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Review Article

The Promotion of Antioxidant and Anti-Inflammatory Activity by Nrf2 Amplifier is A Potential Technique in Diabetic Wound Healing — A Review

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Abstract

Wound healing is a complicated, organised process that includes numerous phases that connect diverse cellular events and activate several intracellular molecular pathways in injured cells and tissues. Delay in wound healing owing to high levels of oxidative stress is a major difficulty in various metabolic illnesses, including diabetes mellitus. Several therapeutic wound dressing materials and methods, such as hyperbaric oxygen treatment and negative pressure wound therapy, have been developed to speed up wound healing and restore cellular homeostasis. A significant advance has been made in locating transcriptional regulators involved in wound healing. The redox-sensitive transcription factor nuclear factor erythroid 2-related factor 2 (Nrf2) is the major regulator of antioxidant defence regulation, inducing the expression of cytoprotective genes and increasing the generation of antioxidants that scavenge free radicals. Activators of Nrf2 have been shown to reduce oxidative stress and improve wound healing in a variety of pathophysiological situations, including diabetes and its consequences such as diabetic foot ulcers, chronic kidney disease, and diabetic nephropathy. Several therapeutic chemicals have been discovered to alleviate oxidative stress and consequently increase cell proliferation. Angiogenesis results in tissue healing through activating the transcription factor Nrf2. This review focuses on the role of Nrf2-mediated antioxidant gene expression in diabetic wound healing.

Introduction

The most serious and life-threatening complication of Type II diabetes mellitus (T2DM) is a diabetic foot ulcer (DFU).[1] Diabetic wounds are produced by chronic inflammation and impose a considerable medical and financial burden on the patient. Nearly 25% of patients with type II diabetes mellitus suffer from diabetic foot ulcers.[2] This is due to dysregulated immune responses, hyperglycaemia, hypoxia, and chronic inflammation.[3] It is estimated that one lower limb is amputated every 30 seconds.[4] Diabetic foot patients are becoming more common in both urban and rural India, with foot ulcers accounting for 85% of amputations. Almost 75% of these amputations are performed on a neuropathic foot, resulting in an infection that could have been avoided. In India, neuropathic lesions account for 80% of foot ulcers, with neuro ischemic lesions accounting for the remaining 20%. Peripheral artery disease (PAD) affects 3.2% of diabetic patients before the age of 50 and 33% of diabetic patients beyond the age of 80. This rise is linked to both age and the duration of diabetes.[5] A wound typically heals in 3–4 weeks; however, this might vary depending on the kind and intricacy of the wound. Chronic wound healing is slowed due to complicated cellular and molecular activities. Reactive oxygen species, ischemia, infection, excessive production of inflammatory cytokines, immunological suppression, depletion of extracellular matrix (ECM), and elevated levels of matrix metalloproteinases (MMP) all contribute to chronic inflammation. The vast majority of chronic wounds are classified as one of three types: venous ulcers, pressure ulcers, and diabetic ulcers, with a fourth kind caused by arterial ischemia. Furthermore, many reports have identified that chronic oxidative stress is associated with the progression of diabetic complications and impaired wound healing.[6] Hence, transcription nuclear factor-E2–related factor (NrF2) regulates the adaptive response to exogenous and endogenous oxidative stress, as well as cell migration, proliferation, apoptosis, and differentiation.[7]

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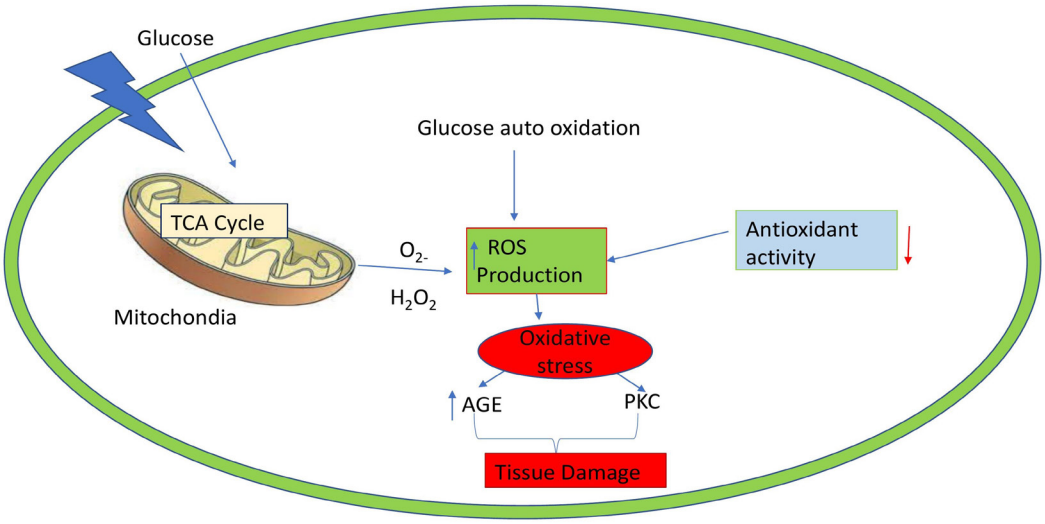

Figure 1. Hyperglycemia induced oxidative stress and tissue damage.

Hyperglycaemia Induced Oxidative Stress and Inflammation

Hyperglycaemia can alter metabolic functions resulting in serious micro and macrovascular dysfunction. The endothelial cells lose their integrity and become susceptible to apoptosis.[8] Monocytes may be activated and induce inflammatory mediators such as diacylglycerol protein kinase C (PKC) and nuclear factor-kB (NF-kB), elevating oxidative stress. Chronic inflammation is the hallmark of diabetes patients, where infiltration of macrophages, lymphocytes, and plasma cells and the release of pro-inflammatory cytokines take place, leading to tissue damage.[9] Hyperglycaemia increases the use of oxygen, resulting in cellular hypoxia and facilitating the formation of reactive oxygen species.[10] The overproduction of ROS causes cellular damage by interacting with mitochondrial DNA and proteins (Figure 1).

Nrf2 and Keap 1

With 605 amino acids and seven domains ranging from Neh1 to Neh7, Nrf2 is a member of the Cap 'n' Collar (CNC) family. (Figure 2a) The Keap1 binding is regulated by the Neh2 domain. The transactivation domains Neh 4, Neh 5, and Neh 3 mediate the interaction between Nrf2 and other coactivators.[11] The cytoplasmic translocation of Nrf2 is controlled by Neh5. The serine-rich Neh6 domain regulates Nrf2 ubiquitination, which leads to proteasomal degradation.[12] The basic portion of the Neh1 domain is a leucine zipper that governs DNA binding and nuclear antioxidant response element (ARE) signalling. By increasing retinoic X receptor binding to Nrf2, Neh7 suppresses Nrf2-ARE binding.[13] The redox homeostasis-maintaining Nrf2/kelch-like Keap1 pathway is impaired in T2DM. During normal conditions, Keap1 interacts with Nrf2 and the cell's actin cytoskeleton to sequester Nrf2 in the cytoplasm and increase ubiquitination and destruction of Nrf2.[14] Certain cysteine-rich oxidant and electrophile sensor areas of Keap1 are covalently changed in the presence of oxidative stress, blocking Nrf2 ubiquitination. It is also found that Nrf2 dissociates from its repressor Keap1 and translocate to the nucleus, where it forms heterodimers with the musculoaponeurotic fibrosarcoma (Maf) protein and binds to Maf recognition element sequences such as the ARE and the electrophile response element (EpRE).[15]

Nrf2 and Keap-1 Interaction

The activity of Nrf2 is strictly controlled by its cytoplasmic repressor protein, Keap1. Keap1, also known as Nrf2 inhibitor, is a 624 amino acid dimeric protein consisting of various domains.[16] (Figure 2b) The domain structures are the N-terminal region (NTR), broad-complex, tram track, and bric-a-brac (BTB) domain, the intervening region (IVR) or BACK domain, the double glycine repeats (DGR) or beta-propeller domain, which is also known as the kelch domain, and the C-terminal region (CTR).[17] The flexible IVR connects the BTB and Kelch domains of Keap1. The interaction of Nrf2 and Keap1, is explained by the "hinge and latch" concept. (Figure 2c) The kelch domain of the homo dimeric Keap1 binds to the Neh2 DLG motif, which has a lower affinity, and the ETGE motif, which has a higher affinity. This makes a complex.[18] This NRF2-Keap1 complex makes it so that a CUL3-dependent E3-ubiquitin ligase adds ubiquitin to Nrf2, which then makes the proteasome break down Nrf2.[19] Hence, Nrf2 is continuously targeted for ubiquitous proteasomal degradation and thus has a very short half-life of fewer than 20 min.[20] The binding of Keap1 to the DLG and ETGE motifs of the Neh2 domain in Nrf2 is essential for Nrf2 ubiquitination and degradation. Once attached, Nrf2 gets properly configured for ubiquitination by Cullin 3 (CuI3).[21] The BTB domain of Keap1 binds to CuI3, resulting in the formation of a ubiquitin 3-ligase complex that ubiquitinates the seven [Asp-Leu-Gly (DLG) and Glu-Thr-Gly-Glu (ETGE)] residues situated between the two motifs in Nrf2. This complex further constitutively polyubiquitinates Nrf2 by adding several ubiquitins to it, until it gets activated, after which it is degraded by the

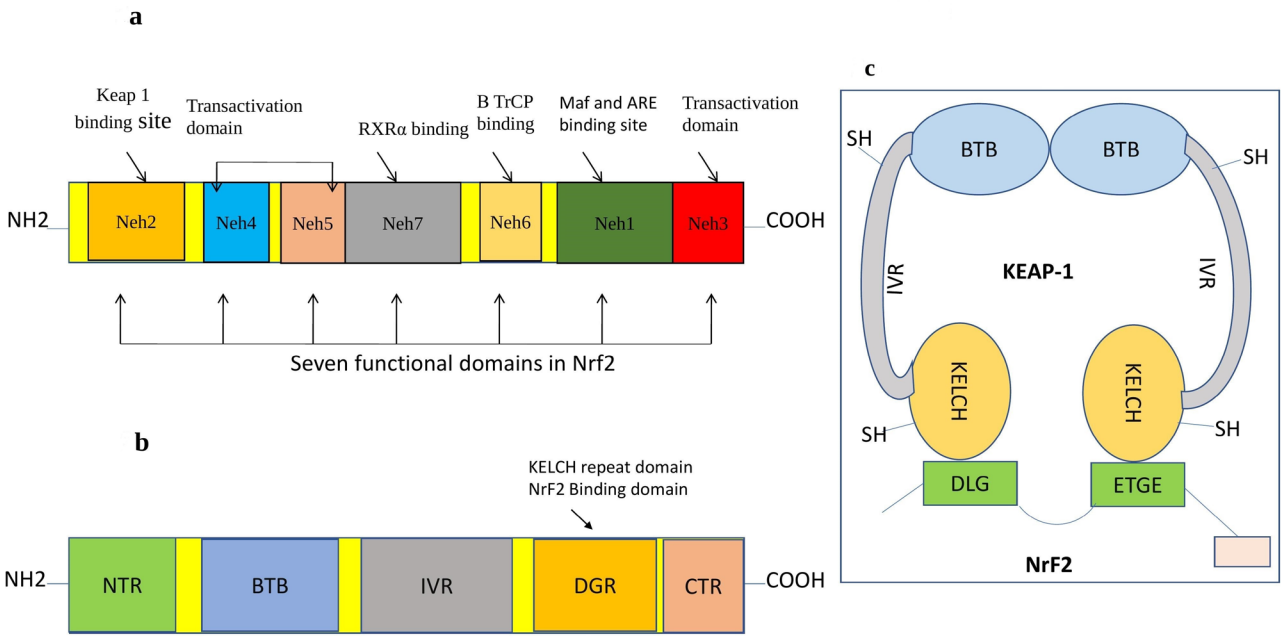

Figure 2. Structure of (a) Nrf2, (b) Keap-1, and (c) hinge and latch concept of KEAP-1 and NrF2 complex.

26S proteasome.[22] Human Keap1 has 27 cysteine residues, and Cys151, Cys273, and Cys288 are important for the ubiquitination of Nrf2 when Keap1 is involved.[23]

Mechanism of Action of Nrf2 Activators

Nrf2 is a transcription factor that controls how many phase I and phase II antioxidant enzymes and anti-inflammatory mediators are made.[24] It is an important part of the body's defence against oxidative stress, inflammation, and other problems that can happen when a diabetic wound heals.[25] Many diseases caused by oxidative stress, such as diabetes, heart disease, and neurological disease, have been linked to Nrf2 dysregulation.[26] This makes Nrf2 activators excellent agents to increase antioxidant capacity, decrease inflammation, and alleviate pathology in diabetic wound healing.[27]

Nuclear factor E2-related factor (Nrf2) is a transcription factor that controls the expression of as many as 200 genes.[28] The proteins encoded by Nrf2 genes control several functions, like anti-inflammation, antioxidant defense, apoptosis, detoxification, removal of oxidised proteins by the proteasome, and DNA repair.[29] Keap-1 is a regulatory protein that regulates the levels of Nrf2 in the cytoplasm of the cell. The Neh2 domain of Nrf2 binds to the barrel structure of Keap-1 in basal conditions.[30] After this, Cullin-3 binds to the Keap-1-Nrf2 complex, which causes the ubiquitin 3-ligase complex to be made.[31] The ubiquitin 3-ligase complex binds to many ubiquitin molecules, resulting in polyubiquitination of Nrf2, which serves as a signal for proteasomal degradation. Keap-1 contains a lot of cysteines in its structure, and the free sulfhydryl (-SH) of cysteine helps Keap-1 act as a sensor of oxidative stress.[32] During oxidative stress, electrophiles alkylate Keap-1 and prevent Keap-1 from degrading Nrf2. This leads to the accumulation of recently synthesised Nrf2, which increases the antioxidant potential by promoting the transcription of antioxidant and detoxifying genes.[33] In an alternative pathway, Nrf2 is degraded by phosphorylation by glycogen synthase kinase 3β (GSK3β). This degradation of Nrf2 by GSK3β is also blocked by elevated levels of oxidants that lead to the accumulation of freshly synthesised Nrf2.[34] In another pathway, Keap-1 itself is degraded by p62. In this pathway, p62 is phosphorylated by TANK-binding kinase 1 (TBK1) and the mechanistic target of rapamycin complex 1 (mTORC1). The phosphorylated p62 forms a complex with KEAP-1, and this complex is degraded by autophagy in cells. All of these pathways are turned on by oxidants, which causes a buildup of newly made Nrf2.[35] Nrf2 escapes breakdown into the nucleus and forms heterodimers with sMaf (Nrf2/sMaf).[36] In the nucleus, the activity of Nrf2 is negatively regulated by Bach-1, which competes with Nrf2 to form heterodimers with sMaf.[37] As many as 200 cytoprotective genes are turned on when Nrf2/sMaf binds to antioxidant response elements.[38] Among the genes activated by Nrf2 in response to oxidative stress are glutathione *S*-transferases (GSTs), nicotinamide adenine dinucleotide phosphate (NAD(P)H), quinone oxidoreductase 1 (NQO1), manganese superoxide dismutase (MnSOD), heme oxygenase 1 (HO-1), glutamate-cysteine ligase (GCL), and GSTs.[39] Hence it produces an antioxidant effect, as shown in Figure 3. Oxidative stress has been linked to many diseases, and the production of ROS is a key part of how inflammatory reactions develop.[40] Several studies have shown that the Nrf2 signalling pathway is important for both cytosolic and mitochondrial ROS production. This is because the mitochondrion is the main place where ROS are made in both healthy and unhealthy cells.[41]

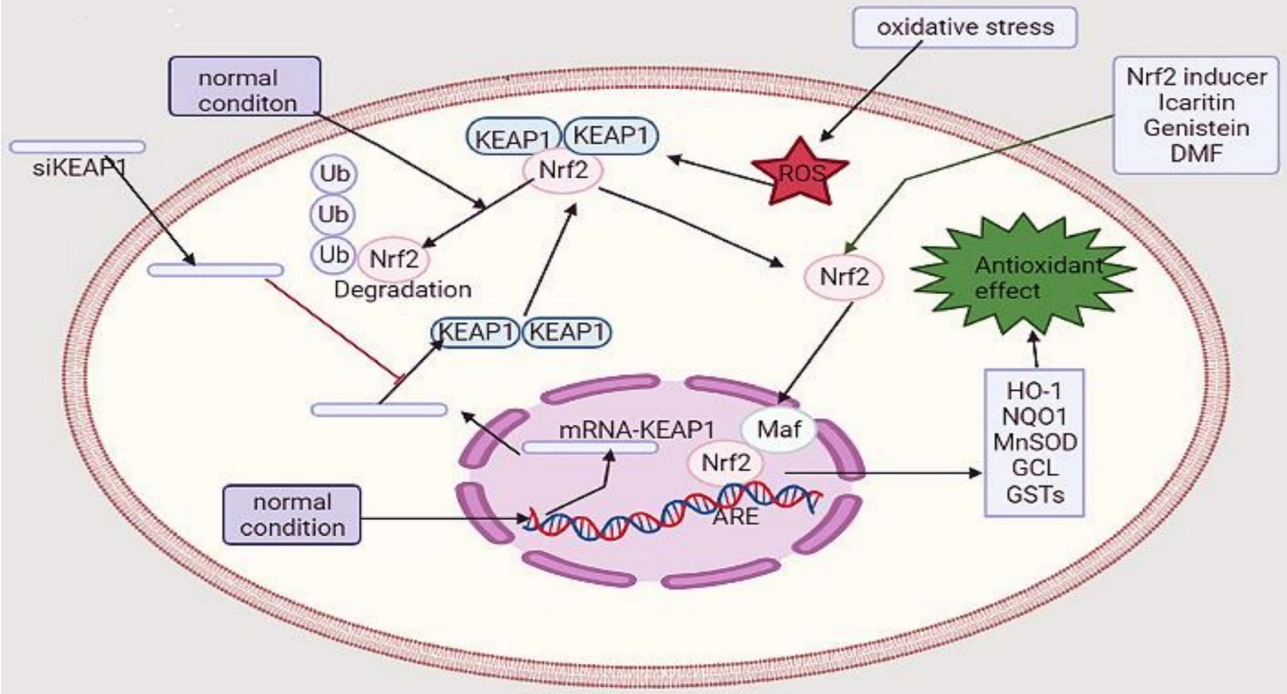

Figure 3. Nrf2 activators and antioxidant gene expression.

Role of NrF2 in Diabetic Wound Healing

The way a diabetic wound heals is different from how a normal wound heals because of pathophysiological problems (like less blood flow and slower healing).[42] Chronic oxidative stress has been associated with the progression of diabetic issues and reduced wound healing as a result of intrinsic (wound contraction and matrix turnover) and exogenous causes (infection and repetitive trauma).[43] Transcriptional controllers are important for diabetic wound healing because they turn on or turn off gene expression in a complex cellular and molecular process at different stages of wound healing.[44] At the wound site, the signal transducer and activator of transcription 3 play critical functions in keratinocyte proliferation and differentiation (STAT3).[45] By activating and maintaining antioxidant proteins, the leucine zipper protein Nrf2 protects cells from oxidative damage. The transcription factor Nrf2 regulates cell migration, proliferation, apoptosis, and differentiation, as well as the adaptive response to external and internal oxidative stress.[46] ARE has unique features, such as cAMP (cyclic adenosine monophosphate) response element-binding protein (CREBP)/p300, which controls ARE-induced antioxidant gene transcription, which decreases oxidative stress.[47] During oxidative stress, Nrf2 separates from Keap1 and dimerizes with the small Maf protein in the nucleus, as well as ARE coactivators such as the CREBP-binding protein CBP/p. As a result, Nrf2 is the primary redox regulator. Nrf2 also suppresses NF-kB translocation to the nucleus, which reduces the production of proinflammatory cytokines, lowering long-term inflammation and facilitating diabetic wound healing[48] (Figure 4). The use of Nrf2 activators as a topical treatment for diabetic wounds is effective.

Nrf2 Activation and Inflammasome Inhibition

In general, Nrf2 activation is thought to have anti-inflammatory effects, but Nrf2 target genes are not directly engaged in inflammation, such as through the control of genes producing proinflammatory cytokines.[49] Inflammation, on the other hand, is related to oxidative stress and ROS, which are essential for pathogen elimination or avoidance. It is plausible to believe that Nrf2 activation minimises the deleterious effects of ROS on inflamed tissue cells and, ultimately, inflammation.[50] Furthermore, the idea that NLR family pyrin domain containing 3 (NLRP3) inflammasome activation is controlled by ROS and oxidative stress provides an even more straightforward explanation for Nrf2 signalling anti-inflammatory action.[51] As a result, multiple studies have been published since the introduction of the hypothesis that ROS regulates NLRP3 inflammasome activation, demonstrating a link between Nrf2 activation and NLRP3 inflammasome suppression in many different disease models associated with inflammation.[52] The majority of this research employed plant-derived compounds that are well-known in Eastern, traditional Chinese medicine for their effectiveness in treating inflammatory diseases in patients. Nonetheless, treatment of cells or animals with these chemicals produces Nrf2 activation and NLRP3 inflammasome suppression in each case.[53] Since the majority of research is based on animal models for inflammatory illnesses in which complete tissues are studied, it is not always clear if Nrf2 activation and NLRP3 inflammasome suppression occur in the same cells, surrounding cells, or even distinct cells.[54]

Nrf2 Activators

Various phytochemicals have also been shown to maintain

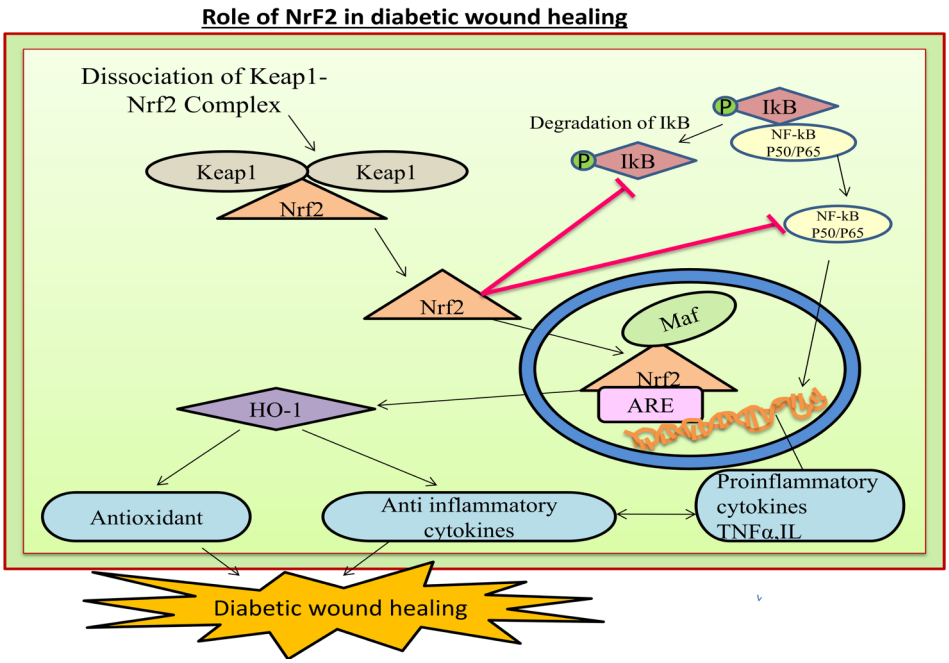

Figure 4. Role of HO-1 gene expression in diabetic wound healing.

Table 1. Nrf2 activators for diabetic wound healing in clinical trials.

No.	Clinical trial ID	Drug /Study	Patients enrolled	Route of administration	Status
1	NCT00815217	Adipose derived stem cell	25	Intramuscular	Recruiting
2	NCT03248466	Autologous BM-MSC Early Phase -I	60	Transplantation	Recruiting
3	NCT00955669	BM-MSC/ MNC	40	Transplantation	Completed
4	NCT02619877	Allogenic AMSC: Phase-II	59	Topical	Completed
5	NCT03865394	Autologous AMSC Phase I & II	20	Topical	Recruiting
6	NCT03267784	Allogenic ABCB-5 positive MSCs Phase I & II	37	Topical	Recruiting
7	NCT02672280	UC-MSC Phase I & II	30	Topical	Unknown
8	NCT01686139	Allogenic BM-MSC	12	Topical and intramuscular	Unknown
9	Autologous bio graft	BM-MSC case study	Unknown	Topical	Unknown
10	Autologous BM derived cells: randomized control studies	BM-MSC case study	48	Topical and intra muscular	CTRI / 2009/ 091/ 000250

redox equilibrium by activating Nrf2 and numerous kinases, which increase phase II antiapoptotic genes and enzymes. Mesenchymal stem cell therapies have also proven to activate NrF2 signalling to promote an antioxidant effect in diabetic wound healing.[55] Some of them are listed below: (Table 1).

Conclusion

Numerous studies have highlighted the promising potential of antioxidant therapy in diabetic wound healing, given the central role of oxidative stress in the pathology of chronic diabetic wounds. The NF-kB and Nrf2/Keap1 pathways are key pathways in oxidative stress; therefore, therapies targeting these pathways have been shown to effectively promote diabetic wound healing. Natural Nrf2 activators derived from plant sources as well as synthetic anti-inflammatory drugs require further experimental validation. Research for efficient therapeutic agents promoting Nrf2 activation came up with some new drugs that have entered clinical trials and will undoubtedly provide advancement in the management of diabetic wound healing in the near future. As a result, the current review would help to refine our understanding of the Nrf2 signalling pathway's interaction with the expression of associated target genes, as well as support the hypothesis that Nrf2 inducers have a high potential as anti-inflammatory therapeutic agents. Despite significant breakthroughs in the treatment of diabetic wounds, their involvement in metabolic diseases such as diabetes mellitus and its repercussions remain uncertain. The activation of NrF2 and HO-1 will be achieved by using NrF2 inducers as nanoparticles and integrating innovative drug delivery

methods, perhaps leading to more effective diabetic wound healing therapies.

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Author Contributions

Tharani Mohanasundaram: Conceptualization, Writing - Original Draft. Vadivelan Ramachandran: Validation, Supervision, Writing - Review & Editing. Bhargav Bhongiri: Formal Analysis, Emdormi Rymbai: Software. Rinu Mary Xavier: Investigation. Gaddam Narasimha Rao: Investigation. Chintha Narendar: Investigation.

Conflict of Interest

The authors report no conflicts of interest.

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