




Diabetic Wound Care: A Concise Review of Diabetic Wound and Skincare Ingredients

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Abstract

Chronic wound healing remains a complicated issue in the world's scientific health society. Alterations in the human body conditions such as biochemical, immunological, and physiological states may lead to non-healing wounds, making the treatment an insurmountably long and expensive procedure. Diabetes mellitus disposes the body to many complicated conditions while preventing diabetic wounds away from the normal wound-healing process. As topical administration is a favorable route of treating wounds, here, in this article, different topical materials and their roles are briefly reviewed.

Keywords: Diabetes, Ingredients, Topical, Mesenchymal Stem Cells, Cosmetic, Wound, Skincare

1. Context

1.1. A Concise Introduction to Diabetes

Diabetes Mellitus (DM) can be described by eccentric high levels of blood glucose. The uprising of glucose in the blood triggers the pancreatic cells to release insulin. For the elimination of glucose from the blood, insulin plays its role by stimulating muscle and fat cells and making the liver metabolize it, which brings the blood glucose back to normal levels. High blood glucose in diabetic patients may be due to the lacked or inadequate levels of insulin production or its improper working.

Based on the latest report of the World Health Organization (WHO) in 2016, an estimated 422 million adults have DM, and its prevalence is on the rise (1). Immune dysfunction that weakens the defensive potential of the body, diabetic neuropathy that decreases the ability to feel outer stimulants, and poor circulation, especially at lower sites of the body, will put these patients at high risk of many infections. However, in patients struggling with advanced DM who might have Peripheral Vascular Disease (PVD), any breakdown and tearing in skin integrity pose a great risk of complicated skin and soft-tissue infections (cSSTI) (2).

1.2. Diabetes Mellitus Affects the Skin

The culmination of diabetic skin defections can lead to long-lasting life complications for patients. The large expense may undergo public health organizational resources under significant draining. Plenty of these complications coincide with dry skin resulted from DM (3). Diminished dermal lipids of diabetic skin can increase transdermal water loss, and the reduced capability of moisture release will result in more dryness of the skin. Furthermore, the absence of collagen deters skin elasticity. Some of these conditions make the skin more vulnerable to cuts and bruises, developing infections, delayed wound healing, and skin problems such as itching (4).

1.3. Diabetic Skin Care Monetary is Pricey

Suffice to say, the refinement of diabetic skin conditions dedicates high costs to either health system accommodators or patients. The estimated cost of Diabetic Foot Ulcer (DFU) treatment is about 18.7 billion dollars annually. Moreover, the DM-related amputation cost is estimated at 3 billion dollars per year (5, 6).

2. Diabetic Skin and Wound Care by Topical Products

2.1. Polymeric Components

2.1.1. Dimethicone

Octamethyltrisiloxane is a group of organosilicon polymers, according to PubChem. Some cosmetic formulations use this colorless oil and related siloxane polymers at concentrations of use up to 15% (7). As a cosmetic rule, it is considered as a skin protectant and emulsifier (8). Otherwise, the FDA indicated that it should not be used over lacerations and wounds (9). Dimethicone can be used to protect the skin against ordinary soap cleaners and other dermal irritants due to its insoluble characteristic (10).

2.2. Metal Components

2.2.1. Ferric Chloride

As a matter, it is an orange to dark brown-black solid. On the other hand, the solution is a colorless to light brown aqueous liquid.

Locally acts as an astringent and hemostatic agent. The study of Hirobe et al. demonstrated that it can stimulate the proliferation of human skin fibroblasts and keratinocytes in culture (11). In 2015, the study of Nouri et al. on rats demonstrated a significant reduction in hemostatic time versus the control group (12).

2.2.2. Calamine

Calamine is a mixture of ZnO and 0.5% Fe₂O₃, which is shown as a Fe₂O₄Zn formula. It is also considered as Chinese traditional medicine (13). Topical Calamine (for the skin) is used to treat itching and skin irritation and decrease sweat levels while helping prevent skin lesions (14).

2.2.3. Zinc

Generally, knowing as Zinc White, Chinese Zinc, and flowers of zinc, crude zinc oxide is a yellow to grey granular solid inorganic compound insoluble in water. The action is provided by making a physical barrier for damaged skin. The topical applying of zinc oxide increases re-epithelialization in partial-thickness wounds in pigs with normal zinc status (15). Often, it can be used as an adjunctive therapy for treating minor skin irritations, cuts and burns, and baby diaper dermatitis. Chiefly described by Martindale, zinc oxide is a mild astringent used as a soothing and protecting agent in eczema, wounds, and slight excoriations (16).

2.2.4. Aluminum Oxide

The compound is an odorless, white, and water-insoluble powder. Aluminum oxide does not penetrate the skin, but it can alter the epidermal barrier. Aluminum oxide is considered as an indirect additive by the FDA. The anodic aluminum oxide membrane could make a more efficient Nano-porous function for keratinocytes and sufficient membrane size for wound healing (17).

2.2.5. Copper

Indeed, copper is an essential trace element for both plants and animals and is shown by the atomic symbol Cu. It is a reddish metallic solid that could be found in various forms, from powder to liquid. It has wound-healing effects. As a rule, its wound-healing effects accommodate VEGF expression and angiogenesis, which could incorporate into wound contraction, extracellular matrix remodeling, and closure. Copper oxide-impregnated dressings enhance wound healing, as shown in a study by Borkow et al. (18).

2.2.6. Iron Sulfate

Ferrous sulfate is a green or yellowish-brown crystal solid. Iron is an astringent in wound healing (19).

2.3. Chemical Components

2.3.1. Iodine

Extraordinary effects on a wide range of microbes and biofilms, in addition to affecting inflammation, have put it a good choice of wound healing (20).

2.3.2. Petrolatum

Helping the skin heal and retain moisture, petrolatum has an immediate barrier-repairing effect on delipidized stratum corneum (21).

2.3.3. Cetyl Palmitate

It is an ester derived from palmitic acid that increases the formation of anisotropic structures (22). It is also known as a thickener and emollient, which smooth and condition dry skin. It is also used as an emulsifier in cosmetics (23).

2.4. Mineral Oils

2.4.1. Paraffin

Liquid paraffin is used in cosmetics and skincare products to lock moisture into the skin. It is well known as a lubricant and emollient and makes a barrier. Among several indications, liquid paraffin could be found in anti-itching products, as well, especially in treating eczema, dry skin, and skin inflammations, in dermatitis and psoriasis products due to its property in preventing water loss (24).

2.5. Herbal Ingredients

2.5.1. Allantoin

It has been used as a moisturizer and keratolytic in the market (25). Pure solutions of allantoin are used for ulcer treatment. Studies have shown positive effects of allantoin on wound healing alone or in combinations (26).

2.5.2. Palmitic Acid

Palmitic acid has many functions in cosmetics, from detergent cleaning agents to emollients. Palmitic acid is a very good emollient despite the possible irritation as an adverse effect (27). A study in 2018 showed the wound-healing effects of palmitic acid in animal models (28).

2.5.3. Menthol

Chiefly, menthol is used as a cooling topical agent and can be described as a heat analgesic (29). The study of Bromm et al. demonstrated the inhibitory effects of cold-sensitive A-delta fiber activation itch (30).

2.5.4. Sorbitol

As a humectant, sorbitol prevents moisture loss by pulling water by osmosis from the air, hydrating the skin; however, when used in extremely dry conditions, sorbitol can instead take the moisture out of the skin and leave it dry or damaged. Sorbitol often is used in modern cosmetics as a humectant, moisturizer, and thickener (31).

2.5.5. Aloe Vera

The botanical name of the plant is *Aloe barbadensis* Miller being used in preventing skin ulcers, burn wounds, genital herpes, psoriasis, and pressure ulcers (32). Aloe vera significantly increases collagen synthesis after topical use, accelerates wound contraction, and stimulates fibroblasts (33). The active compounds are vitamins, enzymes, lignin, saponin, and salicylic acid (34). The antioxidant effect of aloe vera is due to its A, E, C vitamin content (34).

2.5.6. Avocado Oil

Avocado seeds have also been found to have fungicidal and anti-microbial activities (35). In cosmetics, avocado is valuable for its rejuvenate and moisturizing properties. In the study by Werman et al., avocado increased soluble collagen content of the skin (36). Suppressing fungal growth and helping the penetration of other antifungal agents is another effect of aloe vera plant (33)

2.5.7. Shea Butter

It is an extracted fat from the African shea tree or *Vitellaria paradoxa*, which is used in cosmetics as a moisturizer, as well as an analgesic in Africa (37). It is an excellent emollient for dry skin (38). In medical ointments, it is used as a base and showed to have anti-inflammatory effects against different inflammatory conditions (37).

2.5.8. Camellia sinensis

Also known as Tea, it is popular for health benefits for healthy skin. Tea has anti-inflammatory effects and can reduce scars and accelerate wound closure (39). The 2013 study of Asadi et al. showed a positive effect on surgical wounds (40).

2.5.9. Olive Oil

Olive oil is rich in vitamins and polyphenols. A study by Zahmatkesh et al. in 2015 showed the positive healing effects of ointment on burn wounds while preventing infections, accelerating tissue repair, and helping smooth debridement (18). Another study in 2016 demonstrated decreases in oxidative damage and wound healing rates (41).

2.6. Biological Ingredients and Cell-based Therapies

2.6.1. Bacitracin

Is an antibiotic widely used by both the medical profession and the general public. It is most commonly found in a variety of topical ointments and creams used after surgical procedures, for acute skin injuries, and chronic wounds. The incidence of allergies to this agent has been increasing over the last 10 years (42). The United States Food and Drug Administration (FDA) approved the application of bacitracin in the short-term to prevent both acute and chronic wounds from infections (17). While considering the reported adverse effects, some studies suggested safe long term use of bacitracin on wounds (43). Some dressing designs are efficient in healing wounds while having patented formulations, such as the combination of bacitracin and zinc oxide (44).

2.6.2. Benzalkonium Chloride

It is an organic salt that serves as a biocide (45). A study showed that BKC-loaded hydrocolloid wound dressing successfully increased the epithelialization rate compared to control groups (46).

2.6.3. Glycerin

It is a trihydroxy alcohol used as solvent, humectant, and vehicle in various pharmaceutical purposes according to the National Cancer Institute (NCI). In addition, glycerin can be used as a moisturizer (47) for dry skin and scars (48).

In 2002, Loden et al. demonstrated the efficiency of glycerin in atopic skin (49). Studies showed the positive effects of glycerin on wound healing, indicating that it is a bacteriostatic agent at high concentrations that decrease microbial density in the wound (48). Combining glycerin with wound formulations can be helpful due to its anti-itching effects.

2.6.4. Thrombin

Thrombin is an agent that supplies a mechanical formation to facilitate clotting. It has been clinically applied for topical hemostasis and wound management for more than six decades (50). The study by Ofra et al. bounded thrombin to maghemite (γ -Fe₂O₃) nanoparticles to stabilize thrombin (50). A study designed by Carney et al. indicated accelerated wound healing while increasing the capillary quantity and decreasing prolonged inflammation (51).

2.6.5. Urea

Urea is a physiological substance and a component of moisturizing skin factors that holds the skin's hydration and integrity (52). There are many applications for urea in topical formulations. It enhances hydration and ichthyosis, and improves the barrier function of the skin (53). Moisturizers having urea have shown to reduce Transepidermal Water Loss (TEWL) in atopic and ichthyotic patients. By the way, it can make normal and atopic skin less sensitive against irritation to sodium lauryl sulfate (21). Swanbeck et al. used urea to treat dry skin (54).

2.6.6. Keratin

Keratin proteins have been proven to play a fundamental role in wound healing. The expression of the controlled keratin gene promotes cell growth, migration, and differentiation, and the absence of KRT17 has been shown to delay wound closure (55). There are reports of wound healing by using keratin-based dressing in fewer than 100 days (56).

2.6.7. Bone Marrow Mesenchymal Stem Cells (BM-MSCs)

They are heterogeneous cell populations of stromal cells. Direct injection of BM-MSCs to damaged tissues resulted in the amelioration of healing by differentiation accompanied by releasing paracrine factors (57, 58). Bone marrow mesenchymal stem cells can re-epithelize damaged tissue. Nevertheless, being the fundamental source of MSCs, the limitations are conspicuous, i.e., the aspiration method is invasive with fewer quantity of cells where differentiation potential declined with age (59, 60). BM-MSCs could effectively promote corneal alkali burn healing (61).

2.6.8. Umbilical Cord Blood Mesenchymal Stem Cells (UCB-MSCs)

They are more easily obtained than bone marrow with the same angiogenic effects (62) while showing interesting immuno-regulatory properties, which have a key role in treating chronic wounds. In 2016, Qin et al. demonstrated the effective clinical therapy of severe diabetic foot ulcers (63). The 2019 study of Han et al. showed the acceleration of cutaneous wound healing in diabetic rats by HUCB implants (64).

2.6.9. Endometrium Mesenchymal Stem Cells (E-MSCs)

Human endometrium is a possible alternative source of MSCs that can be obtained from menstrual blood or diagnostic curettage after hysterectomy (65). The angiogenesis effect was shown by Murphy et al. (66).

2.6.10. Adipose-Derived Mesenchymal Stem Cells (ADSCs)

Having a fundamental role in basic research and pre-clinical studies, ADSCs are considered an important source of restorative growth factors (67, 68), homing to the injury sites (69). In comparison with BM-MSCs, ADSCs can be harvested in bigger quantities at low risk. ADSCs have been used for wound healing and tissue renovation both in vivo and in vitro (65).

2.6.11. Platelet-Derived Growth Factor (PDGF)

This factor is produced by many cells like fibroblasts, endothelial cells, and keratinocytes in response to injury as a cellular response inducer in all phases of healing (70). The activation of pathways by PDGF generally leads to enhanced cell migration and proliferation and causes increased Vascular Endothelial Growth Factor (VEGF) and Insulin-like Growth Factor (IGF) production. Importantly, it enhanced growth factor receptor expression and extracellular matrix (ECM) (fibronectin, hyaluronic acid) production (70, 71). PDGF-BB is FDA approved for the treatment of diabetic wounds (72).

2.6.12. Fibroblast Growth Factor 2 (FGF-2)

It is produced by many kinds of tissues. FGF-2 is an angiogenic and neurotrophic factor that leads to complete wound healing (73). It has been used in clinical trials for chronic wounds in many formulations, such as hydrogels (74). The 2018 study of Kinoda et al. showed the protective effects of FGF-2 on impaired wound healing in mice (75). In the study by Wu et al. in 2016, FGF-2 facilitated vascular endothelial growth factor in wound healing (76).

2.6.13. Transforming Growth Factor

It is generally named as Tumor Growth Factor (TGF). TGF- β 3 is in use in clinical trials for pressure ulcers (77).

2.6.14. Exosomes

Exosomes are cell-excreted vesicles that could be found in almost all eukaryotic fluids (78). Exosomes have notified the scientific community due to their wonderful features, including their possible function as biomarkers of different diseases and their potential to be used as therapeutic agents. They can carry proteins and nucleic acids to target cells and enhance their uptake through endocytosis (79). They are a novel approach to regenerative medicine and wound therapies. However, the concrete mechanisms that underlie this effect are poorly understood (80). A study done in 2018 reported that ADSC-derived exosomes could rise fibroblast proliferation and migration and hone collagen remodeling via the PI3K/Akt signaling pathway to further accelerate wound healing (80).

3. Results

There is a vast kind of material that is considered for the treatment or healthcare of diabetic wounds and skin conditions. In summary, diabetic skincare is an insurmountable factor in wound prevention. DM wound-healing is a lingering process that has been trapped in repairing phases. This paper discussed different ingredients with the potential of use in formulations as the main components. To design a good formulation, some key points should be considered, including effectiveness, safety, and availability. In conclusion, it can be argued that noticing discrepancies among various components could deter the final result. Due to the chronic nature of DM wounds, complete refinement is usually not achieved, so that investigations for novel treatments are ongoing for accurate and shorter treatment procedures. Hence, this assignment will examine this point of view as a matter of specification in formulations.

4. Conclusions

Diabetes mellitus causes a lot of complications to the skin; hence, choosing the right agents with fewer adverse effects on the body and skin is the main key to designing formulations. The chronic character of diabetic ulcers has made them difficult to manage in a specific way. Cell-based therapies and regenerative medicine are gaining ground in quotidian medical care. They are promising for the repair and/or replacement of damaged tissue and the restoration of lost functionality because they possess many criteria necessary for wound healing. Due to the method and form of application, stem cell therapies could treat the wound in a shorter time and are more effective

than other forms of treatment. By the appearance of regenerative medicine, stem cell-based therapies and ingredients can be a novel and helpful way of treatment for diabetic ulcers, and by expanding our knowledge, there is a strong hope to resolve this problem.

Footnotes

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References

- Roglic G. WHO Global report on diabetes: A summary. *Int J Noncomm Dis.* 2016;**1**(1):3. doi: [10.4103/2468-8827.184853](https://doi.org/10.4103/2468-8827.184853).
- Dryden M, Baguneid M, Eckmann C, Corman S, Stephens J, Solem C, et al. Pathophysiology and burden of infection in patients with diabetes mellitus and peripheral vascular disease: focus on skin and soft-tissue infections. *Clin Microbiol Infect.* 2015;**21** Suppl 2:S27-32. doi: [10.1016/j.cmi.2015.03.024](https://doi.org/10.1016/j.cmi.2015.03.024). [PubMed: [26198368](https://pubmed.ncbi.nlm.nih.gov/26198368/)].
- Sekijima H, Goto K, Hiramoto K, Komori R, Ooi K. Characterization of dry skin associating with type 2 diabetes mellitus using a KK-A(y)/Tajcl mouse model. *Cutan Ocul Toxicol.* 2018;**37**(4):391-5. doi: [10.1080/15569527.2018.1490746](https://doi.org/10.1080/15569527.2018.1490746). [PubMed: [30063844](https://pubmed.ncbi.nlm.nih.gov/30063844/)].
- Bermudez DM, Herdrich BJ, Xu J, Lind R, Beason DP, Mitchell ME, et al. Impaired biomechanical properties of diabetic skin implications in pathogenesis of diabetic wound complications. *Am J Pathol.* 2011;**178**(5):2215-23. doi: [10.1016/j.ajpath.2011.01.015](https://doi.org/10.1016/j.ajpath.2011.01.015). [PubMed: [21514435](https://pubmed.ncbi.nlm.nih.gov/21514435/)]. [PubMed Central: [PMC3081147](https://pubmed.ncbi.nlm.nih.gov/PMC3081147/)].
- Sen CK, Gordillo GM, Roy S, Kirsner R, Lambert L, Hunt TK, et al. Human skin wounds: a major and snowballing threat to public health and the economy. *Wound Repair Regen.* 2009;**17**(6):763-71. doi: [10.1111/j.1524-475X.2009.00543.x](https://doi.org/10.1111/j.1524-475X.2009.00543.x). [PubMed: [19903300](https://pubmed.ncbi.nlm.nih.gov/19903300/)]. [PubMed Central: [PMC2810192](https://pubmed.ncbi.nlm.nih.gov/PMC2810192/)].
- Nussbaum SR, Carter MJ, Fife CE, DaVanzo J, Haught R, Nusgart M, et al. An economic evaluation of the impact, cost, and medicare policy implications of chronic nonhealing wounds. *Value Health.* 2018;**21**(1):27-32. doi: [10.1016/j.jval.2017.07.007](https://doi.org/10.1016/j.jval.2017.07.007). [PubMed: [29304937](https://pubmed.ncbi.nlm.nih.gov/29304937/)].
- O'neil MJ, Smith A, Heckelman P, Budavari S. *The Merck index: an encyclopedia of chemicals, drugs, and biologicals.* Whitehouse Station. 15th ed. Piccadilly, London: NJ: RSC Publishing; 2013.
- Kirk RE, Othmer DF, Grayson M, Eckroth D. *Encyclopedia of chemical technology.* Hoboken, NJ: Wiley; 1982.
- Nair B, Cosmetic Ingredients Review Expert P. Final report on the safety assessment of stearoxy dimethicone, dimethicone, methicone, amino bispropyl dimethicone, aminopropyl dimethicone, amodimethicone, amodimethicone hydroxystearate, behenoxy dimethicone,

- C24-28 alkyl methicone, C30-45 alkyl methicone, C30-45 alkyl dimethicone, cetearyl methicone, cetyl dimethicone, dimethoxysilyl ethylenediaminopropyl dimethicone, hexyl methicone, hydroxypropyldimethicone, stearamidopropyl dimethicone, stearyl dimethicone, stearyl methicone, and vinyl dimethicone. *Int J Toxicol*. 2003;22 Suppl 2:11-35. [PubMed: 14555417].
10. Goodman LS. *Goodman and Gilman's the pharmacological basis of therapeutics*. 1549. New York: McGraw-Hill; 1996.
 11. Hirobe T. Ferrous ferric chloride stimulates the proliferation of human skin keratinocytes, melanocytes, and fibroblasts in culture. *J Health Sci*. 2009;55(3):447-55. doi: 10.1248/jhs.55.447.
 12. Nouri S, Sharif MR, Sahba S. The effect of ferric chloride on superficial bleeding. *Trauma Mon*. 2015;20(1). doi: 10.5812/traumamon.18042.
 13. Sun Y, Chen L, Huang B, Chen K. A rapid identification method for calamine using near-infrared spectroscopy based on multi-reference correlation coefficient method and back propagation artificial neural network. *Appl Spectrosc*. 2017;71(7):1447-56. doi: 10.1177/0003702816685569. [PubMed: 28387134].
 14. Mak MF, Li W, Mahadev A. Calamine lotion to reduce skin irritation in children with cast immobilisation. *J Orthop Surg (Hong Kong)*. 2013;21(2):221-5. doi: 10.1177/230949901302100222. [PubMed: 24014789].
 15. Agren MS. Studies on zinc in wound healing. *Acta Derm Venereol Suppl (Stockh)*. 1990;154:1-36. [PubMed: 2275309].
 16. Sweetman SC. *Martindale: The complete drug reference*. London: Pharmaceutical Press; 2009.
 17. Nguyen R, Khanna NR, Safadi AO, Sun Y. Bacitracin topical. *StatPearls*. 2020. [PubMed: 30725678].
 18. Zahmatkesh M, Manesh MJ, Babashahabi R. Effect of Olea ointment and Acetate Mafenide on burn wounds - A randomized clinical trial. *Iran J Nurs Midwifery Res*. 2015;20(5):599-603. doi: 10.4103/1735-9066.164507. [PubMed: 26457099]. [PubMed Central: PMC4598908].
 19. Rossoff IS. *Handbook of veterinary drugs: A compendium for research and clinical use*. New York: Springer Publishing Company; 1975.
 20. Nesvadbova M, Crosera M, Maina G, Larese Filon F. Povidone iodine skin absorption: an ex-vivo study. *Toxicol Lett*. 2015;235(3):155-60. doi: 10.1016/j.toxlet.2015.04.004. [PubMed: 25858112].
 21. Loden M. Role of topical emollients and moisturizers in the treatment of dry skin barrier disorders. *Am J Clin Dermatol*. 2003;4(11):771-88. doi: 10.2165/00128071-200304110-00005. [PubMed: 14572299].
 22. da Rocha-Filho PA, Maruno M, Ferrari M, Topan JF. Liquid crystal formation from sunflower oil: Long term stability studies. *Molecules*. 2016;21(6). doi: 10.3390/molecules21060680. [PubMed: 27294894]. [PubMed Central: PMC6272883].
 23. Montenegro L, Carbone C, Paolino D, Drago R, Stancampiano AH, Puglisi G. In vitro skin permeation of sunscreen agents from O/W emulsions. *Int J Cosmet Sci*. 2008;30(1):57-65. doi: 10.1111/j.1468-2494.2008.00417.x. [PubMed: 18377631].
 24. Torresani C, Manara GC, Bianchi M, De GP. Treatment of dry skin by the use of a "physiologic" bath oil. *G Ital Dermatol Venereol*. 1989;124(3):VII-XII.
 25. Andreassi M, Stanghellini E, Ettore A, Di Stefano A, Andreassi L. Antioxidant activity of topically applied lycopene. *J Eur Acad Dermatol Venereol*. 2004;18(1):52-5. doi: 10.1111/j.1468-3083.2004.00850.x. [PubMed: 14678532].
 26. Alexandrovich FP, Anatolievich NV, Nikolaevich CY, Vitalievna BA, Ivanovich SA, Ilinichna PS. Preclinical study of the efficacy and safety of wound healing gel containing chitosan, taurine and allantoin. *Res Rsl Pharmacol*. 2017;3(2).
 27. Levin J, Miller R. A guide to the ingredients and potential benefits of over-the-counter cleansers and moisturizers for rosacea patients. *J Clin Aesthet Dermatol*. 2011;4(8):31-49. [PubMed: 21909456]. [PubMed Central: PMC3168246].
 28. Weimann E, Silva MBB, Murata GM, Bortolon JR, Dermargos A, Curi R, et al. Topical anti-inflammatory activity of palmitoleic acid improves wound healing. *PLoS One*. 2018;13(10). e0205338. doi: 10.1371/journal.pone.0205338. [PubMed: 30307983]. [PubMed Central: PMC6181353].
 29. Klein AH, Sawyer CM, Carstens MI, Tsagareli MG, Tsiklauri N, Carstens E. Topical application of L-menthol induces heat analgesia, mechanical allodynia, and a biphasic effect on cold sensitivity in rats. *Behav Brain Res*. 2010;212(2):179-86. doi: 10.1016/j.bbr.2010.04.015. [PubMed: 20398704]. [PubMed Central: PMC2882150].
 30. Bromma B, Scharein E, Darsow U, Ring J. Effects of menthol and cold on histamine-induced itch and skin reactions in man. *Neuroscience Letters*. 1995;187(3):157-60. doi: 10.1016/0304-3940(95)11362-z.
 31. Muizzuddin N, Ingrassia M, Marenus KD, Maes DH, Mammone T. Effect of seasonal and geographical differences on skin and effect of treatment with an osmoprotectant: Sorbitol. *J Cosmet Sci*. 2013;64(3):165-74. [PubMed: 23752031].
 32. Hekmatpou D, Mehrabi F, Rahzani K, Aminian A. The effect of aloe vera clinical trials on prevention and healing of skin wound: A systematic review. *Iran J Med Sci*. 2019;44(1):1-9. doi: 10.30476/ijms.2019.40612.
 33. Tirant M, Lotti T, Gianfaldoni S, Tchernev G, Wollina U, Bayer P. Integrative dermatology - the use of herbals and nutritional supplements to treat dermatological conditions. *Open Access Maced J Med Sci*. 2018;6(1):185-202. doi: 10.3889/oamjms.2018.041. [PubMed: 29484023]. [PubMed Central: PMC5816298].
 34. Surjushe A, Vasani R, Saple DG. Aloe vera: a short review. *Indian J Dermatol*. 2008;53(4):163-6. doi: 10.4103/0019-5154.44785. [PubMed: 19882025]. [PubMed Central: PMC2763764].
 35. Dabas D, Shegog RM, Ziegler GR, Lambert JD. Avocado (*Persea americana*) seed as a source of bioactive phytochemicals. *Curr Pharm Des*. 2013;19(34):6133-40. doi: 10.2174/1381612811319340007. [PubMed: 23448442].
 36. Werman MJ, Mokady S, Nimni ME, Neeman I. The effect of various avocado oils on skin collagen metabolism. *Connect Tissue Res*. 1991;26(1-2):1-10. doi: 10.3109/03080209109152159. [PubMed: 1676360].
 37. Verma N, Chakrabarti R, Das RH, Gautam HK. Anti-inflammatory effects of shea butter through inhibition of iNOS, COX-2, and cytokines via the NF-kappaB pathway in LPS-activated J774 macrophage cells. *J Complement Integr Med*. 2012;9:Article 4. doi: 10.1515/1553-3840.1574. [PubMed: 22499721].
 38. Thomas A, Matthäus B, Fiebig H. Fats and fatty oils. *Ullmann's Encyclopedia Of Industrial Chemistry*. 2015:1-84. doi: 10.1002/14356007.a10_173.pub2.
 39. Hajiaghaalipour F, Kanthimathi MS, Abdulla MA, Sanusi J. The effect of camellia sinensis on wound healing potential in an animal model. *Evid Based Complement Alternat Med*. 2013;2013:386734. doi: 10.1155/2013/386734. [PubMed: 23864889]. [PubMed Central: PMC3705756].
 40. Asadi SY, Parsaei P, Karimi M, Ezzati S, Zamiri A, Mohammadzadeh F, et al. Effect of green tea (*Camellia sinensis*) extract on healing process of surgical wounds in rat. *Int J Surg*. 2013;11(4):332-7. doi: 10.1016/j.ijsu.2013.02.014. [PubMed: 23459184].
 41. Donato-Trancoso A, Monte-Alto-Costa A, Romana-Souza B. Olive oil-induced reduction of oxidative damage and inflammation promotes wound healing of pressure ulcers in mice. *J Dermatol Sci*. 2016;83(1):60-9. doi: 10.1016/j.jdermsci.2016.03.012. [PubMed: 27091748].
 42. Schalock P, Zug KJC. Bacitracin. *cutis*. 2005;76(2):105-7.
 43. Chan JL, Diaconescu AC, Horvath KA. Routine use of topical bacitracin to prevent sternal wound infections after cardiac surgery. *Ann Thorac Surg*. 2017;104(5):1496-500. doi: 10.1016/j.athoracsur.2017.04.017. [PubMed: 28709667].
 44. Dai T, Huang YY, Sharma SK, Hashmi JT, Kurup DB, Hamblin MR. Topical antimicrobials for burn wound infections. *Recent Pat Anti-infect Drug Discov*. 2010;5(2):124-51. doi: 10.2174/157489110791233522. [PubMed: 20429870]. [PubMed Central: PMC2935806].
 45. Lackner M, Guggenbichler JP. Antimicrobial surfaces. *Ullmann's Ency-*

- lopedia of Industrial Chemistry. 2013;1-13. doi: [10.1002/14356007.q03_q01](https://doi.org/10.1002/14356007.q03_q01).
46. Kim JH, Jin SG, Ku SK, Nam DH, Sohn YT, Ryu DS, et al. Wound healing evaluation of benzalkonium chloride-loaded hydrocolloid in the wound infection model. *Int J Pharm Investig*. 2012;**42**(6):327-33. doi: [10.1007/s40005-012-0043-2](https://doi.org/10.1007/s40005-012-0043-2).
 47. Loden M, Wessman W. The influence of a cream containing 20% glycerin and its vehicle on skin barrier properties. *Int J Cosmet Sci*. 2001;**23**(2):115-9. doi: [10.1046/j.1467-2494.2001.00060.x](https://doi.org/10.1046/j.1467-2494.2001.00060.x). [PubMed: [18498456](https://pubmed.ncbi.nlm.nih.gov/18498456/)].
 48. Stout EL, McKessor A. Glycerin-based hydrogel for infection control. *Adv Wound Care (New Rochelle)*. 2012;**1**(1):48-51. doi: [10.1089/wound.2011.0288](https://doi.org/10.1089/wound.2011.0288). [PubMed: [24527279](https://pubmed.ncbi.nlm.nih.gov/24527279/)]. [PubMed Central: [PMC3839013](https://pubmed.ncbi.nlm.nih.gov/PMC3839013/)].
 49. Loden M, Andersson AC, Anderson C, Bergbrant IM, Frodin T, Ohman H, et al. A double-blind study comparing the effect of glycerin and urea on dry, eczematous skin in atopic patients. *Acta Derm Venereol*. 2002;**82**(1):45-7. doi: [10.1080/000155502753600885](https://doi.org/10.1080/000155502753600885). [PubMed: [12013198](https://pubmed.ncbi.nlm.nih.gov/12013198/)].
 50. Ziv-Polat O, Topaz M, Brosh T, Margel S. Enhancement of incisional wound healing by thrombin conjugated iron oxide nanoparticles. *Biomaterials*. 2010;**31**(4):741-7. doi: [10.1016/j.biomaterials.2009.09.093](https://doi.org/10.1016/j.biomaterials.2009.09.093). [PubMed: [19850336](https://pubmed.ncbi.nlm.nih.gov/19850336/)].
 51. Carney DH, Mann R, Redin WR, Pernia SD, Berry D, Heggers JP, et al. Enhancement of incisional wound healing and neovascularization in normal rats by thrombin and synthetic thrombin receptor-activating peptides. *J Clin Invest*. 1992;**89**(5):1469-77. doi: [10.1172/JCI115737](https://doi.org/10.1172/JCI115737). [PubMed: [1373740](https://pubmed.ncbi.nlm.nih.gov/1373740/)]. [PubMed Central: [PMC443017](https://pubmed.ncbi.nlm.nih.gov/PMC443017/)].
 52. Celleno L. Topical urea in skincare: A review. *Dermatol Ther*. 2018;**31**(6):e12690. doi: [10.1111/dth.12690](https://doi.org/10.1111/dth.12690). [PubMed: [30378232](https://pubmed.ncbi.nlm.nih.gov/30378232/)].
 53. Grether-Beck S, Felsner I, Brenden H, Kohne Z, Majora M, Marini A, et al. Urea uptake enhances barrier function and antimicrobial defense in humans by regulating epidermal gene expression. *J Invest Dermatol*. 2012;**132**(6):1561-72. doi: [10.1038/jid.2012.42](https://doi.org/10.1038/jid.2012.42). [PubMed: [22418868](https://pubmed.ncbi.nlm.nih.gov/22418868/)]. [PubMed Central: [PMC3352965](https://pubmed.ncbi.nlm.nih.gov/PMC3352965/)].
 54. Swanbeck G. Urea in the treatment of dry skin. *Acta Derm Venereol Suppl (Stockh)*. 1992;**177**:7-8. [PubMed: [1466188](https://pubmed.ncbi.nlm.nih.gov/1466188/)].
 55. Batzer AT, Marsh C, Kirsner RS. The use of keratin-based wound products on refractory wounds. *Int Wound J*. 2016;**13**(1):110-5. doi: [10.1111/iwj.12245](https://doi.org/10.1111/iwj.12245). [PubMed: [24580740](https://pubmed.ncbi.nlm.nih.gov/24580740/)].
 56. Than MP, Smith RA, Hammond C, Kelly R, Marsh C, Maderal AD, et al. Keratin-based wound care products for treatment of resistant vascular wounds. *J Clin Aesthet Dermatol*. 2012;**5**(12):31-5. [PubMed: [23277802](https://pubmed.ncbi.nlm.nih.gov/23277802/)]. [PubMed Central: [PMC3533319](https://pubmed.ncbi.nlm.nih.gov/PMC3533319/)].
 57. Wu Y, Wang J, Scott PG, Tredget EE. Bone marrow-derived stem cells in wound healing: a review. *Wound Repair Regen*. 2007;**15** Suppl 1:S18-26. doi: [10.1111/j.1524-475X.2007.00221.x](https://doi.org/10.1111/j.1524-475X.2007.00221.x). [PubMed: [17727462](https://pubmed.ncbi.nlm.nih.gov/17727462/)].
 58. Martinello T, Gomiery C, Perazzi A, Iacopetti I, Gemignani F, DeBenedictis GM, et al. Allogeneic mesenchymal stem cells improve the wound healing process of sheep skin. *BMC Vet Res*. 2018;**14**(1):202. doi: [10.1186/s12917-018-1527-8](https://doi.org/10.1186/s12917-018-1527-8). [PubMed: [29940954](https://pubmed.ncbi.nlm.nih.gov/29940954/)]. [PubMed Central: [PMC6019727](https://pubmed.ncbi.nlm.nih.gov/PMC6019727/)].
 59. Rao MS, Mattson MP. Stem cells and aging: expanding the possibilities. *Mech Ageing Dev*. 2001;**122**(7):713-34. doi: [10.1016/s0047-6374\(01\)00224-x](https://doi.org/10.1016/s0047-6374(01)00224-x). [PubMed: [11322994](https://pubmed.ncbi.nlm.nih.gov/11322994/)].
 60. Pittenger MF, Mackay AM, Beck SC, Jaiswal RK, Douglas R, Mosca JD, et al. Multilineage potential of adult human mesenchymal stem cells. *Science*. 1999;**284**(5411):143-7. doi: [10.1126/science.284.5411.143](https://doi.org/10.1126/science.284.5411.143). [PubMed: [10102814](https://pubmed.ncbi.nlm.nih.gov/10102814/)].
 61. Ahmed SK, Soliman AA, Omar SM, Mohammed WR. Bone marrow mesenchymal stem cell transplantation in a rabbit corneal alkali burn model (a histological and immune histo-chemical study). *Int J Stem Cells*. 2015;**8**(1):69-78. doi: [10.15283/ijsc.2015.8.1.69](https://doi.org/10.15283/ijsc.2015.8.1.69). [PubMed: [26019756](https://pubmed.ncbi.nlm.nih.gov/26019756/)]. [PubMed Central: [PMC4445711](https://pubmed.ncbi.nlm.nih.gov/PMC4445711/)].
 62. Du WJ, Chi Y, Yang ZX, Li ZJ, Cui JJ, Song BQ, et al. Heterogeneity of proangiogenic features in mesenchymal stem cells derived from bone marrow, adipose tissue, umbilical cord, and placenta. *Stem Cell Res Ther*. 2016;**7**(1):163. doi: [10.1186/s13287-016-0418-9](https://doi.org/10.1186/s13287-016-0418-9). [PubMed: [27832825](https://pubmed.ncbi.nlm.nih.gov/27832825/)]. [PubMed Central: [PMC5103372](https://pubmed.ncbi.nlm.nih.gov/PMC5103372/)].
 63. Qin HL, Zhu XH, Zhang B, Zhou L, Wang WY. Clinical evaluation of human umbilical cord mesenchymal stem cell transplantation after angioplasty for diabetic foot. *Exp Clin Endocrinol Diabetes*. 2016;**124**(8):497-503. doi: [10.1055/s-0042-103684](https://doi.org/10.1055/s-0042-103684). [PubMed: [27219884](https://pubmed.ncbi.nlm.nih.gov/27219884/)].
 64. Han Y, Sun T, Han Y, Lin L, Liu C, Liu J, et al. Human umbilical cord mesenchymal stem cells implantation accelerates cutaneous wound healing in diabetic rats via the Wnt signaling pathway. *Eur J Med Res*. 2019;**24**(1):10. doi: [10.1186/s40001-019-0366-9](https://doi.org/10.1186/s40001-019-0366-9). [PubMed: [30736851](https://pubmed.ncbi.nlm.nih.gov/30736851/)]. [PubMed Central: [PMC6367839](https://pubmed.ncbi.nlm.nih.gov/PMC6367839/)].
 65. Marfia G, Navone SE, Di Vito C, Ughi N, Tabano S, Miozzo M, et al. Mesenchymal stem cells: potential for therapy and treatment of chronic non-healing skin wounds. *Organogenesis*. 2015;**11**(4):183-206. doi: [10.1080/15476278.2015.1126018](https://doi.org/10.1080/15476278.2015.1126018). [PubMed: [26652928](https://pubmed.ncbi.nlm.nih.gov/26652928/)]. [PubMed Central: [PMC4879897](https://pubmed.ncbi.nlm.nih.gov/PMC4879897/)].
 66. Murphy MP, Wang H, Patel AN, Kambhampati S, Angle N, Chan K, et al. Allogeneic endometrial regenerative cells: an "Off the shelf solution" for critical limb ischemia? *J Transl Med*. 2008;**6**:45. doi: [10.1186/1479-5876-6-45](https://doi.org/10.1186/1479-5876-6-45). [PubMed: [18713449](https://pubmed.ncbi.nlm.nih.gov/18713449/)]. [PubMed Central: [PMC2533293](https://pubmed.ncbi.nlm.nih.gov/PMC2533293/)].
 67. Kapur SK, Katz AJ. Review of the adipose derived stem cell secretome. *Biochimie*. 2013;**95**(12):2222-8. doi: [10.1016/j.biochi.2013.06.001](https://doi.org/10.1016/j.biochi.2013.06.001). [PubMed: [23770442](https://pubmed.ncbi.nlm.nih.gov/23770442/)].
 68. Salgado AJ, Reis RL, Sousa NJ, Gimble JM. Adipose tissue derived stem cells secretome: soluble factors and their roles in regenerative medicine. *Curr Stem Cell Res Ther*. 2010;**5**(2):103-10. doi: [10.2174/157488810791268564](https://doi.org/10.2174/157488810791268564). [PubMed: [19941460](https://pubmed.ncbi.nlm.nih.gov/19941460/)].
 69. Qin JB, Li KA, Li XX, Xie QS, Lin JY, Ye KC, et al. Long-term MRI tracking of dual-labeled adipose-derived stem cells homing into mouse carotid artery injury. *Int J Nanomedicine*. 2012;**7**:5191-203. doi: [10.2147/IJN.S35647](https://doi.org/10.2147/IJN.S35647). [PubMed: [23125528](https://pubmed.ncbi.nlm.nih.gov/23125528/)]. [PubMed Central: [PMC3487538](https://pubmed.ncbi.nlm.nih.gov/PMC3487538/)].
 70. Werner S, Grose R. Regulation of wound healing by growth factors and cytokines. *Physiol Rev*. 2003;**83**(3):835-70. doi: [10.1152/physrev.2003.83.3.835](https://doi.org/10.1152/physrev.2003.83.3.835). [PubMed: [12843410](https://pubmed.ncbi.nlm.nih.gov/12843410/)].
 71. Bennett SP, Griffiths GD, Schor AM, Leese GP, Schor SL. Growth factors in the treatment of diabetic foot ulcers. *Br J Surg*. 2003;**90**(2):133-46. doi: [10.1002/bjs.4019](https://doi.org/10.1002/bjs.4019). [PubMed: [12555288](https://pubmed.ncbi.nlm.nih.gov/12555288/)].
 72. Fang RC, Galiano RD. A review of becaplermin gel in the treatment of diabetic neuropathic foot ulcers. *Biologics*. 2008;**2**(1):1-12. doi: [10.2147/btt.s1338](https://doi.org/10.2147/btt.s1338). [PubMed: [19707423](https://pubmed.ncbi.nlm.nih.gov/19707423/)]. [PubMed Central: [PMC2727777](https://pubmed.ncbi.nlm.nih.gov/PMC2727777/)].
 73. Ortega S, Ittmann M, Tsang SH, Ehrlich M, Basilio C. Neuronal defects and delayed wound healing in mice lacking fibroblast growth factor 2. *Proc Natl Acad Sci U S A*. 1998;**95**(10):5672-7. doi: [10.1073/pnas.95.10.5672](https://doi.org/10.1073/pnas.95.10.5672). [PubMed: [9576942](https://pubmed.ncbi.nlm.nih.gov/9576942/)]. [PubMed Central: [PMC20437](https://pubmed.ncbi.nlm.nih.gov/PMC20437/)].
 74. Zhang X, Kang X, Jin L, Bai J, Liu W, Wang Z. Stimulation of wound healing using bioinspired hydrogels with basic fibroblast growth factor (bFGF). *Int J Nanomedicine*. 2018;**13**:3897-906. doi: [10.2147/IJN.S168998](https://doi.org/10.2147/IJN.S168998). [PubMed: [30013343](https://pubmed.ncbi.nlm.nih.gov/30013343/)]. [PubMed Central: [PMC6038860](https://pubmed.ncbi.nlm.nih.gov/PMC6038860/)].
 75. Kinoda J, Ishihara M, Nakamura S, Fujita M, Fukuda K, Sato Y, et al. Protective effect of FGF-2 and low-molecular-weight heparin/protamine nanoparticles on radiation-induced healing-impaired wound repair in rats. *J Radiat Res*. 2018;**59**(1):27-34. doi: [10.1093/jrr/rrx044](https://doi.org/10.1093/jrr/rrx044). [PubMed: [29121251](https://pubmed.ncbi.nlm.nih.gov/29121251/)]. [PubMed Central: [PMC5778538](https://pubmed.ncbi.nlm.nih.gov/PMC5778538/)].
 76. Wu J, Ye J, Zhu J, Xiao Z, He C, Shi H, et al. Heparin-based coacervate of FGF2 improves dermal regeneration by asserting a synergistic role with cell proliferation and endogenous facilitated VEGF for cutaneous wound healing. *Biomacromolecules*. 2016;**17**(6):2168-77. doi: [10.1021/acs.biomac.6b00398](https://doi.org/10.1021/acs.biomac.6b00398). [PubMed: [27196997](https://pubmed.ncbi.nlm.nih.gov/27196997/)].
 77. Hirshberg J, Coleman J, Marchant B, Rees RS. TGF-beta3 in the treatment of pressure ulcers: a preliminary report. *Adv Skin Wound Care*. 2001;**14**(2):91-5. doi: [10.1097/00129334-200103000-00013](https://doi.org/10.1097/00129334-200103000-00013). [PubMed: [11899912](https://pubmed.ncbi.nlm.nih.gov/11899912/)].

78. Keller S, Sanderson MP, Stoeck A, Altevogt P. Exosomes: from biogenesis and secretion to biological function. *Immunol Lett.* 2006;**107**(2):102-8. doi: [10.1016/j.imlet.2006.09.005](https://doi.org/10.1016/j.imlet.2006.09.005). [PubMed: [17067686](https://pubmed.ncbi.nlm.nih.gov/17067686/)].
79. Zhang Y, Liu Y, Liu H, Tang WH. Exosomes: biogenesis, biologic function and clinical potential. *Cell Biosci.* 2019;**9**:19. doi: [10.1186/s13578-019-0282-2](https://doi.org/10.1186/s13578-019-0282-2). [PubMed: [30815248](https://pubmed.ncbi.nlm.nih.gov/30815248/)]. [PubMed Central: [PMC6377728](https://pubmed.ncbi.nlm.nih.gov/PMC6377728/)].
80. Zhang W, Bai X, Zhao B, Li Y, Zhang Y, Li Z, et al. Cell-free therapy based on adipose tissue stem cell-derived exosomes promotes wound healing via the PI3K/Akt signaling pathway. *Exp Cell Res.* 2018;**370**(2):333-42. doi: [10.1016/j.yexcr.2018.06.035](https://doi.org/10.1016/j.yexcr.2018.06.035). [PubMed: [29964051](https://pubmed.ncbi.nlm.nih.gov/29964051/)].