol.*)[53]. Both animal and cellular models regularly provide evidence for the Nrf2 pathway (either by genetic or pharmacologic intervention) to maintain the mitochondrial integrity, lessen the neuroinflammation and recover conduction velocity as well as nociceptive thresholds; hence, such a finding strongly indicates that the pathway is a causally important

one, and also, therapeutically accessible for diabetic neuropathy[54]. When oxidative stress and microvascular leakage caused by hyperglycaemia in the retina are aggravated to the point that Nrf2 nuclear activity is compromised: the diminished antioxidant gene expression results in glutathione depletion, raises the production of cytokines (such as TNF- α) and provides a local microvasculature environment dominated by capillary dropout, pericyte loss and abnormal neovascular signalling which are the changes leading diabetic retinopathy[42]. When we look at the evidence from blood vessels, kidneys, nerves, and retina, all of it is in line with a single model where diabetes-related disturbances (metabolic, epigenetic and proteostatic) gradually reduce Nrf2-driven cell protection, thus changing oxidative insults from being transient to becoming persistent inflammation, fibrosis, and irreversible organ dysfunction - a model that not only clarifies the multisystem diabetic complications but also suggests selective, time-dependent Nrf2 activation as a potent therapeutic approach. (Exhaustive reviews and translational discussions)[55].

VII. PHARMACOLOGICAL MODULATION STRATEGIES

Targeting the Nrf2-Keap1 signalling pathway through the use of drugs is a potential method to treat the diabetes-related complications by activating the body's own antioxidant, anti-inflammatory, and anti-fibrotic systems. In several experimental settings, various small molecules and natural substances have been tested: for instance, administration of sulforaphane (SFN) and cinnamic aldehyde in streptozotocin-induced diabetic nephropathy not only improved metabolic parameters but also lowered ROS injury and repressed the release of TGF- β 1, fibronectin, collagen IV, and P21 in Nrf2 wild-type mice, whereas no effect was detected in Nrf2 knockout mice[37]. Digitoflavone in the same way mitigated glomerular inflammation in diabetic nephropathy through Nrf2-dependent inhibition of MCP-1, ICAM-1/VCAM-1 and downregulation of ECM proteins, thus alleviating renal inflammation and fibrosis[56]. Naturally-occurring polyphenols give extra benefit from combinations: An experiment with diabetic mice demonstrated that the expression of Nrf2 target genes HO-1, NQO1, and GPx-1 was elevated by salvianolic acid A (SAA) not only as a single agent but also in a co-administration with metformin. Besides that macrovascular relaxation, and endothelial function were also better, indicating the existence of a link between metabolic (glucose-lowering) and Nrf2-based interventions[57]. Bardoxolone methyl (CDDO-Me), a synthetic triterpenoid, has been extensively preclinical / translational the most broadly tested through experiments in diabetic kidney disease. In a phase 2 study, patients with type 2 diabetes and chronic kidney disease who received bardoxolone methyl doses (25-150 mg) showed

significant positive changes in estimated GFR between weeks 24 and 52 compared when given placebo. Nevertheless, these improvements in kidney function were also associated with adverse events such as fluid retention or cardiac risk observed at the advanced stages[58]. The BEACON study, which was the phase 3 trial of bardoxolone in patients with stage 4 CKD and type 2 diabetes, was stopped prematurely. The decision was based on the observation of increased incidence of heart failure and other cardiovascular events in the bardoxolone group even though there were certain improvements in GFR[59]. While sulforaphane has demonstrated considerable success in human trials as well as synthetic activators: one trial involving T2DM patients revealed that the compound suppressed liver gluconeogenesis and elevated glycaemic control through the activation of Nrf2 pathway[60].

7.1. Synthetic Modulators of Nrf2 (E.G., Bardoxolone Methyl, Dimethyl Fumarate)

Many researchers have focused on the use of synthetic activators of the Nrf2–Keap1 pathway in diabetic conditions. Bardoxolone methyl (BM), a synthetic triterpenoid, and dimethyl fumarate (DMF) as well as related fumarates, are some of the main agents that have been tried with varying results in preclinical and clinical studies. The drug Bardoxolone methyl showed evidence of renal function recovery in a type 2 diabetic chronic kidney disease (CKD) scenario, thereby causing a rise in eGFR in the BEAM trial. Here, patients who were given BM treatment exhibited a dose- and time-dependent increase in eGFR in comparison with baseline, along with decreases in serum creatinine and blood urea nitrogen[61]. Nevertheless, the later BEACON study in advanced CKD has been cut short because of safety issues such as increased cardiovascular risk and fluid overload, showing that the treatment window of BM is limited and dependent on the stage or situation[61]. Mechanistically, BM modulates the Keap1-Nrf2 binding, stabilizes Nrf2, promotes its nuclear translocation, increases the expression of ARE genes (HO-1, NQO1, GCL etc.), mitigates oxidative stress markers, and inhibits the occurrence of ferroptosis in RTECs, thus opening up a pathway for its pharmacological and translational effects to be confirmed at the molecular level[62]. Besides that, BM substantially enhanced several functional outcomes in neural tissues of diabetic neuropathy animal (STZ rats) models, thus it basically restored the abnormalities of electrophysiology, nerve Fiber density, mitochondria dysfunction, ROS production and hyperalgesia induced by high glucose, which suggested that the reactivation of Nrf2 signalling pathway was the core mechanism of these neuroprotective effects[63]. Along with the synthetic drugs/fumarates related to dimethyl fumarate (DMF), the latter a compound of Nrf2 with known applications in diabetes or diabetes-derived pathologies could likewise be considered as potential synthetic modulation tools. In several studies on rodent models of STZ diabetes, the administration of DMF has been demonstrated to

normalize the vascular redox state; Abstract:(Bullet Point Form) DMF reduced serum triglycerides and AGEs, lowered ROS and MDA in aorta, improved antioxidant enzyme activities (GSH, SOD), and restored Nrf2 expression in the aortic tissue while suppressing TXNIP, NLRP3 and NF- κ B signalling, thus ameliorating diabetic vascular complications[64]. Just recently, one more research was carried out where diroximel fumarate (a fumarate prodrug) substantially lessened MGO-induced sensitization of the nerves in diabetic mice, diminished ISR activation in dorsal root ganglia and the effect was Nrf2-dependent (knockout prevented the protection), thus showing that agents from DMF class can accomplish their work through Nrf2 in brain pain/neuropathy scenarios[65]. Moreover, for instance, in a diabetic non-alcoholic fatty liver disease (NAFLD) model, the conjunction of DMF and glibenclamide has such an effect that after the DMF-induced activation of the Nrf2/ARE pathway, inflammation is mitigated, liver histology is ameliorated, oxidative damage is decreased, and overall, the data suggest that fumarates may modulate the Nrf2 pathway not only in the kidneys and nerves but also in different organs such as the liver in diabetes[66].

7.2. Natural Bioactive Compounds (E.G., Sulforaphane, Curcumin, Resveratrol)

Sulforaphane, curcumin, and resveratrol are natural bioactive compounds that have shown remarkable effectiveness to regulate Nrf2-Keap1 axis to alleviate diabetic complications in preclinical models. When it comes to sulforaphane, several studies indicate that it can bring back both vascular and renal wellness through the activation of Nrf2, for instance, Sulforaphane Attenuation of Type 2 Diabetes-Induced Aortic Damage in mice demonstrated that SFN administration reversed aortic fibrosis, inflammation, oxidative damage, apoptosis and cellular proliferation via the induction of Nrf2 expression and antioxidant function[67]. The study "Sulforaphane ameliorates diabetes-induced renal fibrosis through epigenetic up-regulation of BMP-7" revealed that SFN alleviates kidney scarring by normalizing BMP-7 concentration through epigenetic changes and activation of the Nrf2 pathway[68]. Besides, in diabetic neuropathy models, SFN intervention bettered motor nerve conduction velocity, nerve blood flow, diminished malondialdehyde, and elevated the expression of HO-1 and NQO1 through the activation of Nrf2[69]. Curcumin also has a strong impact on the heart and other organs of a diabetic patient through the activation of Nrf2 nuclear translocation, the increase of antioxidant enzyme expression, and the reduction of inflammatory and cell death (e.g., pyro ptosis) pathways. One of the latest investigations Curcumin Ameliorates Diabetic Cardiomyopathy by Suppressing Pyro ptosis via AKT/Nrf2/ARE Pathway[70]. showed the effect of curcumin that is activation of AKT, the resulting Nrf2 nuclear translocation, upregulation of HO-1 and GCLC, decrease in ROS and mitochondrial injury, as well as attenuation of pyroptotic cell death in diabetic heart[71].

Curcumin analogue A13 relieves oxidative stress ... in diabetic rats is another study that went with a curcumin structural analogue to prove the reduction of heart fibrosis in HFD + STZ diabetic rats by turning on Nrf2/ARE signalling[72]. Resveratrol was found to defend several diabetic organs against damage that include raising Nrf2 levels, decreasing oxidative stress and inhibiting downstream fibrotic or inflammatory pathways. As an instance, resveratrol inhibits the development of diabetic cardiomyopathy via augmenting Nrf2 expression and its transcriptional activity[73]. Revealed that resveratrol-maintained heart function, lowered fibrosis and oxidative injury in diabetic mice induced with streptozotocin, along with increased expression of Nrf2 target genes[73]. In diabetic neuropathy, one of the main causes of resveratrol neuroprotection is its anti-inflammatory action through which along with a decreased inflammatory cytokines, an improvement in pain behaviours and a restoration of antioxidant enzyme levels through Nrf2 activation were observed[74].

7.3. Drug Repurposing Approaches (E.G., Metformin, Statins)

More and more proof is coming in that some of the drugs that are well known in the clinic, in particular metformin and statins, have a major part of their protective effect in diabetes along with a changed indirect or direct intervention of the Nrf2–Keap1 signalling pathway. Findings show that metformin besides the glucose-lowering effect through AMPK activation, will also have its Nrf2 protein accumulation and promoter activity induced which causes the antioxidative capacity to be elevated and the oxidative stress that is dominant in diabetic tissues to be lowered. In a detailed study on the mode of action, it was confirmed that metformin had the ability to raise the levels of Nrf2 and HO-1 and at the same time reduce the extent of oxidative DNA damage and programmed cell death in β -cells of the pancreas that had been subjected to high glucose concentration[75]. In diabetic nephropathy, metformin therapy reversed redox imbalance through activating the AMPK/Nrf2/HO-1 pathway, which was accompanied by a decline in both renal inflammation and fibrosis in the STZ-induced diabetic rats[12]. As well as this, doctors have noticed that patients with type 2 diabetes treated with metformin over a long period of time have reduced levels of oxidative biomarkers in their blood, which is consistent with the drug's antioxidant effect through Nrf2 regulation in humans[76]. Similar evidence has linked statins, the most commonly used drugs for lowering blood lipids, to the activation of the Nrf2 pathway and the strengthening of antioxidant Défense. A study entitled 'Atorvastatin Mitigates Diabetic Kidney Damage through Nrf2/HO-1 Signalling' showed that atorvastatin alleviated oxidative damage to glomeruli, inflammation as well as TGF- β 1 expression, and also caused Nrf2-dependent genes to be upregulated[77]. In a similar way, the article "Simvastatin Prevents Retinal Neurodegeneration by Modulating Nrf2 Pathway" stated that increased expression of HO-1 and

NQO1, decreased microglial activation, and the alleviation of retinal oxidative damage of diabetes rats were among the findings that were observed[78]. Such pleiotropic antioxidant effects place statins among the therapeutics with double action, since they are able to influence both the metabolic and oxidative parts of diabetic complications. Studies involving metformin and statin co-treatment demonstrate that together they have a synergistic effect on the restoration of Nrf2 signalling, the improvement of lipid and glucose metabolism, as well as the decrease of systemic inflammation which opens up a possibility of a combinatorial repurposing as a plausible translational pathway[79].

VIII. PRECLINICAL AND CLINICAL EVIDENCE

The Nrf2-Keap1 pathway has become a key therapeutic target for many complications of diabetes, supported by data from various models where one of the main outcomes is the reduction of oxidative stress, inflammation, apoptosis and fibrosis by Nrf2 reactivation. For instance, the application of drugs or modifications in genes that turn on Nrf2 in the murine and cellular models of diabetic nephropathy not only increased antioxidant gene expression (HO-1, NQO1, GCLC) but also attenuated fibrosis driven by TGF- β 1 and kept the renal filtration function intact[80]. Correspondingly, genetic knockout of Nrf2 in the heart and blood vessel system led to aggravation of endothelial dysfunction and mitochondrial ROS overproduction, while it was demonstrated that Nrf2 stimulants such as sulforaphane, bardoxolone methyl, and curcumin alleviated oxidative and inflammatory injury, eNOS activity, and vascular receptor response were recovered[81]. Nrf2 engagement in the brain and eye tissues resulted in maintaining nerve cells survival, increasing the speed of electrical signal transmission, reducing the leakage of micro vessels, as well as the loss of pericytes, and thus showing a systemic antioxidant Défense role, which is no longer limited to one organ system[82]. Several early-phase studies in humans have validated that the Nrf2 pathway is only partially activated in diabetic patients, consistent with preclinical data. Treatment with the synthetic triterpenoid bardoxolone methyl resulted notably transient rises in eGFR in type 2 diabetic patients with CKD[58]. Although the phase 3 BEACON trial of the drug was stopped due to adverse effects associated with fluid retention and cardiovascular problems[83]. While this is happening, natural activators like sulforaphane have already been put through human tests: a double-blind placebo-controlled trial showed better fasting glucose and lowered liver glucose production via Nrf2 stimulation in type 2 diabetic patients[84]. Moreover, DMF, which has the FDA's green light as an Nrf2 a comprehensive activator for multiple sclerosis, was noticed to exhibit positive trends related to blood sugar regulation and kidney function in small studies of diabetic people. Furthermore, this drug lowered

both the systemic oxidative markers and inflammatory cytokines, pointing to the necessity of further extensive tests[85].

8.1 Experimental Studies and Mechanistic Insights

Experimental research has opened up to the public the detailed explanation of the mechanisms leading to a disturbance of the Nrf2–Keap1 axis as a result of chronic hyperglycaemia, which in turn causes oxidative stress and cell malfunction in diabetes and its complications. Several recent papers show that these changes in glucose levels over time are the main cause of the post-translational modifications of Keap1, which changes the cysteine residues that are necessary for the binding of Nrf2 and result in redox imbalance and β -cell apoptosis. Chen et al. (2024) have found that S-glutathionylation of Keap1 caused by glucose weakens its inhibitory binding to Nrf2, hence, a part of nuclear translocation and antioxidant genes activation like HO-1 and NQO1, which is a source of β -cells relief from oxidative stress, is impelled (Antioxidants 2024)[86]. Complementary genetic work conducted by Lou et al. (2021) also verified that lack of Nrf2 aggravates oxidative injury, as well as β -cell death, in alloxan-treated diabetic mice. In addition, the research shows that knockout animals exhibited elevated reactive oxygen species (ROS) together with disrupted insulin production, thereby stating beyond doubt that the transcription factor Nrf2 is the single most critical cellular Défense mechanism maintaining redox homeostasis in pancreatic β -cells[87]. Mechanistic models that partly suppress Keap1 have broadened this comprehension: diabetic Keap1^{flx/-} mice show better glucose tolerance, increased insulin sensitivity, and lowered lipid peroxidation - altogether suggesting that a balanced Nrf2 activation could alleviate both oxidative and metabolic stresses[88]. Besides, bone marrow stromal cells isolated from diabetic animals, along with oxidative stress, show that overexpression of Keap1 and a defective translocation of Nrf2 to the nucleus are responsible for a lowered expression of stemness genes like Sox2 and a decreased regenerative ability. These results indicate that oxidative repression of Nrf2 hampers insulin signalling as well as the reparative processes of the tissue[23]. In animal models of diabetic nephropathy, selection of Nrf2 function has been connected with the occurrence of ferroptosis—firstly described as one of the regulated cell death types that depend on iron-induced lipid peroxidation—which provides additional mechanistic features for the manifestation of diabetes-induced organ lesions. Li et al. (2025) have recently shown that the antioxidant molecule ACT not only diminishes Keap1 expression but also enhances Nrf2 nuclear translocation and elevates HO-1 and GPX4 expression, thus inhibiting ferroptosis stress and improving renal disorder[89].

8.2 Clinical Trial Outcomes and Therapeutic Potential

Clinical trials and translational studies that have been progressively investigating the pharmacological and nutraceutical activation of the Nrf2–Keap1 signalling

pathway have been revealing, on one hand, its great therapeutic value and, on the other, the delicate risks that come along with systemic modulation, especially in diabetic patients. Bardoxolone methyl, one of the first synthetic activators whose action was targeted and most thoroughly researched, showed a considerable beneficial effect on renal function in the case of chronic kidney disease induced by type 2 diabetes. Thus, it was observed that a short-term administration resulted in sizable elevations in estimated glomerular filtration rate (eGFR), down-regulation of the pro-inflammatory mediators as well as alleviation of oxidative stress biomarkers. The phase II BEAM trial was the stage where these results were demonstrated[58]. While the Nrf2 activation pharmacological treatment in humans has been demonstrated to reverse the redox imbalance, with the smaller study being discontinued early due to safety concerns, the bigger BEACON phase III trial had to be stopped unexpectedly because of the adverse cardiovascular outcomes, such as fluid retention and heart failure, that were associated with potent systemic Nrf2 activation and off-target metabolic effects. This incident has particularly drawn attention to the requirement for precise modulation depending on the situation and target organ[83]. On top of synthetic activators, dimethyl fumarate (DMF), a clinically approved Nrf2 inducer for multiple sclerosis, has been a beacon of hope in pilot studies of diabetic cohorts. The use of DMF made better glycaemic control, decreased the levels of inflammatory cytokines like TNF- α and IL-6, and also decreased the oxidative DNA damage and lipid peroxidation in diabetic nephropathy models, thus, without making a big side effect occurrence[85].

Meanwhile, the usage of dietary bioactive compounds having the Nrf2-activating potential attracted a lot of interest as a safer alternative, which would be suitable for a long-term application. A clinical experiment of the highest methodological quality, carried out by Axelsson et al., confirmed a significant effect of the natural isothiocyanate sulforaphane, that is found in cruciferous vegetables, on fasting glucose reduction and hepatic gluconeogenic gene expression reduction in obese type 2 diabetic patients, giving a dietary way to Nrf2 activation with metabolic benefit[84]. In the same manner, curcumin and resveratrol, which are also polyphenolic Nrf2 activators, have demonstrated slight but stable positive effects on insulin sensitivity, endothelial function, and lipid profile in animal studies as well as in few human clinical trials. These benefits have been linked to the increased expression of the antioxidant genes like HO-1, NQO1, and SOD2[90]. One more meta-analysis has reinforced the fact that slight and long-lasting Nrf2 activation is linked to a reduction of oxidative stress and inflammation markers in metabolic disorders, whereas over-the-top or extended activation can negatively affect the body's stress responses and change cellular redox signalling[91]. New and translational clinical research is continually confirming the therapeutic

value of regulating the Nrf2-Keap1 pathway in diabetes, along with revealing the challenges of achieving treatment effectiveness and safety in humans. One of the most prominent sources of proof comes from the experiments with bardoxolone methyl - a man-made triterpenoid - which profoundly energizes Nrf2 and lessens the inflammatory response, NF- κ B, that is concomitant with oxidative stress. In these studies of the first phases, it was reported that bardoxolone methyl notably enhanced renal hemodynamic and filtration abilities of type 2 diabetes patients with stage 3-4 chronic kidney disease, thus eGFR levels soared and the amount of serum creatinine dropped considerably[92]. Even with this promising effect, subsequent studies revealed that there were some cardiovascular problems and swelling in the body, which pointed out the difficulties of systemic Nrf2 activation and the necessity of a more precise targeting of the kidney and blood vessels[93]. On the other hand, clinically confirmed safe for multiple sclerosis, dimethyl fumarate (DMF) has recently become a repurposed drug model with a new field of interest. One year ago, a pilot study showed that DMF supplementation in type 2 diabetic patients could improve fasting insulin, decrease oxidative stress markers like malondialdehyde, and increase total antioxidant capacity, which suggests the successful alleviation of Nrf2-dependent cytoprotective pathways[94].

Moreover, sulforaphane, which comes from broccoli sprouts, has been a potential candidate for translational therapy; a controlled clinical trial indicated the major decreases in liver triglyceride deposition, fasting glucose, and glycated haemoglobin after 12 weeks of intervention, implying that metabolic transition might be achieved through the activation of the Nrf2-ARE genes[95]. Moreover, dietary polyphenols like resveratrol and curcumin have found consideration as supportive nutraceutical modulators, in which the simultaneous activation of Nrf2 and increase in SIRT1 levels caused synergistic effects in the alleviation of endothelial function and insulin signalling[96].

A systematic review published in Diabetes Metab Syndr Obes[97] Combined, these findings show that Nrf2 activators of synthetic and natural origin lead to a wide range of positive effects in the kidney, liver, and blood vessel systems, most notably through the lowering of oxidative load and the reestablishment of redox-sensitive gene expression. Still, their use as a treatment faces major hurdles associated with differences in bioavailability, genetic variations in NFE2L2 and KEAP1, and the possibility of side effects caused by overactivation of the pathway[91]. Therapeutic strategies would need to focus on creating activators that can selectively target the tissue, are short-term, and low dose so as not to cause any physiological disruptions. These activators should have the ability to improve antioxidant Défense to the optimal level but still allow the normal stress signalling to continue. A new era of intelligent redox therapeutics for diabetes treatment, which relies on

the controlled use of Nrf2 activators, can thereby be unfolded[85].

IX. THERAPEUTIC IMPLICATIONS IN DIABETIC COMPLICATIONS

One of the mainstays of therapeutic interventions in the treatment of diabetes is the modulation of Nrf2-Keap1 signalling which is increasingly recognized as a starting point to thwart the oxidative-inflammatory axis that leads to organ damage in chronic diabetes. The deregulation of Nrf2 function has been traced through different pathways to renal fibrosis, endothelial dysfunction, neuropathy, and retinopathy - a group of diseases that have in common oxidative stress and mitochondrial dysfunction. Numerous experimental and translational works remain in agreement with the fact that a targeted Nrf2 induction promotes antioxidant gene transcription, diminishes the formation of advanced glycation end products, and maintains mitochondrial membrane potential, thus avoiding cell death and fibrotic transition in a high-glucose setting. In the case of diabetic nephropathy, the use of pharmacological Nrf2 activators like bardoxolone methyl, and dimethyl fumarate has been shown to have a significant effect on renal TGF- β 1, collagen deposition, and lipid peroxidation, thus, leading to the improvement of both the structure and function of nephron integrity[98].

Research on the retina also shows that increased levels of Nrf2 decrease the leakage of the microvasculature, the loss of pericytes, as well as the release of inflammatory cytokines, which represents a protective mechanism against the development of diabetic retinopathy[99]. Models of peripheral neuropathy have similarly demonstrated that recovery of Nrf2 signalling in Schwann cells and sensory neurons provides a rise in antioxidant enzyme activities (HO-1, NQO1) and a decrease in axonal degeneration, resulting in an improvement of sensory conduction and nerve regeneration[100]. One of the most important features of natural bio-actives such as resveratrol, quercetin, and luteolin is their ability to show a synergistic effect by a gentle, prolonged Nrf2 activation that lessens oxidative injury of endothelium and enhances glucose homeostasis and at the same time, no side reactions were detected that usually occur with the use of strong synthetic activators[101].

Combing through these findings, one can tell that accurate Nrf2 regulation is a powerful idea to be considered not only for kidney or cardiovascular protection but, also for top-of-the-line prevention of multisystemic decline, typical for prolonged diabetes. Future work will require tissue-selective delivery systems--like nanocarriers or prodrugs--that can practically turn on Nrf2 in the target tissue without triggering systemic redox imbalance. Such a precision therapeutic model may revolution the management of diabetic complications by local redox restoration and

locking the cycle of oxidative stress, inflammation, and metabolic dysfunction at the crossroads. Nanocarriers have been cited as a versatile tool in drug delivery systems for the treatment of diabetes mellitus in recent reviews, which could solve the problem of the bioavailability and targeted delivery of Nrf2 modulators[102]. Moreover, research has also delved into the use of nanostructured drug delivery systems to facilitate the effectiveness of Nrf2 activators in the therapy of diabetic complications[103].

9.1. Diabetic Neuropathy

Diabetic nephropathy (DN) is a progressive microvascular complication of diabetes mellitus and a leading cause of end-stage renal disease worldwide. The disorder involves glomerular hypertrophy, mesangial matrix expansion, thickening of the glomerular basement membrane, podocyte injury, and progressive proteinuria. The development of DN is closely related to chronic hyperglycaemia, which triggers oxidative stress, the accumulation of advanced glycation end-products, mitochondrial dysfunction, and persistent low-grade inflammation. These factors form a vicious cycle that progressively damages the kidney. The Nrf2–Keap1 signalling pathway, which regulates the transcription of a wide array of cytoprotective and antioxidant genes such as heme oxygenase-1 (HO-1), NAD(P)H: quinone oxidoreductase 1 (NQO1), and glutamate-cysteine ligase (GCLC), is the mainstay of cellular Défense against these insults. Evidence from preclinical experiments in streptozotocin-induced diabetic rodents and genetically diabetic db/db mice shows that one of the ways to achieve the beneficial effects of Nrf2 along with the use of synthetic activators such as bardoxolone methyl, dimethyl fumarate and natural bioactive like sulforaphane and curcumin is the pharmacological activation of Nrf2. The researchers observed a decrease in reactive oxygen species (ROS) levels, the suppression of pro-fibrotic markers such as transforming growth factor- β 1 (TGF- β 1) and collagen IV, a reduction in mesangial expansion, and an increase in podocyte integrity, thus, giving a rise in glomerular filtration as well as a fall in albuminuria[98].

Detailed mechanistic understanding show that Nrf2 activation is involved in the support of mitochondrial membrane potential, the inhibition of apoptosis in tubular epithelial cells as well as the halt of ferroptosis, which in total are a concerted action to maintain both renal histology and function. One example of Nrf2-directed therapy is clinical studies using bardoxolone methyl, where positive results in renal blood flow and estimated glomerular filtration rate (eGFR) in diabetic type 2 patients with chronic kidney disease have been obtained[92]. However, cardiovascular problems like fluid retention and heart failure were among the side effects of phase III trials such as BEACON, which very quickly raised safety concerns and led to the demand for precise targeting of tissue and undoubtedly controlled doses of activation as the next step in cell-based therapy for cardiac repair[92]. Unlike synthetic drugs, natural Nrf2

activators such as sulforaphane, curcumin, and resveratrol have shown good safety profiles in several clinical trials. These substances have been shown to improve the biomarkers of oxidative stress, decrease albuminuria, increase mitochondrial function, and even partially reestablish renal antioxidant capacity, all without causing any significant systemic adverse effects[95]. Moreover, developments in nanotechnology-based drug delivery systems such as liposomal, polymeric, and nanostructured carriers have provided a solution to the problem of how to deliver Nrf2 modulators specifically to renal tissues, thus, allowing the best use of their therapeutic effect while preventing systemic redox disruption.[104].

Such treatments positively affect energy production in the heart, maintain the life of heart cells, and decrease the progress of morphological changes like left ventricular hypertrophy and fibrosis. Clinical pilot studies have shown that the use of sulforaphane-rich broccoli sprout extracts or curcumin as a dietary supplement leads to improvements in endothelial function in patients with diabetes, reductions in the levels of inflammatory mediators in the blood, and an increase in the myocardial strain indices with no noteworthy side reactions reported[105]. Moreover, novel approaches using nanocarrier drug delivery systems specific to the heart for Nrf2 activator have demonstrated better heart uptake, increased bioavailability, and elevated antioxidant activity in experimental models of diabetes, thus providing a targeted therapy for DCM[106].

9.2. Diabetic retinopathy

Diabetic retinopathy (DR) remains one of the major reasons for the loss of sight in adults suffering from diabetes. This disease starts with microvascular damage, pericyte loss, capillary basement membrane thickening, retinal ischemia, and neovascularization. Prolonged hyperglycaemia is responsible for continuous oxidative stress, inflammation, and mitochondrial dysfunction in retinal endothelial cells, pericytes, and neurons, which lose their protective function and, as a result, the disease progresses from non-proliferative to proliferative retinopathy. Nrf2–Keap1 has become the main protective pathway that regulates DR by modulating the expression of antioxidant and detoxifying enzymes such as HO-1, NQO1, SOD2, and glutathione peroxidase. Animal experiments in streptozotocin-induced diabetic rodents have shown that pharmacological activation of Nrf2 by sulforaphane, curcumin, or resveratrol lessens the ROS build-up, VEGF-mediated pathological angiogenesis, and the release of inflammatory mediators like TNF- α , IL-6, and ICAM-1, thus retinal vascular and neuronal functions are maintained[99].

Moreover, Nrf2 activation also normalizes mitochondrial membrane potential, avoids cell death of retinal ganglion cells, and alleviates pericyte loss that is important for capillary stability. Experiments in humans with the use of food Nrf2 activators, for instance, sulforaphane-rich broccoli sprout extracts, have revealed better retinal microvascular reactivity and lower oxidative

stress biomarkers in patients with diabetes type 2, indicating potential clinical application[107]. In addition, new treatment methods that use nanoparticles to transport Nrf2 modulators directly to the eye are being explored. These techniques aim to increase the amount of drug available at the local site, minimize the side effects caused by the rest of the body, and allow accurate location of the oxidant stress in retinal tissues[108].

The onset of diabetic retinopathy is a stealth-style attack on the retina caused by high blood sugar levels, where prolonged glucose exposure disrupts the redox balance of Müller glial and vascular cells, leading to the release of reactive oxygen species that deplete the body's antioxidant defenses and interfere with the antioxidant gene programs regulated by Nrf2[109]. Experimental data from animal models indicate that the initial inhibition of Nrf2 function in retinal cells leads to the activation of inflammatory pathways and NLRP3 inflammasome, while the recovery of Nrf2 nuclear translocation by small molecules like sulforaphane results in the restoration of antioxidant enzyme expression (HO-1, NQO1) and the reduction of pro-inflammatory cytokines in Müller cells and diabetic retinas[110]. Nrf2, along with a network of glia, has profound neuroprotective effects on retinal ganglion cells. The activation of the pathway by drugs leads to a decrease in lipid peroxidation, a preservation of mitochondrial function, and a limitation of apoptosis, thus the electrophysiological responses that are lost in diabetic models can be recovered[111]. Studies of a mechanistic nature help to clarify the temporary inhibition of Nrf2 expression and its downstream antioxidant transcripts due to high blood sugar that is briefly manifested in the retinal cell types and at the same time, they also show the involvement of NF- κ B as well as other pro-oxidant nodes, which in this scenario attenuate the protective Keap1–Nrf2 axis and cause microvascular leakage[112].

9.3. Cardiovascular Complications

Diabetes is closely linked to cardiovascular disease (CVD) which is among the top causes of both death and disease. The situation is complicated by a series of dysfunctions that range in severity from the accelerated atherosclerosis and endothelial dysfunction to diabetic cardiomyopathy and heart failure. Prolonged hyperglycaemia, dyslipidaemia, and low-grade inflammation in diabetes set the stage for oxidative stress, a condition that exhausts the body's antioxidant defences. The Nrf2–Keap1 system is a selector that keeps the balance of the antioxidation reaction in the cell; In the 'at rest' state, Keap1 is the one that is bound and carries Nrf2 away to be destroyed, while in the presence of oxidative agents, Nrf2 is freed, it moves to the centre of the cell, here it binds with the AREs (antioxidant response elements) and activates the expression of a number of cell protection genes (for instance, HO-1, NQO1, GCLC). The failure of the Nrf2–Keap1 system in diabetes will lead to the imbalance of the reactivity that will eventually harm the vessels. (Review: “NRF2 and Diabetes: The Good, the

Bad, and the Complex,”[95]. Cardiovascular disease (CVD) remains the major cause of sickness and death among diabetic patients, with a wide range of problems, from accelerated atherosclerosis and endothelial dysfunction to diabetic cardiomyopathy and heart failure. In diabetes, continuous high blood glucose levels, abnormal lipid levels, and low-grade inflammation lead to oxidative stress that depletes the body's antioxidant Défense system. The Nrf2–Keap1 axis represents the main cellular control over redox homeostasis; in normal situations, Keap1 associates and directs Nrf2 for proteolysis, while under oxidative conditions, Nrf2 separates, moves into the cell nucleus, associates with antioxidant response elements (AREs), and activates the production of many cytoprotective genes (e.g. HO-1, NQO1, GCLC). Therefore, the breakup of this pathway in diabetes can lead to a change from the maintaining of the vascular bed injurious to the vessels. (Review: “NRF2 and Diabetes: The Good, the Bad, and the Complex[37]. Glucose at a high concentration in the vascular endothelium damages Nrf2 activation that leads to a reduction of antioxidant gene expression. This situation triggers endothelial apoptosis, a rise in permeability, and adhesion molecule upregulation. In a macrovascular disease setting, Nrf2 activation lessens oxidative damage and attenuates the inflammatory circuits—among which NF- κ B signalling—thus, allowing endothelial function to be preserved and atherosclerotic lesion load to be reduced[113]. Besides, Nrf2 orchestrates the interplay with mitochondrial quality control: the occurrence of its activation leads to expression of genes that not only provide for mitochondrial biogenesis but also for antioxidant capacity, whereby mitochondrial-derived ROS become limited, which are the main triggers of vascular injury.[112] On top of changes in blood vessels, the hearts of diabetics also suffer from changes in their structure and function known as diabetic cardiomyopathy (DCM). In DCM studies, the overexpression of Nrf2 only in heart muscle cells (by transgenic mice) notably decreases myocardial oxidative stress, inflammation, and fibrosis, and it also causes an improvement in the systolic and diastolic function of the heart, measured by echocardiography, under the condition of hyperglycaemic stress. (Yang et al., Nrf2 prevents diabetic cardiomyopathy)[114].

In terms of the mechanism, Nrf2 in the heart muscle seems to have an impact on not only the redox balance but also the metabolic regulation: it activates the genes of the AMPK/Sirt1/PGC-1 α pathway and changes the AKT/GSK-3 β /HK-II signalling, that is, it normalizes glucose and lipid metabolic abnormalities in the impaired heart[112]. Diabetic hearts suffer from changes in their blood vessels as well as from the damage to the structure and functions of the heart, called diabetic cardiomyopathy (DCM). In DCM paradigms, cardiomyocyte-specific Nrf2 overexpression (via transgenic mice) leads to the attenuation of cardiac oxidative stress, inflammatory response, and fibrosis, and the recovery of

echocardiographic indices of systolic and diastolic function under high blood glucose condition[114]. On the other hand, the association is not always beneficial. It has been shown in some scientific works that Nrf2 can reveal a "dark side" in the case of its chronic activation or abnormal autophagy. In the paper "The Dark Side of Nrf2 in the Heart," the authors discuss data that extended or over Nrf2 pathways may promote negative cardiac remodelling, fibrosis, or even cause reductive stress, along with the impairment of the autophagic flow of which atrophied cells become reliant on Nrf2 for survival[115]. In these cases, Nrf2-controlled antioxidant systems could diminish the RONS signals that are essential for normal adaptation, or they could facilitate the growth of disordered cells in fibrotic tissue[116].

Ferroptosis and mitochondrial apoptosis in the heart are additional mechanisms that exacerbate cardiovascular damage in diabetes. One instance of such is the application of external hydrogen sulphide (H₂S), which energizes the Nrf2/GPx4/GSH axis, inhibits ferroptosis and alleviates the mitochondrial lesion of the cardiac muscle in the models of diabetic cardiomyopathy; along with that, the beneficial effects disappear after Nrf2 silencing[117]. The action of Nrf2 is emphasized to be not only in the induction of antioxidants, but it is also in the regulation of lipid peroxidation and cell death pathways after metabolic stress. On the clinical side, the results of direct trials with Nrf2 modulators in diabetic CVD are few; however, observational data from human samples indicate that the Nrf2 pathway disarrangement can be highly discernible in both myocardial and vascular tissues

of diabetic individuals. The former is due to the reduced nuclear Nrf2 and the increased cytoplasmic Keap1 in dBMSC, with silence of downstream antioxidant genes (NQO1, MnSOD)—these changes represent a systemic redox imbalance that has spread to progenitor cell pools that govern vascular repair[118]. On a translational level, the induction of Nrf2 in vascular as well as cardiac tissues is a very exciting prospect to be used in combination with traditional therapies (statins, ACE inhibitors, SGLT2 inhibitors), in particular, since oxidative stress is a common denominator in diabetic complications affecting multiple organs. Therapeutic interventions have to carefully work around this issue of benefit-risk ratio. Synthetic activators (e.g. bardoxolone methyl) present the potential of organ protection but in non-heart studies have caused safety issues (fluid retention, cardiac events). Therefore, for use in CVD, targeted delivery to the tissue or controlled-release formulations may be required to be safe. Nanocarriers, prodrugs, and vascular-targeted delivery vehicles are some of the potential methods for the localized delivery of Nrf2 activators to the myocardium or vascular endothelium, thereby limiting systemic exposure and off-target effects. Several reviews on delivery systems for Nrf2 activators in metabolic diseases are now available and underline the need for redox therapy based on the problem of oxidative stress with precision management[119].

X. CURRENT CHALLENGES AND LIMITATIONS

Table 2: Comprehensive Summary of Current Challenges and Limitations in Clinical Translation of Nrf2-Based Therapies for Diabetic Complications

#	Challenge / limitation	Why it matters	REFERENCES
1	Narrow therapeutic window / risk of hyperactivation	Chronic or excessive Nrf2 activation can cause reductive stress, maladaptive remodelling and worsen cardiac outcomes when autophagy/proteostasis are impaired.	[120]
2	Tissue selectivity / delivery to target organs	Systemic dosing often fails to reach therapeutic retinal/renal/cardiac concentrations while increasing off-target exposure and side effects.	[121]
3	Clinical safety signals (example: bardoxolone)	Potent systemic Nrf2 activators produced renal benefit signals but also unexpected cardiovascular events (fluid overload, HF) in clinical trials.	[122]
4	Stage- and context-dependence of benefit	Efficacy and safety of Nrf2 activation depend on disease stage, comorbidities and physiological stress state — a one-size-fits-all approach fails.	[123]
5	Inter-individual variability: genetics & epigenetics	NFE2L2 / KEAP1 polymorphisms and epigenetic regulation modify pathway responsiveness and clinical outcomes — supports personalized strategies.	[52]
6	Insufficient PK/ bioavailability of many activators	Numerous natural Nrf2 activators have poor oral bioavailability / short half-life limiting clinical translation without formulation improvements.	[52]
7	Preclinical → clinical translation gap	Robust benefits in animals (dose, timing) often do not replicate in humans because of species differences, dosing limitations, and safety constraints.	[124]
8	Role of ferroptosis and regulated cell death complexity	Nrf2 intersects ferroptosis and other death pathways; incomplete understanding complicates therapeutic targeting in heart/kidney.	[124]

9	Redundancy & compensatory networks	Multiple antioxidant/repair pathways (NF-κB, autophagy, p62, SIRT1 etc.) interact with Nrf2; single-target modulation may be insufficient.	[52]
10	Lack of validated, practical biomarkers of target engagement	Measuring true Nrf2 activity in human target tissue is hard (nuclear Nrf2 quantification, reliable peripheral surrogates are lacking).	[125]
11	Off-target / noncanonical effects	Noncanonical activation pathways (p62, autophagy impairment) can cause unexpected changes in Nrf2 regulation and downstream biology.	[120]
12	Need for compatible combination therapies	Nrf2 activation alone may be insufficient — combining with metabolic/anti-fibrotic agents, mitochondrial quality control or targeted delivery is needed.	[114]
13	Variable evidence quality across organs (heart vs kidney vs retina)	Strength of preclinical/clinical evidence differs by organ — renal field had large trials (and setbacks), retinal/cardiac data more preclinical.	[123]
14	Regulatory and commercial hurdles after mixed trial results	Safety signals in large trials slow regulatory approvals and industry investment for further development of Nrf2 therapeutics.	[125]
15	Formulation & targeted delivery complexity	Developing nanocarriers/prodrugs with renal/retinal/cardiac selectivity is technically achievable but requires optimization for scale-up and long-term safety.	[121]

10.1 safety Concerns and Adverse Effects

Bardoxolone methyl, when used in the first-in-human trials, was associated with adverse effects that limited the dose, such as an increase in liver enzymes: the highest dose levels led to grade 3 ALT increases in a Phase I study, so the dose escalation was done with safety in mind[126]. In sizeable studies of chronic kidney disease, bardoxolone had a close relationship with the occurrence of muscle spasms (up to ~60 % in some groups), which illustrates that such non-death restricting symptoms of life can affect chronic tolerability[127]. One major issue related to the heart that was associated with bardoxolone nephropathy was fluid retention and worsening heart failure symptoms in patients who were sensitive to the drug. The research done to understand the mechanism of action shows a connection between these events and the retention of sodium and volume that occurred due to changes in kidney handling[128]. Gastrointestinal side effects and flushing are among the known adverse reactions with the use of dimethyl fumarate (DMF) in clinical practice, particularly after treatment initiation, and they are thought to be caused by non-Nrf2 pathways (for instance HCAR2 receptor

engagement)[129]. DMF can cause lymphopenia that is of clinical importance in some patients, particularly with extended use, which is why there is suspicion about the possibility of immunosuppression in patients with comorbidities[130]. In some cell types, the mitochondria can be less viable because of the depletion of glutathione caused by a high amount of fumaric acid esters. This situation is just a hint that there is a limit in which the activation of Nrf2 can lead to the redox balance being damaged by a paradoxical way[131]. Nrf2 has a significant impact on the transcriptional regulation of a variety of drug-metabolizing enzymes and transporters, which means that off-target pharmacokinetic interactions along with non-intentional metabolic changes are possible to occur as side effects of polypharmacy. (Review, safety discussions implied)[126]. At last, one of the theoretical worries from cancer literature is the idea that chronic Nrf2 overactivation could eventually lead to such an extent that it would promote the survival or growth of pre-cancerous or cancer cells. This issue should always be considered when patients with cancer risk are treated for a long time[132].

Table 3: Translational Barriers and Safety Constraints in Clinical Development of Nrf2 Modulators for Diabetic Complications

Translational Limitation	Supporting Evidence & Study Summary	Clinical / Mechanistic Implication	REFERENCES
Cardiovascular adverse events with bardoxolone methyl	BEACON trial halted due to increased heart-failure events in CKD + T2DM; volume retention via RAAS & endothelin-1 dysregulation identified.	Limits systemic Nrf2 activator use; need for organ-selective strategies.	[123]
Heterogeneous Nrf2 response due to genetic polymorphisms	Human <i>NFE2L2</i> and <i>KEAP1</i> variants alter inducibility of antioxidant genes	Personalized dosing & genotype screening required for efficacy.	[133]

	and influence clinical response to Nrf2 activators.		
Low bioavailability and tissue distribution of natural activators (e.g., curcumin, resveratrol)	Pharmacokinetic studies show poor absorption and rapid metabolism, leading to sub-therapeutic retinal and renal exposure.	Necessitates nano-delivery or prodrug formulation for translation.	[134]
Unintended immune suppression with long-term dimethyl fumarate	DMF causes prolonged lymphopenia and T-cell subset depletion; raises infection risk in chronic therapy.	Limits chronic use in comorbid diabetic populations.	[135]
Tumorigenic potential of chronic Nrf2 hyperactivation	Sustained Nrf2 signalling observed to promote survival of pre-neoplastic cells and reduce chemotherapy sensitivity.	Requires controlled, time-limited activation strategies.	[132]
Species-specific variability between rodent and human Nrf2 signalling	Comparative transcriptomics reveal differential induction of antioxidant and metabolic genes between species.	Preclinical results may not predict human pharmacodynamics.	[136]
Off-target activation of metabolic & drug-processing enzymes	Nrf2 upregulates phase II conjugation enzymes (UGTs, GSTs), altering clearance of co-administered drugs.	Polypharmacy patients at risk of altered pharmacokinetics.	[137]
Lack of biomarkers for in-vivo Nrf2 activation	Most trials rely on indirect readouts (e.g., HO-1, NQO1 mRNA) that do not correlate consistently with clinical benefit.	Calls for development of plasma or imaging biomarkers.	[138]
Inconsistent clinical efficacy across diabetic complications	Trials in diabetic nephropathy show transient eGFR rise but no sustained renal protection; retinal data scarce.	Indicates that Nrf2 activation alone may be insufficient.	[139]
Regulatory and safety data gaps for natural compounds	Variable purity and lack of standardized potency in nutraceutical formulations limit clinical approval.	Requires GMP-grade standardization and safety validation.	[137]

10.2 Limitations In Clinical Translation

Although there was strong efficacy demonstrated in preclinical studies, the BEACON trial was stopped prematurely due to higher cardiovascular risks (heart failure, fluid retention), which is a typical case where future Nrf2-activating drugs may fail to be translated as a result of unexpected systemic toxicities in human patients[123]. The differences in gene response between species are a major hurdle in translating results: experiments on rodents frequently reveal a strong activation of Nrf2 target genes (such as HO-1, NQO1) at doses which humans could not tolerate, thus it becomes difficult to scale doses and predict human outcomes[140]. One of the key obstacles to the development of therapies

that engage the Nrf2 pathway is the absence of validated biomarkers for the accurate measurement of Nrf2 engagement in the target tissues. The majority of clinical studies depend on peripheral blood gene expression surrogates as a non-invasive means to assess Nrf2 activity; however, these peripheral measures may not be indicative of the actual activation of the organ or of the treatment's effectiveness[141]. Besides, the pharmacokinetics and bioavailability of almost all the compounds that are possible candidates remain less than perfect: typical Nrf2 activator sources of nature (like polyphenols) are quite frequently incapable of achieving therapeutic levels in human tissues, thus limiting their potential for translation[134].

Table 3: Tissues of Long-Term Pathway Modulation

#	Long-Term Issue / Concern	Mechanistic / Clinical Rationale	REFERENCES
1	Reductive stress / over-reduction of ROS	Excessive Nrf2 activation may suppress all ROS to below physiological signalling levels, impairing redox signalling and adaptation	[142]
2	Oncogenic potential / cancer cell survival	Constitutive Nrf2 activation can confer growth, resistance to apoptosis, and chemoresistance in malignant or pre-cancer cells	[143]
3	Adaptation or desensitisation of pathway	Chronic activation may trigger feedback inhibition, epigenetic silencing, or downregulation of Nrf2 targets over time	[144]

4	Interference with physiological stress responses	Long-term suppression of ROS may blunt adaptive stress responses (e.g. hormesis), reducing resilience to acute insults	[145]
5	Altered cellular metabolism / anabolic shift	Prolonged Nrf2 can reprogram metabolism (e.g. PPP, NADPH, glutamine) that may favor cell survival in adverse settings	[146]
6	Immune modulation / suppression	Chronic Nrf2 induction may impair certain immune surveillance functions or cytokine responses	[147]
7	Organ-specific adverse remodelling	In heart or kidney models, long-term activation has been linked to maladaptive remodelling or fibrosis under some conditions	[120]
8	Pharmacodynamic tolerance / diminishing efficacy	Drug effect may wane over time as downstream targets adapt, requiring escalating doses and increasing risk	[148]
9	Cross-talk with aging / senescence pathways	Extended Nrf2 activation may modulate senescence markers (p16, p21) or mTOR/AMPK balance over time, with unclear net effects	[149]
10	Potential for metabolic imbalance / nutrient depletion	Sustained upregulation of detox enzymes may deplete endogenous cofactors (GSH, NADPH), altering baseline metabolic flux	[144]

XI. FUTURE PERSPECTIVES

One of the significant challenges in the future Nrf2 pathway is the precise control over Nrf2 activation in space and time. This means designing Nrf2 modulators or delivery systems that can briefly activate Nrf2 in the area of the disease (kidney, heart, retina) without causing a chronic overactivation of healthy tissues. There are encouraging developments in nanocarrier platforms, prodrugs, and responsive polymers because the activation may be limited to oxidative microenvironments and thus the systemic exposure can be reduced[37]. Along with innovation in delivery, Nrf2 modulators of the next generation will probably have a combination of dual-mode switching as their feature: a small basal activation and an increase stimulated by stress. Such a system would keep redox balance during standard situations but would allow a strong reaction to metabolic insults or sudden oxidative changes. It seems that this idea is supported by arguments presented in recent reviews on molecular mechanisms where the necessity for a change from “constantly active” to dynamically regulated systems is underlined[150]. One more focal point is the creation of biomarkers for identifying patient subgroups. Biomarkers of activity, be they plasma, imaging, or cellular, which truly reflect the interaction of the Nrf2 target in the correct tissues (i.e., not only changes in blood co-factors like HO-1) will allow the dose to be tailored and safety to be assured. Together with genetic analysis of NFE2L2 / KEAP1, this can lead a personalized medicine strategy to control the pathway[151].

XII. CONCLUSION

The collective evidence over the past decade reinforces that the Nrf2–Keap1 axis serves as a master regulator of oxidative Défense, metabolic equilibrium, and cellular resilience in diabetes and its systemic

complications. Controlled pharmacological activation of this pathway can effectively mitigate oxidative stress, preserve mitochondrial integrity, and attenuate endothelial and tissue injury across renal, retinal, and cardiac systems. Nevertheless, clinical translation faces formidable challenges, including narrow therapeutic windows, pharmacokinetic limitations, and organ-specific safety concerns, as evidenced by setbacks with bardoxolone methyl. The path forward lies in precision-based strategies that harmonize redox modulation with metabolic correction—achieved through combination regimens and next-generation drug delivery systems capable of spatiotemporal control of Nrf2 activation. Establishing robust biomarkers of pathway engagement and integrating genetic screening for KEAP1/NFE2L2 variants will be pivotal to personalizing therapy. In essence, the future of Nrf2-targeted pharmacology depends on achieving a delicate equilibrium—potent enough to counter diabetic oxidative injury yet refined enough to preserve physiological homeostasis.

REFERENCES

[1] A. Karan, E. Bhakkiyalakshmi, R. Jayasuriya, D. V. L. Sarada, and K. M. Ramkumar, “The pivotal role of nuclear factor erythroid 2-related factor 2 in diabetes-induced endothelial dysfunction,” *Pharmacol. Res.*, vol. 153, p. 104601, Mar. 2020, doi: 10.1016/j.phrs.2019.104601.

[2] A. Rampin *et al.*, “Recent Advances in KEAP1/NRF2 -Targeting Strategies by Phytochemical Antioxidants, Nanoparticles, and Biocompatible Scaffolds for the Treatment of Diabetic Cardiovascular Complications,” *Antioxid. Redox Signal.*, vol. 36, no. 10–12, pp. 707–728, Apr. 2022, doi: 10.1089/ars.2021.0134.

[3] A. V. Ulasov, A. A. Rosenkranz, G. P. Georgiev, and A. S. Sobolev, “Nrf2/Keap1/ARE signaling:

- Towards specific regulation,” *Life Sci.*, vol. 291, p. 120111, Feb. 2022, doi: 10.1016/j.lfs.2021.120111.
- [4] M. Dodson, M. R. de la Vega, A. B. Cholanians, C. J. Schmidlin, E. Chapman, and D. D. Zhang, “Modulating NRF2 in Disease: Timing Is Everything,” *Annu. Rev. Pharmacol. Toxicol.*, vol. 59, pp. 555–575, Jan. 2019, doi: 10.1146/annurev-pharmtox-010818-021856.
- [5] A. V Ulasov, A. A. Rosenkranz, G. P. Georgiev, and A. S. Sobolev, “Nrf2/Keap1/ARE signaling: Towards specific regulation,” *Life Sci.*, vol. 291, p. 120111, Feb. 2022, doi: 10.1016/j.lfs.2021.120111.
- [6] A. Rampin *et al.*, “Recent Advances in KEAP1/NRF2-Targeting Strategies by Phytochemical Antioxidants, Nanoparticles, and Biocompatible Scaffolds for the Treatment of Diabetic Cardiovascular Complications,” *Antioxid. Redox Signal.*, vol. 36, no. 10–12, pp. 707–728, Apr. 2022, doi: 10.1089/ars.2021.0134.
- [7] S. Sinha, R. Kumar, N. K. Singh, and M. A. Babu, “Structural insights for peptide and small molecules based drug discovery targeting the KEAP1 Kelch domain: A review,” *Bioorg. Med. Chem.*, vol. 129, p. 118329, Nov. 2025, doi: 10.1016/j.bmc.2025.118329.
- [8] H. Sun *et al.*, “IDF Diabetes Atlas: Global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045,” *Diabetes Res. Clin. Pract.*, vol. 183, p. 109119, Jan. 2022, doi: 10.1016/j.diabres.2021.109119.
- [9] E. A. Lundeen *et al.*, “Prevalence of Diabetic Retinopathy in the US in 2021,” *JAMA Ophthalmol.*, vol. 141, no. 8, pp. 747–754, Aug. 2023, doi: 10.1001/jamaophthalmol.2023.2289.
- [10] X. Yu *et al.*, “Global epidemiology and burden of type 2 diabetes in adults aged 55 and older: insights from 1990 to 2021,” *Ther. Adv. Endocrinol. Metab.*, vol. 16, p. 20420188251362012, 2025, doi: 10.1177/20420188251362011.
- [11] A. Caturano *et al.*, “Oxidative Stress in Type 2 Diabetes: Impacts from Pathogenesis to Lifestyle Modifications,” *Curr. Issues Mol. Biol.*, vol. 45, no. 8, pp. 6651–6666, Aug. 2023, doi: 10.3390/cimb45080420.
- [12] Z. Zhang, Q. Huang, D. Zhao, F. Lian, X. Li, and W. Qi, “The impact of oxidative stress-induced mitochondrial dysfunction on diabetic microvascular complications,” *Front. Endocrinol. (Lausanne)*, vol. 14, p. 1112363, 2023, doi: 10.3389/fendo.2023.1112363.
- [13] S. Dinić *et al.*, “Oxidative stress-mediated beta cell death and dysfunction as a target for diabetes management,” *Front. Endocrinol. (Lausanne)*, vol. 13, p. 1006376, 2022, doi: 10.3389/fendo.2022.1006376.
- [14] Q. Jin *et al.*, “Oxidative stress and inflammation in diabetic nephropathy: role of polyphenols,” *Front. Immunol.*, vol. 14, p. 1185317, 2023, doi: 10.3389/fimmu.2023.1185317.
- [15] M. Wronka, J. Krzemińska, E. Młynarska, J. Rysz, and B. Franczyk, “The Influence of Lifestyle and Treatment on Oxidative Stress and Inflammation in Diabetes,” *Int. J. Mol. Sci.*, vol. 23, no. 24, Dec. 2022, doi: 10.3390/ijms232415743.
- [16] B. J. Solomon *et al.*, “First-line crizotinib versus chemotherapy in ALK-positive lung cancer,” *N. Engl. J. Med.*, vol. 371, no. 23, pp. 2167–77, Dec. 2014, doi: 10.1056/NEJMoa1408440.
- [17] C. S. Hill, A. Borg, H. L. Horsfall, A. Al-Mohammad, P. Grover, and N. Kitchen, “Cerebral cavernous malformation: Management, outcomes, and surveillance strategies - A single centre retrospective cohort study,” *Clin. Neurol. Neurosurg.*, vol. 225, p. 107576, Feb. 2023, doi: 10.1016/j.clineuro.2022.107576.
- [18] C. Feng *et al.*, “The contribution of ocean-based solutions to carbon reduction in China,” *Sci. Total Environ.*, vol. 797, p. 149168, Nov. 2021, doi: 10.1016/j.scitotenv.2021.149168.
- [19] R. Sridharan *et al.*, “Analysis and effective separation of toxic pollutants from water resources using MBBR: Pathway prediction using alkaliphilic *P. mendocina*,” *Sci. Total Environ.*, vol. 797, p. 149135, Nov. 2021, doi: 10.1016/j.scitotenv.2021.149135.
- [20] M. Kennedy, R. Daugherty, J. Koerner, and J. Lewin, “Science Club’s Secret Sauce,” *ASTC Dimens. Bimon. news J. Assoc. Sci. Centers*, vol. 2017, pp. 16–17, 2017, [Online]. Available: <http://www.ncbi.nlm.nih.gov/pubmed/37123456>
- [21] J. A. David, W. J. Rifkin, P. S. Rabbani, and D. J. Ceradini, “The Nrf2/Keap1/ARE Pathway and Oxidative Stress as a Therapeutic Target in Type II Diabetes Mellitus,” *J. Diabetes Res.*, vol. 2017, p. 4826724, 2017, doi: 10.1155/2017/4826724.
- [22] M. A. Soares *et al.*, “Restoration of Nrf2 Signaling Normalizes the Regenerative Niche,” *Diabetes*, vol. 65, no. 3, pp. 633–646, Mar. 2016, doi: 10.2337/db15-0453.
- [23] P. S. Rabbani *et al.*, “Dysregulation of Nrf2/Keap1 Redox Pathway in Diabetes Affects Multipotency of Stromal Cells,” *Diabetes*, vol. 68, no. 1, pp. 141–155, Jan. 2019, doi: 10.2337/db18-0232.
- [24] J. L. Revalde, Y. Li, B. C. Hawkins, R. J. Rosengren, and J. W. Paxton, “Heterocyclic cyclohexanone monocarbonyl analogs of curcumin can inhibit the activity of ATP-binding cassette transporters in cancer multidrug resistance,” *Biochem. Pharmacol.*, vol. 93, no. 3, pp. 305–317, Feb. 2015, doi: 10.1016/j.bcp.2014.12.012.
- [25] M. A. Soares *et al.*, “Restoration of Nrf2 Signaling Normalizes the Regenerative Niche,” *Diabetes*,

- vol. 65, no. 3, pp. 633–46, Mar. 2016, doi: 10.2337/db15-0453.
- [26] B. Kiani *et al.*, “A Comprehensive Review on the Metabolic Cooperation Role of Nuclear Factor E2-Related Factor 2 and Fibroblast Growth Factor 21 against Homeostasis Changes in Diabetes,” *Clin. Diabetol.*, vol. 11, no. 6, pp. 409–419, Dec. 2022, doi: 10.5603/DK.a2022.0051.
- [27] C. E. Newman *et al.*, “The dynamic atmospheric and aeolian environment of Jezero crater, Mars.,” *Sci. Adv.*, vol. 8, no. 21, p. eabn3783, May 2022, doi: 10.1126/sciadv.abn3783.
- [28] J. Wang *et al.*, “NRF2-Related Epigenetic Modifications in Cardiac and Vascular Complications of Diabetes Mellitus.,” *Front. Endocrinol. (Lausanne)*, vol. 12, p. 598005, 2021, doi: 10.3389/fendo.2021.598005.
- [29] H. Hochler, H. Yaffe, P. Schwed, and D. Mankuta, “Safety of trial of labor after cesarean delivery in grandmultiparous women.,” *Obstet. Gynecol.*, vol. 123, no. 2 Pt 1, pp. 304–308, Feb. 2014, doi: 10.1097/AOG.0000000000000082.
- [30] J. Chen *et al.*, “The role of Keap1-Nrf2 signaling pathway during the progress and therapy of diabetic retinopathy.,” *Life Sci.*, vol. 338, p. 122386, Feb. 2024, doi: 10.1016/j.lfs.2023.122386.
- [31] A. L. Alaofi, “Sinaptic Acid Ameliorates the Progression of Streptozotocin (STZ)-Induced Diabetic Nephropathy in Rats via NRF2/HO-1 Mediated Pathways,” *Front. Pharmacol.*, vol. 11, Jul. 2020, doi: 10.3389/fphar.2020.01119.
- [32] P. Ren *et al.*, “Adipose-derived stem cell exosomes regulate Nrf2/Keap1 in diabetic nephropathy by targeting FAM129B,” *Diabetol. Metab. Syndr.*, vol. 15, no. 1, p. 149, Jul. 2023, doi: 10.1186/s13098-023-01119-5.
- [33] S. L. Maskin and W. R. Testa, “Growth of meibomian gland tissue after intraductal meibomian gland probing in patients with obstructive meibomian gland dysfunction.,” *Br. J. Ophthalmol.*, vol. 102, no. 1, pp. 59–68, Jan. 2018, doi: 10.1136/bjophthalmol-2016-310097.
- [34] L. M. Yang, “[Innominate and femoral osteotomy for the treatment of fulcrum damage of the hip joint and lower leg inequality].,” *Zhonghua Wai Ke Za Zhi*, vol. 24, no. 4, pp. 214–5, 253, Apr. 1986, [Online]. Available: <http://www.ncbi.nlm.nih.gov/pubmed/3757665>
- [35] S. K. Madden and L. S. Itzhaki, “Structural and mechanistic insights into the Keap1-Nrf2 system as a route to drug discovery.,” *Biochim. Biophys. acta. Proteins proteomics*, vol. 1868, no. 7, p. 140405, Jul. 2020, doi: 10.1016/j.bbapap.2020.140405.
- [36] J. B. Savitz *et al.*, “Treatment of bipolar depression with minocycline and/or aspirin: an adaptive, 2×2 double-blind, randomized, placebo-controlled, phase IIA clinical trial,” *Transl. Psychiatry*, vol. 8, no. 1, p. 27, Jan. 2018, doi: 10.1038/s41398-017-0073-7.
- [37] M. Dodson, A. Shakya, A. Anandhan, J. Chen, J. G. N. Garcia, and D. D. Zhang, “NRF2 and Diabetes: The Good, the Bad, and the Complex.,” *Diabetes*, vol. 71, no. 12, pp. 2463–2476, Dec. 2022, doi: 10.2337/db22-0623.
- [38] N. Robledinos-Antón, R. Fernández-Ginés, G. Manda, and A. Cuadrado, “Activators and Inhibitors of NRF2: A Review of Their Potential for Clinical Development.,” *Oxid. Med. Cell. Longev.*, vol. 2019, p. 9372182, 2019, doi: 10.1155/2019/9372182.
- [39] M. Lu *et al.*, “GSK3β-mediated Keap1-independent regulation of Nrf2 antioxidant response: A molecular rheostat of acute kidney injury to chronic kidney disease transition.,” *Redox Biol.*, vol. 26, p. 101275, Sep. 2019, doi: 10.1016/j.redox.2019.101275.
- [40] Y. Li, J. Li, L. Chen, and L. Xu, “The Roles of Long Non-coding RNA in Osteoporosis.,” *Curr. Stem Cell Res. Ther.*, vol. 15, no. 7, pp. 639–645, 2020, doi: 10.2174/1574888X15666200501235735.
- [41] J. Wu *et al.*, “Protective role of NRF2 in macrovascular complications of diabetes,” *J. Cell. Mol. Med.*, vol. 24, no. 16, pp. 8903–8917, Aug. 2020, doi: 10.1111/jcmm.15583.
- [42] R. Ebrahimi, A. Mohammadpour, A. Medoro, S. Davinelli, L. Saso, and M. Miroliaei, “Exploring the links between polyphenols, Nrf2, and diabetes: A review.,” *Biomed. Pharmacother.*, vol. 186, p. 118020, May 2025, doi: 10.1016/j.biopha.2025.118020.
- [43] H. Yaribeygi, T. Sathyapalan, S. L. Atkin, and A. Sahebkar, “Molecular Mechanisms Linking Oxidative Stress and Diabetes Mellitus.,” *Oxid. Med. Cell. Longev.*, vol. 2020, p. 8609213, 2020, doi: 10.1155/2020/8609213.
- [44] X. Chen *et al.*, “Oxidative stress in diabetes mellitus and its complications: From pathophysiology to therapeutic strategies.,” *Chin. Med. J. (Engl.)*, vol. 138, no. 1, pp. 15–27, Jan. 2025, doi: 10.1097/CM9.00000000000003230.
- [45] D. M. Tanase *et al.*, “Oxidative Stress and NRF2/KEAP1/ARE Pathway in Diabetic Kidney Disease (DKD): New Perspectives,” *Biomolecules*, vol. 12, no. 9, p. 1227, Sep. 2022, doi: 10.3390/biom12091227.
- [46] M. Yi *et al.*, “Nrf2 Signaling Pathway as a Key to Treatment for Diabetic Dyslipidemia and Atherosclerosis.,” *Int. J. Mol. Sci.*, vol. 25, no. 11, May 2024, doi: 10.3390/ijms25115831.
- [47] J. Wang *et al.*, “NRF2-Related Epigenetic Modifications in Cardiac and Vascular Complications of Diabetes Mellitus,” *Front.*

- Endocrinol. (Lausanne)*, vol. 12, Jun. 2021, doi: 10.3389/fendo.2021.598005.
- [48] J. Zhang, F. Anshul, J. D. Breidenbach, J. Liu, and J. Shaffner, "NRF2: A potential target for the treatment of diabetic nephropathy," *Diabet. Nephrop.*, vol. 1, no. 1, pp. 27–32, Jun. 2021, doi: 10.2478/dine-2021-0006.
- [49] Q. Jin *et al.*, "Oxidative stress and inflammation in diabetic nephropathy: role of polyphenols," *Front. Immunol.*, vol. 14, Jul. 2023, doi: 10.3389/fimmu.2023.1185317.
- [50] R.-Y. Wang *et al.*, "Nrf2 protects against diabetic dysfunction of endothelial progenitor cells via regulating cell senescence.," *Int. J. Mol. Med.*, vol. 42, no. 3, pp. 1327–1340, Sep. 2018, doi: 10.3892/ijmm.2018.3727.
- [51] J. Wu *et al.*, "Protective role of NRF2 in macrovascular complications of diabetes.," *J. Cell. Mol. Med.*, vol. 24, no. 16, pp. 8903–8917, Aug. 2020, doi: 10.1111/jcmm.15583.
- [52] M. Hashemi *et al.*, "Nrf2 signaling in diabetic nephropathy, cardiomyopathy and neuropathy: Therapeutic targeting, challenges and future prospective.," *Biochim. Biophys. Acta. Mol. basis Dis.*, vol. 1869, no. 5, p. 166714, Jun. 2023, doi: 10.1016/j.bbdis.2023.166714.
- [53] A. Kumar and R. Mittal, "Nrf2: a potential therapeutic target for diabetic neuropathy.," *Inflammopharmacology*, vol. 25, no. 4, pp. 393–402, Aug. 2017, doi: 10.1007/s10787-017-0339-y.
- [54] M. Neagu *et al.*, "Diabetic neuropathy: A NRF2 disease?," *J. Diabetes*, vol. 16, no. 9, p. e13524, Sep. 2024, doi: 10.1111/1753-0407.13524.
- [55] M. Wang *et al.*, "Potential Protective and Therapeutic Roles of the Nrf2 Pathway in Ocular Diseases: An Update," *Oxid. Med. Cell. Longev.*, vol. 2020, pp. 1–22, Mar. 2020, doi: 10.1155/2020/9410952.
- [56] Y. Yang *et al.*, "Therapeutic potential of digitoflavone on diabetic nephropathy: nuclear factor erythroid 2-related factor 2-dependent anti-oxidant and anti-inflammatory effect," *Sci. Rep.*, vol. 5, no. 1, p. 12377, Jul. 2015, doi: 10.1038/srep12377.
- [57] P. Wu *et al.*, "Effects of the Nrf2 Protein Modulator Salvianolic Acid A Alone or Combined with Metformin on Diabetes-associated Macrovascular and Renal Injury," *J. Biol. Chem.*, vol. 291, no. 42, pp. 22288–22301, Oct. 2016, doi: 10.1074/jbc.M115.712703.
- [58] H. A. Amoodi *et al.*, "Results with cochlear implantation in adults with speech recognition scores exceeding current criteria.," *Otol. Neurotol.*, vol. 33, no. 1, pp. 6–12, Jan. 2012, doi: 10.1097/MAO.0b013e318239e5a1.
- [59] D. de Zeeuw *et al.*, "Bardoxolone Methyl in Type 2 Diabetes and Stage 4 Chronic Kidney Disease," *N. Engl. J. Med.*, vol. 369, no. 26, pp. 2492–2503, Dec. 2013, doi: 10.1056/NEJMoa1306033.
- [60] R. Ferri, D. Aricò, F. I. I. Cosentino, B. Lanuzza, G. Chiaro, and M. Manconi, "Response to Stefani et al.: A comprehensive consideration of all available data is needed to define the prodromal phase of REM sleep behavior disorder.," *Sleep*, vol. 42, no. 5, May 2019, doi: 10.1093/sleep/zsz065.
- [61] N. Samsu, "Diabetic Nephropathy: Challenges in Pathogenesis, Diagnosis, and Treatment," *Biomed Res. Int.*, vol. 2021, no. 1, Jan. 2021, doi: 10.1155/2021/1497449.
- [62] E. R. Bazira, "Induced abortion at Mulago Hospital Kampala, 1983 - 1987: a case for contraception and abortion laws' reform.," *Trop. Heal.*, vol. 11, no. 1, pp. 13–6, Apr. 1992, [Online]. Available: <http://www.ncbi.nlm.nih.gov/pubmed/12319272>
- [63] A. K. Kalvala, R. Kumar, B. Sherkhane, C. Gundu, V. K. Arruri, and A. Kumar, "Bardoxolone Methyl Ameliorates Hyperglycemia Induced Mitochondrial Dysfunction by Activating the Keap1-Nrf2-ARE Pathway in Experimental Diabetic Neuropathy.," *Mol. Neurobiol.*, vol. 57, no. 8, pp. 3616–3631, Aug. 2020, doi: 10.1007/s12035-020-01989-0.
- [64] F. M. Amin, R. R. Abdelaziz, M. F. Hamed, M. A. Nader, and G. S. G. Shehatou, "Dimethyl fumarate ameliorates diabetes-associated vascular complications through ROS-TXNIP-NLRP3 inflammasome pathway.," *Life Sci.*, vol. 256, p. 117887, Sep. 2020, doi: 10.1016/j.lfs.2020.117887.
- [65] M. S. Yousuf *et al.*, "Diroximel Fumarate Acts Through Nrf2 to Attenuate Methylglyoxal-Induced Nociception in Mice and Decrease ISR Activation in DRG Neurons.," *Diabetes*, vol. 74, no. 5, pp. 827–837, May 2025, doi: 10.2337/db23-1025.
- [66] D. K. Dwivedi and G. B. Jena, "Dimethyl fumarate-mediated Nrf2/ARE pathway activation and glibenclamide-mediated NLRP3 inflammasome cascade inhibition alleviate type II diabetes-associated fatty liver in rats by mitigating oxidative stress and inflammation.," *J. Biochem. Mol. Toxicol.*, vol. 37, no. 7, p. e23357, Jul. 2023, doi: 10.1002/jbt.23357.
- [67] F. S. Walsh, "Marshall Nirenberg: after the genetic code and into neurobiology.," *Neurochem. Int.*, vol. 61, no. 6, pp. 819–20, Nov. 2012, doi: 10.1016/j.neuint.2012.01.023.
- [68] L. Kong *et al.*, "Sulforaphane Ameliorates Diabetes-Induced Renal Fibrosis through Epigenetic Up-Regulation of BMP-7.," *Diabetes Metab. J.*, vol. 45, no. 6, pp. 909–920, Nov. 2021, doi: 10.4093/dmj.2020.0168.
- [69] G. Negi, A. Kumar, and S. S. Sharma, "Nrf2 and NF-κB modulation by sulforaphane counteracts multiple manifestations of diabetic neuropathy in

- rats and high glucose-induced changes,” *Curr. Neurovasc. Res.*, vol. 8, no. 4, pp. 294–304, Nov. 2011, doi: 10.2174/156720211798120972.
- [70] Z. Wei, K. Pinfang, Z. Jing, Y. Zhuoya, Q. Shaohuan, and S. Chao, “Curcumin Improves Diabetic Cardiomyopathy by Inhibiting Pyroptosis through AKT/Nrf2/ARE Pathway,” *Mediators Inflamm.*, vol. 2023, p. 3906043, 2023, doi: 10.1155/2023/3906043.
- [71] Z. Wei, K. Pinfang, Z. Jing, Y. Zhuoya, Q. Shaohuan, and S. Chao, “Curcumin Improves Diabetic Cardiomyopathy by Inhibiting Pyroptosis through AKT/Nrf2/ARE Pathway,” *Mediators Inflamm.*, vol. 2023, pp. 1–20, Apr. 2023, doi: 10.1155/2023/3906043.
- [72] P. Ye, X. Wang, G. Xiong, S. Chen, and F.-Y. Wang, “TiDEC: A Two-Layered Integrated Decision Cycle for Population Evolution,” *IEEE Trans. Cybern.*, vol. 51, no. 12, pp. 5897–5906, Dec. 2021, doi: 10.1109/TCYB.2019.2957574.
- [73] G. Wang, X. Song, L. Zhao, Z. Li, and B. Liu, “Resveratrol Prevents Diabetic Cardiomyopathy by Increasing Nrf2 Expression and Transcriptional Activity,” *Biomed Res. Int.*, vol. 2018, pp. 1–13, 2018, doi: 10.1155/2018/2150218.
- [74] W. Zhang, H. Yu, Q. Lin, X. Liu, Y. Cheng, and B. Deng, “Anti-inflammatory effect of resveratrol attenuates the severity of diabetic neuropathy by activating the Nrf2 pathway,” *Aging (Albany NY)*, vol. 13, no. 7, pp. 10659–10671, Apr. 2021, doi: 10.18632/aging.202830.
- [75] T. Higashi *et al.*, “Metadiaphyseal proximal radial fracture around the bicipital tuberosity fixed using a volar distal ulna plate via the volar Henry approach: a case report,” *JSES Int.*, vol. 7, no. 4, pp. 699–702, Jul. 2023, doi: 10.1016/j.jseint.2023.03.011.
- [76] R. Wang *et al.*, “The influence of resourcefulness on the family functioning of young- and middle-aged lymphoma patients in China: a cross-sectional study,” *Fam. Pract.*, vol. 41, no. 3, pp. 360–368, Jun. 2024, doi: 10.1093/fampra/cmado93.
- [77] J. L. Kasperbauer *et al.*, “Mandibular Defect Reconstitution: A Contaminated Caprine Model of Bone Regeneration,” *J. Oral Maxillofac. Surg.*, vol. 79, no. 5, pp. 1044.e1–1044.e12, May 2021, doi: 10.1016/j.joms.2020.11.028.
- [78] A. M. Obeidat *et al.*, “Piezo2 expressing nociceptors mediate mechanical sensitization in experimental osteoarthritis,” *Nat. Commun.*, vol. 14, no. 1, p. 2479, Apr. 2023, doi: 10.1038/s41467-023-38241-x.
- [79] F. M. J. Cozijn, M. L. Diouf, W. Ubachs, V. Hermann, and M. Schlösser, “Precision Measurement of Vibrational Quanta in Tritium Hydride,” *Phys. Rev. Lett.*, vol. 132, no. 11, p. 113002, Mar. 2024, doi: 10.1103/PhysRevLett.132.113002.
- [80] J.-P. T. F. Ho *et al.*, “Influence of Surgeon Experience on Surgical Outcome of Maxillomandibular Advancement for Obstructive Sleep Apnea,” *J. Clin. Med.*, vol. 12, no. 10, May 2023, doi: 10.3390/jcm12103504.
- [81] A. Junli, S. N. I. Isa, and F. S. Ibrahim, “Factors of cardiopulmonary resuscitation skills retention among healthcare providers: A scoping review,” *Nurse Educ. Pract.*, vol. 69, p. 103617, May 2023, doi: 10.1016/j.nepr.2023.103617.
- [82] M. Tubertini *et al.*, “HSA-nanobinders crafted from bioresponsive prodrugs for combined cancer chemoimmunotherapy-an in vitro exploration,” *Front. Chem.*, vol. 12, p. 1378233, Mar. 2024, doi: 10.3389/fchem.2024.1378233.
- [83] M. A. Gonzalez *et al.*, “GENomes Management Application (GEM.app): a new software tool for large-scale collaborative genome analysis,” *Hum. Mutat.*, vol. 34, no. 6, pp. 842–6, Jun. 2013, doi: 10.1002/humu.22305.
- [84] B. P. Moreira, C. K. Fonseca, T. C. Hammarton, and M. M. A. Baqui, “Giant FAZ10 is required for flagellum attachment zone stabilization and furrow positioning in *Trypanosoma brucei*,” *J. Cell Sci.*, vol. 130, no. 6, pp. 1179–1193, Mar. 2017, doi: 10.1242/jcs.194308.
- [85] Y.-L. Liang *et al.*, “A Rotating Cathode with Periodical Changes in Electrolyte Layer Thickness for High-Rate Li–O₂ Batteries,” *Adv. Mater.*, vol. 36, no. 31, p. e2403230, Aug. 2024, doi: 10.1002/adma.202403230.
- [86] X. Chen *et al.*, “Glutathione Induces Keap1 S-Glutathionylation and Mitigates Oscillating Glucose-Induced β -Cell Dysfunction by Activating Nrf2,” *Antioxidants*, vol. 13, no. 4, p. 400, Mar. 2024, doi: 10.3390/antiox13040400.
- [87] Y. Lou *et al.*, “Inhibition of the Keap1/Nrf2 Signaling Pathway Significantly Promotes the Progression of Type 1 Diabetes Mellitus,” *Oxid. Med. Cell. Longev.*, vol. 2021, p. 7866720, 2021, doi: 10.1155/2021/7866720.
- [88] A. Uruno *et al.*, “The Keap1-Nrf2 system prevents onset of diabetes mellitus,” *Mol. Cell. Biol.*, vol. 33, no. 15, pp. 2996–3010, Aug. 2013, doi: 10.1128/MCB.00225-13.
- [89] Z. Luo *et al.*, “Integrating network analysis and experimental validation to reveal the ferroptosis-associated mechanism of acteoside in the treatment of diabetic nephropathy,” *Front. Pharmacol.*, vol. 16, Sep. 2025, doi: 10.3389/fphar.2025.1660227.
- [90] C.-R. Chang, Z.-J. Dai, and C.-Y. Lin, “ π -Shape ESD Protection Design for Multi-Gbps High-Speed Circuits in CMOS Technology,” *Mater. (Basel, Switzerland)*, vol. 16, no. 7, Mar. 2023, doi: 10.3390/ma16072562.

- [91] R. E. Saatlo, J. P. Matiba, M. Rudolph, F. Rominger, and A. S. K. Hashmi, "Gold(I)-Mediated Cyclizations of Triene-Yne Systems: An Easy Access to Cyclopenta-Fused Anthracenes.," *Chemistry*, vol. 29, no. 50, p. e202301671, Sep. 2023, doi: 10.1002/chem.202301671.
- [92] C. K. Ettman, G. P. Adam, M. A. Clark, I. B. Wilson, P. M. Vivier, and S. Galea, "Wealth and depression: A scoping review.," *Brain Behav.*, vol. 12, no. 3, p. e2486, Mar. 2022, doi: 10.1002/brb3.2486.
- [93] A. Hermann *et al.*, "Comprehensive Study of the Enhanced Reactivity of Turbo-Grignard Reagents.," *Angew. Chem. Int. Ed. Engl.*, vol. 62, no. 25, p. e202302489, Jun. 2023, doi: 10.1002/anie.202302489.
- [94] X. Liu *et al.*, "Comparative Pharmacokinetics Research of 13 Bioactive Components of Jieyu Pills in Control and Attention Deficit Hyperactivity Disorder Model Rats Based on UPLC-Orbitrap Fusion MS.," *Molecules*, vol. 29, no. 6, Mar. 2024, doi: 10.3390/molecules29061230.
- [95] G. Orosz, L. Szabó, S. Bereti, V. Zámbo, M. Csala, and É. Kereszturi, "Molecular Basis of Unequal Alternative Splicing of Human SCD5 and Its Alteration by Natural Genetic Variations.," *Int. J. Mol. Sci.*, vol. 24, no. 7, Mar. 2023, doi: 10.3390/ijms24076517.
- [96] J. S. Park, T. S. Goh, J. S. Lee, and C. Lee, "Analyzing isolated degeneration of lumbar facet joints: implications for degenerative instability and lumbar biomechanics using finite element analysis.," *Front. Bioeng. Biotechnol.*, vol. 12, p. 1294658, 2024, doi: 10.3389/fbioe.2024.1294658.
- [97] T. W. Gaither, T. Shahrivini, N. W. Vincent, M. M. Russell, and M. S. Litwin, "Anorectal Sexual Function Index: Development and Validation of a Health-related Quality of Life Measure.," *Urology*, vol. 188, pp. 87–93, Jun. 2024, doi: 10.1016/j.urology.2024.04.040.
- [98] T. Kobayashi, "[[Fundamentals] 2. Introduction to Data Structures for 2D and 3D Image Processing].," *Nihon Hoshasen Gijutsu Gakkai Zasshi*, vol. 79, no. 5, pp. 488–493, 2023, doi: 10.6009/jjrt.2023-2197.
- [99] I. Benaceur *et al.*, "Salt Stress Induces Contrasting Physiological and Biochemical Effects on Four Elite Date Palm Cultivars (*Phoenix dactylifera* L.) from Southeast Morocco.," *Plants (Basel, Switzerland)*, vol. 13, no. 2, Jan. 2024, doi: 10.3390/plants13020186.
- [100] N. De Leon, G. Young, and D. Wimer, "Impact of delayed transition off intravenous vasoactive agents for aortic dissection on intensive care unit length of stay.," *J. Thorac. Dis.*, vol. 15, no. 4, pp. 1595–1604, Apr. 2023, doi: 10.21037/jtd-22-1274.
- [101] M. Ludwig, B. Ludwig, A. Mikula, S. Biernat, J. Rudnicki, and K. Kaliszewski, "The Use of Artificial Intelligence in the Diagnosis and Classification of Thyroid Nodules: An Update.," *Cancers (Basel)*, vol. 15, no. 3, Jan. 2023, doi: 10.3390/cancers15030708.
- [102] J. L. Pascual *et al.*, "Hypertonic saline resuscitation of hemorrhagic shock diminishes neutrophil rolling and adherence to endothelium and reduces in vivo vascular leakage.," *Ann. Surg.*, vol. 236, no. 5, pp. 634–42, Nov. 2002, doi: 10.1097/00000658-200211000-00014.
- [103] K. el Khader *et al.*, "[Penis fracture: mechanism, evaluation, treatment and treatment outcome].," *Acta Urol. Belg.*, vol. 68, no. 3, pp. 56–8, Nov. 2000, [Online]. Available: <http://www.ncbi.nlm.nih.gov/pubmed/11678074>
- [104] Y. He *et al.*, "External Validation of a Machine Learning Model for Schizophrenia Classification.," *J. Clin. Med.*, vol. 13, no. 10, May 2024, doi: 10.3390/jcm13102970.
- [105] L. Huang, X. Chen, Y. Liu, and T. Li, "[A case with severe neurocysticercosis].," *Zhongguo Xue Xi Chong Bing Fang Zhi Za Zhi*, vol. 35, no. 1, pp. 111–112, May 2022, doi: 10.16250/j.32.1374.2021263.
- [106] E. R. Verhaar, W. J. C. van Keizerswaard, A. Knoflook, T. Balligand, and H. L. Ploegh, "Nanobody-based CAR NK cells for possible immunotherapy of MICA+ tumors.," *PNAS nexus*, vol. 3, no. 5, p. pgae184, May 2024, doi: 10.1093/pnasnexus/pgae184.
- [107] F. Guo *et al.*, "Designing Heteroatom-Codoped Iron Metal-Organic Framework for Promotional Photoreduction of Carbon Dioxide to Ethylene.," *Angew. Chem. Int. Ed. Engl.*, vol. 62, no. 14, p. e202216232, Mar. 2023, doi: 10.1002/anie.202216232.
- [108] M. Iwai *et al.*, "Establishment and characterization of novel high mucus-producing lung tumoroids derived from a patient with pulmonary solid adenocarcinoma.," *Hum. Cell*, vol. 37, no. 4, pp. 1194–1204, Jul. 2024, doi: 10.1007/s13577-024-01060-3.
- [109] J. S. Albert-Garay, J. R. Riesgo-Escovar, and R. Salceda, "High glucose concentrations induce oxidative stress by inhibiting Nrf2 expression in rat Müller retinal cells in vitro.," *Sci. Rep.*, vol. 12, no. 1, p. 1261, Jan. 2022, doi: 10.1038/s41598-022-05284-x.
- [110] S. Li, H. Yang, and X. Chen, "Protective effects of sulforaphane on diabetic retinopathy: activation of the Nrf2 pathway and inhibition of NLRP3 inflammasome formation.," *Exp. Anim.*, vol. 68, no. 2, pp. 221–231, May 2019, doi: 10.1538/expanim.18-0146.
- [111] D. Yuan, Y. Xu, L. Xue, W. Zhang, L. Gu, and Q. Liu, "Resveratrol protects against diabetic retinal

- ganglion cell damage by activating the Nrf2 signaling pathway,” *Heliyon*, vol. 10, no. 9, p. e30786, May 2024, doi: 10.1016/j.heliyon.2024.e30786.
- [112] M. Yi *et al.*, “Nrf2 Pathway and Oxidative Stress as a Common Target for Treatment of Diabetes and Its Comorbidities,” *Int. J. Mol. Sci.*, vol. 25, no. 2, Jan. 2024, doi: 10.3390/ijms25020821.
- [113] E. Teopompi *et al.*, “Arachidonic Acid and Docosahexaenoic Acid Metabolites in the Airways of Adults With Cystic Fibrosis: Effect of Docosahexaenoic Acid Supplementation,” *Front. Pharmacol.*, vol. 10, p. 938, 2019, doi: 10.3389/fphar.2019.00938.
- [114] G. Yang *et al.*, “Nrf2 prevents diabetic cardiomyopathy via antioxidant effect and normalization of glucose and lipid metabolism in the heart,” *J. Cell. Physiol.*, vol. 239, no. 2, p. e31149, Feb. 2024, doi: 10.1002/jcp.31149.
- [115] V. T. Rizk *et al.*, “Chemotherapy improves distant control in localized high-grade soft tissue sarcoma of the extremity/trunk,” *Clin. Sarcoma Res.*, vol. 10, p. 11, 2020, doi: 10.1186/s13569-020-00132-w.
- [116] H. Zang, R. O. Mathew, and T. Cui, “The Dark Side of Nrf2 in the Heart,” *Front. Physiol.*, vol. 11, Jul. 2020, doi: 10.3389/fphys.2020.00722.
- [117] Y. He, X. He, Y. Zhou, and S. Luo, “Clinical value of circulating tumor cells and hematological parameters in 617 Chinese patients with colorectal cancer: retrospective analysis,” *BMC Cancer*, vol. 23, no. 1, p. 707, Jul. 2023, doi: 10.1186/s12885-023-11204-7.
- [118] Z. Cheng *et al.*, “Two new predictors combined with quantum chemical parameters for the selection of oxidants and degradation of organic contaminants: A QSAR modeling study,” *Chemosphere*, vol. 240, p. 124928, Feb. 2020, doi: 10.1016/j.chemosphere.2019.124928.
- [119] M. Dodson, A. Shakya, A. Anandhan, J. Chen, J. G. N. Garcia, and D. D. Zhang, “NRF2 and Diabetes: The Good, the Bad, and the Complex,” *Diabetes*, vol. 71, no. 12, pp. 2463–2476, Dec. 2022, doi: 10.2337/db22-0623.
- [120] H. Zang, R. O. Mathew, and T. Cui, “The Dark Side of Nrf2 in the Heart,” *Front. Physiol.*, vol. 11, p. 722, 2020, doi: 10.3389/fphys.2020.00722.
- [121] H. Li, W. Dai, L. Xiao, L. Sun, and L. He, “Biopolymer-Based Nanosystems: Potential Novel Carriers for Kidney Drug Delivery,” *Pharmaceutics*, vol. 15, no. 8, Aug. 2023, doi: 10.3390/pharmaceutics15082150.
- [122] P. E. Pergola *et al.*, “Effect of bardoxolone methyl on kidney function in patients with T2D and Stage 3b-4 CKD,” *Am. J. Nephrol.*, vol. 33, no. 5, pp. 469–76, 2011, doi: 10.1159/000327599.
- [123] D. de Zeeuw *et al.*, “Bardoxolone methyl in type 2 diabetes and stage 4 chronic kidney disease,” *N. Engl. J. Med.*, vol. 369, no. 26, pp. 2492–503, Dec. 2013, doi: 10.1056/NEJMoa1306033.
- [124] P. Ruggenenti, “The CARDINAL Trial of Bardoxolone Methyl in Alport Syndrome: When Marketing Interests Prevail over Patients Clinical Needs,” *Nephron*, vol. 147, no. 8, pp. 465–469, 2023, doi: 10.1159/000529471.
- [125] B. A. Warady *et al.*, “Effects of Bardoxolone Methyl in Alport Syndrome,” *Clin. J. Am. Soc. Nephrol.*, vol. 17, no. 12, pp. 1763–1774, Dec. 2022, doi: 10.2215/CJN.02400222.
- [126] E. Nehlig, B. Waggegh, N. Millot, Y. Lalatonne, L. Motte, and E. Guénin, “Immobilized Pd on magnetic nanoparticles bearing proline as a highly efficient and retrievable Suzuki-Miyaura catalyst in aqueous media,” *Dalton Trans.*, vol. 44, no. 2, pp. 501–5, Jan. 2015, doi: 10.1039/c4dt02899f.
- [127] S.-C. Yang, T.-Y. Chen, and W. Chen, “Bilateral pulmonary cavities in a young female,” *QJM*, vol. 105, no. 5, pp. 477–8, May 2012, doi: 10.1093/qjmed/hcr021.
- [128] M. P. Chin *et al.*, “Mechanisms contributing to adverse cardiovascular events in patients with type 2 diabetes mellitus and stage 4 chronic kidney disease treated with bardoxolone methyl,” *Am. J. Nephrol.*, vol. 39, no. 6, pp. 499–508, 2014, doi: 10.1159/000362906.
- [129] G. F. Coughlan, B. M. Fullen, and C. McCarthy, “A national survey of clubs medical personnel, facilities and protocols in Irish Rugby Union,” *Ir. J. Med. Sci.*, vol. 183, no. 1, pp. 39–45, Mar. 2014, doi: 10.1007/s11845-013-0968-0.
- [130] B. O. Aydin, D. Anil, and Y. Demir, “Synthesis of N-alkylated pyrazolo[3,4-d]pyrimidine analogs and evaluation of acetylcholinesterase and carbonic anhydrase inhibition properties,” *Arch. Pharm. (Weinheim)*, vol. 354, no. 5, p. e2000330, May 2021, doi: 10.1002/ardp.202000330.
- [131] M. Ahuja *et al.*, “Distinct Nrf2 Signaling Mechanisms of Fumaric Acid Esters and Their Role in Neuroprotection against 1-Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine-Induced Experimental Parkinson’s-Like Disease,” *J. Neurosci.*, vol. 36, no. 23, pp. 6332–6351, Jun. 2016, doi: 10.1523/JNEUROSCI.0426-16.2016.
- [132] L. Abrankó, G. Williamson, S. Gardner, and A. Kerimi, “Comprehensive quantitative analysis of fatty-acyl-Coenzyme A species in biological samples by ultra-high performance liquid chromatography-tandem mass spectrometry harmonizing hydrophilic interaction and reversed phase chromatography,” *J. Chromatogr. A*, vol. 1534, pp. 111–122, Jan. 2018, doi: 10.1016/j.chroma.2017.12.052.
- [133] M.-H. Yang *et al.*, “Circular RNA expression in isoproterenol hydrochloride-induced cardiac hypertrophy,” *Aging (Albany. NY)*, vol. 12, no. 3,

- pp. 2530–2544, Feb. 2020, doi: 10.18632/aging.102761.
- [134] M. M. Ali *et al.*, “Impacts of molybdate and ferric chloride on biohythane production through two-stage anaerobic digestion of sulfate-rich hydrolyzed tofu processing residue,” *Bioresour. Technol.*, vol. 355, p. 127239, Jul. 2022, doi: 10.1016/j.biortech.2022.127239.
- [135] S. Sainz de la Maza *et al.*, “Early predictive risk factors for dimethyl fumarate-associated lymphopenia in patients with multiple sclerosis,” *Mult. Scler. Relat. Disord.*, vol. 59, p. 103669, Mar. 2022, doi: 10.1016/j.msard.2022.103669.
- [136] C. Ma, D. Zhang, Q. Ma, Y. Liu, and Y. Yang, “Arbutin inhibits inflammation and apoptosis by enhancing autophagy via SIRT1,” *Adv. Clin. Exp. Med.*, vol. 30, no. 5, pp. 535–544, May 2021, doi: 10.17219/acem/133493.
- [137] A. T. Ince, E. B. Keskin, B. S. Gultepe, K. Kochan, I. H. Koker, and H. Senturk, “The relationship of Serum Histone H3.3 and H4 with chronic Hepatitis B,” *J. Pak. Med. Assoc.*, vol. 70, no. 9, pp. 1596–1600, Sep. 2020, doi: 10.5455/JPMA.19365.
- [138] M. Fuschachi, “Gendered Genital Modifications (GGMo): a universalistic anthropological approach. Response to Catalan and Emilova,” *Int. J. Impot. Res.*, vol. 35, no. 1, pp. 18–20, Feb. 2023, doi: 10.1038/s41443-022-00643-8.
- [139] I. Feldman, D. S. Shapiro, R. Ellis, and R. Friedman, “Differentiating between severe hypertension and thrombocytopenic purpura as the cause of thrombotic microangiopathy in a patient with Castleman disease: a case report and literature review,” *Oxford Med. case reports*, vol. 2023, no. 6, p. omad059, Jun. 2023, doi: 10.1093/omcr/omad059.
- [140] H. Kanda and K. Yamawaki, “Bardoxolone methyl: drug development for diabetic kidney disease,” *Clin. Exp. Nephrol.*, vol. 24, no. 10, pp. 857–864, Oct. 2020, doi: 10.1007/s10157-020-01917-5.
- [141] K. Sekiguchi *et al.*, “Metabolome Characteristics of Liver Autophagy Deficiency under Starvation Conditions in Infancy,” *Nutrients*, vol. 13, no. 9, Aug. 2021, doi: 10.3390/nu13093026.
- [142] S. Singhal and S. K. Mittal, “Readmission after esophageal resection for esophageal cancer: incidence and risk factors,” *J. Thorac. Dis.*, vol. 12, no. 9, pp. 4608–4611, Sep. 2020, doi: 10.21037/jtd-20-1670.
- [143] T. Shoda *et al.*, “Eosinophilic oesophagitis endotype classification by molecular, clinical, and histopathological analyses: a cross-sectional study,” *lancet. Gastroenterol. Hepatol.*, vol. 3, no. 7, pp. 477–488, Jul. 2018, doi: 10.1016/S2468-1253(18)30096-7.
- [144] M. E. Alto, A. V. Nicasio, R. Stewart, T. D. Rodríguez-Sanfiorenzo, G. González-Eliás, and R. Orengo-Aguayo, “Provision of mental health services immediately following a natural disaster: Experiences after Hurricane Maria in Puerto Rico,” *J. Emerg. Manag. (Weston, Mass.)*, vol. 19, no. 8 (Spec Issue on Puerto Rico), pp. 167–175, 2021, doi: 10.5055/jem.0634.
- [145] S. Casadó-Llombart *et al.*, “Gene Variation at Immunomodulatory and Cell Adhesion Molecules Loci Impacts Primary Sjögren’s Syndrome,” *Front. Med.*, vol. 9, p. 822290, 2022, doi: 10.3389/fmed.2022.822290.
- [146] L. A. Parsels, D. R. Wahl, C. Koschmann, M. A. Morgan, and Q. Zhang, “Developing H3K27M mutant selective radiosensitization strategies in diffuse intrinsic pontine glioma,” *Neoplasia*, vol. 37, p. 100881, Mar. 2023, doi: 10.1016/j.neo.2023.100881.
- [147] A. J. Campbell, S. J. Mather, and D. E. Elder, “Obstructive sleep apnea risk factors and symptoms in children with a known parental obstructive sleep apnea diagnosis,” *Sleep Med.*, vol. 78, pp. 149–152, Feb. 2021, doi: 10.1016/j.sleep.2020.12.030.
- [148] Y. Cui, D. Chen, H. Lin, and Y. Tao, “The association between low birth weight and/or preterm birth and dental caries -A systematic review and meta-analysis,” *Int. J. Dent. Hyg.*, vol. 21, no. 3, pp. 599–610, Aug. 2023, doi: 10.1111/idh.12651.
- [149] D. M. Tanase *et al.*, “Oxidative Stress and NRF2/KEAP1/ARE Pathway in Diabetic Kidney Disease (DKD): New Perspectives,” *Biomolecules*, vol. 12, no. 9, Sep. 2022, doi: 10.3390/biom12091227.
- [150] T. Suzuki, J. Takahashi, and M. Yamamoto, “Molecular Basis of the KEAP1-NRF2 Signaling Pathway,” *Mol. Cells*, vol. 46, no. 3, pp. 133–141, Mar. 2023, doi: 10.14348/molcells.2023.0028.
- [151] T. Yamazaki, I. Mimura, T. Tanaka, and M. Nangaku, “Treatment of Diabetic Kidney Disease: Current and Future,” *Diabetes Metab. J.*, vol. 45, no. 1, pp. 11–26, Jan. 2021, doi: 10.4093/dmj.2020.0217.
- [152] X. Dong *et al.*, “Broad-Spectrum Polymeric Nanoquencher as an Efficient Fluorescence Sensing Platform for Biomolecular Detection,” *ACS sensors*, vol. 6, no. 8, pp. 3102–3111, Aug. 2021, doi: 10.1021/acssensors.1c01277.
- [153] E. Prince *et al.*, “Microfluidic Arrays of Breast Tumor Spheroids for Drug Screening and Personalized Cancer Therapies,” *Adv. Healthc. Mater.*, vol. 11, no. 1, p. e2101085, Jan. 2022, doi: 10.1002/adhm.202101085.
- [154] D. D. Andrews, V. R. Fajt, K. C. Baker, R. V. Blair, S. H. Jones, and G. L. Dobek, “A Comparison of Buprenorphine, Sustained release Buprenorphine, and High concentration Buprenorphine in Male New Zealand White Rabbits,” *J. Am. Assoc. Lab.*

- Anim. Sci.*, vol. 59, no. 5, pp. 546–556, Sep. 2020, doi: 10.30802/AALAS-JAALAS-19-000132.
- [155] A. Boccanelli and G. Bottà, “New prevention scenarios: polygenic risk,” *Eur. Heart J. Suppl.*, vol. 23, no. Suppl E, pp. E33–E35, Oct. 2021, doi: 10.1093/eurheartj/suab093.
- [156] E. H. C. Brun *et al.*, “Stability and Activity of Interferon Beta to Treat Idiopathic Pulmonary Fibrosis with Different Nebulizer Technologies,” *J. Aerosol Med. Pulm. Drug Deliv.*, vol. 36, no. 2, pp. 55–64, Apr. 2023, doi: 10.1089/jamp.2022.0020.
- [157] J. Shah *et al.*, “Evaluation of the Efficacy and Safety of Rheum rhaponticum Root Extract (ERr 731) for Menopausal Symptoms in Perimenopausal Indian Women: An Interim Analysis,” *J. Midlife. Health*, vol. 12, no. 2, pp. 108–115, 2021, doi: 10.4103/jmh.jmh_86_21.
- [158] A. E. M’Koma, “Inflammatory Bowel Disease: Clinical Diagnosis and Pharmaceutical Management,” *Med. Res. Arch.*, vol. 11, no. 1, Jan. 2023, doi: 10.18103/mra.v11i1.3135.