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Topical Hesperidin and *Rubia Cordifolia* (Manjistha) in Cutaneous Barrier Support, Venous-Stressed Skin and Post-Laser Recovery [HESPERIDIN CREAM]: A Critical Narrative Review

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Abstract:

Background: Flavanones and botanical quinones exhibit distinct biological actions in the stratum corneum and viable skin compartments. This narrative review critically evaluates the scientific rationale for topically applied hesperidin combined with *Rubia cordifolia* (Manjistha) extract as a candidate formulation for cutaneous barrier maintenance, dermal support under chronic venous stress, and post-laser skin recovery.

Evidence scope: Oral flavonoid preparations, including micronised purified flavonoid fraction (MPFF), were excluded, restricting evidence to dermal, explant and cell-based topical exposure. In murine models, topical native hesperidin accelerated epidermal permeability-barrier repair, increased differentiation markers, stimulated lamellar-body secretion and mitigated age- and glucocorticoid-associated barrier defects. Cutaneous cell and tissue assays indicate antioxidant, photoprotective and matrix-protective activity, including modulation of selected matrix metalloproteinases (MMPs) and increased fibroblast migration; several of these findings derive from hesperetin or hesperidin methyl chalcone (HMC) rather than native hesperidin, which are not interchangeable. In human skin explants, topically applied HMC reduced local vessel dilation and interleukin-8 (IL-8) production. Preclinical studies of *Rubia cordifolia* and its constituent alizarin show complementary antioxidant, anti-inflammatory and barrier-restorative activity.

Translational boundaries and conclusions: No controlled trial of a finished hesperidin–*Rubia cordifolia* topical formulation was identified. The mechanisms align closely with the demands of intact skin under chronic venous hypertension and of laser-disrupted skin, establishing ingredient-level rationale that product-specific testing can now convert into efficacy data. Such a combination is therefore positioned as a candidate cutaneous-support formulation, complementary to rather than a replacement for treatment of deep venous reflux and standard post-procedure care. Product characterisation, dermal-penetration, irritation and sensitisation data and controlled clinical studies remain necessary.

Keywords: hesperidin; *Rubia cordifolia*; Manjistha; epidermal barrier; chronic venous insufficiency; post-laser recovery; cutaneous microcirculation

Abbreviations:

CISD2, CDGSH iron–sulfur domain-containing protein 2; COX-2, cyclo-oxygenase-2; CXCL9, C-X-C motif chemokine ligand 9; CXCL10, C-X-C motif chemokine ligand 10; ERK1/2, extracellular signal-regulated kinase 1/2; GPX4, glutathione peroxidase 4; HMC, hesperidin methyl chalcone; HSPA1L, heat shock protein family A (Hsp70) member 1-like; IL-6, interleukin-6; IL-8, interleukin-8; JAK1, Janus kinase 1; MEDLINE, Medical Literature Analysis and Retrieval System Online; MITF, microphthalmia-associated transcription factor; MMP, matrix metalloproteinase (MMP-1, MMP-2, MMP-3); MPFF, micronized purified flavonoid fraction; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; Nrf2, nuclear factor erythroid 2-related factor 2; PVA, polyvinyl alcohol; Rab27A, Ras-related protein Rab-27A; STAT1, signal transducer and activator of transcription 1; STAT3, signal transducer and activator of transcription 3; TEWL, transepidermal water loss; TRP-1, tyrosinase-related protein 1; TRP-2, tyrosinase-related protein 2; UV, ultraviolet; UVA, ultraviolet A; UVB, ultraviolet B; Wnt, wingless-related integration site.

1. Introduction

Hesperidin is a citrus flavanone glycoside with physicochemical and biological properties relevant to externally applied skincare. Topical interest centres on its interaction with the epidermal barrier and viable cutaneous tissues rather than gastrointestinal absorption or circulating metabolites. Oxidative stress, inflammatory signalling, extracellular-matrix degradation, and epidermal-barrier dysfunction contribute to photoaging, wound repair, post-procedural recovery, and the cutaneous manifestations of chronic venous disease [1-2].

The evidence requires careful interpretation. Native hesperidin, hesperetin and hesperidin methyl chalcone (HMC) are chemically related but non-interchangeable topical interventions. Evidence from hesperetin or HMC is included only when the route is topical, local, cutaneous or skin-explant-based and is explicitly labelled. Systemic and oral preparations are outside the scope of this cream-focused review.

This review evaluates a two-ingredient topical cream in which hesperidin is the principal evidence-bearing ingredient and *Rubia cordifolia* (Manjistha) the complementary botanical. Related hesperidin derivatives and combination preparations are included only where they clarify pharmacology or define the evidence boundary. The question this review addresses is whether the ingredient-level cutaneous and vascular-supportive biology of such a cream justifies two specific therapeutic positioning claims: (1) adjunctive topical support for the dermis and skin in varicose-vein-associated and chronic-venous-stress settings; and (2) a candidate adjunctive post-laser treatment to assist recovery of the epidermal barrier, skin comfort, hydration and erythema control.

2. Formulation Overview and Review Scope

The formulation evaluated here (Biotexlife Hesperidin Cream, Biotex Life Solutions Pvt. Ltd., Secunderabad, India) is a topical preparation containing Hesperidin Powder and *Rubia cordifolia* (Linn.) Manjistha Extract in a cream base. Throughout the remainder of this review, it is referred to as the HESPERIDIN CREAM. The exact concentrations, botanical plant part, extract ratio, solvent system, hesperidin assay and full excipient composition were not available for this review. Consequently, the manuscript evaluates the scientific rationale of the declared ingredients without assuming product-specific pharmacological equivalence to any published study.

Hesperidin Powder is treated as the principal active ingredient because it has the most direct evidence for epidermal-barrier recovery, keratinocyte differentiation, antioxidant signalling, and vascular-supportive biology. Manjistha extract is evaluated as a complementary botanical with traditional dermal use and modern preclinical evidence for antioxidant and inflammatory modulation. Efficacy of the finished cream will be established by product-specific data; the ingredient evidence set out below defines what that testing should measure. Table 1 summarises the declared composition and the ingredient-level mechanistic rationale attributed to each component.

The intended evidence-based positioning is topical support for skin comfort, barrier integrity, moisture balance and antioxidant-inflammatory homeostasis, including skin exposed to chronic venous stress. The cream is positioned as skin-directed care. Correction of venous reflux, closure of structural

varicose veins, replacement of established venous treatment and application to open ulcers fall outside this positioning. Table 2 sets out the six application domains evaluated in this review together with their mechanistic rationale and claim boundaries; the finished product is shown in Figure 1.

Table 1: Declared formulation overview and ingredient-level scientific focus.

Component	Declared identity	Ingredient-level mechanistic rationale (evidence source)
Principal active	Hesperidin Powder	Keratinocyte differentiation and lamellar-body secretion (topical native hesperidin, murine skin); modulation of selected matrix metalloproteinases (hesperidin and hesperetin, cultured fibroblasts)
Complementary botanical	*Rubia cordifolia* (Linn.) Manjistha Extract	Quinone- and anthraquinone-associated suppression of IL-6, IL-8 and chemokine responses (alizarin, an isolated constituent); antityrosinase activity reported for an anthraquinone-enriched stem fraction rather than for the declared extract
Vehicle	Cream base; full excipient composition not available for this review	Emollient and occlusive contribution is expected; formal characterisation is pending

Note: Nrf2-associated antioxidant responses are attributed to a topical hesperidin methyl chalcone formulation. Native hesperidin, hesperetin and hesperidin methyl chalcone are reported here as distinct topical interventions.

Table 2: Proposed topical application domains and translational positioning.

Application domain	Mechanistic rationale	Evidence-based claim boundary
Epidermal barrier and reactive skin	Topical hesperidin stimulates differentiation and lamellar-body secretion; alizarin restored barrier-associated markers in inflamed mouse skin.	Preclinical rationale established; clinical effect on transepidermal water loss (TEWL) and hydration requires finished-product testing.
Cutaneous inflammation and erythema	HMC reduced vessel dilation and IL-8 in human skin explants; Manjistha quinones suppress inflammatory chemokines	Supports a local soothing and anti-redness rationale; rosacea and other dermatoses are separate clinical indications
Dermal and venous-stressed skin	Fibroblast migration, MMP modulation and local vascular-inflammatory moderation	Adjunctive support for intact overlying skin; venous reflux and valve competence are addressed by vascular treatment.
Photoaging and dermal matrix	Antioxidant signalling and MMP modulation across keratinocyte, fibroblast and murine models	Antioxidant and dermal-supportive rationale; sunscreen function and wrinkle reduction are separate claims
Post-laser skin recovery	Overlaps post-procedure requirements: barrier renewal, radical scavenging and comfort	Investigational adjunct; immediate use on ablated skin requires microbial, preservative and tolerability validation
Pigmentation and tone uniformity	Docking-predicted blockade of Rab27A–melanophilin with melanosome aggregation; ERK1/2-mediated MITF degradation; antityrosinase stem fraction	Investigational tone-support rationale; melasma and post-inflammatory hyperpigmentation require clinical testing

Fig 1: The HESPERIDIN CREAM, the finished topical formulation evaluated in this review (20 g pack).

3. Literature-Search Approach

PubMed/MEDLINE-indexed literature available through 2026 was searched using combinations of "hesperidin," "topical hesperidin," "hesperetin," "hesperidin methyl chalcone," "skin penetration," "skin barrier," "keratinocyte," "fibroblast," "wound healing," "photoaging," "cutaneous microvasculature," "skin explant," "chronic venous disease," "stasis dermatitis," "post-laser," "laser resurfacing," "safety" and "phototoxicity." Reference lists of eligible primary studies and reviews were cross-checked. Eligible evidence comprised topical administration, cutaneous cell or tissue models, human skin explants, dermal delivery systems and clinical studies of externally applied post-laser agents. Oral supplementation, beverages, systemic dosing, micronised purified flavonoid fraction (MPFF) and orally administered venoactive combinations were excluded. Manufacturer pages, ingredient-supplier pages, commercial skincare websites and bare database homepages were not accepted as academic references. No language restriction was imposed, but only publications with accessible English full text or abstracts were formally assessed.

4. Chemistry, Sources and Pharmacokinetic Considerations

Hesperidin is hesperetin-7-O-rutinoside. Its rutinoside moiety increases molecular size, while low aqueous solubility can restrict dissolution, vehicle release and partitioning into the stratum corneum. For a cream, the relevant exposure sequence is release from the vehicle, deposition on or within the stratum corneum, and—if the formulation permits—delivery to viable epidermal or superficial dermal compartments. These processes depend on concentration, particle characteristics, vehicle composition, pH, occlusion, application time and barrier status.

Citrus species and plant parts differ substantially. Sweet-orange peel and albedo are common sources, while *Citrus aurantium* materials may range from flavonoid-rich non-volatile extracts to essential-oil fractions. Botanical identity, plant part, extraction solvent and hesperidin assay are therefore essential. Purified hesperidin and citrus essential oil are distinct materials with different safety profiles. Phototoxic furocoumarins such as bergapten are mainly associated with certain volatile citrus fractions and *Citrus bergamia* cold-pressed peel oil [3-4].

Topical delivery is formulation dependent. Hesperidin's low aqueous solubility and molecular properties can limit release from the cream and partitioning into the stratum corneum. Vehicle composition, particle size, pH, occlusion and barrier status can alter local deposition and penetration. The manufacturer has indicated an approximate 20–30 minute "absorption" period; however, no finished-product tape-stripping, Franz-cell, confocal or pharmacokinetic study was available to verify the depth, amount or rate of cutaneous delivery. Accordingly, 20–30 minutes is best described as a product-use or skin-feel interval; tape-stripping, Franz-cell or confocal study would establish the corresponding dermal delivery profile. Freshly laser-treated skin is substantially more permeable than intact skin, so immediate post-procedure use warrants tolerability data generated in that setting rather than extrapolated from ordinary cosmetic use.

5. Epidermal-Barrier Biology

The strongest direct topical evidence concerns epidermal permeability-barrier function. In normal murine skin, topical hesperidin accelerated barrier recovery after acute disruption and increased epidermal differentiation markers and lamellar-body secretion[5]. Related studies in aged mice showed improvement in epidermal function, while topical hesperidin mitigated glucocorticoid-induced abnormalities in barrier homeostasis[6-7]. A broader review concluded that hesperidin benefits multiple cutaneous functions including barrier repair, wound healing, anti-inflammatory responses and moisture retention [8].

These studies provide a coherent mechanism: keratinocyte differentiation and lamellar-body secretion support delivery of lipids required for restoration of the stratum corneum. Improved barrier function can reduce TEWL and support hydration. However, most direct evidence is preclinical. A claim that topical hesperidin maintains barrier function is biologically well supported; a quantitative claim about human hydration or TEWL requires a controlled trial with the finished product.

In mice, topical hesperidin co-applied with glucocorticoid prevented abnormalities in permeability-barrier recovery, stratum-corneum acidification, filaggrin expression and epidermal proliferation [7]. This was observed during experimental co-treatment, which positions the ingredient for investigation in steroid-stressed barrier models. A corresponding Manjistha study remains to be reported.

Barrier support is particularly relevant to chronic venous disease, where oedema, inflammation and altered microcirculation can contribute to dryness, itch, erythema and stasis-associated skin changes. It is also relevant after laser procedures, in which deliberate epidermal or dermal injury temporarily increases water loss and sensitivity.

A 2024 overview identified antioxidant, inflammation-modulating, barrier, pigment and repair-related research as the principal cutaneous evidence domains for hesperidin [9]. In cultured normal human dermal fibroblasts, hesperidin and hesperetin reduced selected matrix metalloproteinase (MMP)-1 and MMP-2 responses, while both compounds inhibited elastase and hyaluronidase in biochemical assays[10]. These findings establish matrix-related activity at the experimental level and identify elastic-fibre preservation and clinical anti-ageing effect as endpoints for finished-product study. Separately, hesperetin increased CISD2-associated mitochondrial and redox responses in keratinocytes and improved ageing-related endpoints in mice[11]. Because hesperetin is the aglycone rather than the declared hesperidin powder, this evidence is mechanistically supportive rather than formulation-equivalent.

6. Antioxidant, Inflammatory and Photoaging Mechanisms

Cutaneous models indicate that hesperidin-class flavanones can moderate oxidative and inflammatory signalling. Native hesperidin reduced oxidative and cytokine responses in ultraviolet (UV)-exposed keratinocyte and murine skin models[12]. In human dermal fibroblasts, hesperetin reduced reactive oxygen species, MMP-1 and MMP-3, interleukin-6 (IL-6) and cyclooxygenase-2 (COX-2) after UVA exposure; this evidence is attributed to the aglycone hesperetin[13]. Comparative skin models further show that hesperidin and hesperetin differ in potency, so each is reported here under its own name [10].

In a UVB-exposed hairless-mouse model, a topical HMC formulation reduced oedema, oxidative injury, lipid peroxidation and cytokine production while preserving glutathione- and Nrf2-related antioxidant responses [14]. This demonstrates local activity for a modified hesperidin derivative in a defined vehicle. These Nrf2-associated findings are attributed to HMC; the corresponding delivery and effect for native hesperidin in a cream base is a defined question for finished-product study.

Several cutaneous models converge on matrix and stress-response pathways. Native hesperidin limited oxidative and inflammatory injury in keratinocyte and murine UV models[12]. A topical, hesperidin-containing *Citrus sinensis* peel-extract nanoformulation reduced MMP-1-associated photoaging changes in UV-exposed mice; the outcome is attributed to the multi-constituent extract as a whole[15]. A 2026 study using cultured cells and three-dimensional skin organoids additionally linked Chenpi-derived hesperidin with HSPA1L/GPX4-associated control of ferroptotic stress[16]. These results support photodamage-related mechanisms, but none is a clinical trial of the finished cream.

Local-delivery studies extend the anti-inflammatory and repair rationale but remain formulation-specific. Hesperidin- and naringin-containing hydrogels reduced NF-κB/COX-2-associated inflammatory

signalling and improved repair outcomes in an experimental deep-dermal wound model[17]. A hesperidin-loaded polyvinyl alcohol (PVA)/alginate hydrogel also reduced oxidative and inflammatory markers in a human skin-cell system[18]. An in vitro and ex vivo study of fixed-ratio quercetin: hesperidin combinations reported antioxidant and anti-inflammatory activity under visible-light and UVA challenge; the work was conducted in vitro and ex vivo, hesperidin alone was characterised for cytocompatibility, and the reported activity was attributed primarily to quercetin, the dominant component[19]. These studies establish local biological plausibility; efficacy for wounds or photodermatoses is a matter for product-specific study.

The most defensible interpretation is that hesperidin has ingredient-level potential to support cutaneous antioxidant balance and moderate excessive inflammatory signalling. Sunscreen remains the appropriate agent for photoprotection and skin-cancer prevention.

7. Keratinocytes, Fibroblasts, Dermal Matrix and Wound Repair

Hesperidin-related activity extends beyond the stratum corneum. In cultured human keratinocytes and dermal fibroblasts, hesperidin increased cellular migration, and in a mouse wound model it accelerated re-epithelialization through Wnt/β-catenin-associated signalling [20]. These findings establish ingredient-level wound-repair biology. Application to open wounds is a separate question requiring product-specific safety and clinical data.

Across UV-exposed keratinocyte, murine-skin, topical nanoformulation and dermal-fibroblast models, hesperidin, hesperidin-containing citrus extract or hesperetin reduced selected matrix metalloproteinases and limited oxidative or structural injury [10,12-13,15]. The convergence of these findings supports a dermal matrix-protection hypothesis. Clinical collagen rebuilding, scar reversal and wound healing are endpoints for product-specific studies.

Dermal repair evidence spans distinct interventions, each reported here under its own preparation. Hesperetin protected UVA-exposed human dermal fibroblasts against oxidative stress, MMP induction and apoptosis[13]. Topical hesperidin reduced hypertrophic-scar formation in a rabbit-ear model[21]. Hesperidin incorporated into nanofiber or cubogel delivery systems improved wound-repair outcomes in preclinical models[22-23]. Together, these studies support fibroblast and repair-related plausibility, while leaving human efficacy, vehicle equivalence and use on compromised skin unresolved.

The distinction between wound-repair biology and wound treatment is important. Cell migration and faster closure in an animal model justify further study, whereas application to open ulcers or freshly ablated skin requires microbial, preservative, irritation and clinical safety evidence for the complete formulation. Manjistha has traditional and preclinical wound-related support [24-25], but neither the declared extract nor the cream vehicle has been tested on open wounds.

8. *Rubia cordifolia* (Linn.) Manjistha Extract: Complementary Cutaneous Rationale

Rubia cordifolia L. (family Rubiaceae), known as Manjistha, contains anthraquinones and other quinones, naphthohydroquinones, terpenoids, phenolics, flavonoids, cyclic peptides and polysaccharides. More than 100 constituents have been reported, while the extraction method and plant part can substantially change the phytochemical profile[24]. Botanical authentication, plant-part disclosure and quantitative marker selection are therefore essential for reproducibility.

Modern reviews describe antioxidant and anti-inflammatory activity for Manjistha extracts and constituents, but human topical evidence is limited[24]. Experimental work with alizarin and related quinones showed suppression of cytokine and chemokine expression in inflammatory keratinocyte and macrophage models. In a psoriasiform animal model, topical alizarin reduced lesions and supported restoration of barrier-associated changes through JAK1/STAT3-related mechanisms, providing the most direct topical skin evidence for Manjistha-type quinones[26]. These findings belong to alizarin as an isolated constituent rather than to the declared extract.

In a 2025 mouse model of vitiligo, *Rubia cordifolia* extract reduced inflammatory signalling associated with the CXCL10/CXCL9/STAT1 axis and limited melanocyte loss [27]. This provides disease-model evidence for Manjistha-related immune modulation and identifies confirmation in human skin as the next step.

Rubia cordifolia has also been discussed within traditional and experimental wound-repair literature [25]. This supports a complementary dermal-homeostasis rationale for intact skin; application to open venous ulcers or freshly ablated skin requires separate evidence. In the cream under review, the most defensible role of Manjistha is complementary antioxidant, soothing and inflammation-modulating support alongside hesperidin's more direct barrier evidence.

9. Application-Level Evidence Appraisal

9.1 Two-ingredient interpretation of the proposed topical applications

The combined formulation may be described as supporting epidermal renewal, local cutaneous vascular-inflammatory homeostasis and pigment-distribution biology. Wording such as "supports local vascular-inflammatory balance" and "influences pigment-distribution biology" matches the evidence as it stands: the vascular findings are local and largely HMC-based, while the pigment findings arise from cell, reconstructed-epidermis, enzyme and ex vivo models. The stronger forms await a finished-product human study. Figure 2 maps each ingredient onto the cutaneous compartments and mechanisms for which experimental evidence exists.

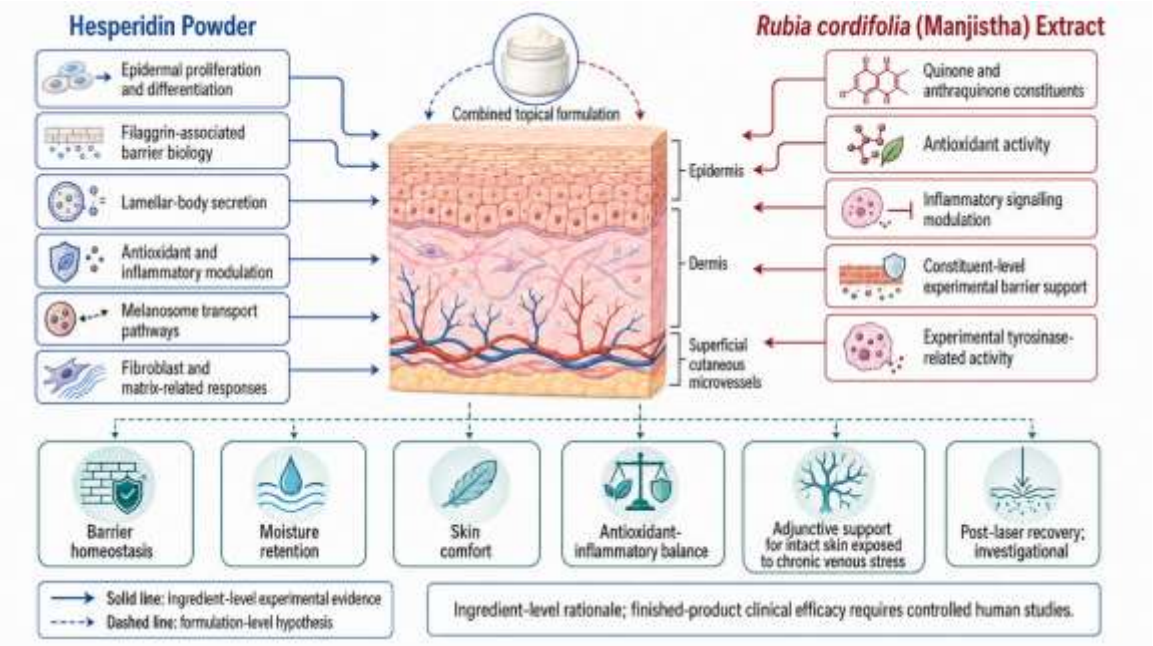

Fig 2: Integrated topical rationale for the HESPERIDIN CREAM. Hesperidin (left) is mapped to epidermal proliferation and differentiation, filaggrin-associated barrier biology, lamellar-body secretion, antioxidant and inflammatory modulation, melanosome transport and fibroblast/matrix responses. Rubia cordifolia (Manjistha, right) is mapped to complementary quinone- and anthraquinone-associated antioxidant, inflammatory, barrier and pigment-enzyme findings. Solid arrows denote directly studied ingredient-level effects; dashed arrows denote formulation-level hypotheses.

9.2 Epidermal barrier and reactive skin

Topical native hesperidin accelerated barrier recovery in murine skin and increased epidermal proliferation, differentiation and lamellar-body secretion [5]. In aged and glucocorticoid-stressed murine skin, topical hesperidin improved selected barrier abnormalities, including filaggrin- and acidification-related endpoints[6-7]. These studies support epidermal renewal and lipid-delivery biology, and identify ceramide quantification and atopic-dermatitis endpoints as targets for finished-product study. Manjistha-derived alizarin provides complementary preclinical evidence because it restored barrier-associated changes in inflamed mouse skin [26].

9.3 Redness, sensitive skin and cutaneous inflammation

Hesperidin-class compounds have reduced oxidative and inflammatory mediators in cutaneous systems, while topical HMC suppressed UVB-associated oedema and cytokine production [14]. Manjistha contributes a distinct but complementary pathway: alizarin and related quinones reduced IL-6, IL-8 and chemokine responses in stimulated keratinocyte and macrophage models, and topical alizarin improved inflammatory lesions and barrier-associated changes in psoriasiform mouse skin[26]. In human skin explants, HMC applied alone at 0.02% reduced the proportion of dilated dermal vessels, total vessel area and IL-8 production relative to substance-P stimulation[28]. Together, the ingredients provide a coherent soothing and anti-redness rationale; rosacea treatment is a separate clinical indication.

9.4 Pigment synthesis, melanosome transport and skin tone

Hesperidin affected two pigment-related processes in experimental systems. It was predicted by molecular docking to block the Rab27A–melanophilin interaction and induce perinuclear melanosome aggregation in melanocytes, with reduced pigmentation in a pigmented reconstructed-epidermis model; in that study, it inhibited neither mushroom tyrosinase nor α-melanocyte-stimulating-hormone-stimulated melanin synthesis [29]. A separate cellular investigation reported ERK1/2-associated MITF degradation with reductions in tyrosinase, TRP-1, TRP-2 and melanin synthesis[30]. The apparent discrepancy between these two reports is assay-dependent—cell-free mushroom tyrosinase in the first, cellular tyrosinase activity in the second—and is acknowledged by the latter authors. Manjistha supplies a different experimental rationale: an anthraquinone-enriched *Rubia cordifolia* stem fraction containing purpurin and ellagic acid showed antityrosinase activity and was incorporated into a gel evaluated by in vitro and ex vivo permeation methods[31]; this activity belongs to the enriched fraction rather than to the declared extract. Conversely, a *Rubia cordifolia* vitiligo model suggested melanocyte-preserving activity[27], demonstrating that pigment effects are context-dependent. The combined evidence gives tone uniformity a defined mechanistic basis across two independent pigment pathways, making it a priority endpoint for finished-product testing.

9.5 Photoaging, dermal matrix and oxidative stress

Hesperidin carries most of the ingredient-level evidence for this application through keratinocyte, fibroblast, murine-skin and topical-delivery studies involving reactive oxygen species, inflammatory mediators and selected matrix metalloproteinases[8-10,12-19]. Manjistha adds complementary antioxidant and inflammation-modulating phytochemistry, but direct photoaging evidence for the declared extract remains limited[24,26]. The combination therefore provides an antioxidant and dermal-supportive rationale; sunscreen function and wrinkle reduction are distinct claims with their own evidence requirements. Table 3 sets out the resulting evidence hierarchy across intervention types.

Table 3: Evidence hierarchy for hesperidin and related preparations.

Evidence domain	Intervention studied	Evidence strength	Meaning for the finished cream
Epidermal barrier	Topical native hesperidin	Strong preclinical	Direct mechanistic support for barrier recovery
Cutaneous antioxidant and inflammation	Topical hesperidin or topical HMC models	Preclinical	Local biological plausibility; each derivative reported under its own name
Fibroblast, matrix and wound repair	Cutaneous cells, topical delivery systems and animal wounds	Preclinical	Dermal-support rationale established; open-wound use requires separate evidence
Cutaneous vascular inflammation	HMC in human skin explants	Ex vivo human	Local cutaneous evidence in human tissue

Post-laser recovery	Other externally applied antioxidants and barrier agents	Limited clinical	Establishes the topical strategy; finished-product efficacy pending
Native hesperidin after laser	Not directly studied	No direct evidence	Candidate use, defined for trial
Rubia cordifolia topical biology	Topical quinone and cutaneous models	Preclinical	Complementary rationale

10. Dermal Support and Varicose-Vein-Associated Skin Changes

Proposed product use. The HESPERIDIN CREAM may be used as adjunctive topical care on intact skin overlying or surrounding varicose veins to support hydration, epidermal-barrier integrity, skin comfort and antioxidant-inflammatory homeostasis. The intended cutaneous targets are dryness, irritation, pruritus, redness, oxidative stress and progressive dermal stress associated with chronic venous hypertension. This is supportive skin care directed at the cutaneous burden of venous disease.

Dermal relevance. Hesperidin and hesperetin influence fibroblast oxidative stress, MMP-related matrix remodelling, and wound-associated cell migration in experimental systems. Manjistha contributes complementary preclinical antioxidant and inflammation-modulating activity. These mechanisms provide a rationale for supporting the dermal extracellular matrix environment and overlying epidermis in areas exposed to chronic venous stress.

Clinical boundary. The cream should be applied only to intact skin unless separate evidence supports use on wounds. Valve competence, venous reflux and vein calibre are addressed by compression, exercise, weight management, sclerotherapy, endovenous ablation and vascular assessment; the cream complements rather than replaces these. Improvement in pain, heaviness, oedema, pigmentation or quality of life must be demonstrated in a product-specific trial.

Varicose veins are structural manifestations of chronic venous disease characterised by venous dilation, valvular incompetence and reflux. Persistent venous hypertension alters endothelial shear stress, promotes leukocyte adhesion and inflammatory signalling, increases microvascular permeability and contributes to oedema and extracellular-matrix remodelling. Cutaneous consequences may include dryness, pruritus, erythema, pigmentation, stasis dermatitis, lipodermatosclerosis and, in advanced stages, venous leg ulcers [32-35].

At the local cutaneous level, HMC reduced substance-P-associated vessel dilation, total vessel area and IL-8 production in human skin explants [28]. This establishes local vascular-inflammatory activity for HMC at the cutaneous level, which is the compartment this formulation is designed to reach. Chronic venous disease reviews describe sustained venous hypertension, oedema, leukocyte-endothelial activation and tissue remodelling as contributors to overlying skin changes[34-35]. Skin-directed care should therefore remain adjunctive to management of the underlying venous disorder.

Together with topical antioxidant, anti-inflammatory and barrier evidence, this creates a reasonable rationale for hesperidin as supportive care for skin exposed to chronic venous stress. The scientifically defensible positioning is: “Topical hesperidin may support skin comfort, barrier integrity and antioxidant-inflammatory homeostasis in areas affected by chronic venous stress.” Closure of varicose veins and reversal of venous reflux are outside this positioning and are not claimed here; compression, sclerotherapy, endovenous ablation and medical evaluation remain the appropriate means of addressing the underlying venous disorder, alongside which this skin-directed care is proposed.

11. Candidate Adjunctive Post-Laser Treatment and Skin-Recovery Formulation

Proposed post-laser treatment use. The HESPERIDIN CREAM may be investigated as a candidate adjunctive topical treatment during post-laser recovery because hesperidin-related barrier restoration, antioxidant activity, inflammatory modulation and keratinocyte/fibroblast migration overlap with the biological requirements of recovering skin. Potential outcomes include improved hydration and comfort and reductions in TEWL, erythema and recovery time after fractional or ablative procedures.

Timing and supervision. Routine immediate application to freshly ablated skin awaits finished-product tolerability data, because laser treatment increases permeability and changes exposure to every ingredient and excipient. Until the finished product has passed microbial, preservative-efficacy, irritation, sensitisation, and relevant phototoxicity testing, use after ablative laser should remain under dermatological supervision. A non-ablative or fully re-epithelialized setting carries lower immediate risk.

Evidence boundary. Published post-laser trials establish antioxidant and barrier-repair topical care as an effective recovery strategy, and this formulation enters that category as a candidate. The product is therefore described here as a "candidate adjunctive post-laser treatment" and an "investigational post-laser skin-recovery formulation," pending completion of a finished-product trial.

Ablative and fractional laser procedures intentionally disrupt epidermal and/or dermal architecture. Early responses may include increased TEWL, erythema, oedema, oxidative stress and inflammation, followed by re-epithelialization and collagen remodelling [36-37]. Controlled studies of other topical antioxidant or barrier-supportive regimens show that recovery endpoints can be modified. A topical antioxidant triad shortened several post-resurfacing recovery measures in a comparative study[38]. In a randomised split-face pilot trial, a laser-assisted vitamin C, vitamin E and ferulic acid serum reduced erythema on postoperative days 3 and 5 and oedema on day 7[39]. A beta-glucan regimen improved hydration and TEWL at selected follow-up points and reduced the haemoglobin index on day 7 after fractional laser treatment[40]. Each of these agents demonstrates that the category can move recovery endpoints.

Clinical studies of other externally applied agents show that early post-laser recovery can be modified by topical care. Split-face or controlled studies have reported improvements in erythema, discomfort, hydration, TEWL or re-epithelialization with enoxolone, hypochlorous acid mist, and a vitamin C–vitamin E–ferulic acid serum[41-43]. These products are hesperidin-free; their role here is to establish that antioxidant, anti-inflammatory and barrier-directed topical strategies can affect post-laser endpoints. Efficacy and immediate-use safety for the HESPERIDIN CREAM require its own trial.

Hesperidin overlaps the relevant targets of these established agents: antioxidant defence, moderation of excessive inflammation, keratinocyte differentiation, lamellar-body secretion, fibroblast/keratinocyte migration and matrix protection. These studies collectively illustrate that topical antioxidant and anti-inflammatory agents can meaningfully accelerate post-laser recovery—an established category into which hesperidin's ingredient-level pharmacology fits mechanistically—pending a finished-product evidence base.

Immediate application after ablative procedures should remain investigational until the finished formulation has appropriate microbial quality, preservative efficacy, irritation/sensitization testing and, where citrus-derived materials warrant it, phototoxicity assessment. A controlled split-face study could measure TEWL, corneometry, erythema, crusting, re-epithelialization, pigment change, adverse events and patient comfort.

12. Integrated Formulation Rationale

At the epidermal level, hesperidin provides direct preclinical evidence for differentiation, lamellar-body secretion and barrier recovery, while the cream vehicle may provide emollient and occlusive support. At the dermal level, evidence for hesperidin and hesperetin supports fibroblast, extracellular matrix, and wound-repair mechanisms; Manjistha adds complementary antioxidant and inflammatory-modulating phytochemistry.

For skin affected by chronic venous stress, the formulation rationale is local rather than structural. Venous hypertension can produce oedema, inflammation, oxidative stress and progressive barrier impairment in the overlying skin. Topical hesperidin evidence supports barrier and cutaneous-homeostasis mechanisms, while topical HMC skin-explant findings provide limited evidence of local vascular-inflammatory modulation. Manjistha may contribute complementary antioxidant and anti-inflammatory activity. The product is therefore framed as an adjunct for maintaining comfort and skin quality in areas exposed to chronic venous burden.

For post-laser use, the combination has a plausible barrier and antioxidant rationale. However, increased permeability after laser treatment makes finished-product safety decisive. Immediate post-

procedure use requires product-specific microbial quality, preservative efficacy, irritation/sensitization assessment and controlled clinical evidence. Figure 3 summarises both translational pathways together with the evidence boundaries that apply to each.

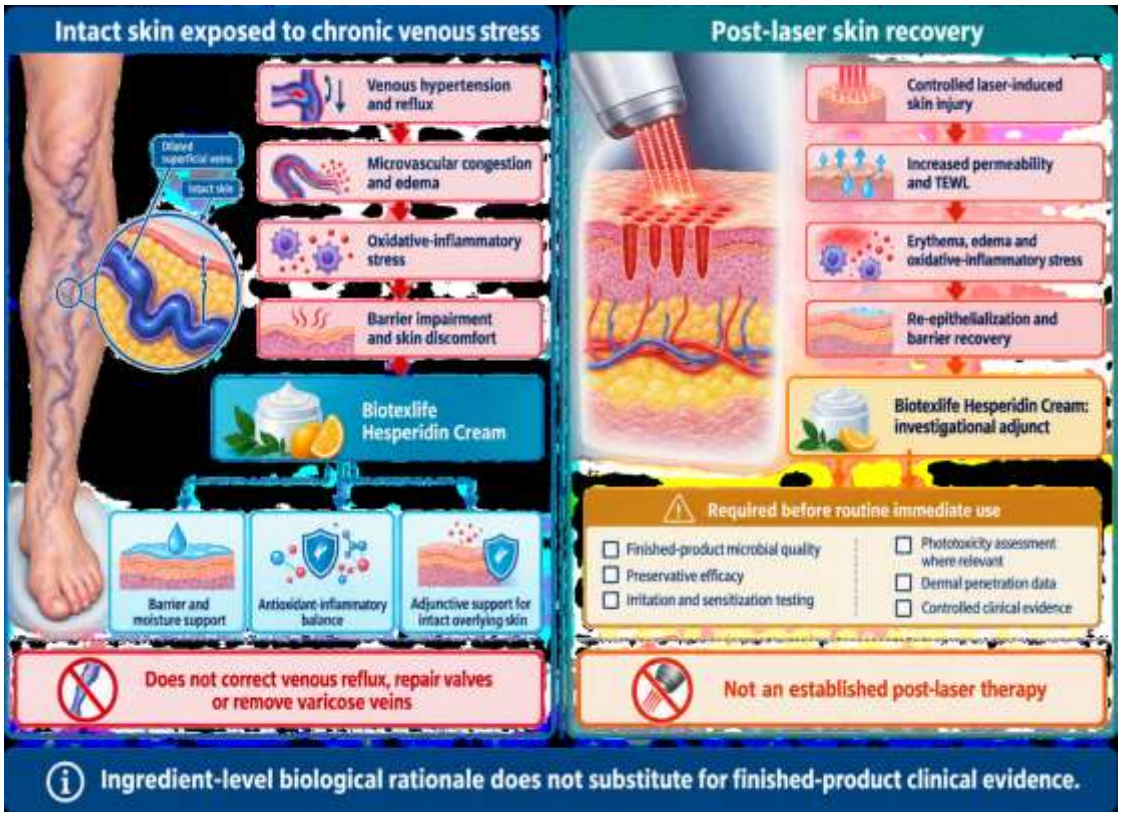

Fig 3: Translational positioning and evidence boundaries for the HESPERIDIN CREAM. Left: chronic venous hypertension leads to microvascular congestion, oedema, oxidative-inflammatory stress and barrier impairment in the intact overlying skin, where the cream is positioned as adjunctive skin support and not as treatment of reflux or varicose-vein anatomy. Right: laser-induced skin injury increases permeability, transepidermal water loss, erythema and oxidative-inflammatory stress during re-epithelialization, where the cream is classified as an investigational adjunct pending finished-product microbial quality, preservative efficacy, irritation and sensitisation testing, phototoxicity assessment where relevant, dermal penetration data and controlled clinical evidence.

13. Safety, Quality and Formulation Requirements

Topical safety is determined by the complete formulation rather than by hesperidin alone. Purity, concentration, particle characteristics, vehicle, preservatives, fragrance, pH and co-extracted citrus constituents can influence irritation, sensitisation, penetration and photoreactivity. A product intended for compromised or recently laser-treated skin requires stricter microbial, preservative and tolerability controls than an ordinary intact-skin cosmetic.

Analytical documentation should include botanical source and plant part, extract type, quantitative hesperidin assay, chromatographic identity, stability, microbial limits, heavy metals, pesticides and residual solvents. If a *Citrus aurantium*-derived material includes volatile fractions, relevant furocoumarins, particularly bergapten, should be controlled [3-4].

Phototoxicity is a property of certain volatile citrus fractions rather than of purified hesperidin. Furocoumarin content should therefore be specified for the finished formulation rather than assumed in either direction. Patch testing and, where appropriate, photopatch or validated in-vitro phototoxicity assessment are reasonable before broad post-procedure use.

14. Evidence Appraisal and Claim Boundaries

Evidence is strongest for experimental epidermal-barrier recovery and cutaneous homeostasis after topical hesperidin exposure. Antioxidant, inflammatory, fibroblast and matrix mechanisms are supported mainly by cutaneous cell, tissue and animal models. Local vascular-inflammatory evidence comes from a human skin-explant study of HMC and applies at the cutaneous level. No peer-reviewed controlled trial was identified that evaluated the HESPERIDIN CREAM or an equivalent finished topical formulation.

Acceptable ingredient-level language includes "supports antioxidant balance," "supports epidermal-barrier homeostasis," "provides a dermal matrix-protective rationale," and "may provide adjunctive support for skin comfort in areas exposed to chronic venous stress." Unsupported language includes "cures varicose veins," "repairs venous valves," "restores circulation" without qualification, "heals venous ulcers," or "clinically proven post-laser treatment." Table 4 applies this appraisal to each proposed application domain.

Table 4: Two-ingredient evidence appraisal and claim-language conclusion by application domain.

Application domain	Two-ingredient evidence appraisal and conclusion
Epidermal barrier and reactive skin	Hesperidin: differentiation, filaggrin and lamellar-body evidence in murine skin. Manjistha: alizarin restored barrier-associated changes in a psoriasiform model. Conclusion: strong preclinical rationale; finished-product human efficacy is the next step.
Cutaneous inflammation and erythema	Hesperidin and HMC: local cytokine and skin-explant vascular-inflammatory effects. Manjistha: alizarin suppressed inflammatory mediators. Conclusion: coherent soothing rationale; rosacea is a separate clinical indication.
Dermal and venous-stressed skin	HMC supplies limited local vascular-inflammatory evidence; both ingredients offer cutaneous antioxidant and anti-inflammatory rationale. Conclusion: adjunctive skin care, complementary to vascular treatment of reflux and valve incompetence.
Photoaging and dermal matrix	Hesperidin has cutaneous antioxidant, MMP and fibroblast evidence; Manjistha adds complementary antioxidant and anti-inflammatory rationale. Conclusion: antioxidant and dermal support; sunscreen activity and wrinkle reversal are separate claims.
Post-laser skin recovery	Both ingredients provide barrier and anti-inflammatory plausibility, but the combination has no direct post-laser trial. Conclusion: a defined investigational use, pending finished-product safety and efficacy testing.
Pigmentation and tone uniformity	Hesperidin affects Rab27A–melanophilin and MITF-related targets in experimental models. Manjistha fractions show antityrosinase activity, while whole-extract data are melanocyte-preserving in one disease model. Conclusion: a promising, context-dependent tone-support rationale; clinical lightening requires product testing.

15. Limitations and Research Priorities

The principal research priority is product-specific controlled human evidence, for which this review defines the rationale and the endpoints. Native hesperidin, hesperetin and HMC differ in chemistry, vehicle compatibility, dermal delivery and local exposure. Much of the eligible topical evidence is preclinical, and studies of other post-laser agents establish the treatment strategy into which hesperidin fits mechanistically. The venous-stressed-skin rationale therefore rests on cutaneous pathophysiology, direct barrier studies and local skin-explant evidence, all of which operate in the skin itself.

Priority studies should first establish concentration, release, skin penetration and safety on intact and barrier-disrupted skin. A randomised vehicle-controlled study in venous-stressed intact skin could assess TEWL, hydration, erythema, pruritus, pigmentation and quality of life while documenting venous disease stage and standard care. A separate post-laser split-face study should use standardised laser parameters and objective recovery measures. Both studies should follow completion of analytical characterisation, preservative efficacy, microbial quality and irritation/sensitisation assessment.

16. Conclusion

This review identifies two clearly defined translational applications for a topical hesperidin–Manjistha formulation: (1) adjunctive topical support for the dermis and intact skin affected by varicose veins or chronic venous stress, and (2) use as a candidate adjunctive post-laser treatment and skin-recovery formulation. The first application targets the secondary cutaneous burden of venous disease rather than the structural vein. The second targets barrier recovery, hydration, oxidative stress and inflammatory control during laser-induced re-epithelialization.

Hesperidin is a scientifically credible citrus bioflavonoid for external application. Direct topical experimental evidence supports epidermal-barrier recovery, keratinocyte differentiation and lamellar-body secretion. Cutaneous cell, tissue, animal and topical-delivery studies further support antioxidant, anti-inflammatory, photoprotective, fibroblast, wound-repair and matrix-protective mechanisms. Local HMC activity in human skin explants provides a rationale for reducing cutaneous vascular-inflammatory stress at the skin surface, which is the compartment a topical formulation reaches.

For chronic venous disease, the cream is best positioned as an externally applied adjunct for the intact skin overlying areas of chronic venous stress. Its role is maintenance of skin comfort, hydration, barrier integrity and antioxidant-inflammatory balance in the skin overlying affected areas. For post-laser use, it is a candidate adjunctive skin-recovery formulation with a coherent topical mechanistic basis, awaiting its first controlled trial. Analytical characterisation, finished-product safety, dermal-delivery data and controlled clinical studies form the defined route to converting either positioning into product-specific efficacy claims.

Declarations

Author contributions: All authors contributed to the conception and scope of the review, literature evaluation, interpretation of evidence, drafting and critical revision of the manuscript. All authors reviewed and approved the final manuscript and accept responsibility for its content.

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Consent to participate: Not applicable.

Consent for publication: Not applicable.

Data availability: No new datasets were generated or analysed for this narrative review. All evidence discussed is available in the cited publications.

Use of artificial intelligence-assisted tools: Artificial intelligence-assisted tools were used to support literature discovery, information organisation, grammar and language refinement. AI-generated outputs were not treated as scientific evidence. The authors independently checked the cited publications, verified the scientific interpretation, critically revised the manuscript and approved the final version. The authors retain full responsibility for the accuracy, integrity and conclusions of the work.

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