

Palm-Derived Tocotrienols and Squalene for Skin-Barrier Repair and Wound Healing: From Redox Biology to Nanoenabled Dermatologic Translation - A Review

Loso Judijanto

IPOSS Jakarta, Indonesia

*Corresponding Author: Loso Judijanto, IPOSS Jakarta, Indonesia. <https://orcid.org/0009-0007-7766-0647>.

Submitted: 08 October 2026

Accepted: 15 October 2026

Published: 22 October 2026

Citation: Judijanto, L. (2026). Palm-Derived Tocotrienols and Squalene for Skin-Barrier Repair and Wound Healing: From Redox Biology to Nanoenabled Dermatologic Translation - A Review. *Journal of Clinical Medicine*, 1(5), 01-17.

Abstract

Impaired skin-barrier function and delayed wound healing arise from interacting disturbances in redox homeostasis, inflammation, keratinocyte migration, fibroblast activity, extracellular-matrix remodelling, vascular responses, microbial ecology, and cutaneous lipid organisation. Palm-derived tocotrienols and squalene are lipid-soluble phytonutrients with complementary properties that make them attractive for topical dermatologic and wound-care development. This qualitative literature review synthesises recent evidence published primarily from 2020 onward and evaluates nanoenabled delivery as a translational strategy. Tocotrienols show comparatively strong mechanistic evidence for antioxidant and anti-inflammatory activity, protection of keratinocyte barrier proteins, modulation of cellular migration, and support of experimental wound repair. Squalene has a complementary profile related to skin-surface lipid physiology, emolliency, redox interactions, formulation compatibility, and limited but encouraging experimental repair data. Nanoemulsions, ethosomes, solid lipid nanoparticles, nanostructured lipid carriers, and nanoemulgels can improve dispersion, stability, local deposition, controlled release, and retention of lipophilic bioactives. However, the evidence base remains dominated by *in vitro*, *ex vivo*, and animal studies, while randomized human evidence is scarce. Chronic and diabetic wound care represents a compelling translational opportunity because oxidative stress, persistent inflammation, cellular dysfunction, vascular impairment, and infection coexist. Future development should prioritize standardized raw materials, mechanistically controlled formulations, human-relevant skin models, safety and pharmacokinetic studies, and indication-specific randomized trials using clinically meaningful endpoints.

Keywords: Palm Oil, Tocotrienols, Squalene, Skin Barrier, Wound Healing, Oxidative Stress, Chronic Wounds, Diabetic Wounds, Nanostructured Lipid Carriers, Nanoemulsions.

JEL Classification: I10; I12; L65; O31; O32

Introduction

The skin is simultaneously a mechanical shield, water-retaining barrier, immunological interface, sensory organ, and metabolically active surface. Failure of this barrier can range from subtle increases in transepidermal water loss to inflammatory dermatoses and open wounds in which loss of structural integrity increases the risks of infection, persistent inflammation, fibrosis, and delayed repair. Wound healing is not a single biological event but a coordinated progression involving hemostasis, inflammation, proliferation, re-epithelialization, angiogenesis, extracellular-matrix deposition, and remodeling. Disturbance at

any of these stages can convert a normally self-limiting injury into a chronic non-healing state, particularly when diabetes, ischemia, aging, infection, repeated trauma, or immune dysregulation are present [1-3].

A recurring biological feature across impaired barrier function, photoaging, inflammatory dermatoses, burns, and chronic wounds is dysregulated oxidative signaling. Reactive oxygen species are not intrinsically pathological because physiologic ROS participate in antimicrobial defense, cell signaling, angiogenesis, and migration. The problem emerges when ROS pro-

duction exceeds antioxidant buffering and produces sustained lipid peroxidation, mitochondrial dysfunction, protein modification, DNA damage, extracellular-matrix injury, and amplification of inflammatory pathways. Antioxidant-based dermatology should therefore aim to restore a functional redox range rather than indiscriminately eliminate all ROS [4-7].

Chronic wounds illustrate this dysregulation particularly clearly. Macrophages that normally change functional states as repair progresses may remain trapped in inflammatory programs, while keratinocytes show defective migration, fibroblasts exhibit abnormal proliferation and matrix production, endothelial responses deteriorate, and polymicrobial communities can organize into persistent biofilms. These environments therefore contain interconnected oxidative, inflammatory, metabolic, vascular, and microbiological abnormalities rather than a single pharmacological target [8-13].

Against this background, lipid-soluble natural compounds have attracted attention because cutaneous physiology is itself strongly lipid-dependent. Natural bioactives may combine antioxidant or anti-inflammatory effects with favorable partitioning into skin lipids, while lipid-based formulations can provide occlusion, hydration, sustained release, and improved local retention. Nevertheless, biological plausibility must be separated from clinical efficacy because favorable changes in antioxidant assays, cell migration, or animal-wound closure do not automatically demonstrate better complete healing, recurrence, infection control, pain, scar quality, or quality of life in human patients [14-16].

Palm-derived tocotrienols are especially relevant to this translational question. Tocotrienols belong to the vitamin E family and differ from tocopherols through an unsaturated isoprenoid side chain that influences membrane localization and biological behavior. Palm oil is an important natural source of tocotrienol-rich fractions that can contain alpha-, gamma-, and delta-tocotrienols together with alpha-tocopherol. Recent work has associated tocotrienols with redox modulation, anti-inflammatory signaling, membrane protection, keratinocyte responses, and experimental tissue repair, while topical formulations have been evaluated in dermatitis, burn, wound-healing, and cutaneous-delivery models [17-20].

Squalene provides a different but potentially complementary profile. It is an unsaturated triterpene intermediate in sterol biosynthesis and is naturally present in human sebum and the skin-surface lipid film. Squalene should not be presented as one of the dominant structural extracellular lipids of the stratum corneum, which are primarily ceramides, cholesterol, and free fatty acids; its dermatologic relevance is instead related to surface lubrication, emolliency, redox chemistry, and compatibility with lipid-based formulations [21-24].

The physicochemical properties of tocotrienols and squalene create both opportunity and constraint. Their lipophilicity is compatible with cutaneous lipid environments, but it can complicate aqueous formulation, dose uniformity, oxidative stability,

release, and penetration. Nanoemulsions, ethosomes, solid lipid nanoparticles, nanostructured lipid carriers, and lipid-polymer hybrid systems may protect labile ingredients, improve dispersion, enhance skin contact, alter deposition, and provide sustained release. At the same time, the vehicle itself can contribute to hydration, occlusion, barrier permeability, or irritation, meaning that favorable outcomes cannot automatically be attributed only to the encapsulated active compound [25-28].

This qualitative literature review evaluates whether palm-derived tocotrienols and squalene have a sufficiently coherent biological and pharmaceutical evidence base to justify continued development for skin-barrier repair and wound healing. The analysis focuses on oxidative stress, inflammatory signaling, keratinocyte and fibroblast biology, extracellular-matrix remodeling, skin-surface lipids, topical pharmacology, and nanoenabled delivery. It also distinguishes cosmetic or biophysical outcomes from medically meaningful therapeutic endpoints and proposes a staged development framework, with particular attention to chronic and diabetic wounds as a high-need translational indication [29-31].

Literature Review: Conceptual and Theoretical Foundations

Skin-Barrier Architecture and Lipid Organization

The outer barrier of the skin is frequently explained through the brick-and-mortar model in which corneocytes provide cellular bricks and a highly organized extracellular lipid matrix provides the mortar. Although simplified, the model captures the dependence of permeability control on ceramides, cholesterol, and free fatty acids within lamellar structures of the stratum corneum. Disturbances in lipid composition, molecular organization, hydration, natural moisturizing factors, and terminal keratinocyte differentiation can increase permeability and transepidermal water loss, thereby increasing susceptibility to irritants and inflammation [32, 33].

Barrier function also depends on proteins produced during keratinocyte differentiation. Filaggrin contributes to corneocyte architecture and natural moisturizing factor generation, involucrin contributes to the cornified envelope, and transglutaminase activity promotes cross-linking of structural proteins. In atopic dermatitis, type 2 inflammatory signaling can suppress several barrier-related pathways while altering lipid composition and antimicrobial defense. Barrier failure and inflammation can therefore reinforce each other because increased permeability facilitates entry of irritants and allergens, while inflammatory cytokines further impair differentiation and lipid homeostasis [34, 35].

The skin surface contains another lipid compartment produced partly by sebaceous glands. Sebum includes triglycerides, wax esters, free fatty acids, cholesterol-related lipids, and squalene, and these materials contribute to lubrication, surface hydrophobicity, microbial ecology, and environmental interactions. Recent lipidomic and biophysical literature emphasizes that skin-surface lipids are heterogeneous and should not be conflated with the ordered extracellular lipids of the stratum corneum.

Recent lipid-focused reviews further reinforce the need to distinguish epidermal barrier lipids from sebaceous surface lipids. Terminal keratinocyte differentiation generates specialized ceramides and lamellar structures that limit water loss and penetration by allergens and microorganisms, while the broader cutaneous lipid environment also interacts with pH and the skin microbiome. These observations support evaluating palm-derived formulations not only through hydration endpoints but also through lipid organization, barrier biomarkers, and microbiome-aware outcomes [36, 37].

This distinction matters for the interpretation of squalene-containing topical products. An emollient can improve spreadability, mechanical flexibility, comfort, and hydration-associated properties without necessarily reconstructing the lamellar architecture of a diseased stratum corneum. Experimental work on emollient structure confirms that biomechanical effects depend on molecular characteristics and formulation context, so claims of barrier restoration require direct measures such as transepidermal water loss, hydration, lipid organization, or barrier-related biomarkers rather than compositional assumptions alone [38].

Wound Healing as an Integrated Sequence

Normal cutaneous healing proceeds through overlapping biological phases. Hemostasis limits blood loss and creates a provisional matrix; inflammatory cells then remove damaged material and coordinate antimicrobial defense. During proliferation, keratinocytes migrate to restore epidermal continuity, fibroblasts synthesize and reorganize extracellular matrix, endothelial cells establish neovasculature, and granulation tissue fills the defect. Remodeling subsequently changes collagen architecture, tensile strength, cellularity, and tissue mechanics over weeks to months.

Macrophages occupy a pivotal position because their functions evolve during healing. The classic M1/M2 shorthand is useful pedagogically but underestimates the diversity and plasticity of real wound macrophages, which respond to microbial signals, hypoxia, damaged-cell products, cytokines, and matrix cues. Persistent inflammatory macrophage programs can maintain protease activity and cytokine production, while failure to transition toward reparative states can delay tissue formation and angiogenesis. Fibroblasts are similarly heterogeneous. They regulate collagen synthesis, matrix organization, wound contraction, paracrine signaling, and scar formation, but subpopulations can contribute differently to regeneration and fibrosis. Consequently, describing a candidate intervention as simply pro-collagen is insufficient: an effective therapy should support appropriately organized matrix deposition and remodeling rather than indiscriminate fibrotic accumulation.

The biology of wound repair also depends on the balance between host defense and tissue preservation. Controlled inflammatory and oxidative responses help suppress microbes and recruit repair cells, but excessive or prolonged activity damages viable tissue and extracellular matrix. This dual role explains why interventions that modulate redox or inflammation should

be evaluated across time and dose rather than treated as uniformly beneficial at all stages of healing.

Why Diabetic and Chronic Wounds Fail to Heal

Diabetes alters nearly every major component of tissue repair. Chronic hyperglycemia promotes oxidative stress and advanced glycation, reduces endothelial responsiveness, impairs immune-cell function, alters keratinocyte and fibroblast behavior, and contributes to peripheral neuropathy. Ischemia and repeated unnoticed trauma can then combine with infection to sustain ulceration, while poor angiogenesis and persistent inflammation prevent orderly progression through normal healing phases [39].

Recent pathway-oriented analyses further indicate that diabetic wound failure reflects simultaneous dysregulation of VEGF, TGF-beta, NF-kappaB, MAPK, PI3K/Akt, matrix metalloproteinases, and other repair networks rather than a single oxidative lesion. Parallel biomaterials research shows that multifunctional hydrogels are increasingly designed to combine antioxidant, antibacterial, angiogenic, oxygen-modulating, and stimulus-responsive functions around this complex wound microenvironment. These developments strengthen the rationale for multifunctional local delivery while also raising the evidentiary standard for any tocotrienol-squalene platform proposed for diabetic wounds [40, 41].

Redox dysfunction is central but nuanced. Controlled ROS generation supports antimicrobial defense and signaling, yet chronic ROS excess damages membranes, proteins, mitochondria, and matrix components. Antioxidant strategies therefore need to restore physiological balance rather than maximally suppress oxidants, because excessive antioxidant exposure could theoretically interfere with signaling or host defense. This concern is especially relevant for potent lipid-soluble antioxidants delivered at high local concentrations.

Microbial ecology adds another layer of complexity. Chronic wounds may host polymicrobial communities that form structured biofilms, tolerate host defenses, and display increased resistance to antimicrobial treatment. Biofilms can perpetuate inflammation, alter oxygen gradients and pH, and interfere with granulation and epithelial migration. Any new topical antioxidant or lipid formulation intended for chronic wounds should therefore be evaluated in the context of debridement, infection control, and standard wound-care practice rather than as a stand-alone solution.

Tocotrienol Pharmacobiology Relevant to Skin

Tocotrienols combine a chromanol antioxidant head group with an unsaturated side chain that influences their distribution within lipid membranes. Their biological effects extend beyond direct radical scavenging and include modulation of inflammatory and stress-responsive signaling pathways, although responses differ by isoform, concentration, tissue, and experimental model. Contemporary reviews therefore support broad therapeutic interest while cautioning against extrapolating findings from unrelated organs directly to skin or wounds.

The most persuasive cutaneous evidence is increasingly mechanistic. In human epidermal keratinocytes exposed to urban particulate matter, tocotrienol-rich fraction reduced intracellular ROS, suppressed ERK, JNK, and p38 MAPK activation, reduced COX-2-associated inflammatory signaling, and improved the expression of barrier-related proteins including filaggrin, involucrin, and transglutaminase-1. This observation connects redox control with epidermal differentiation rather than relying solely on generic antioxidant-capacity assays.

Tocotrienols have also been investigated in repair models. A tocotrienol-rich nanoemulsified system accelerated closure of keratinocyte scratch wounds and promoted regeneration in a zebrafish model, supporting a formulation-enabled effect on repair-associated cellular behavior. Experimental burn studies combining tocotrienol-rich fraction with epidermal growth factor have reported improved histological and gene-expression patterns, although those combination designs prevent precise attribution of efficacy to tocotrienols alone [42, 43].

Dermatitis-related delivery work adds another layer of relevance. Advanced delivery approaches have been used to increase cutaneous exposure to alpha-tocopherol and gamma-tocotrienol, highlighting the barrier as both a therapeutic target and a pharmacokinetic obstacle. These data strengthen the rationale for local tocotrienol delivery but also underscore the importance of dose, vehicle, and disease state when interpreting skin penetration and efficacy [44, 45].

Squalene as a Dermatologic Lipid and Formulation Component
Squalene is an unsaturated triterpene that occupies a distinctive position in cutaneous biology because it is naturally abundant in human sebum and participates in the chemistry of the skin-surface lipid film. Its hydrophobic character supports emollient and formulation functions, while its multiple double bonds create both antioxidant potential and susceptibility to oxidation. Oxidized squalene products may have biological effects that differ substantially from the parent molecule, making oxidative control a formulation requirement rather than a purely manufacturing concern.

The strongest evidence for squalene in healthy skin concerns surface physiology rather than replacement of structural barrier lipids. Surface lipids can influence hydration, lubrication, and interactions with environmental radiation, whereas the deeper permeability barrier remains dominated by ceramides, cholesterol, and free fatty acids. Thus, squalene-containing systems should be evaluated for functions they can plausibly perform, including emolliency, surface protection, delivery compatibility, and redox effects.

Direct tissue-repair evidence is encouraging but comparatively limited. A squalene-loaded agar-based emulgel improved wound contraction, revascularization, macrophage-associated responses, and collagen deposition in an experimental full-thickness burn model. A vitamin C-squalene bioconjugate also increased epidermal thickness and collagen production in human skin

models, demonstrating that squalene-containing molecular constructs can support skin-related outcomes, although such conjugate effects cannot be assumed to represent unconjugated squalene [46, 47].

The combined tocotrienol-squalene concept should consequently be described as complementary rather than proven synergistic. Tocotrienols currently have the stronger direct evidence for keratinocyte redox regulation and wound-related biological effects, whereas squalene contributes physiologic relevance to the skin surface and practical advantages as a lipid-phase component. A recent review of both compounds supports their multifunctional dermatologic potential, but direct combination-specific therapeutic studies remain scarce [48].

Nanoenabled Topical Delivery

Nanoenabled delivery is relevant because lipophilic compounds can be difficult to disperse reproducibly in aqueous formulations and may be vulnerable to oxidation or limited release. Nanoemulsions provide a large interfacial area and can improve dispersion and skin contact, while ethosomes use phospholipids and high ethanol content to alter cutaneous penetration. Solid lipid nanoparticles and nanostructured lipid carriers use lipid matrices to protect hydrophobic compounds and provide sustained release, and nanoemulgels combine nanoscale delivery with the residence and rheological properties of gels [49].

NLCs are particularly attractive because they combine solid and liquid lipids to create a less ordered matrix than classical solid lipid nanoparticles, potentially increasing active loading and reducing expulsion during storage. Their behavior depends on lipid composition, surfactant selection, particle size, polydispersity, zeta potential, crystallinity, and interaction with the active compound. Reviews focused on natural bioactives and skin applications emphasize that no single nanocarrier is universally optimal; the formulation should be selected according to target tissue, desired residence, release profile, stability, and manufacturing constraints.

Recent reviews focused specifically on wound-healing NLCs confirm that their principal advantages include protection of active compounds from degradation, controlled local release, high loading potential, and compatibility with topical gels, but they also identify scale-up, sterilization, stability, and clinical validation as persistent constraints. A 2026 review of NLC-gels likewise concluded that most wound-healing evidence still derives from *in vitro* and animal models despite increasingly sophisticated formulation strategies. This evidence strengthens the case for using NLCs as enabling delivery technologies while maintaining a clear separation between formulation performance and demonstrated clinical efficacy [50, 51].

The wound field provides proof that lipid nanocarriers can be functionally relevant beyond cosmetic delivery. Lipid nanoparticles have been investigated for antibacterial activity, controlled release, growth-factor support, and tissue repair, while NLC-based approaches have been explored for diabetic foot applications. These broader studies do not validate tocotrienols

or squalene specifically, but they establish a plausible platform logic for a lipid-compatible palm-derived formulation.

Hybrid systems may add further functionality. Hydrogels can maintain a moist environment and retain nanocarriers at the tissue surface, while electrospun nanofibers and nanocellulose can provide structural coverage and local release. These materials illustrate an important principle: delivery platforms can influence wound biology by changing moisture, oxygen exchange, mechanical protection, and residence time, so the vehicle must be considered part of the intervention rather than an inert container [52-55].

As summarized in Table 1, the principal evidence domains supporting the proposed tocotrienol-squalene dermatologic platform differ substantially in interpretive strength. The comparison is intended to prevent mechanistic or preclinical observations from being read as equivalent to human therapeutic efficacy.

Table 1: Evidence Domains Supporting the Proposed Tocotrienol-Squalene Dermatologic Platform

Evidence domain	Representative evidence	Interpretive strength
Keratinocyte redox/barrier biology	Reduced ROS/MAPK signaling and improved filaggrin, involucrin, and transglutaminase-1 expression.	Direct skin-cell evidence; clinically indirect
Repair-associated migration	Tocotrienol-rich nanoemulsion accelerated keratinocyte scratch closure and experimental regeneration.	Direct preclinical proof of concept
Burn repair	Tocotrienol-rich fraction with EGF and squalene-based emulgel improved experimental burn-healing outcomes.	Integrated in-vivo evidence; attribution limitations
Human-relevant delivery	Tocotrienol ethosomes evaluated with Strat-M membrane and excised human skin.	Useful translational pharmacokinetic evidence
Skin-surface lipid physiology	Squalene recognized as an important sebaceous/surface lipid with redox and emollient relevance.	Strong physiological plausibility; limited wound-specific evidence
Nanoenabled platform science	NLCs, nanoemulsions, and hybrid carriers support controlled local delivery of lipophilic actives.	Strong enabling-platform evidence
Human therapeutic efficacy	Few direct randomized therapeutic studies of palm tocotrienol-squalene systems in chronic wounds.	Major evidence gap

Method

This study employed a structured qualitative literature review rather than a systematic literature review or meta-analysis. The purpose was interpretive synthesis: to integrate mechanistic, dermatologic, wound-healing, pharmaceutical, and nanotechnology evidence into a coherent translational framework. Accordingly, the review did not use PRISMA-based claims of exhaustive retrieval, formal systematic risk-of-bias scoring, or quantitative pooling, because its central objective was to compare biological mechanisms and translational implications across heterogeneous evidence domains.

The primary evidence window was January 2020 to October 2026, with emphasis on peer-reviewed articles in reputable biomedical, dermatologic, pharmaceutical, biomaterials, and wound-healing journals. Conceptual searches were organized around four interacting blocks: tocotrienols and palm vitamin E; squalene and skin; skin barrier and wound healing; and nanoenabled topical drug delivery. Representative terms included tocotrienol, tocotrienol-rich fraction, palm vitamin E, squalene, kera-

tinocyte, fibroblast, skin barrier, wound, burn, diabetic wound, chronic wound, nanoemulsion, nanoemulgel, ethosome, solid lipid nanoparticle, and nanostructured lipid carrier.

Priority was given to original studies directly evaluating skin, wound, dermal delivery, or dermatologic outcomes. High-quality reviews were used to establish conceptual background on skin-barrier architecture, redox biology, inflammatory signaling, fibroblast and macrophage functions, biofilms, and lipid nanocarriers. Papers were interpreted according to their biological proximity to clinical application: biochemical and cell studies, reconstructed or ex vivo skin studies, animal wound models, human penetration or tolerability studies, and therapeutic clinical studies.

The qualitative synthesis was organized around six predefined themes: redox-inflammatory regulation, epidermal and skin-surface lipid biology, cellular wound repair, nanoenabled delivery, indication-specific translation, and evidence gaps. The unit of interpretation was not simply whether a study reported a statis-

tically significant effect, but what type of claim that result could legitimately support. For example, faster keratinocyte scratch closure was interpreted as evidence of a repair-associated cellular response rather than as evidence of clinical ulcer healing, while increased ex vivo skin penetration was treated as a pharmaceutical performance outcome rather than a therapeutic endpoint.

Particular attention was paid to attribution. Many topical systems are multicomponent and may combine tocotrienols or squalene with growth factors, polyphenols, surfactants, polymers, or other biologically active excipients. When studies did not include matched vehicle and single-component controls, the review treated reported benefits as formulation-level evidence rather than proof of a specific molecular mechanism. This distinction is necessary for developing testable hypotheses and avoiding promotional interpretations of complex natural-product formulations.

This review has limitations that follow from its qualitative design. It cannot claim exhaustive retrieval, pooled treatment effects, or formal comparative ranking of formulations. The evidence base is heterogeneous in tocotrienol isoform, squalene source, concentration, carrier composition, experimental model, wound type, comparator, and outcome, and some potentially relevant studies remain outside the direct skin and wound literature. These limitations are treated as part of the translational analysis rather than as grounds for overgeneralization.

Results: Thematic Findings

Evidence Landscape and Hierarchy

The contemporary evidence base is uneven. Tocotrienols have direct mechanistic support in keratinocytes, formulation studies using human skin or skin surrogates, experimental burn models, and wound-related nanoemulsion systems. Squalene has strong physiological relevance to skin-surface lipids and promising experimental formulation data, but fewer studies directly test wound-healing efficacy. Across both compounds, human randomized therapeutic evidence is much thinner than the mechanistic and preclinical literature, which means the field should be described as translationally promising rather than clinically established.

This hierarchy matters because different evidence levels answer different questions. Cell studies can identify signaling and cytotoxicity; ex vivo human skin can characterize penetration and deposition; animal wounds can test integrated healing in living tissue; and clinical trials determine whether benefits occur in real patients receiving standard care. The strongest manuscript therefore does not flatten these levels into a single claim but explicitly maps how each level contributes to or limits a therapeutic conclusion.

Theme 1: Redox and Inflammatory Modulation

The most consistent biological argument for tocotrienols is modulation of oxidative and inflammatory stress. In keratinocytes exposed to urban particulate matter, tocotrienol-rich fraction re-

duced intracellular ROS, decreased activation of ERK, JNK, and p38 MAPK, and reduced downstream COX-2-related inflammatory signaling while improving barrier-protein expression. These observations directly link antioxidant activity to stress signaling and epidermal differentiation in a skin-relevant system.

This mechanism is relevant to wounds because persistent ROS can damage cellular membranes, mitochondria, proteins, and matrix components while amplifying cytokine and protease pathways. However, the same literature indicates that controlled ROS generation supports host defense and repair signaling. Tocotrienol-based interventions should therefore be optimized for redox normalization, with attention to concentration and timing, rather than assuming that maximal antioxidant capacity is desirable throughout all healing phases.

Squalene may contribute to redox biology, but its unsaturation also creates susceptibility to peroxidation. This duality means that the quality and oxidation state of a squalene-containing formulation are likely to influence biological behavior. Studies of squalene should therefore characterize the parent compound and oxidative degradation products rather than assuming that all squalene-containing materials are equivalent.

Theme 2: Epidermal Differentiation and Barrier Protection

Barrier repair requires restoration of both lipid organization and epidermal differentiation. The finding that tocotrienol-rich fraction can improve filaggrin, involucrin, and transglutaminase-1 expression in stressed keratinocytes provides a mechanistic bridge between redox signaling and structural barrier biology. Because these proteins contribute to cornified-envelope formation and hydration-related functions, they provide more biologically specific endpoints than generic total-antioxidant assays.

Squalene contributes most plausibly at the level of skin-surface lipids and formulation behavior. The skin-surface film can influence hydration, lubrication, friction, and environmental exposure, but it should be analytically separated from the stratum-corneum lipid lamellae. This distinction supports a complementary model in which tocotrienols act primarily through cellular and signaling mechanisms while squalene supports the local lipid environment and delivery system.

Clinical claims should match these mechanisms. Improved hydration or reduced transepidermal water loss can represent meaningful barrier outcomes, but they are not equivalent to resolution of inflammatory dermatitis or closure of a chronic ulcer. The literature on barrier-repair moisturizers reinforces the importance of defining whether a formulation is intended as a dermocosmetic adjunct, a medical device-like wound dressing, or a medicinal product with disease-modifying claims.

Theme 3: Cellular Migration, Matrix Repair, and Tissue Regeneration

The wound-healing literature provides direct evidence that formulated tocotrienols can influence repair-associated behavior. Chong et al. reported faster keratinocyte scratch closure and en-

hanced zebrafish regeneration with a tocotrienol-rich nanoemulsified system. Scratch assays cannot reproduce immune, vascular, mechanical, and microbial features of chronic wounds, but they provide a useful first indication that a formulation can alter migration- or proliferation-associated processes.

Burn studies extend the evidence to living mammalian tissue. Tocotrienol-rich fraction combined with epidermal growth factor improved healing-related outcomes in deep partial-thickness experimental burns, and a related study reported gene-expression changes consistent with accelerated repair. These studies are valuable because burn healing requires coordinated epithelial, inflammatory, vascular, and matrix responses, yet the presence of epidermal growth factor means the observed benefits should be attributed to the combination until factorial controls isolate the tocotrienol contribution.

Squalene-containing systems also show preclinical repair activity. A squalene-loaded agar-based emulgel improved contraction, revascularization, macrophage-associated responses, and collagen deposition in an experimental full-thickness burn model. Meanwhile, a vitamin C-squalene bioconjugate increased epidermal thickness and collagen production in human skin mod-

els. Together, these findings justify continued investigation of squalene-containing formulations while underscoring that the evidence is still formulation-specific and not yet sufficient for broad clinical claims.

Matrix outcomes require particularly careful interpretation. Fibroblast activation and collagen production are necessary for wound strength, but excessive matrix deposition can promote fibrosis and poor scar quality. Future tocotrienol-squalene studies should therefore examine collagen organization, matrix metalloproteinase balance, mechanical properties, and scar architecture in addition to total collagen content or early wound contraction.

Figure 1: Mechanistic Integration

Figure 1 integrates the proposed biological roles of palm-derived tocotrienols and squalene across the wound-healing continuum. The figure places excessive ROS and persistent inflammation upstream of impaired keratinocyte, fibroblast, macrophage, endothelial, and extracellular-matrix responses, and it distinguishes evidence-supported links from relationships that remain translational hypotheses. This architecture is intentionally conservative: it does not claim that a combined tocotrienol-squalene product has already demonstrated synergy or clinical efficacy.

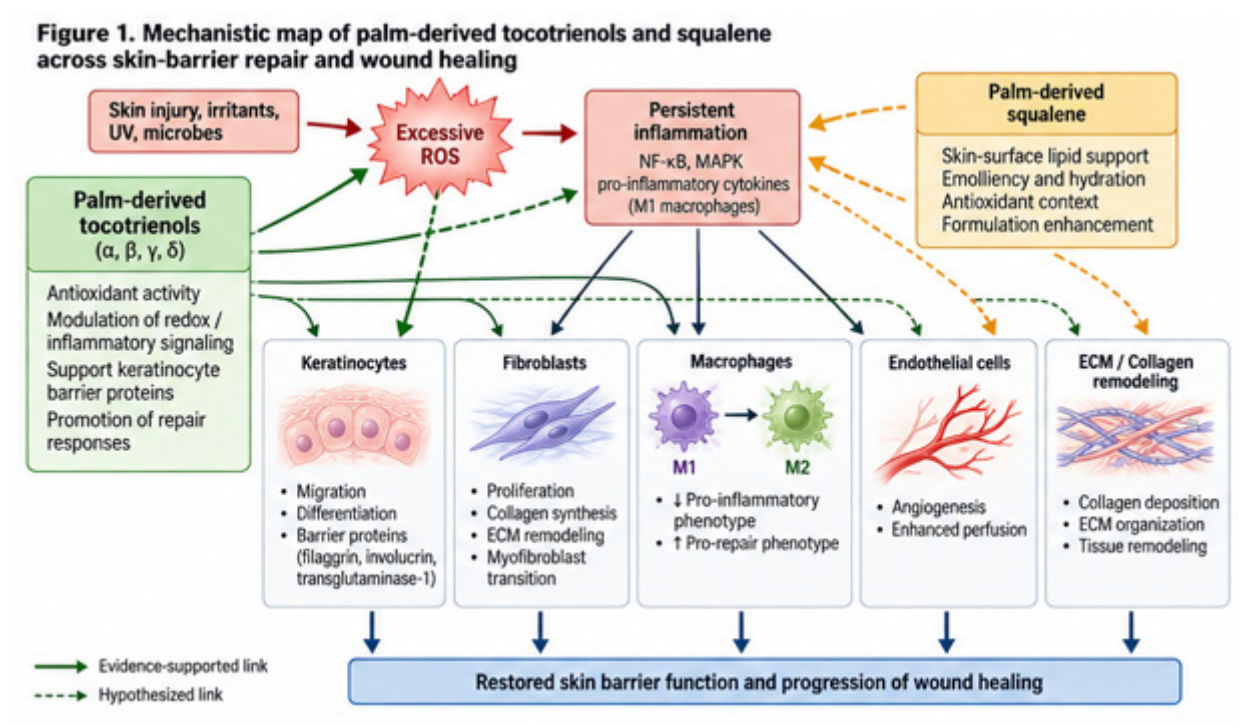


Figure 1: Mechanistic Map of Palm-Derived Tocotrienols and Squalene Across Skin-Barrier Repair and Wound Healing. Solid Relationships Summarize Comparatively Direct Evidence; Dashed Relationships Denote Hypotheses Requiring Stronger Validation.

The synthesis in Figure 1 shows why a combined platform should not be reduced to an antioxidant narrative. The intended therapeutic effect would depend on coordination across epithelial, inflammatory, vascular, and matrix compartments, and the balance between these responses may differ in intact barrier injury, acute burns, and infected chronic ulcers. Accordingly,

mechanistic studies should evaluate multiple cell types and tissue-level outcomes rather than rely on a single ROS assay or wound-closure endpoint.

Theme 4: Nanoemulsions and Nanoemulgels as Delivery Strategies

Nanoemulsions are attractive for tocotrienols because they disperse lipophilic actives within small droplets and can increase contact area with skin. The tocotrienol-rich nanoemulsion reported by Chong et al. combined pharmaceutical formulation with biological testing, making it one of the most directly relevant examples in the current evidence base. However, its pre-clinical results should be interpreted as proof of concept for a delivery-enabled biological response rather than proof of improved chronic-wound outcomes in patients.

The tocotrienol-rich naringenin nanoemulgel developed for diabetic-wound management illustrates both promise and attribution challenges. The system demonstrated favorable nanoscale properties, topical characteristics, and release behavior, showing that tocotrienol-rich components can be integrated into a gel-based platform suitable for local delivery. Because naringenin is itself bioactive and the carrier components can influence release and barrier interaction, the formulation should be considered a multicomponent intervention that requires appropriately matched controls before synergy is claimed.

Nanoemulgels also address practical wound-care issues. A gel can improve residence at the treatment site, reduce runoff, and support controlled local delivery, while the internal nanoemulsion can improve dispersion of hydrophobic molecules. These advantages are particularly relevant to peri-wound skin and superficial wounds, although open chronic ulcers may require additional properties such as exudate management, sterility, dressing compatibility, and resistance to dilution by wound fluid.

Theme 5: Ethosomes, SLNs, NLCs, and Hybrid Systems

Ethosomal delivery provides a complementary approach. Tocotrienol ethosomes have been evaluated using Strat-M membrane and excised human skin, demonstrating the importance of studying deposition and permeation in models that are more relevant than simple dialysis release assays. Such work is especially useful for intact skin and peri-wound applications, where the stratum corneum remains the dominant transport barrier.

tum corneum remains the dominant transport barrier.

Solid lipid nanoparticles and NLCs provide structured lipid matrices that can protect hydrophobic compounds and prolong release. NLCs use mixtures of solid and liquid lipids to create an imperfect matrix that may increase loading and reduce expulsion during storage. Reviews of topical natural bioactives emphasize that performance depends on composition, particle size, polydispersity, crystallinity, surface charge, and storage conditions rather than on the NLC label itself.

Evidence from other wound actives supports the broader platform logic. Simvastatin-loaded NLCs have been investigated for wound-healing purposes, and lipid-based nanocarriers are being studied across diabetic-foot applications for small molecules and other therapeutics. These studies demonstrate that lipid nanoparticles can achieve sustained local exposure and influence wound outcomes, but they should be used as platform precedents rather than as substitute evidence for tocotrienols or squalene [56].

Hybrid matrices can further modify clinical usability. Hydrogels, nanofibers, and nanocellulose systems can provide moisture control, physical coverage, or localized release, and a bacterial nanocellulose wound cover has been used to deliver a vitamin-E-derived metabolite in a controlled manner. Such systems highlight the possibility of integrating antioxidant chemistry with wound-dressing functionality, but they also reinforce the need to distinguish the biological effect of the active compound from the structural effects of the carrier.

As shown in Table 2, the main nanoenabled platforms relevant to topical tocotrienol-squalene delivery offer different functional advantages and formulation-specific limitations. Platform selection should therefore follow the target tissue and clinical use case rather than the assumption that any nanosystem is inherently superior.

Table 2: Nanoenabled platforms and their potential roles in topical tocotrienol-squalene delivery

Platform	Potential advantages	Key limitations / questions
Nanoemulsion	High interfacial area; dispersion of lipophilic actives; adaptable to gel conversion.	Oxidation, surfactant irritation, physical stability, attribution of vehicle effects.
Ethosome	Enhanced interaction with intact stratum corneum; useful for skin deposition studies.	Ethanol-related irritation; may be less relevant to open wound beds.
Solid lipid nanoparticle	Protection of hydrophobic actives; controlled release; occlusive potential.	Crystallization and active expulsion during storage.
Nanostructured lipid carrier	Higher loading through mixed solid/liquid lipid matrix; sustained release; good compatibility with lipophilic actives.	Composition-sensitive stability; scale-up and sterilization challenges.
Nanoemulgel / lipid-hydrogel hybrid	Improved residence, spreadability, moisture management, and local retention.	Gel matrix can alter release; exudate and dressing compatibility must be tested.
Nanofiber / nanocellulose hybrid	Structural coverage with localized controlled release.	Manufacturing complexity, sterility, mechanical-property requirements.

Figure 2: Skin Compartments and Sites of Action

Figure 2 separates the stratum-corneum lipid matrix from sebaceous and skin-surface lipids. This distinction is important because ceramides, cholesterol, and free fatty acids form the principal extracellular barrier lipids, whereas squalene is pre-

dominantly associated with sebum and the surface film. Tocotrienols are positioned at keratinocyte and signaling targets, while squalene is positioned primarily at the surface-lipid and formulation interface.

Figure 2. Skin-barrier compartments and proposed sites of action of tocotrienols and squalene

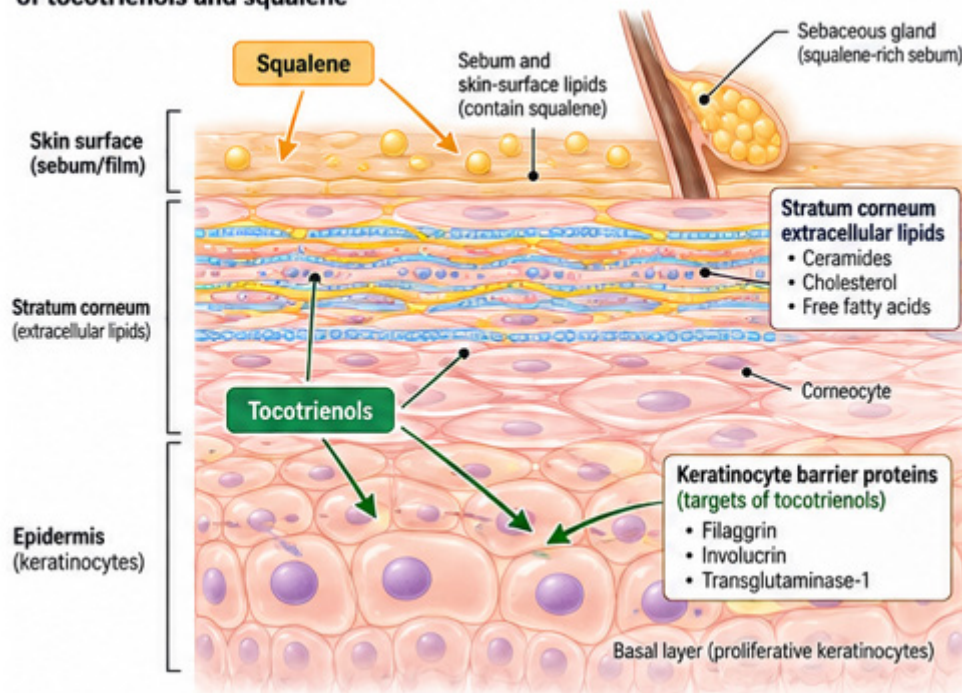


Figure 2: Skin-Barrier Compartments and Proposed Sites of Action of Tocotrienols and Squalene. Squalene is Positioned Primarily within the Skin-Surface Lipid Context, whereas Tocotrienols are Linked to Keratinocyte and Barrier-Protein Responses.

Figure 2 also clarifies a key terminology issue for future manuscripts and product claims. Describing squalene as a surface lipid with emollient and formulation roles is biologically more accurate than presenting it as a major structural stratum-corneum lipid. This distinction helps align experimental endpoints with mechanism and reduces the risk of overclaiming barrier reconstruction from surface hydration alone.

Theme 6: The Carrier is Part of the Biological Intervention

A critical result of the formulation literature is that the vehicle cannot be assumed to be biologically inert. Lipid particles can alter occlusion, hydration, adhesion, residence, and barrier permeability; surfactants can alter membrane organization or cause irritation; and gels can modify moisture and mechanical protection. A nanoformulation may therefore outperform a simple solution even if the intrinsic molecular potency of the active compound has not changed.

This issue makes control design central to future tocotrienol-squalene studies. At minimum, mechanistic experiments should compare an unloaded carrier, tocotrienol-only system, squalene-only system, combined formulation, and clinically relevant comparator where feasible. Factorial designs can then

determine whether the combined system is additive, synergistic, neutral, or antagonistic rather than assuming synergy from co-formulation.

Natural-product nanoformulation studies provide useful methodological examples. Naringenin-loaded chitosan-coated nanoemulsions have been developed for wound-healing applications, showing how particle engineering, surface modification, and topical compatibility can be evaluated before clinical translation. Such precedents are important because a palm-derived formulation should be benchmarked against contemporary pharmaceutical-development standards rather than against unformulated natural ingredients alone [57].

Theme 7: Diabetic Wounds as the Highest-Priority Translational Indication

Among potential indications, diabetic wounds provide the strongest conceptual justification for a multifunctional topical system. Oxidative stress, prolonged inflammation, reduced keratinocyte migration, fibroblast dysfunction, impaired angiogenesis, ischemia, neuropathy, and infection frequently coexist, creating a setting in which a redox-active and locally retained formulation could be relevant. This complexity also means that a single

antioxidant mechanism is unlikely to be sufficient on its own.

The tocotrienol-rich naringenin nanoemulgel demonstrates that a tocotrienol-containing system can be engineered specifically with diabetic-wound management in mind. Nevertheless, the existing evidence is substantially stronger for pharmaceutical feasibility and in vitro performance than for healing of human diabetic ulcers. Development should therefore proceed through disease-relevant models and controlled clinical studies rather than extrapolate directly from formulation performance.

Biofilms impose an additional requirement. Chronic diabetic ulcers often contain organized microbial communities that can perpetuate inflammatory signaling and resist therapy, so a formulation that addresses oxidative stress but lacks compatibility with infection control may have limited clinical value. Studies should test interactions with debridement, antiseptics, antibiotics, dressings, and microbial biofilms, while avoiding assumptions that lipid-rich formulations are automatically antimicrobial.

Clinical endpoints should also be chosen carefully. Redox biomarkers, inflammatory markers, and histological changes are valuable mechanistic outcomes, but later-stage trials should prioritize time to complete closure, proportion of ulcers healed within a defined period, wound-area trajectories, infection, recurrence, pain, adverse events, and patient-reported function. This endpoint hierarchy would align pharmaceutical development with clinically meaningful benefit rather than surrogate improvement alone.

Secondary Indications: Burns, Inflammatory Dermatoses, and Environmental Injury

Burns represent a secondary indication with relatively direct preclinical evidence. Experimental studies combining tocotrienol-rich fraction with epidermal growth factor and separate studies using squalene-loaded emulgels have reported improve-

ments in repair-associated outcomes. The challenge is to identify which wound depth, treatment window, and formulation can provide benefit beyond modern burn care, because experimental closure alone does not establish reduced infection, scarring, pain, or reconstructive requirements.

Inflammatory dermatoses provide another potential application because barrier disruption and immune activation reinforce each other. Tocotrienol-related delivery work in dermatitis and broader vitamin E literature support anti-inflammatory plausibility, while squalene-containing emollient systems may support surface comfort and hydration. Such products should be positioned as adjunctive candidates rather than replacements for evidence-based anti-inflammatory treatment until comparative human studies are available.

Environmental barrier injury and photoaging are more appropriate for preventive or dermocosmetic development. Tocotrienol-rich fraction has protected keratinocytes from particulate-matter-induced oxidative and barrier-related damage, while skin-surface lipids participate in interactions with solar radiation. These findings support a plausible role in environmental skin protection but should not be conflated with medical treatment of chronic wounds, because the target populations, risk-benefit thresholds, and clinical endpoints differ substantially.

Figure 3: Nanoenabled Development Pathway

Figure 3 maps the pharmaceutical development sequence from standardized palm-derived raw material through characterization, nanocarrier development, functional performance, tissue delivery, biological response, and ultimately clinical translation. The figure emphasizes that successful translation requires multiple sequential achievements: chemical standardization, oxidative protection, reproducible formulation characteristics, appropriate release, local deposition, cellular compatibility, mechanistic activity, and clinically meaningful repair.

Figure 3. Nanoenabled development pathway for palm-derived tocotrienols and squalene

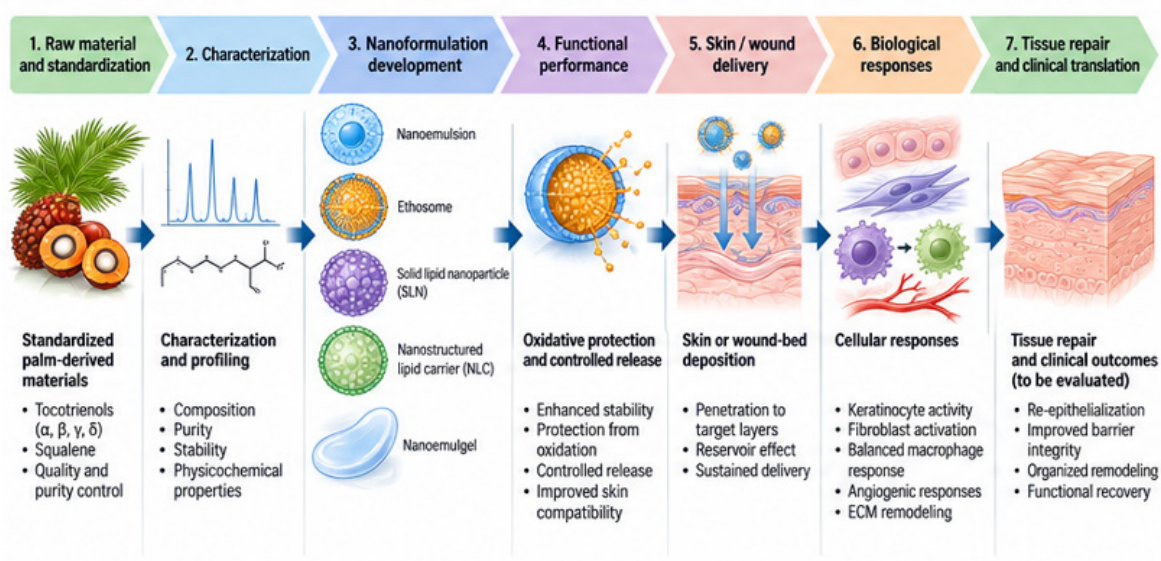


Figure 3: Nanoenabled Development Pathway for Palm-Derived Tocotrienols and Squalene, From Raw-Material Standardization to Tissue Repair and Clinical Translation.

The pathway in Figure 3 is intentionally sequential. A formulation should not proceed to efficacy claims if the raw material is not standardized, if oxidation is uncontrolled, or if the delivery system does not provide reproducible release and local exposure. This sequencing also helps identify failure points early, reducing the risk that expensive animal or clinical studies are conducted with poorly characterized formulations.

Safety, Stability, and Manufacturing Considerations

Natural origin does not guarantee dermatologic safety. Topical products can cause irritation, sensitization, follicular effects, or interactions with concomitant therapies, and surfactants or permeation enhancers can contribute independent toxicity. Diseased or wounded skin may also permit greater exposure than intact skin, making safety studies on normal volunteers insufficient for some final indications.

Oxidative stability is especially important for unsaturated lipids. Tocotrienols and squalene can undergo oxidation, and degradation products may have different biological activities from their parent compounds. Development programs should therefore incorporate stability-indicating chromatography, appropriate oxidation markers, photostability assessment, oxygen and temperature stress testing, packaging studies, and defined shelf-life specifications.

Manufacturing scale-up is another translational bottleneck. Particle size and polydispersity that are easy to control at laboratory scale may change with mixing energy, temperature history, raw-material variability, sterilization, or storage. Quality-by-design approaches should define critical material attributes and process parameters early so that later efficacy studies use a formulation that can actually be reproduced in larger batches.

Discussion and Analysis

Tocotrienols as the Principal Pharmacological Anchor

The integrated evidence suggests that tocotrienols should be treated as the principal pharmacological anchor of a palm-derived dermatologic platform. Their relevance is supported by direct keratinocyte data, wound-related nanoemulsion research, experimental burn studies, dermatitis-focused delivery work, and a broader literature on redox and inflammatory modulation. This pattern is stronger than a generic natural-antioxidant argument because several studies address cutaneous cells, barrier proteins, or wound models directly.

The most compelling mechanism is the integration of redox control with inflammatory signaling and epidermal differentiation. Reduction of ROS and MAPK activation accompanied by restoration of filaggrin, involucrin, and transglutaminase-1 provides a coherent biological narrative: environmental oxidative stress disrupts signaling and barrier maturation, while the tocotrienol-rich fraction partially normalizes both processes. This mechanism is highly relevant to barrier injury, but its relevance to deep infected chronic wounds still requires validation in more complex models.

Wound-specific evidence remains heterogeneous. Combination formulations, different tocotrienol compositions, and varied experimental endpoints make it difficult to define a universal active concentration or mechanism. The field would benefit from studies that report complete tocotrienol isoform profiles, free versus encapsulated exposure, local tissue concentration, and dose-response relationships so that reproducibility and mechanistic interpretation improve across laboratories.

Squalene as a Complementary Rather than Co-Equal Component

Squalene is scientifically attractive but should not be given an evidentiary status equal to tocotrienols. Its strongest support concerns skin-surface physiology, emolliency, antioxidant chemistry, and formulation compatibility, with a smaller direct wound-healing literature. This asymmetry can strengthen rather than weaken the proposed concept if each compound is positioned according to its best-supported role.

A rational combined formulation could use tocotrienols primarily as bioactive ingredients and squalene as a supportive lipid phase with potential additional biological effects. Such a design fits modern formulation science, in which excipients can influence deposition, occlusion, sensory properties, and stability. However, complementarity inferred from mechanism is not the same as synergy, which requires direct comparison of single-component and combined systems.

Source provenance should also be explicit. Squalene can be obtained from different biological sources and by biotechnology, so claims about palm-derived squalene require documentation of origin, purification, purity, oxidation status, and contaminants. Molecular evidence about squalene can support mechanistic plausibility, but source-specific claims should only be made when the material actually studied is characterized as palm-derived.

Nanoformulation as Enabling Technology, not Evidence of Efficacy

The nanoenabled component of this field is persuasive because it addresses genuine physicochemical constraints. Lipid nanocarriers can increase apparent solubility, reduce exposure to destabilizing environments, sustain release, improve contact with the skin, and modify local deposition. These are real pharmaceutical advantages and they justify continued formulation research.

However, nanoformulation can also generate exaggerated therapeutic language. Smaller particles, higher encapsulation efficiency, or greater ex vivo penetration are not clinical endpoints. Increased penetration may even be undesirable if the therapeutic objective is prolonged local retention rather than systemic absorption. An evidence-based development pathway should therefore move sequentially from pharmaceutical performance to target-site exposure, mechanistic activity, integrated preclinical repair, safety, and clinical benefit.

Localization is particularly important in wound care. For intact

peri-wound skin, the stratum corneum is the dominant transport barrier, whereas the open wound bed lacks this layer and may permit much greater absorption. A formulation optimized for intact-skin permeation may therefore be inappropriate for direct application to an ulcer, and separate target product profiles may be needed for peri-wound barrier support and wound-bed therapy.

Figure 4: Translational Evidence Pyramid

Figure 4 summarizes the evidence hierarchy and proposed clinical-development roadmap. The base consists of chemistry, formulation, and molecular mechanisms, followed by cell systems, reconstructed or ex vivo human skin, animal wound models, early human safety studies, proof-of-concept randomized trials, and definitive indication-specific randomized trials. The current evidence for palm-derived tocotrienols and squalene is concentrated primarily in the lower and middle levels, explaining why the field is promising but not yet clinically mature.

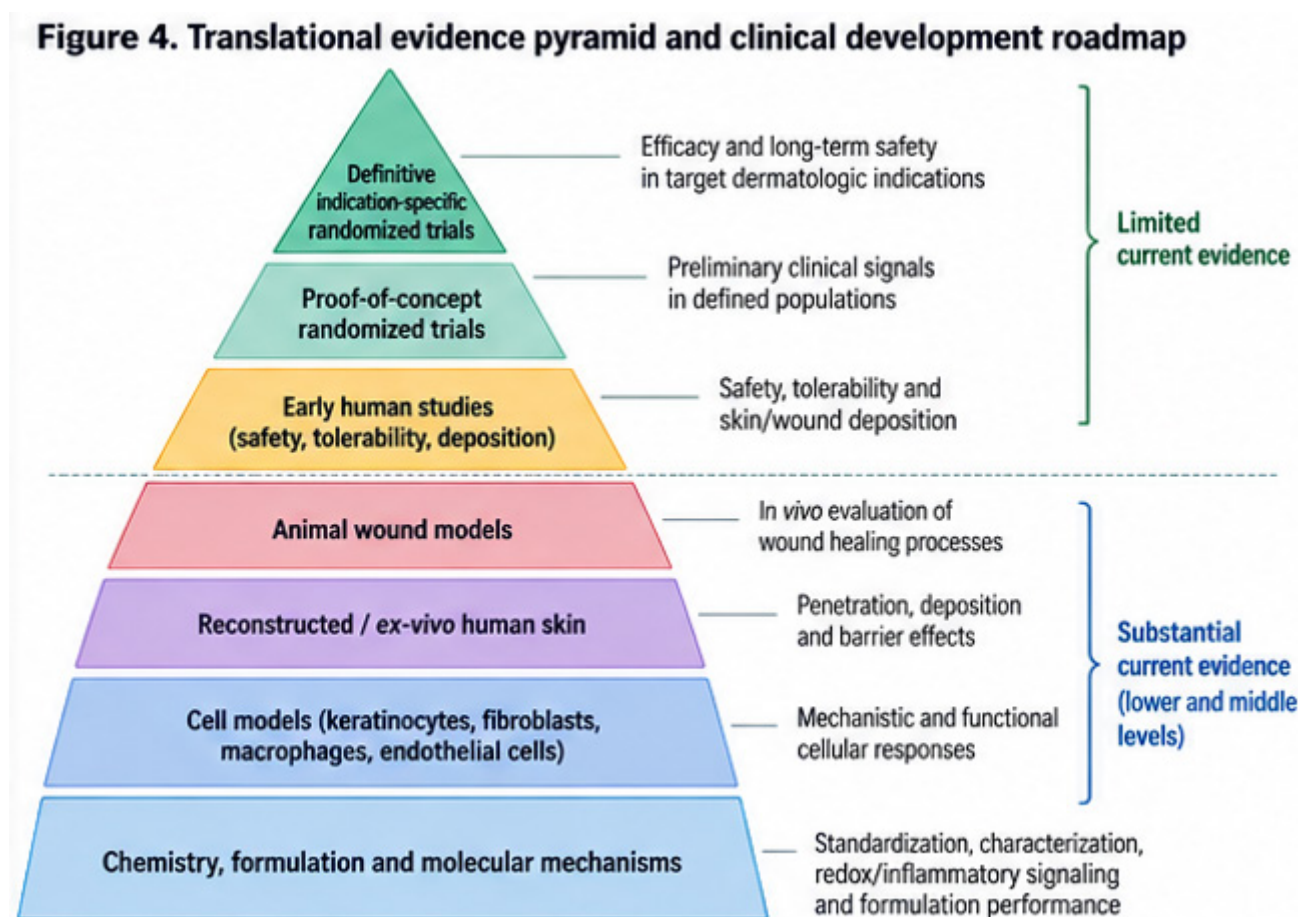


Figure 4: Translational Evidence Pyramid and Clinical-Development Roadmap. Current Evidence is Concentrated in Chemistry, Formulation, Cellular, Ex Vivo, and Animal Levels, with Limited High-Level Clinical Evidence.

Figure 4 highlights the central conclusion of this review: the field has enough mechanistic and formulation evidence to justify structured clinical development, but not enough randomized human evidence to justify broad therapeutic claims. Closing this gap requires movement upward through the evidence pyramid rather than continued accumulation of similar low-level antioxidant assays.

A Target Product Profile for Diabetic Wound Care

The diabetic-wound opportunity should be approached through a target product profile rather than by starting with a favored nanocarrier. The first question is what clinical problem the product is intended to solve: accelerating closure of neuropathic ulcers, improving wound-bed quality, supporting peri-wound barrier integrity, reducing inflammation, or functioning as an adjunct

after debridement. Each objective requires different formulation properties and different clinical endpoints.

A product intended primarily for peri-wound skin may prioritize barrier repair, hydration, low irritation, and ease of application. A product applied directly to an ulcer requires additional attention to microbiological quality, wound cytocompatibility, exudate compatibility, interactions with dressings, and the consequences of applying lipid-rich materials to an environment with altered microbial ecology. The same formulation should not be assumed optimal for both contexts.

A clinically credible program would use biomarkers as secondary mechanistic outcomes rather than the sole evidence of success. Later-stage trials should prioritize complete epithelial clo-

sure, time to healing, recurrence, infection, pain, adverse events, and patient-reported function. This approach would prevent a common translational failure in which statistically significant changes in ROS or cytokines are presented as equivalent to patient benefit.

A Staged Translational Development Roadmap

The first development stage should be raw-material characterization. Tocotrienol preparations should specify alpha-, beta-, gamma-, and delta-tocotrienol content where applicable, tocopherol content, total concentration, purification method, oxidation status, and relevant contaminants. Squalene should likewise be characterized for source, purity, oxidation products, and batch consistency. Standardization at this stage is essential because variation in natural raw materials can otherwise become a hidden source of biological variability.

The second stage should be formulation engineering. Candidate systems should be compared for particle or droplet size, polydispersity, zeta potential where relevant, encapsulation or solubilization capacity, rheology, spreadability, release kinetics, oxidative stability, and compatibility with packaging and dressings. The optimal platform may differ by indication; for example, an NLC gel may be suitable for prolonged residence, while a simpler nanoemulsion may offer manufacturing and scale-up advantages.

The third stage should be mechanistic validation using disease-relevant cell systems. Keratinocyte migration and differentiation should be evaluated alongside fibroblast viability and matrix behavior, macrophage inflammatory state, and endothelial responses. Co-culture and three-dimensional models are preferable once initial screening is complete because chronic wounds are multicellular environments in which paracrine interactions can determine whether an intervention is reparative or harmful.

The fourth stage should use human-relevant tissue models. Reconstructed epidermis can evaluate irritation and barrier markers, excised human skin can quantify deposition and penetration, and advanced wound equivalents can reproduce aspects of diabetic inflammation, matrix damage, or infection. These models can reduce overreliance on simple scratch assays and help define concentrations that are biologically active without being cytotoxic. The fifth stage should consist of early human studies focused on tolerability, sensitization, deposition, and systemic exposure where relevant. Studies on intact skin or peri-wound skin can establish initial safety before direct application to open ulcers. The design should anticipate that diseased skin and open wounds may absorb more active compound or excipient than healthy skin.

The sixth stage should involve proof-of-concept randomized trials in a clearly defined indication. For diabetic foot ulcers, the experimental formulation should be added to standardized wound care and compared with a matched vehicle plus the same standard care. Stratification by wound size, perfusion, infection status, glycemic control, and off-loading can reduce confound-

ing and make mechanistic findings interpretable.

The final stage should include adequately powered multicenter trials, manufacturing validation, and health-economic evaluation. Chronic wounds create substantial costs and patient burden, so a successful product must demonstrate not only biological activity but also reproducible safety, usability, manufacturing consistency, and clinically meaningful benefit. This broader innovation perspective is also why interdisciplinary JEL categories related to health, pharmaceuticals, and technological innovation can be relevant for an article positioned at the interface of biomedical science and product development.

Priority Research Gaps

The first major research gap is dose definition. Concentrations used in cell culture or animal wounds cannot be transferred directly to patients, and a dose that improves antioxidant markers may not optimize migration, matrix formation, or microbial defense. Dose-response experiments should therefore identify local concentration ranges that preserve keratinocyte and fibroblast viability while providing measurable biological benefit.

The second gap is attribution of effect. Multicomponent formulations are common, but they make causal interpretation difficult. Future work should use factorial comparisons that separate tocotrienol effects, squalene effects, carrier effects, and combination effects before synergy is claimed. The third gap is limited human exposure data. Skin deposition, wound-bed residence, metabolism, and systemic absorption of tocotrienols in nanoenabled topical formulations remain insufficiently characterized. Human skin models and early clinical pharmacokinetic studies are therefore essential bridges between formulation science and efficacy trials.

The fourth gap is indication selection. Acute superficial wounds, deep burns, atopic dermatitis, photoaging, pressure injuries, venous ulcers, and diabetic foot ulcers differ profoundly in pathophysiology and treatment requirements. A single formulation should not be assumed to address all these conditions simply because oxidative stress appears in each. The fifth gap is microbial compatibility. Chronic wounds often contain structured polymicrobial biofilms, and lipid-rich formulations could influence microbial ecology in ways that are not fully predictable. Antibiofilm and microbiome-aware testing should accompany chronic-wound development rather than being added only after efficacy studies.

The sixth gap is long-term stability. Both tocotrienols and squalene are oxidation-sensitive, so oxygen exposure, light, temperature, trace metals, emulsifier selection, and packaging may materially affect shelf life and biological performance. Stability-indicating assays should be connected to biological testing so that degradation is not mistaken for batch-to-batch variability.

The seventh gap concerns scar and remodeling outcomes. Faster early closure is desirable, but accelerated proliferation without appropriate remodeling could theoretically worsen fibrosis or

produce weak tissue. Long-term studies should therefore assess collagen architecture, mechanical properties, pigmentation, and scar quality in addition to early wound area reduction.

As summarized in Table 3, the principal translational gaps can be paired with concrete next-step studies spanning dose, effect attribution, safety, biofilm compatibility, stability, and clinically meaningful efficacy. This structure converts the narrative critique into a practical development agenda.

Table 3: Translational Evidence Gaps and Recommended Next-Step Studies

Gap	Why it matters	Recommended study
Dose and tissue exposure	Cell/animal concentrations may not represent safe human exposure.	Dose-response studies plus skin/wound-bed deposition and systemic-exposure measurements.
Effect attribution	Multicomponent formulations obscure the source of benefit.	Factorial vehicle, tocotrienol-only, squalene-only, and combination controls.
Human safety	Diseased skin and open wounds may increase exposure and irritation.	Early-phase tolerability, sensitization, and wound cytocompatibility studies.
Biofilm compatibility	Chronic wounds often contain polymicrobial biofilms.	Biofilm models plus compatibility testing with debridement, antiseptics, and antibiotics.
Long-term stability	Unsaturated lipids are oxidation-sensitive.	Stability-indicating chemistry linked to retained biological activity.
Clinically meaningful efficacy	Mechanistic endpoints do not equal healing.	Indication-specific randomized trials with closure, infection, recurrence, pain, and function outcomes.

Translational Interpretation: Cosmetic Claims Versus Medical Outcomes

One of the most important contributions of this review is the distinction between cosmetic, biophysical, mechanistic, and therapeutic outcomes. Increased hydration, smoother skin feel, reduced oxidative markers, greater penetration, or higher collagen expression can all be useful findings, but none alone establishes medical wound-healing efficacy. Claims should therefore be matched to the level of evidence and to the regulatory context in which the product is intended to be used.

For dermocosmetic products, endpoints such as hydration, transepidermal water loss, elasticity, irritation, and environmental protection may be appropriate. For inflammatory skin disease, validated severity scores, pruritus, flare frequency, barrier function, and rescue medication use become more relevant. For chronic wounds, complete closure, time to closure, infection, recurrence, pain, and function should dominate. Keeping these endpoints separate will make future palm-derived product development more rigorous and more credible.

This distinction also clarifies the role of nanotechnology. A nanoformulation is not inherently more therapeutic than a conventional formulation; its value depends on whether it solves a relevant delivery, stability, or usability problem. The strongest development strategy is therefore problem-driven rather than technology-driven: define the clinical need, identify the local pharmacological target, select the simplest formulation that achieves the required exposure and stability, and then demonstrate patient benefit.

Conclusion

Palm-derived tocotrienols and squalene form a scientifically plausible but incompletely validated platform for dermatologic and wound-healing applications. Tocotrienols possess the stron-

ger direct pharmacological evidence, particularly for modulation of oxidative stress, inflammatory signaling, keratinocyte barrier responses, and experimental tissue repair. Squalene provides complementary value through its physiological relationship with skin-surface lipids, emollient properties, redox chemistry, and suitability for lipid-based formulations.

Nanoenabled delivery offers a rational means of addressing important physicochemical limitations of these lipophilic compounds. Nanoemulsions, ethosomes, solid lipid nanoparticles, nanostructured lipid carriers, and nanoemulgels can protect actives, control release, increase local residence, and alter cutaneous deposition. These pharmaceutical advantages, however, do not by themselves establish therapeutic efficacy.

The most compelling medical opportunity is chronic and diabetic wound care, where oxidative stress, persistent inflammation, impaired cell migration, vascular dysfunction, and microbial persistence coexist. The same complexity that makes this indication attractive also requires unusually rigorous development. Standardized raw materials, mechanistically controlled formulations, human-relevant tissue models, safety studies, and indication-specific randomized trials are needed before clinical claims can be justified.

The field should therefore move away from broad statements that natural antioxidants promote healing and toward testable therapeutic hypotheses linked to clinically meaningful outcomes. A successful palm-derived tocotrienol-squalene platform would need to demonstrate not only mechanistic elegance and formulation sophistication, but also reproducible manufacturing quality, local safety, compatibility with standard care, and superior patient outcomes.

References

1. Almadani, Y. H., Vorstenbosch, J., Davison, P. G., Murphy, A. M. (2021). Wound healing: A comprehensive review. *Seminars in Plastic Surgery*, 35(3), 141-144. <https://doi.org/10.1055/s-0041-1731791>.
2. Dasari, N., Jiang, A., Skochdopole, A., Chung, J., Reece, E. M., Vorstenbosch, J., & Winocour, S. (2021). Updates in diabetic wound healing, inflammation, and scarring. *Seminars in Plastic Surgery*, 35(3), 153-158. <https://doi.org/10.1055/s-0041-1731460>.
3. Willenborg, S., Injarabian, L., Eming, S. A. (2022). Role of macrophages in wound healing. *Cold Spring Harbor Perspectives in Biology*, 14(12), Article a041216. <https://doi.org/10.1101/cshperspect.a041216>.
4. Comino-Sanz, I. M., Lopez-Franco, M. D., Castro, B., Pancorbo-Hidalgo, P. L. (2021). The role of antioxidants on wound healing: A review of the current evidence. *Journal of Clinical Medicine*, 10(16), Article 3558. <https://doi.org/10.3390/jcm10163558>.
5. Deng, L., Du, C., Song, P., Chen, T., Rui, S., Armstrong, D. G., & Deng, W. (2021). The role of oxidative stress and antioxidants in diabetic wound healing. *Oxidative Medicine and Cellular Longevity*, 2021, Article 8852759. <https://doi.org/10.1155/2021/8852759>.
6. Wang, G., Yang, F., Zhou, W., Xiao, N., Luo, M., & Tang, Z. (2023). The initiation of oxidative stress and therapeutic strategies in wound healing. *Biomedicine & Pharmacotherapy*, 157, Article 114004. <https://doi.org/10.1016/j.biopha.2022.114004>.
7. Papaccio, F., D'Arino, A., Caputo, S., Bellei, B. (2022). Focus on the contribution of oxidative stress in skin aging. *Antioxidants*, 11(6), Article 1121. <https://doi.org/10.3390/antiox11061121>.
8. Schilrreff, P., Alexiev, U. (2022). Chronic inflammation in non-healing skin wounds and promising natural bioactive compounds treatment. *International Journal of Molecular Sciences*, 23(9), Article 4928. <https://doi.org/10.3390/ijms23094928>.
9. Knoedler, S., Broichhausen, S., Guo, R., Dai, R., Knoedler, L., Kauke-Navarro, M., Diatta, F., Pomahac, B., Machens, H.-G., Jiang, D., & Rinkevich, Y. (2023). Fibroblasts—the cellular choreographers of wound healing. *Frontiers in Immunology*, 14, Article 1233800. <https://doi.org/10.3389/fimmu.2023.1233800>.
10. Roman, J. (2023). Fibroblasts—warriors at the intersection of wound healing and disrepair. *Biomolecules*, 13(6), Article 945. <https://doi.org/10.3390/biom13060945>.
11. Durand, B. A. R. N., Pouget, C., Magnan, C., Molle, V., Lavigne, J.-P., & Dunyach-Remy, C. (2022). Bacterial interactions in the context of chronic wound biofilm: A review. *Microorganisms*, 10(8), Article 1500. <https://doi.org/10.3390/microorganisms10081500>.
12. Thaarup, I. C., Iversen, A. K. S., Lichtenberg, M., Bjarnsholt, T., Jakobsen, T. H. (2022). Biofilm survival strategies in chronic wounds. *Microorganisms*, 10(4), Article 775. <https://doi.org/10.3390/microorganisms10040775>.
13. Uberoi, A., McCready-Vangi, A., Grice, E. A. (2024). The wound microbiota: Microbial mechanisms of impaired wound healing and infection. *Nature Reviews Microbiology*, 22, 507-521. <https://doi.org/10.1038/s41579-024-01035-z>.
14. Trinh, X.-T., Long, N.-V., Anh, L. T. V., Nga, P. T., Giang, N. N., Chien, P. N., Nam, S.-Y., & Heo, C.-Y. (2022). A comprehensive review of natural compounds for wound healing: Targeting bioactivity perspective. *International Journal of Molecular Sciences*, 23(17), Article 9573. <https://doi.org/10.3390/ijms23179573>.
15. Nair, A. B., Gorain, B., Pandey, M., Jacob, S., Shinu, P., Aldhubiab, B., Almuqbil, R. M., Elsewedy, H. S., & Morsy, M. A. (2022). Tocotrienol in the treatment of topical wounds: Recent updates. *Pharmaceutics*, 14(11), Article 2479. <https://doi.org/10.3390/pharmaceutics14112479>.
16. Lin, Y., Chen, Z., Liu, Y., Wang, J., Lv, W., & Peng, R. (2022). Recent advances in nano-formulations for skin wound repair applications. *Drug Design, Development and Therapy*, 16, 2707-2728. <https://doi.org/10.2147/DDDT.S375541>.
17. Szewczyk, K., Chojnacka, A., Gornicka, M. (2021). Tocopherols and tocotrienols—bioactive dietary compounds; what is certain, what is doubt? *International Journal of Molecular Sciences*, 22(12), Article 6222. <https://doi.org/10.3390/ijms22126222>.
18. Harun, M. S., Wong, T. W., Fong, C. W. (2021). Advancing skin delivery of alpha-tocopherol and gamma-tocotrienol for dermatitis treatment via nanotechnology and microwave technology. *International Journal of Pharmaceutics*, 593, Article 120099. <https://doi.org/10.1016/j.ijpharm.2020.120099>.
19. Chong, W. T., Tan, C. P., Cheah, Y. K., Lai, O. M. (2022). In-vitro and in-vivo evaluations of tocotrienol-rich nanoemulsified system on skin wound healing. *PLOS ONE*, 17, Article e0267381. <https://doi.org/10.1371/journal.pone.0267381>.
20. Neo, J. R. E., Teo, Z. N., Yeo, J. S. E., Ng, C. K. S., Teo, C. W. L., Ung, Y. W., & Yap, W. N. (2022). Tocotrienols improve urban particulate matter-induced skin damages by regulating skin barrier function and ROS/MAPK signaling pathway in keratinocytes. *Atmospheric Pollution Research*, 13(10), Article 101564. <https://doi.org/10.1016/j.apr.2022.101564>.
21. Micera, M., Botto, A., Geddo, F., Antoniotti, S., Berteza, C. M., Levi, R., Gallo, M. P., & Querio, G. (2020). Squalene: More than a step toward sterols. *Antioxidants*, 9(8), Article 688. <https://doi.org/10.3390/antiox9080688>.
22. Assi, A., Michael-Jubeli, R., Duplan, H., Baillet-Guffroy, A., Jacques-Jamin, C., & Tfayli, A. (2023). Effects of solar radiations on stratum corneum hydration: Part I, protective role of skin surface lipids. *Journal of Biophotonics*, 16(8), Article e202300055. <https://doi.org/10.1002/jbio.202300055>.
23. Mijaljica, D., Townley, J. P., Spada, F., Harrison, I. P. (2024). The heterogeneity and complexity of skin surface lipids in human skin health and disease. *Progress in Lipid Research*, 93, Article 101264. <https://doi.org/10.1016/j.plipres.2023.101264>.

24. Schild, J., Kalvodova, A., Zbytovska, J., Farwick, M., Pyko, C. (2024). The role of ceramides in skin barrier function and the importance of their correct formulation for skincare applications. *International Journal of Cosmetic Science*, 46(4), 526-543. <https://doi.org/10.1111/ics.12972>.
25. Ferreira, K. C. B., Valle, A. B. C. S., Paes, C. Q., Tavares, G. D., Pittella, F. (2021). Nanostructured lipid carriers for the formulation of topical anti-inflammatory nanomedicines based on natural substances. *Pharmaceutics*, 13(9), Article 1454. <https://doi.org/10.3390/pharmaceutics13091454>.
26. Akombaetwa, N., Ilangala, A. B., Thom, L., Memvanga, P. B., Witika, B. A., & Buya, A. B. (2023). Current advances in lipid nanosystems intended for topical and transdermal drug delivery applications. *Pharmaceutics*, 15(2), Article 656. <https://doi.org/10.3390/pharmaceutics15020656>.
27. Motsoene, F., Abrahamse, H., Kumar, S. S. D. (2023). Multifunctional lipid-based nanoparticles for wound healing and antibacterial applications: A review. *Advances in Colloid and Interface Science*, 321, Article 103002. <https://doi.org/10.1016/j.cis.2023.103002>.
28. Safta, D. A., Bogdan, C., Moldovan, M.-L. (2024). SLNs and NLCs for skin applications: Enhancing the bioavailability of natural bioactives. *Pharmaceutics*, 16(10), Article 1270. <https://doi.org/10.3390/pharmaceutics16101270>.
29. Deng, H., Li, B., Shen, Q., Zhang, C., Kuang, L., Chen, R., Wang, S., Ma, Z., & Li, G. (2023). Mechanisms of diabetic foot ulceration: A review. *Journal of Diabetes*, 15(4), 299-312. <https://doi.org/10.1111/1753-0407.13372>.
30. Kandregula, B., Narisepalli, S., Chitkara, D. (2022). Exploration of lipid-based nanocarriers as drug delivery systems in diabetic foot ulcer. *Molecular Pharmaceutics*, 19(7), 1977-1998. <https://doi.org/10.1021/acs.molpharmaceut.1c00970>.
31. Yeo, E., Yew Chieng, C. J., Choudhury, H., Pandey, M., Gorain, B. (2021). Tocotrienols-rich naringenin nanoemulgel for the management of diabetic wound: Fabrication, characterization and comparative in vitro evaluations. *Current Research in Pharmacology and Drug Discovery*, 2, Article 100019. <https://doi.org/10.1016/j.crphar.2021.100019>.
32. Yoshida, T., Beck, L. A., De Benedetto, A. (2022). Skin barrier defects in atopic dermatitis: From old idea to new opportunity. *Allergology International*, 71(1), 3-13. <https://doi.org/10.1016/j.alit.2021.11.006>.
33. Sagrafena, I., Morin, M., Paraskevopoulos, G., Nilsson, E. J., Hrdinova, I., Kovacik, A., Bjorklund, S., & Vavrova, K. (2024). Structure and function of skin barrier lipids: Effects of hydration and natural moisturizers in vitro. *Biophysical Journal*, 123(22), 3951-3963. <https://doi.org/10.1016/j.bpj.2024.10.006>.
34. Beck, L. A., Cork, M. J., Amagai, M., De Benedetto, A., Kabashima, K., Hamilton, J. D., & Rossi, A. B. (2022). Type 2 inflammation contributes to skin barrier dysfunction in atopic dermatitis. *JID Innovations*, 2(5), Article 100131. <https://doi.org/10.1016/j.xjidi.2022.100131>.
35. Elias, P. M. (2022). Optimizing emollient therapy for skin barrier repair in atopic dermatitis. *Annals of Allergy, Asthma & Immunology*, 128(5), 505-511. <https://doi.org/10.1016/j.anai.2022.01.012>.
36. Berdyshev, E. (2024). Skin lipid barrier: Structure, function and metabolism. *Allergy, Asthma & Immunology Research*, 16(5), 445-461. <https://doi.org/10.4168/aaair.2024.16.5.445>.
37. Siqueira, R. A. G. B., Hradkova, I., Leite-Silva, V. R., Andreo-Filho, N., Lopes, P. S. (2025). Skin lipids and their influence on skin microbiome and skin care. *ACS Omega*, 10(27), 28534-28546. <https://doi.org/10.1021/acsomega.4c11687>.
38. Berkey, C., Oguchi, N., Miyazawa, K., Dauskardt, R. H. (2020). Emollient structure and chemical functionality effects on the biomechanical function of human stratum corneum. *International Journal of Cosmetic Science*, 42(6), 605-614. <https://doi.org/10.1111/ics.12656>.
39. Spampinato, S. F., Caruso, G. I., De Pasquale, R., Sortino, M. A., Merlo, S. (2020). The treatment of impaired wound healing in diabetes: Looking among old drugs. *Pharmaceutics*, 13(4), Article 60. <https://doi.org/10.3390/ph13040060>.
40. Kamal, R., Awasthi, A., Pundir, M., Thakur, S. (2024). Healing the diabetic wound: Unlocking the secrets of genes and pathways. *European Journal of Pharmacology*, 975, Article 176645. <https://doi.org/10.1016/j.ejphar.2024.176645>.
41. Yang, Y., Zhong, S., Meng, F. Cui, X. (2024) 'Multi-functional hydrogels to promote diabetic wound healing: A review', *Chemical Engineering Journal*, 497, 154855. <https://doi.org/10.1016/j.cej.2024.154855>.
42. Guo, H.F., Hamid, R.A., Ali, R.M., Chang, S.K., Rahman, M.H., Zainal, Z. & Khaza'ai, H. (2020) 'Healing properties of epidermal growth factor and tocotrienol-rich fraction in deep partial-thickness experimental burn wounds', *Antioxidants*, 9(2), 130. <https://doi.org/10.3390/antiox9020130>.
43. Guo, H.F., Mohd Ali, R., Abd Hamid, R., Chang, S.K., Rahman, M.H., Zainal, Z. & Khaza'ai, H. (2022) 'Epidermal growth factor and tocotrienol-rich fraction cream formulation accelerates burn healing process based on its gene expression pattern in deep partial-thickness burn wound model', *International Journal of Lower Extremity Wounds*, 21(4), pp. 544-554. <https://doi.org/10.1177/1534734620971066>.
44. Nair, R.S., Billa, N., Leong, C.O. Morris, A.P. (2021) 'An evaluation of tocotrienol ethosomes for transdermal delivery using Strat-M membrane and excised human skin', *Pharmaceutical Development and Technology*, 26(2), pp. 243-251. <https://doi.org/10.1080/10837450.2020.1860087>.
45. Teo, C.W.L., Tay, S.H.Y., Tey, H.L., Ung, Y.W. Yap, W.N. (2021) 'Vitamin E in atopic dermatitis: From preclinical to clinical studies', *Dermatology*, 237, pp. 553-564. <https://doi.org/10.1159/000510653>.
46. Shanmugarajan, T.S., Kalai Selvan, N. Uppuluri, V.N.V.A. (2021) 'Development and characterization of squalene-loaded topical agar-based emulgel scaffold: Wound healing potential in full-thickness burn model', *International Journal of Lower Extremity Wounds*, 20(4), pp. 364-373. <https://doi.org/10.1177/1534734620921629>.
47. Gref, R., Delomenie, C., Maksimenko, A., Gouadon, E., Percoco, G., Lati, E., Desmaele, D., Zouhiri, F. & Couvreur, P. (2020) 'Vitamin C-squalene bioconjugate promotes epidermal thickening and collagen production in human

- skin', *Scientific Reports*, 10, 16883. <https://doi.org/10.1038/s41598-020-72704-1>.
48. Morgan, N.R., Magalingam, K.B., Radhakrishnan, A.K., Arumugam, M., Jamil, A. & Bhuvanendran, S. (2024) 'Explicating the multifunctional roles of tocotrienol and squalene in promoting skin health', *Skin Health and Disease*, 4(5), e448. <https://doi.org/10.1002/ski2.448>.
 49. Shamsuddin, N.A.M. Zulfakar, M.H. (2023) 'Nanostructured lipid carriers for the delivery of natural bioactive compounds', *Current Drug Delivery*, 20(2), pp. 127-143. <https://doi.org/10.2174/1567201819666220324094234>.
 50. Wathoni, N., Suhandi, C., Elamin, K.M., Lesmana, R., Hasan, N., Mohammed, A.F.A., El-Rayyes, A. & Wilar, G. (2024) 'Advancements and challenges of nanostructured lipid carriers for wound healing applications', *International Journal of Nanomedicine*, 19, pp. 8091-8113. <https://doi.org/10.2147/IJN.S478964>.
 51. Alquraisy, A., Ramadhani, K., Mohammed, A. F. A., Wilar, G., Osman, W., Elamin, K. M., & Wathoni, N. (2026). Nanostructured lipid carrier-gels for wound healing: A narrative review of formulation strategies, mechanisms, and translational potential. *Nanotechnology, Science and Applications*, 19, Article 585159. <https://doi.org/10.2147/NSA.S585159>.
 52. Jacob, S., Nair, A. B., Shah, J., Sreeharsha, N., Gupta, S., & Shinu, P. (2021). Emerging role of hydrogels in drug delivery systems, tissue engineering and wound management. *Pharmaceutics*, 13(3), Article 357. <https://doi.org/10.3390/pharmaceutics13030357>.
 53. Jeckson, T. A., Neo, Y. P., Sisinthy, S. P., Gorain, B. (2021). Delivery of therapeutics from layer-by-layer electrospun nanofiber matrix for wound healing: An update. *Journal of Pharmaceutical Sciences*, 110(2), 635-653. <https://doi.org/10.1016/j.xphs.2020.10.003>.
 54. Hoff, J., Karl, B., Gerstmeier, J., Beekmann, U., Schmolz, L., Borner, F., Kralisch, D., Bauer, M., Werz, O., & Fischer, D. (2021). Controlled release of the alpha-tocopherol-derived metabolite alpha-13'-carboxychromanol from bacterial nanocellulose wound cover improves wound healing. *Nanomaterials*, 11(8), Article 1939. <https://doi.org/10.3390/nano11081939>.
 55. Farasati Far, B., Naimi-Jamal, M. R., Sedaghat, M., Hoseini, A., Mohammadi, N., & Bodaghi, M. (2023). Combinational system of lipid-based nanocarriers and biodegradable polymers for wound healing: An updated review. *Journal of Functional Biomaterials*, 14(2), Article 115. <https://doi.org/10.3390/jfb14020115>.
 56. Mousavi-Simakani, S. M., Azadi, A., Tanideh, N., Omidifar, N., Ghasemiyeh, P., & Mohammadi-Samani, S. (2023). Simvastatin-loaded nanostructured lipid carriers as topical drug delivery system for wound healing purposes: Preparation, characterization, and in vivo histopathological studies. *Advanced Pharmaceutical Bulletin*, 13(4), 761-771. <https://doi.org/10.34172/apb.2023.083>.
 57. Akrawi, S. H., Gorain, B., Nair, A. B., Choudhury, H., Pandey, M., Shah, J. N., & Venugopala, K. N. (2020). Development and optimization of naringenin-loaded chitosan-coated nanoemulsion for topical therapy in wound healing. *Pharmaceutics*, 12(9), Article 893. <https://doi.org/10.3390/pharmaceutics12090893>.

Copyright: ©2026 Loso Judijanto. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.