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Review

Mechanisms of Sensitive Skin and the Soothing Effects of Active Compounds: A Review

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Abstract: The incidence of skin sensitivity issues in human populations has increased steadily because of external factors, such as environmental changes and emotional stress. Skin sensitivity refers to a state of skin hyperreactivity that occurs under certain physiological or pathological conditions. Sensitive skin may manifest as redness, itching, and pain and even trigger skin diseases, such as eczema or dermatitis, in severe cases. This review discusses the sensitization mechanisms and characteristics of sensitive skin, with a focus on symptom alleviation through three key strategies: skin-barrier repair, reduction in TRPV1 receptor activity, and anti-inflammatory interventions utilizing active substances. The findings will enhance public knowledge regarding sensitive skin, promote further research and practical prevention and treatment methods, and provide theoretical support for developing soothing cosmetic products for sensitive skin.

Keywords: sensitive skin; skin-barrier repair; TRPV1; inflammation; skin soothing; active substances; TRPV1 receptor; cosmetic ingredients; natural compounds; therapeutic skincare

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1. Introduction

Sensitive skin refers to skin hyperreactivity that occurs under certain physiological or pathological conditions and primarily affects facial skin. When stimulated by chemical and mental factors, sensitive skin will manifest as a burning sensation, stinging pain, itching, and tightness, which are accompanied or unaccompanied by objective signs, such as erythema, skin scaliness, and capillary dilation [1]. The expert position paper formulated by the Special Interest Group on Sensitive Skin at the International Forum for the Study of Itch in 2017 [2] defined sensitive skin as a skin sensory syndrome. Such skin has high reactivity and poor tolerance, allowing for it to become easily allergic and reflect damage to the skin-barrier function [3].

Sensitive skin, once considered uncommon, is now widely observed, with studies indicating a global prevalence of up to half or more of the population. In recent years, there has been a gradual rise in the number of research papers on sensitive skin and skin soothing in the Web of Science Core Collection (WoSCC) database (Figure 1). The results of the correlation analysis performed on the retrieved publications in VOSviewer 1.6.18.0 revealed that transient receptor potential vanilloid 1 (TRPV1), inflammation, capsaicin, skin barrier, and pain are focal areas of recent research on sensitive skin (Figure 2).

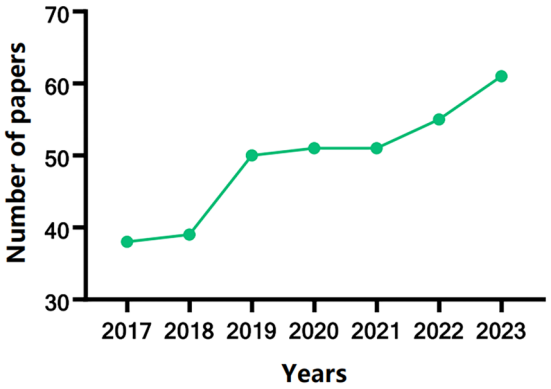

Figure 1. Line chart of annual publications on sensitive skin in the WoSCC database from 2017 to 2023. Using pertinent keywords (skin, sensitive, and active substances) and years of publication (2017–2023) as search criteria, the number of papers related to keywords in the WoSCC database was determined for each year and plotted on the line chart in GraphPad Prism 8.0.

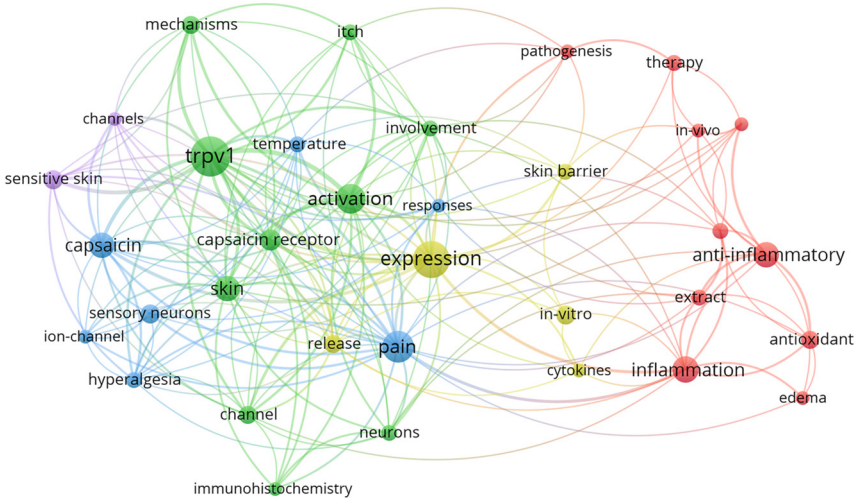

Figure 2. Correlation analysis of papers related to sensitive skin. Search results obtained with pertinent keywords (skin, sensitive, and active substances) in the WoSCC database were analyzed in VOSviewer 1.6.19 (Leiden, The Netherlands). Keywords were extracted from articles of the highest reference significance in the dataset and used to create a network visualization map. Different bubble colors denote different categories, with larger bubbles indicating higher correlation between articles.

In this review, we delve into the intricate mechanisms and unique characteristics of sensitive skin. We focus on three pivotal strategies: enhancing skin-barrier repair, reducing TRPV1 receptor activity, and utilizing specific active ingredients for anti-inflammatory interventions to alleviate symptoms effectively. Our goal is to provide a scientific foundation for the cosmetic industry, aiding in the development of safer and more effective products for sensitive skincare.

2. Causes of Sensitization and Characteristics of Sensitive Skin

2.1. Factors of Sensitization

The causes of sensitive skin are multifactorial, encompassing intrinsic factors and external environmental influences (Figure 3). Intrinsic factors include differences in genetic background, age, and gender. Sensitive skin is a common skin condition that is highly prevalent worldwide. And women are more prone to experiencing sensitive skin conditions than men. Prevalence rates of sensitive skin reported in the literature are as follows: United States women: 60–70%, United States men: 50–60% [4,5]; British women: 51%, British men: 38% [6]; Russian women: 25.01%, Russian men: 5.4% [7]; Indian women: 36.7%,

Indian men: 27.9% [8]; Chinese women: 36.1% [1]. The *2020 White Paper on the Current State of Sensitive Skin in Chinese Women* indicated that sensitive skin was the most prevalent in the 26–30 age group [9]. A UK-based study on the determinants of self-perceived sensitive skin in the population showed that the prevalence of sensitive skin decreases with age [10]. The observed decrease in the prevalence of sensitive skin with aging may be attributed to an overall reduction in susceptibility to skin irritation, as well as a diminished capacity for displaying visible signs of dermatological irritation [11]. Irregular lifestyles, frequent consumption of spicy food, and stress in life and work are common features of young individuals with sensitive skin. In addition, a lack of skincare habits and misuse of household chemicals will further aggravate stress in the skin and trigger young people's sensitive skin responses.

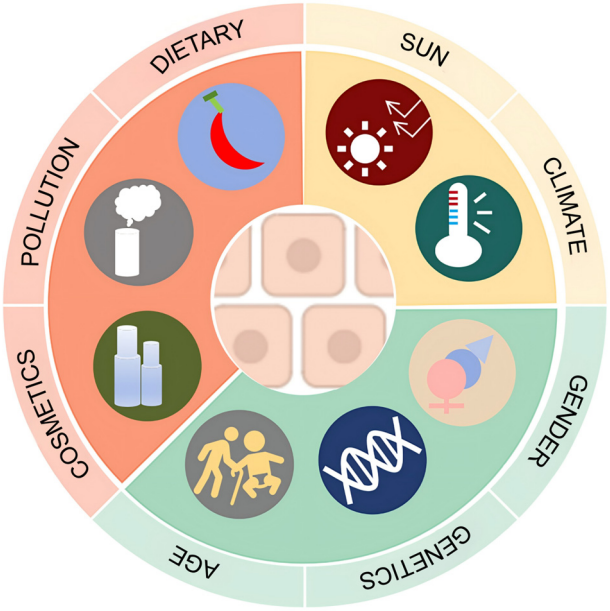

Figure 3. Factors affecting skin sensitization. Causes of sensitive skin include intrinsic factors, such as genetic background, age, and gender, and external environmental factors, such as climatic fluctuations, changes in season, the use of household chemicals, environmental pollution, and dietary habits of consuming irritating foods.

External environmental factors include seasonal changes, climatic fluctuations (e.g., temperature fluctuations), and other natural conditions. Chemical substances, such as cosmetics, fragrances, and hair dyes used in everyday life; disinfectants; and air pollutants in the environment, are also key influencing factors of skin sensitivity. Sensitive skin may be secondary to certain skin diseases, such as atopic eczema, acne, contact dermatitis, and eczema [12].

2.2. Manifestations and Characteristics of Sensitive Skin

The formation of sensitive skin is a complex and subtle process involving multiple processes, such as skin-barrier impairment, abnormal neurovascular excitation, and the activation of immune inflammation (Figure 4). Interactions among these factors increase the sensitivity of the skin to external stimuli, triggering a series of discomforting clinical symptoms, such as burning, stinging, itching, and tightness.

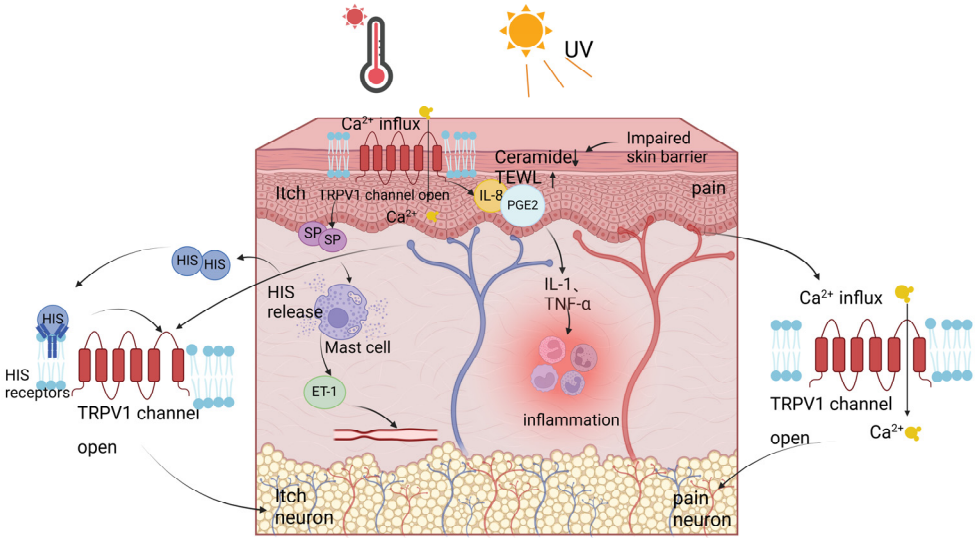

Figure 4. Characterization of sensitive skin. When the skin is exposed to UVB radiation and other factors that damage the skin barrier, ceramide levels decrease and transepidermal water loss (TEWL) increases. The TRPV1 channels are activated, resulting in the generation of action potentials and a significant influx of Ca^{2+}, which activate nociceptive neurons and cause a tingling sensation. The activation of TRPV1 also promotes the local release of substance P (SP), which triggers mast cells to degranulate and release histamine (HIS). HIS binds to HIS receptors, activating itch neurons and producing an itching sensation. Mast cells also enhance the production of endothelin-1 (ET-1), leading to vascular hyperreactivity and skin redness and swelling. Furthermore, TRPV1 activation promotes the production of interleukin-8 (IL-8) and prostaglandin E2 (PGE2), which in turn stimulate the release of interleukin-1 (IL-1) and tumor necrosis factor-alpha (TNF-α), triggering an inflammatory response.

2.2.1. Impairment of Skin-Barrier Function

The skin barrier is a natural protective membrane. Normal skin-barrier function is critical for maintaining physiological skin functions. Besides blocking the invasion of harmful chemical, physical, or biological factors from the external environment, the skin barrier can also prevent the loss of nutrients, water, and electrolytes [13]. In sensitive skin, reduced ceramide content is common because of impaired stratum corneum integrity and imbalanced lipid content in epidermal cells. A reduction in ceramide content damages the skin barrier, increasing water loss and weakening the defense capacity of the skin against bacteria. Skin physiological indices, such as TEWL and water content in the stratum corneum, can indicate the degree of the impairment of the skin-barrier function. Pinto et al. [14] developed TEWL desorption curves to compare the evaporation half-life period and dynamic water mass between sensitive and normal skin. The sensitive skin and healthy control groups exhibited significant differences in cutaneous barrier integrity, demonstrating that sensitive skin is strongly associated with impaired stratum corneum barrier function.

2.2.2. Dysfunction of Sensory Nerves in Skin

In sensitive skin, the weakened protective capacity of nerve endings, decreased density of nerve fibers, and heightened reactivity of sensory nerves result in the dysfunction of sensory nerves. Weakening the protective capacity of nerve endings renders sensitive skin more susceptible to influences by external stimuli. The skin is innervated by peripheral nerve fibers, which include three types of sensory nerve fibers. Among them, A-δ fibers and C fibers transmit signals to the central nervous system in response to various physical and chemical stimuli [15]. Studies indicate that selective stimulation of C fibers with a 5 Hz current decreases the sensory threshold only in individuals with sensitive skin, suggesting a correlation between C-fiber instability and abnormal sensations [16]. Research also shows lower intra-epidermal nerve fiber density, particularly of peptidergic C fibers, in sensitive

skin [17]. These changes, which lead to neuropathic pain and a lowered threshold for detecting heat-induced pain, indicate an increased sensitivity of nerve endings in response to environmental stimuli. Therefore, Misery et al. concluded that sensitive skin can be considered as a neurological disorder [18].

The dysfunction of sensory nerves in the skin is usually closely associated with the transient receptor potential vanilloid (TRPV) family. TRPV1 is a multimodally activated, calcium-permeable, non-selective cationic channel that transmits sensitivity-related sensory symptoms. TRPV1 is expressed in various cell types, including keratinocytes, fibroblasts, mast cells, endothelial cells, A-δ fibers, and sensory C fibers [15]. Upon activation of TRPV1 receptors, action potentials are generated by TRPV1 channels, leading to a massive influx of Ca^{2+} [19] and causing symptoms such as a burning sensation, stinging pain, and itching in sensitive skin [20]. Overactivation of TRPV1 in the skin can also regulate the release of related proinflammatory factors in localized neuroinflammation [21], accelerating the death of epithelial cells and damaging the epidermal barrier. Bodó et al. [22] found that Ca^{2+} influx caused by TRPV1 activation led to apoptosis in keratinocytes. These changes are important physiological triggers for elevating skin sensitivity toward external stimuli.

TRPV1 can be activated by various types of endogenous and exogenous factors [23], with the former including arachidonic acid, 2-arachidonoylglycerol, and lysophosphatidic acid and the latter including vanillin compounds, capsaicin, temperatures exceeding 42 °C, low pH ($\leq$5.9), and high concentrations of ethanol [24].

2.2.3. Skin Inflammatory Responses

Immune cells (e.g., mast cells, macrophages, and lymphocytes) are abundant in the epidermal and dermal skin layers and primary participants in skin inflammatory responses [13]. These cells, closely associated with the pathogenesis of sensitive skin, play an important role in the skin's defenses against external stimuli and maintain skin homeostasis. The symptoms of inflammation and itching in sensitive skin can be co-regulated by sensory nerve fibers and immune cells through TRPV1 receptor mediation [25]. Such neuroimmune interactions play a crucial role in skin inflammatory responses. The activation of TRPV1 can promote the localized release of SP from the skin and the discharge of vasoactive intestinal peptide and neurotensin [26]. It also induces the release of interleukin-23 (IL-23) and interleukin-31 (IL-31) by keratinocytes and mast cells near sensory nerve endings [27]. Consequently, antigen-presenting cells and T cells are activated, leading to skin immune and inflammatory responses [28]. SP, which can trigger mast cell degranulation and HIS release, mediates acute inflammation and hypersensitivity in the skin. HIS can bind to HIS receptors on keratinocytes and neurons, triggering signaling pathways related to inflammation and itching. This leads to TRPV1 stimulation, which induces Ca^{2+} influx into cells and generates action potentials. These processes ultimately form a vicious circle that maintains and aggravates the inflammatory process [29–31].

3. Active Substances with Skin-Soothing Effects and Their Mechanisms of Action

Given the mechanisms of sensitization and characteristics of sensitive skin, it is evident that sensitive skin is closely associated with skin-barrier impairment, vascular hyperreactivity, and inflammatory responses arising after TRPV1 receptor activation. Therefore, skin-barrier repair, reduction in TRPV1 receptor activity, and inhibition of inflammation are critical targets for treating sensitive skin. The ensuing sections of this paper summarize the active substances with skin-soothing, anti-inflammatory, and moisturizing effects that address these three key targets (Figure 5).

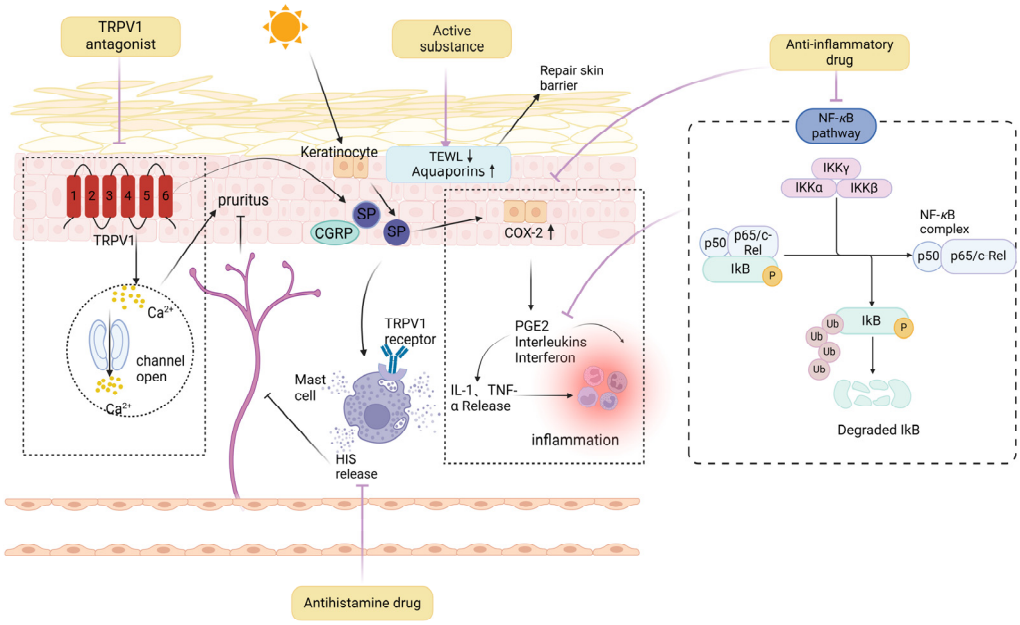

Figure 5. Mechanisms of action of active substances with soothing effects. TRPV1 inhibitors reduce pain and itching sensation by inhibiting the activity of TRPV1 receptors, which closes the TRPV1 channels and decreases the calcium ion influx. They also reduce the release of calcitonin-gene-related peptide (CGRP) and SP, leading to decreased cyclooxygenase-2 (COX-2) levels and subsequently inhibiting the release of inflammatory factors (IL-1 and TNF-α), thereby alleviating inflammation. Antihistamines relieve itching by inhibiting the release of HIS from mast cells. Active substances repair damaged skin barriers by reducing TEWL and increasing aquaporin levels. Anti-inflammatory medications decrease inflammation by inhibiting the NF-kappa-B (NF-κB) signaling pathway.

3.1. Skin-Barrier Repair

3.1.1. Oils

Oils have long been used in the care and medical treatment of the skin because of their ability to protect the skin barrier through blocking effects, which enable the preservation of the skin's water content and a reduction in TEWL. An in vitro study by Varma et al. revealed that coconut oil inhibited proinflammatory cytokines at both the protein and gene expression levels [32]. Green thorn fruit oil contains abundant unsaturated fatty acids and a fatty acid composition extremely close to that of human skin. Its good affinity, moisturizing properties, and permeability make it an excellent basic raw material for cosmetics [33]. Green thorn fruit oil promotes the expression of acid ceramidase in the epidermis of nude mice, reduces TEWL, and increases the water and sebaceous contents of the epidermis, aiding the repair of the skin barrier [34]. Job's tears (*Coix lacryma-jobi*) seed oil significantly reduced ear swelling and scratching episodes in mice, which indicated considerable alleviation of skin inflammation and good reparation effects toward the mouse skin barrier [35]. *Nageia nagi* seed oil could reduce the TWEL, impedance, and redness of sodium-lauryl-sulfate-exposed skin [36]. *Matricaria chamomilla* essential oil exhibits antibacterial properties and free-radical-scavenging capabilities and promotes wound healing [37].

3.1.2. Polysaccharides

Hyaluronic acid (HA) is a non-species-specific acidic mucopolysaccharide that is prevalent in the skin and the intercellular matrices of muscles, bones, and tissues [38]. Lee et al. [39] performed in vitro and ex vivo experiments on 25 subjects with mild atopic dermatitis or dry skin to investigate the effects of a novel emollient containing HA and a soluble proteoglycan on the skin-barrier function, wrinkles, and skin hydration. The novel emollient reduced itching and improved the skin-barrier integrity. The *Compendium of Ma-*

teria Medica (Bencao Gangmu) states that cactus provides therapeutic effects on burn injuries. Cactus is commonly used in folk remedies to treat inflammation, pain, and skin itching, attributable to its aromatic amines and saccharides. Polysaccharide extracts from cacti (*Opuntia ficus-indica*) enhanced skin wound healing in rats [40]. False starwort (*Pseudostellaria heterophylla* (Miq.) Pax) polysaccharides prepared by Liu et al. [41] significantly inhibit lipopolysaccharide-induced NO secretion in RAW264.7 cells, ameliorate skin damage symptoms in mice with atopic dermatitis, and inhibit the expressions of the inflammatory factors IL–4, IL–13, and interferon-γ (IFN–γ). Common Bletilla (*Bletilla striata*) polysaccharides promote the proliferation, differentiation, and migration of cells in wound tissue, increase the synthesis and secretion of type I collagen, and promote granulation tissue formation. This enables the regeneration and restoration of the dermis, promoting skin wound healing in rats [42].

3.1.3. Others

Aloe vera (*Aloe vera*) is a widely recognized medicinal plant with vast applications in treating various skin diseases. Aloe vera leaf gel has been investigated in many in vitro, in vivo, and clinical studies. Wahedi et al. explored the wound-healing effects of aloesin, an aromatic C-glycosylated 5-methylchromone found in aloe vera, through in vitro and in vivo experiments in cell and mouse models. Aloesin increased cell migration, enhanced angiogenesis in endothelial cells, and accelerated wound closure in hairless mice, demonstrating its skin repair effects [43]. Razia et al. treated human epidermal keratinocytes (HaCaT cells) with aloe vera flower water extract (AFWE) and observed that AFWE modulates filaggrin, aquaporin expression, and HA synthesis via a balanced regulation of hyaluronan synthase 1 (HAS1) and hyaluronidase 1 (HYAL1) proteins, enhancing the skin-barrier function [44]. Indian chrysanthemum (*Chrysanthemum indicum*) also possesses skin-barrier-protecting and repair-promoting functions. Indian chrysanthemum extract ameliorates atopic dermatitis and ear swelling in mice [45,46] and effectively slows the progression of skin inflammation. Li et al. found that ginsenosides alleviate UVB-induced increases in epidermal thickness and TEWL and decreases in dorsal skin dehydration in BALB/c hairless mice, effectively restoring the physiological state of the skin surface and strengthening the protection against UVB-induced skin-barrier impairment in the mice [47]. Zhuang et al. utilized a hydrogen peroxide (H_2O_2)-induced HaCaT cell injury model to demonstrate that *Centella asiatica* extract (CAE) significantly reduces the levels of human claudin 1 and human tight junction protein 1. Furthermore, through network pharmacology predictions, CAE is suggested to potentially improve skin-barrier damage by modulating the phosphoinositide 3-kinase-protein kinase B (PI3K-Akt), vascular endothelial growth factor (VEGF), and mitogen-activated protein kinase (MAPK) signaling pathways [48].

3.2. Reduction in TRPV1 Receptor Activity

3.2.1. Synthetic Compounds

Synthetic TRPV1 antagonists, including trans-4-tert-butylcyclohexanol, asivatrep, and capsazepine, can accelerate the repair of skin-barrier injury. Trans-4-tert-butylcyclohexanol is a TRPV1 receptor antagonist developed by Symrise AG, a German chemical company. It can effectively inhibit Ca^{2+} influx induced by capsaicin, phenoxyethanol, and retinol, relieving symptoms of irritation, such as stinging pain and a burning sensation [49]. Skincare products containing trans-4-tert-butylcyclohexanol are already available on the market, including Eucerin's anti-rose creams and Avène's face creams; however, these products are still relatively rare. Asivatrep is a TRPV1 antagonist developed by Amorepacific Corporation, a South Korean beauty and cosmetic conglomerate. Asivatrep effectively inhibits Ca^{2+} influx in keratinocytes; attenuates symptoms of discomfort, such as itching and redness; and ameliorates skin-barrier injury. However, asivatrep has not yet been used in cosmetic products [50].

3.2.2. Natural Compounds

Peptides

In recent years, peptide antagonists of TRPV1 have become a focal topic of research in developing active substances with skin-soothing effects. Analgesic polypeptide HC1 (APHC1), derived from sebae anemone (*Heteractis crispa*), is the first reported peptide antagonist that binds to TRPV1 channels. It strongly inhibits capsaicin-induced TRPV1 activation and provides significant analgesic effects in different in vivo pain models [51]. Kang et al. developed a novel TRPV1-targeting peptide (TIP) that effectively inhibits capsaicin-induced Ca^{2+} influx and TRPV1 activation. TIP also attenuates UV-induced erythema and the expression of inflammatory factors in human skin in vivo, providing a promising approach for treating UV-induced inflammation and photoaging [52].

Others

Researchers have also derived extracts with antagonistic effects on TRPV1 from various plant species. Zhou et al. obtained an extract of tangerine (*Citrus reticulata*) fruit and examined its effects on a recombinant hTRPV1-overexpression cell line. The tangerine fruit extract inhibits TRPV1 expression, alleviates lactic-acid-induced skin discomfort in the nasolabial folds or cheek areas, and reduces skin irritation or sensitivity [53]. Ge et al. treated a mouse model of eczema with common purslane (*Portulaca oleracea L.*) extract. Measurements of Ca^{2+} concentrations and immunohistochemical staining of TRPV1 showed that purslane extract treats acute eczema-associated itching by reducing TRPV1 activity [54]. Zhang et al. extracted an active substance primarily consisting of spilanthol from paracress (*Acmella oleracea*) and demonstrated its significant inhibitory effect on TRPV1 expression through an in vitro experiment [55].

3.3. Anti-Inflammatory Activity

Medications to treat skin inflammation include steroidal and non-steroidal anti-inflammatory drugs. Although both types provide extremely strong anti-inflammatory and pain alleviation effects [56], they produce significant side effects and may damage human organs. In recent years, natural plants have been widely applied to treat skin inflammation, as they slow skin disease development, control inflammation, and have a good safety profile and milder side effects. Developing safe and effective anti-inflammatory medications from natural plants is a focal research topic.

Cellular and mouse models are the mainstream methods for identifying skin anti-inflammatory substances and elucidating their mechanisms of action. At the cellular level, lipopolysaccharide (LPS) is commonly used to induce inflammation in mouse macrophages and HaCaT cells and examine the NO content; release of pro-inflammatory cytokines, such as IL-6 and IL-8; and the expression and phosphorylation levels of proteins involved in inflammatory signaling pathways. Alternatively, 1-fluoro-2,4-dinitrobenzene (DNFB) is used to induce skin inflammation in mice and analyze the anti-inflammatory efficacy of active substances by measuring skin thickness and inflammatory markers in skin tissue. Table 1 lists various active substances, including asiaticoside, madecassoside, Asiatic acid, quercetin, isoflavones, rutin, curcumin, dipotassium glycyrrhizinate, glabridin, and alkaloids, all of which have been validated for their anti-inflammatory activities at the cellular or mouse level.

Additionally, numerous active substances have been verified for their anti-inflammatory properties through human trials involving parameters such as TEWL values, the number of non-inflammatory and inflammatory acne lesions, red/melanin pigmentation levels, and collagen density. Examples include madecassoside, *Aescus chinensis* extract, *Castanea sativa* shell extract, *Aloe barbadensis* extract, *Ginkgo biloba* leaf extract, *Sphaeranthus indicus* polyphenols, *Punica granatum* seed oil extract, and *Actinidia arguta* leaf extract (see Table 2).

Table 1. Anti-inflammatory active substances evaluated at cellular and animal levels.

Source(s)	Main Active Ingredient	Mechanism(s) of Action	Model(s)	Skin Protective Effect(s)	Reference
Centella asiatica	Madecassoside	Filamentous protein, aquaporin 3, Claudin-1, and HA↑ IL-1α, IL-6, TNF-α, and PGE2↓	HaCaT cells, Raw264.7 cells, and 3D-skin model	Promotes sensitive skin repair and anti-inflammation	[57]
		Glutathione (GSH) and Hydroxyproline↑ NO and malondialdehyde (MDA)↓	ICR mice	Antioxidant activity, collagen synthesis, and angiogenesis	[58]
	Asiaticoside	IL-23, IL-22, and IL-17a↓	BALB/c mice	Anti-inflammatory	[59]
	Asiatic Acid	COX-2, IL-6, TNF-α, IL-8 NF-κB, and MAPK ↓ Thickness of the dermis and epidermis, collagen deposition, and mast cells↓	HaCaT cells and BALB/c mice	Anti-inflammatory	[60]
		Phosphorylation of IκB-α, vascular cell adhesion molecule-1 (VCAM-1), and cell adhesion molecules (CAMs) ↓	HAEC cells	Anti-inflammatory and protective skin barrier	[61]
Fruits, vegetables, and flowers	Quercetin	TNF-α, IL-1β, IL-6, NO, and reactive oxygen species (ROSs)↓	RAW264.7 cells	Anti-inflammatory and antioxidant	[62]
		Chemoattractant cytokine ligand-17 (CCL17), CCL22, IL-4, IL-6, IFN-γ, and TNF-α↓	HaCaT cells and C57BL/6 mice	Anti-inflammatory	[63]
Glycine max L. Merr.	Isoflavone	IL-22, IL-17a, and TNF-α↓ TEWL, erythema, blood flow velocity, and ear thickness↓ Hydration↑ Inhibition of MAPK, NF-κB, and JAK-STAT pathways	HaCaT cells and BALB/c mice	Anti-inflammatory	[64]
		IL-6, TNF-α, and P-cadherin↓	C57BL/6 mice	Anti-inflammatory	[65]
Casearia decandra Jacq.	Rutin-casein	2,2-Diphenyl-1-picrylhydrazyl (DPPH), NO, and dermal thickness↓	Swiss mice	Anti-inflammatory and antioxidant	[66]
Citrus limon (L.) Osbeck		TNF-α, IL-6, and IL-17a↓, improved skin lesions and inhibited cell proliferation, regulation of the AGE-RAGE signaling pathway	HaCaT cells and BALB/c mice	Anti-inflammatory	[67]
Curcuma longa	Curcumin	ROSs and GSH↓, catalase activity↓	Swiss mice	Anti-inflammatory and antioxidant	[68]
Glycyrrhiza uralensis	Glycyrrhiza glabra	TNF-α, IL-6, and IL-1β↓ Inhibition of phosphorylation of signal transducer and activator of transcription 1 (STAT1), AKT, inhibitor of NF-κB (IκB), NF-κB	RAW264.7 cells	Anti-inflammatory	[69]
	Dipotassium glycyrrhizinate	TNF-α, COX-2, IL-8, NF-κB, and IL-1↓ Tissue reepithelization, total collagen and IL-10↑	Wistar mice	Anti-inflammatory and repair	[69]
Litsea cubeba	Alkaloid	iNOS, TNF-α, IL-1β, and NO↓	RAW264.7 cells, Zebrafish, and C57BL/6 J mice	Anti-inflammatory and promotes tissue repair	[70]

↑—Up-regulated expression; ↓—Down-regulated expression.

Table 2. Anti-inflammatory active substances evaluated at the cellular and animal levels.

Source	Main Active Ingredient(s)	Mechanism(s) of Action	Model	Skin Protective Effect(s)	References
C. asiatica	Madecassoside	TEWL, a* values, Red pigmentation, the numbers of non-inflammatory acne and inflammatory acne↓	Human	Promotes sensitive skin repair and anti-inflammation	[57]
A. chinensis	*A. chinensis* extract	a* values, Red pigmentation and melanin↓ Collagen density↑	Human	Improves skin-barrier function and whitening	[71]
C. sativa	*C. sativa* shell extract	Wrinkle depth and volume and skin roughness↓ skin Firmness and skin Hydration↑	Human	Improves skin-barrier function	[72]
A. barbadensis	*A. Barbadensis* extract	TEWL↓ skin firmness and elasticity and skin hydration↑	Human	Improves skin-barrier function	[73]
G. biloba	*G. biloba* leaf extract	DPPH and wrinkle volume↓ Skin firmness↑	Human	Improves skin-barrier function	[74]
S. indicus	Polyphenols	Skin erythema, melanin, sebum, and skin pores↓ Skin hydration and elasticity↑	Human	Anti-inflammation and whitening	[75]
P. granatum	Pomegranate seed oil extract	Collagenase, elastase, hyaluronidase, tyrosinase, NO, MDA, and COX-2↓	Human	Anti-inflammation	[76]
A. Arguta	*A. arguta* leaf extract	Skin hydration↑	Human	Moisturizing	[77]

a* value—the a* axis value in the CIELAB color space. It quantifies the color deviation of skin along the red-green dimension and is used to assess conditions such as erythema and pigmentation.

The inhibition of HIS synthesis reduces the release of inflammatory factors, resulting in anti-inflammatory and skin-soothing effects. Xu et al. observed that HIS-induced scratching behaviors in mice were alleviated by injections of sophorolipid (SL) extract. HIS-induced HaCaT cells treated with different concentrations of SL extract also significantly inhibit Ca^{2+} influx [13]. Koh et al. performed intradermal injections of HIS diphosphate and topical applications of tea tree oil on the forearms of 27 volunteers. By measuring flare and weal diameters and double skin thickness, they found that tea tree oil significantly inhibits HIS-induced flare and weal, indicating an effective reduction in HIS-induced skin inflammation [78]. Formononetin inhibits HIS release and the secretions of TNF-α, IL-1β, and IL-6 and ameliorates allergic inflammation caused by the release of histamines by mast cells. These effects are closely associated with reducing the intracellular Ca^{2+} content, suppressing NF-κB activation and upstream IκKα phosphorylation, and inhibiting caspase-1 activity [79].

4. Methods to Assess Skin-Soothing Effects

4.1. Methods for In Vitro Measurement of Skin-Soothing Effects

In vitro measurement methods for skin-soothing effects include the in vitro hyaluronidase inhibition assay, mast cell HIS release assay, β-hexosaminidase inhibition assay, immune cell rejuvenation, and serum IgE antibody inhibition assay [80], with in vitro hyaluronidase inhibition being the most commonly used method. Hyaluronidase is an enzyme that degrades HA. During inflammation and tissue injury, hyaluronidase breaks down the polysaccharide HA into low-molecular-weight fragments, which trigger proinflammatory

immune responses [81]. Therefore, skin-soothing effects can be assessed by measuring the inhibition of the hyaluronidase activity.

4.2. Assessment of the Effects of Skin-Soothing Cosmetics on the Human Body

Subjective and semi-subjective assessments are commonly used to assess the effects of skin-soothing cosmetics. The former is typically performed using a questionnaire to self-assess the skin's condition by individuals with sensitive skin, which usually includes items assessing symptoms of discomfort, such as skin itching, redness, and stinging pain, caused by various physical and chemical stimuli. However, given that assessments solely based on subjective feelings lack objectivity, assessing sensitive skin in clinical practice is usually performed by combining subjective and semi-subjective approaches. Semi-subjective assessments mainly include the lactic-acid-stinging and capsaicin-stinging tests. Additionally, sodium dodecyl sulfate can regulate tension in the dermis and increase blood flow in the skin, increasing its surface permeability [82]. Therefore, it is also commonly used in semi-subjective assessments of skin-soothing cosmetics.

5. Conclusions and Future Directions

Sensitive skin is a syndrome that can be classified into primary and secondary types. Its formation mechanisms are complex and multifactorial, and the treatment of the condition is usually difficult. Numerous active substances have been developed to target different mechanisms, such as promoting skin-barrier repair, reducing neurovascular hyperreactivity, and controlling inflammatory responses to alleviate corresponding symptoms. This review consolidates and summarizes these functional ingredients. However, there is still a lack of comprehensive summaries on the sensitizing potential of other cosmetic ingredients. For instance, certain functional ingredients with whitening effects may also increase skin sensitivity. Therefore, the balance and selection of the efficacy and safety of cosmetic ingredients will be crucial considerations in developing specialized cosmetics for individuals with sensitive skin.

Although studies around the world on sensitive skin and soothing cosmetics have demonstrated remarkable achievements, there are certain challenges that remain: (1) Exploration of novel active ingredients: the continuous search for and validation of new active ingredients with skin-soothing, anti-inflammatory, and skin-barrier-repairing effects, especially ingredients derived from non-traditional sources (e.g., marine organisms and microorganisms); (2) Enhancement of bioavailability: the utilization of nanotechnology to improve the penetrability and stability of active ingredients to enhance their transfer and absorption rates in the skin; (3) Research and development of multi-functional products: the development of compound skincare products with skin-soothing, anti-inflammatory, and moisturizing effects to meet the needs of different skin issues; (4) Investigation of relationships between environmental factors and sensitive skin: the elucidation of the influences of external factors, such as environmental pollution and climate change, on sensitive skin and the exploration of relevant prevention and protection measures; (5) Psychological skin interactions: the determination of the influences of psychological stresses and mood swings on skin sensitivity and the development of corresponding intervention measures.

With the deepening of our understanding of the mechanisms of sensitive skin and progress in research on active substances with skin-soothing effects, we will be able to identify and deal with sensitive skin more effectively and provide a better scientific basis to prevent and treat sensitive skin. This will contribute to further innovations in the cosmetic industry, aid consumers in managing sensitive skin better, and enhance the quality of life of sensitive-skin sufferers.

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