American Journal of Biochemistry and Biotechnology

Research Article

Exploring the Relationship Between Skin Barrier Function, Sensitivity, and Repair Mechanisms

Xiaoqing Yan, Yusong Shi and Jiguang Yang

Department of Medicine, Jinan Dermatosis Prevention and Control Hospital, China, Jingsan Road, Huaiyin District, Jinan City, China

Article history
Received: 05-02-2025
Revised: 07-05-2025
Accepted: 23-05-2025

Corresponding Author:
Yusong Shi
Department of Medicine, Jinan Dermatosis Prevention and Control Hospital, China, Jingsan Road, Huaiyin District, Jinan City, China
Email: jiaqiyan1@outlook.com

Abstract: For healthy skin, the skin's barrier function must remain maintained. Many different molecular while immunological signaling mechanisms are involved in skin barrier control. The control of a healthy skin barrier, particularly acid mantle maintenance and proper amounts of ceramides, may help dermatologists develop remedies for skin barrier disruption disorders. In contrast, new medicines could focus on signaling pathways to offer more effective treatment for patients by identifying which skin barrier alterations are related with certain illnesses. For example, psoriasis and atopic dermatitis. A functioning model of the epidermis barrier has been recently published, and the skin's anatomical layers are well delineated. Many skin disorders include disturbance of the skin's protective barrier, and for some, like atopic dermatitis, moisturization is the first line of defense. The purpose of this study was to examine the skin barrier through the lens of the function approach, paying special attention to how moisturizers aid in the maintenance and repair of the skin barrier's many functional layers. The construction and function of the skin barrier are maintained by four interdependent layers: chemical, microbiologic, physical, and immunologic. More than one study found that moisturisers improved transepidermal water loss by targeting disturbance that affected all four of these layers via different pathways. To further fortify the skin's physical barrier, occlusives obstruct the Stratum Corneum (SC) surface, humectants attract water from the dermis to the epidermis, and emollients absorb into the SC. By promoting normal enzymatic activity, raising ceramide synthesis, and creating an optimum environment for commensal microbes, acidic moisturizers strengthen the skin's chemical barrier. By lowering permeability and, by extension, allergen penetration and sensitization, regular moisturizing may fortify the immunologic skin barrier. Disruptions to the skin barrier have distinct effects on the physical, chemical, microbiological, and immunologic layers. In order to keep everything in balance and make repairs easier, moisturizers work by penetrating all seven layers of the skin's protective barrier. Age, gender, race/ethnicity, and skin type are some of the factors that influence skin characteristics. Furthermore, lifestyle factors and body mass index may affect skin features, which in turn vary by place on the body. Despite the skin's primary role as a barrier, it is nonetheless able to allow the absorption of some chemicals Changes in skin function along with general well-being may result from a wide range of environmental and lifestyle variables. The characteristics and functions of the skin are closely related.

Keywords: Skin Barrier Function; Transepidermal Water Loss; Moisturizers; Ceramides; Atopic Dermatitis; Psoriasis; Dermatology; Stratum Corneum

Introduction

Changes in the environment and emotional stress are two of the external variables that have contributed to the steady growth in the occurrence of skin sensitivity concerns in human populations. Hyperreactivity of the skin, known as skin sensitivity, may manifest under certain normal or abnormal physiological or pathological circumstances. In extreme circumstances, sensitive skin may cause skin illnesses like eczema or dermatitis, which present as redness, itching, and discomfort (Ljosaa *et al*., 2020). hazardous proteins, accompanied by varying degrees of 2, 5, and CD7 deletion. There is no evidence of 4, 30, CD56, or EBV-encoded small RNA. The presence of red blood cell fragments (hemophagocytosis) and karyorrhectic nuclear waste (cytophagocytosis) by histiocytes that seem normally may also be seen. Despite the lack of sensitivity and specificity, hemophagocytosis in subcutaneous tissue should be considered a diagnostic indicator of cutaneous T-cell lymphomas (Tan ***et al.***, 2021). Low tolerance and strong responsiveness characterize sensitive skin. Unique skin care functionality is found in natural compounds like madecassoside and paeoniflorin. Although paeoniflorin and madecassoside have anti-inflammatory and skin barrier repair-enhancing properties, they are unable to penetrate the stratum corneum due to the skin barrier (Laskin *et al*., 2023). Sensitivity of the face skin is a symptom of inflammatory papulopustular rosacea. Consequently, rosacea medicines need meticulous vehicle construction to guarantee the most effective drug delivery in a setting conducive to barrier restoration (Porto Ferreira *et al*., 2023). The military and civilian populations are equally at risk from Sulfur Mustard (SM). For humans, SM triggers a series of symptoms including delayed erythema, swelling, and inflammatory cell infiltration, culminating in the formation of massive blisters filled with fluid. After blistering, the skin takes longer to heal, which might make the barrier less effective. The creation of animal models with a human-like pathophysiology is crucial for understanding how SM acts in the skin, as it allows for quantitative evaluations of the effectiveness of treatment medications (Zhou *et al*., 2024). Although the precise mechanisms of action of topical dexpanthenol are not fully understood, it is known to have moisturizing characteristics and to maintain and restore the skin barrier function (Evidence-Based Complementary and Alternative Medicine, 2023). Concerns for sensitive skin have been raised by the widespread use of mask-wearing in the post-COVID-19 period. This randomized controlled trial examined the effects of a moisturizer containing biological lipids and probiotics on 30 female volunteers with sensitive skin, looking at changes in skin barrier function and microbiome composition as a result of wearing a mask. At baseline, three hours after masking, post-tape removal, and after twenty-four hours, the masked and unmasked regions' skin physiological indicators were measured, including transepidermal water loss, erythema index, stratum corneum moisture, pH, and temperature (Evidence-Based Complementary and Alternative Medicine, 2023). Flares caused by exposome variables characterize rosacea, a prevalent face dermatosis. Hyaluronic acid, tocopherol, niacinamide, probiotic fractions, Vichy mineralizing water, and M89PF all work together to strengthen the skin's defenses and rebuild the skin barrier (Nagrik *et al*., 2024). It is well-known that exposuresome aggressions diminish the skin's barrier and defensive capabilities, among others. Percolating via magmatic and volcanic rocks in France's Auvergne area, Vichy Volcano Mineralizing Water (VVMW) becomes a clean, highly mineralized water with a total mineral concentration of 5.2 g/L and 15 different minerals (Peng *et al*., 2023). Accumulation of cancerous T cells in the skin is the hallmark of the terrible lymphoid tumor known as Cutaneous T-Cell Lymphoma (CTCL). In addition to being entrance points for bacterial infections, which are a leading cause of morbidity and death in advanced illness, skin lesions produce severe symptoms that impair quality of life. It is still unclear what causes the pathological processes that damage the skin's protective barrier (Johnson *et al*., 2023). Clinical signs including redness, burning, and dryness are shared with other inflammatory dermatoses like rosacea and dermatitis, however the exact pathophysiology of sensitive skin is yet understood (Naik, 2021). The release of mediators from skin-resident cells aids in the repair of the skin barrier after abrasive stress. This process has only been studied in simplified human systems or in mice, and the few biomarkers that have been studied so far have been somewhat small (Zaric *et al*., 2019). We examined cosmetics using Artemisia annua extract to see whether it helped heal sensitive skin, as consumer skin sensitivity has been on the rise in recent years. The results of the trial with xylene-induced ear swelling in mice showed that three groups of cosmetics containing Artemisia annua extract had inhibition rates of xylene-induced ear swelling in mice that were close to the positive drug group: 60.40 percent, 73.36, and 74.01%, respectively. A human clinical experiment was conducted with 25 volunteers who volunteered to have their skin examined for TEWL value, cuticle moisture degree, and skin heme (ultra-high concentration) (Hu *et al*., 2020). The need for biocompatible, safe, and effective therapies has boosted the need for formulations based on natural ingredients in chronic wound care. Vegetable oil-enriched natural polysaccharide emulsions show promise as a skin restoration aid because they provide structural support and protective barriers that are well-suited to delicate wound settings (Tring and Jolly, 1973). Many synthetic materials have been developed as a result of human

society's progress for the sake of improved convenience; yet, these innovative items often release unnatural substances into the environment as side effects. The skin is the body's first line of protection against harmful substances and germs, so keeping it healthy has implications for both outward appearance and internal well-being. A refined diet and excessive housekeeping habits do not enhance the quality of life for many individuals who have hectic lives (Rinnov *et al*., 2023). Formulations for dermo-cosmetics have increasingly incorporated bioactive compounds derived from plants. The result is a wide variety of cutting-edge solutions that address a wide range of issues, such as anti-aging, antioxidant, depigmenting, and moisturizing. The mechanism of action of the natural bioactive elements inside dermo-cosmetics is still up for dispute, despite the fact that many methods using science and nature are used to produce these effective molecules (Lacerda Brito *et al*., 2023). Psoriasis is a prevalent chronic skin illness that may lead to skin lesions that are thicker and scaley, red, inflamed, and may include painful sores, fissures, pustules, and blisters. Psoriasis was formerly thought to be a skin ailment that did not cause any discomfort (Chen *et al*., 2024).

Motivation

Atopic dermatitis, dermatitis, and seborrheic dermatitis are frequent inflammatory skin illnesses that may have a significant impact on a person's quality of life. These disorders are based on the interconnected functions of the skin barrier, environmental assaults, and genetic origins. When it comes to management, topical treatment is often the go-to option. Medicinal formulation at an adequate dose is thought to be necessary for effective topical therapy, since it must penetrate the stratum corneum and diffuse to the desired region in order to exert therapeutic effects. The physicochemical characteristics of the active ingredient, the makeup of the product's base, and the skin barrier's limits and circumstances (particularly in inflammatory skin) are among the several elements that might impact this process. Inflammatory skin disease remedies are discussed in this article, which also offers a concise overview of the relevant research on the topic.

Impacts of Skin Barriers

Mammals on land rely on their skin, which is constantly changing and repairing itself, as a primary barrier from the elements. Alterations to the Stratum Corneum (SC) integrity and an increase in Transepidermal Water Loss (TEWL) are common symptoms of impaired skin barrier function. Damage to the skin that leads to a split in the SCand/or a loss of SC lipids or their malfunction is a common cause of impaired skin barrier function. Skin dryness and flakiness is the most frequent skin condition. This results from a number of causes, including mechanical failure, impairment of SC cell maturation and desquamation, and a reduction in the SC's water-holding capacity, as well as direct injury to the SC. Moisturizers, particularly those that augment SC barrier function, may cure dry, flaky skin, which is linked to several physiological and pathological problems.

Hypothesis

The working idea is that several variables may disturb the skin barrier, which in turn increases skin sensitivity and hinders its healing processes. This, in turn, causes inflammatory processes, more damage, and a decrease in the effectiveness of the barrier.

Research Questions

- How to Study the mechanisms that influence the many routes that restore the skin's barrier
- How to investigate the skin microbiota contributes to the maintenance and healing of the skin barrier
- How to creating novel approaches to enhancing skin health and treating a range of skin disorders by mending and fortifying the skin barrier

Related Work

The three main tactics for alleviating symptoms—skin-barrier restoration, decrease in TRPV1 receptor activity, and anti-inflammatory treatments using active compounds—are discussed in this review, along with the sensitization processes and features of sensitive skin. This study's results will increase awareness of sensitive skin, spur further studies and real-world approaches to prevention and treatment, and provide theoretical backing for the creation of cosmetics that calm sensitive skin (Lu *et al*., 2023). To enhance their delivery efficiency, stimulate sensitive skin regeneration, and counter inflammation, we created nanoemulsions (PM-NEs) laden with paeonol and madecassoside. Efficacy was also thoroughly assessed in clinical studies, 3D skin models, and cell line models. By increasing cellular absorption and improving transdermal penetration and retention, PM-NEs rendered madecassoside glucoside and paeonol more effective. The secretion of filamentous protein, aquaporin 3, Claudin-1, and hyaluronic acid was greatly enhanced by the PM-NEs in cellular assays and 3D epidermal models, while the secretion of interleukin 1α, interleukin 6, tumor necrosis factor-α, and prostaglandin E2 was considerably inhibited, in comparison to the free components. Evidence from clinical trials shown that PM-NEs considerably decreased a* values, erythropoietin, transepidermal water loss, non-inflammatory acne, and inflammatory acne on the face. Nanoemulsions containing both paeoniflorin and madecassoside show promise as a means to enhance the topical delivery

efficiency and anti-inflammatory healing effectiveness in sensitive skin, according to three tiers of systematic research (Draelos, 2021). Subjects with inflammatory rosacea were included in this phase 1 trial to better understand the barrier effects of a topical minocycline anhydrous gel 3% that was under evaluation. METHODS Thirty-one male and female subjects of various complexion types were included in this single-site study to assess the effects of a newly developed topical 3% minocycline anhydrous gel vehicle on skin barrier function. The gel is an investigational product that has already completed a phase 2b study in rosacea patients. Once the individuals had adjusted to the conditions for 30 minutes, they measured their Transepidermal Water Loss (TEWL) for one minute on one cheek and their pin probe corneometry for three times on the other. On days 1, 2, and 4, subjects returned to the study facility after using the 3% minocycline anhydrous gel topically every evening. 30 out of 31 participants were able to finish the trial. On day one, the study medicine increased skin hydration by 23% (P=0.003). By week two, it maintained this gain, increasing skin hydration by 22% (P=0.003), and by week four, it increased skin hydration by 20% (P=0.001). On the same note, skin barrier function was shown to improve with an 11% drop in TEWL on day 1, an 18% drop at week 2 (P=0.001), and a 28% drop at week 4 (P<0.001). The skin-healing and moisturizing effects of the topical 3% minocycline anhydrous gel medicine that was studied in this research contributed to the improvement of the skin barrier (Berardesca *et al*., 2023).

Using protective face masks, this research evaluated the efficacy of M89PF in rosacea patients who also had erythema and sensitive skin during the COVID-19 pandemic. Participants in a 30-day randomized, split-face trial with erythema-associated rosacea and sensitive skin were compared to those who received standard skin care products. Redness, scaling, tightness, dryness, heat, itching, stinging, stinging test, and local tolerability were all included of the clinical assessments. Erythema, skin moisture, and TEWL were the instruments used for assessment. Also evaluated was the level of subject satisfaction. Both time periods showed a substantial improvement in erythema while using M89PF ($p<0.01$ at D15 and $p<0.001$ at D30). At 30 days after starting M89PF, skin sensitivity as measured by the skin stinging test showed a substantial improvement ($p<0.01$) when contrasted with baseline and regular skin care. Compared to baseline and the untreated side, M89PF substantially reduced skin redness, tightness, dryness, hydration, and TEWL at D15 and D30 ($p\leq0.05$). At D15 and D30, subjects reported very high levels of satisfaction with M89PF. Across the board, tolerance was excellent. Conclusions: M89PF improves skin hydration and sensitivity, decreases redness, tightness, dryness, and TEWL in rosacea participants, and this is true even when the subjects use protective masks. Users have reported a high level of satisfaction with M89PF (Rasmont *et al*., 2022).

To better understand how VVMW mitigates exposome aggressions on the skin, we summarize the relevant findings from in vitro and ex vivo investigations (using keratinocyte cultures, a 3D reconstructed skin model, skin explants, and clinical trials) that assessed its impact on essential skin functions. The skin-protecting properties of VVMW include an increase in the production of keratinocyte differentiation markers and tight junction proteins in vitro. By increasing skin hydration and speeding up cell turnover, VVMW showed promise in clinical trials. Features that enhance the skin's antioxidant defense: VVMW boosted the production of antioxidant defense markers and outperformed competing thermal water in stimulating the expression of glutathione peroxidase, superoxide dismutase, and catalase in keratinocytes in vitro. Exposure to UVA radiation restored endogenous catalase activity in vivo using VVMW. In terms of anti-inflammatory effect, VVMW decreased inflammation created by substance P both in vitro and in vivo, as well as stinging caused by lactic acid. Subjects with sensitive skin reported less redness and dryness after applying VVMW topically, indicating a calming and decongestant action. Applying VVMW after sodium lauryl sulfate disrupted the skin barrier resulted in quicker recovery from redness and erythema than either water or untreated skin, according to a previous study (Brink *et al*., 2024).

we looked at the potential of EIS as a non-invasive way to test the epidermal barrier function of HEE. We used 24-transwell cell culture equipment with a specially-made cover that has 12 pairs of electrodes arranged on it. There was no effect on epidermal morphology after seven days of serial EIS measurements, and the results were in line with those of single-measurement HEEs. The resultant impedance spectra showed two distinct frequency ranges, one associated with stratum corneum thickness and the other with keratinocyte terminal differentiation (EISdiff, lower frequency range) that is independent of epidermal thickness. The absence of FLG, TFAP2A, AHR, or CLDN1 in HEEs produced by CRISPR/Cas9 altered keratinocytes demonstrated that keratinocyte terminal differentiation is the primary criterion for EISdiff. Keratinocyte differentiation marker expression and EISdiff were both decreased after exposure to cytokine mixtures associated with atopic dermatitis or psoriasis, both of which are inflammatory skin conditions. Stimulation with therapeutic agents restored the EISdiff reduction associated with cytokines (Zang *et al*., 2024).

This study aims to examine the C-xyloside-enriched face cream for its anti-aging effects on the skin and to determine how it works by mending and reducing wrinkles. The 3D epidermal skin model was used to study

the healing effectiveness, while ex-vivo human skin was used to study the antiaging efficacy. Chinese women participated in two clinical trials. The first trial had 49 participants, ranging in age from 30 to 50, who were all worried about wrinkles. They were given 8 weeks to use the experimental cream that contained C-xyloside. The dermatologist examined the wrinkles and their characteristics. Furthermore, skin hydration, transepidermal water loss (TEWL), and skin elasticity were assessed using instruments. Thirty participants, ranging in age from 25 to 60, who reported having sensitive skin and redness on their faces were included in the second trial and told to use the cream for a duration of four weeks. Facial tape strips were used to analyze biomarkers in the stratum corneum. The 3D skin model's histomorphology was enhanced following SLS stimulation by using the cream, and the expression of LOR and FLG was greatly increased (Gluud *et al*., 2023).

Areas close to TOX positive T cells in CTCL skin lesions show impaired expression of the skin barrier proteins filaggrin and filaggrin-2, and there is an increase in transepidermal water loss. In order to activate STAT3 signaling and downregulate filaggrin and filaggrin-2 expression in human keratinocytes and rebuilt human epithelium, malignant T cells release mediators, which include cytokines like IL-13, IL-22, and Oncostatin M. Therefore, a combination of antibodies targeting these cytokines/receptors, siRNA-mediated reduction of JAK1/STAT3, and JAK1 inhibitors might counterbalance the regulation of filaggrins. Importantly, we demonstrate that filaggrin expression is upregulated in lesional skin from mycosis fungoides patients treated with Tofacitinib, a clinically licensed JAK inhibitor. These results suggest that cytokines secreted by malignant T cells cause epidermal barrier abnormalities via a JAK1/STAT3 dependent pathway. Based on our research, clinical grade JAK inhibitors provide new hope for patients with advanced CTCL who also have a damaged skin barrier, as they significantly reduce the harmful impact of cancer cells on these proteins (García-Millan *et al*., 2022).

This study was aimed to provide some early evidence that Endoret-Serum (ES) works as an autologous treatment for sensitive skin changes that may be applied topically. Techniques and Materials for three months, five patients had a topical ES therapy once day. Reliable dermatological questionnaires (DLQI, IGA, Likert, PGI-I) were used for clinical evaluation. In addition, we used reflectance confocal imaging and high-resolution topographic mapping to assess the moisture levels of the skin. The results showed that there were no side effects from the therapy. After the follow-up period ended, surveys showed a significant improvement in therapy efficacy when compared to the beginning. Topographic imaging revealed a reduction in the patient's underlying inflammatory and vascular state, and skin hydration was also enhanced. Endoret-Serum may be helpful in managing clinical symptoms caused by sensitive skin modifications, according to this early investigation (Baumann *et al*., 2021).

We show how a human ex vivo skin model may be utilized to study early events triggered by skin-barrier breakdown. Skin microdialysis was used to extract ten useful biomarkers from the interstitial fluid, which were then analyzed utilizing a multiplex platform. Microdialysis biomarker profiles were compared to skin biopsy homogenate profiles as a control. When exposed to abrasive trauma, nine out of ten biomarkers (GM-CSF, CXCL1/GROα, CXCL8/IL-8, CXCL10/IP-10, IL-1α, IL-6, MIF, TNF-α, and VEGF) showed a substantial increase in expression. There was a complete absence of effect of skin abrasion on CCL27/CTACK dialysate levels. The concentrations of biomarkers in the homogenates were seen to match those in the dialysate for CCL27/CTACK, CXCL1/GROα, CXCL8/IL-8, and IL-6. The levels of MIF in biopsy samples remained stable, whereas IL-1α exhibited a shift in the other direction in response to trauma. The biopsy homogenates did not include GM-CSF, CXCL10/IP-10, TNF-α, or VEFG. Our findings provide credence to the idea that studying the skin barrier's early events in a human ex vivo model is a valid method (Mijaljica *et al*., 2024).

Understanding the structural and functional aspects of important phytosphingosine-based ceramides (CERs), such as [EOP], [NP], and CER[AP], and how they contribute to the health of atopic skin is the goal of this study. In this article, we will go over the ways in which these crucial lipids of the stratum corneum (SC) help keep the skin's barrier function in check and how they add to the barrier's cohesion and durability. We also think about how CER[EOP], CER[NP], and CER[AP] might help keep skin hydrated and soothe dry, itchy, or sensitive skin. The next step is to investigate the relationship between the distinctive features of atopic skin illnesses like eczema and an imbalance or insufficiency of [EOP], [NP], and CER[AP]. In addition, we go over the significance of Free Fatty Acids (FFAs) and cholesterol (CHOL), two lipids that dwell in the SC and are essential for the proper functioning of the CER (Trindadeb *et al*., 2024).

Incorporating oils of avocado (Persea gratissima) and blackcurrant (Ribes nigrum), respectively, into semisolid polysaccharide emulsions for wound healing was the goal of this work. The biocompatibility and gel-forming capabilities of both Gellan Gum (GG) and Kappa-Carrageenan (KC) made them suitable stabilizers. We used an in vitro scratch test to measure the physicochemical characteristics, spreadability, rheology, antioxidant activity, biocompatibility, and wound healing efficiency of four different formulations (F1-GG-AO, F2-KC-AO, F3-GG-BO, and F4-KC-BO). Findings: FTIR verified excipient compatibility, and pH levels ranging

from 4.74 to 5.06 were appropriate for topical use on the skin. The formulations exhibited proper spreadability (7.13-8.47 mm2/g), decreased occlusive potential, and pseudoplastic behavior with thixotropy. Less bioadhesion meant it was easier to apply and remove, which meant the user was more comfortable. Stabilized with KC, the formulations showed better antioxidant activity (DPPH scavenging), were biocompatible with fibroblasts (CC50% 390-589 µg/mL), and did not hemolyze. By encouraging cell migration, F2-KC-AO and F4-KC-BO both outperformed other formulations in in vitro wound healing (Barnes *et al*., 2022). By metabarcoding the universal V3-V4 16S rRNA region from tape strip skin samples, we examined the skin-associated bacterial populations of healthy volunteers, as well as lesional and nonlesional skin of AD patients. For both healthy controls and Alzheimer's Disease (AD) patients, we measured the spatial-temporal variation (across individuals, different skin depths, different time points) of the skin-associated bacteria, taking into account the relative change caused by AD in each group. The bacterial community had the strongest interindividual correlation with skin depth and AD state, after which skin depth and AD status were the next most important variables. Within the AD population and the healthy control group, no statistically significant temporal change was detected. There was a significant difference in the bacterial community between patients with and without filaggrin mutations, and this difference was also associated with the severity of AD. In order to better understand the function of the skin bacterial community in the etiology of Alzheimer's disease, future research should not view AD as a presence-absence problem but rather sample subsurface epidermal populations while taking AD severity and the host genome into account. IMPORTANCE It is possible that skin-associated bacteria affect immune response and skin barrier function. Researchers have looked at the spatiotemporal variation of skin bacteria in healthy skin in an effort to deduce what variables control skin bacterial populations (Baldi *et al*., 2023).

The research examined the effects of a postbiotic mix of three probiotic strains, TYCA06/AP-32/CP-9 (TAC), on Staphylococcus aureus growth suppression and anti-inflammatory cytokine stimulation in vitro, including Transforming Growth Factor (TGF)-β and Interleukin (IL)-10. Wound healing in keratinocytes HaCaT cell culture and skin moisture content in vivo were both improved by this TAC formulation. The human clinical experiment included administering a cosmetic lotion containing the TAC mixture to the hands and faces of volunteers who had Atopic Dermatitis (AD). Skin hydration, irritation, and brightness were all positively affected by the TAC lotion. Also, the broken skin wound healing in AD participants was enhanced by using TAC lotion. Worst of all, this TAC lotion reduced the appearance of wrinkles and speckles on the face. By combining these postbiotic TAC ingredients, we may improve skin health and reduce redness and itching in AD patients' skin (Zhang *et al*., 2019). Synergistic uses of natural active substances for the treatment of common but specialized skin problems are the subject of this review, which summarizes the primary biological processes behind their action. Givaudan Active Beauty is a global leader in pioneering research on natural actives; 28 of their plant-derived bioactives were chosen for this study. The firm is based in Argenteuil, France. Using a variety of keywords, we searched PubMed for articles discussing their biological function. Restrictions were not imposed based on language or publication date. Information from Givaudan Active Beauty was also taken into account. Ten prevalent skin disorders that dermo-cosmetics have the potential to treat were analyzed in terms of the pathogenetic pathways behind the bioactive components. According to research in the scientific literature, bioactive compounds produced from plants have several biological functions, including protecting the skin barrier and promoting collagen formation, as well as anti-inflammatory, antioxidant, and moisturizing effects. Consequently, various dermo-cosmetic bioactive combinations may be designed to address the underlying pathogenetic pathways of various skin disorders all at once (Ho *et al*., 2021).

Skin Sensitivity and Barrier Function

Skin health is supported by numerous systems that include sensitive skin, the skin microbiota, along with the function of the skin barrier. A common skin ailment, sensitive skin is more reactive and easily damaged by physical, chemical, or environmental irritants. Symptoms include feeling uneasy in reaction to things that normally shouldn't make you feel that way. Dryness, redness, itching, combustion, and stinging are some of the symptoms that people with sensitive skin may encounter. Skin sensitivity is thought to be caused by an abnormal skin barrier and an overactive cutaneous nerve system. Cosmetic topical solutions for sensitive skin can undergo a paradigm shift with the adoption of a therapy strategy that places a premium on restoring the skin's barrier function, in conjunction with the use of specifically formulated topical actives that increase skin tolerance and reduce inflammatory responses. This approach might completely transform skincare practices, leading to skin that is healthier and more robust.

New insights from the field of skin research have highlighted the importance of the skin microbiota in this regard. The skin is constantly bombarded with a multitude of things that might break down its protective barrier function. It is the biggest organ in our body. Inflammatory disorders, infections, allergies, and autoimmune illnesses

are only some of the skin issues that may be brought on by these aspects, which fall into the exogenous, endogenous, and lifestyle categories. A breakdown of the skin's protective barrier may result from the complex interplay among microbial communities as well as host tissue, with bacterial variety and the relative numbers of various microorganisms on the skin likely playing a key role.

Skin dryness and a weakened skin barrier are common symptoms of sensitive skin. Inflammation, itching, and pain may result from these causes because they may heighten mast cell degranulation with cause hyper-reactivity in the blood vessels and the nervous system. Alterations to stratum corneum maturation along with thinner skin are two biochemical variations between normal and sensitive skin, which may make sensitivity even worse.

The construction and purpose of the skin barrier are maintained by four interconnected layers: physical, chemical, microbiologic, and immunologic. More than one study found that moisturisers improved transepidermal water loss by targeting disturbance that affected all four of these layers via different pathways. A physical skin barrier is strengthened by occlusives, which obstruct the surface of the Stratum Corneum (SC), humectants, which pull water from the dermis into the epidermis, and emollients, which assimilate into the SC. Moisturizers with an acidic pH improve the skin's chemical barrier by encouraging healthy enzyme activity, raising ceramide formation, and creating an environment where commensal microbes thrive. By lowering permeability and, in turn, allergen penetration and sensitization, regular moisturizing may fortify the immunologic skin barrier. Changes in the environment and psychological strain are two of the external variables that have contributed to the steady growth in the occurrence of skin sensitivity concerns in human populations. When certain physiologic or pathological variables cause an overreaction of the skin, this condition is known as skin sensitivity. Extreme instances of sensitive skin may cause redness, itching, and discomfort, and can even set off skin illnesses like eczema or dermatitis.

Factors of Sensitization

There are a lot of internal and external variables that might contribute to skin sensitivity. Genetics, chronological age, and gender are all examples of intrinsic variables. A very common skin ailment, sensitive skin affects a large percentage of the global population. When compared to males, women have a higher risk of developing sensitive skin problems. According to the research, the prevalence instances of sensitive skin are: The following percentages are for women and men in the US: 60–70% for women and 50–60% for males, 51% for British women and 38% for British men, 25.01 percent for Russian women and 5.4% for Russian men, 36.7% for Indian women and 27.9% for Indian men, and 36.1% for Chinese women: Yes. Among Chinese women, those between the ages of 26 and 30 had the highest prevalence of sensitive skin, according to a 2020 white paper on the topic. According to research conducted in the United Kingdom on the factors that influence people's perceptions of their own skin sensitivity, the incidence of sensitive skin tends to decrease as people become older. In general, people become less sensitive to skin irritation and less able to show outward symptoms of dermatological irritation as they get older, which may explain why sensitive skin becomes less common as people get older.

Young people who have sensitive skin often have hectic lives, consume spicy food often, and deal with a lot of stress at work and at home. Also contributing to skin stress and the heightened reactions seen in young individuals is an absence of proper skincare practices and the inappropriate usage of common home chemicals. Natural phenomena, such as variations in the seasons and weather (such as shifts in average temperature), are examples of external environmental influences. Environmental air pollutants, disinfectants, and common household chemicals like hair colors, perfumes, and cosmetics may all aggravate skin sensitivity. Atopic dermatitis, acne, contact dermatitis, along with eczema are among the skin conditions that may cause sensitive skin as a secondary symptom.

Manifestations and Characteristics of Sensitive Skin

Multiple factors, including weakening of the skin-barrier, aberrant neurovascular stimulation, and the activation of immunological inflammation, contribute to the development of sensitive skin. This process is intricate and nuanced. When these elements interact, they make the skin more sensitive to outside stimuli, which in turn cause a cascade of unpleasant clinical sensations including stinging, burning, itching, and tightness.

Impairment of Skin-Barrier Function

One such natural protective membrane is the skin's barrier. The proper functioning of the skin barrier is essential for the preservation of the skin's physiological activities. In addition to preventing the entry of potentially dangerous physical, chemical, or biological elements from the outside world, the skin barrier also helps to retain electrolytes, water, and nutrients. Due to compromised stratum corneum integrity and unbalanced lipid levels in epidermal cells, sensitive skin often has lower ceramide concentration. The skin's barrier is compromised when ceramide levels drop, leading to increased water loss and a diminished ability to fight off microorganisms. The extent to which the skin-barrier function is impaired may be revealed by skin physiological indicators including TEWL and stratum corneum water content. Changes in cutaneous barrier integrity between the healthy control

group and the sensitive skin group were statistically significant, showing that decreased stratum corneum barrier performance is a hallmark of sensitive skin.

An important factor in skin sensitivity is the skin microbiota, a diverse ecology that differs across various parts of the body. Bacteria on human skin interact with both the adaptive and innate immune systems. They create vitamins, organic acids, along with neurotransmitters, and are affected by the temperature and pH of healthy human skin. One possible cause of skin sensitivity is the interplay between the skin microbiota and neuropeptides generated by skin nerve endings, which in turn modulate bacterial virulence. The cutaneous nerve system may be infected by germs, according to the research. The live epidermis contains commensal microorganisms, which are also found in nociceptors and pruriceptors. Both sensory receptors and mast cells contain pattern recognition receptors, which may include Toll-Like Receptors (TLRs). Due to their ability to directly activate nociceptors and pruriceptors, microorganisms may play a role in the pathogenesis of sensitive skin. For the skin barrier to continue to work effectively, a diverse cutaneous microbiota is required. The intercellular lipid makeup is crucial to the skin barrier's integrity; when this barrier is compromised, allergies, irritants, and microbes are able to penetrate more easily. Dysbiosis may occur when either internal or external events upset the delicate balance that exists between resident and transitory bacterial populations and host cells. Atopic dermatitis, rosacea, psoriasis, with acne are chronic inflammatory skin illnesses that have been shown to include dysbiosis.

Essential to good skincare is the regulation of the skin's protective barrier and microbiome. Therefore, creating successful skincare products relies on maintaining a healthy skin microbiome. Skincare products may affect bacterial development by include important actives, including targeted prebiotic compounds, and different skin environments create different "culture mediums" for bacterial growth. Recent advances in skincare have led to improved hydration and skin surface quality, as well as the development of novel formulations for the management of inflammation with neuro-mediator activation. Lastly, it is crucial to note that a good skin barrier is dependent on a balanced microbiota, and that skincare products may play a part in this complex relationship. There has to be continuous study into dysbiosis since it may lead to inflammatory skin problems. Skin sensitivity, the skin microbiota, as well as the function of the skin barrier are all interconnected, and understanding this complex web has the potential to completely transform the cosmetics industry. We are about to uncover ground-breaking findings in the rapidly growing subject of skin microbiota with skin barrier dynamics, specifically in relation to sensitive skin, therefore it goes without mentioning that you should remain tuned. These discoveries might revolutionize current skincare practices and bring topical therapies to a whole new level of effectiveness.

Materials and Methods

Novel approach to improving skin barrier function. The preservation of the skin's natural equilibrium and protective function, known as homeostasis, may prove to be highly advantageous in dealing with various skin concerns such as dryness, irritation, acne, eczema, and premature aging. This is because a robust protective barrier is essential for the well-being of the skin and can aid in warding off environmental harm.

According to our preliminary testing, Chinese skin is more sensitive to capsaicin, and CAT users are more likely to suffer burning feelings. In order to make the CAT more suitable for use on Chinese skin, this research made many adjustments. Among these modifications were:

(1) Samples: The vehicle and placebo were chosen as a single combination of capsaicin with 5% ethanol. The approach was uniform, easy to implement, and promoted with little effort. Ethanol, at concentrations ranging from 10% to 4%, served as a placebo by reducing skin irritation and experimental interference
(2) Methodology: We used a 6-minute procedure that was easier to follow and saved time. The dosage was precisely controlled using the pipette. It is possible to get a consistent and long-lasting concentration by using filter paper
(3) Testing / Evaluation: As demonstrated in Table 1, capsaicin caused itching, stinging, and burning sensations. Intensity level 3 was the most common reporting level for burning. Burns with a duration of 30 seconds or longer and a score of 3 were considered CATP in this research. Just four out of ninety-three women reported scorching ratings of five. It seems that the CAT procedure was safe since the burning went away after 5 minutes of washing with water

Data Collection

A number of foreign research have looked at this, but they've only used traditional Chinese evaluation instruments on a Chinese patient group. The goals of this research were to ascertain whether the capsaicin testing (CAT) was applicable to a Chinese population and, secondarily, to establish a correlation between the CAT and instrumental measures for the evaluation of SS in Chinese patients. Our sample size for this research was 97 healthy Chinese women, ranging in age from 20 to 45. After rinsing their faces with water, the individuals gently patted their skin dry. Participants thereafter relaxed for 20 minutes in a room with a temperature range of 20–22.8°C

and a relative humidity of 40–60%. Next, we used Tewameter1 to quantify transepidermal water loss on both sides, one centimeter from the nasolabial fold. At the same locations, a Corneometer1 was used to measure capacitance (Cap). The two tests were run three times each. So, after that, the CAT was run for six minutes. Facial washing wipes impregnated alongside the vehicle were used five times to clean the nasolabial creases during minutes 0–2.

Equipped with distilled water and absolute ethanol (99.85%; Beijing, China: Tiangen Biological Technology Co.), the vehicle was a 5% ethanol/95% water (v/v) solution. In minutes 2-4, if the individual did not complain of any pain, the researcher used a single-use cotton-tipped applicator to apply the vehicle solution in a split-face fashion across the nasolabial folds. In this stage, the subject was prepared to feel the wet, cold, and wiping sensations that would accompany the use of the impregnated applicators.

Participants who experienced any pain throughout this portion of the test were subsequently removed from further administration. Fifty microliters of a 1/104% capsaicin water solution were applied to the two layers of 0.8 cm diameter filter paper two minutes after the vehicle was applied to both sides. Made using 98.0% pure capsaicin powder from Haida Chemical Co., Qingdao, China (8-methyl-N-vanillyl-6-nonenamide). The nasolabial fold was treated with this solution in a random fashion. On the other side, the car was finished. Within two minutes of the application, we asked the subjects to note any changes in feeling or similarities between the test locations. On a scale from 1 (not at all detectable), 2 (not at all noticeable), 3 (moderately noticeable), 4 (strongly perceptible), and 5 (very painful), subjects were additionally prompted to characterize the kind and degree of facial feeling on each side. The capsaicin experiment was Considered Positive (CATP) if the burning sensation on the capsaicin side persisted for more than 30 seconds at a degree of 3. All things considered; the capsaicin test came out negative (CATN). After a brief 5-minute break, the TEWL along with SC were remeasured. Applying an Ultrasound B Ultrascan1, the density of SC was assessed 2 cm distant from the nasolabial fold. In order to determine the impact of a higher capsaicin concentration, this research used the 5 gradient approaches. After 30 seconds at level 3, the test was terminated due to the capsaicin side feeling lasting longer than expected. In every other case, the experiment proceeded to the next solution concentration. Increases in attention were made until the participant felt a change. Every stage was separated by 2 minutes. "Nonresponders" were those who did not show any response even at the greatest concentration. The whole time of the exam was between six and fourteen minutes.

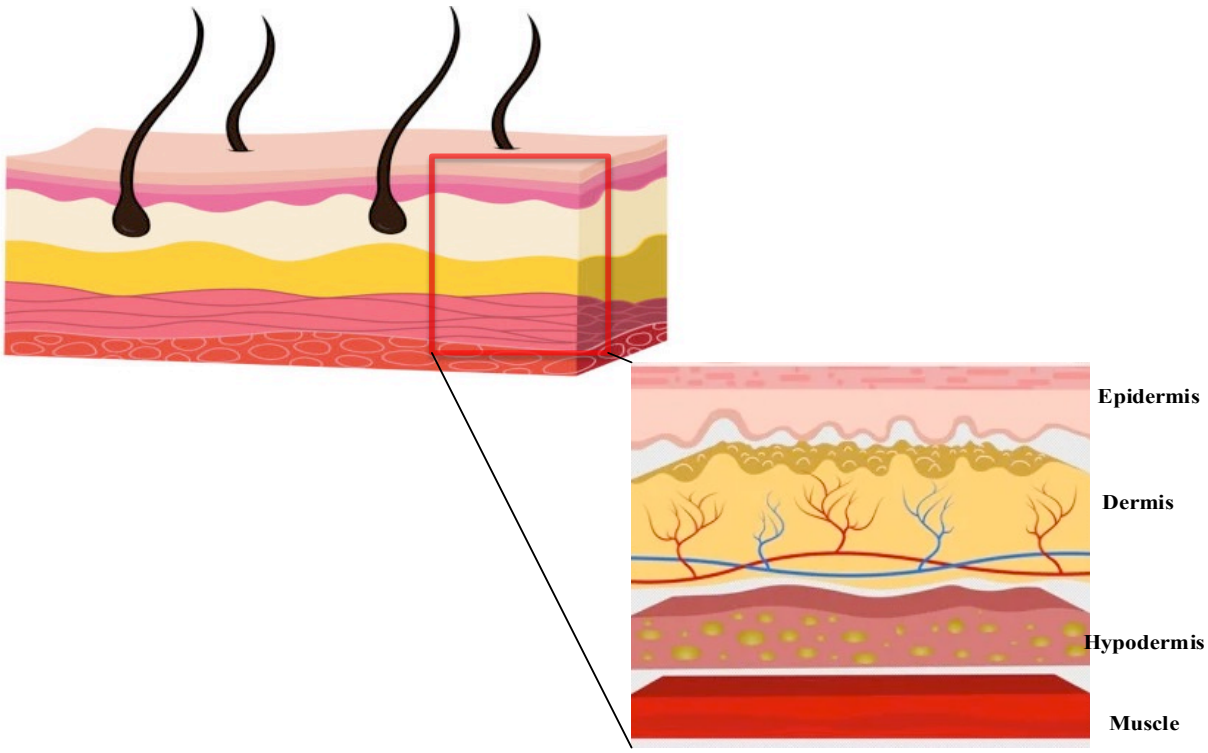

Fig. 1: Sensitive Skin Model

Environmental Pollutants Considerations

Air pollution impacts the physiology of the human skin in two ways: directly, via transcutaneous digestion, and indirectly, through systemic dispersion after inhalation or consumption. Billions of people continue to be exposed to this harmful cocktail of pollutants. Benzene, Particulate Matter (PM), ground-level ozone (O3), Aromatic Polycyclic Hydrocarbons (PAHs), sulfur dioxide (SO2), nitrogen dioxide (NO2), carbon monoxide (CO), and other gaseous pollutants, heavy metals, and Volatile Organic Compounds (VOCs) are among the air pollutants that are a worldwide concern.

Ultraviolet Radiation (UVR) is another kind of physical stress that may harm the skin. Sunlight-induced photodamage on regions that are constantly exposed to the sun speeds up the physiological aging process and increases the risk of skin cancer, making Ultraviolet Radiation (UVR) the most detrimental environmental element affecting skin biology. The skin health of the general public is negatively affected by air pollutants and photopollution. Through a variety of pathways, they weaken the structural integrity of the skin, interact with the microbiota of human skin, and cause or worsen a variety of skin illnesses. For the best results in treating xerotic skin changes, it may be best to use a moisturizing agent that targets specific SC abnormalities. These agents should include humectants, occlusive agents, and emollients in the right amounts and combinations. They should also contain physiological lipids or substances that enhance skin lipid synthesis, and, if necessary, agents like NMF components that restore the skin's permeability barrier.

Mechanisms of Moisturization

Therapy for AD and other skin conditions that are inflammatory mostly involves the use of moisturizers. Reduce the requirement for topical corticosteroid medication in AD by improving barrier function with daily use of moisturizers containing a mix of emollient, humectant, and occlusive components. More research into the skin barrier might lead to the development of moisturizers that address certain gaps in the skin's protective layer. The current skin functional barrier model provides insight into the effectiveness of moisturizers.

Moisturizers and the Physical Barrier

Moisturizers help maintain the skin's physical barrier due to its occlusive, emollient, and humectant characteristics. The mechanics of the commonly used occlusives, such petrolatum, that are applied to babies to strengthen their skin barrier have been better understood. In addition to forming an occlusive barrier to the epidermis, Czarnowicki *et al.* discovered that applying petrolatum increased the production of AMPs and keratinocyte differentiation markers (such as filaggrin and loricrin) and lowered the numbers of epidermal T cells. The term "emollient" may also refer to the emulsifying components found in moisturizers, which help make the product easier to apply. These ingredients, which are usually alcohols or esters, may make the moisturizer thicker, harder to spread, as well as more occlusive, or thinner, easier to spread, and less occlusive, depending on the formulation.

The skin's protective chemical layer contains acidic pH, AMPs, and moisturizing chemicals. When added to moisturizers, urea, a breakdown product of filaggrin and an NMF component, improves skin moisture and decreases TEWL. The buffer capacity of the moisturizer is another factor that affects the pH of the SC, along with the moisturizer's pH. A material's buffering capacity is its ability to withstand an acidic or basic insult without causing its pH to change.

More recent moisturizers have been designed with the idea of using sites of skin barrier disturbance as therapeutic targets, so there's hope that this trend will continue. As our knowledge of the skin barrier expands, we may be able to create more complex formulations that target patterns of barrier disruption seen in different disease phenotypes; moisturizers play a crucial role in the treatment of skin diseases.

Skin Cleansers

For maximum results, whether you have healthy skin or skin plagued by illness, use a mild skin cleanser that eliminates excess sebum and exogenous and exfoliated detritus without changing the skin's pH and with little harm to the SC.96,101–106, 95 A gentle skin cleanser and other patient-specific adjunctive skin care products can improve the therapeutic response to treatment for a range of skin conditions, including rosacea and AD, and lessen the likelihood of side effects:

- Participants were selected using the following exclusion criteria
- Pregnant or breast-feeding women, and women using potential for pregnancy
- Individuals via topical steroid-containing dermatological plans for more than one month for skin scenario treatment
- Participants who have got involved in the identical clinical trial within the previous 6 months
- Subjects presenting using cutaneous abnormalities like as pigmentation spots, acne, erythema, while telangiectasia
- Individuals who have used the same or similar effectiveness cosmetics or pharmaceutical items on the test site within 3 months earlier to investigation initiation
- Subjects who have experienced processes on the evaluate site within 6 months before to investigation initiation

- Other individuals deemed inappropriate for the trial at the principal investigator's choice

Student's T-Test Method

A Student's t-test as well as analysis of variance were used to compare the results from the instrumental measures. For the correlational study, the spearman-test was used. P < 0.05 was the criterion of significance. The CAT was finished by 93 girls from China. Three were not included because they experienced pain throughout the adaptation period, and one was not followed up on. Forty-three individuals were classified as CATN and forty as CATP. A comparison was made among the CATP of CATN individuals and the findings of objective measures (Table 1). Pre- and post-test, the CATP group exhibited noticeably more TEWL, lesser Cap, and lower SC density ($p < 0.05$). Itching, tingling, and burning were noted during the CAT. Table 2 shows that out of all the symptoms, burning was the most common, affecting 47 (50.54%) of the females. Cap and SC density were inversely associated to burn severity. we see that TEWL has a positive correlation with the degree of burns in Table 3.

Statistical Analysis

The arithmetic mean +/- standard deviation is used to represent values. To examine differences before and after application, we used parametric, two-tailed, paired Student's t-tests or nonparametric Wilcoxon signed-rank tests. Minitab 19 (Minitab® 19.2, Minitab Inc.) was used for all statistical analyses. A 95% confidence interval was used, and p values less than 0.05 were deemed statistically significant.

Table 1: Pre-and post-CAT instrumental measurement values. (Mean ± S.D.)

		CATP	CATN	p
Cap	Before	41.39±11.40	49.40±16.98	0.04
	After	42.68±10.44	47.18±8.74	0.02
TEWL	Before	27.37±8.91	15.22±5.06	0.01
	After	35.65±17.70	21.24±15.16	0.03
		186.23±14.34	154.91±17.16	0.00

Table 2: The dissemination of many feelings of Cap (N, %)

	Itching	Sting	Burning
0	91(98.85)	66(73.44)	46(54.46)
1	1(1.48)	19(16.13)	1(1.49)
2	1(1.55)	6(6.65)	6(6.45)
3	0	2(3.15)	29(30.11)
4	0	2(4.15)	8(9.60)
5	0	0	4(7.30)

Table 3: The relationship between the two sets of instrumental data for burn severity

		r	p
Burning degree (0-5)	Cap	-0.28	0.02
	TEWL	0.59	0.04
	Density	-0.23	0.02

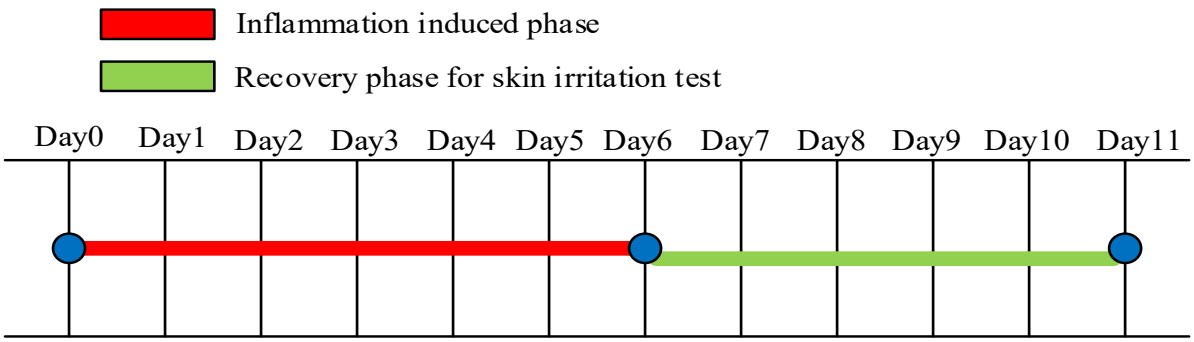

Fig. 2: Test Result

The following is a calculation of the alteration in each parameter: TEWL while skin redness was remeasured after 4 weeks of the item consumption:

Inflammatory Skin and Irritation Test

In order to determine which formulation is most appropriate for the next stage of topical pharmaceutical development, researchers conduct safety studies such as the skin irritation test. The dorsal skin of healthy, untreated mice is often chosen as the material by researchers. To determine whether the chosen formulation caused an inflammatory reaction, researchers wait at least three days after applying it before looking at skin tone and histological samples. On the other hand, inflammatory skin has a very different barrier function than untreated healthy skin. As a result, normal skin may not react to even a little number of irritants that are designed to cause redness and irritation. However, in inflammatory skin, even a minute number of irritants may trigger significant transepidermal water loss, reddening of the skin, and an

inflammatory reaction. One study found that compared to a healthy control group, those who had previous instances of Atopic Dermatitis (AD) lost more water through the skin's surface after being exposed to an irritant. It is possible that the patients' poor barrier function and/or dry skin state contributed to their heightened susceptibility to irritants. The candidate formulations should not have caused or sustained the irritation/inflammation response in mice, as shown by scales, erythema, and dryness on the dorsal skin. Additionally, the histopathology findings should not have included any formulations that retained the hallmarks of epidermal hyperplasia.

According to our preliminary testing, Chinese skin is more sensitive to capsaicin, and CAT users are more likely to suffer burning feelings. In order to make the CAT more suitable for use on Chinese skin, this research made many adjustments. Among these modifications were: (1) The reagent's nature and concentration The vehicle and placebo were chosen as a single method for capsaicin and 5% ethanol. The approach was uniform, easy to implement, and promoted with little effort.

Among the neuropeptides released by the nociceptive C-fibers are substance P while calcitonin gene-related peptide, while capsaicin is a naturally occurring chemical that works on vanilloid receptors. Symptoms of sensitive nerves are the hallmark of sensitive skin, a prevalent disease seen globally. A neurogenic origin is suggested by the neuro-sensory indications, such as the typical pattern of capsaicin responsiveness of skin.

Conclusion

The skin sensitivity syndrome may be categorized into two main types: primary and secondary. As a result of the complexity and multiple nature of its development processes, the illness is sometimes difficult to cure. In order to relieve symptoms associated with various processes, a plethora of active compounds have been produced. These medicines aim to promote skin-barrier repair, reduce neurovascular hyperreactivity, and moderate inflammatory reactions. This review compiles and summarizes all of these useful components. While certain cosmetic components may cause sensitization, there is a dearth of thorough summaries on the subject. As an example, skin sensitivity might be exacerbated by certain functional substances that have whitening properties. So, while making cosmetics specifically for those with sensitive skin, it will be important to strike a balance between the components' effectiveness and safety.

Even though there have been a lot of successful research on sensitive skin and calming cosmetics, there are still certain obstacles:

(1) Exploration of fresh active ingredients: the continuous search for while validation of fresh active ingredients with skin-soothing, anti-inflammatory, while skin-barrier-repairing effects, especially ingredients developed from non-traditional sources (e.g., marine creatures and microorganisms)
(2) Improvement of bioavailability: the utilization of nanotechnology to enhance the penetrability while stability of active ingredients to improve their transfer and absorption prices in the skin
(3) Research and growth of multi-functional products: the growth of compound skincare products using skin-soothing, anti-inflammatory, while moisturizing impacts to meet the requires of different skin issues
(4) Investigation of relationships among environmental factors while sensitive skin: the elucidation of the influences of external variables, like as environmental pollution while climate change, on sensitive skin while the exploration of relevant avoidance and protection metrics
(5) Psychological skin interactions: the determination of the impacts of psychological stresses while mood swings on skin sensitivity and the growth of corresponding intervention measures

Better identification and management of sensitive skin, as well as a stronger scientific foundation for prevention and treatment, will be possible as our knowledge of the processes of sensitive skin grows and as research into active compounds with skin-soothing properties advances. As a result, the cosmetics sector will continue to innovate, customers will be able to better manage their sensitive skin, and people with sensitive skin will have an improved quality of life.

Authors Contribution

All authors contributed to the study conception and design, Material preparation, data collection, and analysis. All authors read and approved the final manuscript.

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