Medical Science
The International Weekly journal
ISSN 2321 – 7359 EISSN 2321 – 7367

REVIEW

# Potential Use of Herbal Medicines in the Treatment of Diabetic Foot Ulcers

Kollipara Radhakrishna[#], Narayana Reddy Karri VVS[#], Mahendran Baskaran, Gowthamarajan Kuppusamy[*]

Department of Pharmaceutics, JSS College of Pharmacy, Ootacamund, JSS University, Mysore, India – 643001

[#]These authors contributed equally.

[*]**Address for Correspondence:** Gowthamarajan Kuppusamy, Department of Pharmaceutics, JSS College of Pharmacy, Ootacamund, JSS University, Mysore, India – 643001. E-mail: gowthamsang@gmail.com; Phone: +91 423 2443393 Ext.216.

**Publication History**
Received: 02 October 2014
Accepted: 14 November 2014
Published: 19 November 2014

**Citation**
Kollipara Radhakrishna, Narayana Reddy Karri VVS, Mahendran Baskaran, Gowthamarajan Kuppusamy. Potential Use of Herbal Medicines in the Treatment of Diabetic Foot Ulcers. *Medical Science*, 2014, 14(56), 34-42

## ABSTRACT

The complications of diabetes became a heavy burden to the patient as well as physician. Among the various complications, diabetic foot ulcer (DFU) is important since the major deaths in diabetes are due to DFU, which arises as a consequence of complicated and multi-factorial pathologies. The treatments using a single strategy may unlikely less effective and also the overall costs of these therapies are high. From long since, many commonly used herbs and spices are claimed to have wound healing effects with various mechanisms. Hence their application in the treatment of DFU may not only synergize the diabetic wound healing but also reduce the overall cost. This review discusses the possible use of herbs in treating DFUs with their mechanisms.

**Key Words:** Diabetes Mellitus, Diabetic foot ulcer, Diabetic neuropathy, Herbal.

## 1. INTRODUCTION

Diabetes mellitus (DM) is the major issue in the world wide and it is the chronic disorder which occurs due to the inadequate amount of insulin uptake (or) release. The occurrence of the DM is increased considerably (Shaw et al. 2010). The main factors for the increasing DM are inactive lifestyle, obesity, ageing and in few cases it was genetical. The negligence of DM condition will result in a number of consequences which include neuropathy, retinopathy, endothelial dysfunction, atherosclerosis, myocardial infractions, diabetic foot etc., (Bays et al. 2004). This results with many problems in foot such as neuropathy, peripheral arterial disease, DFU, osteomyelitis, gangrene and amputation (Blakytny et al. 2011; Botek et al. 2011; Howell and Goulston, 2011). In the past decade the DM patients with leg complications are increased. A major

complication of this is diabetic foot having ulcer healing difficulties, which are clinically significant and challenging. It was estimated that approximately 15% of total diabetic patient will be affected by DFU. (Powlson and coll, 2011; Nilforoushzadeh et al. 2012) DM is considered as the major cause of non-traumatic lower extremity amputation that reduces the survival of patient and cause huge burden to the society (Tentolouris et al. 2004). To improve the healing process of a DFU, there are several antibiotics (moxifloxacin, enrofloxacin and Pregabalin), neuropathic drugs (tricyclic anti depressant, anticonvulsant, serotonin reuptake inhibitors) and biomedical devices (epligraft, dermagrafte.tc) are available. The use of oral or I.V antibiotics were found to be resistant to most of the pathogens. Hence this requires repeated and high doses. Medical devices require skilled practitioners and hospitalization of the patient which associated with high cost. Apart from this the treatment of DFU using a single strategy may unlikely less effective since DFU arises as a consequence of multi-factorial pathologies. To overcome these hurdles herbal compounds can be used which are biocompatible, biodegradable and less or non-toxic. Several extracts of plants, minerals and animal origin are described in the traditional texts of Indian systems of medicine like "Ayurveda" for their healing properties under the term 'Vranaropaka'. Some of these plants have been screened scientifically for the evaluation of their wound healing activity in different pharmacological models and human subjects. However their capacity in treating DFU is remains unexplored (Kumar et al. 2007). Numerous studies have reported the use of herbals in active wound healing but very few explained the herbal products in chronic wound healing. Plant constituents and herbal extracts are known to be the rich source of anti-oxidants to counter act Reactive Oxygen Species (ROS). Hence antioxidants are helpful in treating many diseases such as arteriosclerosis, inflammatory disorders, cancer, coronary disease and DM. Hence natural antioxidants due to their free radical scavenging property gives possible protection against many chronic diseases as well as lipid per oxidation (Ak T et al. 2008). The herbs also enhance the rate of tissue healing by providing different vital substances (vitamins, proteins and minerals) required at different stages of wound regeneration and proliferation. Herbals are also found to be safe and cost effective than allopathic drugs. This review discusses the possible use of herbs in treating DFUs with their mechanisms.

## 2. HERBAL MEDICINES FOR THE TREATMENT OF DFUs (Figure 1 and Table 1)


**Figure 1**
Images of various parts of herbals for treating DFU

## 2.1. Turmeric

Turmeric (C*urcuma longa*) is an herb belonging to the family Zingiberaceae. Since from ancient time it was used as the coloring agent, dietary spice and as antibiotic (Chattopadhyay et al. 2004). Rhizome (root) is the most important part of *C. longa* which is used as the ancient medicine for several diseases (Chattopadhyay et al. 2004; Patwardhan et al. 2005). The paste of lime mixed with curcumin is used to treat inflammation and wounds, which is known to be one of the popular Indian home remedy (Anamika, 2012). *C. longa* consists of three principle curcuminoids, among which curcumin (diferuloylmethane 77%) is the major constituent. In more recent times, curcumin has been studied extensively for its use as an anti-cancer (Agrawal and Mishra, 2010; Shehzad et al. 2013), anti-aging (Lima et al. 2011; Bala et al. 2006), diabetic retinopathy (Pathak et al. 2014), anti-infective and wound healing activity (Maheshwari et al. 2006). Curcumin act against and protects the wound tissue from bacterial infections and induces cell proliferation. It reduces inflammation to help in the restoration of damaged tissue (Kulac et al. 2013). It acts as an ideal antioxidant as the free radicals are considered to be the major cause of inflammation during wound healing process of DFUs (Mohanty et al. 2012). The potency of curcumin in wound healing is attributed to its biochemical effects such as anti-infectious (Mun et al. 2013; Singh et al. 2010), antioxidant (Ak T and Gulcin, 2008; Meng et al. 2013) and anti-inflammatory (Liang et al. 2009) activities. Curcumin also improves cutaneous wound healing by involving in the tissue remodeling, collagen deposition, and granulation tissue formation (Joe et al. 2004). The exact mechanisms by which curcumin modulates inflammation is by inhibiting the production of tumor necrosis factor alpha- α (TNF-α) and interleukin-1 (IL-1), two major cytokines released from monocytes and macrophages that play important roles in the regulation of inflammatory responses. Oxidative stress is a significant factor in the chronic wound healing process and generally inhibits tissue remodeling (Thangapazham et al. 2013). As free radicals, ROS result in oxidative damage, DNA breakage and enzyme inactivation, leading to lipid per oxidation all of which inhibit optimum wound healing. ROS are considered to be the major cause of inflammation during chronic wound healing activity (Mohanty et al. 2012). It has been found that anti-oxidants with free radical scavenging potential like curcumin can significantly improve wound healing when applied topically (Martin, 1996). Kant V et al., 2014 studied effect of curcumin (0.3%) in streptozotocin-induced diabetic rats. The results revealed that topical curcumin application increased the wound contraction and decreased the expressions of inflammatory cytokines/enzymes i.e. TNF-α, interleukin (IL)-1β and matrix metalloproteinase-9 (MMP-9). It also has shown increased levels of anti-inflammatory cytokine (IL-10) and antioxidant enzymes (superoxide dismutase, catalase and glutathione peroxidase). Curcumin treated wounds showed better granulation tissue dominated by marked fibroblast proliferation and collagen deposition, and thus wounds were covered by thick regenerated epithelial layer. These findings shown that the anti-inflammatory and antioxidant potential of curcumin caused faster and better wound healing in diabetic rats and they also further confirmed that curcumin could be an additional novel therapeutic agent in the management of impaired wound healing in diabetics (Kant v et al. 2014).

## 2.2. Avocado

The *Persea Americana (P. americana)* also known as avocado fruit belonging to the family Lauraceae. The fruit pulp contains monounsaturated fatty acids with the highest content of lutein (70% of the measured carotenoids) (Ortiz et al. 2004; Salazar et al. 2005). These play significant role in reducing the risk of cancer, Wound healing (Nayak et al. 2008) and hepatoprotective action (Kawagishi et al. 2001). It is also a rich source for vitamin A, Vitamin E, phospholipids and glycolipids. Vitamin A is required for epithelial formation, cellular differentiation and immune function, and vitamin E is the major lipid-soluble antioxidant in the skin. Monounsaturated fatty acids, topical and systemic carotenoids and vitamin E promote wound healing. Derivatives of phospholipids and glycolipids also found to have wound-healing properties (Nayak et al. 2008). Phytochemical screening of the *P. americana* discovered the presence of flavonoids which are helpful in antioxidant property. Extracts of *P. americana* has shown both antifungal and antibacterial properties (Jacob et al. 1971). Aqueous extract of *P. Americana* reported to have vasorelaxation depending up on the concentration. This vasorelaxant effect may be produced by the inhibition of $Ca^{+}$ mobilization through voltage-dependent channels and to a lesser extent through receptor-operated channels. (Owolabi et al. 2005) *P. americana* will show anti-inflammatory activity by the inhibition of prostaglandin synthesis in platelets (Adeyemi et al. 2002). Extract of *P. americana* significantly increases the rate of wound contraction/epithelialisation, and the weight of the granulation tissue. These tissues are mostly composed of fibroblasts, collagen, edema and new small blood vessels. The pro-inflammatory activity of the constituents of *P. americana* could attract macrophages to the wound site. Macrophages stimulate the chemotaxis and proliferation of fibroblasts and attract endothelial cells to the wound and stimulate their proliferation to promote angiogenesis.

## 2.3. Aloe vera

Aloe vera is botanical known as *Aloe barbadensis* (*A. barbadensis*) belonging to the family of Xanthorrhoeaceae. *A. barbadensis* gel contains chemical constituents such as saponins, naftoquinones, anthroquinones, sterols, and triterpenoids. (Rosenthal, 1968) These compounds are useful to show beneficial effects (anti-inflammatory activity) and promote wound healing (Davis et al. 1994). Glucomannan, a mannose-rich polysaccharide, and gibberellin, a plant growth hormone, interact with growth factor receptors of the fibroblast, thereby stimulating their activity and proliferation, which in turn significantly increase collagen synthesis after topical administration of *A. barbadensis* gel. This gel not only increases collagen content of the wound but also changes collagen composition (type III) and increases the extent of collagen cross-linking. Due to this, it accelerates wound contraction and increases the breaking strength of resulting scar tissue. An increase in the synthesis of hyaluronic acid and dermatan sulfate in the granulation tissue of a healing wound following oral or topical application of *A. barbadensis* has been reported. The mechanism involved in *A. barbadensis* in diabetic wound healing (Chithra et al. 1998; Mendonca et al. 2009; Takzare et al. 2009) is by hydrolyzing enzymes like prostaglandin, bradykinin, carboxypepditase and bardykinase that are hypothesized to reduce inflammation and pain (Steenkamp and Stewart, 2007; Takzare et al. 2009). *A. barbadensis* derived polysaccharides such as mannose-6-

phosphate has been postulated to be active growth substances, especially in epithelialisation (Davis et al. 1994; Boudreau and Beland, 2006; Steenkamp and Steward, 2007). Acemannan, another polysaccharide in *A. barbadensis*, has been shown to up-regulate white blood cell activity in the wound healing process (Boudreau and Beland, 2006; Tamura et al. 2009). Anti-bacterial properties of anthraquinones, an organic compound responsible for the natural pigment of *A. barbadensis*, are beneficial in minimizing infections (Tamura et al. 2009; Kuzuya et al. 2001). Hotkar et al., 2013 have studied the use of *A. barbadensis* as gel base using Nitroglycerin as active molecule in streptozotocin-induced DFU and rat excision wound models. They found that the wound size in animals of all treated groups was significantly reduced compared with that of the diabetic control and marketed treated animals. They also further conformed that the gel (carbopol 974p (1%) and Aloe vera) treated animals promotes significant wound healing and closure in diabetic rats compared with the commercial product and provided a promising product to be used in diabetes-induced foot ulcer (Hotkar et al. 2013).

### 2.4. Papaya

*Carica papaya (C. papaya)* belonging to family Caricaceae (Banerjee et al. 2007). The major phytochemical constituents of this fruit are flavonols, nicotine, tannins, and terpinenes as well as enzymes such as papain and chymopapain (Brocklehurst et al. 1985; Tona et al. 1998). Traditionally different parts of this plant are used in many treatments. The *C. papaya* seed extract having effective bactericidal action against the *Staphylococcus aureus*, *Pseudomonas aeurginosa*, *Escherichia coli*, *Bacillus cereus* and *Shigella flexneri* (Emeruwa, 1982). The unripe matured *C. papaya* fruit is reported to have anti diabetic effects and studies are conducted in several animals (Olagunju et al. 1995) and humans (Olapade, 1995; Salau et al. 2003). There is an adequate report on the hypoglycemic and/or antidiabetic effects of the *C. papaya* seed despite its extensive and historical use in the traditional management of diabetes and obesity. *C. papaya* is used as the debridement agent and it convert proline to hydro proline and it act as anti bacterial which together enhance wound healing. Nayak et al, 2007 examined the effect of *C. papaya* in experimentally induced diabetic rats. The reduction of wound area in *C. papaya* treated animals was reported to be 77% when compared to control which is 59%. The *C. papaya* treated wound was found to epithelize faster than the control and also a significant increase in wet and dry granulation tissue weight and hydroxyproline content was observed (Nayak et al. 2007).

### 2.5. Chinese Herbal Medicine

Chinese Herbal medicine contains *Astragali Radix* (AR) and *Rehmanniae radix* (RR). AR is extracted from the dried roots of *Astragalus membranaceus* belonging to the family Leguminosae. The main constituents of AR are polysaccharides, flavonoids, saponins, amino acids and trace elements (Ma et al. 2002; Yu et al. 2007). AR is used as the cardioprotective (Xu et al. 2008; Zhao et al. 2008), immunomodulatory (Zhang et al. 2009; Liu et al. 2010), as well as insulin-sensitizing agent (Xu et al. 2009; Hoo et al. 2010). *AR* promotes fibroblast proliferation and increasing the rate of diabetic wound healing. *RR* is extracted from the *Rehmannia glutinosa* belonging to the family of Scrophulariaceae. RR having wide range of pharmacological actions on the immune system, endocrine system, blood system, cardio vascular system and nervous system (reviewed by Zhang et al. 2008). RR can remove pathogenic heat from blood, nourish and promote production of body fluid. Therefore, it is widely prescribed to relieve febrile diseases, diabetes, epistaxis and skin eruption. AR and RR stimulate fibroblast and inhibit cellular inflammation by synergestic action. lau et al, 2012 described the synergistic interaction between AR and RR in a chemically induced DFU rat model. Their examination showed that AR and RR as a separate formulation with a clinical relevant dose of 0.98g/kg dose not promote diabetic wound healing. But when they are used as combination a synergistic interaction was demonstrated and reduced the wound area in rats significantly (lau et al, 2012).

### 2.6. Manuka honey

Manuka honey botanically known as the *Leptospermum scoparium* belongs to the family Myrtaceae (stephens, 2006). It is also called as Monofloral honey produced from the nectar of the manuka tree. Manuka Honey is considered as a medicine in wound healing from the ancient times. In 2007 USFDA has approved Manuka honey for wound management. It act as an antimicrobial, antioxidant and immune modulator with both pro- and anti-inflammatory effects, hence it is used in the treatment of a broad spectrum of wounds. The active constituent present in the Manuka honey is methylglyoxal that show excellent anti-bacterial action (Lo et al. 1994). Methylglyoxal has been reported to react with arginine, lysine and cysteine residues of structural proteins such as collagen giving origin to AGEs that disturb extracellular matrix remodeling, promote fibrosis in chronic tissue infections, impair immune response and microcirculation, promote atherosclerosis and neovascularisation, induce endothelial cell dysfunction and impair wound closure. In a case study conducted by Mohamed H et al., 2013 in a 65 years old female-Egyptian diabetic patient presented with a neuropathic plantar ulcer with honey dressing at 16$^{th}$ week showed complete ulcer healing. Honey used topically has provided antibacterial activity and moisture environment, thereby accelerating tissue repair, less scarring and less pain and no symptoms were reported by the patient which could be attributed to advanced diabetic peripheral neuropathy (Mohamed et al. 2013).

### 2.7. Curculin

Curculin is botanically known as *Curculigo orchioides* (*C. orchioides*) belongs to the family Hypoxidaceae (Singh A and Singh PK, 2009). It is a tiny herbal plant widely distributed in China, Malaysia, Japan, Australia and also in subtropical Himalayas region of India. *C. orchioides* contains phytoconstituents such as flavonoids, tannins, saponins and phenolic compounds which are important plant metabolites that play prominent role in diabetic wound healing. Tannins act as free radical scavengers, triterpenoids and flavonoids will promote wound healing due to their astringent and antimicrobial property. Flavonoids also possess potent antioxidant and free radical scavenging effect that enhances the levels of anti oxidant enzyme in granulation tissue. Saponins, due to their antioxidant and antimicrobial activity appear to be responsible for wound

contraction and elevated rate of re-epithelialization. Singh A et al, 2014 found the wound healing activity of standardized extract of *C. orchioides* in streptozotocin induced diabetic mice. The results showed that the root tubers of *C. orchioides* are potent source of anti-oxidants. The root tuber of *C. orchioides* increases the level of superoxide dismutase and nitric acid significantly and decreases lipid peroxidation in granulose tissues of diabetic mice. They also found that the rate of angiogenesis and levels of anti-oxidant enzymes were increased by *C. orchioides* (Singh et al. 2014).

### 2.8. Martynia annua

Martynia annua (*M. annua*) belongs to the family of Martyniaccae (Khare, 2007). *M. annua* contain phytoconstituents such as glycosides, tannins, carbohydrates, phenols, flavonoids and anthocyanins. Flavonoids are reported to have free radical scavenging effect and anti-bacterial activity. Luteolin exerts a various pharmacological activities including anti-oxidant properties associated with its ability to scavenge oxygen and potent anti-inflammatory (Chatpalliwar et al. 2002) Luteolin is a flavone widely distributed in the plant kingdom, showed a concentration-dependent inhibitory activity in several models of oxidative stress. The antioxidant potential of luteolin is twice stronger than that of vitamin E and has strong scavenging properties for superoxide radicals. Lodhi and Singhai, 2013 explored Wound healing effect of flavonoid rich fraction and luteolin isolated from *M. annua* in streptozotocin induced diabetic rats. The results confirmed that percentage wound contraction was observed significantly ($p<0.01$) greater in flavanoid fraction and 0.5% w/w of luteolin treatment groups. In their histopathological studies matured collagen fibers and fibroblasts with better angiogenesis were observed possibly due to free-radical scavenging activity of plant (Lodhi and Singhai, 2013).

### 2.9. Rosmarinus officinalis

*Rosmarinus officinalis* (*R. officinalis*) commonly known as the rosemary belonging to the Family Lamiaceae (al-sereiti et al. 1999). It is a perennial herb which is commonly used as the spice and flavoring agent. The major constituent present in the *R. officinalis* are caffeic acid and its derivative rosmarinic acid. *R. officinalis* have a rich source of antioxidants and anti-inflammatory compounds (Takaki et al. 2008) which enhances memory and concentration, neurological protection, prevent brain aging, cancer, protection against macular degeneration. The carnosic acid in *R. officinalis* is able to fight against free radical damage in the wound. Mariam A and Abu-Al-Basal 2010, studied Healing potential of *R. officinalis* on full-thickness excision cutaneous wounds in alloxan-induced-diabetic BALB/c mice. Their study showed reduced inflammation and facilitated wound contraction, re-epithelialization, regeneration of granulation tissue, angiogenesis and collagen deposition were detected in the *R. officinalis* extract treated wounds. This indicates that the extract of *R. officinalis* is more potent in healing diabetic wound (Abu-Al-Basal, 2010).

### 2.10. Grape seed extract

Grape seed extract (GSE) is botanically known as *Vitis vinifer*. GSE have a high concentration of flavonoids, Vitamin E, linoleic acid and phenolic procyanidins (oligomeric procyanidins). The GSE (proanthocyanidin or condensed tannins) contains poly phenols which are widely distributed throughout the plant kingdom. GSE is an effective hydrophilic peroxy radical, especially radical scavenger in the aqueous system. The proanthocyanidin were found to be much stronger than the vitamin C and E. GSE is widely used in the treatment of cardiac disorders (atherosclerosis), protective agent for gastric mucosa (gastric ulcer), cataracts, diabetes (diabetic neuropathy) and reduces hypoxic ischemic brain injury. Proanthocyandins (or condense tannins) and other tannins are well known for their acceleration of wound healing property (Root-Bernstein, 1982; Hupkens et al. 1995). However the mechanism of action is not known (Bagchi, et al. 1997; Bagchi et al. 1999; Ye et al. 1999 Ray et al. 1999). The expected mechanism is found to be anti-oxidant and potentially induced (Vascular endothelial growth factor) VEGF expression in human keratinocytes (Khanna et al. 2001; Sen et al. 2002). It also considerably increase the motor nerve conductive velocity mechanically, superoxide dismutase and reduce the advanced glycation end products (AGEs) and tissue malondialdehyde. It decreases the inflammation and viscosity of the blood in diabetic patient and thereby increases the nutrient supply to wound and accelerate wound healing. It also helps in lowering the blood glucose levels and improves the micro circulation. Alpha-glycosidase, an enzyme in GSE which breaks down carbohydrates into glucose molecule can delay glucose absorption to a greater extent.

### 2.11. Kiwi Fruit

Kiwi fruit botanically known as *Actinidia deliciosa* belongs to the family Actinidiaceae. It is a rich source of vitamin C, E, K and carotenoids, such as provitamin A beta-carotene, lutein and zeaxanthin. It also contains proteolytic enzymes (actinidin) (Low et al. 2004) and ascorbic acid. It is believed that Kiwi fruit contains potent protein-dissolving property that acts as debridement agent. Kiwifruit is probably a rich source of angiogenesis modulators that are commonly required for wound healing. It contains antibacterial (Basile et al. 1997) and scavenger agents in addition to proteolytic enzymes, which may improve the wound healing. Mohajeri et al, 2014 explored the topical use of kiwifruit on neuropathic DFU. They reported a mean reduction in surface area of foot ulcer in kiwifruit treated group when comparing with the control. They also found a significant increase in collagen and granulation tissues similarly higher levels of angiogenesis and vascularization were found in kiwifruit treated patients. Actinidin, a protein dissolving enzyme in kiwifruit have shown improved wound healing property (Mohajeri et al. 2014).

**Table 1**

Herbals in treating DFUs with their mechanisms

| Scientific Name of the Plant | Common Name | Family Name | Major Constituents | Mechanism of Action |
|---|---|---|---|---|
| Curcuma longa | Turmeric | Zingiberaceae | Curcumin, desmethoxycurcumin and bis-desmethoxy curcumin. | Reduce the activity of NF-(κ)B, TNF-α and IL-1 cytokines. Increase fibroblast proliferation, fibroblast migration, granulation tissue formation and collagen deposition |
| Persea americana | Avocado | Lauraceae | Monosaturated fatty acis, leutin, Vitamin A and E, phospho and glycolipids. | Promotes wound healing by collagen formation at the proliferative stage of wound healing. Vitamins A and E, proteins, beta-carotene, lecithin, fatty acids and potassium which acts as nutrient support in wound healing. |
| Aloe barbadensis | Aloe vera | Xanthorrhoeaceae | Saponons, naftoquinones, anthroquinones, sterols and triterpenoids. | Reduce inflammation and pain, Increased blood flow to the wound. Bactericidal and bacteriostatic. |
| Carica papaya | Papaya | Caricaceae | Papain, cystatin, chymopapain, tocopherol, flavonoids, cyanogenic glucosides and glucosinolates. | Debridiment agent (convert proline to hydro proline) and it act as antimicrobial. |
| Astragali Radix and Rehmanniae Radix | Chinese herbal medicine | Leguminosae and Scrophulariaceae | Flavanoids, Saponins, aminoacids and trace elements. | Stimulate fibroblast proliferation and inhibit cellular inflammation. |
| Leptospermum scoparium | Manuka honey | Myrtaceae | Methylglyoxal | Methylglyoxal, effective antimicrobial active against forms of MRSA. Debridement action. |
| Curculigo orchioides | Curculin | Hypoxidaceae | Curculigosides Flavanoids, tannins and phenolic compounds. | Free radical scavenger, antimicrobial, decreases lipid peroxidation in granulose tissues. |
| Martyina annua | Martynia annua | Martyniaccae | Steroid, palmitic acid, oleic acid, arachidic acid and chlorogenic acid. | Inhibitory activity on oxidative stress. Luteolin have antioxidant potential twice stronger than that of vitamin E and has strong scavenging properties for superoxide radicals. |
| Rosmarinus officinalis | Rosemary | Lamiaceae | Carnosic acid and rosmarinic acid | Reduce inflammation and facilitate wound contraction and re-epithelialization, regeneration of granulation tissue, angiogenesis and collagen deposition |
| Vitis vinifera | Grape seed extract | Vitaceae | Oligomeric procyanidins | Oligomeric procyanidins induced vascular endothelial growth factor and accelerated healing of injured skin. |

| | | | | |
|---|---|---|---|---|
| Actinidia deliciosa | Kiwi fruit | Actinidiaceae | Lutein, beta-carotene, fisetin, Vitamin C, E, K and ascorbic acid. | Protein-dissolving property (Debridement action) and antimicrobial. |

## 3. CONCLUSION

Treatment and management of DFUs are challenging to medical practitioners till today. Treatment is much costly and most of the ulcers are reluctant to treat with standard wound care. Herbals are better alternatives for the treatment of DFUs because of their safer profiles, low cost, widespread availability, reduced risk of side effects and effectives with chronic conditions. Herbal drugs will act by various mechanisms unlikely allopathic drugs and hence synergize the overall wound healing effects. An alternate therapy with herbal drugs will be the best solution to address the complications associated with the treatment of DFUs.

## REFERENCES


1. Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. *Diabetes Res Clin Pr* 2010, 87, 4–14.
2. Bays H, Mandarino L, DeFronzo R A. Role of the adipocyte, free fatty acids, and ectopic fat in pathogenesis of type 2 diabetes mellitus: peroxisomal proliferator-activated receptor agonists provide a rational therapeutic approach *J Clin Endocrinol Metab* 2004, 89, 463–478.
3. Blakytny R, Spraul M, Jude EB. Review: the diabetic bone: a cellular and molecular perspective. *Int J Low Extrem Wounds* 2011, 10, 16–32.
4. Botek G, Anderson MA, Taylor R. Charcot neuroarthropathy: an often overlooked complication of diabetes. *Cleve Clin J Med* 2011, 77, 593–599.
5. Howell W R, Goulston C. Osteomyelitis. *Hosp Pract* 2011, 39, 153-160
6. Powlson AS, Coll AP. The treatment of diabetic foot infections. *J Antimicrob Chemother* 2010, 65, iii3-iii9.
7. Nilforoushzadeh MA, Jaffary F, Ansari N, Siadat AH, Heidari A, Adibi N. Treatment of recalcitrant diabetic foot ulcers using trichloroacetic acid. *J Res Med Sci* 2012, 17, S287-S291.
8. Tentolouris N, Al-Sabbagh S, Walker MG, Boulton AJ, Jude EB. Mortality in diabetic and nondiabetic patients after amputations performed from 1990 to 1995 a 5-year follow-up study. *Diabetes care* 2004, 27, 1598-1604.
9. Kumar B, Vijayakumar M, Govindarajan R, Pushpangadan P. Ethnopharmacological approaches to wound healing—exploring medicinal plants of India. *J Ethnopharmacol* 2007, 114, 103-113.
10. Ak T, Gülçin İ. Antioxidant and radical scavenging properties of curcumin. *Chem Biol Interact* 2008, 174, 27-37.
11. Chattopadhyay I, Biswas K, Bandyopadhyay U, Banerjee R. Turmeric and curcumin:biological actions and medicinal applications. *Curr Sci* 2004,87,44–53.
12. Patwardhan B, Warude D, Pushpangadan P, Bhatt N. Ayurveda and traditional Chinese medicine: a comparative overview. *Evid Based Complement Alternat Med* 2005,631, 465–473.
13. Anamika B. Extraction of curcumin. *J Environ Sci Toxicol Food Technol* 2012, 1, 1–16.
14. Agrawal DK, Mishra PK. Curcumin and its analogues: potential anticancer agents. *Med Res Rev* 2010,30,818–860.
15. Shehzad A, Lee J, Lee YS. Curcumin in various cancers. *Biofactors* 2013, 39, 56–68.
16. Lima CF, Pereira-Wilson C, Rattan SI. Curcumin induces heme oxygenase-1 in normal human skin fibroblasts through redox signaling: relevance for anti-aging intervention. *Mol Nutr Food Res* 2011, 55, 430–442
17. Bala K, Tripathy BC, Sharma D. Neuroprotective and anti-ageing effects of curcumin in aged rat brain regions. *Biogerontology* 2006, 7, 81–89.
18. Pathak D, Kumar P, Kuppusamy G, Gupta A, Kamble B, Wadhwani A. Physicochemical characterization and toxicological evaluation of plant-based anionic polymers and their nanoparticulated system for ocular delivery. *Nanotoxicology 2014, 8*, 843-855.
19. Maheshwari R, Singh A, Gaddipati J, Srimal R. Multiple biological activities of curcumin: a short review. *Life Sci* 2006, 78, 2081–2087.
20. KulacM, Aktas C, Tulubas F, Uygur R, KanterM, ErbogaM, ozen OA. The effects of topical treatment with curcumin on burn wound healing in rats. *J Mol Histol* 2013, 44, 83–90.
21. Mohanty C, Das M, Sahoo S. Sustained wound healing activity of curcumin loaded oleic acid based polymeric bandage in a rat model. *Mol Pharm* 2012, 9, 2801–2811.
22. Mun SH, Joung DK, Kim YS, Kang OH, Kim SB, Seo YS, Kwon DY. Synergistic antibacterial effect of curcumin against methicillin-resistant Staphylococcus aureus. *Phytomedicine* 2013, 20,714–718.
23. Singh RK, Rai D, Yadav D, Bhargava A, Balzarini J, De Clercq E. Synthesis, antibacterial and antiviral properties of curcumin bioconjugates bearing dipeptide, fatty acids and folic acid. *Eur J Med Chem* 2010, 45, 1078–1086.
24. Meng B, Li J, Cao H. Antioxidant and antiinflammatory activities of curcumin on diabetes mellitus and its complications. *Curr Pharm Des* 2013, 19, 2101–2113.
25. Liang G, Yang S, Zhou H, Shao L, Huang K, Xiao J, Li X. Synthesis, crystal structure and anti- inflammatory properties of curcumin analogues. *Eur J Med Chem* 2009, 44, 915–919.
26. Joe B, Vijaykumar M, Lokesh B. Biological properties of curcumin-cellular and molecular mechanisms of action. *Crit Rev Food Sci Nutr* 2004, 44, 97–111
27. Thangapazham R, Sharad S, Maheshwari R. Skin regenerative potentials of curcumin. *Biofactors* 2013, 39, 141–149.
28. Martin P. Wound healing-aiming for perfect skin regeneration. *Science* 1997, 276, 75–81.
29. Kant V, Gopal A, Pathak NN, Kumar P, Tandan SK, Kumar D. Antioxidant and anti-inflammatory potential of curcumin accelerated the cutaneous wound healing in streptozotocin-induced diabetic rats. *Int Immunopharmacol* 2014, 20, 322-330.
30. Ortiz MA, Dorantes AL, Gallndez MJ, Cardenas SE. Effect of a novel oil extraction method on avocado (Persea americana Mill) pulp microstructure. *Plant Foods Hum. Nutr* 2004, 59,11-14.
31. Salazar MJ, El Hafidi M, Pastelin G, Ramírez-Ortega MC, Sánchez-Mendoza MA. Effect of an avocado oil-rich diet over an angiotensin II-induced blood pressure response. *J. Ethnopharmacol* 2005, 98, 335-338.
32. Nayak BS, Raju SS, Chalapathi Rao AV. Wound healing activity of Persea americana (avocado) fruit: a preclinical study on rats. *J. Wound Care* 2008, 17, 123-126.
33. Kawagishi H, Fukumoto Y, Hatakeyama M, He P, Arimoto H. Liver injury suppressing compounds from avocado (Persea americana). *J Agric Food Chem* 2001, 49, 221-521.
34. Jacob B, Biale JB, Young RE .The avocado pear. In: Hulme AC, ed., The Biochemistry of Fruits and Their Products. *London, Academic Press* 1971, 3–22.
35. Owolabi MA, Jaja SI, Coker HA. Vasorelaxant action of aqueous extract of the leaves of Persea Americana on isolated thoracic rat aorta. *Fitoterapia* 2005, 76, 567–73.
36. Adeyemi OO, Okpo SO, Ogunti OO. Analgesic and anti-inflammatory effects of the aqueous extract of leaves of Persea americana Mill (Lauraceae) *Fitoterapia* 2002,73,375–380
37. Rosenthal SP. Acceleration of primary wound healing by insulin.Archives of *Surgery* 1968, 96, 53-55.
38. Davis RH, Didonato JJ, Hartman GM, Haas RC. Anti-inflammatory and wound healing activity of a growth substance in aloe vera. *J Amer Podiatric Med Assoc* 1994, 84, 77–81.

39. Chithra P, Sajithal G, Chandrakasan G. Influence of aloe vera on the healing of dermal wounds in diabetic rats. *J Ethnopharmacol* 1998, 59, 195–201.
40. Mendonça F, Passarini Jr J, Esquisatto M, Mendonça J, Franchini C, Dos Santos G. Effects of the application of Aloe vera (L.) and microcurrent on the healing of wounds surgically induced in Wistar rats [Efeitos da aplicação de Aloe vera (L.) e microcorrente no reparo de lesões cirúrgicas induzidasem ratos Wistar]. *Acta Cir Bras*. 2009, 24,150–155.
41. Takzare N, Hosseini M, Hasanzadeh G, Mortazavi H, Takzare A, Habibi P. Influence of aloe vera gel on dermal wound healing process in rat. *Toxicol. Mech. Methods*. 2009,19,73–77
42. Steenkamp V, Stewart M. Medicinal applications and toxicological activities of aloe products. *Pharm Biol* 2007, 45,411–420.
43. Boudreau M, Beland F. An evaluation of the biological and toxicological properties of Aloe Barbadensis (Miller), Aloe Vera. *J Environ Sci Health* 2006, 24, 103–154.
44. Tamura N, Yoshida T, Miyaji K, Sugita-Konishi Y, Hattori M. Inhibition of infectious diseases by components from Aloe vera. *Biosci., Biotechnol., Biochem* 2009, 73,950–953.
45. Kuzuya H, Tamai I, Beppu H, Shimpo K, Chihara T. Determination of aloenin, barbaloin and isobarbaloin in aloe species by micellar electrokinetic chromatography. *J. Chromatogr. B, Biomed.Sci*. 2001, 752, 91–97.
46. Hotkar MS, Avachat AM, Bhosale SS, Oswal YM. Preliminary investigation of topical nitroglycerin formulations containing natural wound healing agent in diabetes-induced foot ulcer. *Int Wound J* 2013.
47. Banerjee A, Vaghasiya R, Shrivastava N, Padh H, Nivsarkar M. Antihyperlipidemic effect of Carica papaya L. in Sprague Dawley rats. Nigerian *J Natl Prod Med* 2007, 10, 69-72.
48. Brocklehurst K, Salih E, McKee R, Smith H. Fresh non-fruit latex of Carica papaya contains papain, multiple forms of chymopapain A and papaya proteinase omega. *Biochem J* 1985, 228, 525-527.
49. Tona L, Kambu K, Ngimbi N, Cimanga K, Vlietinck AJ. Antiamoebic and phytochemical screening of some Congolese medicinal plants. *J Ethnopharmacol* 1998, 61, 57-65.
50. Emeruwa AC. Antibacterial substance from Carica papaya fruit extract. *J Nat Prod* 1982, 45, 123-127.
51. Olagunju JA, Ogunlana CO, Gbile ZO. The hypoglycemic activity of ethanolic extracts of unripe, mature fruits of Carica papaya in alloxan-induced diabetic rats. *Nig J Biochem Mol Biol* 1995,10, 21-23.
52. Olapade EO. Foods and herbs on diabetes mellitus: NARL Specialist. *Clinic Publications. Ibadan*.1995, 1-5.
53. Salau BA, Osilesi O, Idowu GO, Musa S, Ajani EO. Effects of fruits and vegetables on cardiovascular disease risk factors in non-insulin dependent diabetes mellitus (NIDDM) subjects. *Afr J Med pharm sci* 2003, 7, 21-26.
54. Nayak BS, Pereira LP, Maharaj D. Wound healing activity of Carica papaya L. in experimentally induced diabetic rats. *Indian J Exp Biol* 2007, 45,739.
55. Ma XQ, Shi Q, Duan JA, Dong TT, Tsim KW. Chemical analysis of Radix Astragali (Huangqi) in China: a comparison with its adulterants and seasonal variations. *J. Agric. Food Chem* 2002, 50, 4861–4866.
56. Yu QT, Qi LW, Li P, Yi L, Zhao J, Bi Z. Determination of seventeen main flavonoids and saponins in the medicinal plant Huang-qi (Radix astragali) by HPLC-DAD-ELSD. *J Sep Sci* 2007, 30, 1292–1299.
57. Xu XL, Ji H, Gu SY, Shao Q, Huang QJ, Cheng YP. Cardioprotective effects of Astragali Radix against isoproterenol-induced myocardial injury in rats and its possible mechanism. *Phytother Res* 2008, 22, 389–394.
58. Zhao P, Su G, Xiao X, Hao E, Zhu X, Ren J. Chinese medicinal herb Radix Astragali suppresses cardiac contractile dysfunction and inflammation in a rat model of autoimmune myocarditis. *Toxicology Letters* 2008, 182, 29–35.
59. Zhang RP, Zhang XP, Ruan YF , Ye SY, Zhao HC, Cheng QH, Wu DJ. Protective effect of Radix Astragali injection on immune organs of rats with obstructive jaundice and its mechanism. *World J. Gastroenterol* 2009, 15, 2862–2869
60. Liu J, Hu X, Yang Q, Yu Z, Zhao Z, Yi T, Chen H. Comparison of the immunoregulatory function of different constituents in radix astragali and radix hedysari. *J. Biomed. Biotechnol* 2010.
61. Xu A, Wang H, Hoo RL, Sweeney G, Vanhoutte PM, Wang Y, Wu D, Chu W, Qin G, Lam KS. Selective elevation of adiponectin production by the natural compounds derived from a medicinal herb alleviates insulin resistance and glucose intolerance in obese mice. *Endocrinology* 2009,150, 625–633.
62. Hoo RL, Wong JY, Qiao C, Xu A, Xu H, Lam KS. The effective fraction isolated from Radix Astragali alleviates glucose intolerance insulin resistance and hypertriglyceridemia in db/db diabetic mice through its anti-inflammatory activity. *Nutrition & Metabolism* 2010, 7, 67–78.
63. Zhang RX, Li MX, Jia ZP. Rehmannia glutinosa: review of botany chemistry and pharmacology. *J Ethnopharmacol* 2008, 117,199–214.
64. Lau KM, Lai KK, Liu C, Tam JCW, To MH, Kwok HF, Lau CBS.Synergistic interaction between Astragali Radix and Rehmanniae Radix in a Chinese herbal formula to promote diabetic wound healing. *J Ethnopharmacol* 2012, 141,250-256.
65. Stephens JMC. The factors responsible for the varying levels of UMF® in mānuka (Leptospermum scoparium) honey (Doctoral dissertation, The University of Waikato).2006.
66. Lo TW, Westwood ME, McLellan AC, Selwood T, Thornalley PJ. Binding and modification of proteins by methylglyoxal under physiological conditions. A kinetic and mechanistic study with N alpha-acetylarginine, N alpha-acetylcysteine, and N alpha-acetyllysine, and bovine serum albumin. *J. Biol chem* 1994.*269*, 32299-32305
67. Mohamed, H., El Lenjawi, B., Salma, M. A., & Abdi, S. (2014). Honey based therapy for the management of a recalcitrant diabetic foot ulcer. Journal of tissue viability, 23(1), 29-33.
68. Singh A, Singh PK. An ethnobotanical study of medicinal plants in Chandauli district of Uttar Pradesh, India. *J Ethnopharmacol* 2009, 121, 324-329.
69. Singh A, Bajpai S, Singh N, Kumar V, Gour JK, Singh PK, Singh RK. Wound healing activity of standardized extract of Curculigo orchioides in streptozotocin–induced diabetic mice. *Asian Pac J Trop Dis* 2014,4, S48-S53.
70. Khare CP. Indian Medicinal Plants: An Illustrated Dictionary. Heidelberg: *Springer-Verlag*. 2007, 399-400
71. Chatpalliwar VA, Joharapurkar AA, Wanjari MM, Chakraborty RR, Kharkar VT. Antiinflammatory activity of Martynia diandra GLOX. *Ind Drugs* 2002, 39, 543-545.
72. Lodhi S, Singhai AK. Wound healing effect of flavonoid rich fraction and luteolin isolated from Martynia annua Linn. On streptozotocin induced diabetic rats. *Asian Pac J Trop Med* 2013, 6, 253-259.
73. al-Sereiti MR, Abu-Amer KM, SenP.Pharmacologyofrosemary(Rosmarinus officinalis Linn.) anditstherapeuticpotentials. *Indian J Exp Biol* 1999,37,124–130.
74. Takaki I,Bersani-Amado LE,Vendruscolo A, Sartoretto SM, Diniz SP, Bersani-Amado CA, CumanRK.Anti-inflammatoryandantinociceptiveeffects of Rosmarinus officinalis. L.essentialoilinexperimentalanimalmodels. *J Med Food* 2008,11,741–746.
75. Abu-Al-Basal MA. Healing potential ofRosmarinus officinalis L. on full-thickness excision cutaneous wounds in alloxan-induced-diabetic BALB/c mice. *J Ethnopharmacol* 2010,*131*,443-450.
76. Root-Bernstein R S. Tannic acid, semipermeable membranes and burn treatment. *Lancet* 1982, 320, 1168.
77. Hupkens P, Boxma H, Dokter J. Tannic acid as a topical agent in burns: historical considerations and implications for new developments. *Burns* 1995, 21, 57–61.
78. Bagchi D, Garg A, Krohn RL, Bagchi M, Tran MX, Stohs SJ. Oxygen free radical scavenging abilities of vitamins C and E, and a grape seed proanthocyanidin extract in vitro. *Res. Commun. Mol. Pathol. Pharmacol* 1997, 95, 179–189.
79. Bagchi M, Balmoori J, Bagchi D, Ray SD, Kuszynski C, Stohs SJ. Smokeless tobacco, oxidative stress, apoptosis, and antioxidants in human oral keratinocytes .*Free Radic. Biol. Med* 1999,26,992-1000.
80. Ye X, Krohn RL, Liu W, Joshi SS, Kuszynski CA, McGinn TR, Bagchi M, Preuss HG, Stohs SJ, Bagchi D. The cytotoxic effects of a novel IH636 grape seed proanthocyanidin extract on cultured human cancer cells. *Mol. Cell. Biochem* 1999, 196, 99–108.
81. Ray SD, Kumar MA, Bagchi DA. Novel proanthocyanidin IH636 grape seed extract increases in vivo Bcl-XL expression and prevents acetaminophen-induced programmed and unprogrammed cell death in mouse liver. *Arch. Biochem. Biophys* 1999,369,42–58.

82. Khanna S, Roy S, Bagchi D, Bagchi M, Sen CK. Upregulation of oxidant-induced VEGF expression in cultured keratinocytes by a grape seed proanthocyanidin extract. *Free Radic. Biol.Med* 2001, 31, 38–42.
83. Sen CK, Khanna S, Venojarvi M, Trikha P, Ellison EC, Hunt TK, Roy S. Copper-induced vascular endothelial growth factor expression and wound healing. *Am. J. Physiol. Heart Circ. Physiol* 2002, 282, H1821–H1827.
84. Low C, Webb C, Thomas L, Ramos E, Panarese A, Clarke RW,Goodwin WJ. The efficacy of fruit juices in disimpacting meat bolus obstruction. *Otolaryngol Head Neck Surg* 2004,131,166.
85. Basile A, Vuotto ML, Violante U, Sorbo S, Martone G, Castaldo- Cobianchi R. Antibacterial activity in Actinidia chinensis, Feijoa sellowiana and Aberia caffra. *Int J Antimicrob Agents* 1997,8,199-203.
86. Mohajeri G, Safaee M, Sanei MH. Effects of topical Kiwifruit on healing of neuropathic diabetic foot ulcer. *J Res Med Sci* 2014,*19*,520-524