

Development And Assessment of Ointment Formulation for Enhancing the Wound Healing Activity in Diabetic Animal

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Abstract

Diabetes mellitus, a chronic metabolic condition characterized by persistent hyperglycemia that poses significant clinical and socioeconomic challenges, frequently results in ulcers, infections, and even amputations. Diabetes severely impairs normal wound healing, which goes through the phases of hemostasis, inflammation, proliferation, and remodeling, due to oxidative stress, vascular insufficiency, neuropathy, and decreased angiogenesis. Together, these factors hinder the formation of granulation tissue, postpone epithelialization, and make people more vulnerable to infections. Alternative approaches are taken into consideration when conventional therapy fails. Ointment compositions have demonstrated potential as topical therapies because they can enhance the penetration of active ingredients, extend the release of medication, and preserve a moist wound environment that promotes healing. In diabetic wound models, herbal-based ointments including extracts from plants like *Centella asiatica*, *Curcuma longa*, and *Aloe vera*, as well as formulations employing nanocarrier systems like silver nanoparticles, have demonstrated increased fibroblast proliferation, collagen synthesis, and angiogenesis. Effective ointment formulations require the steady addition of active chemicals like growth factors, antimicrobials, or nanocarriers, as well as the selection of suitable bases, such as water-removable for better patient compliance or oleaginous for optimum occlusivity. Preclinical evaluations in rats with streptozotocin-induced diabetes often measure hydroxyproline concentration, wound contraction rate, and epithelialization time to assess

therapy efficacy. Taken together, modern ointment formulations, like hydrogel-ointment hybrids and nano-herbal formulations, offer a possible strategy to speed up the healing of diabetic wounds and reduce associated issues.

Keywords: Diabetes Mellitus, Wound Healing, Diabetic Wound, Ointment Formulation, Hyperglycemia, Nano-herbal Ointments.

1. Introduction

Diabetes mellitus, a chronic metabolic condition, is characterized by persistent hyperglycemia caused by reduced insulin secretion, action, or both. One of its most debilitating adverse effects is impaired wound healing, which typically leads to infections, persistent ulcers, and in severe cases, amputations. With a reported lifetime prevalence of 15–25% among diabetes patients, diabetic foot ulcers represent a significant clinical and socioeconomic burden [1]. Normal wound healing occurs in four coordinated, overlapping stages: hemostasis, inflammation, proliferation, and remodeling. Due to peripheral vascular insufficiency, neuropathy, oxidative stress caused by glucose, and inadequate angiogenesis, these mechanisms are disrupted in diabetic environments. This leads to poor formation of granulation tissue, delays in epithelialization, and increased susceptibility to infections [2, 3].

Conventional wound treatment methods, such as bandages, systemic antibiotics, and surgery, are often inadequate for diabetic patients. Alternative treatment approaches that could speed healing, restore normal tissue architecture, and reduce issues are therefore becoming more and more in demand. Ointment formulations augmented with herbal extracts, bioactive compounds, and nanocarrier systems have attracted a lot of interest because they can improve active agent penetration, sustain medication release, and provide a moist wound environment [4,5].

Recent research has demonstrated that herbal-based ointments (such as aloe vera, curcuma longa, and centella asiatica) and nano-formulations (such as silver nanoparticles and nanostructured lipid carriers) can stimulate angiogenesis, fibroblast proliferation, and collagen production in diabetic wound models [6,7]. These findings highlight the importance of developing ointment formulations, particularly for the treatment of diabetic wounds.

2. Pathophysiology of Diabetic Wound Healing

Hemostasis, inflammation, proliferation, and remodeling are the four overlapping stages of the closely controlled biological process of wound healing. Each stage is controlled by cellular and molecular mechanisms, including platelet aggregation, cytokine release, fibroblast proliferation, collagen production, angiogenesis, and tissue remodeling. Diabetes conditions significantly impair this phase, leading to chronic wounds that do not heal [8,9].

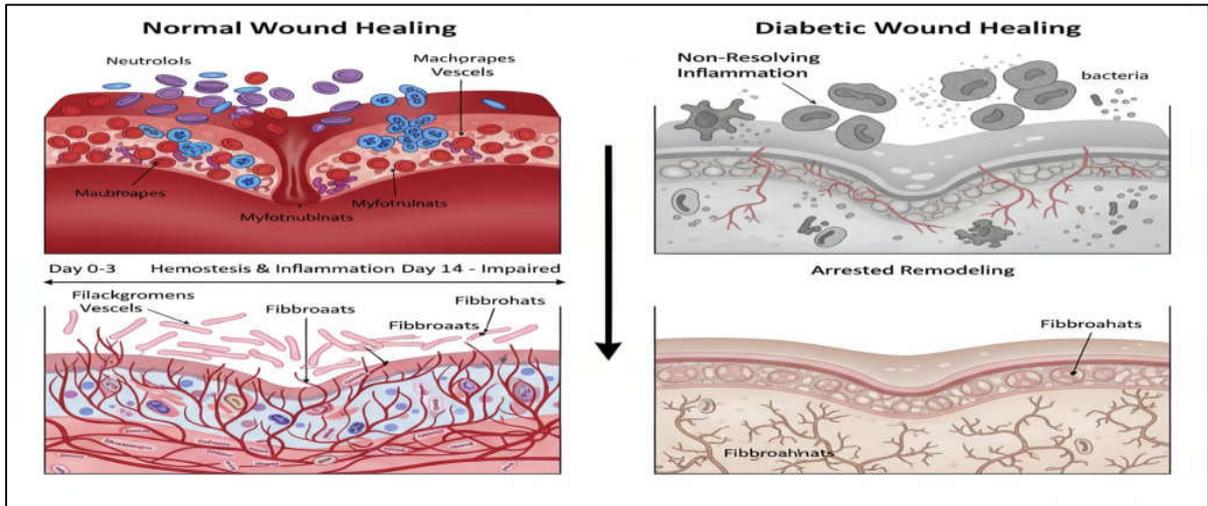


Fig 1: Pathophysiology of Diabetic Wound Healing

2.1 Hemostasis Phase

As soon as an injury occurs, platelet aggregation and clot formation halt bleeding and establish a framework for cellular infiltration. Diabetes resulted in unstable fibrin networks and delayed wound stabilization because of inadequate clot formation and poor platelet activity [10].

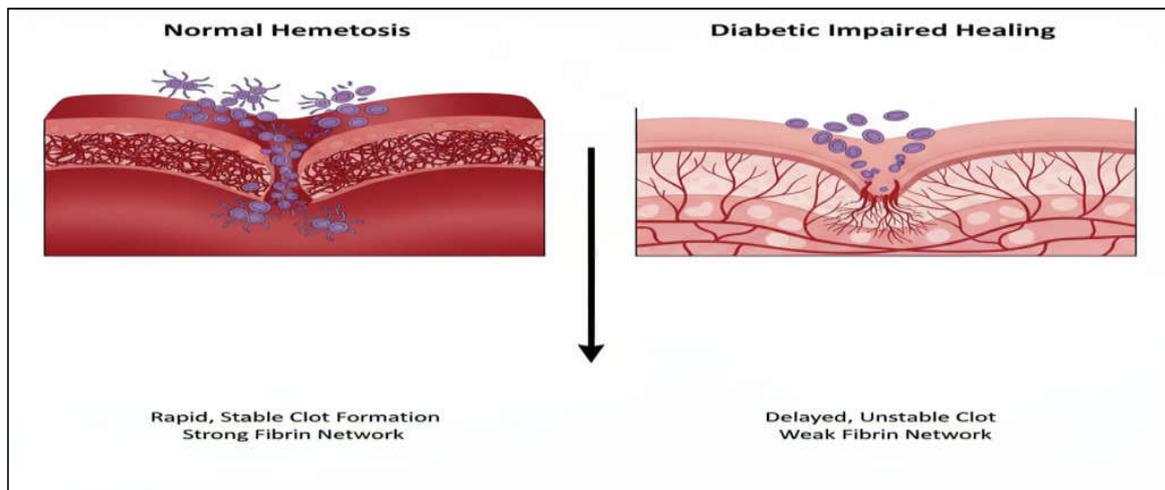


Fig 2: Hemostasis Phase

2.2 Inflammatory Phase

Normal wound healing requires a short inflammatory response characterized by neutrophil and macrophage infiltration. In diabetic wounds, oxidative stress brought on by hyperglycemia

results in severe and persistent inflammation. The pro-inflammatory (M1) to pro-healing (M2) phenotypic transition of macrophages is inhibited by the overproduction of pro-inflammatory cytokines like TNF- α , IL-6, and IL-1 β [11].

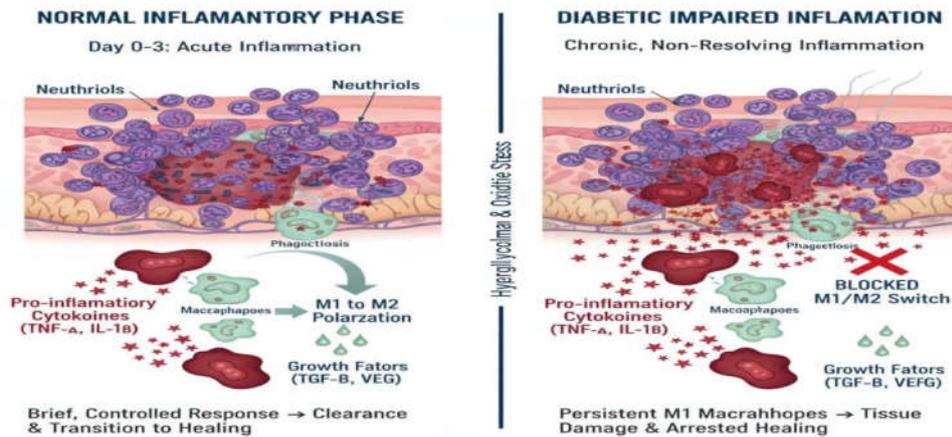


Fig 3: Inflammatory Phase

2.3 Proliferation Phase

This stage includes fibroblast proliferation, epithelialization, angiogenesis, and extracellular matrix (ECM) deposition. Fibroblast migration, keratinocyte proliferation, and angiogenesis are all impaired in diabetic wounds due to the downregulation of vascular endothelial growth factor (VEGF). Significant reductions in collagen synthesis and deposition hinder the formation of granulation tissue. [12]

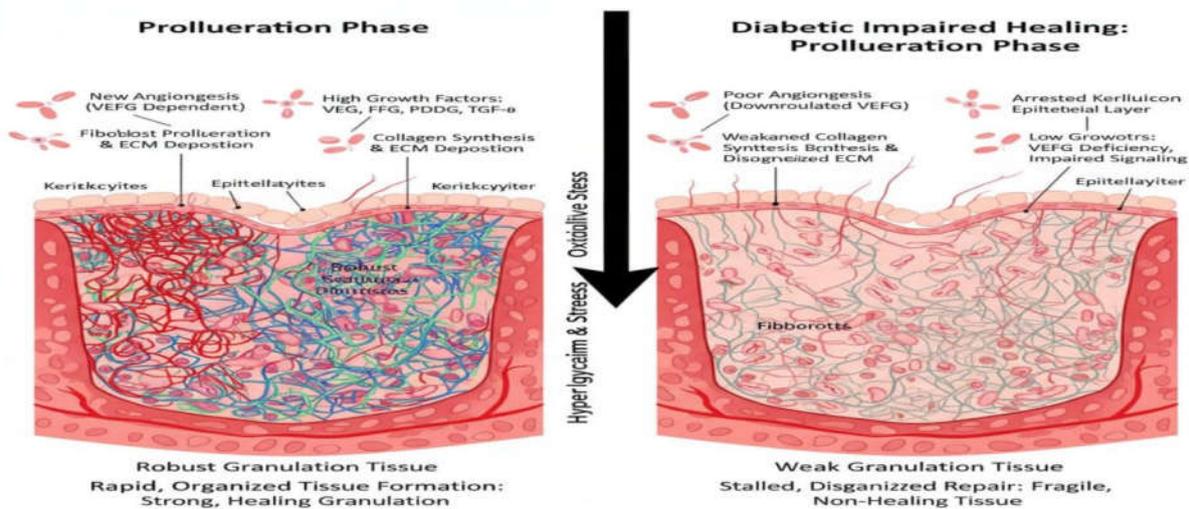


Fig 4: Proliferation Phase

2.4 Remodeling (Maturation) Phase

When type I collagen replaces type III during remodeling, tensile strength is restored. In diabetics, inadequate collagen fiber cross-linking, decreased matrix metalloproteinase (MMP) regulation, and continuous extracellular matrix degradation result in fragile scar formation and recurrent wound recurrence.[13].

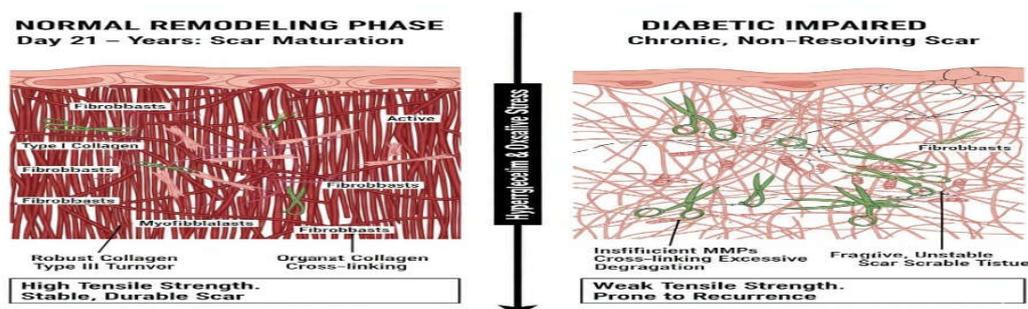


Fig 5: Remodeling (Maturation) Phase

2.5 Additional Contributing Factors

Microbial infection, ischemia, and neuropathy all worsen the wound environment in diabetics. Recurrent injuries are more likely when neuropathy causes a loss of protective sensation. While peripheral arterial dysfunction lowers perfusion and oxygen supply, high glucose levels promote bacterial growth, raising the risk of infection in wounds [14].

Together, these pathogenic pathways account for the aberrant healing of diabetic wounds, which results in persistent, non-healing ulcers.

3. Role of Ointment Formulations in Wound Healing

Because topical medicine distribution permits direct and localized action at the site of injury, it remains one of the finest approaches for treating wounds. Ointments are semisolid preparations that provide protective and occlusive surface coverage for wounds. By keeping the region moist, ointments decrease desiccation, accelerate the re-epithelialization process, and encourage keratinocyte migration [15].

3.1 Occlusive and Moisturizing Effect

Ointments' occlusive base keeps tissue hydrated, stops transepidermal water loss, and promotes the cellular and enzymatic processes required for tissue regeneration. Epithelialization can occur up to 50% more quickly in a moist environment than in a dry one [16].

3.2 Vehicle for Active Agents

Numerous bioactive substances can be administered through ointments, such as:

- Herbal extracts that encourage angiogenesis and collagen synthesis, such as Aloe vera, Curcuma longa, and Centella asiatica.
- Antimicrobials that lower microbial load and infection-related delays, such as fusidic acid and silver sulfadiazine.
- Growth factors that promote cell division include platelet-derived growth factor and epidermal growth factor.
- Lipid carriers and nanoparticles, which improve poorly soluble drugs' tissue penetration, prolonged release, and bioavailability [17,18].

3.3 Sustained and Controlled Drug Release

Topical ointments guarantee localized medicinal concentration with few systemic side effects, in contrast to systemic therapy. Long-term therapeutic effects at the wound site may be possible with formulations designed to offer prolonged pharmacological release. When sustained exposure to antioxidants, antimicrobials, or angiogenic agents is required to overcome delayed healing, this is especially helpful for diabetic wounds [19].

3.4 Enhanced Patient Compliance

Compared to intricate wound dressings or systemic drugs, ointments are less expensive, simpler to use, and non-invasive. Patient compliance and quality of life are enhanced by their capacity to lessen pain, infection, and healing time [20].

3.5 Comparative Advantages

Research has demonstrated that ointments offer better occlusivity and hydration when compared to different topical formulations (creams, gels, and films). But in other situations, their avarice can make them less acceptable. Combining the benefits of both systems is the goal of creative hybrid formulations, such as herbal ointment-nanogel combinations [21].

In conclusion, by acting as both effective medication delivery systems and protective barriers, ointments might greatly improve the outcomes of wound healing in diabetic patients.

4. Formulation Strategies for Ointments

How successfully an ointment heals wounds is greatly influenced by its formulation approach, which determines medicine stability, penetration, release profile, and patient acceptance. An ideal formulation must maintain the necessary consistency, spreadability, and therapeutic efficacy while efficiently dispersing the active component during the course of treatment [22].

4.1 Selection of Ointment Base

Both medication release and skin penetration are impacted by base selection.

- Maximum occlusivity and hydration are made possible by oleaginous bases (white petrolatum, paraffin, etc.).

- Aqueous solutions can be included using absorption bases like lanolin.
- Polyethylene glycols and other water-soluble bases are easy to wash and non-greasy.
- Water-removable bases, such as hydrophilic ointments, are more visually pleasing and facilitate medicine diffusion [23].

4.2 Incorporation of Active Agents

Many types of wound-healing agents can be found in ointments, such as:

- Herbal extracts: Aloe vera, Centella asiatica, and Curcuma longa (angiogenesis, collagen production).
- Fusidic acid and silver sulfadiazine are antimicrobials that stop infections.
- Bioactive substances: antioxidants, growth factors, and peptides (ECM synthesis, fibroblast proliferation).
- Liposomes, nanostructured lipid carriers, and silver nanoparticles (longer release, higher penetration) are examples of nanocarrier systems [24, 25].

4.3 Stability Considerations

Ointments must be able to withstand changes in temperature, pH, and microbial contamination. Viscosity measurements, pH calculations, spreadability and extrudability tests, and microbiological stability tests are common evaluation methods [26].

4.4 Optimization of Drug Release and Penetration

Drug diffusion across the skin barrier can be greatly increased by using nanocarrier systems and permeation enhancers (such ethanol and surfactants). For diabetic wounds where extended local medication availability is necessary, controlled-release ointments are particularly beneficial [27].

4.5 Patient-Centered Formulation Approaches

To achieve great wound healing outcomes in diabetic circumstances, formulation solutions essentially need to comprise base selection, active agent integration, stability, and patient acceptability. Current approaches focus on developing non-greasy hybrid ointments (ointment-gel or ointment-nanogel systems) that maintain occlusivity while improving application ease because oily textures may decrease compliance [28].

5. Herbal and Synthetic Agents Used in Ointment Formulations

Aloe vera, Centella asiatica, curcumin, and honey are examples of herbal remedies that promote angiogenesis, collagen synthesis, and tissue regeneration. Growth hormones, antibiotics, and silver sulfadiazine are examples of synthetic substances that aid in healing and guard against infection. Nano formulations are useful in the treatment of diabetic wounds because they enhance bioavailability, maintain release, and speed wound closure.

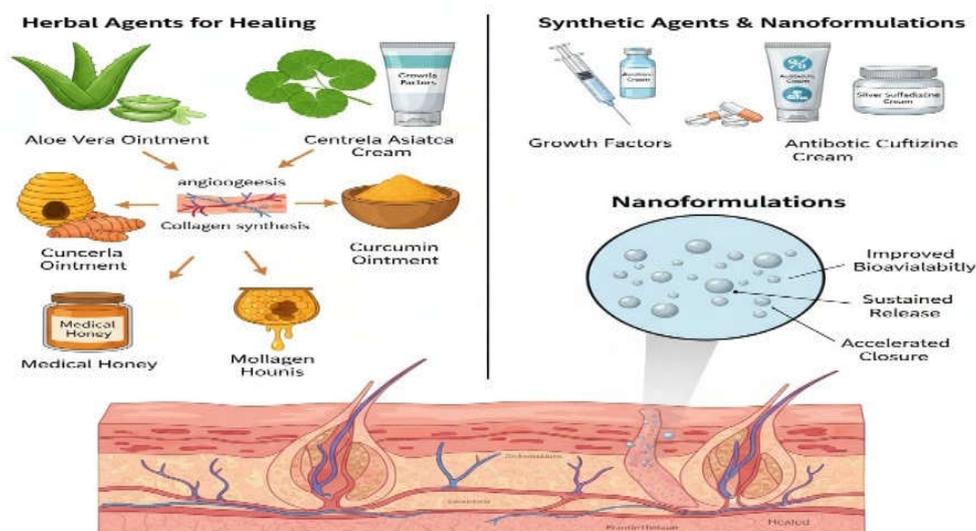


Fig 6: Herbal and Synthetic Agents Used in Ointment Formulations

6. Preclinical Assessment of Ointments in Diabetic Animals

7. Mechanism of Action in Enhancing Wound Healing

Ointments promote fibroblast proliferation, angiogenesis, and collagen synthesis in addition to producing a moist healing environment and supplying bioactive compounds that reduce oxidative stress and prevent microbial infection in chronic wounds.

8. Recent Advances in Ointment Formulation

Advance	Description
Nano-herbal ointments	Herbal extracts are added to nanoparticle systems to improve the bioavailability, stability, and prolonged release of nano-herbal ointment
Combination formulations	Using antimicrobials and antioxidants in ointments to reduce oxidative stress and infection in a synergistic manner.
Hydrogel-ointment hybrids	combining hydrogels and ointments to enhance tissue hydration, oxygen exchange, and medicine penetration

Parameter	Description / Detai
Animal Models	Streptozotocin (STZ)-induced diabetic rats are commonly used to mimic diabetic wound healing deficits.
Wound Induction	To evaluate the healing process, models of burn, incision, or excision wounds are created.
Wound Contraction Rate	By estimating the percentage decrease in wound area over time, this statistic assesses the efficacy of healing.
Epithelialization Period	The time it takes for a wound to completely heal and for new epithelium to form is called the epithelialization period.
Hydroxyproline Content	The hydroxyproline content biochemical test can be used to quantify collagen deposition in healed tissue.
Histopathological Studies	microscopic evaluation of granulation tissue, angiogenesis, fibroblast proliferation, and overall tissue regeneration.
Smart ointments	The development of temperature-responsive or pH-sensitive devices that enable site-specific and controlled drug release is known as "smart ointments."

9. The challenges and opportunities of maintaining the bioactive ingredients in ointments throughout time.

- Overcoming diabetic tissues' low pharmacological penetration. Standardization of preclinical and clinical processes is necessary.
- Converting animal models into human applications

10. Conclusion

Ointment formulations provide a practical therapeutic option for the management of diabetic wounds. With the correct formulation techniques, integration of bioactive chemicals, and careful testing in diabetic animal models, these formulations can significantly improve wound healing and reduce the effects of diabetes.

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