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"Nature's Cure: Herbal innovations for Diabetic Foot Infection Treatment"

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ABSTRACT:
Infection, a common and serious complication of diabetic foot wounds, is a major cause of physical disabilities in diabetic patients. It usually begins in foot ulcers, which are associated with neuropathy, vasculopathy, and various metabolic disturbances. These infections are potentially limb and sometimes life threatening. Antibiotic therapy is the main stay of treatments for patients with deep and surrounding tissue infection. Among the various complications, diabetic foot ulcer (DFU) is important since the major deaths in diabetes are due to Diabetic Foot Ulcer, 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 Diabetic Foot Ulcer may not only synergize the diabetic wound healing but also reduce the overall cost. Present study is a review of some herbal products for wound treatment and management and medicinal properties of some commonly used spices such as aloe vera, turmeric, garlic, ginger, neem, amla, fenugreek, peepal, green tea have been taken into consideration. Spices enhance the antimicrobial, preservative and antioxidant properties.

KEYWORDS: Diabetic Foot Ulcer, Neuropathy, Wound Healing, Amputation, Gangrene.

I. INTRODUCTION :

Diabetes is the most common metabolic disorder worldwide, linked to various connective tissue abnormalities, and remains incurable to this day [1,2]. Both the International Diabetes Federation (IDF) and the World Health Organization (WHO) have reported a growing global incidence, particularly in developing nations [3]. India, with the largest diabetic population around 19million, projected to rise to 57 million by 2025 faces significant challenges. Poorly controlled diabetes increases the risk of skin infections, as elevated blood sugar impairs the function of bacteria fighting cells. Additionally, reduced collagen biosynthesis or accelerated degradation leads to a decrease in skin collagen. These qualitative and quantitative collagen abnormalities contribute to impaired wound healing, often resulting in foot ulcers, and 85% of major leg amputations begin with thesse ulcers [4,5]. Foot infections also account for 20% of hospitalizations among diabetic patients annually, worsening wound conditions, delaying healing, and compromising the body's defense mechanisms.

Unhealed wounds persistently release inflammatory mediators, leading to pain and swelling at the injury site. These wounds provide a breeding ground for infections, which can delay the recovery process in affected individuals. In severe cases, chronic wounds may lead to multiple organ failure or even death [6]. It is important to understand why diabetic patients are more prone to developing foot infections. As shown in Figure 1, various physiological and metabolic disturbances contribute to the development of these infections [7]. While the diagnosis is primarily clinical, it is crucial to distinguish between infection and bacterial colonization, a natural process involving minimally virulent bacteria from the skin flora, endogenous sources, or the environment [1]. This phenomenon can be further complicated by diabetes mellitus. In diabetes, carbuncles, boils, and various skin infections can become serious if not treated appropriately.

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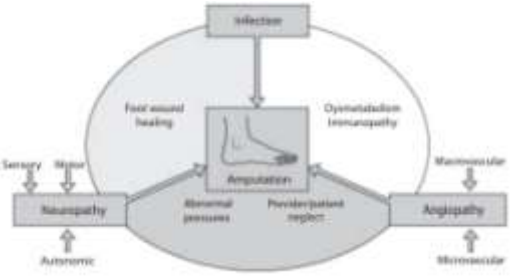

Figure 1: Factor causing foot disorders [7]

Even a small cut can progress into a deep, open sore called an ulcer [1]. Ulceration often occurs when protective sensation is lost, meaning the person may not feel the injury that cause the skin to break down.

Once a patient develops an ulcer, infection often follows. The progression of foot infection occurs in several stages. Initially, in the stage of cellulitis, swelling and edema develop in the foot following an injury or infection. As the infection progresses, it enters the stage of spreading cellulitis, where the infections spreads upwards along the fascial planes. In the stage of abscesses, secondary infections caused by mixed organisms, including anaerobes and non-clostridial gas-forming bacteria, lead to the formation of multiple abscesses. The next stage, gangrene, is characterized by tense edema and vascular compromise, which results in ischemia and the development of gangrenous patches on the skin and toes. If the infection continues to spread, it can reach the bone, leading to osteomyelitis. Finally, in untreated cases, the infection can lead to septicaemia, a severe condition where rapidly spreading cellulitis and gangrene result in widespread infection, predisposing the patient to complications such as ketoacidosis [8,9,10].

Pathophysiology:

Diabetic foot ulcers (DFU) result from various risk factors such as peripheral vascular disease, neuropathy, biomechanical abnormalities, previous ulcers, poor glucose control, and long-standing diabetes. Key triggers include diabetic neuropathy, poor circulation, and heightened infection risk [11,12].

Diabetic neuropathy: Diabetic foot ulcers (DFUs) are major diabetes complications, accounting for over 60% of neuropathy cases and 50-75% of non-traumatic amputations. Metabolic disruptions, such as reduced aldose reductase and sorbitol dehydrogenase activity, limit glucose-6-phosphate dehydrogenase activity, hindering NADPH synthesis. This converts glucose into sorbitol and fructose, reducing myoinositol in nerve cells, leading to nerve cells, leading to nerve damage, reduced sensation, and epidermal cracks [13,14,15].

Autonomic neuropathy can cause anhidrosis, leading to dry, cracked skin that may serve as an entry point of bacteria. While most diabetic patients maintain sufficient circulation for healing, autonomic dysfunction often dominates, presenting as a hot, swollen foot. Sensory neuropathy initially causes tactile allodynia and thermal hyperalgesia, progressing to loss of sensation and proprioceptive dysfunction as myelinated fibers are damaged. Motor neuropathy results in muscle atrophy, foot deformities, and altered biomechanics, redistributing pressure and increasing the risk of claw toes, hammertoes, and prominent metatarsal heads [16,17,18]. People with diabetes are prone to peripheral neuropathy involving sensory, autonomic, and motor components, driven by mechanisms such as nitric oxide inhibition and maillard reaction between sugars and amino acids [19].

Nitric oxide blocking: Hyperglycemia, dyslipidemia, insulin resistance, and oxidative stress contribute to cellular damage, endothelial dysfunction, and diabetes complications. Hyperglycxidatemia specifically inhibits nitric oxide production by preventing endothelial nitric oxide synthase activation, leading to increased reactive oxygen species like superoxide. Superoxide is converted to hydrogen peroxide by superoxide dismutases, which is further reduced to hydroxyl radicals in the presence of ferrous or cuprous ions. Superoxide anions bind to nitric oxide, forming peroxynitrite, which reduces its bioavailability and disrupts endothelial function. This leads to lipid peroxidation, proatherogenic LDLs, platelet aggregation, and atherothrombosis. Additionally, glucoxidation and lipoxidation of vascular proteins promote atherogenesis and neuropathy in small vessels [19,20].

Maillard reaction: The Maillard reaction is a slow interaction between reducing sugars and amino groups in biomolecules, forming advanced glycation end products (AGEs). This reaction is linked to diabetes complications, aging, and protein modifications, contributing to atherosclerosis development. Excess glucose is converted to sorbitol by aldose reductase in the polyol pathway, using NADPH. Activation of the hexosamine biosynthetic pathway reduces NADPH and inhibits glucose-6-phosphate dehydrogenase. Neuropathy causes foot deformity and limited joint mobility,

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leading to abnormal pressure, callus formation, tissue injury, inflammation, necrosis, and ulceration [19,21].

Figure 2: Diabetic neuropathic feet [19]

PAD: peripheral arteries disease (PAD): Hyperglycemia induced peripheral disease (PAD) leads to endothelial dysfunction and reduced vasodilator production, causing atherosclerotic stenosis in lower limb arteries. It raises thromboxane A2, increasing hypercoagulation and the risk of ischemia and ulcers. Factors affecting endothelial cell proliferation include basement membrane thickening, increased blood viscosity, smooth muscle cell growth, altered microvascular tone, and decreased antioxidant activity and angiogenesis. Noninvasive tests like the Ankle-Brachial Index (ABI) are effective in diagnosing PAD [11,22,23].

Immunopathy: In diabetes, a weakened immune response slows inflammation and increases infection risk. Compared to non-diabetics, diabetics show reduced neutrophil function , impaired chemotaxis, weakened phagocytosis, and lower T-cell activity. These changes also affect leucocyte function, macrophage morphology, and pro-inflammatory cytokine production, worsening diabetic foot ulcers (DFU) [11].

Foot Architecture: The foot unique structure increases it's suspectibility to DFUs, often affecting plantar tendons, muscle sheaths, aponeurosis, and fascia. A sterile metal probe can detect bone infection, will CT scans, MRI, radioisotope scans, and radiographs offer high-resolution imaging of bone and soft tissue infections [11,15].

Treatment:

Uninfected wounds: Some experts prescribe antibiotic for uninfected wound, fearing high surface bacteria may hinder healing or mask infection in diabetic. However, trials show systemic antibiotic neither aid healing nor prevent infections. Due to a lack of evidence and potential clinical, microbiological, and financial risks, guidelines advise against their use [24,25,26].

Infected wounds: Diabetic foot infection treatment require multiple interventions. While antibiotics are essential, they are often insufficient alone. Effective management includes debridement, pressure offloading,and sometimes surgery to cleanse wounds, remove necrotic tissue, and drain pus. Edema is controlled with limb elevation and compression, while revascularization may be needed for arterial insufficiency to improve nutrient, immune cell, and antibiotic delivery [24].

Antimicrobial therapy:

Empirical therapy: Initial antibiotic therapy is usually empiric, and infection severity guides the choice of agents and treatment route [24].

Table 1: Antibiotic for empirical treatment of diabetic foot infection [27]

Severity of infection	Expected pathogens	Potential antibiotic agents	Route	Duration of treatment
Mild	Staphylococcus aureus, streptococci	Cephalosporins, Clindamycin, Co-amoxiclav	Oral	1-2 weeks
Moderate	Staphylococcus aureus, streptococci, Enterobacteriaceae	Co-amoxiclav, combination of quinolone + clindamycin	Oral or parenteral	2-3 weeks
Sever	All pathogens, maybe anaerobes and pseudomonas aeruginosa	Piperacillin-tazobactam, Cefepime, carbapenem	Parenteral, with oral switch when stable	2-3 weeks

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Various Plants: Some plants could be the treatment in the future for wound healing in diabetes. Different traditional & medicinal plants that have a natural origin used in diabetic wound healing.

1. Aloe vera:

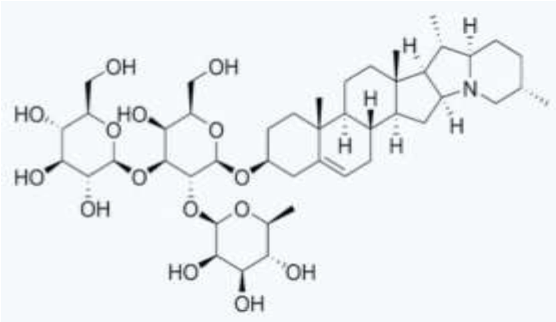

Figure 5: Structure of saponin [28]

The commercial source of saponin is aloe vera (aloe, Musabbar, Kumari) leaves. Aloe is the dried juice collected by incision from the bases of leaves of Aloe babadensis. It is belonging to the Liliaceae family. Aloe vera contains saponin, naftoquinones, anthroquinones, sterols, triterpenoids. This bioactive molecule present multiple biological activities [29,30,31].

Uses: Anti-inflammatory activity, promote wound healing, increase collagen synthesis, anti-bacterial properties.

Study: The effect of aloe vera on the DFU (Conducted in 2023). Involved 66 patients with DFU. The study involved 66 patients diagnosed with diabetic foot ulcers (DFU). These patients were divided into two groups for comparison. The first group, known as the intervention group, received treatment with aloe vera gel. The second group, the control group, received standard care for their condition. After three week intervention group improved healing compared to the control group [32,33]. This study is combination of aloe vera/plantago (conducted in 2019). These patients were divided into two groups. The first group, known as the intervention group, received topical plantavera gel in addition to routine care. The second group, the control group, received a placebo gel. Intervention was carried out twice a day four weeks. Plantavera gel significantly reducing the ulcer surface area compared to control group [34]. The effect of aloe vera on the DFU (conducted in 2014). In this study model are divided into four groups. The first group, known as the control group. The second group, untreated group. Third group is rats treated with an ethanol extract, extracted from aloe vera. The forth group, rats whose diabetic foot ulcers were treated with aloe vera gel. After four weeks in the groups where aloe vera gel and ethanol extract were used, a faster reduction in the extent of ulceration was observed compared to rat not treated with these substance [35,36].

2. Turmeric:

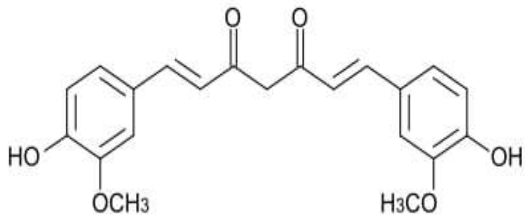

Figure 6: Structure of Curcuminoid [37]

The synonym for turmeric is haldi, saffron indian, rhizome curcumae, which is commonly used in india. It is dried, rhizome of curcuma longa Linn. It is belonging from zingiberaceae family. Turmeric contain curcumin, curcuminoids, cymene, tumeron [38,39,40].

Use: Anti-ulcer properties, anti-inflammation activity, anti-bacterial, wound healing properties during DFUs, improve cutaneous wound healing by involving in the tissue remodelling, collagen deposition.

Study: In a 2014 study on the effect of turmeric on diabetic foot ulcers (DFU), researchers investigated the role of turmeric in diabetic wound healing. The study involved wistar rats that were induced with diabetes using streptozotocin. These rats were divided into three group, a control group, a gel-treated group receiving 25% pluronic F-127 gel, and a curcumin-treated group. The treatments were applied once daily for 19 days. Curcumin application increased the wound contraction. Curcumin also increases a level of anti-oxidant enzymes. Curcumin caused faster and better wound healing in diabetic rats insulin more effective [29,41]. The study investigated the effect of turmeric on diabetic wound healing using different pastes: turmeric paste, insulin paste, and honey paste (2015). The experiment was conducted on alloxan-induced diabetic male albino mice, which had a blood glucose level greater than 180mg/dl. The mice were divided in to five groups, each consisting of six animals. Group A (positive control) was treated with insulin paste, Group B

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(positive control) was treated with turmeric extract paste, Group C (positive control) was treated with honey paste, Group D (diabetic control) received no treatment, and Group E consisted of non-diabetic, normal animals. The effects of the topical application paste on diabetic wound healing were evaluated at different day intervals: 0, 3, 6, and 9 days. Results showed that honey paste was more effective than insulin paste. At the 6th day , wound healing percentages, depending on this size of the wound, were as follows: turmeric at 68.86% honey at 62.45% and insulin at 47.65% all compared to the diabetic control, turmeric, rich in polyphenols, enhances the healing activity in diabetic wounds by improving glucose sensitivity, thus promoting faster and more effective wound recovery [42,43,44].

3. Amla:

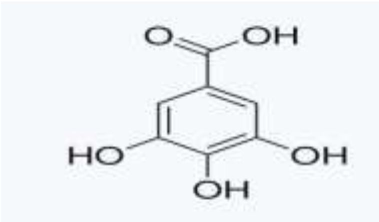

Figure 7: Structure of Gallic acid [45]

The synonym for amla is aonla, gooseberry. It is dried, leaf, seed and fruit of Embica officinalis/phyllanthus Embica. It is belonging from euphorbiaceae family. Amla contain gallic acid, gallotanin, ellagic acid, corilagin [46,47].

Use: Antioxidant, immunomodulatory, hepatoprotective, anti-microbial, anti-inflammatory.

Study: Oral admistration 100 mg/kg body weight reduced the blood sugar level in normal and in alloxan induced diabetic rats [48,49,50].

4. Green tea:

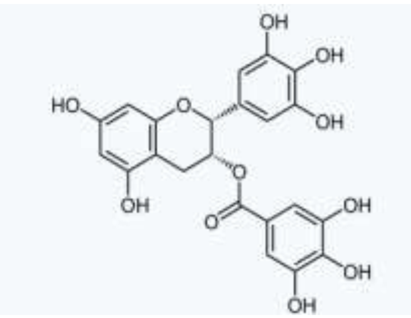

Figure 8: structure of Epigallocatechin-3-gallate [51]

The synonym for green tea is chai, Tea, Te. It is produced from the leaves, buds, or delicate stems of the plants of the camellia sinensis Lin. It is belongs to the Theaceae family. Green tea contain Epigallocatechin-3-gallate, epicatechin-gallate, epicatechin-Catechin, Epigallocatechin, gallic acid [52].

Use: anti-cancer, cardioprotective, antidiabetic.

Study: 75, 150 and 300 mg/kg body weight caused a significant decrease in blood glucose levels of alloxan-induced diabetic mice [53].

5. Fenugreek:

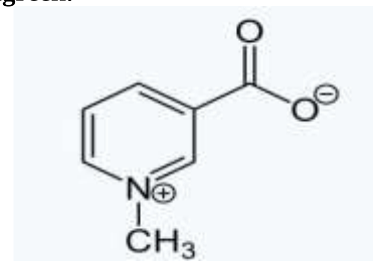

Figure 9: Structure of Trigonelline [54]

The synonym for Fenugreek is Methi (hindi), Methika or chandrika (Sanskrit), vendayan (tamil). It is obtained from seeds and green leaves of Foenum Graceum. It is belonging from Fabaceae family. Fenugreek contain diosgenin, galactomannan, trigoneosides, trigonelline, choline [46].

Use: Hypoglycemic, hypocholestrolemic, antiulcerative, antibacterial, antioxidant.

Study: Oral admistration of ethanol extract of seed at 2 g/kg, 1 g/kg, 0.5 g/kg and 0.1 g/kg dose, in diabetic rats [55].

6. Garlic:

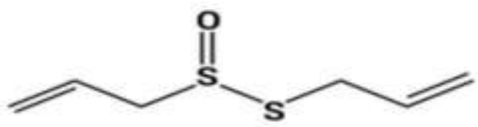

Figure 10: Structure of Allicin [56]

The synonym for garlic is Lahasun, Rasona, Lasan, Lassun. The roots of Allium sativum plants were obtained from those cultivated in the farm of aromatic and medicinal plants. It is belonging from alliaceae/liliaceae. Garlic contain allin (diallyldisulfide oxide), allicin, APDS (allyl propyl disulphide), S-allyl cysteine, S-allyl, Mercaptocysteine [57].

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Use: antioxidant, antimicrobial, anticancer.
Study: Oral dose of 0.25 mg/kg of ethanol, petroleum ether and ethyl acetate extract in alloxanized rabbits, shows antihyperglycemic activity [58].

7. Peepal:

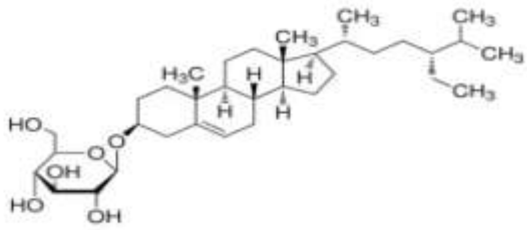

Figure 11: Structure of β-Sitosteryl-d-glycoside [59]

The synonym for Peepal is piparo, pipalo, arlo, ashwatha. It is obtained from dried leaves, flowers, fruits of Ficus religosa. It is belonging from Moraceae. Peepal contain β-Sitosteryl-d-glucoside, flavonols (kaempeferol, quercetine, myricetin) [60].
Use: Antiulcer, antibacterial, antiprotozoal, anti-viral**.**
Study: The ethanolic extract of the fruit, at a dosage of 250 mg/kg body weight, showed antidiabetic activity [61].

8. Ginger:

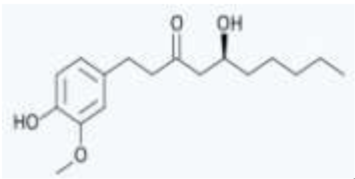

Figure 12: Structure of Gingerol [62]

The synonym for ginger is adrak (Hindi), Ingwer (German), Jengibre (Spanish). The most important part of the Zingiber officinale (ginger) plant is its rhizome (underground stem), which is thick, fleshy, and aromatic. It is belonging from zinzibaraceae. Ginger contain gingerol, shogaol, gingerols, zingiberene, zingiberols, zingerone [63].
Use: Antioxidant, antiviral, antibacterial, antifungal.
Study: Oral admistration of the juice (4 ml/kg of body weight/day) for 6 weeks on streptozotocin induced diabetic rats significantly reduced blood glucose level [46].

9. Neem:

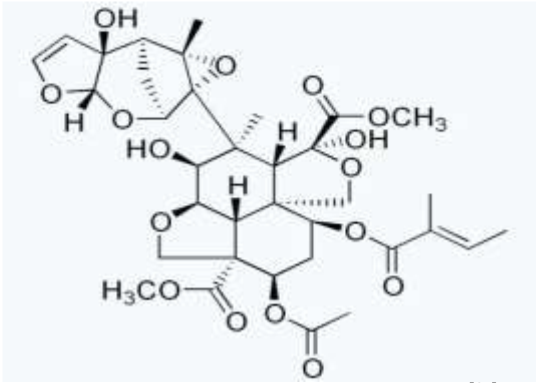

Figure 13: Structure of Azadirachtin [64]

The synonym for neem is Nimba, Holy tree, Vembu, Arishtha, Indian lilac, Margosa tree. It is obtained from leaves, bark, seeds of Azadirachta indica Linn. It is belonging from meliaceae. Neem contain isopreinoids, azadirone, azadirachtin, polyphenolic, flavonoids, glycoside, terpenoids, caumarin, tannin [46].
Use: Anti-inflammatory, antifungal, antibacterial, antioxidant.
Study: Aqueous leaves extract at a dose of 250 mg/kg body weight for 16 weeks resulted significant fall in blood glucose and improvement in serum total, LDL and HDL cholesterol and triacylglycerol which increased in diabetic rats [65].

II. CONCLUSION:

The goals of wound care include reducing risk of side effects, enhancing the healing process. Many plants have been found useful in wound healing. We discussed some antibiotics used in treatment of DFUs. Apart from synthetic drugs used in the healing process, this review also talk about different traditional & medicinal plants that have a natural origin used in diabetic wound healing. The active phytoconstituents of the plant are mainly responsible for the activity of wound healing. Clinical trial studies on diabetic wound healing are also discussed. Plants and plant extracts in this review have been used in preclinical trials, and have shown a positive response in the treatments of wound healing in diabetes- induced animals. These plants could be the treatments in the future for wound healing in diabetes.

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ABBREVATION:
DFU- Diabetic foot ulcer
IDF- International diabetics federation
PAD- Peripheral Arteries Diseases
ABI- Ankle Brachial Index
STZ- Streptozotocin
MRSA- Methicillin Resistant Staphylococcus aureus

REFERENCES:

[1]. Manish K Gautam, Anamika Gupta, RK Goel.Diabetic foot infection and its herbal treatment. Recent advances in microbiology, 155, 2012.
[2]. Lipsky, Pecoraro, Larson, Hanley, and Ahroni. Outpatient management of uncomplicated lower- extremity infections in diabetic patients. Archives of internal medicine 1990;150,790-7.
[3]. Larijani, B., Ranjbar, H.S. Overview of diabetic foot; novel treatments in diabetic foot ulcer. Daru volume 16, supplement 1,2008.
[4]. Boulton., AJ. The diabetic foot: a global view. Diabetes Metabolism Research Review. 2000; volume 16.
[5]. Ramani, Shivananda, and Kundaje. Bacteriology of diabetic foot ulcers. Indian journal of pathology & Microbiology 34:1991;(81-87).
[6]. Roberts Pamela R., Kimberly Ward Black, Jean T. Santamauro and Gary P. Zaloga. Dietary peptides improve wound healing following surgery. Nutrition, 1998;Volume14: 266-269.
[7]. Lipsky, B.A. A Current Approach to Diabetic Foot Infections. Current Infectious Disease Reports 1999, Volume 1:253–260.
[8]. Girish M Bengalorkar, Kumar Tayur Nagendra. International Journal of biological and medical Research 2(1): 453-460 2011.
[9]. Reiber GE, Lipsky BA, Gibbons GW. The burden of diabetic foot ulcers. The American Journal of Surgery 1998; Volume 176(supplement l):5S–10S.
[10]. Shenoy KR, editor. Manipal Manual of Surgery. New Delhi: CBS publisher and Distributors ; 2002.53-56.
[11]. Suman Kumar, Alakesh Bharali, Himangshu Sarma, Susankar Kushari, Sameeran Gam, Iswar Hazarika, Satyendra, Prasad, Damiki Laloo. Traditional complementary and alternative medicine for diabetic foot ulcer management: A systematic review. Journal of Ayurveda and Integrative Medicine 14 (2023) 100745.
[12]. Fard AS, Esmaelzadeh M, Larijani B. Assessment and treatment of diabetic foot ulcer. International Journal of Clinical Practice 2007;61:1931e8.
[13]. Larijani B, Hasani Ranjbar S. Overview of diabetic foot; novel treatments in diabetic foot ulcer. Daru Journal of Pharmaceutical Science 2008;16:1e6.
[14]. Syafril S. Pathophysiology diabetic foot ulcer. IOP Conference Series Earth & Environmental Science 2018;125:012161.
[15]. Aumiller WD, Dollahite HA. Pathogenesis and management of diabetic foot ulcers. Journal of the American Academy of Physician Assist. 2015;28:28e34.
[16]. JJ Mendes, J Neves. Diabetic Foot Infections: Current Diagnosis and Treatment The Journal of Diabetic Foot Complications, 2012; Volume 4, Issue 2, No. 1, Pages 26-45.
[17]. Frykberg RG. Diabetic foot ulcers: current concepts. Journal of Foot Ankle Surgery 1998;37:440-6.
[18]. Corbin DO, Young RJ, Morrison DC. Blood flow in the foot, polyneuropathy and foot ulceration in diabetes mellitus. Diabetologia 1987;30:468-73.
[19]. Afsaneh Alavi, Gary Sibbald, Dieter Mayer, Laurie Goodman, Mariam Botros, David G. Armstrong, Kevin Woo, Thomas Boeni, Elizabeth A. Ayello, and Robert S. Kirsner, Diabetic foot ulcers Part I. Pathophysiology and prevention International Journal of the American Academy of Dermatology. Volume 70; Issue 1; 2014;240-1280.
[20]. Apelqvist J, Ragnarson-Tennvall G, Persson U, Larsson J. Diabetic foot ulcers in a multidisciplinary setting. An economic analysis of primary healing and healing with amputation. Journal of Internal Medicine 1994;235:463-71.
[21]. Erbersdobler HF, Faist V. Maillard reaction products: uptake, metabolic transit and selected parameters of biopotency and safety. Forum of Nutrition 2003;56:353-5.
[22]. Tresierra-Ayala MA, García Rojas A. Association between peripheral arterial

disease and diabetic foot ulcers in patients with diabetes mellitus type 2. Medicina Universitaria 2017;19:123e6.

[23]. Syafril S. Pathophysiology diabetic foot ulcer. IOP Conference Series Earth Environmental Science 2018;125:012161.

[24]. Edgar J.G. Peters, Benjamin A. Lipsky. Diagnosis and Management of Infection in the Diabetic Foot. Medical Clinics of North America 97 (2013) 911–946.

[25]. Berendt AR, Lipsky BA. Should antibiotics be used in the treatment of the diabetic foot? The Diabetic Foot 2003;6:18–28.

[26]. Edmonds M, Foster A. The use of antibiotics in the diabetic foot. The American Journal of Surgery 2004;187(5):25S–8S.

[27]. Uckay¸ z. Gariani, Z. Pataky & B. A. Lipsky. Diabetic foot infections: state-of-the-art Diabetes, Obesity and Metabolism 2013.

[28]. Structure of Saponin: https://images.app.goo.gl/R2D8XdyGtW7PCZmFA.

[29]. 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.

[30]. Rosenthal SP. Acceleration of primary wound healing by insulin. Archives of Surgery 1968, 96, 53-55.

[31]. Davis rh, Didonato jj, Hartman gm, Haas rc. Anti-inflammatory and wound healing activity of a growth substance in aloe vera. The Journal of the American Podiatric Medical Association 1994, 84, 77–81.

[32]. Dr. Ruhul Amin, Dr. Ronald Darwin, Mr. Izaz Hussain, Mr. Lakhyajit Borah. Foot Ulcer: An Effect of Aloe Vera.

[33]. Irani PS, Ranjbar H, Mehdipour-Rabori R, Torkaman M, Amirsalari S, Alazmani-Noode F. The Effect of Aloe Vera on the Healing of Diabetic Foot Ulcer: A Randomized, Double-blind Clinical Trial. Current Drug Discovery Technologies. 2023. Volume; 21,56-63c8.

[34]. Najafian Y, Khorasani ZM, Najafi MN, Hamedi SS, Mahjour M, Feyzabadi Z. Efficacy of Aloe vera/ Plantago Major Gel in Diabetic Foot Ulcer: A Randomized Double-Blind Clinical Trial. Current Drug Discovery Technologies. 2019;16(2):223-31.

[35]. Kania, Anna, kaluzynski, grzegorz, pelka, maciej, fijalkowska, Justyna and ciulkiewicz, lukasz. An overview of Aloe vera impact on the healing process of Diabetic Foot Ulcer. Journal of Education, Health and Sport. 2024;54:67-82.

[36]. Daburkar M, Lohar V, Rathore AS, Bhutada P, Tangadpaliwar S. An in vivo and in vitro investigation of the effect of Aloe vera gel ethanolic extract using animal model with diabetic foot ulcer. Journal of Pharmacy and Bioallied Sciences. 2014 Jul;6(3):205-12.

[37]. Structure of Curcuminoid: https://images.app.goo.gl/3rFsfNL8UnCshzZj6.

[38]. Chattopadhyay I, Biswas K, Bandyopadhyay U, Banerjee R. Turmeric and curcumin:biological actions and medicinal applications. Current Science. 2004,87,44–53.

[39]. Agrawal DK, Mishra PK. Curcumin and its analogues: potential anticancer agents. Medicinal Research Review 2010,30,818–860.

[40]. Shehzad A, Lee J, Lee YS. Curcumin in various cancers. Biofactors 2013,39, 56–68.

[41]. 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. International Immunopharmacology 2014, 20, 322-330.

[42]. M. A. Khan1, T. Shahzadi1, S. A. Malik, M. Shahid1, M. Ismail1, M. Zubair1* and S. Iqbal. pharmacognostic evaluation of turmeric (curcuma longa) extracts in diabetic wound healing. The Journal of Animal & Plant Sciences, 29(1): 2019, Page: 68-74.

[43]. Chaovanalikit, A. and R.E. Wrolstad . Total Anthocyanins and Total Phenolics of Fresh and Processed Cherries and Their Antioxidant Properties. Journal of Food Science. 2004;69(1): FCT67-FCT72.

[44]. Takemoto, K., W. Doi and N. Masuoka . Protective effect of vitamin E against alloxan- induced mouse hyperglycemia. Biochimica et Biophysica Acta, 2016;1862(4): 647–650.

[45]. Structure of Gallic acid: https://images.app.goo.gl/fhDSsiT74KPgztcP7
[46]. Neha Gupta1, Tejovathi Gudipati2* and G.B.K.S. Prasad3.Plant Secondary Metabolites of Pharmacological Significance in Reference to Diabetes Mellitus: An Update. International Journal of Current Microbiology and Applied Sciences. (2018) 7(5): 3409-3448.
[47]. Jain, S.K., and Khurdiya, D.S. Vitamin C enrichment of fruit juice based ready-to-serve beverages through blending of Indian gooseberry (Emblica officinalis Gaertn.) juice. Plant Foods for Human Nutrition. 2004;59(2): 63-66.
[48]. Suryanarayan, P., Saraswat, M., Petrash, J.M., and Reddy, G.B. Emblica officinalis and its enriched tannoids delay streptozotocin-induced diabetic cataract in rats. Molecular Vision. 2007; 24(13): 1291-1297.
[49]. Khan, K.H., 2009. Roles of Emblica officinalisin Medicine - A Review. Botany Research International 2 (4): 218-228.
[50]. Tirgar, P.R., Shah, K.V., Rathod, D., Desai, T.R., and Goyal, R.K. Investigation Into Mechanism of Action of Anti-Diabetic Activity of Emblica Officinalis on Streptozotocin Induced Type I Diabetic Rat. Pharmacologyonline. 2011;2: 556-575.
[51]. StructureofEpigallocatechin-3-gallate:https://images.app.goo.gl/zpt4jfzpsGzzhAb46.
[52]. Han, Q., Yu, Q.Y., Shi, J., Xiong, C.Y., Ling, Z.J., and He, P.M. 2011. Molecular characterization and hypoglycemic activity of a novel water-soluble polysaccharide from tea (Camellia sinensis) flower. Carbohydrate Polymers. 86(2): 797–805.
[53]. Eidia, A., Eidib, M., and Esmaeilia, E. Antidiabetic effect of garlic (Allium sativum Linn.) in normal and streptozotocin-induced diabetic rats. Phytomedicin. 2006;13: 624-629.
[54]. Structure of Trigonelline: https://images.app.goo.gl/bZ26Tya9uZ1dYExY6.
[55]. Sarasa, D., Sridhar, S., and Prabakaran, E. Effect of an antidiabetic extract of Trigonella foenum graecum on normal and alloxan induced diabetic mice. International Journal of Pharmacy and Pharmaceutical Sciences. 2012;4(1): 63-65.
[56]. Structure of Allicin: https://images.app.goo.gl/bZ26tya9uZ1dYExY6.
[57]. S. Palani , Nisha Mary Joseph , Yonatan Tegene and Anish Zacharia. Garlic - a concise review. International journal of pharmacognosy, 2014; Vol. 1(11): 691-695. 2014; Vol. 1(11): 691-695.
[58]. Eidia, A., Eidib, M., and Esmaeilia, E. Antidiabetic effect of garlic (Allium sativum L.) in normal and streptozotocin-induced diabetic rats. Phytomedicin. 2006;13: 624-629.
[59]. Structure of β-sitosteryl-d-glycoside: https://images.app.goo.gl/SD61t7TwFdjZ8MYa7.
[60]. Choudhary, S., Pathak, A.K., Khare, S., and Kushwah, S. Evaluation of antidiabetic activity of leaves and fruits of Ficus religiosa Linn. International Journal of Pharmaceutical and Life Sciences. 2011;2(12): 1325-1327.
[61]. Shailendra Singh. A review on ficus religiosa - an important medicinal plant. International journal of life sciences and review (2016), Vol. 2, Issue 1.
[62]. Structure of gingerol: https://images.app.goo.gl/6gPo7ZCrmfDk1jjZA.
[63]. Khani, S.P., Vishwakarma, S.L., and Goyal, R.K. Anti-diabetic activity of Zingiber officinale in streptozotocin-induced type I diabetic rats. The Journal of pharmacy and pharmacology. 2004;56(1): 101-105.
[64]. Structure of Azadirachtin: https://images.app.goo.gl/9xkieW52g1kXKMYA8.
[65]. Eshrat, H.M., and Hussain, A. Reversal of diabetic retinopathy in streptozotocin induced diabetic rats using traditional indian anti-diabetic plant, Azadirachta indica (Linn.). Indian Journal of Clinical Biochemistry. 2002;17 (2): 115-123.