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Review

Insight into polyol pathway for diabetic wound care supported by applications of scaffolds

Vadivelan Ramachandran [1]*, Tharani Mohanasundaram [1], Monika Gunasekaran [1], Darshan Karnakaran [1], Ruchi Tiwari [2]

[1] Department of Pharmacology, JSS College of Pharmacy, JSS Academy of Higher Education & Research, Ooty, The Nilgiris, Tamilnadu, India

[2] Pranveer Singh Institute of Technology (Pharmacy), Kanpur, Uttar Pradesh, India

* Correspondence to: Vadivelan Ramachandran, Department of Pharmacology, JSS College of Pharmacy, JSS Academy of Higher Education & Research, Ooty, The Nilgiris, Tamilnadu, 643001, India. E-mail: vadivelanr@jssuni.edu.in

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Abstract

Diabetes foot ulcer (DFU) affects around one-third of diabetic patients, which are mostly caused by peripheral neurovascular disease or peripheral neuropathy. Since diabetic foot ulcers are persistent and difficult to cure, the present study contains a literature review for a better understanding of the neuropathic and ischemic characteristics of diabetes, their control, prevention, and treatment. The researchers discovered that the inhibitors of sorbitol dehydrogenase, AR, Protein Kinase C (PKC) activation, activators of myo-inositol bisphosphatase, nitric oxide synthase and many other enzymes were found to play salient roles in the polyol pathway of diabetic neuropathy. It can be concluded that key elements of the polyol pathway play a vital role in the control, prevention, management, and treatment of diabetic foot ulcers.

Keywords: diabetic foot ulcer, polyol pathway, diabetic foot neuropathy, neurotrauma, scaffolds.

Introduction

Diabetes is a long-term metabolic illness marked by high blood glucose levels that cause irreversible, catastrophic damage to the nerves, heart, kidneys, eyes and blood vessels [1]. Diabetic neuropathy is a serious and widespread condition that affects people mainly beneath the knee. The chances of having diabetic wounds during the course of a person's life are between 19–34%. After initial healing, recurrence is common, roughly 40% within one year, 60% within three years, and 65% within five years. Infection occurs in 50–60% of ulcers and is the most common cause of diabetic foot injury [2].

Around 20% of the moderate or severe infections of diabetic foot account for lower extremity amputations. Osteomyelitis accounts for around 20% of diabetic wounds. A lower leg is amputated every 20 seconds owing to diabetic complications [3]. Because of diabetic wounds, around 50–70% of lower limb amputations occur, and a leg is amputated every 30 seconds [4]. There is a higher risk of 2.5 times death of people with a diabetic foot ulcer than diabetic people without a foot ulcer after 5 years. Diabetic neuropathy is a complex condition that includes a wide variety of symptoms.

The most common neurological consequence of diabetes mellitus is diabetic peripheral neuropathy (DPN). Reduced nerve blood flow, which affects functional and morphological nerve alterations, appears to be a crucial element in DPN pathophysiology. The trinity of variables that lead to diabetic wounds involves peripheral neuropathy, foot abnormalities, and acute or chronic repeated trauma. DFUs are a dangerous consequence of diabetes mellitus that is open to amputations of the lower extremities. Because diabetes mellitus (DM) produces significant anomalies in all four phases of wound healing, it has been suggested that impaired wound healing is a primary cause of chronic DFUs (hemostasis, inflammation, proliferation and

remodeling). Regular debridement, pressure unloading, revascularization where indicated, sufficient infection therapy, and local wound care are the foundations of DFU treatment.

Polyol pathway

Under hyperglycemic circumstances, the polyol route of glucose metabolism is accelerated, which digests around 30% of the intracellular glucose in the polyol pathway [5]. Under normoglycemic conditions, only 3% of the aldohexose will be converted to sorbitol [6]. In humans, AR (AR) is encoded by the gene AKR1B1 which normally causes the reduction of toxic aldehydes in the cell to inactive alcohols. In contrast, in this pathway, the rate-determining enzyme utilizes nicotinamide adenine dinucleotide phosphate (NADPH) as the cofactor and catalyzes the reduction of glucose to sorbitol (Figure 1). Further, the reversible oxidation of sorbitol to fructose is driven by sorbitol dehydrogenase, which employs (NAD+) nicotinamide adenine dinucleotide as the cofactor [7].

Three pathways contribute to hyperglycemia-induced oxidative damage via the polyol system [8]. For starters, AR's usage of NADPH may reduce the amount of cofactor available to glutathione reductase (GR), which is essential for maintaining the reduced glutathione intracellular pool. As a result, the polyol pathway reduces glutathione disulfide (GSH) synthesis, impairing cells' ability to react to oxidative stress. Second, increased sorbitol dehydrogenase activity raises NADH levels, which serves as a substrate for the nicotinamide adenine dinucleotide phosphate-dependent oxidase, leading in the generation of superoxide anion [9]. Third, fructose can be transformed to fructose-3-phosphate (Fr-3-Po4) and 3-deoxyglucosone, resulting in the formation of advanced glycation endproducts (AGE) and, as a result, an increase in reactive oxygen species (ROS) production. Preclinical cellular and animal researchers are gathering evidence that glucose flows through the polyol pathway could be a key origin of the oxidative stress implicated in the etiology of diabetes sequelae, including diabetic retinopathy and diabetic nephropathy. In genetically engineered diabetic mice with AR deficiency, there is a decrease in the excretion of urine albumin, overexpression of collagen IV growth of mesangial matrix, and an increase in the size of the glomerulus, all of which are linked with diabetic nephropathy.

AR ablation causes the reduced activity of PKC and transforming growth factor (TGF-1), which are essential for accumulating extracellular matrix [10]. Furthermore, recent *in vitro* evidence supports the relationship between AR overexpression and high blood pressure. Renal damage caused by glucose. Further high glucose concentrations enhance AR 390 in renal tubular cells [11].

Diabetic foot neuropathy

Diabetic foot neuropathy manifestation occurs via the autonomic, motor and sensory nervous system. About 50% of cases of foot ulcers are contributed by peripheral arterial disease, which affects the calf's peroneal arteries and tibial arteries. However, hyperlipidemia, hypertension and smoking contribute to peripheral artery disease. Callus formation, insensitivity and high foot pressure lead to clawing of the affected toes (Figure 2) [12].

Neurotrauma – diabetic foot ulcers

Microorganisms which are found in the acute diabetic foot infection are β-hemolytic *Streptococcus* (A, B, C and G) and *Staphylococcus aureus*, whereas the microorganisms found in chronic infection are *Streptococcus sp.*, *Staphylococcus sp.*, *Enterococcus sp.*, *Escherichiacoli*,*Enterobacteriaceae.*,*Pseudomonasaeruginosa*, *Clostridium sp.*, *Peptococcus sp.*, *Peptostreptococcus sp.*, *Fusobacterium sp.*, and *Bacteroides sp.* Neurotrauma causes infection of the wound that could lead to abnormal extensor and flexor tendons leading to extension of ligaments, distension of the joint, microfractures and dislocation of the bones and neurovascular damage of the autonomic neuron resulting in hyperemia [13]. Arteriovenous shunts cause increased vascular flow leading to bone resorption and osteopenia. None of the theories accounts for the unilateral presentation of diabetic foot ulcers.

Therapeutic targets

The most prevalent therapeutic target for the polyol pathway is AR. The AR-deficient mice have shown symptoms of recuperation from the sensory and motor nerve conduction abnormalities [14]. Apart from restoring MNCV, AR inhibitors (ARIs) were demonstrated lower sorbitol building, improve blood flow in nerves (NBF) and decrease sorbitol buildup. The Cyclic amides of

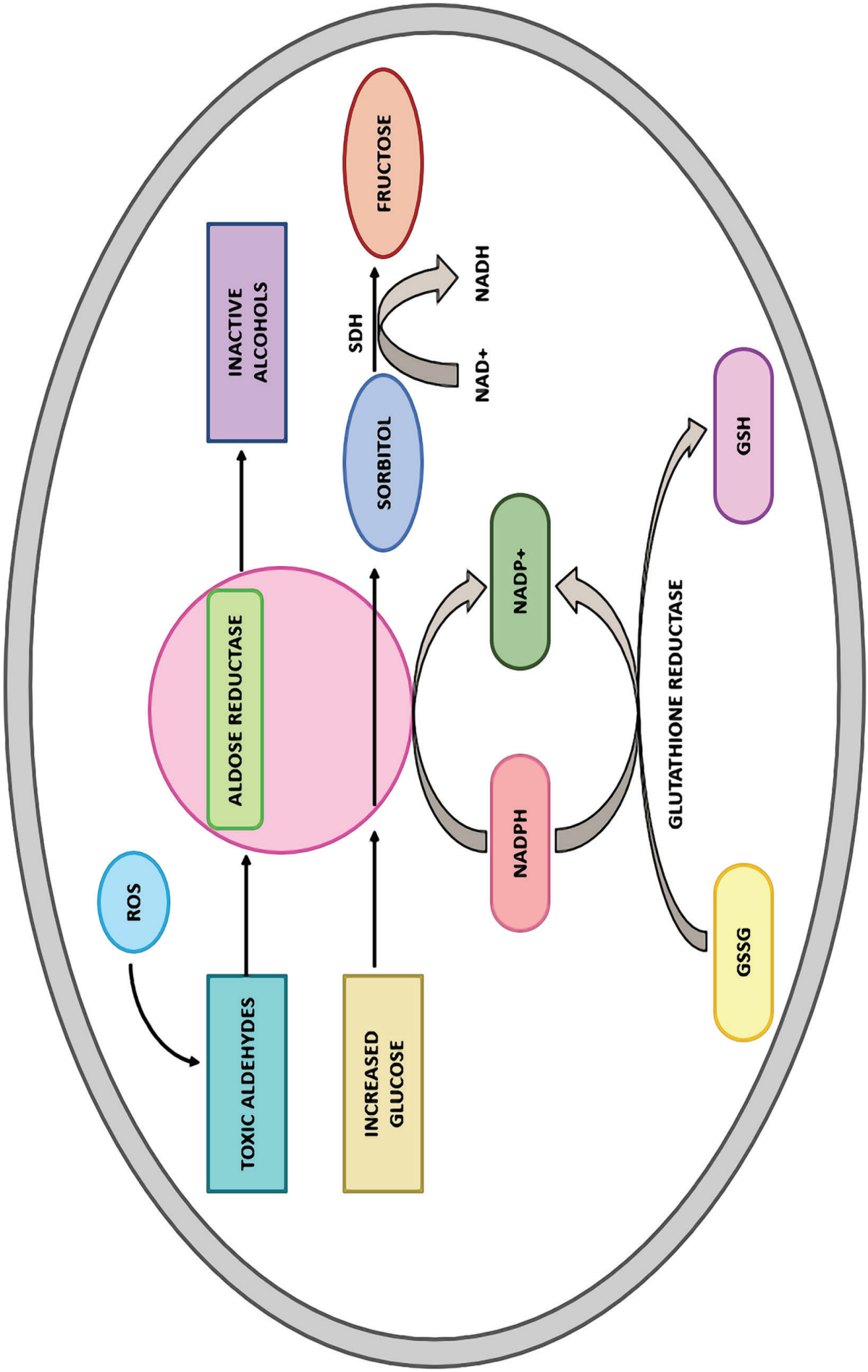

Figure 1: Hyperglycemia increases flux through the polyol pathway. GSH – Glutathione; GSSG – Glutathione disulfide; NAD+ – Nicotinamide Adenine Dinucleotide; NADP+ – Nicotinamide Adenine Dinucleotide Phosphate (oxidized form of NADPH); NADPH – Nicotinamide Adenine Dinucleotide Phosphate; ROS – Reactive Oxygen Species; SDH – Succinate Dehydrogenase.

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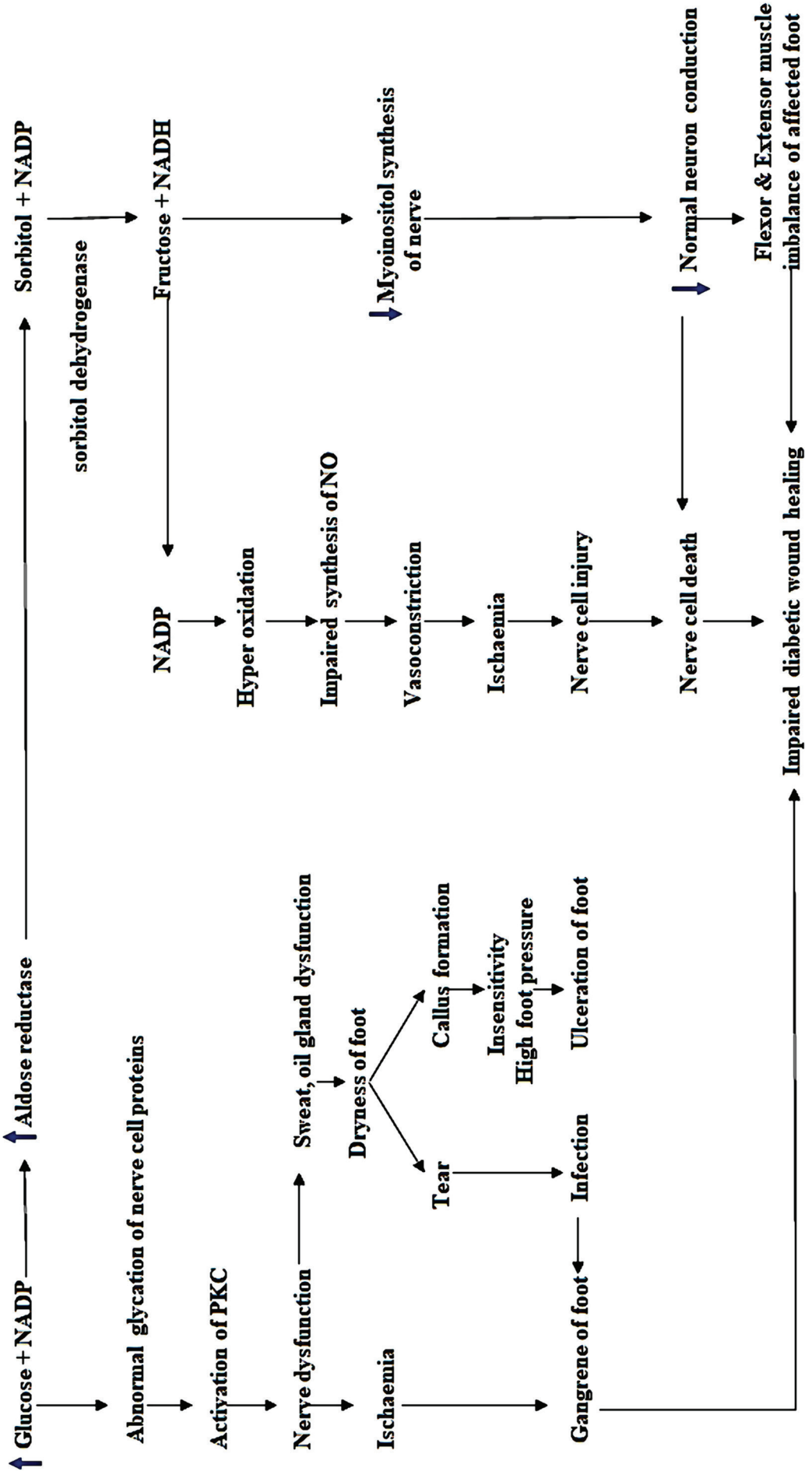

Figure 2: Schematic representation of hyperglycemia-induced ischaemic-neuropathy of diabetic foot ulcer.

Spiro hydantoin, Sorbinil, Fidarestat, Minalrestat and the Carboxylic acid derivatives, Ponarelstat, Eparelstat and the Phenolic derivatives showed AR inhibition [15].

Sorbinil is an ARI prototype that has been proven in animal models to block diabetes-induced neuronal conduction deficits; however, it has not been replicated in humans. Sorbinil increased the regeneration of nerve fibers in diabetic NCV patients much more. The development of skin rashes is its side effect. In rats induced with Streptozotocin, treatment with fidarestat restored the NCV deficit in a dose-dependent manner. Treatment of fidarestat at a dosage of 2 mg/kg averted the myelin sheath damage of paranodal areas and the degeneration of axons to normal levels [16]. *Zenarestat* decreased the accumulation of Fructose and Sorbitol in the neurons of diabetic rats in a dose-dependent manner; however, at doses of 250–500 mg, zenarestat lowered sorbitol levels in humans but failed to reduce fructose levels. A higher dose of zenarestat (1000 mg) was more effective in lowering nerve cell conduction (NCV) [17]. In another investigation, zenarestat therapy lowered sorbitol levels in the dorsal root area of the ganglia and the spinal cord in diabetic rats [18].

Epalrestat, a carboxylic acid ARI that has recently hit the Japanese market, has fewer adverse effects. Hotta *et al.* performed a randomized, placebo-controlled research of a dosage of 150 mg that showed suppression of nerve deformation as well as the production of various diabetes neuropathic symptoms, such as limb numbness and cramps [19]. In the past decades since its introduction, epalrestat was found to be a constructive treatment for diabetic neuropathy with few adverse effects [20]. *Ranirestat* is one of the few medications that has had any clinical effectiveness in diabetic nephropathy too far. However, a full picture of clinical reports on phase II and phase III is necessary [21]. As a result, the search for new ARIs with greater efficacy and safety, ideally from plants and vegetables, continues. α-lipoic acid's ability to treat diabetes, foot ulcer and renal disease was investigated in several studies (Jiang *et al.*, 2015, 2016; Han *et al.*, 2012;). A study on 236 subjects demonstrated clinical improvement in 73% of patients treated with α- lipoic acid, compared to 18% of the placebo-treated group.

Pain, muscular weakness, and burning sensation were dramatically reduced compared to the control and placebo groups. Furthermore, at the conclusion of the experiment, HbA1c (glycated hemoglobin) levels were determined to be quite low (Gu *et al.*, 2010) [22]. In various countries, L-carnitine and ALC were also studied for their efficiency in treating diabetic foot neuropathy and its associated consequences. L-carnitine aids in the production of energy in the mitochondria. The exogenic L-carnitine forms can be found in many supplements and meat, but a sufficient amount of it will be secreted by the body of humans to keep physiological processes running smoothly [23].

Scaffold applications in wound healing

Scaffolds are novel carriers of drug and cell delivery that causes the enhancement of wound healing, epithelial and endothelial cell differentiation and angiogenic growth factors production in cutaneous wounds [24]. The use of polymeric fiber scaffold structures with encapsulated anti-infectious compounds like nanoparticles, antibiotics, essential oils and anti-microbial peptides) as wound dressings have shown tremendous promise in speeding wound healing and preventing infection [25].

Scaffolds based on biomaterials are widely applied in biomedical applications in the healing of wounds, delivery of drugs, tissue engineering DNA/gene/plasmid delivery, health care, biotechnology, energy storage, environmental engineering, defense security and in various research methods [26]. Scaffolds are three-dimensional structures, apart from providing nourishment for the growth of the tissue, they may also cover a wound, acting as an effective "fence" in opposition to external pollution.

Scaffolds must offer physical assistance and cell contact to activate physiological functions of Adhesion of cells, cell proliferation, and cell differentiation, which give to an assembly of the cell into a working unit of great importance [27]. Because of cell attachment and migration through the networks, porosity and biocompatibility are essential for the scaffolds. Hence preparation of scaffolds for the application of wound healing must contain these features in order to maintain high productivity and low-cost fabrication (Figure 3) [28].

Wound healing scaffolds often help with purposes of (i) allowing cell communication a link by conventional attachment and migration of the cells; (ii) helping in cell and other biochemical substance delivery and retention; (iii) permitting free flux of critical cell nutrients and ATP, carbon dioxide and water; (iv) altering the activity of the cells by applying biological and mechanical stimuli; (v) further creasing a micro-environment that is similar to the extracellular matrix in three dimensions [29].

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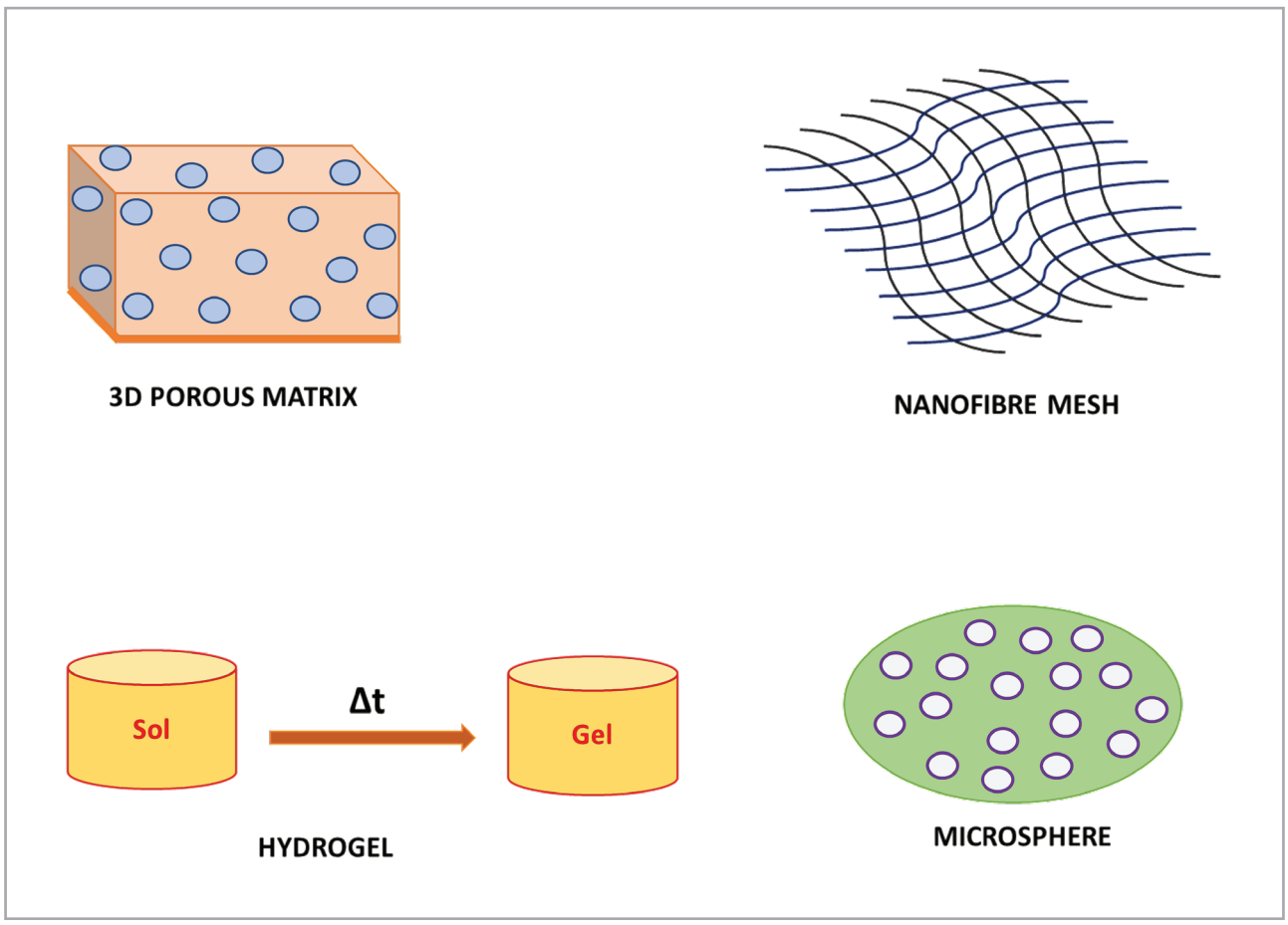

Figure 3: Various types of scaffolds used in diabetic wound healing.

Table 1: Outcomes of various studies using drug-loaded scaffolds to treat diabetic foot ulcers.

Drug	Types of scaffolds	*In vitro*/*In vivo* studies	Outcomes
Allontoin & lidocaine	Chitosan/collagen composite scaffold	*In vitro* tests revealed no toxicity and the migration of cells increased when the collagen ratio scaffold was raised.	Adding Allantoin and Lidocaine Hydrochloride to the wound dressing might be assessed as a substitute to the commercial preparation, improving patient compliance by speeding up the healing process and helping patients survive the pain and suffering.
Andrographolide	Chitosan/hyaluronic acid composite sponge scaffold	*In vivo* testing in rats showed improved wound healing by preventing scarring and improving tissue quality.	It is linked to the chitosan and hyaluronic acid combined antioxidant and anti-inflammatory effects as well as andrographolide action.
Norfloxacin	Collagen/chitosan scaffolds	A scaffold region contains the same concentration as determined by the Terahertz Pulsed Imaging studies. Further regeneration of the tissues was reported to be faster after wound dressing for 28 days with the scaffold compared to the untreated wounds.	They demonstrated non-toxic and long-term biodegradability. Furthermore, the manufactured scaffolds accelerated the healing of wounds while causing no noticeable inflammation or any other negative effects.

Table 1: Continued.

Drug	Types of scaffolds	*In vitro*/*In vivo* studies	Outcomes
Frutalin	Hydrogel and membrane scaffold	The ideal combination recovered the region of the lesions with hastened angiogenesis and enhanced keratinocyte and fibroblast proliferation.	It was found to be a possible medicinal biomolecule for healing wounds and skin restoration and other injuries and skin diseases. Further, they are cost-effective substitutes for existing burns, wounds and surgical treatment of wounds and burns.

Scaffolds such as 3D-porous matrix, Hydrogels, Microspheres and Nanofibers have been created for wound healing applications. The designed tissue scaffolds' capacity for absorbing a large volume of fluid while keeping the wound bed wet is critical for skin regeneration and wound healing. Standard cotton pads' fluid retention capacity is typically restricted to 67% of the dry weight. A good absorbent scaffold is required to limit the replacement of the pad during the surgical intervention as well as for chronic wounds that will produce large volumes of exudates.

Further, the elastic deformation of the scaffold materials influences the cell responses through biomedical transmission; hence, mechanical qualities like soft elasticity are critical in the applications of tissue-engineered skin [30]. The low fiber stiffness encourages cells to actively recruit adjacent fibers, facilitating the migration of the cells [31]. Studies on tissue engineering have revealed the importance of matrix complaisance in cell migration soft three-dimensional matrices facilitated quicker migration of cells than rigid ones. Cells are said to "feel" in a softer backdrop way, allowing them to migrate [32].

Theranostic materials which cause the integration of bioactive and interactive methods with diagnostic and therapeutic functions into a scaffold can be used in the next generation of wound healing scaffolds. Many new technologies are expected to incorporate the targeted biomarkers into the scaffolds for monitoring wound healing [33]. Table 1 summarises various studies carried out using drug-loaded scaffolds in the treatment of diabetic foot ulcers.

Conclusion

In diabetic foot ulcer treatments, the polyol pathway has been and continues to be a focus of pharmacological intervention. Collectively, all the studies suggest that scaffolds are an effective way to promote diabetic wound healing and are also convenient to use. Future therapy possibilities for diabetic wound healing, boosting the possibility of individualized treatment, would assist in revolutionizing present treatment choices.

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Conflict of interest

The authors declare no conflict of interest.

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