Literature Review *Open Access*

Journal of Innovative Clinical Trials and Case Reports

ISSN: 3068 - 1936

DOI: doi.org/10.63721/26JCTC0163

When Biological Promise Meets a Neutral Trial: Palm-Derived Tocotrienols, Dermal Exposure, and Postoperative Scar Prevention—A Critical Review

Loso Judijanto

IPOSS Jakarta, Indonesia

Citation: *Loso Judijanto (2026) When Biological Promise Meets a Neutral Trial: Palm-Derived Tocotrienols, Dermal Exposure, and Postoperative Scar Prevention—A Critical Review. J. of Inn Clin Trail Case Reports 2(5), 1-17. WMJ/JCTC-163*

Abstract

Background: *Palm-derived tocotrienols have plausible antioxidant and anti-inflammatory activities, yet an early randomised trial found no statistically significant scar-prevention benefit for a 5% topical formulation. Objective: To explain the apparent translational discordance and establish a clinically testable research agenda for postoperative incisional scars.*

Methods: *A critical qualitative literature review integrated purposively selected journal studies from 2020–2026 with the landmark 2011 trial. Evidence was organised thematically across scar biology, formulation science, comparative treatments, outcome instruments and trial design.*

Results: *The neutral clinical signal remains the most directly relevant efficacy evidence. Laboratory wound closure, animal regeneration, topical delivery feasibility and mechanistic fibrosis research are informative but indirect. Unmeasured dermal exposure, molecular target engagement, timing after epithelialisation, wound tension and scar-risk heterogeneity hinder causal interpretation. Modern scar measurement increasingly combines patient-reported measures with objective assessments; comparator studies illustrate both possibilities and methodological limits.*

Discussion: *A staged formulation–exposure–target engagement–clinical outcome model can prevent promising mechanisms from being mistaken for proven patient benefit.*

Conclusions: *Routine preventive use of tocotrienol cream cannot be justified on current evidence. Before another definitive trial, botanical identity, formulation stability, tissue exposure, early human safety and patient-important endpoints should be prospectively validated.*

***Corresponding author**: Loso Judijanto, IPOSS Jakarta, Indonesia.

Submitted: 16.10.2026 **Accepted**: 24.10.2026 **Published**: 30.10.2026

Keywords: Palm Oil, Tocotrienols, Postoperative Scars, Hypertrophic Scarring, Qualitative Literature Review, Topical Bioavailability, Scar Prevention, Fibroblast Mechanotransduction, POSAS 3.0, Translational Clinical Trials

JEL Classification: I10; I12; I18; O31; Q56.

Introduction

Clinical Problem, Outcome Distinctions and Relevance

A postoperative scar is not simply an aesthetic mark. It can change cutaneous sensation, restrict movement where tension is substantial, cause itch or tenderness, influence clothing choices and alter the way a patient perceives the outcome of an otherwise successful operation. Normal scar maturation is expected after dermal injury, yet excessive connective-tissue deposition can produce elevated, symptomatic hypertrophic scars. Keloids differ in their tendency to extend beyond the original wound margin and their biological behaviour, so evidence concerning keloids must not be casually transferred to prevention of linear incisional hypertrophic scars. These distinctions matter when defining a realistic intervention target and choosing a study population [1-3].

Surgical scars vary markedly in depth, orientation, anatomical position, local tension, closure technique, infection exposure and individual tissue response. An incision over a mobile joint is not a biological duplicate of one on the lower abdomen; a chest incision is not interchangeable with a small dermatological excision. Skin pigmentation can influence the visibility and personal impact of erythema or postinflammatory pigment change, while the external appearance of a scar may be weakly aligned with discomfort. Research needs to capture both the trajectory of physical maturation and the way patients value its consequences, rather than treating every scar as a uniform structural endpoint [1,3,4].

Wound closure, scar prevention and revision of an established scar represent three different therapeutic projects. Faster keratinocyte migration could shorten the interval to epidermal closure without preventing excessive collagen deposition several months later. A substance that improves a mature scar's pliability might not interrupt the processes responsible for forming that scar. Conversely, temporary suppression of inflammation could benefit one stage while impairing another stage of normal repair. This review therefore restricts its central effectiveness question to topical prevention of undesirable postoperative scarring after appropriate wound closure, while drawing mechanistic insights from adjacent but non-equivalent models [2,5,6].

Palm Tocotrienols and the Unresolved Clinical Contradiction

Palm oil contains a mixture of vitamin E constituents, including tocopherols and tocotrienols. Tocotrienol isoforms possess an unsaturated isoprenoid side chain, a feature that influences membrane interactions and formulation behaviour. Antioxidant activity and modulation of inflammatory signalling provide a plausible reason to investigate these compounds during repair. Nevertheless, biological plausibility is an entry condition for clinical testing, not evidence of clinical effectiveness. A preparation applied to the skin must remain chemically stable, reach an appropriate tissue compartment in sufficient amount and influence a pathway that actually determines an outcome patients notice [7-9].

The pivotal direct clinical test remains an earlier randomised, double-blinded study of topical 5% tocotrienol cream for prevention of hypertrophic scars. The trial randomised 122 patients, and 85 completed the assessments reported in the publication. No statistically significant differences emerged between treatment and placebo for the scar appearance and vascularity measures assessed. The responsible interpretation is narrow but important: the tested topical strategy did not demonstrate superior clinical scar outcomes in its analysed participants. This does not establish that every tocotrienol isoform, concentration, vehicle or treatment schedule is ineffective, nor does it provide a licence to ignore the negative result in favour of attractive experimental mechanisms [10,11].

Since that study, cell-based work, non-human wound models and new topical carrier systems have expanded the landscape of possible tocotrienol interventions. A 2022 nanoemulsion study reported relevant activity in keratinocyte assays and an animal regeneration model,

while other experimental investigations considered tocotrienol-rich preparations alongside growth factors in burns. These results generate hypotheses about delivery or tissue responses. They do not answer whether an incision treated after surgery is less likely to develop symptomatic fibrosis, and combining an active with another agent prevents attribution of effects to tocotrienol alone. This difference in evidential distance is the central problem addressed here [7,12,13].

Aim and Argumentative Contribution

The objective is to reconcile the neutral randomised trial with subsequent biological and technological advances without selecting only favorable evidence. Six guiding questions concern the meaning of the clinical signal, distinctions among scar phenotypes, local exposure, effect modification, relevant clinical comparators and the evidence required before another trial. Rather than declaring topical tocotrienol an effective or ineffective class of treatments, this review asks what additional observations would discriminate between biologically different explanations for the existing outcome. The contribution is a practical, falsifiable framework joining reproducible formulation quality to local pharmacology and longitudinal patient experience [7,10,14].

Literature Review

Scar Formation as a Temporally Organised Process

Repair proceeds through overlapping episodes of haemostasis, immune-cell recruitment, proliferative matrix formation, epithelialisation and long-term remodelling. These are not independent stages triggered by a single switch. Fibroblasts respond to chemokines, extracellular-matrix architecture, mechanical load and the cellular neighbourhood; immune cells themselves can support host defence, debris clearance and subsequent resolution. The objective of scar prevention cannot be generalized as maximal suppression of all inflammation or all collagen production. Excessive inhibition could plausibly compromise tensile strength and wound integrity, particularly if applied before secure epithelial closure [1,2,15].

Reactive oxygen species illustrate the same contextual problem. Excess oxidative stress may contribute to persistent inflammation and abnormal matrix deposition, but physiological redox signals support antimicrobial defence, cell migration and repair coordination. Antioxidants therefore require an appropriate concentration, location and exposure window. Demonstrating radical-scavenging activity in a chemical assay is insufficient to establish that the net response of a human postsurgical dermis will be favorable. The relevant question is whether a defined preparation produces a measurable and beneficial modification of the redox environment in the scar-forming compartment without disturbing essential repair functions [6,8,13].

Transforming growth factor-beta signalling, collagen organisation, matrix turnover and myofibroblast persistence all contribute to hypertrophic scar development. Yet even these labels conceal diverse temporal activities and cell-specific effects. A therapeutic concept might aim to temper excessive fibrosis rather than disable the signalling axis entirely. Contemporary molecular accounts of tissue repair underscore interactions among epidermis, vascular cells, immune cells and multiple fibroblast populations. This complex ecology makes a single-biomarker explanation of clinical scar outcomes unlikely and challenges simplistic extrapolation from cultured fibroblasts alone [2,15,16].

Fibroblast Heterogeneity and Mechanics

Single-cell investigations increasingly portray fibroblasts not as one homogeneous target but as transcriptionally and functionally distinct populations. Research in keloid and fibrotic skin reports expansion or reorganisation of mesenchymal, inflammatory and matrix-producing fibroblast states. Such findings help identify candidate pathways and biomarkers but do not establish that an isolated dermal incision will respond similarly. Disease stage, anatomical compartment and tissue type influence the cellular composition, while single-cell RNA profiles measure transcriptional states rather than proving that a compound engages those states in vivo [17-20].

Biomechanical forces shape dermal repair and may help explain why certain sites scar disproportionately. Mechanotransduction studies link tissue tension to intracellular pathways such as YAP and focal adhesion kinase, while experimental models demonstrate that altering mechanical signals can reduce fibrotic responses. Particularly influential laboratory work concerning Engrailed-1-associated fibroblast activation

has shifted attention toward the conditions under which regenerative rather than fibrotic repair may occur. However, these interventions were not trials of topical palm tocotrienols, and some evidence derives from animal systems or engineered tissue conditions. The conceptual relevance is mechanistic, not confirmatory [21-24].

Further experimental work on material-based control of mechanical environments, spatial delivery systems and Engrailed-1 modulation reinforces the possibility of changing scar trajectories. The novelty of these studies should not conceal differences in species, wound depth, devices and treatment routes. Core-shell microneedles, mechanically engineered biomaterials and genetic pathway modulation are interventions with different exposure mechanisms from a cream applied to a healed incision. They may reveal testable biological targets or inspire comparators, but claims of equivalence are unjustified. A future tocotrienol trial must establish its own target engagement rather than borrowing the efficacy narrative of another therapeutic technology [25-27].

Chemical Identity and the Topical Formulation Problem

The expression palm-derived vitamin E can mask substantial variation in chemical composition. Alpha-, gamma- and delta-tocotrienols should be distinguished from one another and from tocopherols, and each tested formulation should identify its relative proportions rather than reporting only a generic vitamin E percentage. Botanical source, extraction process, oxidative handling and storage can further influence reproducibility. Importantly, the 5% figure in an applied cream reports formulation concentration, not drug mass deposited in viable dermis. Without composition-specific assay and stability testing, even nominally identical batches may deliver different local chemical environments [7,28].

The intact stratum corneum provides a highly organised barrier to passive movement of compounds. Tocotrienols are lipophilic, and their partitioning into surface lipid domains cannot automatically be equated with penetration to fibroblasts deeper in the dermis. The barrier may behave differently in recently epithelialised skin, inflamed tissue and a stable mature scar. Vehicle viscosity, occlusion, solvent systems and local surface hydration also modify drug release and partitioning. Therefore, the critical pharmacological denominator is exposure at the relevant wound interface or viable dermal compartment over time, rather than the concentration printed on a cream label [7,9,29].

Novel carriers may address several obstacles, but each technology introduces new parameters to control. Nanoemulsions and vesicular formulations can modify droplet size, distribution, dissolution, adhesion, release and stability, sometimes improving measured deposition in laboratory models. Reviews of nanodelivery systems describe strategies for skin disorders, and recent advances in topical nanoemulsions illustrate the formulation possibilities. Yet a higher amount appearing in an ex-vivo receptor fluid, a cell culture or an animal wound need not predict improved scar appearance in a patient. Carrier irritation, preservative effects and systemic absorption remain relevant to comparative safety [12,29-31].

A defensible clinical-development program therefore requires analytical measurements at multiple levels: confirmed isoform composition before packaging, degradation across expected storage conditions, uniformity of content, application-dose reproducibility, and ex-vivo or otherwise ethically supported evidence of dermal deposition. If a nanoemulsion increases release in a laboratory assay, the interpretation should be that an exposure-related assumption became more plausible, not that scar prevention was proven. Clinical pharmacology must ultimately bridge these measurement systems, with appropriate attention to tolerability and potentially altered uptake through healing tissue [7,9,28].

Clinical Interventions and Outcome Instruments as Comparators

Silicone gels and sheets are commonly discussed as scar management measures and provide the most relevant practical comparison for a new topical preventive product. A meta-analysis of fluid silicone gels reports outcomes that are generally favourable, although included studies have methodological limitations and treatment settings differ. Separate clinical studies include patients with deep hand burns or paediatric burns, where scar biology and co-treatment may not resemble uncomplicated elective surgery. These studies help define realistic standard care, tolerability, feasibility and comparison conditions; they cannot confer their

measured benefits on tocotrienols [14,32-36].

The evidence for pressure garments provides an instructive example of persistent uncertainty despite longstanding use. A contemporary Cochrane review found that confidence in preventing hypertrophic scarring after burns remains limited. Similarly, injections, toxin-based approaches and lasers show context-specific clinical results but differ in cost, pain, treatment setting and potential adverse effects. The emerging small-interfering-RNA microneedle evidence also highlights that promising innovation must be assessed in direct clinical comparisons with existing management. These modalities broaden the menu of candidate comparators while reinforcing the need to avoid transferring efficacy claims across intervention classes [37-41].

Newer injection-based approaches and trials of laser therapy provide lessons in selecting realistic endpoints. A study of botulinum toxin after mastectomy in transgender men is informative regarding surgical-scarring prevention but uses a population and anatomical setting that may not generalize to all patients. Reports concerning fractional carbon-dioxide laser, comparative laser effectiveness and triamcinolone microneedle delivery primarily address particular scars or treatment contexts. Their relative invasiveness, operator dependence and time of application should inform feasibility rather than suggest a simple hierarchy of efficacy against tocotrienols, for which direct head-to-head evidence is not established [42-47].

Patient and observer assessments capture complementary dimensions of scar quality. POSAS 3.0 was developed with qualitative patient input to improve relevance and interpretability, while SCAR-Q offers a patient-reported assessment with psychometric development across scar types. Objective measurements of pigmentation, vascularity, thickness, flexibility or perfusion can add precision, but may not correlate perfectly with symptoms or satisfaction. Device reliability, anatomical positioning and repeatability need prespecification. An informative trial therefore requires a coherent hierarchy of patient and objective outcomes rather than adding many loosely related measurements after the results are known [4,48-51].

Method

Critical Qualitative Literature Review Design

This study adopts a critical qualitative literature review, not a systematic literature review, scoping review or meta-analysis. Its unit of analysis is the explanatory proposition connecting topical palm tocotrienol exposure to postoperative scar outcomes. Interpretative synthesis examines why evidence with different methodological structures appears to conflict or answer different questions. An abductive approach moves iteratively between the neutral randomised trial and biological, formulation and measurement explanations, while requiring each proposed explanation to be expressed as a hypothesis that could in principle be disproved. No numerical pooled treatment effect is estimated, and no exhaustive search or PRISMA-style flow is claimed [2,7,10].

Journal literature published from January 2020 through 15 October 2026 provides the primary contemporary corpus, supplemented by the seminal randomised 2011 tocotrienol trial because it remains indispensable direct human evidence. Sources were assembled purposively across clinical scar prevention, skin biology, pharmacology, wound repair, advanced formulations and validated measurement. Search concepts comprised tocotrienol, tocotrienol-rich fraction, palm vitamin E, surgical scar, hypertrophic scar, keloid, wound repair, nanoemulsion, cutaneous penetration, silicone, mechanotransduction, POSAS and SCAR-Q. Relevant references were traced from article bibliographies and forward citation links where accessible [1,7,10,52].

The purpose of purposive inclusion was to capture methodological contrast rather than to infer prevalence from a complete census of studies. Direct topical intervention studies in people were accorded the highest relevance for postoperative efficacy. Evidence from burns, keloids, other topical agents and patient-reported instruments provided context, while cell and animal experiments informed plausible biological targets. A study was not treated as direct proof when its route, population, outcome, formulation or comparator differed materially from the proposed intervention. This explicit boundary aims to reduce a common interpretative error in translational reviews: replacing absent clinical evidence with abundant but distant mechanistic evidence [1,12-14].

Appraisal, Coding and Synthesis

Evidence was appraised qualitatively across study design, directness, participant selection, intervention description, outcome validity, duration of follow-up, uncertainty and the possibility of missing data or confounding. Random allocation reduces some forms of bias but does not repair an inadequately characterised product or unmeasured drug deposition. For uncontrolled or laboratory studies, plausible confounding and non-equivalence to an incision were treated as central limitations. The present paper does not assign numerical quality scores or imply that a narrative synthesis can quantify comparative certainty with the precision of a formal meta-analysis [10,11,14].

Contemporary reporting standards provide useful lenses for appraising the transparency of existing trials, without turning this qualitative review into a systematic quality-scoring exercise. CONSORT 2025 highlights participant flow, missing outcomes, intervention description and prespecified analyses, whereas CONSORT-Surrogate warns against presenting a biomarker as a substitute for patient-important benefit without adequate validation [53,54].

Thematic categories were specified around five causal transitions: product identity to formulation, formulation to local exposure, exposure to biological target response, tissue response to scar phenotype, and scar phenotype to patient-valued outcome. Additional cross-cutting codes captured application timing, tissue tension, phototype, risk of adverse reactions, cointerventions and feasibility. Evidence was compared within each category, then assembled across categories into alternative explanations for trial results. For every inference, the analysis asks whether the cited study measures the proposed transition directly, indirectly or not at all [5,9,23,48].

This approach offers a transparent conceptual account but has limitations. Purposive sampling may miss eligible articles, publication practices can privilege positive laboratory findings, and the rapidly evolving formulation literature may have inconsistent analytical standards. The review does not invent an evidence-screening count, imply that all sources possess equivalent rigor, or claim that a theory-derived pathway predicts human efficacy. Conclusions concern the interpretation of currently cited evidence and the design of future tests; they should be updated when additional blinded clinical results or well-characterised dermal-exposure studies become available [2,7,11].

Table 1 provides an evidential hierarchy for reading the results that follow. The central distinction is between studies that directly assess prevention of postoperative scars in humans and adjacent research that informs mechanisms, delivery feasibility, standards of care or measurement. The latter evidence is valuable for designing subsequent investigations but cannot be promoted into a statement of tocotrienol efficacy [7,10,14].

Table 1: Evidential directness and permissible conclusions

Evidence category	What it can establish	What it cannot establish
Human randomized scar-prevention trial	Clinical performance of the tested 5% regimen	Effectiveness of untested formulations or doses
Preclinical tocotrienol formulations	Potential release, deposition and tissue response	Prevention of human incision scars
Fibroblast/mechanics studies	Biological targets or experimental repair pathways	Topical tocotrienol target engagement
Silicone, laser and injection trials	Comparator pathways, feasibility and endpoints	Transfer of comparative efficacy to tocotrienol
POSAS, SCAR-Q and objective devices	Defined measurement constructs and reliability	Clinically important difference without validation

This hierarchy structures the interpretation of all five result themes and keeps uncertainty visible across the full translational argument. In particular, preclinical target engagement would justify further testing, whereas only appropriately designed human prevention trials can establish patient benefit.

Results: Thematic Findings

Theme One: The Neutral Human Signal is the Anchor

The original randomised study remains the most direct evaluation of the headline prevention claim. It compared a 5% tocotrienol cream with a control cream after surgery and followed the appearance of the resulting scars. From 122 randomised participants, 85 were available for the completed-assessment analysis. Reported differences in scar assessments and measures of vascularity were not statistically significant. This should be reported as failure to demonstrate the anticipated benefit of that regimen, rather than proof of equivalence or evidence of a beneficial effect hidden somewhere in the available outcomes [10].

The difference between randomised and analysed populations is important. Participants who complete scar follow-up may differ from those who do not in recovery, symptoms, satisfaction or ability to return, and missing outcomes can change the credibility of an estimated intervention effect. At the same time, attrition alone does not establish the direction or size of bias. Without fully reconstructing unpublished participant-level data, it is inappropriate to declare that missing observations necessarily concealed an effect. The transparent statement is that the published completed-assessment result was neutral and the attrition narrows the strength of generalisable inference [10,11].

The CONSORT 2025 reporting framework further emphasises clear disclosure of numbers randomised, numbers analysed and missing-outcome handling, making these omissions material to interpretation rather than merely administrative. This appraisal does not retroactively require that the 2011 trial complied with a guideline issued in 2025; it uses current principles to identify what any replication would need to report [53].

Several explanatory possibilities remain unresolved by the trial report. The product might have had insufficient biological activity at the tested dose; it might have been active but not delivered to fibroblast-rich tissue; or the timing after surgery might have missed a decisive phase of scar programming. A genuine effect could also have been limited to particular high-risk anatomical settings or patient groups, or obscured by endpoint variability. These are mutually compatible hypotheses in places, not established explanations. Their value lies in specifying discriminating experiments rather than rescuing a favourite conclusion after a nonsignificant result [2,9,10].

Theme Two: Plausible Biology is not Equivalent to Clinical Prevention

Preclinical studies show that tocotrienol-rich preparations can influence cellular processes relevant to wound repair. A nanoemulsified system has been evaluated through keratinocyte-related work and a zebrafish regeneration model, while combinations of tocotrienol-rich material and growth factors have been examined in experimental burns. Yet migration into an artificial scratch, restoration of an injured animal appendage, and closure of a thermal wound are not validated surrogates for reducing raised, itchy or cosmetically distressing human incision scars at six or twelve months. Both the tissue architecture and causal endpoint change when moving between these models [7,12,13].

Mechanistic reviews highlight oxidative stress, TGF-beta signalling, extracellular-matrix remodelling, inflammation and the balance between fibroblast activation and resolution. Even if tocotrienols modulate one of these pathways in an experimental setting, the magnitude and direction of its effect may depend on local concentration and the stage of repair. For example, antioxidants could be beneficial in a context dominated by damaging oxidative stress yet irrelevant where inflammation is already resolving physiologically. The appropriate mechanistic question is not whether oxidative activity exists, but whether topical dosing shifts an abnormal pathway toward an improved healing state in human tissue [6,8,15,16].

Human skin-fibrosis single-cell datasets reveal a broader biological challenge: a scar comprises multiple cellular states with different behaviour, and not all fibroblasts need to be suppressed. Keloid transcriptomic studies identify matrix-associated and inflammatory

subpopulations, but population proportions differ according to tissue type and sampling time. Comparing these profiles against experimental incision models might generate useful biomarkers. However, a molecular signature observed in a keloid is not yet an established predictor of response to a tocotrienol cream placed on an early postoperative scar. A mechanistic translational program must address target selection, localization and timing before assuming biological relevance [17-20].

Theme Three: Formulation can be a Hidden Mediator

The phrase topical tocotrienol leaves substantial formulation uncertainty. An active may crystallise, oxidise, separate from the base, remain trapped at the skin surface or partition into lipids without reaching the relevant dermis. Two creams containing the same nominal active percentage may expose skin differently if their emulsifiers, occlusives or manufacturing conditions differ. The observed outcome in a trial is consequently an effect of a complete product-and-use regimen, not an intrinsic characteristic of the molecule considered independently of delivery. This distinction is particularly relevant when proposing a new carrier following neutral results with a conventional cream [7,9,30].

Nanovesicles and nanoemulsions may increase the scientific plausibility of adequate delivery, but claims must be calibrated to what was measured. Small droplet size or improved release kinetics describes formulation properties. Skin deposition in a laboratory model demonstrates the next link in the chain, while drug detection within an appropriate living compartment would provide a more clinically proximate exposure measure. Biological target engagement requires a further step, such as a prespecified change in scar-associated molecular activity. None of these alone proves that a patient experiences less itch, a flatter scar or greater satisfaction [12,28,29,31].

Delivery innovations may also modify risk. Surfactants, preservatives, solvents and occlusion can influence irritation or sensitisation in recently healed skin. Diseased or disrupted skin can exhibit different absorption from healthy volunteers, creating uncertainty about systemic exposure and local tolerability. Because preventive therapy would often be used by relatively healthy individuals, the acceptable threshold for adverse events is especially low. Studies should report not merely the absence of serious toxicity but also local erythema, contact dermatitis, discomfort, delayed wound problems and treatment discontinuation [7,9,30].

Safety is more than the absence of serious adverse events. Future studies should prospectively define irritation, allergic contact dermatitis, delayed epithelial integrity, treatment cessation and any other local or systemic unwanted effects, reporting denominators and monitoring windows as carefully as they report scar scores. The updated CONSORT Harms framework offers a transparent structure for this purpose, although it does not itself establish the safety of tocotrienol formulations [55].

Theme Four: Clinical Comparisons Improve Design, not Molecule Efficacy

Conventional scar prevention commonly includes instructions about wound support, sun protection and selected topical measures, with silicone-based products often occupying a practical role. Evidence summaries of silicone gel, gel sheets and scar-related over-the-counter products identify potential benefits alongside variable methods, heterogeneous scar types and limitations in certainty. When a palm-derived intervention is introduced, it should be evaluated against realistic existing care rather than compared only with an untreated or poorly defined control if this would undermine applicability. Crucially, the benefit of silicone does not imply tocotrienol will work because both can be rubbed onto the skin [11,14,34,52].

Evidence from paediatric burns, deep hand burns and pressure garments provides additional context but also cautions against indiscriminate pooling. Thermal wounds can have different depth, inflammation, grafting requirements and tension than elective linear incisions. Some interventions are applied only after extensive scar formation, whereas a preventive cream is proposed during early maturation. A Cochrane assessment of pressure therapy also demonstrates that longstanding clinical use does not automatically generate high-certainty evidence. Future trials must therefore define the relevant incision population and avoid importing baseline event rates from unlike burn cohorts [32,33,37].

Minimally invasive approaches, toxin injections and

lasers offer another set of comparisons. A facial surgery trial, a post-mastectomy scar intervention, a hypertrophic-keloid treatment series and a fractional laser study can use similar scar scales yet address distinct therapeutic decisions. Current reviews of botulinum toxin and lasers, as well as microneedle steroid studies, suggest possible options for selected contexts but cannot resolve the tocotrienol question. A head-to-head design must be tied to actual practice: preventive treatment should be compared with an accepted preventive regimen, and rescue therapy for established scars should be defined in advance as an intercurrent event or secondary outcome [38-40,42-45].

Theme Five: Measurements can Mask or Magnify Apparent Effects

Scar scores can disagree because the construct measured differs. An observer may rate vascularity or thickness as improved while the patient still experiences pruritus and social discomfort. A device can reliably identify a subtle change in colour or elasticity that does not constitute a meaningful clinical improvement. Conversely, a modest physical difference may matter greatly for a particular patient depending on location and functional requirements. The revised POSAS patient scale and SCAR-Q emphasise that rigorous research should begin with an explicit construct of benefit, not with whichever numerical measure is most convenient for an investigator [4,48,49].

Instrument selection alone is insufficient. Assessments should take place at clinically meaningful intervals and under repeatable lighting, temperature and positioning; scars change naturally over months. Objective devices for pliability, colour and related properties provide valuable adjuncts where validated, but interobserver disagreement and device-specific variation deserve study planning. An early difference in perfusion at a few weeks is not interchangeable with prevention of hypertrophic scarring after a year of remodelling. A trial needs a prespecified primary endpoint, carefully defined secondary outcomes and appropriate multiplicity management [10,50,51].

Surrogate measurements require the same discipline. Changes in dermal deposition, redox markers, collagen architecture or observer-rated colour should be interpreted as intermediate signals unless the relationship to symptoms and later scar outcomes has been directly established. The CONSORT-Surrogate extension underscores why an intervention effect on a surrogate need not predict its effect on the outcome of interest to patients [54].

Scar characteristics and experience also vary across phototypes and cultural settings. The salience of pigmentary contrast differs from the salience of erythema, and photographs interpreted through one skin-colour distribution may not be equally informative in another. Studies should report and analyse baseline phototype and relevant sociodemographic characteristics without assuming homogeneous preferences. Equity in outcome instruments and recruitment is a methodological concern: a treatment cannot confidently be recommended to a diverse population if measurement favours only the scar features most visible in the original sample [3,4,48].

Discussion and Analysis

A Disciplined Explanation of Translational Discordance

The most defensible interpretation of the evidence is neither that tocotrienols are established scar-preventive agents nor that the biochemical class has been definitively refuted. The actual result is narrower: one tested postoperative topical product did not outperform placebo on the reported clinical assessments. New preclinical delivery research increases understanding of potential failure points, but it does not reclassify the trial as successful. When researchers respond to neutral evidence by changing several assumptions simultaneously, they risk creating an unfalsifiable narrative in which every unsuccessful intervention becomes proof only of a suboptimal dose. Progress requires experiments capable of rejecting specific rescue explanations [7,10,12].

An exposure problem could be tested with a predeclared threshold for stable formulation identity and relevant skin deposition. A target-selection problem would require a measurable biological signature connecting achieved concentrations to inflammatory or matrix-remodelling changes. A clinical-response problem would require evidence that target modulation alters outcomes beyond normal maturation. If exposure is documented but target engagement fails, further work should not automatically escalate the dose without a safety rationale. If target engagement occurs without

patient benefit, the chosen pathway may be insufficient, redundant or temporally irrelevant. Each scenario should lead to a different decision [2,5,9].

Mechanotransduction research adds an especially important limitation to antioxidant-centred accounts. Mechanical load can drive fibroblast activation even where oxidative markers are favourably modified, and different fibroblast states may require distinct interventions. The physical environment of an incision could therefore swamp a modest biochemical signal. It would be useful to measure wound orientation, closure tension and anatomical motion prospectively, rather than explaining subgroup patterns after seeing the results. Future tocotrienol studies could also be designed as add-on interventions to consistent mechanical support, provided interaction hypotheses are set before the trial begins [21-24].

The Formulation–Exposure–Target–Outcome Framework

Figure 1 distinguishes the clinical events that are often collapsed into the broad term wound healing. It shows that successful epithelial closure, the evolution of early redness and thickening, and final scar maturation are separate landmarks. The time axis is deliberately schematic because healing rates depend on procedure and patient factors. This visual separation supports a central claim: an intervention administered during one phase cannot be declared effective for a later phase unless that later outcome is measured [1,2,48].

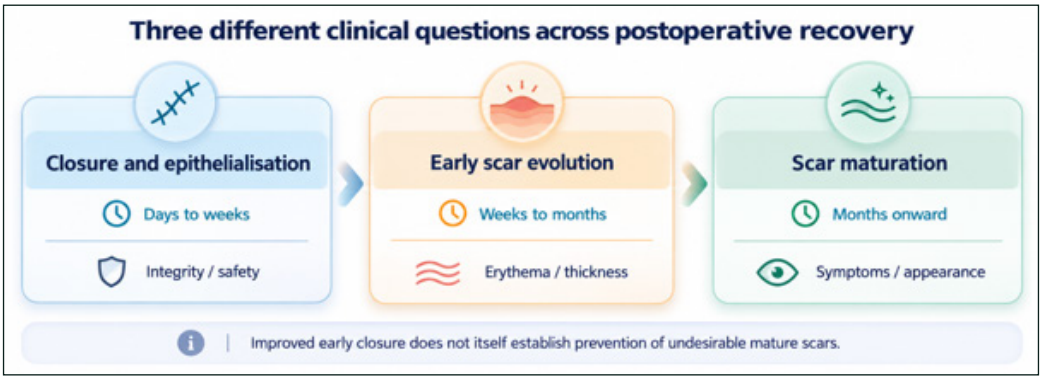


Figure 1: A schematic separation of wound closure, early scar evolution and mature scar outcomes. These are distinct clinical objectives; intervals are illustrative, not universal.

In Figure 1, closure is represented by the restoration of an intact surface and an immediate safety objective. The second period concerns changes in redness and tissue elevation that may fluctuate even in otherwise satisfactory repair. The third period concerns symptoms, contour and patient experience when collagen architecture has matured further. The arrows indicate a temporal relationship, not proof of a single mechanism or a universal deadline. Intervention timing, endpoint timing and the condition being prevented must be aligned explicitly in any future human study [1,2,48].

The proposed causal framework in Figure 2 begins with a chemically authenticated palm-derived product rather than a generic ingredient name. Every subsequent arrow represents an empirical question: release from its vehicle, access to viable tissue, engagement of a fibrosis-related pathway, and improvement in a patient-valued scar outcome. Contextual factors such as anatomical tension, application timing and phototype enter as moderators. The framework prevents an encouraging intermediate result, such as smaller nanoemulsion droplets or a favourable cell assay, from being mistaken for the terminal clinical finding [4,7,9,12].



Figure 2: Proposed formulation–exposure–target engagement–clinical outcome framework for topical palm-derived tocotrienols. Every causal transition must be validated experimentally or clinically.

Figure 2 also indicates why botanical traceability and independent replication are scientific rather than merely marketing concerns. The clinical meaning of a positive result depends on knowing what was administered and whether another laboratory can produce comparable exposure. A reproducible formula should report composition, degradation products where relevant, batch-to-batch variation, packaging and actual use in the trial. Comparative analyses should clearly distinguish palm-derived isoforms from similar vitamin E products originating elsewhere. This precision is necessary for any conclusion about an economically and environmentally specific supply chain [7,28,30].

Trial Design: From Attractive Hypothesis to Decision-Ready Evidence

The proposed program includes three sequential stages with predeclared stop/go decisions, illustrated in Figure 3. In Stage A, the product should pass identity, stability, quality, release and ex-vivo deposition criteria under reproducible application conditions. Even successful completion would justify only an early human assessment, not efficacy claims. Stage B should address local safety, tolerability, adherence, possible systemic exposure and preferably a prespecified tissue-relevant mechanistic indicator. Only when these requirements are met should Stage C test clinical scar prevention against appropriate standard care, with blinded assessment where feasible [7,9,28].

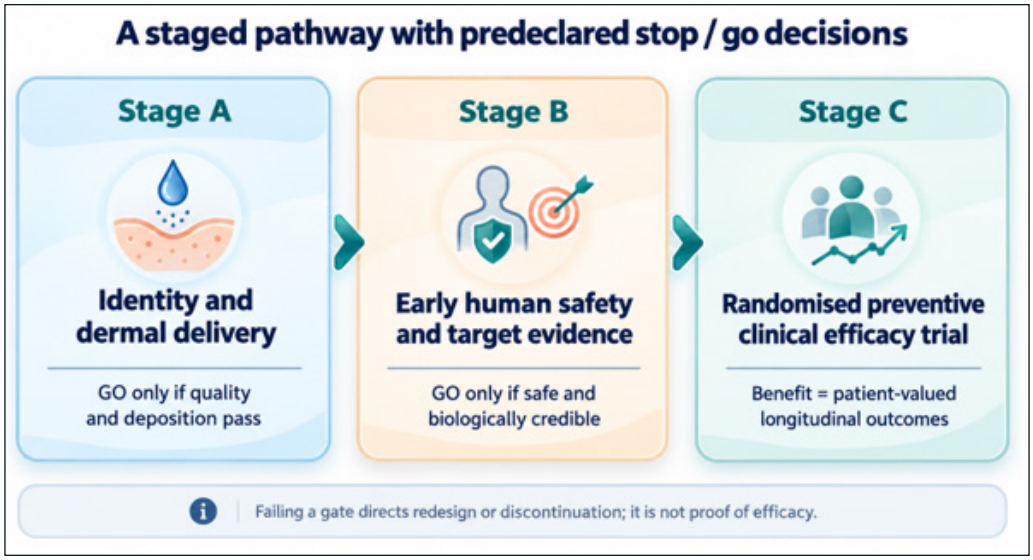


Figure 3: Translational go/no-go pathway: formulation quality and delivery, early human safety and target evidence, then a patient-centred randomized clinical trial.

A pragmatic definitive study could enrol patients undergoing a clearly defined procedure associated with a meaningful incidence of undesirable scars. Randomisation would occur at a consistent post-epithelialisation time, with standardised wound closure and co-intervention instructions. The trial should prespecify whether tocotrienol is an add-on to silicone or an alternative to it, since an add-on design estimates incremental benefit and an alternative design may raise different ethical and noninferiority questions. Scar history, phototype and anatomical tension could be stratification variables; participants with active wound complications or known formulation allergy would require clearly justified screening [3,11,14].

A definitive study should be preceded by a publicly accessible protocol that states the primary estimand, recruitment criteria, formulation identity, allocation scheme, comparator and cointervention policy, safety monitoring, analysis plan and follow-up schedule. SPIRIT 2025 provides contemporary guidance for designing and reporting such protocols, and CONSORT 2025 provides complementary guidance for transparent final reporting. These are standards for the proposed future trial, not methodological labels for the present qualitative literature review [53,56]. Blinding deserves explicit attention because creams can differ in smell, colour, viscosity and skin feel. A matched vehicle control needs comparable sensory properties, while outcome photographs should be assessed under standardised conditions without visible identifiers. Contamination by concurrent oils, silicone gels, scar massage, injections or energy-based treatment may obscure the contrast between allocated groups. Rescue care should never be withheld when clinically indicated; instead, treatment escalation needs prospective recording and an estimand that specifies how rescue treatment will affect interpretation. Trial reporting should make missing observations and reasons for discontinuation accessible rather than relying solely on completed-case summaries [10,14,52].

To prevent differential ascertainment, outcome assessors should be blinded when feasible, and digital scar photographs should be standardised for distance, lighting, colour calibration, posture and timing. Unmasking from a distinctive product odour or colour should be assessed rather than assumed absent. Transparent descriptions of intervention implementation and participant flow will be essential to interpreting any apparent benefit [53].

The primary clinical endpoint should reflect a benefit that would matter to patients and clinicians, perhaps a validated patient component of POSAS or a prespecified composite whose rationale and interpretation are established before recruitment. Observer measures, standardised photography, pigmentation and pliability indices, pruritus, pain, treatment burden and quality of life can serve as complementary outcomes. A twelve-month horizon is reasonable for studying scar maturation in many contexts, although timing should be tailored to procedure and pilot evidence. The target difference and sample size should be derived from meaningful change and event rates in a comparable population, not from optimism about laboratory effect sizes [4,48-51].

Biomarker changes should occupy prespecified secondary or mechanistic positions in the endpoint hierarchy rather than displacing long-term patient-reported improvement. The rationale for any surrogate must state the clinical outcome it is intended to predict and the limits of the validation evidence. This reduces the chance that a statistically promising tissue assay is incorrectly presented as successful postoperative scar prevention [54].

Mechanistic endpoints should be incorporated selectively rather than multiplying surrogate outcomes without a plan. Where ethically and practically possible, investigators might examine minimally invasive tissue sampling, non-invasive imaging, biomarkers of inflammation or matrix activity, and measurement of deposited tocotrienol. Their purpose is to distinguish delivery failure from downstream lack of effect, not to replace the patient-centred primary endpoint. The analysis should assess heterogeneity only for prespecified plausible modifiers, with restraint given expected imprecision. All unexpected local reactions, delayed healing events and rescue procedures should be reported regardless of whether the intervention group appears cosmetically superior [5,6]; [7,15].

Comparators, Clinical Adoption, Safety and Fairness

A central clinical ethical principle is that experimental prevention should not displace reasonable established scar-management care without adequate evidence.

Patients are often concerned about visible scars and may be susceptible to claims grounded in phrases such as natural, antioxidant or regenerative. These descriptors do not convey effect size, applicability or safety. A responsible patient discussion would state that the original randomised tocotrienol trial was neutral, that later formulation studies remain indirect, and that routine use cannot currently be presented as evidence-based scar prevention. This communication need not discourage research; it establishes informed expectations [10,11,14].

The choice of comparator should follow the actual decision faced at a clinical service. A low-cost topical add-on might be compared against optimally delivered routine advice plus silicone where appropriate, while a product claiming to replace standard care requires a design that protects participants from preventable worsening. Trials examining lasers or injections commonly involve procedure-related pain, greater cost and practitioner skill, making them imperfect direct economic substitutes for a preventive cream. Researchers should avoid simplistic rankings that ignore treatment timing, burdens and residual uncertainty in each evidence stream [37,38,43,44].

Patient heterogeneity has ethical as well as statistical consequences. Procedures performed on high-tension regions may create more visible scars and a larger possibility of absolute benefit but also represent a different mechanism of failure. Darker skin phototypes require outcome measures that adequately capture pigmentation and patient concerns rather than relying disproportionately on redness. Socioeconomic factors affect access to repeated follow-up and ability to purchase treatment, with missingness potentially related to the same burdens that determine satisfaction. Recruitment, retention, translation of patient instruments and reporting of skin-type representation therefore belong in the research protocol [3,4,48].

Product provenance raises additional responsibilities. Palm-derived inputs should be traceable and reproducibly manufactured, with attention to contaminants, oxidation and relevant supply-chain claims. A formulation does not become environmentally sustainable simply because its lipid source is agricultural, and environmental arguments do not establish clinical benefit. Conflict-of-interest declarations should identify material supply, product development ownership and study funding, while any positive result should be reproducible by investigators independent of the supplier. These measures improve confidence that product attributes, rather than unreported commercial assumptions, explain observed trial outcomes [7,28].

Interpretation Limits and a Prioritized Research Agenda

This review deliberately resists numerical synthesis because the evidence spans unlike designs, exposures and scar phenotypes. Interpretative breadth is useful for identifying failed causal links but does not replace an exhaustive search or formally graded evidence certainty. Some cited comparator reviews aggregate studies using their own structured methods, but the present review does not inherit the status of a systematic review by discussing them. Selective availability of positive basic-science research remains a concern; the neutral randomised clinical result therefore retains a disproportionate role when judging current claims of postoperative efficacy [10,11,14].

The most urgent research question is not whether a newer cream can change an attractive molecular biomarker, but whether a reproducible topical regimen achieves exposure in tissue relevant to clinical scar formation. The next question is whether that exposure changes a defined scar-associated biological process without compromising safe repair. Only after both are addressed does a costly long-term preventive trial become scientifically well grounded. Pilot work should also calibrate the natural variability of POSAS and objective instruments in the chosen surgical population, estimate adherence and inform missing-data procedures. Such investments may reduce the risk of another informative but mechanistically indeterminate negative result [7,9,48,50].

A development programme can reduce avoidable uncertainty by publishing prespecified, auditable decision gates and reporting both benefit and harms. Early human protocols should follow current SPIRIT guidance, later trial publications should implement CONSORT 2025, and adverse-event documentation should follow the updated harms reporting principles. In this way, an exposure-positive but efficacy-neutral result can still inform a disciplined stop, redesign or

progression decision without overstating clinical value [53,55,56].

Conclusion

Substantive Synthesis and Recommendations

The direct randomised evidence reviewed here does not establish a postoperative scar-prevention advantage for the previously tested 5% topical tocotrienol preparation. Modern studies of wound biology and topical carriers enlarge the set of plausible explanations, but they cannot convert surrogate improvements into demonstrated clinical benefit. A scientifically productive response to the neutral result is to clarify the exposure, timing and target assumptions that were not resolved by the initial clinical test.

Future research should authenticate the palm-derived tocotrienol profile, establish reproducible release and dermal deposition, and document local safety before advancing to a patient-centred efficacy trial. Such a trial should distinguish prevention from mature-scar treatment, use an appropriate comparator, predefine relevant follow-up and include validated patient-reported outcomes alongside objective assessments. Careful evaluation across skin phototypes and surgical sites should be integral rather than optional. The most useful contribution of topical tocotrienol research may initially be the creation of a falsifiable development pathway that prevents repeated clinical uncertainty.

For present practice, tocotrienol creams should not be advertised as proven postoperative scar preventives. Clinicians and investigators should communicate the existing neutral evidence, preserve established care, and publish confirmatory as well as negative findings. Only clinically meaningful benefit demonstrated with a fully characterised formulation could justify changing that position.

References

1. Manjula P Mony, Kelly A Harmon, Ryan Hess, Amir H Dorafshar, Sasha H Shafikhani (2023) An Updated Review of Hypertrophic Scarring. Cells 12: 678.
2. Peña, Martin (2024) Cellular and molecular mechanisms of skin wound healing', Nature Reviews Molecular Cell Biology 25: 599-616.
3. Devaun Reid, Samantha Malak, Monica Khadka, Rana Hanna, Trevor Pharr, et al. (2025) 'Keloids and hypertrophic scars in individuals with darker Fitzpatrick skin types: a systematic review of treatment efficacy and quality of life outcomes', Archives of Dermatological Research 317: 795.
4. Natalia I Ziolkowski, Andrea L Pusic, Joel S Fish, Lily R Mundy, Richard Wong She, et al. (2020) Psychometric Findings for the SCAR-Q Patient-Reported Outcome Measure Based on 731 Children and Adults with Surgical, Traumatic, and Burn Scars from Four Countries', Plastic and Reconstructive Surgery 146: 331e-338e.
5. Heather E Talbott, Shamik Mascharak, Michelle Griffin, Derrick C Wan, Michael T Longaker (2022) Wound healing, fibroblast heterogeneity, and fibrosis. Cell Stem Cell 29: 1161-1180.
6. Gang Wang, Feifei Yang, Weiying Zhou, Nanyang Xiao, Mao Luo, et al. (2023) The initiation of oxidative stress and therapeutic strategies in wound healing', Biomedicine & Pharmacotherapy 157.
7. Anroop B Nair, Bapi Gorain, Manisha Pandey, Shery Jacob, Pottathil Shinu, et al. (2022) 'Tocotrienol in the Treatment of Topical Wounds: Recent Updates. Pharmaceutics 14: 2479.
8. Nur Izzah Md Fadilah, Shou Jin Phang, Nurkhuzaiah Kamaruzaman, Atiqah Salleh, Mazlan Zawani, et al. (2023) Antioxidant Biomaterials in Cutaneous Wound Healing and Tissue Regeneration: A Critical Review. Antioxidants 12: 787.
9. Neubert (2024) Mechanisms of penetration and diffusion of drugs and cosmetic actives across the human Stratum corneum', European Journal of Pharmaceutics and Biopharmaceutics 202.
10. TL Khoo, AS Halim, Z Zakaria, AZ Mat Saada, LY Wu, et al. (2011) A prospective, randomised, double-blinded trial to study the efficacy of topical tocotrienol in the prevention of hypertrophic scars. Journal of Plastic, Reconstructive & Aesthetic Surgery 64: 6e137-e145.
11. Grigoryan, Kampp (2020) Summary and evidence grading of over-the-counter scar treatments. International Journal of Dermatology 59: 1136-1143.
12. Wai Ting Chong, Chin Ping Tan, Yoke Kqueen Cheah, Oi Ming Lai (2022) In-vitro and in-vivo evaluations of tocotrienol-rich nanoemulsified system on skin wound healing. PLOS ONE 17: e0267381.
13. Hui-fang Guo, Roslida Abd Hamid, Razana

Mohd Ali, Sui Kiat Chang, Mohammed Habibur Rahman, et al. (2020) Healing Properties of Epidermal Growth Factor and Tocotrienol-Rich Fraction in Deep Partial-Thickness Experimental Burn Wounds. Antioxidants 9: 130

14. Ignace De Decker, Henk Hoeksema, Jozef Verbelen, Els Vanlerberghe, Petra De Coninck, et al. (2022) The use of fluid silicone gels in the prevention and treatment of hypertrophic scars: a systematic review and meta-analysis. Burns 48: 491-509
15. Yizhao Ma, Zhifang Liu, LinLin Miao, Xinyu Jiang, Hongyu Ruan, et al. (2023) Mechanisms underlying pathological scarring by fibroblasts during wound healing. International Wound Journal 20: 2190-2206.
16. Wang Xiaojie, Joshua Banda, Hui Qi, Alan K Chang, Canol Bwalya, et al. (2022) Scarless wound healing: Current insights from the perspectives of TGF-β, KGF-1, and KGF-2', Cytokine & Growth Factor Reviews 66: 26-37.
17. Cheng-Cheng Deng, Yong-Fei Hu, Ding-Heng Zhu, Qing Cheng, Jing-Jing Gu, et al. (2021) Single-cell RNA-seq reveals fibroblast heterogeneity and increased mesenchymal fibroblasts in human fibrotic skin diseases. Nature Communications 12: 3709.
18. Xuanyu Liu, Wen Chen, Qingyi Zeng, Baihui Ma, Zhujun Li, et al. (2022) Single-Cell RNA-Sequencing Reveals Lineage-Specific Regulatory Changes of Fibroblasts and Vascular Endothelial Cells in Keloids. Journal of Investigative Dermatology 142: 124-135.
19. Daishi Li, Zhaohuai Li, Sitao Liu, Xiaozhen Chen, Xuanlin Che, et al. (2025) Single-cell RNA sequencing highlights the role of proinflammatory fibroblasts, vascular endothelial cells, and immune cells in the keloid immune microenvironment. International Journal of Dermatology 64: 890-900.
20. Xinwei Cheng, Zhen Gao, Shengzhou Shan, Haoyu Shen, Hongkun Zheng, et al. (2024) 'Single cell transcriptomics reveals the cellular heterogeneity of keloids and the mechanism of their aggressiveness. Communications Biology 7: 1647.
21. Britta Kuehlmann, Clark A Bonham, Lukas Prant, Isabel Zucal, Geoffrey C Gurtner (2020) Mechanotransduction in Wound Healing and Fibrosis', Journal of Clinical Medicine 9: 1423.
22. Jiayi Yin, Shiming Zhang, Chao Yang, Yan Wang, Bing Shi, et al. (2022) Mechanotransduction in skin wound healing and scar formation: Potential therapeutic targets for controlling hypertrophic scarring. Frontiers in Immunology 13: 1028410.
23. Shamik Mascharak, Heather E desJardins-Park, Michael F Davitt, Michelle Griffin, Mimi R Borrelli, et al. (2021) Preventing Engrailed-1 activation in fibroblasts yields wound regeneration without scarring. Science 372: eaba2374.
24. Kellen Chen, Dominic Henn, Michael Januszyk, Janos A Barrera, Chikage Noishiki, et al. (2022) Disrupting mechanotransduction decreases fibrosis and contracture in split-thickness skin grafting. Science Translational Medicine 14.
25. Ying-Ying Li, Shuai-Fei Ji, Xiao-Bing Fu, Yu-Feng Jiang, Xiao-Yan Sun (2024) Biomaterial-based mechanical regulation facilitates scarless wound healing with functional skin appendage regeneration. Military Medical Research 11: 13.
26. Ying Zhang, Shenqiang Wang, Yinxian Yang, Sheng Zhao, Jiahuan You, et al. (2023) Scarless wound healing programmed by core-shell microneedles. Nature Communications. 14: 3431.
27. Ailing Hao, Xiangyu Dong, Yannian Gou, Aohua Li, Jiajia Li, et al. (2025) Engrailed-1 inactivation leads to scarless skin wound healing through extracellular matrix remodeling. Genes & Diseases 12: 101484.
28. Lefkothea Antonara, Efstathia Triantafyllopoulou, Maria Chountoulesi, Natassa Pippa, Paraskevas P Dallas, et al. (2025) Lipid-Based Drug Delivery Systems: Concepts and Recent Advances in Transdermal Applications. Pharmaceutics 15: 1326.
29. Touitou, Natsheh (2024) The Evolution of Emerging Nanovesicle Technologies for Enhanced Delivery of Molecules into and across the Skin. Pharmaceutics 16: 267.
30. Mingyue Cui, Christian Wiraja, Sharon Wan Ting Chew, Chenjie Xu (2021) Nanodelivery Systems for Topical Management of Skin Disorders. Molecular Pharmaceutics 18: 491-505.
31. Rajvi Shah, Jimil Gandhi, Monit Shah, Prerna Tiwari, Bharat Chaudhary, et al. (2025) Nanoemulsions for topical delivery: formulation, applications and recent advances. Journal of Microencapsulation 42: 660-681.
32. Chatchai Pruksapong, Chairat Burusapat, Natthawoot Hongkarnjanakul (2020) Efficacy of Silicone Gel versus Silicone Gel Sheet in Hypertrophic Scar

Prevention of Deep Hand Burn Patients with Skin Graft: A Prospective Randomized Controlled Trial and Systematic Review. Plastic and Reconstructive Surgery Global Open 8: e3190.

33. Jodie Wiseman, Megan Simons, Roy Kimble, Robert S Ware, Steven M McPhail, et al. (2021) Effectiveness of topical silicone gel and pressure garment therapy for burn scar prevention and management in children 12-months postburn: A parallel group randomised controlled trial. Clinical Rehabilitation 35: 1126-1141.
34. De Oliveira, Gold (2020) Silicone sheets and new gels to treat hypertrophic scars and keloids: A short review. Dermatologic Therapy. 33: 4 e13705.
35. Thunyaluk Meetam, Apichai Angspatt, Pornanong Aramwit (2024) Evidence of Potential Natural Products for the Management of Hypertrophic Scars. Journal of Evidence-Based Integrative Medicine 29.
36. Yuxiao Zhang, E Liua, Hongjin Gao, Qingying He, Anjing Chen, et al. (2024) Natural products for the treatment of hypertrophic scars: Preclinical and clinical studies. Heliyon 10: e37059.
37. Isobel M Harris, Kwang Chear Lee, Jonathan J Deeks, David J Moore, Naiem S Moiemen, et al. (2024) Pressure-garment therapy for preventing hypertrophic scarring after burn injury', Cochrane Database of Systematic Reviews CD013530.
38. Ziyao Fu, Hanzi Huang, Jiuzuo Huang (2022) Efficacy and safety of botulinum toxin type A for postoperative scar prevention and wound healing improvement: A systematic review and meta-analysis. Journal of Cosmetic Dermatology 21:176-190.
39. Shuai Yue, Mengran Ju, Zhe Su (2022) A Systematic Review And Meta-Analysis: Botulinum Toxin A Effect on Postoperative Facial Scar Prevention. Aesthetic Plastic Surgery 46: 395-405.
40. Man-Yun Li, Wen-Kuan Chiu, Hsian-Jenn Wang, I-Fan Chen, Jin-Hua Chen, et al. (2022) 'Effectiveness of Botulinum Toxin Type A Injection on Scars: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Plastic and Reconstructive Surgery 150: 1249e-1258e.
41. Delwyn Zhi Jie Lim, Yong Yao Chun, Faith Nicole Shih Yun Tan, Amelia Yuting Monteiro, Hui Mei Cheng, et al. (2025) Small interfering RNA microneedle patches versus silicone sheets in reducing postoperative scars: a randomized single-blinded intraindividually controlled clinical trial. British Journal of Dermatology 192: 19-26.
42. Waranaree Winayanuwattikun, Vasanop Vachiramon, Teerapong Rattananukrom, Pasita Palakornkitti, Ngamcherd Sitpahul (2023) Efficacy of Botulinum Toxin Type A for Prevention of Post-Mastectomy Scar in Transmen: A Prospective, Randomized Study. Toxins 15: 636.
43. Jose A. Foppiani, Abdulrhman Khaity, Nada Mostafa Al-Dardery, Mohammed Tarek Hasan,
44. Mohamed El-Samahy, et al. (2024) Laser Therapy in Hypertrophic and Keloid Scars: A Systematic Review and Network Meta-analysis. Aesthetic Plastic Surgery 48: 3988-4006.
45. Sihao Shen, Yujia Cai, Xiuzu Song, Wenzhong Xiang (2023) The Efficacy of Fractional Carbon Dioxide Laser in Surgical Scars Treatment: A system Review and Meta-analysis. Aesthetic Plastic Surgery 47 : 340-350.
46. Wareeporn Disphanurat, Nakarin Sivapornpan, Benjaporn Srisantithum, Jeerapond Leelawattanachai (2023) Efficacy of a triamcinolone acetonide-loaded dissolving microneedle patch for the treatment of hypertrophic scars and keloids: a randomized, double-blinded, placebo-controlled split-scar study. Archives of Dermatological Research 315: 989-997
47. Kevin M Klifto, Mohammed Asif, C Scott Hultman (2020) Laser management of hypertrophic burn scars: a comprehensive review. Burns & Trauma 8: tkz002.
48. Alireza Jafarzadeh, Arash PourMohammad, Azadeh Goodarzi (2024) A systematic review of the efficacy, safety and satisfaction of regenerative medicine treatments, including platelet-rich plasma, stromal vascular fraction and stem cell-conditioned medium for hypertrophic scars and keloids. International Wound Journal 21: e14557.
49. ME Carrière, LB Mokkink, Z Tyack, MJ Westerman, A Pijpe, et al. (2023a) Development of the Patient Scale of the Patient and Observer Scar Assessment Scale (POSAS) 3.0: a qualitative study. Quality of Life Research 32: 583-592.
50. ME Carrière, Z Tyack, MJ Westerman, J Pleat, A Pijpe, et al. (2023b) From qualitative data to a measurement instrument: A clarification and elaboration of choices made in the development of the Patient Scale of the Patient and Observer Scar Assessment Scale (POSAS) 3.0. Burns 49: 1541-1556.

51. Rendell M Bernabe, Paloma Madrigal, Deborah Choe, Christopher Pham, Haig A Yenikomshian, et al. (2024) Assessing Scar Outcomes Using Objective Scar Measurement Tools: An Adjunct to Validated Scar Evaluation Scales. Plastic and Reconstructive Surgery 154: 885e-890e.
52. Felix J Klimitz, Hubert Neubauer, Annette Stolle, Sabine Ripper, Simeon C Daeschler, et al. (2023) Objective Burn Scar Assessment in Clinical Practice Using the Cutometer: Introduction and Validation of a Standardized Measurement Protocol. Journal of Burn Care & Research 44: 95-105.
53. Benjamin Tran, Jashin J Wu, Desiree Ratner, George Han (2020) Topical Scar Treatment Products for Wounds: A Systematic Review. Dermatologic Surgery 46: 1564-1571.
54. Hopewell S, Chan AW, Collins GS, Hróbjartsson A, Moher D, et al. (2025) CONSORT 2025 statement: updated guideline for reporting randomised trials. BMJ 389: e081123.
55. Manyara AM, Davies P, Stewart D, Weir CJ, Young AE, et al. (2024) Reporting of surrogate endpoints in randomised controlled trial reports (CONSORT-Surrogate): extension checklist with explanation and elaboration. BMJ 386: e078524.
56. Junqueira DR, Zorzela L, Golder S, Loke Y, Gagnier JJ, et al. (2023) CONSORT Harms 2022 statement, explanation, and elaboration: updated guideline for the reporting of harms in randomised trials. BMJ 381: e073725.
57. Chan AW, Boutron I, Hopewell S, Moher D, Schulz KF, et al. (2025) SPIRIT 2025 statement: updated guideline for protocols of randomised trials. BMJ 389: e081477.

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.