EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 6
Issue: 10
144-155
Year: 2019

DIABETIC FOOT ULCER: A REVIEW ON ITS PATHOPHYSIOLOGY, CLASSIFICATION AND AYURVEDIC TREATMENT

Lalita Chauhan*, Prerna Thakur[1] and Sheetal Sharma[2]

*Assistant Professor (Pharmaceutics), School of Pharmacy and Emerging Sciences, Baddi University of Emerging Sciences and Technology, Village Makhnumajra Baddi District Solan, Tehsil Nalagarh, H.P-173205.
[1,2]School of Pharmacy and Emerging Sciences, Baddi University of Emerging Sciences and Technology, Village Makhnumajra Baddi District Solan, Tehsil Nalagarh, H.P-173205.

***Corresponding Author: Prof. Lalita Chauhan**
Assistant Professor (Pharmaceutics), School of Pharmacy and Emerging Sciences, Baddi University of Emerging Sciences and Technology, Village Makhnumajra Baddi District Solan, Tehsil Nalagarh, H.P-173205.

Article Received on 10/07/2019 **Article Revised on 31/07/2019** **Article Accepted on 20/08/2019**

ABSTRACT
Foot ulcers are one of the main complications in diabetes mellitus in all diabetic patients. The problem and features are infection, ulceration, or gangrene. The three major contributors to the development of diabetic foot are; Neuropathy, poor circulation, and susceptibility to infection which when present, foot deformities or minor trauma can readily lead to ulceration and infection. About 60% of the foot ulcers are caused by neuropathy and affects patients with both Type 1 and Type 2 diabetes mellitus. For the classification of foot ulcers, The Wagner and University of Texas systems are the ones most frequently used and is indicative stage of prognosis. Many different methods have been proposed for the prevention and treatment and their goal is to accelerate the wound healing. These treatments other than standard therapy include local use of epidermal growth factor, tretinoin, human skin equivalents, vacuum-compression therapy (VCT), hyperbaric oxygen and peripheral Stem cell injection. The novel drugs for treatment of this problem are the herbal extracts like aloe vera, neem and guduchi extracts. The World Health Organization (WHO) has listed 21,000 plants, which are used for medicinal purposes around the world. The current review focuses on herbal drugs, plants that are used in the treatment of Diabetic Foot Ulcer and some allopathic marketed preparations.

KEYWORDS: Diabetes mellitus, Diabetic foot ulcer, Herbal plants, Treatment.

INTRODUCTION
Diabetes Mellitus (DM) is a metabolic disorder characterized by hyperglycaemia due to deficiency insulin secretion, insulin action or both.[1] Human life style and food habits have been changed drastically which lead to various chronic diseases. DM causes serious problems to human health.[2] About 200 million people around the world are being diagnosed with DM. According to WHO statistics, it is the sixth leading cause of disease-related death in the world. It leads to many micro and macro vascular complications. Nephropathy, Retinopathy and Neuropathy are considered under the macro vascular complications of DM.

There are three types of DM:

1. Type 1 diabetes (Insulin-dependent diabetes), it is prevalent in 10% of diabetic patients, islet β-cell destruction usually leads to absolute insulin deficiency.[3] Patients are completely reliant upon exogenous insulin to prevent ketosis and thereby preserve life.[4]
2. Type 2 diabetes (Non insulin-dependent diabetes), Accounts for more than 85% of cases worldwide. It is a heterogeneous type, ranging from insulin resistance to insulin deficiency.[5] Also type 2 diabetes is a multifactorial disease with both a genetic component and an important non-genetic component.[6]
3. Gestational diabetes, Diabetes diagnosed in pregnancy, including pre-existing diabetes which develops during pregnancy.[7]

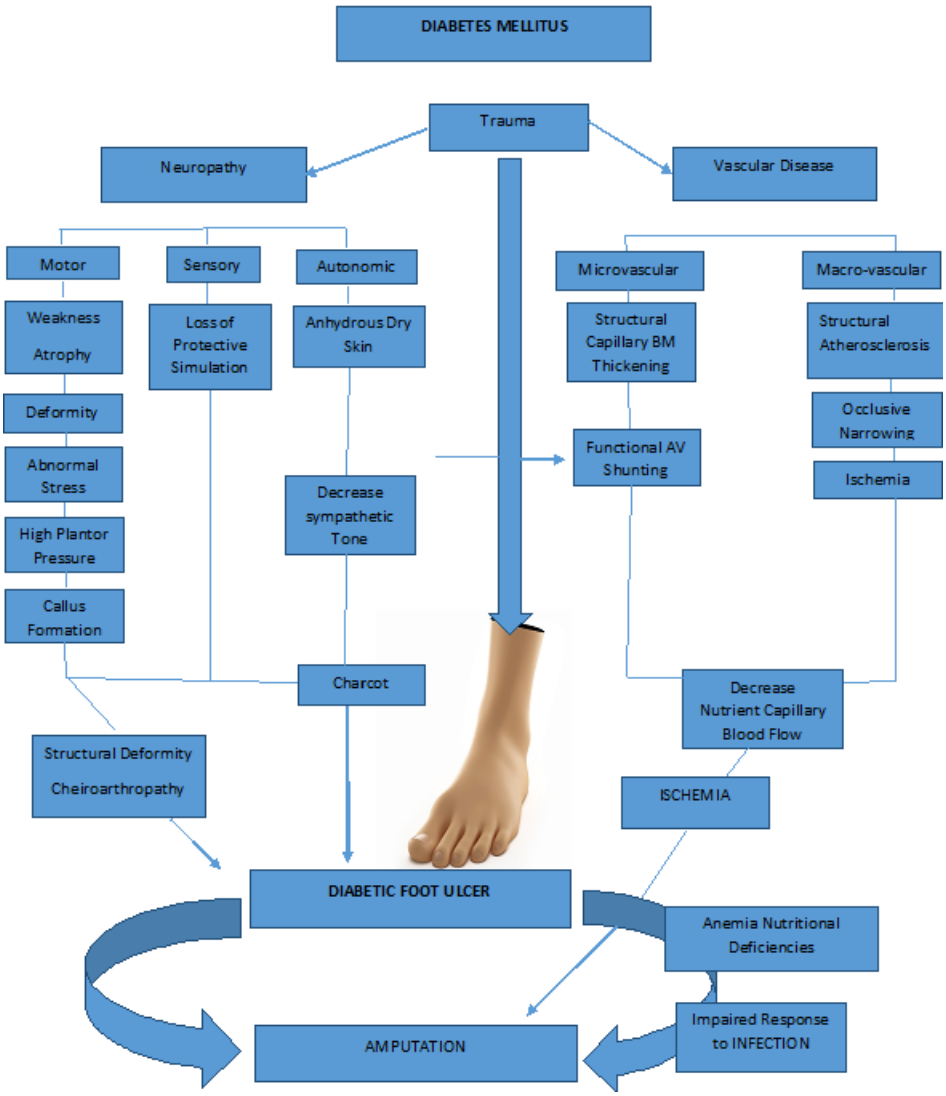

Fig. 1: Diabetes mellitus is responsible for a variety of foot pathologies contributing to the complications of ulceration and amputation. Multiple pathologies may be implicated, from vascular disease to neuropathy to mechanical trauma.

DIABETIC FOOT ULCER

Foot ulcers are the most common medical complications of the suffering from DM, with an estimated prevalence of 12-15% amongst all the individuals with DM.[8] Diabetic foot ulcers (DFU) are responsible for the more hospitalizations than any other complications of the diabetes. Ulcerations can have potential devastating complications as they cause up to 90% of lower extremity amputations in patients with diabetes.

Several factors are involved in the decreased healing potential of a diabetic foot, all of which occur from the metabolic disorders associated with diabetes. The most important factors are:

- Level of uncontrolled hyperglycaemia
- Reduced circulation and arterial blood flow
- Nutrition status
- Inability to offload the affected region of the foot
- Presence of infection.[9]

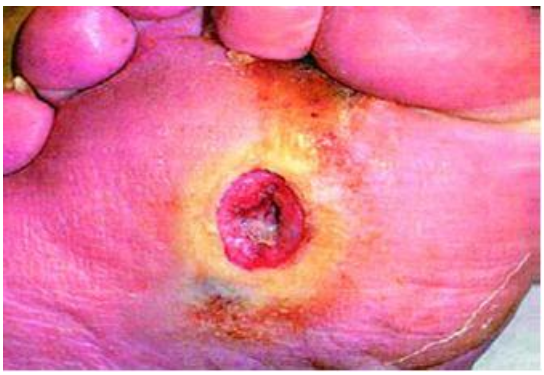

Fig. 2: Typical diabetic foot ulcer caused by high plantar pressures at the second metatarsal head.

Wound may be produced by physical, chemical, thermal, microbial or immunological insult to the tissue. Diabetic foot wounds are defined as any break in the cutaneous barrier, usually extending through the full thickness of

the dermis.[10] There are different methods for infection control and treatment of diabetic foot ulcers. Its main aim is to accelerate the wound healing and tissue repair. The process of wound healing consists of integrated cellular and biochemical events leading to reestablishment of structural and functional integrity with regain of strength of injured tissue.

Over the years, various herbal products have been used in the management and treatment of wounds. Many substances like tissue extracts.[11] vitamins and minerals and a number of plant products have been reported to possess pro-healing effects. Wound healing herbals encourage blood clotting, fight infection and accelerate the healing of wound.

Sign and Symptoms

- Bad odour or pus coming from ulcer.
- Foot weakness or trouble moving foot.
- Pain in foot that had little or no feeling before.
- Redness and warmth, or swelling in your foot.
- Thick, yellow toenails.
- Muscle pain/cramping that occurs with walking/exercising, and goes away with rest. Over time, pain may be felt even at rest.

PATHOPHYSIOLOGY OF DFU

DFU is characterized by a classical triad of neuropathy, ischemia, and immunopathy and mechanical stress.[12] Due to the impaired metabolic mechanisms in DM, there is an increased risk of infection and poor wound healing due to a series of mechanisms which include decreased cell and growth factor responses, diminished peripheral blood flow and decreased local angiogenesis.[13] Thus, the feet are predisposed to peripheral vascular disease, damage of peripheral nerves, deformities, ulcerations and gangrene.[14]

Neuropathy

Neuropathy causes more than 60% of the foot ulcers and affects patients with both Type 1 and Type 2 DM. Rise in blood glucose levels leads to increased enzyme production such as aldose reductase and sorbitol dehydrogenase. These enzymes convert glucose into sorbitol and fructose. As these sugar products accumulate, the synthesis of nerve cell myoinositol is decreased, affecting nerve conduction.[15] Furthermore, hyperglycaemia induced micro angiopathy leads to reversible metabolic, immunologic and ischemic injury of autonomic, motor and sensory nerves.[16]

DM affects the autonomic nervous system, leading to dryness and fissuring of skin, which makes it prone to the infection. Autonomic system also controls the microcirculation of the skin. These changes ultimately contribute to the development of ulcers, gangrene, and limb loss.[17][18]

Vasculopathy

Hyperglycaemia causes endothelial cell dysfunction and smooth cell abnormalities in peripheral arteries. Endothelial cells synthesize nitric oxide which causes vasodilation and protects the blood vessels from endogenous injury. Hence, in hyperglycaemia, there is perturbation of the physiological properties of nitric oxide which usually regulates the endothelial homeostasis, anticoagulation, leukocyte adhesion, smooth muscle cell proliferation and antioxidant capacity. Endothelium-derived vasodilators and nitric oxide are decreased hence leading to constriction of the blood vessels[19] and propensity for atherosclerosis,[20] eventually leading to ischemia. Ischemia can also occur even in the presence of palpable pedal pulses. Hyperglycaemia in DM is also associated with increase in thromboxane A2 leading to plasma hypercoagulability.[21] Clinically the patient may have signs of vascular insufficiency such as claudication, night pain or rest pain, absent peripheral pulses, thinning of skin, loss of limb hair etc.[22]

Immunopathy

DM patients have weaker immune system than a healthy person's immune system. Thus, foot infection in a patient with diabetes is a limb threatening and debilitating condition. The hyperglycaemic state causes an elevation of pro-inflammatory cytokines and impairment of polymorphonuclear cell functions like chemotaxis. Besides that, high blood glucose is a good medium for the growth of bacteria. The predominant organisms in diabetic foot infections are mainly aerobic gram positive cocci like *S. aureus* and *β*-hemolytic streptococci.[23] ABC et al reported that, gram-negative aerobes were the common microorganisms in diabetic foot.[24] The soft tissues of foot like plantar aponeurosis, tendons, muscles sheaths and fascia cannot resist infections. This soft tissue infection can rapidly spread to the bones, causing osteitis. Thus, a simple ulcer on the foot can easily result in complications such as osteitis/ osteomyelitis and gangrene without appropriate care.

Mechanical stress

The movements of the foot like flexion and extension are affected due to the damage to innervations of the foot muscles. Gradually, it leads to an alteration of the anatomical framework of the foot and formation of deformities. Peripheral neuropathy promotes callus formation. The callus (callosity) contributes to high pressure areas and ulcer formation.[25] Duckworth et al reported that[26] "abnormally high pressures are more common in patients with diabetic neuropathy and almost all patients with a history of ulceration show high-pressure areas which correlate well with the site of previous ulceration." Usually, ulcers occur on the plantar aspect of great toe and heel. However, ill-fitting shoes (which are the most common source of trauma)[27] can cause ulcers on the dorsal aspect.[28] Hence neuropathic foot ulcer formation in patients with diabetes has a complex multifactorial aetiopathogenesis wherein areas

of high pressure complimented by peripheral neuropathy and associated skin changes lead to ulcer formation.
Thus, above mentioned factors are responsible for causing severity in DFU.

CLASSIFICATION OF DFU

The most commonly used classification systems are the Wagner-Ulcer Classification system [29] (Table1) and the University of Texas Wound Classification.[30] The University of Texas Wound Classification is a simple classification that considers grade (depth of the lesion) and stage (presence or absence of infection and ischaemia). The 'grade' ranges from 0 (pre- or post-ulcerative completely epithelized lesion) to III (involvement of bone or joint). 'Stage' ranges from A (absence of both infection and ischaemia), B (infection), C (ischaemia) and D (infection and ischaemia). The 'grade and stage' are combined to give the final classification (Table 2).

In both classifications, the higher the grade, the higher the risk of amputation with a longer healing time. Samson et al. found 'The University of Texas Wound classification system' to be better predictor of outcome.[31] However both the systems do not take into account the severity of infection.[32] Another validated classification system for DFUs that includes the severity of infection is The PEDIS (perfusion, extent, depth, infection, and sensation) system.[37]

Wagner Ulcer Classification System

Table 1: Wagner Classification of Diabetic Foot Ulcer.[36]

Grade 0	No ulcer in a high risk foot.
Grade 1	Superficial ulcer involving the full skin thickness but not underlying tissues.
Grade 2	Deep ulcer, penetrating down to ligaments and muscle, but no bone involvement or abscess formation.
Grade 3	Deep ulcer with cellulitis or abscess formation, often with osteomyelitis.
Grade 4	Localized gangrene.
Grade 5	Extensive gangrene involving the whole foot.

University of Texas wound classification system

Table 2: The University of Texas wound classification system.[37]

Stage	**Grade**			
	0	1	**2**	**3**
A	pre- or post-ulcerative completely epithelized lesion	Superficial Wound	Wound penetration upto tendon or capsule	Wound penetration upto bone 0r joint
B	Infection	Infection	Infection	Infection
C	Ischaemia	Ischaemia	Ischaemia	Ischaemia
D	Infection and ischaemia	Infection and ischaemia	Infection and ischaemia	Infection and ischaemia

PREVENTION AND TREATMENT OF ULCERS

Not all diabetic foots are preventable, but appropriate preventive measures can dramatically reduce their occurrences. Awareness of physicians about foot problems in diabetic patients, clinical examination and Para clinical assessment, regular foot examination, patient education, simple hygienic practices and provision of appropriate footwear combined with prompt treatment of minor injuries can decrease ulcer occurrence by 50%.[33] Many different methods have been proposed and their goal is to accelerate the wound healing.

Acceleration the Wound Healing

Basic principles of wound healing include appropriately treated infection, adequate arterial inflow and off loading or removing pressure from the wound.

Control of infection

After classification of ulcers, proper antimicrobial therapy should be done for infective ulcers. Treatment of osteomyelitis and appropriate debridement are necessary. A number of small trials have evaluated the possible efficacy of granulocyte colony-stimulating factor in diabetics with foot infections.[34][35] A meta-analysis was performed on five trials with a total of 167 patients.[36] Although adjunctive G-CSF did not appear to hasten the clinical resolution of infection or ulceration, it reduced the rate of surgical procedures including amputation (relative risk 0.41, CI 95% 0.17-0.95).

Method of debridement

The method of debridement may also be important. Various types of products have been used to keep the wound dry and covered (hydrogels, hydrocolloids, alginates and foams).[37] In a systematic review,

hydrogels were significantly more effective than gauze or standard care in healing foot ulcers among diabetic patients.[38] Larval therapy showed no significant benefit in small size studies. Clinical trials of enzyme preparations and polysaccharide beads are not yet available.

Off loading

Total contact casts and therapeutic shoes are proper options for removal of pressure from the wound.

Revascularization

Adequate arterial inflow plays an important role in the management of diabetic foot ulcers in patients with documented peripheral arterial disease. The efficacy of this approach was evaluated in a report for 29 diabetic patients whounderwent percutaneous transluminal angioplasty followed by therapy with aspirin and warfarin.[39] This study sought to determine whether infrapopliteal transcatheter interventions can salvage ischemic limbs in diabetic patients referred for below the knee amputation. At 12 month follow-up, 23 had experienced wound healing and avoided below the knee amputation. The tissue oxygen partial pressure levels improved in all patients who eventually had healed and healing ulcers, in contrast to the anklebrachial index, served as a useful predictor of outcome.

Topical Agents for Treatment of Diabetic Foot Ulcer

Platelet-derived growth factor

A platelet-derived growth factor gel preparation (Becaplermin) is approved by the US Food and Drug Administration as an adjuvant therapy for diabetic foot ulcers.[40]

Epidermal Growth Factor

In addition, local application of human epidermal growth factor may promote healing of diabetic foot ulcers.[41] Results of one clinical trial revealed that administration of Epidermal Growth Factor (EGF) resulted in statistically significant wound closure in comparison to placebo.[42]After 4 weeks, mean closure was significantly higher in EGF group compared with placebo (71.2% vs. 48.9%, P<0.03). 100% closure was observed in 7 patients (With 30 ulcers) from EGF group and in one patient (With 12 ulcers) from placebo group. EGF showed a greater efficacy in ulcer healing (RR=3.4, 95%Cl: 1.84-13.61).

Tretinoin

The use of tretinoin solution for 10 minutes a day followed by iodine gel for four weeks resulted in complete resolution of 46% of the ulcers in the treatment group (n = 13) compared to 18 % in control group (n = 11).[43]

Human skin equivalents

Human skin equivalents in noninfected, nonischemic regions may be used. In one study of 208 patients, application of the cultured skin equivalent (Graftskin®) for 4 weeks improved the healing rate.[44]

Topical and systematic hyperbaric oxygen

The effect of 2 weeks of topical hyperbaric oxygen (THO) treatment on the healing of diabetic foot ulcers without associated gangrene was evaluated in a prospective, controlled, and randomized manner in 28 patients.[45] Ulcer size changes did not differ statistically between the controls and THO groups. A trend toward slower healing was observed in the THO group. Healing of diabetic foot ulcers was not accelerated by THO in this study. In a randomized trial of systemic hyperbaric oxygen therapy in 70 patients with severely ischemic foot ulcers (Wagner grades 3 and 4), the amputation rate was 9% in the treatment group and 33% in the control group.[46]

Phenytoin

The efficacy of topical phenytoin in the treatment of diabetic foot ulcers was evaluated in a controlled inpatient study. Mean time to complete healing was 21 days with phenytoin and 45 days in control. The observed differences were statistically significant ($P < 0.05$). Phenytoin appears to be useful as a topical agent in promoting the healing of diabetic foot ulcers.[47]

Compression Vacuum Therapy

A single-blind, randomized controlled trial was conducted to evaluate vacuum-compression therapy (VCT) for the healing of diabetic foot ulcers. The experimental group received VCT 1 hour a day, 4 times a week, for 10 sessions [(-75 mmHg) of negative pressure for 60 s, followed by (38.5 mmHg) of positive pressure for 30 s]. The experimental group significantly improved in measures of foot ulcer surface area compared with the control group ($p = 0.024$). Researchers believe that VCT systems do improve total tissue blood flow and oxygenation.[48] In a retrospective study of payer claims data, patients with diabetic foot ulcers in the medicare sample treated with negative-pressure wound therapy had a lower incidence of amputations than those undergoing traditional wound therapy; this finding was evident in wounds of varying depths in both studied populations.[49]

Other Topical therapies

In a trial electrical stimulation, given daily with a short pulsed, asymmetric biphasic waveform, was effective for enhancement of healing rates for patients with diabetes and open ulcers.[50] The semipermeable polymeric membrane dressing and Derma graft are useful therapeutic options for treatment uncomplicated chronic diabetic foot ulcers.[51][52]

The other new therapies that have been studied in diabetic foot ulcer include: gene therapy, protease inhibitors, Angiogenesis stimulants, nitric oxidereleasing agents, adenosine agonists, immunostimulants, vasoactive compounds and granulating agents. These

therapies should be considered when existing treatments have failed to heal ulceration in the diabetic foot.[53]

PLANT PROFILE

Aloe vera

Fig. 3: Aloe vera Plant.

Common Name: Aloe vera
Biological Name: *Aloe barbadensis*
Family: Asphodelaceae (Liliaceae)

Description: Succulent herb with short, thick stem. Leaves alternate, sessile, succulent, green, arising from basal rosette, lanceolate and up to 70 cm long, margins with conspicuous spines andapical point. Flowers 3-parted, tubular, red, up to 4 cm long and borne on a terminal spike. Fruit a brown capsule 15-25 mm long with many small flattened seeds. Flowering and fruiting periods not known in the South Pacific.

Chemical Constituents: Aloe-emodin, aloesin, aloin derivatives, anthrol, 1,8-dihydroxyanthraquinone, chrysophanic acid, amino acids, sugars, barbaloin, enzymes, org anic acids, dehydro-abietal, methyl ester of dehydro-abietic acid, acemannan, aloeferon, glucomannan, aloe peptides, campesterol, cholesterol, stigmasterol, lupeol, benzothiazolone, iso citric acid, para-coumaric acid, cyclohexane derivatives, lipids, aminoacids.[54]

Biological Activity*:* Burn healing, wound healing, antipeptic ulcer, anti-inflammatory, antibacterial, insecticidal, analgesic, antipyretic, toxic, antileukopenic, antitumour, teratogenic, hypoglcemic, antifertility, CNS depressant, embryotoxic, uterine stimulant, antiviral, hair stimulant, antiasthmatic, haemaglutinin, mitogenic, emollient, hypocholesterolemic, hypolipemic, allergenic, local anaesthetic.[55]

Anti-inflammatory activity of Aloe vera

1) Campesterol: It is used for cartilage repair during injuries by generating new cells in the body that helps to heal inflamed area.
2) Bradikinase: it cause blood vessels to enlarge, permitting increased blood flow, relieve pain and swelling by breaking bradykinin.
3) Salicylic acid has pain relieving properties and reduces inflammation by inhibiting the production of prostaglandin hormones which encourage inflammation.[56]

Traditional Uses

The plant has been used as a purgative. Its cathartic action is probably because it promotes peristalsis of the lower bowels. It is used to treat wounds and burns. The sap from the fresh leaves is used to treat sun burns, rashes and x-ray burns. In Tahiti, Cook Islands, Tonga and Samoa, the plant is used in treating cuts, burns and internal ailments such as stomachache.[57]

Neem

Fig. 4: Neem Plant.

Common Name: Neem, Nemtree
Biological Source: *Azadirachta indica*
Family: Meliaceae

Description: Tree 6 to 25 m tall with alternately arranged pinnately compound leaves up to 40 cm long, with 8 to 18 short-petiolate narrowovate, pointed, curved toothed leaflets, 3-10 cm long, 1-4 cm broad. Flowers numerous, borne in long panicles which arise from bases of leaves, each flower fragrant, white, 5-parted, tubular, about 1 cm broad. Fruit a yellowish drupe, oblong, about 1.5 cm long containing thin pulp surrounding a single seed. The leaves and twigs when bruised emit an onion-like odour.

Chemical constituents: Nimbidin, Azadirachtin, Nimbin, Nimbolide, Mahmoodin, Gallic acid, (-) epicatechin and catechin, Cyclic trisulphide and cyclic tetrasulphide, Polysaccharides G1A, G1B, Polysaccharides G2A, G3A, NB-2 Peptidoglucan.[43]

Biological Activity*:* Insect antifeedant, anti-bacterial, insecticidal, antiarthritic, anti-inflammatory, antiulcerative, antitumour, antipyretic, antiviral, cytotoxic, nematocidal, molluscicidal, fish poison, antifertility, anti-implantation, insect repellant, larvicidal, abortifacient, antifungal, spasmolytic, wound healing acceleration, hypotensive, antihyperglycemic, analgesic, CNS depressant, antifilarial, dermatitis producing.

Antibacterial effect of neem

Neem tree extracts has an endodontic anti-microbial agent, an alternative to frequently employed Sodium Hypochlorite and Chlorhexide; both to inhibit the growth of endodontic pathogens.

1) Sodium Hypochlorite is now used in endodontic during root canal treatments. It is the medicament of choice due to its efficacy against pathogenic organisms and pulp digestion.
2) Chlorexide is a chemical antiseptic. It is effective on Gram-positive and Gram-negative bacteria

The effects of Neem on Wound healing

Wounds on our skin heal in a multi-stage process. In the earliest stage of the Wound healing process a provisional matrix or ground substance is laid down which is made up of Glycosaminoglycans. This is followed by the formation of granulation tissue and finally the synthesis of elastin and collagen. Neem oil contains active ingredients that directly deal with the Wound healing process. Because of this Neem directly affects the Wound healing process and helps the skin retain its suppleness as the wound heals. Neem oil has a high content of essential fatty acids, which plays an important role in adding moisture and a soft texture to the skin during the healing process. In addition to the Neem trees ability to affect the restructuring of the skin during the Wound healing process Neem Leaf extracts and Seed Oil have a proven anti-microbial effect. This keeps any Wound or lesion free from infection by bacteria, viruses, parasites, and fungi. Clinical studies show that Neem plays another important role in Wound healing by inhibiting inflammation as effectively as cortisone acetate.[58]

Guduchi Plant

Fig. 5: Guduchi Plant.

Common Name: Guduchi, Gloy
Biological Name: *Tinospora cardifolia*
Family: Menispermaceae
Botanical description

It is a large, deciduous extensively spreading climbing shrub with several elongated twining branches. **Leaves** simple, alternate, exstipulate, long petioles up to 15cm long, roundish, pulvinate, both at the base and apex with the basal one longer and twisted partially and half way around. **Lamina** broadly ovate or ovate cordate, 10-20 cm long or 8- 15 cm broad, 7 nerved and deeply cordate at base, membranous, pubescent above, whitish tomentose with a prominent reticulum beneath. **Flowers** unisexual, small on separate plants and appearing when plant is leafless, greenish yellow on axillary and terminal racemes. Male flowers clustered, female usually solitary. **Sepals** 6, free in two series of three each, the outer ones are smaller than the inner. **Petals** 6 free smaller than sepals, obovate and membranous. **Fruits** aggregate of 1-3, ovoid smooth drupelets on thick stalk with sub terminal style scars, scarlet or orange coloured.

Chemical Constituents: Berberine, Choline, Tembetarine, Magnoflorine, Tinosporin, Palmetine, Isocolumbin, Aporphine alkaloids, Jatrorrhizine, Tetrahydropalmatine, Tinosporon, Tinosporides, 18-norclerodane glucoside, Furanoid diterpene glucoside, Tinocordiside, Tinocordifolioside, Cordioside, Cordifolioside Syringin, Syringin- apiosylglycoside, Pregnane glycoside, Palmatosides, Cordifolioside A, B, C, D and E.[59]

Biological activity: Anti-viral infections, Anticancer, anti-diabetes, inflammation, Neurological, immunomodulatory, psychiatric conditions, Vasorelaxant: relaxes norepinephrine induced contractions, inhibits Ca^{++} influx, anti-inflammatory, anti-oxidant, anti-microbial, antihypertensive, anti-viral, Antiseptic.[60]

Antioxidant property of Guduchi, Giloy

1) Natural antioxidants like phenolic compounds, flavonoids which are secondary plant metabolites present in food products of plant origin.
2) These oxidants can trap the free radicals directly or scavenge them through a series of coupled reactions with antioxidant enzymes and also exhibit a wide range of biological effects, including antiageing.[61]

SOME OTHER HERBAL PLANTS USED FOR DFU

S.No.	Common Name	Biological Name	Family	Chemical Constituents	Biological Activity
1.	Bitter guard	*Momordica charantia*	Cucurbitaceae	Vicine, mycose, steroidal glucoside, momorcharaside A, B, cucurbitane triterpenoids, momordicines I and II, cycloeucalenol, spinasterol, stigmasterol, taraxerol, lophenol, momordicosides.[62]	Antihyperglycemic and also hypoglycemic effect in normal and STZ diabetic rats. This may be because of inhibition of glucose-6-phosphatase besides fructose-1, 6-biphosphatase in the liver and stimulation of hepatic glucose-6-phosphate dehydrogenase activities.[63]
2.	Garlic	*Allium sativum*	Alliaceae	Llicin, phytoncidea, allin, ajoene, isoalliin, methiin.[64]	Hypoglycemic activity due to increased hepatic metabolism, increased insulin release from pancreatic beta cells and/or insulin sparing effect.[65]
3.	Amla	*Emblica officinalis*	Euphorbiaceae	Ellagitannis,Emblicanin A,Emblicanin B, Puniglucanin,Pedunculagin,Punicafalin,Phyllanemblinin A.[66]	Anti-inlammatory, antioxidant and wound healing.[67]
4.	Curcumin	*Zingiber officinale*	Zingiberaceae	Alpha- & delta-atlantones, bisaboladienones, bisabolenes, bisacumol, bisacurone, caryophyllene, curcumenes, curcumenol, curcumenone, curcumins and derivatives, curdinone, curlone, curzerenones, germacron derivatives, beta-sesquiphellandrene, alpha-turmerine, turmeronols.[68]	Anti -inflammatory activity (curcumin), increases bile production, antibacterial,diuretic and antioxidant.[69][43]

ADVANTAGES OF HERBAL FORMULATION

There are a number advantages associated with using herbal medicines as opposed to pharmaceutical products. Examples include the following:

- **Reduced risk of side effects:** Most herbal medicines are well tolerated by the patient, with fewer unintended consequences than pharmaceutical drugs. Herbs typically have fewer side effects than traditional medicine, and may be safer to use over time.
- **Effectives with chronic conditions:** Herbal medicines tend to be more effective for long-standing health complaints that don't respond well to traditional medicine. Such treatments include dietary changes like adding simple herbs, eliminating vegetables from the nightshade family and reducing white sugar consumption.
- **Lower cost:** Another advantage to herbal medicine is cost. Herbs cost much less than prescription medications. Research, testing, and marketing add considerably to the cost of prescription medicines. Herbs tend to be inexpensive compared to drugs.
- **Widespread availability:** Yet another advantage of herbal medicines are their availability. Herbs are available without a prescription. You can grow some simple herbs, such as peppermint and chamomile, at home. In some remote parts of the world, herbs may be the only treatment available to the majority of people.[70]

MARKETED FORMULATION FOR DIABETIC FOOT ULCER

PRODUCT NAME	FORMULATION	INGREDIENTS
Terrasil	Infection conrol wound care ointment	Organic bees wax, peepermint oil, magnesium oxide, silver oxide, jojoba seed oil.[71]
Manuka Honey	Super saturated liquid	Apple cider vinegar, beeswax, beepollen, cacium carbonate, castor oil, german chamomile flower, manuka oil, multifloral honey, olive butter, sodium carbonate, tea tree.[72]
Revita Derm	Wound care gel	Benzalkonium chloride, aloe vera leaf extract, aloe oil extract, collagen, carbomer, glycerine, triethanolamine, methylparaben, ethylparaben, propylparaben, butylparaben.[73]
Zostrix	Diabetic foot pain relief cream	Capsaicin, benzyl alcohol, cetyl alcohol, glyceral state, isopropyl myristate, purified water, sorbitol solution.[74]
Silvrstat	Antibacterial wound dressing gel	32ppm proprietary silver, propylene glycol, triethanolamine, carbomer.[75]
Eucerin	Diabetic foot cream	Water, glycerine, cetaryl alcohol, sodium lactate, triglyceride, lactic acid, phenoxyethone, castor oil, carbomer.[76]
Neosporin	Ointment	Neomycin, bacitracin, polymyrix, coca butter, olive oil, cottonseed oil, sodium pyruvate ,petrolatum.[77]
Derma wound	Ointment	Benzocaine hydrochloride, sucrose, calcium carbonate , glycerine, xanthum gum, PVP-Iodine, methylparaben, water.[78]

CONCLUSION

Diabetic foot problems are common all over the world and have major economic consequences to society, diabetic patients. Most of treatments of diabetic foot ulcer have a partial effect in ulcer improvement and amputation rate and some of the ulcers are retractable to conventional therapy; so more effective and cost benefit i.e. treatments are essential. The above-mentioned plants have been considered for their possible actions in diabetic foot ulcer. Thus many different plants have been used individually or in formulations for treatment of this dreadful disease.

ACKNOWLEDGEMENT

Authors are highly thankful to Dr. Tilak Raj Bhardwaj, Dean of School of Pharmacy and Emerging Sciences for their support and encouragement and Department of Pharmacy, Baddi University for providing library facility during literature survey.

REFERENCES

1. Lakshmi M, Rani SK. Review on Diabetes Milletus and the herbal plants used for its treatment. Asian journal of pharmaceutics and clinical research, 2012; 5(31).
2. Kumar PJ, Clark M. Textbook of Clinical Medicine. Pub: Saunders, London; 2002, pp 1099-1121.
3. Chakrabarti R, Rajagopalan R. Diabetes and insulin reistance associated disorders: Disease and the therapy. Curr Sci, 2002; 83(12): 1533-1538.
4. Lokesh D, Amit SD. Diabetes mellitus-it‟s possible pharmacological evaluation techniques and naturotherapy. International Journal of Green Pharmacy, 2006; 1: 15-28.
5. Yarborough PC, Rodgers ST. Comprehensive pharmacy review. 4th ed., New York; Lippincott Williams and Wilkins: 2001.
6. Torben H. Genetics of Type 2 diabetes. Curr Sci, 2002; 83: 1477-82.
7. Seshiah V, Balaji V. Current Concepts in Management of Diabetes Mellitus in Pregnancy: Role of Insulin Pumps and Analogues. Int J Diab Dev Countries, 2000; 20: 109-11.
8. American Diabetes Association: Diabetes statistics, http//www.diabetes.org/diabetes-statistics.jsp.
9. Boulton AJ, Kirsner RS, Vileikyte L. Clinical practice. Neuropathic diabetic foot ulcers. N Engl J Med, 2004; 351(1): 48-55.
10. Cianci P. Consensus Development Conference on Diabetic Foot Wound Care: a randomized controlled trial does exist supporting use of adjunctive hyperbaric oxygen therapy. Diabetes Care, 2000; 23: 873-4.

11. Udupa SL, Shaila HP, Udupan AL, Ramesh KV, Kulkarni DR. Wound healing properties of some medicinal plants. Biochem Arch, 1991; 7: 207-12.
12. Singh S, Pai DR, Yuhhui C. Diabetic Foot Ulcer - Diagnosis and Management. Clin Res Foot Ankle, 2013; 1: 120.
13. Pendsey SP. Understanding diabetic foot. Int J Diabetes Dev Ctries, 2010; 30(2): 75-79.
14. Brem H, Tomic-Canic M. Cellular and molecular basis of wound healing in diabetes. J Clin Invest, 2007; 117(5): 1219-1222.
15. Clayton W, Elcasy TA. A Review of the Pathophysiology, Classification, Treatment of Foot Ulcers in Diabetic Patients. Cli Diabetes, 2009; 27: 52-58.
16. Younger DS, Rosoklija G, Hays AP. (1998) Diabetic peripheral neuropathy. Semin Neurol, 1998; 18(1): 95-104.
17. Vinik AI, Maser RE, Mitchell BD, Freeman R. (2003) Diabetic autonomic neuropathy. Diabetes Care, 2003; 26(5): 1553-1579.
18. Boyko EJ, Ahroni JH, Stensel V, Forsberg RC, Davignon DR, Smith DG. A prospective study of risk factors for diabetic foot. The Seattle Diabetic Foot Study. Diabetes Care, 22(7): 1036-1042.
19. Creager MA, Lüscher TF, Cosentino F, Beckman JA. Diabetes and vascular disease, pathophysiology, clinical consequences, and medical therapy: Part I. Circulation, 2003; 108(12): 1527-1532.
20. Dokken BB. The Pathophysiology of Cardiovascular Disease and Diabetes: Beyond Blood Pressure and Lipids. Diabetes Spectrum, 2008; 21(3): 160-165.
21. Paraskevas KI, Baker DM, Pompella A, Mikhailidis DP. Does diabetes mellitus play a role in restenosis and patency rates following lower extremity peripheral arterial revascularization? A critical overview. Ann Vasc Surg, 2008; 22(3): 481-491.
22. Armstrong DA, Lavery LA. Diabetic foot ulcers: prevention, diagnosis and classification. AmFamphysician, 1998; 57(6): 1325-1332.
23. Lipsky BA, Berendt AR, Deery HG, Embil JM, Joseph WS, Karchmer AW, LeFrock JL, Lew DP, Mader JT, Norden C, Tan JS. Infectious Diseases Society of America. Diagnosis and Treatment of Diabetic Foot Infections. Clin Infect Dis, 2004; 39(7): 885-910.
24. Gadepalli R1, Dhawan B, Sreenivas V, Kapil A, Ammini AC, Chaudhry R. A clinico-microbiological study of diabetic foot ulcers in an Indian tertiary care hospital. Diabetes Care, 2006; 29(8): 1727-1732.
25. Rosen RC, Davids MS, Bohanske LM, Lemont H. Hemorrhage into plantar callus and diabetes mellitus. Cutis, 1985; 35(4): 339-341.
26. Duckworth T, Boulton AJ, Betts RP, Franks CI, Ward JD. Plantar pressure measurements and the prevention of ulceration in the diabetic foot. J Bone Joint Surg Br, 1985; 67(1): 79-85.
27. Macfarlane RM, Jeffcoate WJ. Factors contributing to the presentation of diabetic foot ulcers. Diabet Med, 1997; 14(10): 867-870.
28. Peters EJ, Armstrong DA, Lavery LA. Risk Factors for Recurrent Diabetic Foot Ulcers:sitematters. Diabetes Care, 2007; 30(8): 2077-2079.
29. Wagner FW Jr. The dysvascular foot: a system for diagnosis and treatment. Foot Ankle, 1981; 2(2): 64-122.
30. Lavery LA, Armstrong DG, Harkless LB. Classification of diabetic foot wounds. J Foot Ankle Surg, 1996; 35(6): 528-531.
31. Oyibo SO1, Jude EB, Tarawneh I, Nguyen HC, Harkless LB, Boulton AJ. A Comparison of Two Diabetic Foot Ulcer Classification Systems. The Wagner and the University of Texas wound classification systems. Diabetes Care, 2001; 24(1): 84-88.
32. Schaper NC1, Dryden M, Kujath P, Nathwani D, Arvis P, Reimnitz P, Alder J, Gyssens IC. Efficacy and safety of IV/PO moxifloxacin and IV piperacillin/tazobactam followed by PO amoxicillin/clavulanic acid in the treatment of diabetic foot infections: results of the relief study. Infection, 2013; 41(1): 175-186.
33. Larijani B, Hasani RS. Overview of diabetic foot; novel treatments in diabetic foot ulcer. DARU, 2008; 16(1): 1-6.
34. Gough A1, Clapperton M, Rolando N, Foster AV, Philpott-Howard J, Edmonds ME.. Randomized placebo-controlled trial of granulocyte colony-stimulating factor in diabetic foot infection. Lancet, 1997; 350(9081): 855-9.
35. Kästenbauer T1, Hörnlein B, Sokol G, Irsigler K. Evaluation of granulocyte-colony stimulating factor (Filgrastim) in infected diabetic foot ulcers. Diabetologia, 2003; 27-30.
36. Cruciani, M, Lipsky, BA, Mengoli, C, de Lalla, F. Are granulocyte colony-stimulating factors beneficial in treating diabetic foot infections: A meta-analysis. Diabetes Care 2005; 28(2): 454-460.
37. Hogge J, Krasner D, Nguyen H, Harkless LB, Armstrong DG. The potential benefits of advanced therapeutic modalities in the treatment of diabetic foot wounds. J Am Podiatr Med Assoc, 2000; 90(2): 57–65.
38. Smith, J. Debridement of diabetic foot ulcers. Cochrane Database Syst Rev 2002; (4): CD003556.
39. Hanna GP1, Fujise K, Kjellgren O, Feld S, Fife C, Schroth G, Clanton T, Anderson V, Smalling RW. Infrapopliteal transcatheter interventions for limb salvage in diabetic patients: Importance of aggressive interventional approach and roles of transcutaneous oximetry. J Am Coll Cardiol, 1997; 30(3): 664-669.
40. Wieman, TJ, Smiell, JM, Su, Y. Efficacy and safety of a topical gel formulation of recombinant human platelet-derived growth factor-BB (becaplermin) in patients with chronic neuropathic diabetic ulcers. A

phase III randomized placebo-controlled double-blind study. Diabetes Care, 1998; 21(5): 822-827.
41. Tsang, MW, Wong, WK, Hung, CS, Lai, KM. Human epidermal growth factor enhances healing of diabetic foot ulcers. Diabetes Care, 2003; 26(6): 1856-1861.
42. Larijani B, Afshari M, Fadaei M, Pajouhi M, Bastan Hagh MH, Baradar Jalili R Effect of local epidermal growth factor on wound healing in diabetic foot. Iran J Diabetes and Lipid Disord, 2003; 18(5): 110-107.
43. Tom WL1, Peng DH, Allaei A, Hsu D, Hata TR The effect of short-contact topical tretinoin therapy for foot ulcers in patients with diabetes. Arch Dermatol, 2005; 141(11): 1373-1377.
44. Veves, A, Falanga, V, Armstrong, DG, Sabolinski, ML. Graftskin, a human skin equivalent, is effective in the management of noninfected neuropathic diabetic foot ulcers: a prospective randomized multicenter clinical trial. Apligraf Diabetic Foot Ulcer Study. Diabetes Care, 2001; 24(2): 290-295.
45. Leslie CA1, Sapico FL, Ginunas VJ, Adkins RH. Randomized controlled trial of topical hyperbaric oxygen for treatment of diabetic foot ulcers. Diabetes Care, 1988; 11(2): 111-115.
46. Faglia, E, Favales, F, Aldeghi, A, et al. Adjunctive systemic hyperbaric oxygen therapy in treatment of severe prevalently ischemic diabetic foot ulcers: a randomized study. Diabetes Care, 1996; 19(12): 1338-1343.
47. Muthukumarasamy, MG, Sivakumar, G. Manoharan, G. Topical phenytoin in diabetic foot ulcers. Diabetes Care, 1991; 14(10): 909-911.
48. Akbari A, Moodi H, Ghiasi F, Sagheb HM, Rashidi H. Effects of vacuum-compression therapy on healing of diabetic foot ulcers: Randomized controlled trial. J Rehabil Res Dev, 2007; 44(5): 631-6.
49. Frykberg RG, Williams DV. Negative-pressure wound therapy and diabetic foot amputations: a retrospective study of payer claims data. J Am Podiatr Med Assoc, 2007; 97(5): 351-9.
50. Baker LL1, Chambers R, DeMuth SK, Villar F. Effects of electrical stimulation on wound healing in patients with diabetic ulcers. Diabetes Care 1997; 20(3): 405-412.
51. Blackman JD, Senseng D, Quinn L, Mazzone T. Clinical evaluation of a semipermeable polymeric membrane dressing for the treatment of chronic diabetic foot ulcers. Diabetes Care, 1994; 17(4): 322-325.
52. Marston, WA, Hanft, J, Norwood, P, Pollak, R. The Efficacy and Safety of Dermagraft in Improving the Healing of Chronic Diabetic Foot Ulcers: Results of a prospective randomized trial. Diabetes Care, 2003; 26(6): 1701-1705
53. Petrova N, Edmonds M. Emerging drugs for diabetic foot ulcers. Expert Opin Emerg Drugs. 2006; 11(4):709-24
54. Winters WD, Bouthet C. Polypeptides of *Aloe barbadensis* miller. Phytother. Res, 1995; 9(6): 395-400.
55. Upupa, S. L., et al., Fitoterapia, 1994; 65(2): 141-145.
56. Grindlay d, Reynolds T. The Aloe vera phenomenon: a review of the properties and modern uses of the leaf parenchyma gel. Journal of ethnopharmacology, 1986; 16(2-3): 117-151.
57. Whistler WA. Polynesian Herbal Medicine. Everbest, Hong Kong, 1992; 123-124.
58. Tembe-Fokunang EA, Charles F, Kaba N, Donatien N, Michael A, Bonaventure N. The Potential Pharmacological and Medicinal Properties of Neem (*Azadirachta indica* A. Juss) in the Drug Development of Phytomedicine. Journal of Complementary and Alternative Medical Research, 2019; 7(1): 1-18.
59. Upadhaya AK, Kumar K, Kumar A, Mishra HS. *Tinospora cordifolia* (Willd.) Hook. F. and Thoms. (Guduchi)-alidation of the Ayurvedic pharmacology through experimental and clinical studies. Int J Ayurveda Res, 2010; 1(2): 112-121.
60. Sriramaneni RN, Omar AZ, Ibrahim SM, Amirin S, Mohd ZA. Vasorelaxant effect of diterpenoid lactones from and rographis paniculata chloroform exract on rat aortic rings. Pharmacognosy Res, 2010; 2(4):242-246.
61. Helle L, Grete B. Spices as antioxidants trends. Food Science Technology, 1995; 6(8): 271-277.
62. Okabe H, Miyahara Y, Yamuchi T. Structure of Momordicosides F1, F2, G, K and L, Novel cucurbitacins in the fruits of *Momordica charantia* L. Tetrahedron Lett, 1982; 23(1): 77-80.
63. Shibib BA, Khan LA, Rahman R. Hypoglycemic activity of *Coccinia indica*and *Momordica charantia* in diabetic rats: depression of the hepatic gluconeogenic Page 26.enzymes glucose-6-phosphatase and fructose-1, 6-biphosphatase and elevation of liver and red-cell shunt enzyme glucose-6-phosphate dehydrogenase. Biochem. J, 1993; 292(1): 267–270.
64. Lyantagave SL. Ethnopharmacological and phytochemical review of Allium species (sweet garlic) and tulbaghia species (wild garlic) from southern Africa. Tanz. J. Sci., 2011; 37: 17-21.
65. Bever BO, Zahnd GR. Plants with oral hypoglycemic action. Quart. J. Crude Drug Res, 1979; 17(3-4): 139–146.
66. Bhattacharya A, Chatterjee A, Ghosal S, Bhattacharya SK. "Antioxidant activity of active tannoid principles of Emblica officinalis (amla)". Indian journal of experimental biology, 1999; 37(7): 676–680.
67. Sumitra M, Manikandan P, Gayathri VS, Mahendran P, Suguna L. Emblica officinalis exerts wound healing action through up-regulation of collagen and extracellular signal-regulated kinases (ERK1/2). Wound Repair and Regeneration, 2009; 17(1): 99-107.

68. Golding BT, Pombo VE. Structures of α- and β-turmerone. J. Chem.Soc. Perkin Trans I, 1992; 12: 1519-1524.
69. Singh YN. Traditional medicine in Fiji: some herbal folk cures used by Fiji Indians. J. Ethnopharmacol, 1986; 15(1): 57-88.
70. http://herbs.lovetoknow.com/Advantages_and_Disadvantages_of_Herbal_Medicine
71. http://www.terrasilwoundcare.com/Ingredients
72. www.comvita.com
73. http://www.drugs.com/otc/117945/revitaderm-wound-care.htm
74. http://www.ebay.com/itm/2-Pack-Zostrix-Diabetic-Foot-Pain-Relieving-Cream- /301381881429
75. https://www.henryschein.com/us-en/Medical/ShopExp/SilvrSTAT.aspx
76. http://www.amazon.com/Eucerin-Diabetics-Relief-Creme-Ounce/dp/B00Q2MYUFG
77. https://www.neosporin.com/products/wound-care/original-antibiotic-ointment
78. http://www.drugs.com/otc/193064/dermawound-wound-care-venous-stasis.htm