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Review Article

Potential effects and mechanistic pathways of sodium-glucose cotransporter 2 inhibitors in diabetic wound healing: A comprehensive review

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Abstract

Diabetes mellitus (DM) and its associated morbidities embody a significant challenge and considerable strain on healthcare sectors globally. Significantly, impaired wound healing is a common complication associated with poorly managed diabetes, often leading to adverse consequences. The diabetic wound results from a perpetual state of localized inflammation induced by the over-accumulation of proinflammatory cells along with their cytokines and proteases. Sodium-glucose cotransporter-2 (SGLT-2) inhibitors represent one of the classes of novel antidiabetic drugs that have shown promising effects in promoting wound healing, largely due to their anti-inflammatory properties. The findings in this review were synthesized using authoritative sources and advanced research tools. Searches on platforms such as Google Scholar, PubMed, Scopus, and JSTOR yielded high-quality peer-reviewed articles. Furthermore, the use of generic medication names referenced in this study, combined with terms such as "wound healing" and "diabetes," facilitated a precise and comprehensive analysis of their therapeutic implications. Reference materials were sourced from eminent journals like ScienceDirect and The Lancet, providing a robust empirical foundation, while esteemed repositories such as the World Health Organization (WHO) enriched the discourse with authoritative insights. This review focused on the potential impact of SGLT-2 inhibitors, namely, empagliflozin and dapagliflozin, on promoting wound healing. It will also discuss the mechanistic pathways by which this process is thought to occur. The current pool of evidence favors the notion that certain antidiabetic medications possess anti-inflammatory properties that aid in preventing wounds from being in a perpetual inflammatory stage; this is thought to be accomplished by the downregulation of proinflammatory cytokines, upregulation of specific growth factors, reduction of metalloproteinases, promotion of angiogenesis, and enhancement of epithelialization. Nevertheless, this remains a fertile area for further research before these antidiabetic medications may be incorporated into clinical guidelines as therapeutic agents in the management of chronic wounds.

Keywords: *Diabetes mellitus (DM), Wound healing, Sodium-glucose cotransporter 2 (SGLT-2) inhibitor, Empagliflozin, Dapagliflozin*

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INTRODUCTION

Wound healing

Overview of wounds and their implications

As the body's most expansive organ, the skin plays a vital role in protecting the moisture-filled internal organs from the dry external environment [1]. As a vital immune system component, the skin provides a protective barrier and an active defense against external threats. Its immune cells maintain balance, prevent infections, and support wound healing. However, disruptions to this process often result in inflammation and delayed recovery of wounds [2]. A wound is characterized by a disruption in the continuous and intact nature of living tissue at the cellular, anatomical, and functional levels, typically presenting as a rupture in the epithelial layer that may further affect the underlying tissue's structure and function [3]. Recent reports indicate that almost one billion people around the world are affected by acute and chronic wounds, a staggering figure that results in significant financial costs [4]. Wounds may arise from a range of causes, such as surgical interventions, physical injuries, external influences like burns, pressure, lacerations, and health issues like vascular disorders or diabetes [5]. The persistence of wounds diminishes the quality of life, driving up healthcare costs by causing psychological strain, prolonged hospital stays, and an elevated risk of both morbidity and mortality. These reasons have led to the designation of wounds as a “Silent Epidemic.” [6]. Notably, diabetes mellitus (DM) is a major contributor to wound complications, as it is linked to numerous pathological alterations that significantly impede the wound healing process [7]. Presently, nearly 500 million individuals are believed to be affected by DM, with projections indicating a substantial rise in prevalence in the coming years. In the United States alone, annual expenditures exceed $300 billion, encompassing both healthcare costs and economic losses from reduced productivity due to DM [8]. Consequently, creating new treatment strategies to enhance the healing process presents a significant challenge.

METHODS

The conclusions presented in this review were meticulously synthesized through the integration of authoritative academic resources and advanced research methodologies. Extensive searches on platforms such as Google Scholar, PubMed, Scopus, and JSTOR were conducted to obtain high-quality, peer-reviewed literature. The inclusion of generic drug names, particularly, *empagliflozin* and *dapagliflozin*, combined with critical terms such as "wound healing" and "diabetes," along with keywords such as "anti-inflammatory" and "antidiabetic," facilitated a detailed and comprehensive exploration of their therapeutic implications. Reference materials were sourced from eminent journals such as ScienceDirect and The Lancet, establishing a robust empirical foundation, while reputable repositories such as the World Health Organization (WHO) enriched the analysis with globally recognized authoritative insights.

Wound healing and its distinct phases

The healing of wounds is a complex and ever-changing mechanism crucial for repairing damaged skin and maintaining tissue balance, requiring the precise orchestration of various cellular elements, including different cell types, as well as key growth factors and cytokines [9]. It involves a series of overlapping and interdependent phases, including hemostasis, inflammation, proliferation, and remodeling. Each of these stages is crucial for ensuring the effective progression of the healing process (Figure 1) [10].

Hemostasis

Primary hemostasis is a crucial initial step in wound healing, where platelets aggregate at the site of injury through their interaction with proteins of the extracellular matrix (ECM), including collagen and fibronectin. This aggregation forms the foundation of a clot, which is subsequently reinforced by secondary hemostasis. During this phase, the coagulation cascade is activated, leading to the conversion of fibrinogen into a fibrin network that captures red blood cells, thereby stabilizing the clot and halting further bleeding [9]. Platelets are crucial in promoting immune cell recruitment to the site of injury. This is achieved either by trapping the immune cells within the eschar or by secreting a variety of factors that stimulate local skin cells, such as fibroblasts and keratinocytes. These growth factors play a significant role in activating the cells, which in turn aids in tissue regeneration and repair [11].

Inflammation

The inflammatory phase generally spans several days and is marked by the critical process of leukocyte chemotaxis, which directs immune cells to the injury site to facilitate the efficient removal of cellular debris and pathogens [9]. Neutrophils are the initial immune cells to

respond to injury, migrating from damaged blood vessels under the influence of various chemoattractants, including bacterial endotoxins such as lipopolysaccharide (LPS) and tumor necrosis factor-alpha (TNF-α). These cells are pivotal in phagocytosis, as well as in releasing reactive oxygen species (ROS), proteolytic enzymes, and eicosanoids, all of which contribute to the defense and decontamination of the wound [12]. Additionally, monocytes from the bloodstream migrate into the wound tissue, where they undergo differentiation into macrophages in response to the surrounding environment [13]. Moreover, pro-inflammatory signals activate macrophages, prompting them to release ROS and inflammatory cytokines [12].

Proliferation

The formation of granulation tissue, re-epithelialization, and neovascularization comprise the essential steps that take place during proliferation, extending over several weeks [9]. In this phase, critical for angiogenesis and ECM formation, the activation of endothelial cells, keratinocytes, macrophages, and fibroblasts plays a crucial role. These cell types are essential for processes such as matrix synthesis, and the formation of new blood vessels [12]. Notably, incorporating unorganized collagen, predominantly the immature type III collagen, into the temporary extracellular matrix, fibroblasts are essential during this phase, contributing to the formation and stabilization of the matrix structure [14]. Enhanced collagen production and promotion of wound contraction are facilitated by the differentiation of fibroblasts into myofibroblasts at the injury site, triggered by specific cytokine signals [14]. During the first few days following the injury, fibroblasts migrate significantly to the wound site [15].

Remodeling

Wound remodeling is a prolonged phase, potentially lasting for years, during which excess collagen is degraded, and wound contraction is initiated. This ultimately promotes increased tissue strength and the restoration of structural integrity [9]. Around 30 to 37 days after the injury, granulation tissue is replaced by scar tissue, with collagen synthesis continuing throughout this period. Over the next year, type I fibrillar collagen gradually becomes the dominant form, replacing type III reticular collagen [14].

Diabetic wound

Diabetic wounds represent a significant clinical challenge, primarily encompassing leg ulcers and diabetic foot ulcers. Diabetes adversely impacts the wound-healing process by disrupting each phase of tissue repair, leading to prolonged healing times and contributing to detrimental effects on quality of life, increased morbidity, and higher mortality rates [16]. In addition, diabetic wounds are marked by insufficient angiogenesis and an extended inflammatory response, both of which significantly impair effective tissue repair [7]. It is anticipated that between one out of three and one out of five people diagnosed with DM will experience a long-lasting, unhealed lesion, such as a diabetic foot ulcer (DFU), over the course of their life [17].

Determinants impacting the healing process in diabetic wounds

The challenges in healing diabetic wounds can be attributed to several factors, including elevated blood glucose levels, endotheliopathy, impaired immune function, neuropathy, and an increased susceptibility to infection [18].

High blood sugar and diabetic endotheliopathy

Endotheliopathy is defined as an abnormal vessel wall function, which in chronic diabetes results in reduced blood flow to distant areas. Interestingly, it also leads to excessive blood flow at the arteriolar level within tissues due to the formation of connections between arteries and veins, known as arteriovenous anastomoses (AVAs) [19].

Moreover, endotheliopathy, driven by hyperglycemia, is strongly linked to the progression of microangiopathy through several key mechanisms. These processes include the build-up of advanced glycation end-products (AGEs), the activation of protein kinase C (PKC) pathways, which directly impact vascular health, and the involvement of the polyol pathway, in addition to the hexosamine biosynthesis pathway [20]. Notably, activating PKC enzymes, predominantly induced by heightened diacylglycerol (DAG) synthesis or directly by hyperglycemic conditions, is instrumental in initiating endothelial dysfunction within micro-arterioles. This enzymatic activation disrupts smooth muscle contractility in vessels that perfuse distal tissues [21]. Furthermore, in diabetes, there is an elevation in serum levels of AGEs, which bind to receptors on endothelial cells, thereby stimulating an overproduction of ROS [22]. However, in the diabetic wound microenvironment, AGEs seem to adversely affect ECM proliferation, extend the inflammatory phase, and hinder wound contraction [23].

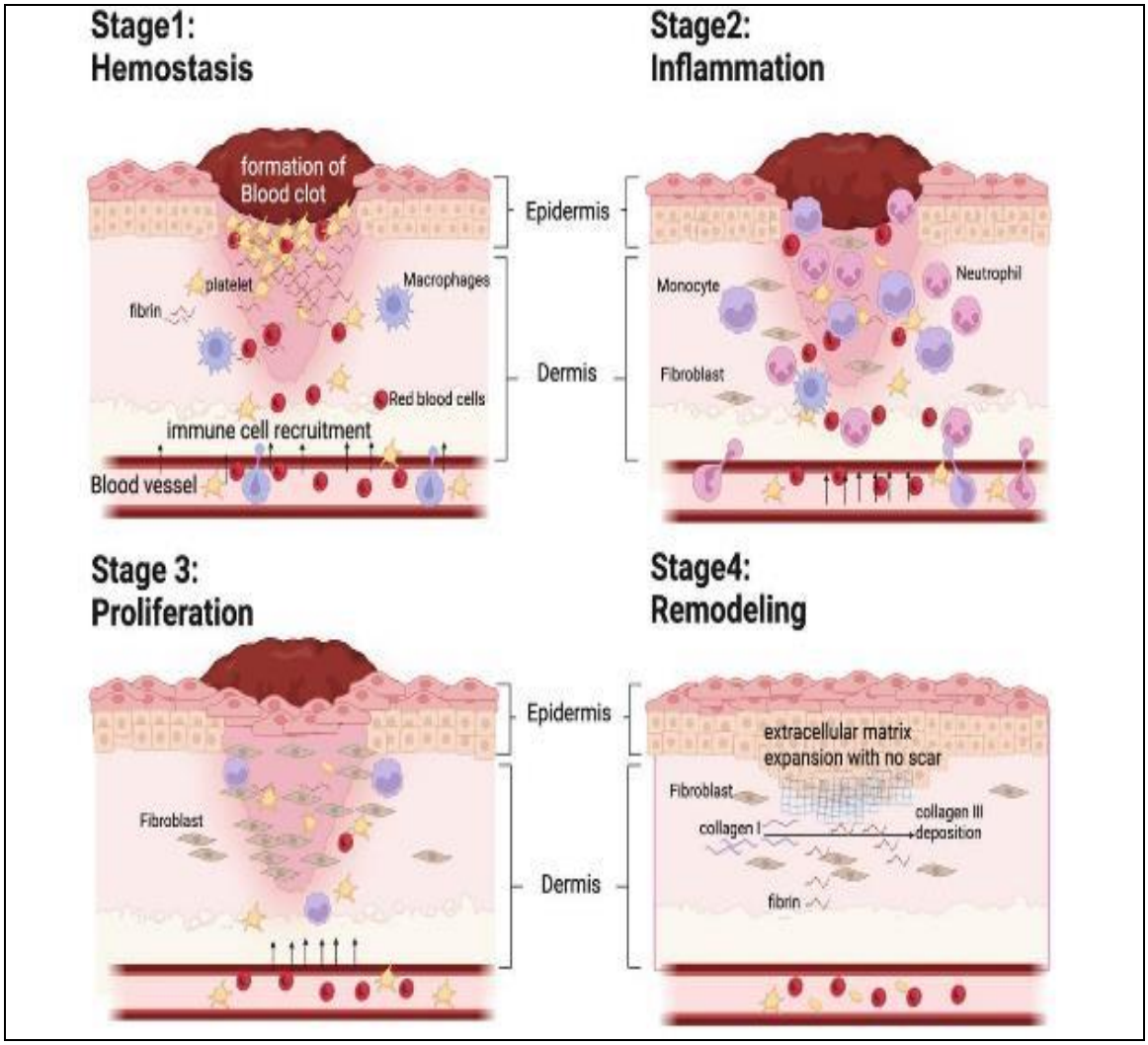

Figure 1: Phases of wound healing

Lastly, the polyol pathway contributes to endotheliopathy by depleting cytosolic Nicotinamide adenine dinucleotide phosphate hydrogen (NADPH), which is crucial for nitric oxide synthase (NOS) activity and the regeneration of glutathione, a key antioxidant. This depletion reduces nitric oxide (NO) availability in dysfunctional blood vessels, impairing normal vascular function [24].

Impairment of immune function

One of the hallmark features of diabetic wound is the chronic persistence of inflammatory conditions, impaired angiogenesis, reduced levels of endothelial progenitor cells, and a dysregulated balance in ECM remodeling [25]. Inflammation at the wound site prompts the infiltration of innate immune cells, such as polymorphonuclear leukocytes and macrophages. Chemokines, including monocyte chemotactic protein-1 (MCP-1) and macrophage inflammatory protein-2 (MIP-2), interact with these immune cells. This interaction ultimately triggers the upregulation of inflammatory mediators, including interleukin-1β (IL-1β) and TNF-α, during the inflammatory phase [26]. One of the reasons for exacerbating tissue damage in diabetes is the increased levels of M1 macrophage polarization and the buildup of CD8+ T-cells. An imbalance between elevated levels of pro-inflammatory cytokines and insufficient levels of anti-inflammatory cytokines is responsible for the exacerbation of tissue damage [27].

Neuropathy

Neuropathy, which includes sensory, motor, and autonomic types, impacts the wound healing process in various ways. Autonomic neuropathy impairs sweat gland function, leading to dry skin. This heightens the risk of pruritus and infection, further hindering wound healing [22].

Additionally, motor neuropathy amplifies pressure on the sole, leading to ischemia and subsequent tissue necrosis. Furthermore, skin affected by neuropathy displays a diminished neuronal density and a significantly reduced ability to heal [8].

Infection

Patients with diabetes are highly susceptible to wound infections, as impaired immune function and compromised blood circulation exacerbate inflammation and disrupt the wound healing process [18]. In the presence of bacteria, elevated levels of pro-inflammatory cytokines are released, which subsequently delay the wound healing process. Consequently, the wound remains in a heightened inflammatory state, increasing the risk of chronicity and hindering complete tissue repair [28].

Repurposing antidiabetic drugs for wound healing applications

Repurposing existing drugs that target one or multiple key molecular events in the healing process offers a promising approach to accelerate therapeutic advancements. Many antidiabetic drugs, such as metformin and sitagliptin, exhibit anti-inflammatory properties in addition to their insulinotropic effects. Considering the link between inflammation and impaired wound healing, it is plausible that these medications could improve the wound healing process [29]. Several antidiabetic medications, including biguanides, such as metformin, sitagliptin (a dipeptidyl peptidase-4 (DPP-4) inhibitor), and dapagliflozin (a sodium-glucose co-transporter-2 (SGLT2) inhibitor), have been investigated for their potential to promote wound healing. Each drug class offers distinct mechanisms that may contribute to improved wound repair processes in diabetic patients.

SGLT2 inhibitors

One of the novel antidiabetic agents, SGLT2 inhibitors, lowers glucose through a unique mechanism by promoting its elimination via urine. This occurs by targeting the proximal renal tubules, where the reabsorption of glucose and sodium is inhibited, ultimately aiding in the maintenance of optimal blood sugar levels [30]. In 2012, the first SGLT-2 inhibitor, dapagliflozin, received approval, marking the introduction of a new class of antidiabetic drugs. Since then, numerous other SGLT-2 inhibitors have been developed, including empagliflozin, canagliflozin, and ertugliflozin, significantly expanding the therapeutic options for managing type 2 diabetes [31]. The renal proximal tubule is the primary site for SGLT proteins, which are responsible for the reabsorption of glucose. SGLT inhibitors increase urinary glucose excretion by blocking this reabsorption process. This process also raises sodium levels in the distal tubules, inhibiting the renin-angiotensin-aldosterone system, which helps reduce both preload and afterload, offering cardioprotective benefits [32]. SGLT2 inhibitors have shown various effects beyond glucose control, including immunomodulatory properties that impact various immune pathways. However, the precise mechanisms driving their cardiovascular and renal benefits remain under investigation, with ongoing efforts to translate these findings into targeted clinical use for patients with inflammatory conditions [33]. Among the SGLT2 inhibitors, dapagliflozin has been explicitly investigated for its potential role in enhancing wound healing, distinguishing it within this drug class for its therapeutic implications in tissue repair, while case reports have also been documented for empagliflozin (Table 1).

Dapagliflozin

A study investigated the synergistic impact of dapagliflozin and zamzam water (ZW) on diabetic wound healing, focusing on anti-inflammatory and angiogenic mechanisms. ZW, a supplement widely consumed by millions of Muslims globally, is alkaline in nature, and contains elements such as zinc, and magnesium, which contribute to the synthesis of antioxidant enzymes. The study involved forty rats divided into five groups: non-diabetic control, untreated diabetic, ZW-treated, dapagliflozin-treated, and combined treatment. The research measured wound closure rates, oxidative stress, immunohistochemical markers, and histological changes. Findings indicate that combined dapagliflozin and ZW treatment significantly promoted wound healing through enhanced antioxidant activity, reduced inflammation, increased angiogenesis, cellular proliferation, and improved tissue remodeling. This is a promising approach to the diabetic wound management [34].

Moreover, an *in vitro* study presents an innovative technique for addressing diabetic wounds by utilizing nanovesicles (NVs) that replicate the function of natural exosomes. Using a specialized extrusion technique, NVs were generated from endothelial cells derived from reprogrammed stem cells. Encapsulating dapagliflozin, the NVs were coated with CXCR4 protein to target and accumulate in endothelial cells. This targeted delivery promoted

angiogenesis and accelerated wound healing through the HIF-1α/VEGFA signaling pathway. In addition, the in vivo study in the same experiment supports the finding of the *in vitro* study [35]. Another study investigated the effects and mechanisms of dapagliflozin on angiogenesis following hindlimb ischemia in rats, which were divided into three groups: the dapagliflozin group (femoral artery resection with dapagliflozin treatment), a positive control group (femoral artery resection with buffer solution), and a negative control group (no resection, buffer solution). Through the stimulation of the PI3K-Akt-eNOS cascade, dapagliflozin treatment was observed to augment capillary density and enhance blood flow [36].

Empagliflozin

Research explicitly examining empagliflozin's contribution to wound repair is, to date, minimal, despite a handful of case reports suggesting its potential efficacy. A report examines the clinical history of a 35-year-old woman with glycogen storage disease type 1b (GSD-1b) and inflammatory bowel disease (IBD), who has been undergoing long-term treatment with granulocyte colony-stimulating factor (G-CSF) to address GSD-associated neutropenia since early life. Following treatment initiation with 20 mg of empagliflozin daily, her neutrophil count and function normalized, allowing G-CSF discontinuation and her long-standing abdominal wound in the skin showed significant healing within 12 weeks. The findings indicate that empagliflozin may represent a safe and effective treatment for neutropenia and neutrophil dysfunction in GSD Ib, promoting wound healing and potentially improving IBD outcomes [37].

Moreover, a retrospective review of empagliflozin therapy in three pediatric patients diagnosed with GSD-1b demonstrated substantial clinical improvements, such as the resolution of recurrent oral mucosal lesions, abdominal pain, infections, and anemia, as well as enhanced wound healing in mucosal lesions. Neutrophil counts increased and stabilized all patients, enabling the discontinuation of G-CSF therapy; two patients exhibited gains in body mass index, and one achieved sustained remission of IBD. Furthermore, decreased inflammatory markers underscored the therapy's effectiveness [38].

Another report highlighted the clinical scenario of a 30-year-old woman diagnosed with Glucose-6-phosphatase catalytic subunit 3 (G6PC3) deficiency, further complicated by severe congenital neutropenia and a five-year history of a refractory wound. Empagliflozin therapy was initiated, leading, within two months, to significant decreases in inflammation, necrotic tissue removal, and new skin formation. Continued treatment produced progressive skin regeneration, complete clearance of necrotic areas, and a substantial wound size reduction from 12.238 cm to 10.535.2 cm over the subsequent four months. Concurrently, blood cell counts stabilized, with a significant rise in neutrophils, underscoring empagliflozin's potential in addressing this complex wound [39].

Potential molecular targets of empagliflozin and dapagliflozin for enhancing the healing of diabetic wounds

Wound healing is a highly intricate process that involves multiple cellular, humoral, and molecular pathways. It is initiated immediately following the occurrence of a lesion and can continue over an extended period, potentially lasting several years [40]. The coordinated release of cytokines and growth factors serves as the principal regulator of wound healing, orchestrating the process across its various stages. Disruptions to this delicate modulation not only hinder proper healing but also predispose to the formation of chronic, non-healing wounds. Various signaling pathways play indispensable roles in regulating the intricate process of wound healing, including Nuclear factor erythroid-2–related factor-2 (Nrf2), protein kinase B (Akt), Sirtuin-1 (SIRT1), and Signal transducer and activator of transcription 3 (STAT3) [41].

Nrf2

One of the members of the basic leucine zipper DNA-binding transcription factor family is Nrf2, which belongs to the Cap 'n' Collar (CNC) subgroup conserved in metazoans. Nrf2, composed of seven functional domains known as Neh, is a 605-amino acid protein associated with N2-erythroid-derived Cap 'n' Collar homology [42]. Within the paradigm of tissue repair, Nrf2 is a critical transcription factor in wound healing by detecting the buildup of ROS in injured and inflamed tissues, subsequently triggering the activation of the antioxidant defense system to counteract oxidative damage and promote tissue repair [43].

Regulation of Nrf2 pathway activation

Nrf2, during typical physiological status, remains a short-lived protein subjected to continuous ubiquitination and subsequent degradation via the proteasomal system.

Table 1: Research studies and clinical case reports have explored the potential wound-healing effects associated with dapagliflozin and empagliflozin

Type of study	Medication	Number of subjects and duration	Conclusion	Ref
Experimental animal study	Oral dapagliflozin was administered at a dosage of 1 mg/kg. Dapagliflozin was prepared by dilution in 0.5 ml saline and given daily throughout the experimental period.	40 rats. The duration of the study was four weeks	The combination of dapagliflozin and zamzam water significantly promoted wound healing by enhancing wound closure, antioxidant levels, angiogenesis, cellular proliferation, and remodeling while reducing inflammation in diabetic rats.	[34]
Experimental laboratory study (*in vitro* and in vivo)	The dapagliflozin-loaded nanovesicles derived from induced pluripotent stem cell-derived endothelial cells with a dapagliflozin concentration of 0.04 mg/mL were subjected to comparative analysis alongside empagliflozin and canagliflozin. Under conditions of elevated glucose levels, their respective impacts on endothelial cell functionality were thoroughly assessed.		Dapagliflozin, through the activation of the HIF-1α/VEGFA signaling pathway, effectively promotes angiogenesis, thereby accelerating the process of wound healing.	[35]
Experimental animal study (in vivo and in vitro)	Oral dapagliflozin (1 mg/kg/d), for 21 days	30 rats were included for 21 days	Dapagliflozin administration increased levels of angiogenic markers, including p-Akt, p-eNOS, and VEGFA, both in vivo and in vitro. The inhibition of PI3K or eNOS activity disrupted these processes, indicating that dapagliflozin facilitates post-ischemic angiogenesis via this specific signaling pathway.	[36]
Case report	Oral empagliflozin (20 mg per day)	One female patient with GSD and IBD	Empagliflozin led to the normalization of both neutrophil count and function and improved wound healing of chromic abdominal wound within 12 weeks.	[37]
Case report	Oral empagliflozin Each patient received empagliflozin at a dose adjusted according to their age: 0.38 mg/kg/day 0.48 mg/kg/day. 0.57 mg/kg/day.	Three pediatric patients, each with a confirmed diagnosis of GSD, complicated by IBD and recurrent oral lesions.	Empagliflozin treatment led to symptom resolution and enhanced wound healing in all patients.	[38]
Case report	Empagliflozin treatment began with 10 mg administered each day for the first two months, subsequently increased to 25 mg per day and maintained for a duration of one year.	A 30-year-old woman with G6PC3 deficiency presented with a chronic, non-healing wound persisting for five years.	After 2 months of treatment, a reduction in inflammation, clearance of necrotic fibrinous tissue, emergence of new epidermal growth, and normalization of white blood cell and neutrophil counts were observed.	[39]

However, through intricate and tightly controlled regulatory mechanisms, Nrf2 is activated in response to oxidative or electrophilic stress [42]. The initiation of the Nrf2 signaling pathway orchestrates anti-inflammatory and antioxidant responses by regulating critical processes, including calcium ion homeostasis and mitochondrial oxidative stress modulation [44].

Calcium (Ca^{2+}) regulation

Oxidative stress and cellular dysfunction begin with an excessive influx of Ca^{2+} into cells, leading to mitochondrial Ca^{2+} overload. This overload can induce apoptosis and activate Ca^{2+}-dependent degradative enzymes [44]. Heme oxygenase 1 (HO-1), an antioxidant functioning to shield vascular endothelial cells from oxidative stress and cellular damage, is upregulated in response to its activation. This heightened expression is facilitated by the stimulation of Nrf2 and the MAPK/ERK pathways, which are activated following Ca^{2+} influx [45].

The connection between mitochondrial oxidative stress and the Nrf2 pathway

A major contributor to cellular senescence is the significant disruption in the balance of mitochondrial reactive oxygen species (mtROS). Scholarly investigations have established that the deacetylase enzyme Sirtuin-3 (SIRT3) plays a key role in regulating mtROS levels, with its expression being controlled by mitochondrial superoxide dismutase 2 (MnSOD) [46]. Enhancing the therapeutic efficacy of mesenchymal stem cells in facilitating skin wound healing through improved oxidative stress regulation could be achieved by targeting Nrf2, which primarily governs the expression of SIRT3 [44].

Targeting Nrf2 signaling pathway in diabetic wound healing

In diabetic rats, macrophages exhibit reduced Nrf2 activity, because of elevated ROS production and the downregulation of Nrf2-regulated genes such as NQO1 and HO1. The dysregulation of Nrf2 signaling is linked to the heightened release of proinflammatory cytokines, such as IL-1β, IL-6, and MCP1, which amplifies inflammation and plays a critical role in impaired wound healing [47]. In the streptozotocin (STZ)-induced diabetic mouse model, the absence of Nrf2 significantly impaired re-epithelialization, demonstrating that Nrf2 deficiency obstructs wound healing and angiogenic processes. This wound impairment is likely due to prolonged inflammation and reduced critical mediators of neovascularization [43]. In opposition, overexpression of Nrf2 enhances angiogenesis, promoting wound healing by reducing inflammation via suppression of ROS and proinflammatory cytokine production (Figure 2) [44]. The activation of Nrf2 by vascular endothelial growth factor (VEGF) has been observed in the BeWo cell line, a human choriocarcinoma cell line originating from placental trophoblastic tissue. This process enhances the expression of crucial antioxidant enzymes, including thioredoxin, thioredoxin reductase, and HO-1, bolstering cellular antioxidant defenses [48]. According to a recent study, the PI3K/Akt signaling pathway experiences downregulation as early as six hours following injury during the initiation of chronic wound development. This downregulation impairs the activation of Nrf2-mediated antioxidant pathways, preventing the effective scavenging of ROS and leading to subsequent tissue damage [49]. Activating Nrf2 can enhance cellular resilience and restore tissue homeostasis in diabetic wounds, offering potential therapeutic benefits in mitigating diabetes-related complications. Remarkably, a previous research studying the potential renoprotective effect of empagliflozin on methotrexate-induced nephrotoxicity showed that therapy with empagliflozin significantly improved several parameters, including enhancement in Nrf2 expression [50].

Moreover, dapagliflozin reduces hypertrophy, inflammation, and cellular stress by activating the Akt pathway and modulating key metabolic, and inflammatory markers, and Nrf2. Its cardioprotective and anti-inflammatory effects underscore its potential in treating cardiovascular and metabolic disorders, including type 2 diabetes [51].

To substantiate the therapeutic potential of empagliflozin and dapagliflozin and elucidate their effects on wound healing, extensive preclinical and clinical investigations remain imperative, as a significant research gap persists. It starts when Nrf2 binds to KEAP1 under normal conditions, but in the presence of ROS, this interaction weakens, allowing Nrf2 to accumulate, pair with MAF, and bind to ARE in DNA.

KEAP1: Kelch-like ECH-associated protein; Nrf2: The nuclear factor-erythroid 2-related factor 2; IL-1β: interleukin 1β; IL-6: interleukin 6; ROS: reactive oxygen species; ARE: antioxidant response element; MAF: musculoaponeurotic fibrosarcoma.

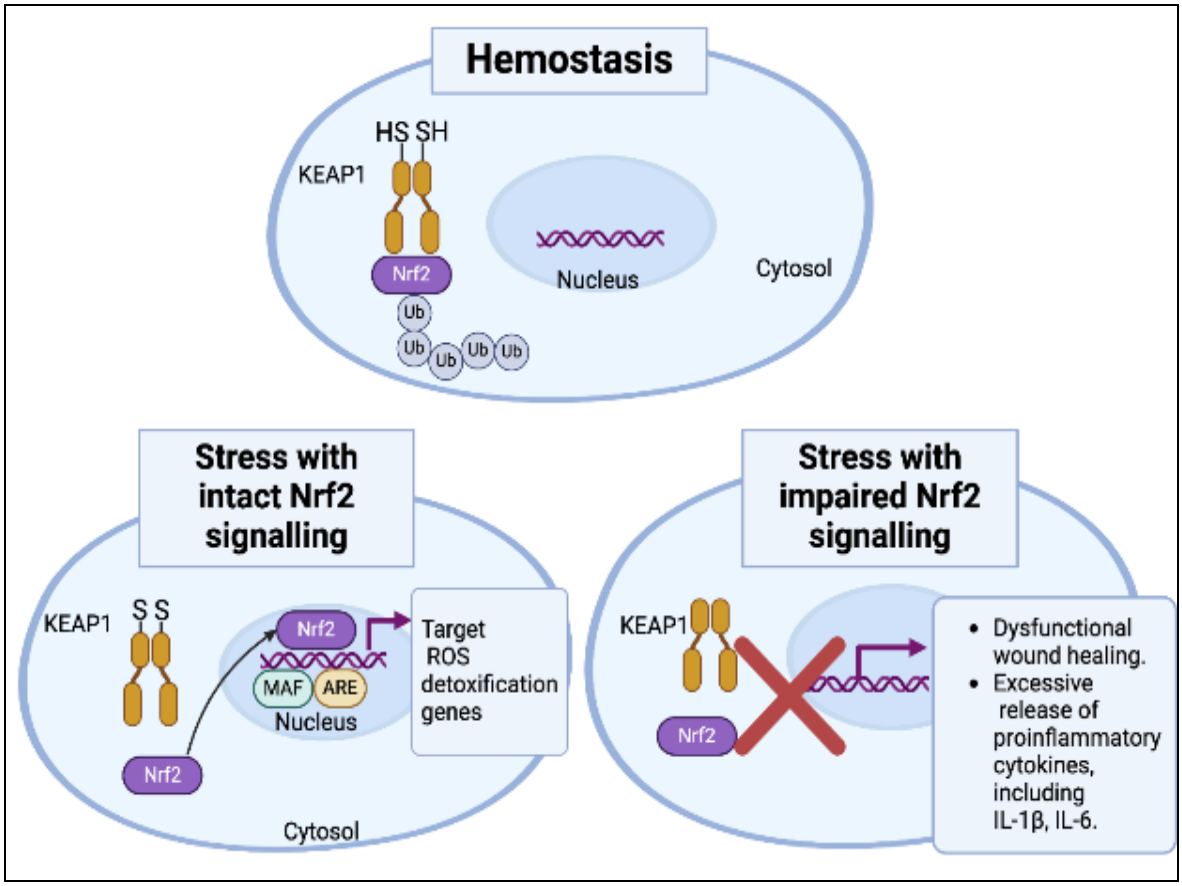

Figure 2: Nrf2 signaling pathway

Akt pathway

Essential to cellular functions such as metabolism, proliferation, and growth, Akt is one of the foremost serine/threonine kinases, acting as a key mediator in these critical processes [52]. Additionally, Akt is a 480-amino acid protein structurally organized with an N-terminal pleckstrin homology (PH) domain [53].

Regulation of Akt pathway activation

Angiogenesis, apoptosis, and proliferation are among the critical cellular functions governed by various downstream pathways, which are further influenced by Akt activation mediated through phosphoinositide 3-kinase (PI3K). These pathways play a core function in promoting growth, maintaining tissue integrity, and facilitating cellular adaptation to stress or damage [54]. The mammalian target of rapamycin (mTOR) and glycogen synthase kinase 3 (GSK3) are among the critical downstream proteins modulated by the PI3K/Akt signaling pathway through activation or inhibition mechanisms. By regulating essential functions such as protein synthesis, metabolism, and cell survival, this modulation underscores the pivotal role of the pathway in preserving cellular homeostasis [54].

By stimulating receptor tyrosine kinases (RTKs), various growth factors and signaling complexes, including epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), and insulin, are capable of activating the PI3K/Akt signaling pathway. This activation triggers autophosphorylation of the receptors, which in turn initiates the downstream signaling cascades essential for cellular processes like proliferation, survival, and metabolism [55]. Phosphorylation-mediated inhibition of GSK3 isoforms (GSK3β and GSK3α) by Akt has critical cellular functions such as the inflammatory response, cell migration, proliferation, and apoptosis. Specifically, inhibition of GSK3β suppresses pro-apoptotic signaling, thereby enhancing cell survival and preventing activation of intrinsic apoptosis pathways, which is crucial for maintaining cellular integrity and promoting growth (Figure 3) [56].

Targeting AKT signaling pathway in diabetic wound healing

Associated metabolic dysfunctions and the progression of the disease are significantly

influenced by disruptions in the PI3K/Akt signaling pathway, which impairs critical cellular functions. Such impairments have been strongly correlated with the onset of DM and its related complications [57]. In the context of wound healing, the PI3K/Akt signaling pathway reaches its highest activity during the inflammatory and proliferative stages of wound healing, and its suppression has been associated with delayed or impaired healing processes. Numerous studies have investigated therapeutic strategies to stimulate the PI3K/Akt pathway to enhance and accelerate wound healing, emphasizing its integral contribution to tissue repair and regeneration [58].

Notably, in a study investigating the renoprotective potential effect of empagliflozin in diabetic nephropathy, empagliflozin showed improvement in the viability of tubular cells through the reduction of oxidative stress by activating the Akt/GSK-3 [59]. To determine the influence of empagliflozin and dapagliflozin on wound healing and validate their therapeutic potential, extensive preclinical and clinical studies are essential, particularly given the persisting gaps in existing research.

SIRT1

SIRT1, SIRT2, SIRT3, SIRT4, SIRT5, SIRT6, and SIRT7 represent the seven identified members of the human SIRT protein family, with SIRT1 being the most thoroughly investigated and comprehensively characterized among them. Sirtuins, classified as class III histone deacetylases, orchestrate a wide array of physiological processes and pathological conditions by modulating the deacetylation of both histone and non-histone substrates. It plays crucial roles in various diseases and conditions, including aging, diabetes, apoptosis, oxidative damage, and inflammation [60].

Regulation of SIRT1 pathway activation

The mitogen-activated protein kinase (MAPK) pathway, which includes extracellular signal-regulated kinases (ERKs), p38 kinases, and c-Jun N-terminal kinases (JNKs 1, 2, and 3), is among the pivotal signaling pathways influencing the regulation and activation of SIRT1 [61].

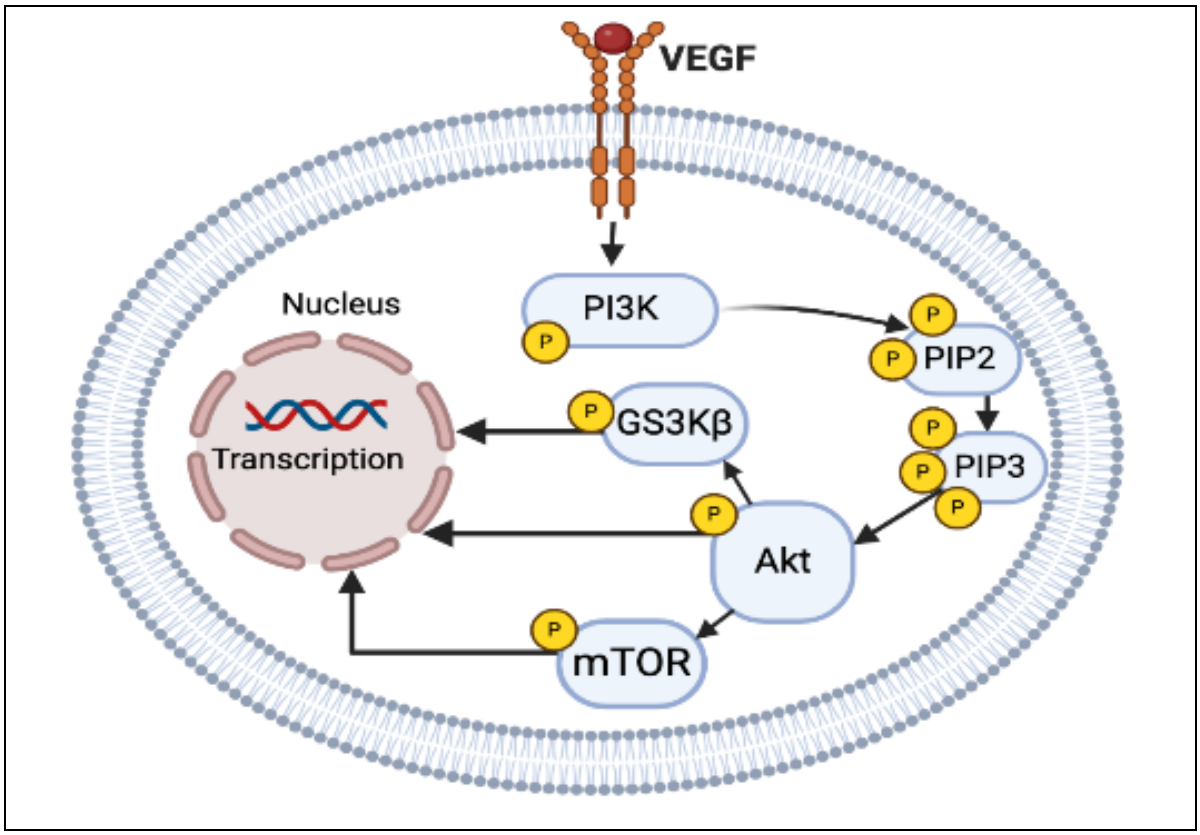

Figure 3: Akt signaling pathway. ***Key:*** VEGF: vascular endothelial growth factor; PI3K: phosphoinositide 3-kinases; PIP2: phosphatidylinositol 4,5-bisphosphate; PIP3: phosphatidylinositol (3,4,5)-trisphosphate; GSK3β: glycogen synthase kinase 3; Akt: protein kinase B; mTOR: mammalian target of rapamycin

By regulating downstream targets, the MAPK signaling pathway may play a significant role in contributing to the activation of SIRT1. SIRT1 may regulate the MAPK-AP-1 pathway, reducing the phosphorylation of key kinases such as JNK, p38, and ERK, while inhibiting the transcription factor AP-1, thereby enhancing its anti-inflammatory effects and promoting wound healing [62].

Targeting SIRT1 signaling pathway in diabetic wound healing

Deficiency of SIRT1 in the epidermis disrupts the recruitment of immune cells and the activation of fibroblasts, impairing the regeneration of both the epidermal layer and dermal stroma, which underscores its critical role in wound healing. Additionally, its deficiency disrupts angiogenesis within the granulation tissue, further inhibiting wound healing [63]. Moreover, hypertrophic scars are hypothesized to be significantly influenced by SIRT1, which is believed to play a critical role in their development. In an experimental wound healing model, the absence of SIRT1 resulted in greater structural disarray within the skin, marked by the accumulation of densely packed collagen fibers.

Conversely, treatment with resveratrol, a known SIRT1 activator, enhances tissue organization and collagen alignment, indicating that SIRT1 is essential for preserving proper tissue structure during healing [64]. Scholarly findings validate the potential of sirtuins as therapeutic targets in wound healing, mainly through a study examining corylin, a significant flavonoid extracted from *Psoralea corylifolia* L. The acceleration of full-thickness skin wound healing, enhancement of collagen deposition, and reduction of inflammatory responses were demonstrated in a mouse model, as indicated by the findings on corylin's efficacy. Mechanistic investigations revealed that corylin activates the PI3K/Akt signaling pathway, which enhances fibroblast proliferation and migration and facilitates wound closure. The study also demonstrated that corylin stimulates SIRT1 signaling, further underscoring its beneficial role in wound healing [65].

Furthermore, the activation of the Nuclear Factor-kappa B (NF-κB) pathway and the promotion of inflammation were associated with SIRT1 deficiency in macrophages, which exacerbated oxidative stress, increased NADPH oxidase 2 (NOX2) levels, and suppressed the Nrf2 pathway in animal and LPS-induced inflammatory cell models. This sequence of processes culminates in the development of excessive scarring. Therefore, one of the potential therapeutic strategies to mitigate inflammation and minimize scarring during wound healing is by enhancing SIRT1 expression in macrophages [66].

Moreover, empagliflozin, through the activation of large-conductance calcium-activated potassium (BK) channels, leads to dose-dependent vasodilation in coronary arteries, a mechanism mediated by the SIRT1-Nrf2 signaling pathway [67].

In addition, dapagliflozin improves endothelial function by stimulating SIRT1, which facilitates the deacetylation of endothelial NOS (eNOS), thereby restoring its activity and enhancing nitric oxide (NO) production. This process reduces the generation of ROS and helps alleviate endothelial dysfunction caused by oxidative stress [68]. Further confirmation of these effects requires additional research, despite these findings supporting the molecular targets of empagliflozin and dapagliflozin in enhancing wound healing.

STAT3

In processes such as cancer, wound healing, angiogenesis, immune responses, and neurodevelopment, one of the most pivotal signal transducers and transcription factors is STAT3, which is integral to regulating these diverse biological functions [69]. Through the regulation of critical profibrotic pathways, STAT3 facilitates fibrosis development and is activated by a range of cytokines and growth factors, such as IL-6 and TGF-β1 [70].

Regulation of STAT3 pathway activation

Phosphorylated STAT3 translocates to the nucleus upon activation by various stimuli, where it associates with the promoter regions of target genes and initiates transcription, while in resting cells, it remains as an inactive monomer in the cytoplasm [71]. Although several tyrosine kinases have been identified as intracellular activators of STAT3, the phosphorylation of STAT3 at tyrosine 705 is primarily governed by Janus-activated kinases (JAKs), with JAK1 serving as a critical regulator of this process [71]. The activation of STAT3 is initiated by the phosphorylation critical key tyrosine residue (Tyr 705), which promotes STAT3 dimerization through mutual interactions between the phosphotyrosine and SH2 domains[72]. In addition, phosphorylation at serine 727 is another mechanism of STAT3 activation, and PKC,

MAPK, and CDK5 predominantly control this process [72].

Targeting STAT3 signaling pathway in diabetic wound healing

In the wound healing process, STAT3 activation is essential for facilitating epithelial cell migration and proliferation, as well as for creating the necessary inflammatory environment. Nevertheless, overstimulation of STAT3 can intensify scar development by driving an excessive inflammatory and cellular growth response [73]. Through direct or indirect mechanisms, STAT3 stimulates the production of growth factors such as VEGF and fibroblast growth factor (FGF), while triggering processes that collectively facilitate wound healing. Following skin injury, STAT3 is rapidly activated in the surrounding tissue. At the wound site, this activation stimulates angiogenesis, supports epithelial cell survival and proliferation, and accelerates the migration of keratinocytes and fibroblasts, thereby aiding in wound closure [73]. By upregulating downstream inflammatory factors such as MCP-1 and IL-6, STAT3 facilitates the recruitment of inflammatory cells, including monocytes and macrophages, to the wound site [74].

Additionally, through the activation of the Chitinase-3-like protein 1/MAPK (CHI3L1/MAPK) axis, the upregulation of STAT3 enhances wound healing by driving fibroblast proliferation and migration. These findings offer new potential drug targets for treating diabetic foot ulcer (DFU) and provide insights into the mechanisms responsible for delayed wound healing in the DFU [75].

Remarkably, the stimulation of the JAK2/STAT3 signaling pathway by empagliflozin has been shown to safeguard against hypoxia-induced cardiomyocyte injury, with suppression of STAT3 negating these protective effects, suggesting that the cardioprotective properties of empagliflozin [76].

Moreover, through the activation of the STAT3 signaling pathway, dapagliflozin enhances the polarization of macrophages towards an anti-inflammatory (M2) state, reducing inflammation in viral myocarditis. This shift mitigates cardiac damage and improves heart function [77].

The effects of empagliflozin and dapagliflozin on wound healing require further investigation, as significant research gaps persist. Comprehensive preclinical and clinical studies are imperative to elucidate their impact and validate their therapeutic potential.

CONCLUDING REMARKS

This review of SGLT-2 inhibitors' potential role in the promotion of wound healing highlights key insights regarding the plethora of molecular pathways that may be targeted for this purpose, as evidenced by multiple preclinical animal studies and case reports. Nevertheless, the pathophysiology behind chronic wounds, especially in diabetic patients, remains a complex area in need of further research. As a result, further preclinical and subsequent clinical studies to support these promising findings are required, focusing on delineating more of these mechanistic pathways and their therapeutic impact systematically and potentially advancing strategies to enhance the clinical outcomes of wound care in practice.

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