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Diabetic Skin Wound Healing and the Use of Medicinal Plants

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ABSTRACT

Skin wound healing occurs through a process of connective tissue repair involving interactions between specialized cells, cytokines and growth factors. Diabetes mellitus is a metabolic disorder characterized by hyperglycemia with impaired carbohydrate, fat, and protein metabolism. This disease is a public health problem due to its high incidence and prevalence, affecting more than 180 million individuals worldwide; this number is projected to double in 15 years. Diabetes mellitus is associated with connective tissue abnormalities, such as decreased angiogenesis, collagen biosynthesis and cell proliferation, which leads to impaired wound healing that can result in amputation. These factors have encouraged the search for new drugs, including herbal drugs, for the treatment of skin injuries in diabetic patients. This review aims to identify the plant species that have been experimentally tested for skin wound healing in diabetic animals, discussing the main therapeutic properties that identify a plant as a promising phytomedicine for wound healing in diabetic patients.

Keywords: Antioxidant,diabetes, Inflammation, Medicinal plants, Natural products, Reepithelization, Skin wound healing.

Introduction

Healing is a biochemical and physiological phenomenon that aims to restore the anatomical integrity of injured tissue. This restoration occurs through cellular

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and molecular responses and/or interactions; due to the high complexity of this process, some authors separate the stages of repair to facilitate understanding (Mandelbaum *et al.*, 2003; Balbino *et al.*, 2005). Healing events can be classified into three stages: 1) hemostasis and inflammation (inflammatory phase), 2) the formation of granulation tissue and epithelialization (proliferation phase) and 3) matrix remodeling (Morin *et al.*, 2012).

The healing process can become even more complicated when it is associated with diabetes mellitus (DM) (Lima *et al.*, 2012). DM is a complex metabolic disease that affects >340 million individuals worldwide (CDCP, 2011). Diabetic patients have an impaired ability to metabolize glucose, and the ensuing hyperglycemia results in many complications, including vasculature damage and the inability to heal wounds (Gooyit *et al.*, 2014).

Wound healing comprises a complex sequence of events involving cell migration, inflammation, the proliferation of different cell types, angiogenesis, and the formation of the components of the extracellular matrix (ECM) involved in remodeling and epithelialization. In DM, many factors interfere with this process, making it slow and prone to complications (Goova *et al.*, 2001). This healing difficulty is related to the delayed onset and long duration of inflammation. Moreover, impaired angiogenesis; the abnormal proliferation of keratinocytes, fibroblasts and endothelial cells; the increased apoptosis of these cells; the decreased migration of fibroblasts; defects in collagen deposition and the decreased production of growth factors also impair wound healing in diabetics (Loots *et al.*, 2002; Deveci *et al.*, 2005).

In addition to the changes directly related to the phases of wound healing, chronic hyperglycemia promotes changes in vascular endothelial cells. The decreased blood flow and endothelial damage caused by decreased tissue oxygenation and nutrition impair the healing process as a whole and are also associated with ischemic lesions (Akbari and Logerfo, 1999). These lesions are associated with metabolic changes that lead to the decreased conduction of sensory stimuli and motor peripheral nerves (Guimarães *et al.*, 2009).

In humans, these injuries occur predominantly in the feet and are prone to infections and recurrent trauma because the patient is often unaware of the damage. The delay in identifying the wound and the search for appropriate treatment hinders the healing process and is responsible for a large number of amputations (Romana-Souza *et al.*, 2009). Apikoglu-Rabus *et al.* (2010) compared the rates of wound contraction, time to complete healing and epithelialization in rats and found a shorter time to complete tissue regeneration in non-diabetic rats than in a diabetes-induced group of rats.

The wounds and ulcers in diabetic individuals have a significant impact on public health and in the investment of public resources. These wounds can lead to various deficiencies in the body parts where they occur or can even result in death (Guo and Dipietro, 2010). Furthermore, individuals with exaggerated scars may suffer physical and psychosocial consequences (Bayat *et al.*, 2003). It is estimated that the morbidity associated with unhealed wounds increases every year. In Brazil, there are no official data, but in the United States chronic wounds affect approximately 6.5 million people, reaching a cost of 25 billion dollars per year (Sen *et al.*, 2009).

Although there are numerous options on the market and curative treatments for chronic wounds, most of these products come from other countries, producing high costs for patients in light of the long duration of most treatments. Moreover, the results obtained from the use of these products are still controversial and deserve in-depth scientific investigation (Ferreira *et al.*, 2003). Because such wounds are resistant to conventional therapies, researchers and industries have tried to explore new therapeutic strategies to solve this problem (Rennert *et al.*, 2013), including the use of plants and natural products (Gál *et al.*, 2009).

Plants have been used for the treatment of various diseases and health problems for thousands of years, and human dependence on plant-derived treatments is growing (Ganeshkumar *et al.*, 2012). Nature is a source of bioactive and efficient products, and a vast number of current medications are extracted from plants (Cragg and Newman, 2002). The use of medicinal plants for treating wounds has been popular since ancient civilization. However, in most cases, the composition and therapeutic efficacy of these products remain to be established (Morin *et al.*, 2012).

Only 1 to 3 per cent of existing drugs are intended to treat wounds and other skin problems. However, almost one third of medicinal plants currently used are intended for such treatments (Mantle *et al.*, 2001). Recently, some species of plants or natural products derived from plants have been successfully tested in experimental wound healing (Cetin *et al.*, 2013; Upadhyay *et al.*, 2013.). The secondary metabolites and active compounds isolated from plants have also been responsible for accelerating cutaneous wound healing in animal models (Fikru *et al.*, 2012; Thangapazham *et al.*, 2013). This review identifies the plant species that have been experimentally used in skin wound healing in diabetic animals with the intention of identifying the plants and pathways that produce effective wound healing to direct future studies in this field.

Material and Methods

The search for the review was carried out on PubMed, Scopus and Web of Science until May 2014, using 'natural products', 'skin wound healing' and 'diabetes' as keywords. Articles published in the last ten years were considered (2004-2014). The results are displayed in Table 18.1 and are discussed below.

Results and Discussion

Table 18.1 summarizes all the plant species experimentally used in the treatment of skin wounds in diabetic animals that were described in the literature. Eleven species of plants, belonging to 11 different families, were found. The parts of the plants used varied between the fruits, flowers, leaves and seeds.

The most used diabetic-inducing method was streptozotocin (STZ) injection.STZ is an antibiotic derived from *Streptomyces achromogenes*. STZ, a glucosamine derivative of nitrosourea, induces hyperglycemia through a cytotoxic effect on pancreatic β-cells. The administration of STZ induces free radical generation, a well-known mechanism involved in diabetogenecity. The advantages of STZ include the induction of sustained hyperglycemia and well-characterized diabetic complications with a low incidence of ketosis and mortality (Ozturk *et al.*, 1996). The intravenous

Table 18.1: Plant Extracts Experimentally Tested in Skin Wound Healing in Diabetic Animals

Plant Species/ Family	*Part of the Plant*	*Diabetes Induction Model*	*Wound Healing Assay*	*Method of Treatment*	*Mechanism of Action*	*Reference*
Acalypha langiana (Euphorbiaceae)	Leaves	Streptozotocin-induced Wistar rats (50 mg/kg)	Excision and incision	0.05 per cent *, 0.1 per cent *, 0.2 per cent, 0.4 per cent and 0.5 per cent solution of aqueous extract t.a.	Diminished edema	Perez Gutierrez e Vargas, 2006
Aloe vera (Liliaceae)	Leaves	Goto-Kakizaki rats (a spontaneous model of diabetes type 2)	Excision	30 mg/rat orally once	Increased growth factor production and angiogenesis	Atiba *et al.*, 2011
Cenostigma macrophyllum (Caesalpiniaceae)	Seeds	Streptozotocin-induced Wistar rats (50 mg/kg)	Excision	0.5 ml of oil-in-water emulsion of seeds t.a.	increased production of nitric oxide; anti-inflammatory effect	Coelho *et al.*, 2013
Ganoderma lucidum (Polyporaceae)	fruits	Streptozotocin-induced Sprague Dawley rats (45 mg/kg)	excision	5 per cent, 10 per cent, 15 per cent, and 20 per cent aqueous extract t.a.	Antioxidant activity	Cheng *et al.*, 2013
Hylocereus undatus (Cactaceae)	Leaves, rind, fruit pulp and flowers	Streptozotocin-induced Wistar rats (50 mg/kg)	Excision and incision	0.05 per cent, 0.1 per cent, 0.2 per cent, 0.4 per cent and 0.5 per cent aqueous extract t.a.	Enhanced collagen synthesis	Perez Gutierrez *et al.*, 2005
Malva sylvestris (Malvaceae)	Flowers	Alloxan-induced Wistar rats (125 mg/kg)	Excision	200 mg/kg diethyl ether extract t.a.	Anti-inflammatory effect	Pirbalouti *et al.*, 2010
Martynia annua (Martyniaceae)	leaves	Streptozotocin-induced Wistar rats (50 mg/kg)	Excision	0.2 per cent and 0.5 per cent of flavonoid fraction t.a.	Antioxidant activity	Lodhi and Singhai, 2013
Momordica charantia (Cucurbitaceae)	Fruits	Streptozotocin-induced Sprague Dawley rats (45 mg/kg)	Excision	50 mg of the extract t.a.	Cellular proliferation	Teoh *et al.*, 2009

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Table 18.1–*Contd...*

Plant Species/ Family	*Part of the Plant*	*Diabetes Induction Model*	*Wound Healing Assay*	*Method of Treatment*	*Mechanism of Action*	*Reference*
Punica granatum (Punicaceae)	Flowers	Alloxan-induced Wistar rats (125 mg/kg)	Excision	200 mg/kg diethyl ether extract t.a.	Decrease in inflammatory cell population	Pirbalouti *et al.*, 2010
Rosmarinus officinalis (Lamiaceae)	Aerial parts	Alloxan-induced-diabetic BALB/c mice (100 mg/kg)	Excision	Intraperitoneal injection of 0.2 ml of 10 per cent aqueous extract or 25 µl of essential oil t.a.	Collagen deposition and anti-inflammatory activity	Abu-Al-Basal, 2010
Withania coagulans (Solanaceae)	Fruits	Streptozotocin-induced Charles Foster rats (70 mg/kg)	Excision	Hydroalcoholic fraction at 10 per cent ointment t.a. or 500 mg/kg orally	Increased collagen synthesis and cell proliferation and antioxidant activity	Prasad *et al.*, 2010

*: Ineffective; t.a.: Topical application.

administration of alloxan (ALX) has also been used for diabetes induction.ALX is a uric acid derivative that acts by selectively destroying pancreatic β-cells,leading to insulin deficiency, hyperglycemia, ketosis, glucosuria, hyperlipidaemia, polyphagia, polydypsia and other symptoms of uncontrolled diabetes.In the long term, the experimental rodents develop complications such as neuropathy, cardiomyopathy and retinopathy. ALX has been replaced by STZ for experimental diabetes induction because of some disadvantages, such as the reversal of hyperglycemia, a variable incidence of diabetes and a high incidence of ketosis and resulting mortality, in addition to its low stability and short half-life (1 minute). However, both drugs have been widely used for anti-diabetic compound screening, including the screening of medicinal plants and natural products (Srinivasan and Ramarao, 2007).

The studied plants exerted skin wound healing effects through a variety of mechanisms; here, we will discuss the predominant ones. Antioxidant and anti-inflammatory activities prevailed. Both effects are involved in wound healing, and the suppression of these activities is related to the development and maintenance of diabetes and other complications.

In type 2 diabetes, excessive nutritional factors, such as glucose and free fatty acids, can induce the generation of oxidative stress (Furukawa *et al.*, 2004), which can in turn induce insulin resistance and diabetes through multiple mechanisms. The excessive generation of reactive oxygen species (ROS),such as superoxide anions ($O_2^{\cdot}$), hydroxyl radicals (OH) and hydrogen peroxide (H_2O_2),leads to damage to and the apoptosis of pancreatic5-cells, decreasing insulin secretion (Evans *et al.*, 2003)and causing insulin resistance (Goldin *et al.*, 2006; Li *et al.*, 2014). In addition, oxidative stress also contributes to the development of chronic,long-term complications from diabetes, such as nephropathy, retinopathy and neuropathy (Rosen *et al.*, 2001).

When insulin demand is constantly elevated, ROS generation is increased by mitochondrial respiration, which saturates the neutralizing capacity of antioxidants, resulting in oxidative stress. Pancreatic β-cells have low levels of antioxidant enzyme expression, making the β-cell population more susceptible to damage when exposed to oxidative stress (Tiedge *et al.*, 1997).

The increased production of ROS also plays a role in skin wound healing, impairing keratinocyte, endothelial cell, fibroblast, and collagen metabolism. In the wound healing process, endogenous and exogenous antioxidants may play an important role, protecting the cell membrane, lipoproteins, and DNA from the damaging effects of free oxygen radicals (Gutteridge and Halliwell, 2000; Cheng *et al.*, 2013). In this review, the species that presented antioxidant activity as part of the wound healing mechanism were *Ganoderma lucidum, Martynia annua* and *Withania coagulans*. These three species were tested in the excision model in STZ-induced diabetic rats and presented promising results in skin wound healing.

The generation of ROS can lead to inflammation, which is a key component in many human diseases, such as type 2 diabetes (Wellen and Hotamisligil, 2005). ROS production in adipocytes leads to the increased production of pro-inflammatory cytokines, which can affect β-cells (Lin *et al.*, 2005; Montane *et al.*, 2014). Recently, results from laboratory studies as well as clinical investigations have shown that

diabetes is in fact an inflammatory disease (Donath and Shoelson, 2011; Xie and Du, 2011).

In the pathogenesis of type 2 diabetes, pro-inflammatory cytokines can be produced by immunocytes (like macrophages) and adipocytes (Gratas-Delamarche *et al.*, 2014). These cytokines, including TNF-α (tumor necrosis factor-α), interleukin-6 (IL-6), and interleukin-1β (IL-1β), lead to insulin resistance in the tissues in which they are produced, such as the liver and adipose tissue, and may also be transported through the circulatory system to induce insulin resistance in more distant sites, including vessel walls, skeletal and cardiac muscle, the kidneys and circulating leukocytes (Donath and Shoelson, 2011). TNF-αand IL-6 are strongly associated with insulin resistance, causing pancreatic dysfunction and accelerating the progression of diabetes (Gratas-Delamarche *et al.*, 2014).TNF-α levels are elevated in individuals with type 2 diabetes. Increased levels of cytokines are associated with an increased risk of developing type 2 diabetes, confirming the inflammatory nature of the disease (Tousoulis *et al.*, 2013).

The inflammation induced by pro-inflammatory cytokines may produce insulin resistance or cause the death of pancreatic β-cells, leading to the development of diabetes (Dixit, 2013).Local cytokine release can also attract macrophages to the pancreas, exacerbating local inflammation (Westwell-Roper *et al.*, 2011).There is increasing evidence that the acute inflammatory response induced by cytokines is closely related to the generation of insulin resistance and the development of diabetes mellitus (Guadarrama-López *et al.*, 2014).

Inflammatory mediators also play a role in skin remodeling (Midwood *et al.*, 2004). Mice that are deficient for TNF-α receptors present increased collagen formation and angiogenesis and rapid skin wound repair (Mori *et al.*, 2002). Ahanger *et al.* (2010) concluded that the inhibition of TNF-α production accelerated the healing of skin wounds. However, some recent studies have shown positive modulatory effects of TNF-α in skin regeneration based on the fact that TNF-α induces the expression of several growth factors, which are signaling molecules important in skin remodeling and regeneration. Recent studies have credited accelerated skin wound healing to the induction of TNF expression (Senapati *et al.*, 2011; Ganeshkumar *et al.*, 2012).*Cenostigma macrophyllum, Malva sylvestris, Punica granatum* and *Rosmarinus officinalis* induced anti-inflammatory activity in rat skin, which contributed to accelerated skin wound healing.

High levels of cytokine production are also involved in the impairment of endothelial nitric oxide synthase (eNOS) activity, resulting in diminished nitric oxide (NO) bioavailability and consequent pro-atherogenic alterations in diabetic conditions (Tousoulis *et al.*, 2012). Together with an anti-inflammatory effect, *Cenostigma macrophyllum* increased the production of NO, which contributed to the wound healing progression in diabetic rats.

Elucidating the modulatory effect of cytokines in skin wound healing can lead to novel and effective therapeutic strategies (Alzoghaibi *et al.*, 2013). Plants and natural products with anti-inflammatory properties exert beneficial effects in the control of type 2 diabetes and also in the cicatrization of skin wounds.

The well-known decreased rate of wound contraction in diabetic individuals can be attributed to several factors, such as decreased angiogenesis, impaired growth factor production, altered inflammatory and immune responses (Nilsson *et al.*, 2008) and an imbalance between the accumulation of extracellular components and their remodeling by matrix metalloproteinases (Lobmann *et al.*, 2002). Hyperglycemic animals present higher concentrations of glycated collagen and higher levels of collagenase activity (Peppa *et al.*, 2009). Bermudez *et al.* (2011) showed that there is decreased collagen content in the diabetic dermis as well as increased gene expression of the enzymes involved in collagen synthesis and a decreased production of factors that promote collagen degradation, suggesting that the defect in the collagen protein content in diabetic skin is at the post-transcriptional level. Successful skin wound healing involves adequate collagen biosynthesis, deposition and maturation, as collagen is the main component of the extracellular matrix (Haifei *et al.*, 2014). *Hylocereus undatus*, *Rosmarinus officinalis* and *Withania coagulans* demonstrated increased collagen synthesis and deposition as part of the skin wound healing mechanism.

Conclusions and Future Directions

The species studied to date exert skin wound healing activity through several mechanisms, reflecting the different pathways involved in the pathogenesis of diabetes and wound healing. The use of medicinal plants in diabetic skin wound healing could provide broader and more efficacious therapeutic strategies. These findings reinforce the importance of ethnopharmacological research, encouraging further research into new phytomedicines as safe and effective treatments for wound healing in diabetic individuals.

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