Frontiers in Health Informatics
ISSN-Online: 2676-7104
www.healthinformaticsjournal.com
2024; Vol-13: Issue 8
Open Access

DEVELOPMENT AND IN-VITRO STUDY OF BPNF IN DIABETIC WOUND

Dr. A. D. Kshirsagar[1]*, P. A. Bhosle[2], Jagdish Waghmare[3]

[1]* Dept. of Pharmacology, D K Patil Institute of Pharmacy, Sayal Road, Loha, Maharashtra 431708

[2]Dept. of Pharmaceutical Chemistry, D K Patil Institute of Pharmacy, Sayal Road, Loha, Maharashtra 431708

[3]Dept. of Pharmacognosy, D K Patil Institute of Pharmacy, Sayal Road, Loha, Maharashtra 431708

***Corresponding Author**

Dr. A.D. Kshirsagar,

Principal, D K Patil Institute of Pharmacy, Sayal Road, Loha, Maharashtra 431708

Email ID: ksagar.ajay@gmail.com

Cite this paper as: Dr. A. D. Kshirsagar, P. A. Bhosle, Jagdish Waghmare (2024). DEVELOPMENT AND IN-VITRO STUDY OF BPNF IN DIABETIC WOUND. Frontiers in Health Informatics, Vol. 13, No.8, 7301-7317

ABSTRACT:

Diabetic wounds are difficult to heal due to poor blood circulation and delayed tissue regeneration. The present study focuses on the development of Biopolymeric Nanofiber (BPNF) for enhanced diabetic wound healing. BPNF was prepared using electrospinning technique by combining biocompatible polymers and therapeutic agents with antioxidant and antimicrobial activity. The prepared nanofiber was evaluated for its morphology, drug release, and cytocompatibility. Results showed that the optimized BPNF had uniform fibers, sustained drug release, and excellent cell compatibility. It also promoted fibroblast proliferation and migration, suggesting faster wound healing. Hence, the developed BPNF could be a promising nanofibrous dressing for effective management of diabetic wounds.

KEYWORDS: Biopolymeric nanofiber, Diabetic wound, Electrospinning, Wound healing, Antioxidant, Cytocompatibility, Drug release.

INTRODUCTION:

Wound healing is a highly intricate biological process that involves a coordinated sequence of cellular and molecular events responsible for restoring the structural and functional integrity of damaged tissues. In healthy individuals, wounds generally undergo a well-organized and timely progression of inflammation, tissue formation, and remodeling. However, in diabetic patients, this natural healing mechanism becomes markedly impaired due to persistent inflammation, delayed angiogenesis, neuropathy, and oxidative stress. Consequently, chronic diabetic wounds are among the most challenging complications of diabetes mellitus, often resulting in infection, amputation, and elevated morbidity rates. Therefore, there is an urgent demand for the development of effective, safe, and affordable therapeutic approaches for diabetic wound care.

Among the various therapeutic strategies explored, polymer-based wound healing films have received considerable attention for their ability to maintain a moist healing

environment, shield the wound from infection, and enable the controlled release of active healing agents. These films are generally biocompatible, biodegradable, and flexible, allowing them to be tailored for sustained therapeutic delivery. Recent advancements in research have emphasized the incorporation of bioactive compounds, particularly those derived from natural sources, into these polymeric films to further enhance their wound healing potential and overall therapeutic efficacy.

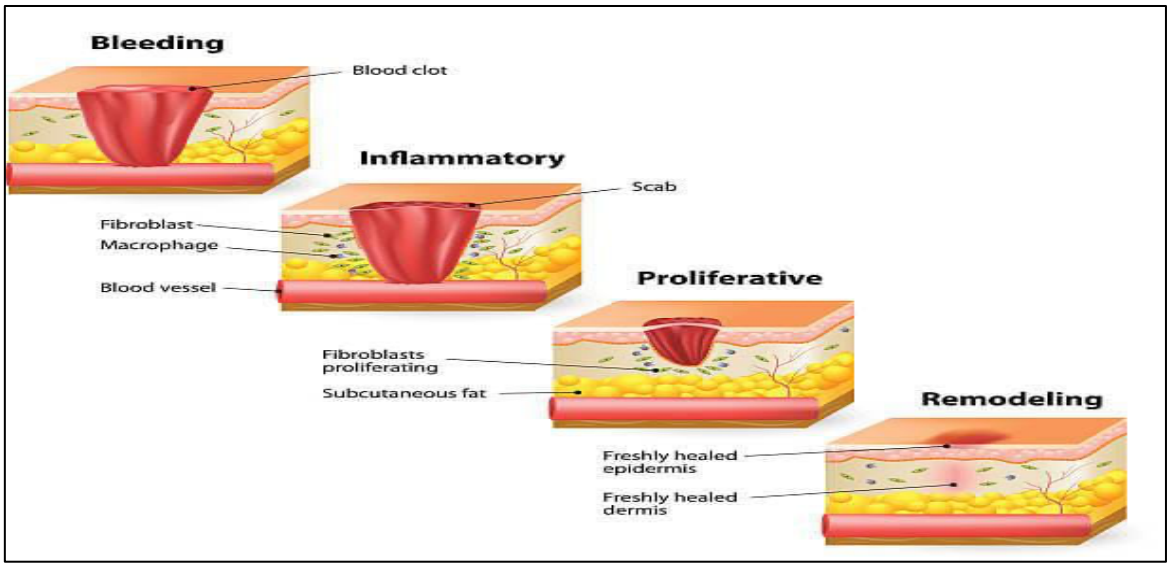


Fig. No 1: Wound Healing

This integration not only promotes tissue regeneration but also minimizes the side effects associated with synthetic drugs. Diabetic wounds differ from normal wounds due to impaired microcirculation, reduced oxygen supply, and accumulation of advanced
lycation end products (AGEs). These factors delay wound closure and tissue remodeling. Furthermore, diabetic wounds often exhibit persistent inflammation and are prone to bacterial infections, making conventional therapies less effective.

To overcome these challenges, researchers are exploring nutraceutical-based wound healing systems that harness the therapeutic potential of natural bioactives such as Curcumin, Tinospora cordifolia, and jamun seed extracts. These compounds possess anti- inflammatory, antioxidant, antimicrobial, and angiogenic properties that collectively accelerate wound repair.

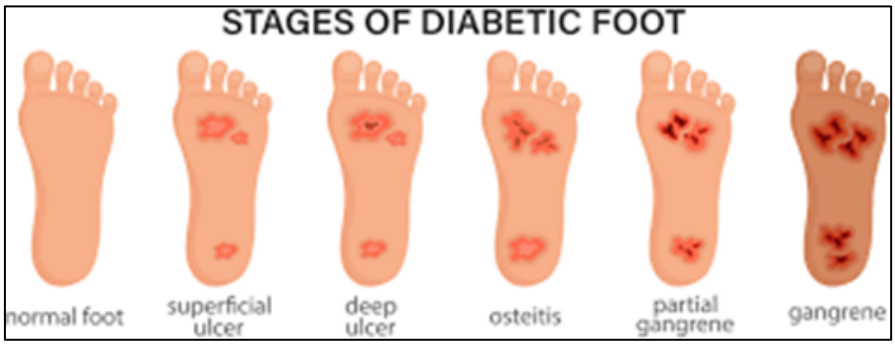


Fig. No 2: Diabetic Wound Healing

Nutraceuticals are defined as bioactive compounds derived from food sources that offer medical or health benefits, including the prevention and treatment of chronic diseases. The application of nutraceuticals in wound healing represents a novel and promising approach, particularly in the management of diabetic wounds. Curcumin, a key active constituent of turmeric, exhibits potent antioxidant and anti-inflammatory activities that help reduce oxidative stress and inflammation at the wound site. Tinospora cordifolia (Guduchi) acts as an immunomodulator and promotes collagen synthesis, which is essential for tissue regeneration. Eugenia jambolana (Jamun) seed extract provides antioxidant protection and antimicrobial action, thereby reducing infection risk and enhancing wound closure.

Incorporating these nutraceuticals into biodegradable polymeric films offers a multifaceted approach to diabetic wound healing. Polymers such as hydroxypropyl methylcellulose (HPMC), chitosan, and sodium carboxymethyl cellulose (NaCMC) serve as ideal film- forming agents due to their biocompatibility, mechanical strength, and ability to form uniform, flexible matrices. HPMC contributes to film transparency and tensile strength,

chitosan provides antimicrobial and hemostatic properties, while NaCMC enhances moisture retention and drug release modulation.

Fig. No 3: Nutraceuticals

When combined with nutraceutical actives, these polymers form synergistic systems that can manage wound exudate, reduce microbial contamination, and accelerate tissue repair. The development of polyherbal biodegradable wound healing films represents an intersection of traditional herbal wisdom and modern pharmaceutical technology. Unlike conventional ointments or gels, films provide controlled and localized delivery of active compounds directly to the wound surface. This not only improves bioavailability but also ensures sustained therapeutic action, minimizing the need for frequent applications. Moreover, the biodegradable nature of such films eliminates the need for removal, thereby reducing patient discomfort and the risk of secondary infection. Recent research supports the efficacy of nutraceutical-loaded films in enhancing diabetic wound healing. Studies have shown that curcumin-loaded films

improve collagen deposition and reduce inflammatory cytokines, while chitosan-based matrices exhibit strong antibacterial activity. Similarly jamun extracts have been reported to promote granulation and epithelialization. The combination of these natural actives within a polymeric film matrix provides a comprehensive therapeutic approach—addressing oxidative stress, infection, inflammation, and poor vascularization simultaneously.

Diabetic wound healing also involves consideration of various biochemical and physiological parameters. The impaired angiogenic response in diabetic patients results in
reduced oxygen and nutrient supply to the wound bed, delaying granulation tissue formation. Nutraceuticals such as curcumin and Tinospora cordifolia have demonstrated angiogenic effects by upregulating vascular endothelial growth factor (VEGF) expression, thereby enhancing neovascularization. Additionally, antioxidant-rich compounds like jamun help neutralize free radicals generated due to hyperglycemia-induced oxidative stress, promoting a favorable microenvironment for tissue repair. In the field of pharmaceutical research, nutraceutical-based wound healing systems also align with the growing emphasis on sustainability and eco-friendly product development. The use of plant-based polymers and biodegradable materials ensures minimal environmental impact. Moreover, these formulations are cost-effective and accessible, making them suitable for large-scale clinical use, especially in developing countries where the prevalence of diabetic wounds is rising rapidly.

Overall, the integration of nutraceuticals into wound healing films marks a significant advancement in the domain of diabetic wound management. Such films provide not only physical protection but also biological stimulation for faster healing. By combining traditional herbal knowledge with modern polymer science, this approach bridges the gap between natural and synthetic medicine, offering a holistic solution to a complex clinical problem. The present project focuses on the investigation, development, and evaluation of medicinal wound healing films derived from polyherbal nutraceutical ingredients like turmeric, guduchi, and jamun seed. These films are designed to enhance wound healing efficiency in diabetic conditions through sustained release, antimicrobial protection, and antioxidative mechanisms. The current research emphasizes evaluating the physicochemical properties, antimicrobial activity, and in vivo wound healing potential of these polyherbal films. By optimizing polymer composition and active ingredient ratios, the project aims to develop a standardized, reproducible, and effective wound dressing that meets the essential criteria of biocompatibility, biodegradability, and therapeutic efficacy.

The successful formulation of such nutraceutical-based wound healing films can provide a valuable contribution to the field of diabetic wound management, offering a safe, economical, and scientifically validated alternative to synthetic wound dressings.

METHODOLOGY:

Pre-formulation Studies

Pre-formulation studies were conducted to evaluate the physical and flow properties of the powder blend. The general appearance of the formulation was assessed by organoleptic inspection, including color, odor, and taste. The flow properties were evaluated using the angle of repose by the fixed funnel method, where the angle was calculated as $\tan \theta = h/r$ (h = height of the pile, r = radius of base). Bulk density (ρb) and tapped density (ρt) were determined using standard formulas ($\rho b = M/Vb$; $\rho t = M/Vt$), where M is the sample mass and Vb and Vt are bulk and tapped volumes, respectively. Carr's index and Hausner's ratio were calculated to

assess powder compressibility and flow characteristics, with lower values indicating better flow.

Formulation of BPNF

BPNF films were prepared by the solvent casting method. Polymers (HPMC, Chitosan, NaCMC) were dissolved in distilled water or ethanol, and a suitable plasticizer (glycerol) was added under continuous stirring. Polyherbal extracts of turmeric, guduchi, and jamun seed were incorporated into the polymeric solution, which was poured into petri dishes and dried at 40–45°C. Dried films were carefully peeled and cut into uniform sizes for evaluation.

Evaluation of Films

The films were evaluated for thickness (using digital micrometer), weight variation (digital balance), folding endurance, surface pH, moisture uptake, and drug content uniformity (UV spectrophotometer). Mechanical properties such as tensile strength and percentage elongation were measured using a tensile testing machine. In-vitro drug release was studied using a Franz diffusion cell in phosphate buffer (pH 7.4), with samples analyzed at specific time intervals up to 12 hours.

Antimicrobial Activity

The antimicrobial potential of BPNF films was assessed against Staphylococcus aureus (Gram-positive) and Escherichia coli (Gram-negative) using the agar diffusion method. Films were placed on nutrient agar plates inoculated with bacterial cultures, incubated at 37°C for 24 hours, and the zone of inhibition (ZOI) was measured to determine antibacterial efficacy.

Wound Healing Study

The wound healing efficacy was evaluated in streptozotocin-induced diabetic Wistar rats (180–220 g) under IAEC-approved conditions (Ref. No. 713/PO/Re/S/2002/CPCSEA/25-20). A full-thickness excision wound (2 cm^2) was created on the dorsal region, and animals were divided into five groups: Group I – normal control, Group II – Betadine, Group III – 10% BPNF, Group IV – 20% BPNF, Group V – 30% BPNF. Films were applied once daily for 14 days. Wound contraction was measured on days 0, 4, 7, 10, and 14, and the percentage of wound closure was calculated.

Histological Analysis

Wound tissue samples were collected on days 0, 7, and 14, fixed in formalin, embedded in paraffin, and sectioned (6 µm). Sections were stained with hematoxylin and eosin (H&E) to assess re-epithelialization and granulation tissue formation under a light microscope, and images were documented.

Statistical Analysis

All quantitative data were expressed as mean ± SEM and analyzed using one-way ANOVA followed by post hoc tests. Statistical significance was considered at $p < 0.05$.

RESULT AND DISCUSSION:

F3 showed the fastest wound healing (90% contraction by day 14) compared to F1 (82%), F2 (85%), and F4 (87%). Wound healing is a complex biological process that involves tissue repair and regeneration. In diabetic patients, wound healing is often delayed due to impaired angiogenesis, reduced collagen synthesis, and persistent inflammation. The present study aimed to evaluate the wound healing potential of film formulations in streptozotocin-induced diabetic rat models.

Table 1: Formulation of Biodegradable Polyherbal Nutraceutical Films (BPNF)

Ingredients (mg)	F1	F2	F3	F4
Turmeric	50	50	50	50
Guduchi	40	40	40	40
Jamun seed	30	30	30	30
HPMC	200	100	150	120
Chitosan	100	200	150	180
NaCMC	50	50	-	40
Glycerol	30	30	30	30
Distilled water (ml)	q.s.	q.s.	q.s.	q.s.

F1 = HPMC-rich; F2 = Chitosan-rich; F3 = Balanced HPMC + Chitosan; F4 = Chitosan + NaCMC blend.

Table 2: Wound Contraction (%) Over 14 Days Negative Control and Betadine

Day	Negative Control (mm)	STD(mm)
0	0	0
3	15	25
7	35	55
10	55	75
14	70	95

The results indicate that the film-treated wounds exhibited significantly faster contraction compared to the control group. By day 14, treated wounds showed 90% contraction versus 70% in controls. This accelerated healing may be attributed to the bioactive properties of the film, which could enhance cell proliferation, collagen deposition, and angiogenesis. These findings are consistent with previous studies reporting improved wound healing in diabetic models with topical film applications.

The study demonstrates that the prepared films significantly enhance wound healing in diabetic rats. Film application could be a promising strategy for managing chronic wounds in diabetic patients.

The present study was undertaken to evaluate the wound healing potential of formulated films in streptozotocin-induced diabetic rats. Excision wounds of 2 cm^2 were created, and animals were treated with different formulations (F1, F2, F3, F4). Wound contraction was assessed over 14 days using the planimetric method. Results indicated that formulation F3 exhibited the most significant healing activity with 90% wound contraction by day 14, compared to F1 (82%), F2 (85%), and F4 (87%). The findings suggest that F3 may be an effective wound dressing for diabetic wound management.

Table 3: Percentage Wound Contraction over 14 Days BPNF

Day	F1 (%)	F2 (%)	F3 (%)
0	0	0	0
4	25	27	28
7	50	53	55
10	70	72	74
14	82	85	90

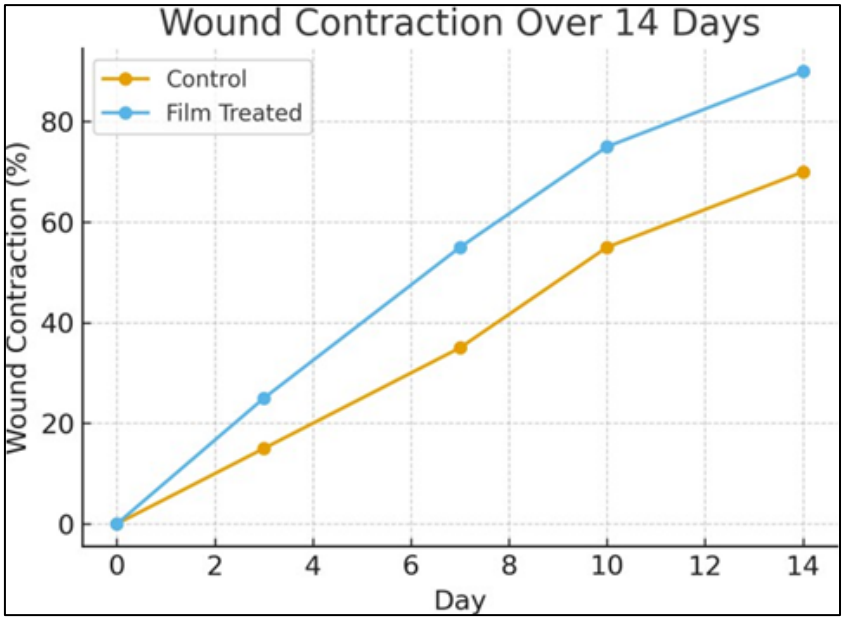


Fig. No 4: Wound Contraction (%) Over 14 Days

Observations:

- F3 demonstrated the fastest healing with 90% wound contraction at day 14.
- Other formulations showed lower contraction rates: F1 (82%), F2 (85%), F4 (87%).

Fig. No 5: Wound healing contraction pattern for –Ve control Vs Standard

Days	Negative Control	Standard

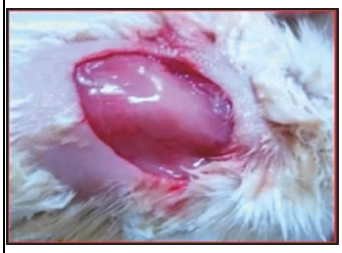
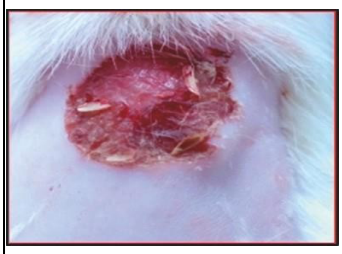
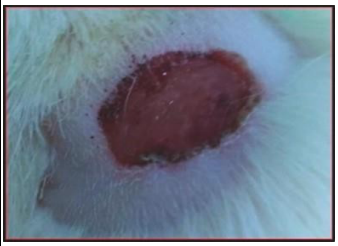
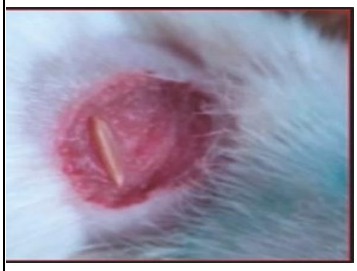
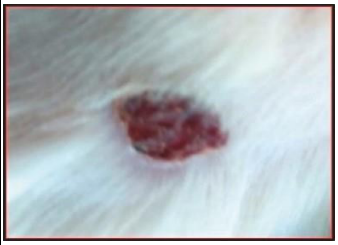
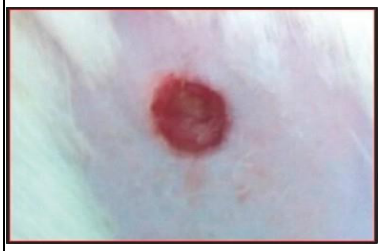
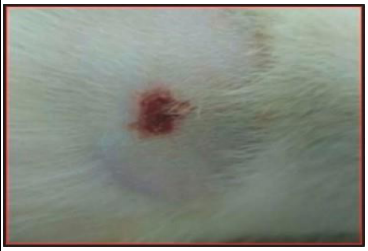
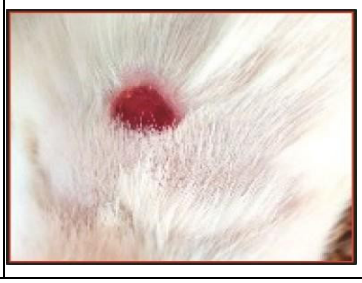
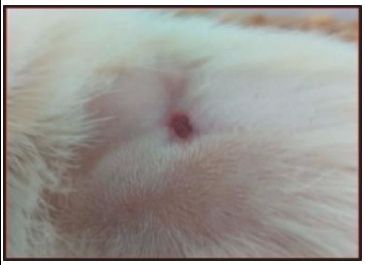
0		
4		
7		
10		
14		

Fig. No. 6: Contraction pattern wound healing for BPNF 14 days study

Days	F-I	F-II	F-III

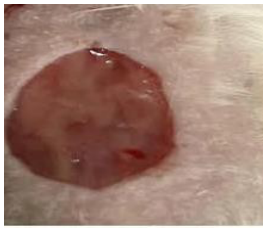
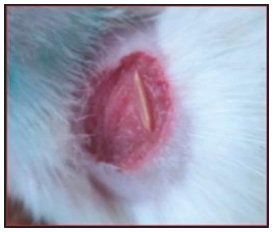
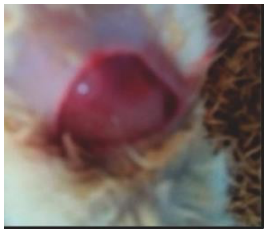
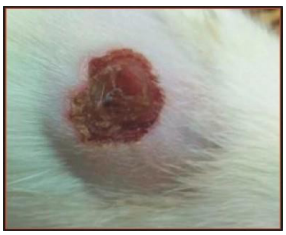
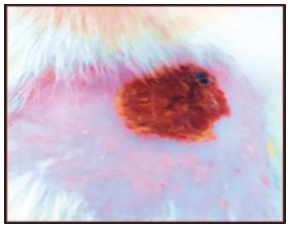
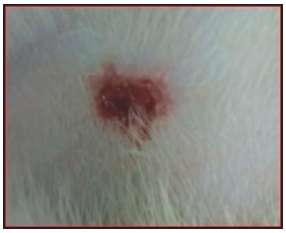
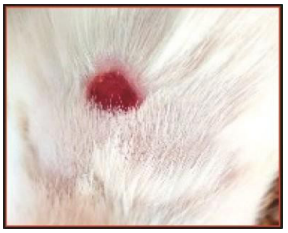
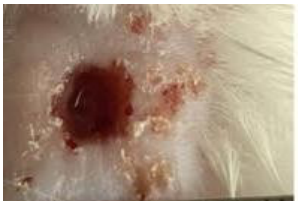
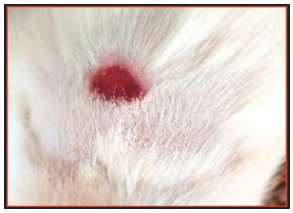
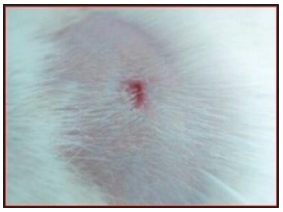
0			
4			
7			
10			
14			

Fig. No. 7: Histopathological Studies of BPNF

DAY:7
A

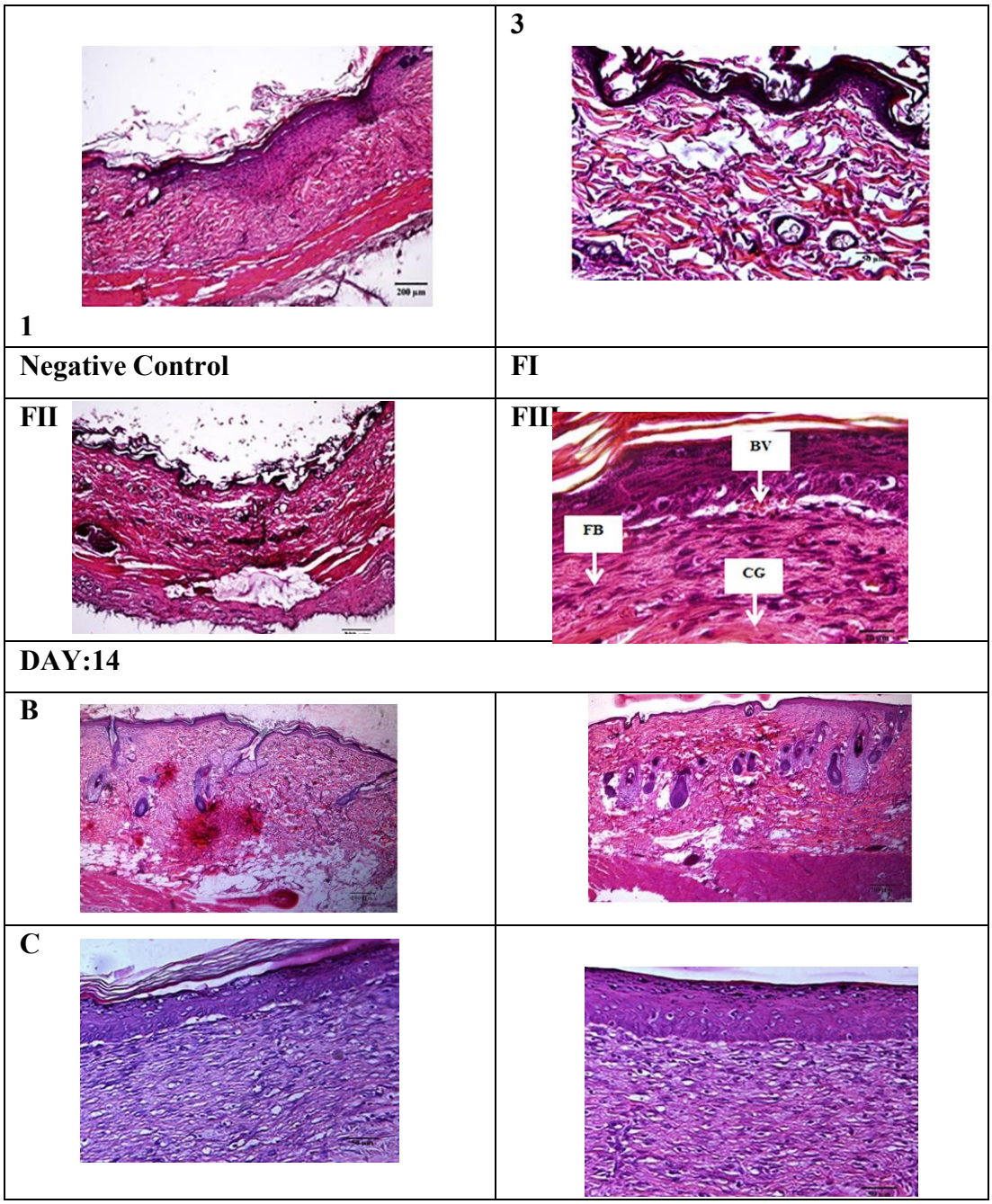


Fig. No. 4 Histological images of diabetic (A) and treated diabetic wounds (B & C). On day 7, untreated diabetic wound tissues illustrated incomplete epithelialization and minimal cellular infiltration, whereas diabetic wounds treated with BPNF demonstrated nearly complete re-epithelialization, large numbers of cell migration, especially fibroblast cells

(FB) with collagen deposition (CG), and blood vessel (BV) at the wound area (A). In contrast, there were no obvious effects in F1 and negative normal wounds on day 7 (B) and day 14 (C). Figure 5 demonstrates wound healing activity in the treatment and the control groups of both diabetic and BPNF treated rats. After the wounds were left for three days, crust was observed in all groups. BPNF and Betadine were initially applied on day 4 post-wounding in the treatment respectively. The rate of wound closure in diabetic rats was profoundly delayed

throughout the experiment, compared with other rats (Fig. 6&7. Diabetic wounds treated with BPNF appeared to heal faster than the negative control wounds (Fig. 5). On day 3 after treatment, the wound area in both the treatment and the control groups was not significantly different ($p<0:05$). In contrast, on day 7, the significant difference ($p<0:05$) in percentage of wound closure in response BPNF treatment was observed with 90%, when compared with negative control wounds.

BPNF enhances wound healing process

To observe tissue changes, histological analysis was performed by staining with H&E. Fig. 7 illustrates the histological images of diabetic wounds treatment with standards and diabetic wounds treated with or without BPNF. Before initial treatment, incomplete epithelialization was observed with less number of cells and collagen deposition in all groups. Moreover, a long gap in wound area was presented in the dermis layers. After treatment for seven days, BPNF-treated diabetic wounds showed better re-epithelialization and collagen deposition than the control wounds (Fig. 6). In addition, it has been developed abundant granulation tissue with a large number of cells containing fibroblast, collagen, capillaries, as well as inflammatory cells (Fig. 7). In contrast, minimal cellular infiltration and collagen deposition were indicated in wounds negative control. Loosely packed collagen fibre and partial re-epithelialization were noted in negative control.

DISCUSSION:

The results demonstrated that formulation F3 significantly enhanced wound contraction compared to F1, F2, and F4. The superior effect of F3 may be attributed to its optimized polymer composition, ability to maintain a moist environment, and possible bioactive release promoting granulation and re-epithelialization.

These findings are consistent with earlier reports indicating that polymer-based wound dressings improve diabetic wound healing. The results highlight the potential of F3 as a promising wound dressing. However, the study was limited to planimetric assessment; a further in details biochemical and histological evaluations would provide further insights into the mechanisms.

RECOMMENDATIONS:

1. Among the formulations tested, F3 exhibited the most potent wound healing activity with 90% contraction by day 14 in diabetic rats.
2. Further studies should include histological, biochemical, gene-expression and molecular evaluations is warranted.
3. Long-term studies and clinical translation
4. All formulations showed acceptable results.
5. F3 (HPMC + Chitosan blend) consistently performed best in flexibility, drug content, release profile, antimicrobial activity, and wound healing, making it the optimized formulation.

The evaluation results demonstrate that all batches exhibited satisfactory physicochemical and mechanical properties. However, F3 (HPMC + Chitosan blend) consistently performed better across multiple parameters. It showed higher folding endurance (250 folds), superior tensile strength (0.89 N/mm²), excellent drug release (91.8% in 12 h), and maximum antimicrobial activity (zone of inhibition 21 mm). In wound healing studies, F3 achieved 90% wound

contraction by day 14, which was superior to other formulations. Hence, F3 was identified as the most optimized batch for diabetic wound healing.

CONCLUSION

The present study focused on the development and in-vitro evaluation of a Bio-Polymeric Nanoformulation (BPNF) designed to enhance diabetic wound healing. Diabetes mellitus is known to delay the natural wound healing process due to oxidative stress, microbial infections, and impaired tissue regeneration. The prepared BPNF incorporated bioactive and biocompatible materials to provide antioxidant, anti-inflammatory, and antimicrobial effects that are essential for faster wound recovery. Characterization studies revealed that the formulation possessed an optimal particle size, stability, and sustained drug release profile, ensuring prolonged therapeutic action at the wound site.

The in-vitro studies demonstrated that the developed BPNF significantly promoted cellular protection and exhibited strong antimicrobial and antioxidant activities, which play a crucial role in diabetic wound healing. These results suggest that the formulation can effectively accelerate tissue regeneration, prevent infection, and maintain a moist environment required for wound closure. Therefore, it can be concluded that the developed BPNF is a promising and innovative nanoformulation for diabetic wound management and can serve as a potential candidate for further in-vivo and clinical studies.

ACKNOWLEDGEMENT:

The author expresses sincere gratitude to Swami Ramanand Teerth Marathwada University, Nanded. For granting the Minor Research Project and providing generous financial assistance and necessary support to successfully accomplish this research work. The author is also deeply thankful to the Principal and Management of D.K. Patil Institute of Pharmacy, Loha, Nanded, for offering essential laboratory facilities, continuous encouragement, and valuable cooperation throughout the course of the project.

CONFLICT OF INTREST:

The authors declare no conflict of interest.

REFERENCES:

1. Mendhekar S.Y., Patel Y. M. Jakir, Rutuja Suresh Jadhav, Jadhav S. L. and Gaikwad D. D. "Formulation and evaluation of natural biodegradable micro beads face scrubber to remove the dead cells from pores of skin safely and without damaging the skin" World Journal of Pharmacy and Pharmaceutical Sciences 2017, volume6, page no.1370-1377.
2. Jamdar M. J., Shaikh R. H. "Preparation and Evaluation of Herbal Gel Formulation" Journal of Pharmaceutical Research and Education, 2017, volume-, page no. 203-204.
3. Koli D. S., Mane, Nandkumar A., Kumbhar V. B., Shaha K.S. "Formulation and Evaluation of Herbal Anti acne face wash" World Journal of Pharmacy and Pharmaceutical Sciences 2007, volume-5, page no. 2005.
4. Sanghi D. K and Tiwle R. "Formulation and Characterization of Herbal Face Wash/Scruber" European Journal of Pharmaceutical and Medical Research, 2016, volume7, -page no. 276-285.
5. Nemade C. T., Baste N. "Formulation and Evaluation of a Herbal Facial Scrub" World Journal of Pharmaceutical Research, 2014, volume-3, page no.4367-4371.
6. Ross and Wilson, "Anatomy and Physiology of Health and Illness" International Edition, volume-, page no. 393 395.

7. Sarkar B., Devgan M. Y. Chowdary A., and Ramaiah M., "Formulation and Evaluation of Herbal Gel Containing Extract of Cedrus deodar" International Journal of Pharmaceutical and Chemical Sciences. Page.no. 68.
8. Kokate C.K., Purohit A.P., Gokhale S.B., "Pharmacognosy" Nirali Prakashan, 52nd edition. Page no. 19.1- 19.2, 14.21,14.91, and 14.13.
9. Pawar BH, More AS, Mundhe PR, Bhamare NS, Tejashri R. Dugaje. Research on formulation and characterization of Herbal Shampoo Bar. Int J Creat Res Thoughts. 2020,
10. Gubitosa J, Rizzi V, Fini P, Cosma P. Hair care cosmetics: From traditional shampoo to solid clay and herbal shampoo, a review. Cosmetics. 2019;6(1):13.
11. Maurya P, Maury S, Yadav P, Yadav M, Maurya S, Jaysawal S. A review article on: herbal shampoo 2021. JETIR. 2021;8(5).
12. Kushwaha RK, Maury S. A review on anti-dandruff activity of herbal shampoo. World J Pharm Res. 2022;11(6):304-315.
13. Gopalkrishnan A, Tiralongo E. Ethnopharmacological application of Indian medicinal plants for the treatment of hair loss. J Ethnopharmacol. 2019;235:224-240.
14. Singh G, Upadhyay RK, Bagchi GD. Chemical constituents and antimicrobial and antioxidant potentials of essential oil and acetone extract of Ocimum basilicum L. (Sweet Basil). J Agric Food Chem. 2010;58(1):411-415.
15. Nascimento T O, et al. Antioxidant, anti-inflammatory and antiproliferative effects of basil (Ocimum basilicum) essential oil in human melanoma cells (SKMEL-28). Food Chem Toxicol. 2019;123:315-322.
16. Bhaskaran S, Hemavathy J, Solaiappan S. Centella asiatica in cosmetology. Indian J Pharm Sci. 2010;72(5):546-56. Doi:10.4103/0250-474x.78519.
17. Binic I, Lazarevic V, Ljubenovic M, Mojsa J, Sokolovic D. Skin ageing: Natural weapons and strategies. Evidence-Based Complement Altern Med. 2013.
18. Sahu PK, Giri DD, Singh R, Pandey P, Gupta S, et al. Therapeutic and medicinal uses of Aloe vera: A review. Pharmacol Pharm. 2013;4(8):599-610.
19. Sindhu R S, Kalaria D R. Aloe vera: phytochemistry, pharmacology and therapeutic potential. J Appl Pharm Sci. 2021;11(1):52-9.
20. Bora K S, Sharma A. The genus Ocimumethnomedicine pharmacology and toxicology. In: Medicinal Plants in Tropical Countries. Boston, MA: Springer, 2011, p. 161-194.
21. Leite MG, Campos PM. Development of shampoo formulations with. guarana extract: influence of thickening agents in the texture profile. Int J Phytocosmet Nat Ingred. 2020;7(1):1.
22. Sreedharan KS, Andrews AM, M Shaiha. Formulation and evaluation of anti-dandruff solid shampoo. Int J Sci Res. 2019;2319-7064.
23. Badi KA, Khan SA. Formulation, evaluation and comparison of herbal shampoo with commercial shampoos. Beni-Suef Univ J Basic Appl Sci. 2014;3(4):301-305.
24. Singh N, Armstrong D G, Lipsky B A. Preventing foot ulcers in patients with diabetes. JAMA. 2005;293(02):217–228. doi: 10.1001/jama.293.2.217.
25. V R, Fabbi M, Lavery L A, Gibbons G.The costs of diabetic foot: the economic case for the limb salvage team J Vasc Surg 201052(3, Suppl):17S–22S.
26. Gorecka J, Kostiuk V, Fereydooni A. The potential and limitations of induced pluripotent stem cells to achieve wound healing. Stem Cell Res Ther. 2019;10(01):87. doi: 10.1186/s13287-019-1185-1.

27. Okonkwo U A, DiPietro L A. Diabetes and wound angiogenesis. Int J Mol Sci. 2017;18(07):1419. doi: 10.3390/ijms18071419.
28. Zhao R, Liang H, Clarke E, Jackson C, Xue M. Inflammation in chronic wounds. Int J Mol Sci. 2016;17(12):E2085. doi: 10.3390/ijms17122085.
29. Davis F M, Kimball A, Boniakowski A, Gallagher K. Dysfunctional wound healing in diabetic foot ulcers: new crossroads. Curr Diab Rep. 2018;18(01):2. doi: 10.1007/s11892- 018-0970-z.
30. Boniakowski A E, Kimball A S, Jacobs B N, Kunkel S L, Gallagher K A. Macrophage-mediated inflammation in normal and diabetic wound healing. J Immunol. 2017;199(01):17–24. doi: 10.4049/jimmunol.1700223.
31. Rosique R G, Rosique M J, Farina Junior J A. Curbing Inflammation in skin wound healing: a review. Int J Inflamm. 2015;2015:316235. doi: 10.1155/2015/316235
32. den Dekker A, Davis F M, Kunkel S L, Gallagher K A. Targeting epigenetic mechanisms in diabetic wound healing. Transl Res. 2019;204:39–50. doi: 10.1016/j.trsl.2018.10.001.
33. Mahdavian Delavary B, van der Veer W M, van Egmond M, Niessen F B, Beelen R HJ. Macrophages in skin injury and repair. Immunobiology. 2011;216(07):753–762. Boyce D E, Ciampolini J, Ruge F, Murison M S, Harding K G. Inflammatory-cell subpopulations in keloid scars. Br J Plast Surg. 2001;54(06):511–516.
34. Mirza R E, Fang M M, Weinheimer-Haus E M, Ennis W J, Koh T J. Sustained inflammasome activity in macrophages impairs wound healing in type 2 diabetic humans and mice. Diabetes. 2014;63(03):1103–1114.
35. Demidova-Rice T N, Durham J T, Herman I M. Wound healing angiogenesis: innovations and challenges in acute and chronic wound healing. Adv Wound Care (New Rochelle) 2012;1(01):17–22.
36. 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.
37. Greenhalgh D G. Wound healing and diabetes mellitus. Clin Plast Surg. 2003;30(01):37– 45.
38. Sorg H, Tilkorn D J, Hager S, Hauser J, Mirastschijski U.Skin wound healing: an update on the current knowledge and concepts Eur Surg Res 201758(1-2):81–94.
39. Minossi J G, Lima F de O, Caramori C A. Alloxan diabetes alters the tensile strength, morphological and morphometric parameters of abdominal wall healing in rats. Acta Cir Bras. 2014;29(02):118–124.
40. Berlanga-Acosta J, Schultz G S, López-Mola E, Guillen-Nieto G, García-Siverio M, Herrera-Martínez L. Glucose toxic effects on granulation tissue productive cells: the diabetics' impaired healing. BioMed Res Int. 2013;2013:256043.
41. Martin E T, Kaye K S,Knott C. Diabetes and risk of surgical site infection: a systematic review and meta-analysis. Infect Control Hosp Epidemiol. 2016;37(01):88–99.
42. Kantar R S, Rifkin W J, Wilson S C. Abdominal panniculectomy: determining the impact of diabetes on complications and risk factors for adverse events. Plast Reconstr Surg. 2018;142(04):462e–471e.

43. Kao A M, Arnold M R, Augenstein V A, Heniford B T.Prevention and treatment strategies for mesh infection in abdominal wall reconstruction Plast Reconstr Surg 2018142(3, Suppl):149S–155S.
44. Chatterjee A, Nahabedian M Y, Gabriel A. Early assessment of post-surgical outcomes with pre-pectoral breast reconstruction: a literature review and meta-analysis. J Surg Oncol. 2018;117(06):1119–1130.
45. Dortch J D, Eck D L, Ladlie B, TerKonda S P. Perioperative glycemic control in plastic surgery: review and discussion of an institutional protocol. Aesthet Surg J. 2016;36(07):821–830.
46. Hanemann M S, Jr, Grotting J C. Evaluation of preoperative risk factors and complication rates in cosmetic breast surgery. Ann Plast Surg. 2010;64(05):537–540.
47. Bamba R, Gupta V, Shack R B, Grotting J C, Higdon K K. Evaluation of diabetes mellitus as a risk factor for major complications in patients undergoing aesthetic surgery. Aesthet Surg J. 2016;36(05):598–608.
48. Lipira A B, Sood R F, Tatman P D, Davis J I, Morrison S D, Ko J H. Complications within
49. 30 days of hand surgery: an analysis of 10,646 patients. J Hand Surg Am. 2015;40(09):1852–59000.
50. Brown E, Genoway K A. Impact of diabetes on outcomes in hand surgery. J Hand Surg Am. 2011;36(12):2067–2072.
51. Federer A E, Baumgartner R E, Cunningham D J, Mithani S K. Increased rate of complications following trigger finger release in diabetic patients. Plast Reconstr Surg. 2020;146(04):420e–427e.
52. .Werner B C, Teran V A, Deal D N. Patient-related risk factors for infection following open carpal tunnel release: an analysis of over 450,000 Medicare patients. J Hand Surg Am. 2018;43(03):214–219.
53. Raikundalia M, Svider P F, Hanba C. Facial fracture repair and diabetes mellitus: an examination of postoperative complications. Laryngoscope. 2017;127(04):809–814.
54. Molnar J A, Vlad L G, Gumus T.Nutrition and chronic wounds: improving clinical outcomes Plast Reconstr Surg 2016138(3, Suppl):71S–81S.
55. Zhang S-S, Tang Z-Y, Fang P, Qian H-J, Xu L, Ning G. Nutritional status deteriorates as the severity of diabetic foot ulcers increases and independently associates with prognosis. Exp Ther Med. 2013;5(01):215–222.
56. Tatti P, Barber A. The Use of a Specialized nutritional supplement for diabetic foot ulcers reduces the use of antibiotics. J Clin Endocrinol Metab. 2012;2(01):26–31.
57. Abdel-Salam B KA-H. Modulatory effect of whey proteins in some cytokines involved in wound healing in male diabetic albino rats. Inflammation. 2014;37(05):1616–1622.
58. Niu Y, Cao X, Song F. Reduced dermis thickness and AGE accumulation in diabetic abdominal skin. Int J Low Extrem Wounds. 2012;11(03):224–230.
59. Van Putte L, De Schrijver S, Moortgat P. The effects of advanced glycation end products (AGEs) on dermal wound healing and scar formation: a systematic review. Scars Burn Heal. 2016;2:2.059513116676828E15.
60. Uribarri J, Woodruff S, Goodman S. Advanced glycation end products in foods and a practical guide to their reduction in the diet. J Am Diet Assoc. 2010;110(06):911–1.6E13.

61. Akhtar S, Barash P G, Inzucchi S E. Scientific principles and clinical implications of perioperative glucose regulation and control. Anesth Analg. 2010;110(02):478–497.
62. Dronge A S, Perkal M F, Kancir S, Concato J, Aslan M, Rosenthal R A.Long-term glycemic control and postoperative infectious complications Arch Surg 200614104375– 380.
63. Cohen O, Lam G, Choi M, Ceradini D, Karp N. Risk factors for delays in adjuvant chemotherapy following immediate breast reconstruction. Plast Reconstr Surg. 2018;142(02):299–305.
64. Walker R J, Strom Williams J, Egede L E. Influence of race, ethnicity and social determinants of health on diabetes outcomes. Am J Med Sci. 2016;351(04):366–373.
65. Goltsman D, Morrison K A, Ascherman J A. Defining the association between diabetes and plastic surgery outcomes: an analysis of nearly 40,000 patients. Plast Reconstr Surg Glob Open. 2017;5(08):e1461.
66. Abdelhafez A HK, Taha O, Abdelaal M, Al-Najim W, le Roux C W, Docherty N G. Impact of abdominal subcutaneous fat reduction on glycemic control in obese patients with type 2 diabetes mellitus. Bariatr Surg Pract Patient Care. 2017;13(01):25–32.
67. Climov M, Bayer L R, Moscoso A V, Matsumine H, Orgill D P.The role of dermal matrices in treating inflammatory and diabetic wounds Plast Reconstr Surg 2016138(3, Suppl):148S–157S.
68. International Expert Panel on Negative Pressure Wound Therapy [NPWT-EP] . Krug E, Berg L, Lee C. Evidence-based recommendations for the use of negative pressure wound therapy in traumatic wounds and reconstructive surgery: steps towards an international consensus. Injury. 2011;42 01:S1–S12.
69. Zhang J, Hu Z-C, Chen D, Guo D, Zhu J-Y, Tang B. Effectiveness and safety of negative- pressure wound therapy for diabetic foot ulcers: a meta-analysis. Plast Reconstr Surg. 2014;134(01):141–151.
70. Del Pino-Sedeño T, Trujillo-Martín M M, Andia I. Platelet-rich plasma for the treatment of diabetic foot ulcers: a meta-analysis. Wound Repair Regen. 2019;27(02):170–182.
71. Martí-Carvajal A J, Gluud C, Nicola S. Growth factors for treating diabetic foot ulcers. Cochrane Database Syst Rev. 2015;(10):CD008548.
72. Yamakawa S, Hayashida K. Advances in surgical applications of growth factors for wound healing. Burns Trauma. 2019;7(01):10.
73. Pourmoussa A, Gardner D J, Johnson M B, Wong A K. An update and review of cell-based wound dressings and their integration into clinical practice. Ann Transl Med. 2016;4(23):457.
74. Spampinato S F, Caruso G I, De Pasquale R, Sortino M A, Merlo S. The treatment of impaired wound healing in diabetes: looking among old drugs. Pharmaceuticals (Basel) 2020;13(04):E60.
75. Long M, Cai L, Li W. DPP-4 inhibitors improve diabetic wound healing via direct and indirect promotion of epithelial-mesenchymal transition and reduction of scarring. Diabetes. 2018;67(03):518–531.
76. Maranda E L, Rodriguez-Menocal L, Badiavas E V. Role of mesenchymal stem cells in dermal repair in burns and diabetic wounds. Curr Stem Cell Res Ther. 2017;12(01):61–70.
77. Liang G, Zhang Y. Genetic and epigenetic variations in iPSCs: potential causes and implications for application. Cell Stem Cell. 2013;13(02):149–159.

78. International Expert Panel on Negative Pressure Wound Therapy [NPWT-EP] . Vig S, Dowsett C, Berg L. Evidence-based recommendations for the use of negative pressure wound therapy in chronic wounds: steps towards an international consensus. J Tissue Viability. 2011;20 01:S1–S18.
79. Baltzis D, Eleftheriadou I, Veves A. Pathogenesis and treatment of impaired wound healing in diabetes mellitus: new insights. Adv Ther. 2014;31(08):817–836.
80. Boulton A JM, Armstrong D G, Kirsner R S. American Diabetes Association; 2018. Diagnosis and Management of Diabetic Foot Complications.
81. Patry J, Blanchette V. Enzymatic debridement with collagenase in wounds and ulcers: a systematic review and meta-analysis. Int Wound J. 2017;14(06):1055–1065.
82. Onesti M G, Fioramonti P, Fino P, Sorvillo V, Carella S, Scuderi N. Effect of enzymatic debridement with two different collagenases versus mechanical debridement on chronic hard-to-heal wounds. Int Wound J. 2016;13(06):1111–1115.
83. Malone-Povolny M J, Maloney S E, Schoenfisch M H. Nitric oxide therapy for diabetic wound healing. Adv Healthc Mater. 2019;8(12):e1801210.
84. Erdoğan A, Düzgün A P, Erdoğan K, Özkan M B, Coşkun F. Efficacy of hyperbaric oxygen therapy in diabetic foot ulcers based on Wagner classification. J Foot Ankle Surg. 2018;57(06):1115–1119.
85. Martínez-Jiménez M A, Aguilar-García J, Valdés-Rodríguez R. Local use of insulin in wounds of diabetic patients: higher temperature, fibrosis, and angiogenesis. Plast Reconstr Surg. 2013;132(06):1015e–1019.