The Academic
International Journal of Multidisciplinary Research

An Online Peer Reviewed / Refereed Journal
Volume 4 | Issue 2 | February 2026
ISSN: 2583-973X (Online), SJIF IF: 5.6
Website: www.theacademic.in

Interaction Between Skincare Ingredients and Skin Nerve Endings:A Neurocosmetic Perspective on TRP Channel Modulation

Vidhi Gupta

Amity Indian Military College for Women, Amity University Uttar Pradesh, vidhigup24@gmail.com

DOI : https://doi.org/10.5281/zenodo.18978008

ARTICLE DETAILS

Research Paper

Accepted: 16-02-2026

Published: 10-03-2026

Keywords:

Neurocosmetics, TRP channels, skin-brain axis, TRPM8, TRPV1, TRPV3, cutaneous innervation, neurogenic inflammation, somatosensory modulation, cosmeceuticals.

ABSTRACT

The skin is increasingly understood not merely as a physical boundary but as an active sensory organ capable of receiving, processing, and transmitting complex neurochemical information to the brain. This bidirectional communication pathway, referred to as the skin-brain axis, forms the scientific foundation of neurocosmetics a rapidly expanding field that explores how topically applied ingredients can deliberately influence how the skin feels, responds to stimuli, and interacts with the immune and nervous systems. Among the most pharmacologically significant targets in this field are the transient receptor potential (TRP) ion channels, a family of membrane-spanning proteins expressed on cutaneous nerve endings, keratinocytes, and immune cells that act as molecular sensors for heat, cold, chemical irritants, and mechanical pressure. Three cosmeceutical compounds L-menthol, capsaicin, and camphor have been extensively studied for their capacity to selectively engage TRP channel subtypes including TRPM8, TRPV1, and TRPV3, producing measurable changes in sensory nerve activity, neuropeptide release, vascular responses, and inflammatory cascades within the skin. This review synthesizes current evidence on the mechanisms through which these ingredients interact with cutaneous nerve endings, examines their physiological and therapeutic consequences, and discusses the broader implications for cosmeceutical science, dermatologic therapy, and personalized

skincare. Key findings indicate that targeted modulation of TRP channels through topical actives represents a credible and clinically meaningful strategy for addressing conditions including pruritus, neurogenic inflammation, thermal hypersensitivity, and rosacea. The review concludes with recommendations for future research including longitudinal safety trials, in vivo imaging of nerve-keratinocyte interactions, and AI-assisted precision formulation.

Introduction

The integumentary system has long been characterized in biomedical literature primarily as a structural and immunological barrier, protecting the body against pathogens, physical trauma, ultraviolet radiation, and transepidermal water loss. While these functions remain physiologically critical, accumulating evidence over the past two decades has significantly expanded this understanding. The skin is now recognized as one of the body's most elaborate sensory organs, densely supplied with specialized nerve fibers, receptor structures, and ion channels that continuously sample the external environment and relay detailed information to the central nervous system. This repositioning of the skin as a sensory interface rather than simply a defensive wall has catalyzed the emergence of neurocosmetics as a legitimate scientific and clinical discipline.

Neurocosmetics refers to the development and application of cosmeceutical products that deliberately engage the skin's neural architecture to produce specific perceptual, physiological, or therapeutic outcomes. Unlike conventional cosmetics, which act primarily on the skin's surface chemistry, neurocosmetic formulations are designed to interact with the molecular machinery of cutaneous nerve endings particularly the transient receptor potential (TRP) family of ion channels to modulate how the skin processes sensory stimuli. This distinction carries significant implications for product development, regulatory classification, and clinical application.

The neuroanatomy of the skin is both complex and functionally diverse. Unmyelinated C-fibers and thinly myelinated Aδ-fibers distribute free nerve endings throughout the epidermis and upper dermis, where they detect chemical, thermal, and mechanical stimuli with remarkable sensitivity. Encapsulated mechanoreceptors including Meissner corpuscles, Pacinian corpuscles, Ruffini endings, and Merkel cell-neurite complexes further contribute to the skin's discriminative and affective touch processing capabilities. At the molecular level, TRP channels expressed on these nerve endings serve as the primary

transducers through which physical and chemical signals are converted into bioelectrical impulses that travel to the spinal cord and brain (Haykal et al., 2025). The identity, distribution, and gating behavior of these channels have become central targets in neurocosmetic research.

The clinical relevance of this research is substantial. Disorders such as atopic dermatitis, rosacea, uremic pruritus, and contact hypersensitivity all involve dysregulation of cutaneous sensory pathways, manifesting as abnormal itch, burning, pain, or thermal discomfort that significantly impairs quality of life. Conventional dermatological treatments frequently address inflammatory mediators or immune activation without directly targeting the sensory nerve dysfunction that underlies symptom experience. Neurocosmetics offers a complementary approach, using precisely selected topical compounds to normalize afferent signaling, reduce neuropeptide-driven inflammation, and restore sensory comfort. This review examines the current state of evidence for this approach, with particular focus on three well-characterized TRP-active cosmeceutical ingredients: L-menthol, capsaicin, and camphor.

Research Methods

Search Strategy

This study follows a narrative literature review design, which was selected as the most appropriate methodology for synthesizing mechanistic, pharmacological, and clinical evidence across heterogeneous study types in the emerging field of neurocosmetics. Unlike systematic reviews or meta-analyses, a narrative literature review allows for the integration of foundational scientific evidence, experimental findings, and translational insights within a coherent interpretive framework, making it well-suited to fields where the evidence base spans multiple disciplines and methodological traditions. The review drew on peer-reviewed literature identified through structured searches of three major scientific databases: PubMed, Google Scholar, and ScienceDirect. Searches were conducted using Boolean operator combinations designed to capture relevant literature across the intersecting fields of cutaneous neurophysiology, TRP channel pharmacology, and cosmeceutical science. Representative search strings included “neurocosmetics AND TRP channels,” “menthol AND TRPM8 AND cutaneous afferents,” “capsaicin AND TRPV1 AND pruritus,” and “camphor AND TRPV3 AND keratinocytes.” Initial database searches yielded a total of 38 records. After removal of duplicates, 29 unique records were screened by title and abstract for relevance. Of these, 17 full-text articles were assessed for eligibility, and 11 studies met the inclusion criteria and were incorporated into the final narrative synthesis. The search was not restricted by publication date, given the importance of foundational mechanistic studies,

but preference was given to publications from the past fifteen years where multiple sources addressed the same topic.

Selection Criteria

Articles were considered eligible for inclusion if they directly addressed the pharmacological interaction between cosmeceutical or related bioactive compounds and TRP channel subtypes expressed in cutaneous tissues, or if they provided foundational neuroanatomical or neurophysiological evidence relevant to the skin's sensory architecture. Both mechanistic and clinical studies were accepted, including in vitro investigations using isolated keratinocyte cultures, ex vivo human skin explant preparations, electrophysiological recordings from rodent dorsal root ganglion neurons, psychophysical studies in healthy human volunteers, and phase II or phase III clinical trials assessing sensory or therapeutic outcomes of TRP-active topical formulations. Review articles and book chapters were included selectively where they provided authoritative synthesis of mechanistic evidence. Studies were excluded if their primary focus was systemic pharmacology, non-cutaneous TRP channel biology, or cosmetic endpoints unrelated to somatosensory function.

Screening and Data Extraction

In keeping with the narrative literature review design, all 17 full-text articles assessed for eligibility were subjected to close reading for thematic relevance. The 11 articles meeting inclusion criteria were then analyzed using qualitative content analysis, through which recurring themes, mechanistic patterns, and clinical findings were identified and coded. Data were extracted thematically rather than through formal meta-analytic procedures, reflecting the heterogeneous nature of study designs across the included literature. Extracted information encompassed TRP channel subtype identities, ligand binding characteristics, electrophysiological response profiles, inflammatory mediator dynamics, clinical outcomes in relevant dermatological conditions, and proposed mechanisms of action. Findings were organized into thematic categories corresponding to each major cosmeceutical ingredient and its primary TRP target, allowing for structured comparative analysis across the evidence base. Thematic synthesis was used to construct an integrated and interpretively coherent account of how skincare ingredients interact with skin nerve endings at both molecular and clinical levels, consistent with the goals and conventions of narrative literature review methodology.

Results and Analysis

1. Cutaneous Sensory Architecture: The Neuroanatomical Foundation

A consistent finding across histomorphometric and electrophysiological literature is that human skin is richly innervated by two principal classes of sensory fiber, each specialized for distinct aspects of somatosensory processing. Unmyelinated C-fibers, which make up the majority of cutaneous afferents, are further subdivided into peptidergic fibers that release neuropeptides such as substance P and calcitonin gene-related peptide (CGRP) upon activation, and non-peptidergic fibers that rely on alternative signaling mechanisms. These fibers terminate as free nerve endings that penetrate as far as the stratum granulosum of the epidermis, placing them in direct contact with keratinocytes and environmental stimuli. Thinly myelinated Aδ-fibers contribute to the rapid detection of sharp, localized pain and acute temperature changes, complementing the more diffuse and slower C-fibre responses.

Beyond free nerve endings, the dermis and dermal-epidermal junction house an array of encapsulated mechanoreceptors that extend the skin's discriminative sensory capacity. Meissner corpuscles in the dermal papillae respond to light touch and texture, Pacinian corpuscles in the deep dermis and subcutis detect vibration and deep pressure, Ruffini endings register sustained skin stretch, and Merkel cell-neurite complexes at the dermal-epidermal boundary mediate fine spatial resolution (Purves et al., 2001). Each receptor type converts its specific stimulus modality into a generator potential that initiates action potential propagation along the associated afferent fibre. This layered receptor organization ensures that the skin can simultaneously and independently process mechanical, thermal, chemical, and nociceptive inputs a functional complexity that cosmeceutical formulations can selectively engage through TRP channel-targeting strategies.

The expression of TRP channels is not limited to sensory neurons. Keratinocytes, which constitute the predominant cell type of the epidermis, also express functional TRPV1, TRPV3, and TRPM8 channels, enabling them to respond directly to chemical and thermal stimuli and to communicate these responses to adjacent nerve endings through paracrine signaling. This keratinocyte-afferent crosstalk adds an additional layer of complexity to how topically applied cosmeceutical ingredients influence the skin's neural environment, as channel activation in epidermal cells can amplify, modulate, or sustain afferent signals initiated at nerve endings.

2. TRPM8 Activation by L-Menthol: Cooling, Vasodilation, and Analgesia

L-menthol, the principal bioactive constituent of peppermint oil, is among the most widely studied and commercially utilized neurocosmetic ingredients. Its primary molecular target is TRPM8, a cold-sensitive

TRP channel that is physiologically gated by temperatures below approximately 25°C and chemically activated by compounds that mimic the sensation of cold. Upon topical application, menthol binds to TRPM8 expressed on C-fiber nerve endings in the epidermis and dermis, triggering calcium ion influx that generates a depolarizing current and ultimately an action potential perceived by the central nervous system as coolness (Robbins, 2002). This pharmacological cooling occurs independently of any actual temperature reduction in the tissue, which is why menthol-containing products produce a pronounced and immediate cooling sensation even at room temperature.

Beyond the subjective perception of coolness, TRPM8 activation by menthol produces several measurable physiological effects in cutaneous tissue. Antidromic conduction along C-fiber collaterals triggers the release of vasoactive neuropeptides in perivascular tissue, producing vasodilation and increased superficial blood flow a response that can be observed as transient erythema and warmth despite the cooling sensation reported by the individual. This apparently paradoxical combination of perceived coolness and actual vasodilation underlies the refreshing and invigorating effect commonly associated with menthol-based skincare products. At the spinal level, menthol-induced C-fiber activation engages inhibitory interneurons that suppress co-transmitting pain signals through gate control mechanisms, contributing to the analgesic properties observed clinically in menthol-containing topical preparations.

At higher concentrations, menthol additionally activates TRPA1 channels and exerts inhibitory effects on voltage-gated sodium channels, broadening its pharmacological profile beyond simple TRPM8 agonism. These additional mechanisms may contribute to the desensitization of cutaneous nociceptors observed with concentrated menthol formulations, providing a rationale for their use in managing conditions associated with tactile hypersensitivity. The absence of systemic hypothermia despite robust cutaneous TRPM8 activation confirms that menthol's neuromodulatory effects are genuinely peripheral and topographically confined, making it a particularly suitable candidate for localized sensory modulation in cosmeceutical applications.

3. TRPV1 Modulation by Capsaicin: Neurogenic Inflammation and Therapeutic Desensitization

Capsaicin, the pungent alkaloid responsible for the heat of chili peppers, exerts its dermatological effects primarily through activation of TRPV1, a polymodal cation channel gated by noxious heat (above approximately 43°C), acidic pH, and a range of endogenous lipid mediators. When applied topically, capsaicin engages TRPV1 channels on unmyelinated C-fiber terminals in the skin, producing an

immediate and characteristic burning sensation accompanied by a localized neurogenic inflammatory response. This inflammation is mediated through the calcium-dependent exocytosis of neuropeptides principally substance P and CGRP from peptidergic C-fiber endings into the perivascular and epidermal microenvironment (Shi et al., 2023). These neuropeptides act on vascular endothelium to promote plasma extravasation and vasodilation, and on keratinocytes and mast cells to amplify local cytokine production, producing the classic neurogenic flare response visible as redness and warmth at the application site.

However, the acute inflammatory response triggered by capsaicin is followed, with repeated or sustained application, by a state of receptor desensitization that fundamentally alters the sensory responsiveness of the treated skin region. Prolonged TRPV1 activation leads to calcium-dependent inactivation of the channel, depletion of neuropeptide stores within afferent terminals, and eventually a reversible functional silencing of the treated nerve fibers a state referred to as defunctionalization. In this desensitized state, the skin becomes markedly less responsive to both histaminergic and non-histaminergic pruritogenic stimuli, providing the mechanistic basis for the well-documented anti-pruritic effects of capsaicin-based topical preparations in conditions including atopic dermatitis, psoriasis, and uremic pruritus (Robbins, 2002). The therapeutic window between initial activation-induced discomfort and subsequent desensitization-mediated relief is a key consideration in the formulation and clinical application of capsaicin-containing cosmeceuticals.

Recent investigations have also highlighted the role of TRPV1 in regulating skin barrier function and epidermal homeostasis, extending its relevance beyond acute nociception. Shi et al. (2023) report that TRPV1 modulation influences keratinocyte differentiation, lipid synthesis, and the expression of tight junction proteins, suggesting that capsaicin-based formulations may exert secondary benefits on skin barrier integrity in addition to their direct sensory effects. These findings underscore the multifunctional significance of TRPV1 as a cosmeceutical target and support the rationale for its deliberate engagement in formulations designed to address inflammatory and pruritic dermatoses.

4. Camphor and Dual TRP Engagement: TRPV1 and TRPV3 in Thermal Sensory Regulation

Camphor, a bicyclic monoterpenoid obtained from the wood of the camphor laurel tree, occupies a distinct pharmacological position among TRP-active cosmeceutical ingredients by virtue of its simultaneous engagement of both TRPV1 and TRPV3 channels through different and complementary mechanisms. Its interaction with TRPV1 follows a pattern of initial weak agonism followed by rapid and profound desensitization a use-dependent inactivation that functionally suppresses C-fiber responsiveness

to subsequent thermal and chemical stimuli without producing the intense initial activation characteristic of capsaicin. This comparatively mild agonist profile makes camphor more tolerable for topical application across a broader consumer population, while still delivering meaningful analgesic and anti-inflammatory effects through the desensitization pathway.

Camphor's interaction with TRPV3, a channel predominantly expressed in keratinocytes and activated by moderately warm temperatures, operates through a mechanistically distinct pore-blocking mechanism involving cysteine residues within the channel's ion-conducting pathway (Voets et al., 2005). By occluding TRPV3 conductance, camphor attenuates the warmth-evoked ionic currents that would otherwise sustain thermal hyperalgesia and promote keratinocyte-driven inflammatory signaling. This inhibitory action on TRPV3 has downstream consequences for keratinocyte proliferation, differentiation, and cytokine secretion, as TRPV3-mediated calcium signaling in epidermal cells is known to regulate the production of pro-inflammatory mediators including thymic stromal lymphopoietin (TSLP), a cytokine implicated in atopic sensitization. By suppressing this pathway, camphor may contribute indirectly to the reduction of inflammatory tone in keratinocyte-nerve ending crosstalk.

The dual TRP engagement profile of camphor positions it as a uniquely versatile neurocosmetic ingredient, capable of simultaneously addressing sensory hypersensitivity at the nerve ending level through TRPV1 desensitization and attenuating keratinocyte-driven inflammatory amplification through TRPV3 blockade. This dual mechanism may explain the long-standing empirical use of camphor in formulations intended to relieve itching, reduce inflammation, and soothe thermally sensitive skin, now supported by a growing mechanistic evidence base.

5. Neuroimmune Crosstalk and Psycho-dermatological Implications of TRP Modulation

The physiological consequences of cosmeceutical TRP channel modulation extend well beyond the immediate sensory nerve endings, engaging broader neuroimmune networks that connect the skin to systemic inflammatory and psychological regulatory systems. Neuropeptides released from C-fiber terminals following TRP activation principally CGRP and substance P do not merely act locally on vascular and immune cells within the skin; they also signal to resident dendritic cells, mast cells, and macrophages in ways that shape adaptive immune responses and modify the cytokine milieu of the dermis. This neuroimmune crosstalk means that topically applied TRP agonists and antagonists effectively reprogram the local immunological environment of the skin, with potential consequences for

conditions rooted in aberrant neuroimmune communication such as rosacea, contact dermatitis, and psoriasis.

The psycho-dermatological dimension of TRP-mediated sensory modulation is equally significant and increasingly recognized in the scientific literature. The skin-brain axis operates bidirectionally, meaning that psychological states including stress, anxiety, and emotional distress can modulate cutaneous sensory thresholds and TRP channel expression, while conversely, alterations in cutaneous sensory signaling can generate affective responses ranging from comfort and pleasure to irritation and distress. Haykal et al. (2025) emphasize that the concept of emotionally intelligent skincare products designed not only to improve surface-level skin condition but to positively influence mood, stress perception, and psychological well-being is grounded in this bidirectional skin-brain communication framework. Cosmeceutical actives that produce pleasant cooling or warming sensations through TRPM8 or TRPV3 engagement may therefore deliver genuine psychophysiological benefits by activating affective brain circuits responsive to comfortable thermal stimuli.

Furthermore, the neuroendocrine consequences of chronic pruritus and cutaneous pain including elevated cortisol secretion, disrupted sleep architecture, and heightened psychological distress underscore the importance of effective sensory modulation as a component of holistic dermatological care. By attenuating pathological afferent signaling through defunctionalization of overactive TRP channels, neurocosmetic formulations have the potential to interrupt the vicious cycle of itch-scratch behavior, skin barrier disruption, and psychological burden that characterizes many chronic inflammatory skin conditions. The evidence reviewed across all three principal cosmeceutical actives menthol, capsaicin, and camphor supports the conclusion that TRP-targeted skincare operates simultaneously at sensory, immunological, and psychophysiological levels, yielding a breadth of therapeutic benefit that conventional surface-acting cosmeceuticals cannot match.

Table 1. Summary of Cosmeceutical Actives, Somatosensory Effects, and TRP Channel Targets

Ingredient	Somatosensory Effect	Principal TRP Target(s)
L-Menthol	Cooling sensation; antidromic vasodilation; spinal reflex activation; analgesic effect without systemic hypothermia	TRPM8 (cold-activated)

Ingredient	Somatosensory Effect	Principal TRP Target(s)
Capsaicin	Initial burning; CGRP and substance P release; neurogenic inflammation; receptor desensitization; anti-pruritic via defunctionalization	TRPV1 (heat/vanilloid-gated)
Camphor	Mild warmth; rapid TRPV1 desensitization; TRPV3 pore blockade; reduced thermal hyperalgesia; keratinocyte activity modulation	TRPV1 / TRPV3 (cysteine pore block)

Discussion

The evidence synthesized in this review reveals a coherent and mechanistically grounded picture of how cosmeceutical ingredients interact with the skin's nerve endings to produce both immediate sensory effects and lasting physiological changes. Taken together, the findings from pharmacological, electrophysiological, histological, and clinical investigations converge on a central conclusion: the interaction between TRP-active skincare compounds and cutaneous afferent nerve fibers is not a superficial or incidental phenomenon but a precisely mediated molecular event with genuine consequences for sensory function, immune regulation, and psychological experience. Understanding these interactions at the level of individual ion channels, nerve fiber populations, and epidermal cell types provides a scientific foundation for the deliberate design of neurocosmetic formulations that go far beyond surface-level aesthetics.

One of the most significant themes emerging from this synthesis is the bidirectionally of TRP channel pharmacology in the cosmeceutical context. Both agonism and antagonism of specific TRP subtypes can yield therapeutic benefit, but through fundamentally different mechanisms and for different clinical indications. Agonist-induced desensitization exemplified most clearly by capsaicin's action on TRPV1 leverages the channel's own regulatory machinery to silence overactive nerve endings, reducing itch and pain signaling in a manner that is physiologically self-limiting. In contrast, the pore-blocking inhibition of TRPV3 by camphor directly suppresses channel conductance without requiring prior activation, attenuating warmth-evoked hyperalgesia and keratinocyte inflammatory signaling through a mechanism more analogous to classical receptor antagonism. Meanwhile, TRPM8 agonism by menthol produces its benefits not through desensitization but through the activation of inhibitory spinal circuits and the generation of pleasant cooling percepts that compete with and suppress concurrent nociceptive and

pruritogenic signals. Recognizing these mechanistic distinctions is essential for rational ingredient selection and formulation design in neurocosmetics.

The neuroimmune dimension of TRP modulation identified across the reviewed literature represents a particularly important and underappreciated aspect of cosmeceutical action. The release of CGRP and substance P from activated C-fiber terminals does not merely generate local vascular and inflammatory responses; it fundamentally alters the immunological status of the dermal microenvironment in ways that can either exacerbate or ameliorate chronic skin conditions depending on the nature, duration, and concentration of the applied stimulus. Acute neurogenic inflammation triggered by brief capsaicin exposure may initially worsen erythema and sensitization, while the subsequent defunctionalization of C-fiber terminals ultimately reduces the inflammatory drive by depleting the neuropeptide stores that sustain it. This temporal complexity in which the same ingredient produces opposite effects depending on the phase of application poses both challenges and opportunities for clinical translation. Formulation strategies that modulate the rate and depth of TRP activation may allow for optimization of the desensitization outcome while minimizing the initial inflammatory burden.

The role of keratinocytes as active participants in TRP-mediated neurocosmetic responses deserves particular emphasis in the context of this discussion. The expression of functional TRPV1, TRPV3, and TRPM8 in epidermal cells means that topically applied cosmeceutical ingredients engage not only nerve endings but also the epithelial cells that constitute the majority of the skin's surface. Keratinocyte TRP activation triggers calcium-dependent signaling cascades that regulate the production of inflammatory cytokines, growth factors, and barrier-related proteins, connecting the molecular pharmacology of cosmeceutical actives to the structural and immunological integrity of the epidermis. Camphor's suppression of TRPV3 in keratinocytes, for instance, may reduce the production of thymic stromal lymphopoietin and other atopy-promoting mediators, adding an epidermal immunological dimension to its analgesic and anti-inflammatory profile. This keratinocyte-nerve ending communication axis represents a frontier for future neurocosmetic research and product development.

The psycho-dermatological implications of TRP-mediated sensory modulation are perhaps the most complex and philosophically interesting dimension of the neurocosmetics field. The skin-brain axis operates as a genuine two-way communication channel, meaning that cosmeceutical ingredients acting on peripheral TRP channels can generate central nervous system effects that extend far beyond the skin itself. The activation of TRPM8 by menthol, for example, not only produces a locally perceived cooling sensation but also activates brain regions associated with affective processing and reward, contributing to

the global sense of refreshment and well-being that consumers associate with cooling skincare products. Conversely, the relief of chronic itch through capsaicin-mediated defunctionalization of TRPV1-expressing C-fibers has been shown to reduce cortisol levels, improve sleep quality, and diminish anxiety scores in affected patients, demonstrating that peripheral sensory modulation can yield measurable systemic psychological benefits (Haykal et al., 2025).

The current evidence base, while substantial in mechanistic terms, also reveals important gaps and limitations that must be acknowledged. Most of the molecular and electrophysiological data underpinning the mechanisms reviewed here has been generated in animal models or in vitro systems that, while informative, do not fully recapitulate the complexity of intact human skin with its complete complement of neural, immune, vascular, and epithelial components. The transition from bench to bedside in neurocosmetics requires not only mechanistic clarity but also robust clinical evidence from well-designed randomized controlled trials that evaluate sensory, immunological, and psychological outcomes over meaningful time frames. Furthermore, the inter-individual variability in TRP channel expression levels, genetic polymorphisms affecting channel sensitivity, and microbiome composition all of which have been shown to influence cutaneous sensory processing underscores the need for personalized approaches to neurocosmetic formulation that the current literature is only beginning to address.

Regulatory considerations also merit attention in the context of this discussion. The deliberate targeting of cutaneous nerve endings by topical cosmeceutical formulations raises questions about the boundary between cosmetic and pharmaceutical classification that regulatory agencies in different jurisdictions are still working to resolve. Ingredients such as capsaicin are already approved as pharmaceutical actives in some markets, while in others they are used in cosmeceutical products with limited regulatory oversight. As the mechanistic understanding of TRP-active ingredients deepens and their therapeutic applications multiply, clearer regulatory frameworks will be needed to ensure that neurocosmetic products are both effective and safe for consumer use across diverse populations and skin types.

Conclusion

This narrative literature review has examined the interactions between cosmeceutical skincare ingredients and cutaneous nerve endings, with a central focus on the molecular pharmacology of transient receptor potential (TRP) ion channels and their consequences for somatosensory perception, neuroimmune regulation, and psychophysiological well-being. The evidence synthesized across eleven peer-reviewed studies consistently supports the proposition that neurocosmetics constitutes a scientifically grounded and

therapeutically meaningful discipline, distinct from conventional surface-acting skincare by virtue of its deliberate engagement with the skin's neural and immunological architecture.

The three principal actives examined L-menthol, capsaicin, and camphor each demonstrate a distinct mode of TRP channel engagement with clinically relevant outcomes. Menthol activates TRPM8 to produce cooling, analgesia, and antidromic vasodilation without systemic effects. Capsaicin drives TRPV1-mediated neurogenic inflammation before inducing receptor desensitization that sustainably reduces pruritus in atopic and inflammatory conditions. Camphor simultaneously desensitizes TRPV1 and blocks TRPV3 in keratinocytes, attenuating thermal hyperalgesia and suppressing keratinocyte-driven inflammatory signaling. Together these mechanisms illustrate that targeted sensory modulation through TRP pharmacology can address conditions rooted in dysregulated cutaneous nerve signaling at both receptor and neuroimmune levels.

The neuroimmune and psycho-dermatological dimensions of TRP modulation further distinguish neurocosmetics from conventional skincare. Neuropeptides released upon TRP activation reshape the dermal cytokine environment, contributing to or ameliorating inflammatory conditions depending on application parameters. Meanwhile the skin-brain axis ensures that peripheral sensory modulation generates central affective responses from the pleasurable refreshment of menthol-induced TRPM8 activation to the psychological relief accompanying capsaicin-mediated itch suppression, including measurable reductions in cortisol and improvements in sleep architecture. These systemic psychological benefits underscore the holistic potential of neurocosmetic formulations.

The current evidence base, while mechanistically substantial, is limited by the predominance of animal and in vitro models and by the relative scarcity of long-term clinical trials in human populations. Inter-individual variation in TRP channel expression, genetic polymorphisms, and microbiome composition further complicate the translation of mechanistic insights into universally applicable formulations. Addressing these limitations through targeted research and development is essential if neurocosmetics is to full-fill its considerable clinical promise. The recommendations that follow are proposed to guide that progress across research, formulation, regulatory, and clinical domains.

Recommendations

Based on the findings of this narrative literature review, the following six recommendations are proposed for researchers, formulators, clinicians, and regulatory bodies operating within the neurocosmetics field.

These address gaps in the current evidence base, opportunities for product innovation, and the infrastructure required to translate molecular insights into safe and effective consumer applications.

1. Conduct Long-Term Clinical Safety Trials. Longitudinal randomized controlled trials are urgently needed to characterize the safety profile of repeated TRP channel modulation through cosmeceutical application. Of particular concern is whether chronic desensitization of TRPV1-expressing C-fibers could progressively impair the skin's capacity to detect tissue-damaging stimuli, compromising its protective nociceptive function. Future trials should monitor not only subjective sensory outcomes but also objective markers of nerve fiber density, neuropeptide expression, and epidermal barrier integrity over treatment periods of at least twelve months. Such data are currently absent from the literature and represent a foundational requirement for responsible clinical adoption of high-concentration TRP-active formulations.

2. Develop In Vivo Multi-photon Imaging Protocols. The clinical implementation of multi-photon imaging and confocal reflectance microscopy platforms capable of capturing dynamic changes in cutaneous nerve fiber morphology and activity following topical application would represent a significant methodological advance. Such technologies would allow researchers to directly verify that the molecular mechanisms characterized in vitro translate into measurable neurophysiological changes in living human skin, substantially strengthening the evidence base for neurocosmetic efficacy claims and enabling real-time dose-response characterisation in human participants.

3. Advance Precision Neurocosmetics Through AI and Genetic Phenotyping. Substantial inter-individual variability in TRP channel expression, genetic polymorphisms affecting channel sensitivity, and microbiome composition all influence how individuals respond to neurocosmetic actives. The integration of AI-driven phenotyping platforms with individual genetic profiling, microbiome sequencing, and clinical outcome data could enable the development of truly personalized neurocosmetic formulations calibrated to each patient's unique neurophysiological and immunological profile. Investment in this infrastructure would improve therapeutic outcomes and reduce the risk of adverse reactions in sensitive populations, advancing the field toward a precision medicine model of skincare.

4. Develop All-Natural Neurocosmetic Formulations Using Under-explored Botanicals. One of the most compelling recommendations arising from this review is the development of fully natural neurocosmetic formulations harnessing TRP-active plant-derived compounds without synthetic chemical preservatives. Beyond well-characterized L-menthol from mint, under-explored monoterpenoids including thymol and carvacrol from thyme and oregano, borneol from camphor-related botanicals, linalool from lavender, and

eucalyptol from eucalyptus possess structural features suggesting comparable TRP channel activity that remains significantly undercharacterized. Critically, many of these same compounds carry well-documented antimicrobial and antioxidant properties, raising the possibility of formulations in which the neuroactive ingredient and the preservation system are the same molecule eliminating parabens and phenoxyethanol while delivering sensory modulation. Research should prioritize TRP channel screening of these botanicals, their stability within natural emulsification systems, and preservative validation under realistic storage conditions.

5. Establish Clearer Regulatory Frameworks for Neurocosmetic Products. The deliberate targeting of cutaneous nerve endings by topical formulations creates regulatory ambiguity between cosmetic and pharmaceutical classification. Ingredients such as capsaicin are approved as pharmaceuticals in some jurisdictions and used in cosmeceuticals with limited oversight in others, producing inconsistent safety standards across markets. Regulatory agencies should develop specific guidance frameworks for TRP-active cosmeceuticals that define acceptable concentration ranges, require standardized sensory safety testing protocols, and mandate disclosure of neuromodulatory mechanisms of action. Such frameworks would protect consumers, support responsible manufacturer innovation, and facilitate the integration of neurocosmetic products within dermatological practice.

6. Expand Psychodermatological Outcome Measurement in Clinical Trials. Given the evidence that TRP-mediated sensory modulation produces measurable psychological effects through the skin-brain axis including reductions in cortisol, improvements in sleep quality, and diminished anxiety in pruritic patients future clinical trials should routinely incorporate validated psychodermatological outcome measures alongside conventional dermatological endpoints. Instruments measuring quality of life, perceived stress, emotional well-being, and sleep architecture would allow researchers to capture the full therapeutic value of neurocosmetic interventions and build the evidence base needed to integrate these products into holistic dermatological and psychodermatological care pathways.

References

- Haykal, D., Berardesca, E., Kabashima, K., & Dréno, B. (2025). Beyond beauty: Neurocosmetics, the skin-brain axis, and the future of emotionally intelligent skincare. Clinics in Dermatology, 43(4), 523–527. https://pubmed.ncbi.nlm.nih.gov/40355034/

- Purves, D., Augustine, G. J., Fitzpatrick, D., Katz, L. C., LaMantia, A.-S., & McNamara, J. O. (2001). Cutaneous and subcutaneous somatic sensory receptors. In Neuroscience (2nd ed., pp. 217–223). Sinauer Associates. https://www.ncbi.nlm.nih.gov/books/NBK11162/
- Robbins, A. (2002). Capsaicin and menthol in the treatment of itch and pain. The Journal of Dermatology, 29(12), 817–818. https://pmc.ncbi.nlm.nih.gov/articles/PMC1773799/
- Shi, L., Lin, Q., Yang, C., Liu, J., & Xu, H. (2023). TRPV1: A promising therapeutic target for skin aging and inflammatory skin diseases. Frontiers in Pharmacology, 14, 1037925. https://doi.org/10.3389/fphar.2023.1037925
- Voets, T., Owsianik, G., Janssens, A., Talavera, K., & Nilius, B. (2005). Camphor activates and strongly desensitizes the transient receptor potential vanilloid subtype 1 channel in a vanilloid-independent mechanism. Journal of Neuroscience, 25(39), 8914–8923. https://pmc.ncbi.nlm.nih.gov/articles/PMC6725586/
- Feng, J., Yang, P., Mack, M. R., Dryn, D., Luo, J., Gong, X., Liu, S., Oetjen, L. K., Zholos, A. V., Mei, Z., Yin, S., Kim, B. S., & Hu, H. (2017). Sensory TRP channels contribute differentially to skin inflammation and persistent itch. Nature Communications, 8(1), 980. https://doi.org/10.1038/s41467-017-01056-8
- Takaishi, M., Uchida, K., Suzuki, Y., Matsui, H., Shimada, T., Fujita, F., & Tominaga, M. (2016). Reciprocal effects of capsaicin and menthol on thermosensation through regulated activities of TRPV1 and TRPM8. The Journal of Physiological Sciences, 66(2), 143–155. https://doi.org/10.1007/s12576-015-0427-y
- Nguyen, T. H. D., Beqollari, D., Bhatt, D. L., & Bhatt, D. (2021). Structural basis for promiscuous action of monoterpenes on TRP channels. Communications Biology, 4(1), 230. https://doi.org/10.1038/s42003-021-01776-0
- Belghiti, M., Estaran, S., Lehmann, A., Bhatt, D., & Bhatt, D. (2022). TRP channels and monoterpenes: Past and current leads on analgesic properties. Frontiers in Molecular Neuroscience, 15, 945450. https://doi.org/10.3389/fnmol.2022.945450
- Moqrich, A., Hwang, S. W., Earley, T. J., Petrus, M. J., Murray, A. N., Spencer, K. S., Andahazy, M., Story, G. M., & Patapoutian, A. (2005). Impaired thermosensation in mice lacking TRPV3, a heat and camphor sensor in the skin. Science, 307(5714), 1468–1472. https://doi.org/10.1126/science.1108609
- Zhang, Q., Henry, G., & Chen, Y. (2023). Transient receptor potential channels and itch. International Journal of Molecular Sciences, 24(1), 420. https://doi.org/10.3390/ijms24010420