CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES
SJIF Impact Factor: 7.187
https://doi.org/10.5281/zenodo.23924233

Available online at: http://www.iajps.com Review Article

THE ROLE OF PLANT-BASED EXTRACTS IN THE HEALING OF DIABETIC FOOT ULCERS

Noorsaba A. Pathan*

*Assistant Professor, Sushganga College of Pharmacy, Wani, Maharashtra.

Abstract:

The purpose of this review is to provide verified data on the various herbal extract that shows healing in diabetic wounds. Herbal products and their active constituents used for diabetic wound healing activity, and various cellular and molecular mechanisms of their actions will also be described. Study shows that depending on the factors that affecting the wound formation and the healing process. The biological factors and the genetic factors affecting the formation diabetic foot ulcer. With the use of active constituents present in the herbal plants made use in the formulations diabetic wound should be cure. Herbal products through different mechanisms of angiogenesis, production of cytokines and growth factors, keratinocytes, and fibroblast migration and fibroblast migration and proliferation may be considered as an important support for substitutes for synthetic drugs and conventional and sustained drugs therapy. This will affecting on both the acute and the chronic wound healing process. As the herbal natural extracts have no adverse effects on the body.

Keywords: *Herbal extracts, diabetic wound, foot ulcer wounds, bacterial wound infection.*

Corresponding author:

Noorsaba Pathan,

Assistant Professor,

Sushganga College of Pharmacy, Wani, Maharashtra.

Email id - nurrpathan@gmail.com

QR CODE

Please cite this article in press *Noorsaba Pathan* ***et al., The Role Of Plant-Based Extracts In The Healing Of Diabetic Foot Ulcers,. Indo Am. J. P. Sci, 2026; 13(11).***

INTRODUCTION:

Diabetic foot ulcer (DFU) is one of the major complicated disease. Diabetes is a metabolic disorder associated with the endocrine system that resulted in hyperglycemic conditions [1]. Diabetes are of two types-diabetes mellitus and diabetes insipidus. Diabetic mellitus (dm) is a chronic disease that occur due to impairment of insulin secretion and sensitivity, destruction of pancreatic beta cell type -1 diabetes and peripherial insulin resistance in type 2 diabetes affecting more than 342 million people worldwide.[2-4].Prolonged and untreated hyperglycemia or uncontrolled glucose levels lead to serious diabetic complications such as nephropathy ,neuropathy , retinopathy , hypertension ,hyperlipidemia, increased risk of cardiovascular disease and heart attack[5] . The most costly and the devastating problem is delayed in wound healing processes which lead to serious complications such as high risk of bacterial infections, gangrene, limb amputations sepsis and even death[6].

Wound healing process related to Diabetes:

Wound healing difficulties in diabetes patients are multidirectional .The hyperglycemic condition in the wound site leads to chronic inflammation, impaired vascularization and tissue regeneration ,reduced production of growth factors ,excessive protease activity and oxidative stress [7]. Hyperglycemia leads to contracted blood vessels which leads to reduced circulation and microvascular dysfunction[8],which ultimately leads to oxidative stress because of superoxide formation [9].due to overactivation of superoxide formation ,the formation of advanced glycation end-products(AGEs) occurs, which interacts with their receptors (RAGE) and gives rise to impaired wound healing[10].diabetic foot ulcers are associated with elevated metalloprotease which are 60 times higher in chronic wound fluid than in acute wounds .This elevated level of protease leads to dysregulated cellular functions are involved in diabetic wounds, such as defects in leukocyte chemotaxis, defective T-cell immunity ,dysfunction of fibroblasts and epidermal cells and phagocytosis and bactericidal capacity which further leads to insufficient bacterial clearance and delays wounds healing in diabetic individuals[11].

In diabetic patients, blood vessels get impaired , which leads to lower leukocyte migration into the wound and creates infections [12].

The production of fibrin plugs achieves recovery of inflammatory cells in the early stages (homeostasis and (inflammation) of healing after injury. The aggregation of platelets releases different growth factors ,including platelets-derived growth factor (PGDF).TGF-BETA1 ,epidermal growth factor (EGF),and proinflammatory cytokines such as interleukin-1 (IL-1) [13]. Which leads to the accumulation if neutrophils and macrophages at the site of injury. These macrophages and neutrophils increases inflammatory responses.[14].,[15].

Neutrophil activation ,along with chemotactic signals, occurs that allows the cell's localization at the wound site , which leads to cell adhesion and leaching of ECM out of the trophil adhesion which elevates the inflammatory phase end delays the healing cascade [16,17].it was concluded that the hypoxia ,dysfunction in fibroblasts and epidermal cells, impaired angiogenesis and neovascularization ,high level of metalloproteases ,damage from ROS and AGEs results in autoimmune diseases and delays in the wound healing process.

The dysregulation in wound healing phase retards the healing process in diabetic patients , which affects the quality of life and increase mortality .The matured granulation tissues are formed by the continuous inflammatory phase, which results in a decline in wound tensile strength that can be due to vascular damage resulting in ischemia[18].

Open wounds are particularly prone to infection, especially by bacteria and provide an entry point for systemic infections. Aerobic or facultative pathogens such as staphylococcus aureus , pseudomonas aeruginosa and beta-haemolytic streptococci are the primary causes of delayed healing and infection in both acute and chronic wounds [19,20]. In control of bacterial infections an important part of the standard treatment of diabetic wounds ,in addition to wound debridement ,revascularization and acceleration of the healing process[21],and amputation.[22]

About 20% of people with a diabetic foot ulcer will undergo a lower extremity amputation , either minor (i.e., above foot)[23] infection and progressive gangrene are the primary causes of lower extremity amputation[24] with approximately 50% of diabetic foot ulcer becoming infected.[25,26]

Healing phages [7,73] :

1) Hemostasis (coagulation which controls excessive blood loss from the damaged vessels) (few minutes)

a) Immediate response: when a wound occurs, the body's immediate response is to stop bleeding .Platelets in the blood gather at the wound site and form a temporary plug to seal the damaged blood vessels (hemostasis).

b) Vasoconstriction: blood vessels near the wound constrict to reduce blood flow , helping to minimize bleeding.

C) clot formulation: the clotting cascade begins, leading to the formation of a stable blood clot (hemostatic plug) composed of fibrin and blood cells. This clot acts as a temporary barrier.

2. Inflammation: (influx of macrophages and proteases to clean up debris and pathogens, secretion of growth factors and pro-inflammatory cytokines) (0-3 days)

i. **Cellular Response:** Inflammation is a crucial

phase for wound healing. White blood cells, primarily neutrophils and macrophages, migrate to the wound to remove debris, dead cells, and potential pathogens.

ii. Cytokine Release: Various signaling molecules, called cytokines, are released to coordinate the inflammatory response. These molecules also stimulate the recruitment of fibroblasts and endothelial cells.

iii. Angiogenesis: New blood vessels (angiogenesis) begin to form, supplying the wound with oxygen and nutrients needed for repair.

iv. Granulation Tissue: Granulation tissue, which is rich in collagen and blood vessels, starts to develop at the wound site.

3) Proliferation (fibroblast migration ,extracellular matrix formation ,granulation ,re-epitheliazation ,neoangiogenesis) (3-21 days)

i. Proliferation: Fibroblast Activity: During this phase, fibroblasts play a key role. They produce collagen, a structural protein that strengthens the wound, and other extracellular matrix components.

ii. Re-epithelialization: Epithelial cells migrate from the wound edges to cover the wound's surface, forming a new epidermal layer.

iii. Contraction: Myofibroblasts contribute to wound contraction, reducing the wound's size.

iv. Continued Angiogenesis: Blood vessels continue to grow into the wound, ensuring adequate blood supply to support tissue repair.

4) Remodelling (Maturation): Maturation or remodelling that occurs within the dermis (collagen) crosslinking and reorganization, increase in the tensile strength of the extracellular matrix , scar formation) (21 days -2 years)[4,102].

Remodelling (Maturation):

a). Tissue Remodelling: This phase can last for several months or even years. The newly formed collagen fibers gradually reorganize and mature, making the wound stronger.

b). Scar Formation: The wound is filled with collagen, and the scar tissue becomes more organized. The scar may initially appear raised and red but tends to flatten and fade over time.

c). Strength Restoration: The wound gradually regains its strength, although it may never reach the full strength of the original tissue.

Functional Recovery: If the wound affected a functional area (e.g., a joint), functional recovery occurs during this phase as tissues adapt and regain their functionality.

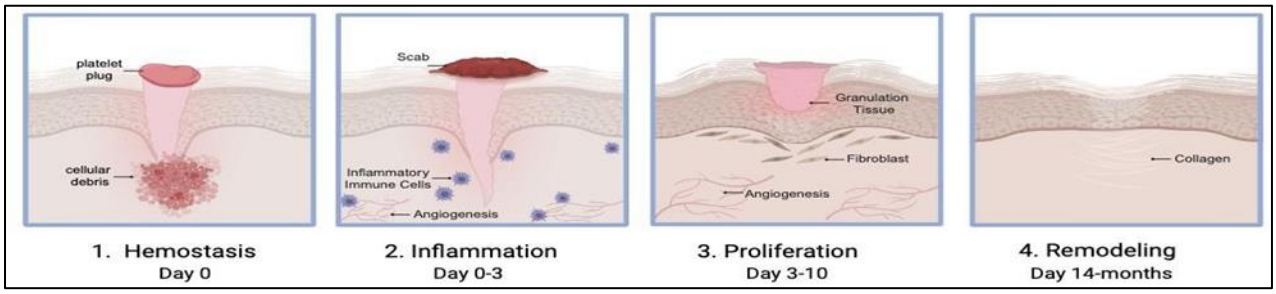


Figure 1.Stages of wound healing (figure made in Biorender)

Mechanism of wound healing :[Image representation] Injury

↓

Platelets release growth factors and cytokines
Neutrophils and macrophages engulf bacteria; release growth factors, cytokines and proteases.

↓

Epithelial cells, fibroblasts and endothelial cells produce growth factors

↓

Synthesis of extracellular matrix and new capillaries

↓

Fibroblasts orchestrate the remodelling of the scar by producing extracellular matrix, matrix metalloproteinases and tissue inhibitor of metalloprotease

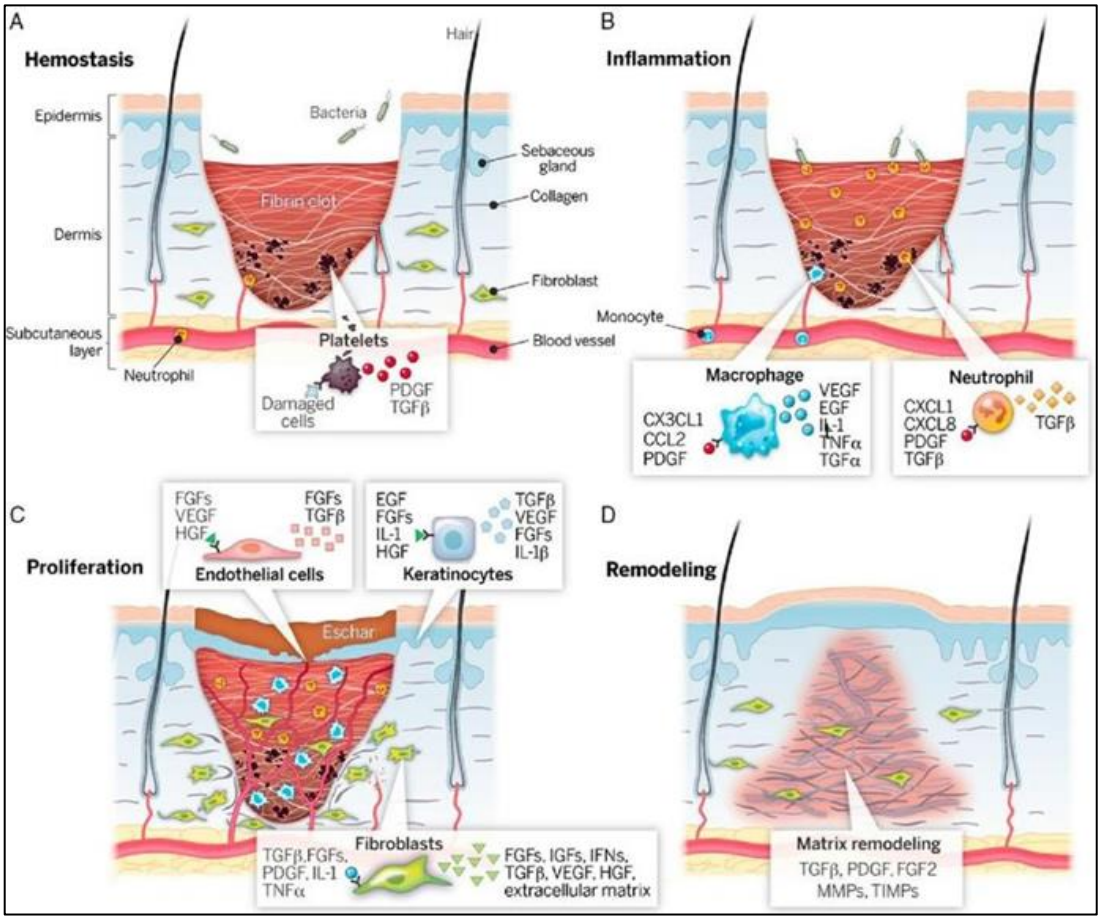


Figure 2.Wound healing process

What happen when Changes occurs in:

Growth factors	Source of activation	Action	Ref
Epidermal growth factor (EGF)	Activated macrophages • Salivary glands. keratinocytes	Keratinocyte and fibroblast mitogen • Keratinocyte migration Granulation tissues formation	[31]
Transforming growth factors (tgf)	• Activated macrophages • t-lymphocytes • keratinocyte	• Hepatocyte and epithelial cell proliferation • Expression of antimicrobial peptides • Expression of chemotactic cytokines. m	[32]
Hepatocytic growth factor	• Mesenchymal cells	• Epithelial and endothelial cell proliferation	[32]
Vascular endothelial growth factors	• Mesenchymal cells	• Vascular permeability • Endothelial cell proliferation	[33]
Platelet derived growth factors	• Platelets • Macrophages • Endothelial cells • Smooth muscle cells • Keratinocytes	• Granulocyte, macrophage ,fibroblast,and smooth muscle cell chemotaxis. • Granulocytes , macrophage ,and fibroblast	[34,35]

		activation • Fibroblast ,endothelial cell proliferation • Matrix metalloproteinase, • fibronectin , hyaluronan production • Angiogenesis • Wound remodeling	
Fibroblast growth factor 1 and 2	Macrophages mast cells T-lymphocytes Endothelial cells Fibroblasts	• Fibroblast chemotaxis Fibroblast and keratinocyte proliferation Keratinocytes migration Angiogenesis Wound contraction Matrix (collagen fibers) deposition	[36]
Transforming growth factors - beta	Platelets T-lymphocytes Macrophages Endothelial cells Keratinocytes Smooth muscles cells Fibroblast	Granulocyte, macrophage, lymphocyte, fibroblast, and smooth muscle cell chemotaxis TIMP synthesis Angiogenesis Fibroplasia Matrix metalloproteinase production inhibition	[37]
Keratinocyte growth factor	Keratinocytes	Keratinocytes migration, proliferation , and differentiation	[38]

Herbal products and their active constituents used for diabetic wound healing :

The described animal studies are based on diabetes induced by streptozotocin (STZ) and alloxan monohydrate . Alloxan monohydrate and STZ are the most popular diabetogenic agents used for assessing the anti-diabetic or hypoglycemic capacity.[37],[39]

STD/Alloxan monohydrate

↓

Cytotoxic glucose analogue

↓

Pancreatic beta cells via the GLUT 2 glucose transporter

↓

1) Hypo-insulinemia 2) Hyperglycemia

Herbals and their activity

Herbs	Model of study	Pharmacological study	Ref
Aloe vera	STZ-induced diabetic BALB/ c mice; excision wound model	A.vera gel control 1 : untreated group ; control untreated diabetic group ; treatment once a day for 9 days Effects : significantly increases level of GAGs and breaking strength on day 9	[40]
Agrimonia Pilosa ;nelumbo nucifera ;Boswellia carteri ;pollen typhae	STZ-induced diabetic C57BL/6 mice ;excision wound model	Accelerated wound healing , promoted vascularization and inhibited inflammation	[41]
Annonas quamosa	STZ-induced diabetic Wistar rats ;excision wound model	A.squamosa ethanolic extracts Better wound healing through increased levels of enzymetic and non-enzymatic antioxidants in wound tissues	[42]
Camellia sinensis	AM-induced diabetic Wistar rats ;incision and excision wound models	Faster wound contraction	[43]
Catharanthus roseus	Invivo study it was observed after 2 months of treatment in diabetic rats	The ethanolic -extract of C.roseus applied on chronic diabetic wounds A 77.7 % declines in blood glucose occurred [44]	[44]
Carica papaya	An excision wound was created and remained open and observed for any infection	Shows contraction of wound more rapidly compared to animals given a placebo[46]	[45],[46]
Punica grantum	Alloxan -induced male wistar rats used[125] .alloxan was injected intraperitoneally after 15 hrs of fasting . Wound was created on rats with glucose >250 mg/dl.	Tissue regeneration	[50]
Radix *rehmanniae*	Female Sprague Dawley rats with diabetic foot ulcers	Deduction of ulcer area from 8-18 days by the extracts	[51]
Rosmarinus officinalis	Alloxan -induced diabetic BALB/c mice	Wound contraction [107]	[52]

Phytochemicals	Sub-class	Mechanism of Action	Ref
Alkaloid	Nicotine	Improve wound healing Accelerate angiogenesis in a small dose . Increase the intracellular level of calcium .	[53],[54]
	Napelline ,songorine and hypaconitine	Fibroblast precursor activation Hyperstimulation growth factors	[55]
	Taspine	The elevated autocrine activity of TGF-beta Increase epidermal growth factor on fibroblasts	[56]
Flavonoid	Quercetin	Activation of collagen matrices in case of dermal WH	[57]
	Isorhamnetin and kaempferol	Improved collegen deposition Maturation Decreased COX-2 level	[58]
	2-(3,4-dihydroxy phenyl-5;7-dihydroxychromen-4)	Accelerates epithelization Scavenging of superoxides Inhibition of mediators of inflammation	[59]
	Vicenin -2	Accelerating proliferation Increase the feasibility of fibroblast cells	[60]
	4,6,7-trimethoxyflavone	Accelerating the movements of kerationocytes	[61]
Terpenes	Genotiopicroside, sweroside and swertiamarine	Trigger collagen production Stimulate mitosis of embryonic fibroblasts	[62]
	Borneol	Suppression of proinflammatory cytokines at the mRNA level	[63]
	Thymol	Modulation of fibroblast metabolism and collagen synthesis	[64]
	Oleanolic acid	Alteration in migration of NH/3T3 fibroblasts and Hecate keratinocytes Enhancement of wound closure	[65]
Phenolics	Asiatic acid ,asiaticoside ,madecassic acid and madecassoside	Evocation of expression of genes influencing angiogenesis Remodelling of the extracellular matrix occurs Introduction of multiple growth factors Elevating collagen synthesis via activation of the TGF-beta	[66,67]
	Cannabinoid	Enhanced epithelial wound closure Helps in intestinal inflammation Suppression inflammation at the early phase if WH	[68,69]
Glycosides	The mixture of 11 saponin glycoside	Accelerating recapitalization of skin wound Enhancing production of collagen in skin fibroblasts Suppress inflammation at the early phase of WH	[70]
	Secoisolariciredesin ol glycoside, ferulic acid glycosides and caffeic acid glycosides	Amplify proliferation Resettling of normal human dermal fibroblasts by the wound scratch assay	[70]

Plant chemicals are regarded as secondary metabolites because the plants that manufacture them may have little need for them. They are synthesized in all the parts of the plant body ; bark, leaves, stem , root, flower, fruits, seeds, etc .any part of the plant body may contain active components.[Solomon Charles et al.,2013]. This chemical work with nutrients and fibres to form an integrated part of defence system against various disease and stress conditions (thilagavathi et al .,2015) . the most important of these bioactive groups of plants are alkaloids, terpenoids, tannins, saponins and phenolic compounds (edeoga et al ., 2005) . correlation between the phytochemical and the bioactivity of plant is desirable to know for the synthesis of compounds with specific activities to treat various health aliments and chronic disease as well.(pandey et al.,2013) [72]

CONCLUSION:

The purpose of this review is to highlight that the herbal approach that could be best suited for the wound healing process in diabetes, without causing any further side effects or with very fewer side effects. In this review we have discussed wound healing , normal wound healing factors that delay wound healing , the effect of diabetes on the delaying of wound healing primary growth factors involved in wound healing.

REFERENCES:

1. Kharroubi, AT,Darwish HM. Diabetics mellitus :The epidermic of the century World J Diabetics 2015; 6(6):850-867
2. Goboza, M.; Aboua, Y.G.; Meyer, S.; Oguntibeju, O.O. Diabetes mellitus: Economic and health burden, treatment and the therapeutical effects of Hypoxis hemerrocallidea plant. Med. Technol. SA.,2016, 30(2), 39-46.
3. Kim, J.E.; Lee, J.H.; Kim, S.H.; Jung, Y. Skin regeneration with self-assembled peptide hydrogels conjugated with substance P in a diabetic rat model. Tissue Eng. Part A, 2018, 24(1-2), 21-33. http://dx.doi.org/10.1089/ten.tea.2016.0517 PMID: 28467735
4. WHO. Global Reports on Diabetes; World Health Organization: Geneva, Switzerland, 2018. 5)Brownlee,M.The Pathobiology of Diabetic Complications. Diabetes 2005,54,1615-1625.[CrossRef][PubMed]
5. Kalan, L.R.; Meisel, J.S.; Loesche, M.; Horwinski, J.; Soaita, I.; Chen, X.; Uberoi, A.; Gardner, S.E.; Grice, E.A.
6. Strain- and Species-Level Variation in the Microbiome of Diabetic Wounds Is Associated with Clinical Outcomes and Therapeutic Efficacy. Cell Host Microbe 2019, 25, 641–655.e5. [CrossRef] [PubMed]
7. Patel,S.;Srivastava,S.;Singh,M.R.;Singh,D.Mechanistic insight into diabetic wounds:Pathogenesis,molecular targets and treatment strategies to pace wound healing.Biomed.Pharmacother.2019,112,108615.[CrossRef][PubMed]
8. Dinh,T.;Elder ,S.;Veves ,A.Delayed wound healing in diabetes Considering future treatments.Diabetes Management,2011,1(5),509. http://dx.doi.org/10.2217/dmt.11.44
9. Vincent,A.M.;Russell, J.W.;Low , P.;Feldman,E.L.Oxidative stress in the pathogenesis of diabetic neuropathya2nd its therapeutic implications. Diabetic Metabolism Research and Review,2004,20,Issue 2, Pages 109-117.
10. Huijberts, M.S.;Schapter,N.C.;Schalkwijk , C.G.(2008).”Advanced glycation end products and diabetic foot disease”.Diabetic metabolism .Research and Review.,2008,24(S1),S19-S24.
11. “Woo,K.;Ayello,E.A.;Sibbald ,R.G.,The edge effect : Current therapeutic options to advance the wound edge.Adv.Skin and Wound care :The Journal for preventation and healing ,2007,Volume 20,Issue 2,pages 99-117”
12. Greenhalgh, D.G. Wound healing and diabetes mellitus.Clin. Plast. Surg.,2003,30(1),37-45.
13. Barrientos, S.;Stojadunovic ,O.;Golinko,M.S.;Brem,H.; Tomic-Canic ,M.Growth factors and cytokines in wound healing.Wound Repair Regen.,2008,16(5),585-601.
14. Hübner, G.; Brauchle, M.; Smola, H.; Madlener, M.; Fässler, R.; Werner, S. Differential regulation of pro-inflammatory cytokines during wound healing in normal and glucocorticoid-treated mice. Cyto-kine, 1996, 8(7), 548-556. http://dx.doi.org/10.1006/cyto.1996.0074 PMID: 8891436
15. Dohan, D.M.; Choukroun, J.; Diss, A.; Dohan, S.L.; Dohan, A.J.; Mouhyi, J.; Gogly, B. Platelet-rich fibrin (PRF): A second-generation platelet concentrate. Part I: Technological concepts and evolution. Oral Surg. Oral Med. Oral Pathol. Oral Radiol. Endod., 2006, 101(3), e37-e44.
16. http://dx.doi.org/10.1016/j.tripleo.2005.07.008 PMID: 16504849
17. Dinh, T.; Veves, A. Microcirculation of the diabetic foot. Curr. Pharm. Des., 2005, 11(18), 2301-2309. http://dx.doi.org/10.2174/1381612054367328 PMID: 16022669
18. Pereira, L.P. Focusing on metabolomic dysregulation and modulation of retinal metabolism to develop novel therapeutic strategies for diabetic retinopathy. 2015
19. Patel, P.; Macerollo, A. Diabetes mellitus:

Diagnosis and screening. Am. Fam. Physician, 2010, 81(7), 863-870. PMID: 20353144
20. Louie, T.J.; Bartlett, J.G.; Tally, F.P.; Gorbach, S.L. Aerobic and Anaerobic Bacteria in Diabetic Foot Ulcers. Ann. Intern. Med. 1976, 85, 461–463. [CrossRef]
21. Lipsky, B.A.; Brendt, A.R.; Deery, H.G.; Embil, W.S.; Joseph, A.W.; Karchmer, B.A. Diagnosis and treatment of diabetic foot infections. Clin. Infect. Dis. 2004, 39, 885–910. [CrossRef]
22. Dang, C.N.; Prasad, Y.D.M.; Boulton, A.J.M.; Jude, E.B. Methicillin-resistant Staphylococcus aureus in the diabetic foot clinic: A worsening problem. Diabet. Med. 2003, 20, 159–161. [CrossRef]
23. Okonkwo, U.A.; DiPietro, L.A. Diabetes and wound angiogenesis. Int. J. Mol. Sci., 2017, 18(7), 1419. http://dx.doi.org/10.3390/ijms18071419 PMID: 28671607
24. McDermott K, Fang M, Boulton AJM, Selvin E,Hicks CW. Etiology, epidemiology, and disparities in the burden of diabetic foot ulcers. Diabetes Care. 2023;46(1):209-221. doi:10.2337/dci22-0043
25. Ndosi M, Wright-Hughes A, Brown S, et al. Prognosis of the infected diabetic foot ulcer: a 12-month prospective observational study. Diabetic Med. 2018;35(1):78-88. doi:10.1111/dme.13537
26. Senneville É, Albalawi Z, van Asten SA, et al. Guidelines on the Diagnosis and Treatment of Foot Infection in Persons With Diabetes: IWGDF/IDSA 2023. Published 2023. Accessed June 12, 2023.https://iwgdfguidelines.org/wp-content/uploads/2023/05/IWGDF-2023-04-Infection-Guideline.pdf
27. Cortes-Penfield NW, Armstrong DG, Brennan MB, et al. Evaluation and management of diabetes-related foot infections. Clin Infect Dis.Published online June 12, 2023. doi:10.1093/cid/ciad255
28. Tan, S. P. et al. Development of a novel antimicrobial seaweed extract-based hydrogel wound dressing. Int J Pharm 456, 10–20 (2013).
29. Khan, A. W. et al. Formulation development, optimization and evaluation of aloe vera gel for wound healing. Pharmacogn Mag 9, S6–S10 (2013).
30. Gavan, A. et al. Development and Evaluation of Hydrogel Wound Dressings Loaded with Herbal Extracts. Processes 10, (2022).
31. Pagano, C. et al. Starch-based sustainable hydrogel loaded with Crocus sativus petals extract: A new product for wound care. Int J Pharm 625, 122067 (2022).
32. Dogan, S.; Demirer, S.E.H.E.R.; Kepenekci, I.; Erkek, B.; Kiziltay, A.Y.S.E.L.; Hasirci, N.E.S.R.˙ I.N.; Müftüoglu, S.; Nazikoglu, A.; Renda, N.; Dincer, U.D.; et al. Epidermal growth factor-containing wound closure enhances wound healing in non-diabetic and diabetic rats. Int. Wound J. 2009, 6, 107–115. [CrossRef]
33. Grazul-Bilska, A.T.; Johnson, M.L.; Bilski, J.J.; A Redmer, D.; Reynolds, L.P.; Abdullah, A.; Abdullah, K.M. Wound healing: The role of growth factors. Drugs Today 2003, 39, 787–800. [CrossRef]
34. Liu, L.; Marti, G.P.; Wei, X.; Zhang, X.; Zhang, H.; Liu, Y.V.; Semenza, G.L.; Harmon, J.W. Age-dependent impairment of HIF-1 α expression in diabetic mice: Correction with electroporation-facilitated gene therapy increases wound healing, an-giogenesis, and circulating angiogenic cells. J. Cell Physiol. 2008, 217, 319–327. [CrossRef] [PubMed]
35. Nishikori, Y.; Shiota, N.; Okunishi, H. The role of mast cells in cutaneous wound healing in streptozotocin-induced diabetic mice. Arch. Dermatol. Res. 2014, 306, 823–835. [CrossRef]
36. Tellechea, A.; Leal, E.C.; Kafanas, A.; Auster, M.E.; Kuchibhotla, S.; Ostrovsky, Y.; Tecilazich, F.; Baltzis, D.; Zheng, Y.; Carvalho, E.; et al. Mast Cells Regulate Wound Healing in Diabetes. Diabetes 2016, 65, 2006–2019. [CrossRef]
37. Peng, C.; Chen, B.; Kao, H.-K.; Murphy, G.; Orgill, D.P.; Guo, L. Lack of FGF-7 Further Delays Cutaneous Wound Healing in Diabetic Mice. Plast. Reconstr. Surg. 2011, 128, 673e–684e. [CrossRef]
38. Roberts, A.B. Transforming growth factor-β: Activity and efficacy in animal models of wound healing. Wound Repair Regen. 1995, 3, 408–418. [CrossRef] [PubMed]
39. Werner, S.; Breeden, M.; Hübner, G.; Greenhalgh, D.G.; Longaker, M.T. Induction of Keratinocyte Growth Factor Expression Is reduced and Delayed During Wound Healing in the Genetically Diabetic Mouse. J. Investig. Dermatol. 1994, 103, 469–473. [CrossRef]
40. Lenzen, S. The mechanisms of alloxan- and streptozotocin-induced diabetes. Diabetologia 2007, 51, 216–226. [CrossRef] [PubMed]
41. Daburkar, M.; Rathore, A.S.; Tangadpaliwar, S.; Bhutada, P.; Lohar, V. An in vivo and in vitro investigation of the effect of Aloe vera gel ethanolic extract using animal model with diabetic foot ulcer. J. Pharm. Bioallied Sci. 2014, 6, 205–212. [CrossRef]
42. Hou, Q.; He, W.-J.; Chen, L.; Hao, H.-J.; Liu, J.-J.; Dong, L.; Tong, C.; Li, M.-R.; Zhou, Z.-Z.; Han, W.-D.; et al. Effects of the Four-Herb Compound ANBP on Wound Healing Promotion in Diabetic Mice. Int. J. Low.

Extrem. Wounds 2015, 14, 335–342. [CrossRef]
43. Ponrasu, T.; Subamekala, M.K.; Ganeshkuma, M.; Suguna, L. Role of Annona squamosa on antioxidants during wound healing in streptozotocin-nicotinamide induced diabetic rats. J. Pharmacogn. Phytochem. 2013, 2, 77–84.
44. Al-Rawaf, H.A.; Gabr, S.A.; Alghadir, A.H. Circulating Hypoxia Responsive microRNAs (HRMs) and Wound Healing Potentials of Green Tea in Diabetic and Nondiabetic Rat Models. Evid.-Based Complement. Altern. Med. 2019, 2019, 9019253. [CrossRef]
45. [118] Nayak, S. Influence of ethanol extract of Vinca rosea on wound healing in diabetic rats. Online J. Biol. Sci., 2006, 6(2), 51-55. http://dx.doi.org/10.3844/ojbsci.2006.51.55
46. Dawkins, G.; Hewitt, H.; Wint, Y.; Obiefuna, P.C.; Wint, B. Antibacterial effects of Carica papaya fruit on common wound organisms. West Indian Med. J., 2003, 52(4), 290-292. PMID: 15040064
47. Morton, J.J.; Malone, M.H. Evaluation of vulneray activity by an open wound procedure in rats. Arch.Int. Pharmacodyn. Ther., 1972, 196(1), 117-126. PMID: 5059357
48. Maquart, F-X.; Bellon, G.; Gillery, P.; Wegrowski, Y.; Borel, J-P. Stimulation of collagen synthesis in fibroblast cultures by a triterpene extracted from Centella asiatica. Connect. Tissue Res., 1990, 24(2), 107-120.
49. Biswas, T.K.; Maity, L.N.; Mukherjee, B. Wound healing potential of Pterocarpus santalinus linn: A pharmacological evaluation. Int. J. Low. Extrem. Wounds, 2004, 3(3), 143-150. http://dx.doi.org/10.1177/1534734604268385 PMID: 15866805
50. Mali, P.C.; Ansari, A.S.; Chaturvedi, M. Antifertility effect of chronically administered Martynia annua root extract on male rats. J. Ethnopharmacol., 2002, 82(2-3), 61-67. http://dx.doi.org/10.1016/S0378-8741(02)00084-3 PMID: 12241978
51. Lodhi, S.; Singhai, A.K. 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(4), 253-259. http://dx.doi.org/10.1016/S1995-7645(13)60053-X PMID: 23608325
52. Bek, E.L.; McMillen, M.A.; Scott, P.; Angus, L.G.; Shaftan, G.W. The effect of diabetes on endothelin, interleukin-8 and vascular endothelial growth factor-mediated angiogenesis in rats. Clin. Sci., 2002; 103, 424S-429S. http://dx.doi.org/10.1042/CS103S424S
53. Firdous, S.M.; Sautya, D. Medicinal plants with wound healing potential. Bangladesh J. Pharmacol.,2018, 13(1), 41-52. http://dx.doi.org/10.3329/bjp.v13i1.32646
54. Morimoto, N.; Takemoto, S.; Kawazoe, T.; Suzuki, S. Nicotine at a low concentration promotes wound healing.
55. J. Surg. Res., 2008, 145(2), 199-204. http://dx.doi.org/10.1016/j.jss.2007.05.031 PMID: 17644111
56. Tournier, J-M.; Maouche, K.; Coraux, C.; Zahm, J-M.; Cloëz-Tayarani, I.; Nawrocki-Raby, B.; Bonnomet, A.; Burlet, H.; Lebargy, F.; Polette, M.; Birembaut, P. α3α5β2-Nicotinic acetylcholine receptor contributes to the wound repair of the respiratory epithelium by modulating intracellular calcium in migrating cells. Am. J. Pathol., 2006, 168(1), 55-68. http://dx.doi.org/10.2353/ajpath.2006.050333 PMID: 16400009
57. Zyuz'kov, G.N.; Krapivin, A.V.; Nesterova, Y.V.; Povetieva, T.N.; Zhdanov, V.V.; Suslov, N.I.;Fomina, T.I.; Udut, E.V.; Miroshnichenko, L.A.; Simanina, E.V.; Semenov, A.A.; Kravtsova, S.S.; Dygai, A.M. Mechanisms of regeneratory effects of baikal aconite diterpene alkaloids. Bull. Exp. Biol. Med.,2012, 153(6), 846-850. http://dx.doi.org/10.1007/s10517-012-1841-2 PMID: 23113300
58. Dong, Y.; He, L.; Chen, F. Enhancement of wound healing by taspine and its effect on fibroblast. Zhong Yao Cai, 2005, 28(7), 579-582. PMID: 16252727
59. Gomathi, K.; Gopinath, D.; Rafiuddin Ahmed, M.; Jayakumar, R. Quercetin incorporated collagen matrices for dermal wound healing processes in rat. Biomaterials, 2003, 24(16), 2767-2772. http://dx.doi.org/10.1016/S0142-9612(03)00059-0 PMID: 12711523
60. Fu, S.C.; Hui, C.W.; Li, L.C.; Cheuk, Y.C.; Qin, L.; Gao, J.; Chan, K.M. Total flavones of Hippophae rhamnoides promotes early restoration of ultimate stress of healing patellar tendon in a rat model. Med. Eng. Phys., 2005, 27(4), 313-321. http://dx.doi.org/10.1016/j.medengphy.2004.12.011 PMID: 15823472
61. Ghosh, S.; Samanta, A.; Mandal, N.B.; Bannerjee, S.; Chattopadhyay, D. Evaluation of the wound healing activity of methanol extract of Pedilanthus tithymaloides (L.) Poit leaf and its isolated active constituents in topical formulation. J. Ethnopharmacol., 2012, 142(3), 714-722. http://dx.doi.org/10.1016/j.jep.2012.05.048 PMID:22683906
62. Muhammad, A.A.; Pauzi, N.A.S.; Arulselvan, P.; Abas, F.; Fakurazi, S. In vitro wound healing potential and identification of bioactive

compounds from Moringa oleifera Lam. BioMed Res. Int., 2013, 2013, 974580.[142] Bui, N.T.; Ho, M.T.; Kim, Y.M.; Lim, Y.; Cho, M. Flavonoids promoting HaCaT migration: II. Molecular mechanism of
63. 4′,6,7-trimethoxyisoflavone via NOX2 activation. Phytomedicine, 2014, 21(4), 570-577.
64. http://dx.doi.org/10.1016/j.phymed.2013.10.010 PMID: 24388604
65. Oztürk, N.; Korkmaz, S.; Oztürk, Y.; Başer, K.H. Effects of gentiopicroside, sweroside and swertiamarine, secoiridoids from gentian (Gentiana lutea ssp. symphyandra), on cultured chicken embryonic fibroblasts. Planta Med., 2006, 72(4), 289-294. http://dx.doi.org/10.1055/s-2005-916198 PMID: 16557467
66. Park, T-J.; Park, Y-S.; Lee, T-G.; Ha, H.; Kim, K-T. Inhibition of acetylcholine-mediated effects by borneol. Biochem. Pharmacol., 2003, 65(1), 83-90. http://dx.doi.org/10.1016/S0006-2952(02)01444-2 PMID: 12473382
67. Riella, K.R.; Marinho, R.R.; Santos, J.S.; Pereira-Filho, R.N.; Cardoso, J.C.; Albuquerque-Junior,R.L.; Thomazzi,
68. S.M. Anti-inflammatory and cicatrizing activities of thymol, a monoterpene of the essential oil from Lippia gracilis, in rodents. J. Ethnopharmacol., 2012, 143(2), 656-663. http://dx.doi.org/10.1016/j.jep.2012.07.028 PMID:22885071
69. Kuonen, R.; Weissenstein, U.; Urech, K.; Kunz, M.; Hostanska, K.; Estko, M.; Heusser, P.; Baumgartner, S. Effects of lipophilic extract of Viscum album L. and oleanolic acid on migratory activity of NIH/3T3 fibroblasts and on HaCat keratinocytes. Evid. Based Complementary Altern. Med., 2013, 2013, 718105.
70. Coldren, C.D.; Hashim, P.; Ali, J.M.; Oh, S-K.; Sinskey, A.J.; Rha, C. Gene expression changes in the human fibroblast induced by Centella asiatica triterpenoids. Planta Med., 2003, 69(8), 725-732. http://dx.doi.org/10.1055/s-2003-42791 PMID: 14531023
71. Liu, M.; Dai, Y.; Li, Y.; Luo, Y.; Huang, F.; Gong, Z.; Meng, Q. Madecassoside isolated from Centella asiatica herbs facilitates burn wound healing in mice. Planta Med., 2008, 74(8), 809-815. http://dx.doi.org/10.1055/s-2008-1074533 PMID: 18484522
72. Wright, K.; Rooney, N.; Feeney, M.; Tate, J.; Robertson, D.; Welham, M.; Ward, S. Differential expression of cannabinoid receptors in the human colon: Cannabinoids promote epithelial wound healing. Gastroenterology, 2005, 129(2), 437-453. http://dx.doi.org/10.1016/j.gastro.2005.05.026 PMID: 16083701
73. Ben-Shabat, S.; Hanuš, L.O.; Katzavian, G.; Gallily, R. New cannabidiol derivatives: Synthesis, binding to cannabinoid receptor, and evaluation of their antiinflammatory activity. J. Med. Chem., 2006, 49(3), 1113-1117. http://dx.doi.org/10.1021/jm050709m PMID: 16451075
74. Kim, Y.S.; Cho, I-H.; Jeong, M-J.; Jeong, S-J.; Nah, S.Y.; Cho, Y-S.; Kim, S.H.; Go, A.; Kim, S.E.; Kang, S.S.; Moon,
75. C.J.; Kim, J.C.; Kim, S.H.; Bae, C.S. Therapeutic effect of total ginseng saponin on skin wound healing. J. Ginseng Res., 2011, 35(3), 360-367. http://dx.doi.org/10.5142/jgr.2011.35.3.360 PMID: 23717081
76. Czemplik, M.; Kulma, A.; Bazela, K.; Szopa, J. The biomedical potential of genetically modified flax seeds overexpressing the glucosyltransferase gene. BMC Complement. Altern. Med., 2012, 12(1),251. http://dx.doi.org/10.1186/1472-6882-12-251 PMID: 23228136
77. Shivashankar, M.; Mani, D. A brief overview of diabetes. Int. J. Pharm. Pharm. Sci., 2011, 3(4), 22-27.
78. V.Nandagopalan, A.Doss and C.Marimuthu,2016.Phytochemical Analysis of Some Traditional Medicinal Plants. Bioscience Discovery,7(1):17-20
79. Gantwerker,E.A.;Hom,D.B.Skin: Histology and Physiology of Wound Healing .Facial Plast.Surg.Clin.N.Am.2011,19,441-453.[CrossRef][Pubmed]