Review on Diabetic Wound Healing with Emphasis on Plants Having Diabetic Wound Healing Potential

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Abstract: Diabetic wound healing presents a major clinical challenge due to hyperglycemia, neuropathy, microvascular disease, impaired immune response, altered inflammatory response and other conditions. These diabetic wounds are chronic wounds associated with serious complications and increased risk of infections leading to severe morbidity and mortality. Conventional therapies including debridement, infection control, and advanced dressings often fail to achieve complete healing, highlighting the need for alternative and adjunctive treatment strategies. Recent researches have highlighted the therapeutic potential of medicinal plants having bioactive components such as flavonoids, alkaloids, triterpenoids, polyphenols, tannins with antioxidant, anti-inflammatory, and angiogenic properties. These phytoconstituents promote wound healing at different phases and improves wound closure in diabetic patients. The current review summarizes the phathophysiology of diabetic wounds, current therapeutic limitations and promising role of plant-derived active constituents in tissue regeneration and repair. A better understanding of these phytochemicals and their mechanism could aid in developing cost-effective and biocompatible plant-based formulations for the management of diabetic wounds.

Keywords: diabetic wound healing, diabetes mellitus, impaired healing, phytoconstituents, hyperglycemia.

I. INTRODUCTION

Diabetes mellitus is a chronic metabolic illness which is due to irregular insulin production or defects in insulin secretion or action and or glucose sensing. Basically, it is of two types, type-I diabetes mellitus(T1DM): due to auto immune mediated cell destruction and type-II (T2DM): because of insufficient peripheral insulin resistance compensation. The characteristic classical symptom is three polyps and one loss i.e., polydipsia, polyphagia, polyuria and weight loss[1,2].

Of these two prevalent types 10-15% of diabetics suffer from T1DM and the rest 85-90% suffers from T2DM [3]. Despite variations in pathogenesis among these sub types the underlying pathological basis remains the body's inability to properly handle and utilize glucose resulting in elevated blood glucose levels [2] (hyperglycemia) a characteristic feature of diabetes mellitus has detrimental impact on long-term health of an individual [4] as it leads to a serious complication-poor wound healing which presents a significant challenge for individuals with diabetes. In recent estimates 20% diabetic patients suffer from poor wound healing worldwide [5].

Wound is nothing but the destruction of living tissue produced by cut, blow or break[6] .Wound healing is defined as a natural process by which wounds return to their normal state with the support of complicated cellular and biomolecular processes (haemostasis, inflammation, proliferation, and remodelling) that restore damaged wound tissue into its original state [7,8].However diabetic wounds are skin and tissue damage caused by prolonged hyperglycemia that hinders the normal wound healing process due to disruption in skin regeneration which prevents normal wound healing. If left untreated and unmanaged more than half of diabetic wounds develop into chronic wounds with increased risks of amputation and death[5].

Traditionally different parts of plants were used to cure cuts, chronic wounds and burns. These medicinal plants contain a number of bioactive constituents which have proliferative, migratory, anti-oxidative, anti-bacterial, pro-angiogenic, antiseptic and immune modulatory properties that promotes wound healing, can help even treat ulcers, skin infections, scabies leprosy, and venereal diseases. This may be due to the synergism (positive

herb-herb interaction) of primary active component with other components present [9,10,11,12]. Nowadays health care professionals around the world are using numerous plants and herb species in the treatment of both diabetic and non-diabetic wounds because of the assumption that the ingredients from medicinal plants are less toxic and have fewer side effects compared to the therapeutic agents [6].

Wound and diabetic wound:

Damage to the skin is known as wound. Generally, they are categorised into two groups on the basis of time of healing as acute wounds (which heal quickly) and chronic wounds (which heal slowly). Diabetic wounds are chronic non healing wound which damages the skin and tissue because of prolonged hyperglycemia [6,8]. According to recent estimates one in every five individuals suffering from diabetes experience chronic non-healing wound during their lifetime [13].

Causes for problematic healing of diabetic wounds:

The reasons of problematic wound healing are multifactorial but here are the primary causes listed below

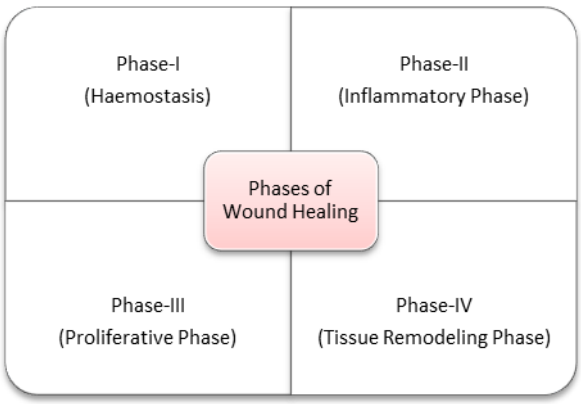
1. Hyperglycemia: the persistent chronic high blood glucose level can constrict and harden blood vessels leading to reduced blood, oxygen and nutrient supply to the injured site thus affecting wound repair.
2. Neuropathy: diabetic neuropathy affects the sensory nerve and autonomic nervous system leading to loss of sensation as a result patient becomes unaware of injuries and treatment gets delayed.
3. Microvascular disease: poor circulation in diabetic patients make them more prone to microvascular disease which damages the microcirculation around the wound causing insufficient blood supply.
4. Impaired immune response: diabetes impairs the immune response leading to decreased patients' resistance in fighting infections, making them more prone to infections which further complicates wound healing.
5. Altered inflammatory response and other complications: diabetic wounds have chronic inflammation which disrupts normal healing process and prolongs the inflammatory phase. Besides presence of other complications such as hypertension and arteriosclerosis further impairs wound healing process [8,14].

Factors affecting diabetic wound healing [1,6,15]:

1. Wound site:
   The place of wound plays an important role in wound healing. As the patients suffering from diabetes usually presents with diabetic foot infection as the commonest and most serious complication which further delays wound healing. The bacteria present at the chronic diabetic wound site include S. aureus and Pseudomonas aeruginosa[6,15].
2. Reactive oxygen species:
   Increased concentration of reactive oxygen species and oxidative stress retards normal diabetic wound healing process by damaging DNA, proteins and lipids.
3. Age:
   With advancing age, the wound healing process gets delayed may be because the growth and activity of fibroblast decreases and also the collagen synthesis which leads to slower wound contraction.
4. Stress:
   Psychological stress slows down the process of wound healing in diabetics.
5. Immune state:
   Anti-oxidant system that has bactericidal activity gets impaired in patients of diabetes which makes them more susceptible to infections.

Mechanism of wound healing [2,6,16,17]:
Wound healing is divided into four stages:

1. Haemostasis phase
2. Inflammatory phase
3. Proliferative phase
4. Tissue remodelling phase



Phases	Haemostasis phase	Inflammatory phase	Proliferative phase	Tissue remodelling phase
Duration	0 hours after injury	1-14 days	14-21 days	21 days or more
Key events	Constriction of blood vessels and platelet aggregation. Release of pro inflammatory mediators with formation of thrombi.	Vasodilation due to release of histamine and 5-HT from mast cells W.B.C initiate's inflammatory phase Recruitment of neutrophils along with macrophages-engulfs bacteria (phagocytosis) and remove debris which causes inflammation at wound site.	Inflammation subsides and fibroblasts moves to wound site. Granulation, Contraction, and Epithelialization Granulation: formation of new fresh capillaries and bed of collagen. Contraction: side margins of wound contracts and closes. Epithelialization: formation of epithelial and scar tissue.	Formation of new collagen with increased tissue tensile strength.

Mechanism of Diabetic Wound Healing [17,18]

In general healing of diabetic wounds are challenging because of presence numerous factors that alter the normal process of wound healing such as hypoxia, impaired angiogenesis, chronic inflammation and excessive expression of matrix metalloproteinases which leads to delayed wound healing in diabetics with increased risk of infections. Below is the discussion of how these effect different phases of wound healing.

Haemostasis: in case of diabetes hyperglycemia and oxidative stress interferes with platelet aggregation and clotting factors causing endothelial dysfunction which impairs haemostasis.

Inflammatory phase: here because of improper function of neutrophils and macrophages inflammatory phase gets prolonged. If it is not controlled and inflammatory cells persist in the wound site, diabetic wound becomes chronic.

Proliferative phase: persistent hyperglcemia in diabetics leads to delayed angiogenesis which limits the supply of nutrients and oxygen to the tissues. Hypoxia prolongs the proliferative phase by increasing oxygen free radical levels causing delayed tissue regeneration.

Remodeling phase: microvascular complications and impaired angiogenesis (due to reduced availability of VEGF [14]) delays remodeling phase resulting in weakened wound contraction and decreased wound strength.

Management and therapeutic approach [19,20,21]:

The management of diabetic wounds include:

1. Local wound care (surgical debridement): it is the removal of necrotic and devitalized tissue from wound and should be repeated every 24 to 72 hours [21].
2. Wound dressings: these are required to maintain a moist environment and protect the wound.
3. Wound offloading: it includes shoe modification, boots and orthotic walkers
4. Treatment of active infection: use of 1–2-week broad spectrum antibiotic therapy for mild infections and 2-3 weeks for moderate to severe infection.
5. Vascular assessment: local ischemia due to microvascular complications delays wound healing in diabetics [19].one such example is of peripheral artery disease (PAD) which causes slow healing of diabetic foot ulcer with increased rates of amputation and mortality [21].
6. Glycemic control: in case of diabetics control of blood glucose levels improves healing and limits adverse effects on cellular immunity and infection.
7. Topical antiseptics and anti-microbials: examples include povidone iodine 10% solution, acetic acid, hydrogen peroxide, honey and plant extracts.
8. Advanced therapies: includes application of topical growth factor-based therapy [6] leukocyte and platelet rich fibrin patch, hyperbaric oxygen therapy, negative pressure therapy [21], skin substitutes, platelet rich plasma, stem cell therapy (bone marrow derived stem cell, adipose derived stem cell, umbilical cord derived stem cell, blood derived stem cell, placenta derived stem cell [22]).

Plant extract derivatives or role of herbal products and their active constituents used for diabetic wound healing [23-50]:

S.No	Botanical name	Vernacular name	Family	Part used	Phytoconstituent
1.	Euphorbia hirta linn	Baridudhi	Euphorbiaceae	Whole plant	Flavonoids [23,24]
2.	Byrsonima crassifolia	Nanche	Malpighiaceae	Fruit and Seeds	Byrsonine-A [23,25,26]
3.	Glycyrrhiza glabara	Liquorice	Fabaceae	Stem and root	Isoflavones, glycyrrhizin [9,27]
4.	Tipha angustifolia	Cattail	Typhaceae	Whole plant	Flavonoids, glycosides, terpenoids [9,28]
5.	Crocus sativus	Saffron	Iridaceae	Petals	Crocin, crocetin, safranal[10,29]
6.	Carica papaya	Papaya	Caricaceae	Seeds	Sterols, alkaloids and flavonoids[6,30]
7.	Rosmarinus officinalis	Rosemary	Lamiaceae	Aerial parts	Essential oil[6,31]
8.	Annona squamosa	Custard apple	Annonaceae	Leaves and seeds	Flavonoids[6,31,32]
9.	Catharanthus roseus	Vinca rosea	Apocynaceae	Flower	Tannins and alkaloids[6,33]
10.	Centella asiatica	Indian penny wart	Apiaceae	Herb	Flavonoids[6,34]
11.	Acalypha langiana	Indian acalypha	Euphorbiaceae	Leaves	Cyanogenic glucosides and alkaloids[6,35]
12.	Hylocereus undatus	Dragon fruit	Cactaceae	Leaf and floral extract	Phenols, flavonoids[36]
13.	Punica granatum	Pomegranate	Punicaceae	Peels	Ellagitannin, punicalin, punicalagin[37]
14.	Azadirachta indica	Neem	Meliaceae	Leaves	Flavonoids, alkaloids[35,38]
15.	Aloe vera	Gheekumari	Liliaceae	Leaves	Aloe emodin, barbaloin[35,39]
16.	Cassia fistula	Golden shower	Fabaceae	Leaves Pods	Anthraquinones, beta-sitosterol, sennosoides A and B[36,40]
17.	Butea monosperma	Flame of forest	Fabaceae	Flowers	Tannins, flavonoids and triterpenoids [35,41,42]
18.	Datura alba	Thorn apple	Solanaceae	Leaves	Flavonoids, alkaloids[43,44]
19.	Ocimum sanctum	Holy basil	Lamiaceae	Leaves	Alkaloids, flavonoids, tannins[45]
20.	Solanum xanthocarpum	Indians nightshade	Solanaceae	Whole plant	Polyphenols, flavonoids[46]
21.	Matynia annua	Bichchhu	Martyniaccae	Leaves	Terpenoids, flavonoids, alkaloids, tannins[47]
22.	Tephrosia purpurea	Sarpunkha	Fabaceae	Aerial parts	Terpenoids, flavonoids[47]
23.	Ipomoea batatas	Sweet potato	Convolvulaceae	Peels	Plyphenols[48]
24.	Curcuma longa	Turmeric	Zingiberaceae	Rhizomes	Alkaloids, glycosides, saponins[49]
25.	Sida cordifolia	Bala	Malvaceae	Aerial parts	Flavonoids, glycosides, alkaloids[50]

Available polyherbal formulations with wound healing property[12]

S.No	Name of polyherbal formulation	Composition of polyherbal formulation
1.	Aab-e- Shifa	Allium sativum, Zingiber officinale, and Curcuma longa
2.	Derma heal cream	Natural honey, olive oil and beeswax
3.	Aris wound healing cream	Glycyrrhiza glabra, Ficus infectoria, Shorea robusta, Curcuma longa, Berberis eristata, Rubia cordifolia, Azadirachta indica, Pongamia glabra, and Yashad Bhasma
4.	Amarantha wound healing cream	Jatyadi oil, Yashad Bhasma, Ficus religiosa, Ficus bengalensis, Centella asiatica, Shorea robusta, Glycyrrhiza glabra, Azadirachta indica, Pongamia glabra
5.	Herboheal	Azadirachta indica, Acacia nilotica, Ocimum sanctum, Annona squamosa, Curcuma longa, Ricinus communis, Beewax.

Possible mechanism of action of herbal products and their active constituents:

S.No	Name of phytoconstituent	Possible mechanism of action
1.	Flavonoids	Scavenges free radicals[51]
2.	Saponins	Reduces oxidative stress which promotes faster tissue regeneration[52]
3.	Triterpenoids	Contracts the wound and increases rate of epithelization by their inhibitory effect on production and activation of inflammatory mediators[53]
4.	Tannins	Suppress lipid oxidation by scavenging different radicals[54]

II. CONCLUSION

Impaired wound healing in diabetes is one of the serious and commonest complication. Health professionals globally see it as a serious health challenge may be because of non-specific etiology in some cases. Therefore, one of the therapeutic approaches for treatment is the application of medicinal plants.

Throughout human history herbal medicines have been essential for treating various diseases even the ayurvedic system of medicine promotes the use of natural products for healthy living by preventing unnecessary ailments. The present review highlights the medicinal plants and active constituents which can be employed in treating diabetic wounds.

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