

Review Article

Brief analysis of causes of sensitive skin and advances in evaluation of anti-allergic activity of cosmetic products

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Abstract

This review focuses on the causes of sensitive skin and elaborates on the relationship between skin sensitivity and skin irritations and allergies, which has puzzled cosmetologists. Here, an overview is presented of the research on active ingredients in cosmetic products for sensitive skin (anti-sensitive ingredients), which is followed by a discussion of their experimental efficacy. Moreover, several evaluation methods for the efficacy of anti-sensitive ingredients are classified and summarized. Through this review, we aim to provide the cosmetic industry with a better understanding of sensitive skin, which could in turn provide some theoretical guidance to the research on targeted cosmetic products.

Résumé

Cette revue se concentre sur les causes de la peau sensible et des précisions sur la relation entre la sensibilité de la peau et des irritations cutanées et des allergies, qui ont intrigué les cosmétologues. Ici, une vue d'ensemble est présentée de la recherche sur les ingrédients actifs dans les produits cosmétiques pour la peau sensible (des ingrédients anti-sensibles), qui est suivie d'une discussion de leur efficacité expérimentale. En outre, plusieurs méthodes d'évaluation de l'efficacité des ingrédients anti-sensibles sont classées et résumées. Grâce à cet examen, nous visons à fournir l'industrie cosmétique avec une meilleure compréhension de la peau sensible, qui pourrait à son tour fournir quelques indications théoriques à la recherche sur les produits cosmétiques ciblés.

Introduction

Sensitive skin is defined as skin that exhibits high reactivity and low tolerance, allowing the skin to easily become allergic. Sensitive skin, which is associated with subjective sensory symptoms induced by a predisposition to a variety of factors, is generally treated as a skin condition rather than a skin disease in the medical field. However, concerns regarding skin sensitivity have gradually increased due to worsening environmental pollution, development of diverse cosmetic products and increased awareness of skin health.

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Sensitive skin occurs primarily on the face, but is also often found on the hands, feet and scalp [1]. Sensitive skin is characterized by dryness of texture, constriction and erythema, without the presence of skin lesions or diseases. Moreover, even mild irritation can lead to itching, desquamation, and burning or prickly sensations. In severe cases of sensitive skin, negative emotions or psychiatric symptoms may also occur. Because the causes and pathogenesis of sensitive skin are complex, no effective treatments for sensitive skin have been developed [2]. Therefore, the use of targeted cosmetic products and careful attention to daily skin care play important roles in alleviating the symptoms of sensitive skin.

In this review, we survey a series of related research literature and present a comprehensive overview of the progress achieved in research on sensitive skin while focusing on existing research on cosmetic products commonly used for the treatment of sensitive skin.

Causes and symptoms of sensitive skin

Sensitive skin, with its high reactivity and low tolerance, is not caused by contact or reaction with any specific materials. Instead, it is an established state of the skin's inherent structure and nerve sensations. Some of the possible factors are listed below.

Barrier function

The skin acts as a barrier that effectively prevents the invasion of external harmful factors and the loss of nutrients from the body. Damage to the skin's barrier function is a major factor behind sensitive skin [3]. It has been suggested that compared to normal skin, sensitive skin shows a weaker barrier function of the stratum corneum [4]. When a reduction of keratinocytes leads to a thinner corneum, the percutaneous penetration rate increases, causing the skin have higher responsivity [5, 6]. Combined use of a facial skin cleanser and moisturizers with functional extracts can strengthen the skin barrier and improve the overall skin condition, thereby benefiting sensitive skin according to the response of the subjects [7].

Neurobiological factors

On studying the characteristics of sensitive skin through a non-invasive method, it was observed that the growth amount of all types of nerves in the corneum were higher than that of non-sensitive skin

[8], leading to the belief that allergic responses of sensitive skins were closely related to the nerve factor. In recent years, studies have shown that the occurrence of sensitive skin was associated with functional abnormalities of the peripheral nerves and functional changes to the central nervous system [9, 10]. Neuromediators are also involved in all phases of skin wound healing (inflammatory, proliferative and remodelling phases). Numerous experimental observations indicate that after surgical resection or disease, damage to the peripheral nervous system will delay wound healing and repair [11]. Transient receptor potential vanilloid type 1 (TRPV-1), the recently popular research topic within the cosmetic industry, belongs to the subject of neurobiological factors analysis.

Inflammatory response

As sensitive skin has the characteristics of barrier function impairments or neurological abnormalities, it has poorer defence against attacks from exogenous stimuli and allergens compared to normal skin. As such, it is easy for sensitive skin to have a series of inflammations caused by irritations or allergies. The inflammations will further damage the barrier structure and nerve endings, resulting in a vicious cycle. Yokota *et al.* categorized sensitive skin into three types according to the presence of inflammation or damage to the skin's barrier function and treated, respectively, and then, they found that the classification process is more conducive to improving skin conditions, which proves inflammation to be an important factor of sensitive skin [12].

Differences and links between skin sensitivity, irritation and allergy

Contact dermatitis (CD) is an acute or chronic inflammation induced when the skin is exposed to particular substances. Based on the pathogenesis, CD can be divided into two major categories: allergic CD (ACD) and irritant CD (ICD).

Allergic CD, commonly known as skin allergy, is an antigen-specific response of the skin that is mediated by thymus-dependent lymphocyte cells (T-cells); it consists of two phases. The initial phase is when the skin is first exposed to the hapten. The latter is engulfed by the Langerhans cells (LC) or transported by the carrier protein in cell membrane of other epidermal cells, subsequently moving from the epidermis to the lymph nodes. The T-cells become activated and turn into effector and memory T-cells, which are then distributed over the entire body through blood circulation. This phase takes approximately 10 days. Next is the stimulation phase, when the skin contact with the same hapten once again. The memory T-cells rapidly differentiate into large numbers of effector T-cells. Within one to two days, inflammation mediated by T-helper cells (CD4+Th1) and cytotoxic effects mediated by cytotoxic T-cells (CD8+CTL) will occur. The various cells and substances involved in skin allergies are shown in Fig. 1.

Irritant CD, commonly known as skin irritation, refers to damage of the histiocytes caused by exposure to irritants. In terms of its pathogenic path, after an irritant enters the corneum, the keratinocytes become activated or mildly damaged producing various cytokines including IL-1, IL-2 and IFN- γ . These cytokines directly initiate leucocyte chemotaxis on a dose-dependent basis, and even activate non-specific T-cells [13]. ICD has varied manifestations: During the acute stage, it is mainly expressed as skin erythema, oedema, desquamation, and keratinocytes forming cell vesicles or undergoing amyloidosis. During the chronic stage, the main

expressions are skin fissures, lichenification and excessive keratinization [14] (Fig. 2).

A summary of the differences and links between skin sensitivity, irritation and allergy is presented in Table I.

Common anti-sensitive ingredients in cosmetic products

'Anti-sensitivity' usually refers to a series of restorative effects targeting sensitive skin, including daily care and improvement, suppression of response to irritants, and relief of inflammations or allergies. The cosmetic industry had carried out extensive researches on natural substances with this ability. Table II lists the functional ingredients generally used in the industry for anti-allergy or anti-irritation, as well as their respective main efficacies.

Efficacy evaluation methods for anti-sensitive ingredients

Presently, researches focusing on evaluation methods for the efficacy of anti-sensitive ingredients are complex and diverse. The methods cover basic in vitro, animal, human, as well as small number of cells experimentations, targeting different aspects of efficacy, including barrier repair, nerve sedation and anti-inflammation. The following is an overview of existing experiments aimed at efficacy evaluation based on different target classifications.

Experiments related to the maintenance and restoration of skin barrier function

Skin barrier function is a complex concept, which we believe involves the structure, composition, and status of various cells and intercellular lipids of the epidermis.

Hyaluronidase (HAase)

Hyaluronic acid (HA), the largest constituent of extracellular matrix [48], is distributed across many tissues of the human body, especially in the dermis, cartilage and joint fluids. HA has very strong water-binding capacity and viscosity. It maintains extracellular volume and regulates the secretion of cell growth factors,

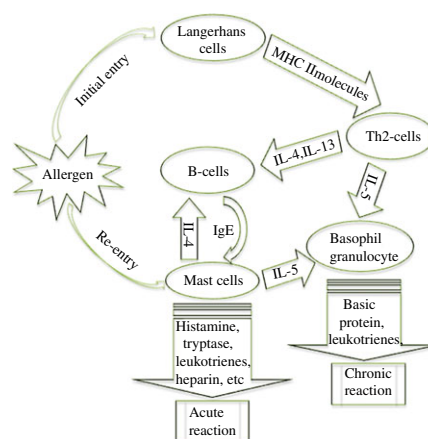


Figure 1 Processes involved in skin allergic reaction.



Figure 2 Images depicting skin allergy (left) and irritation (right).

Table I Differences and links between skin sensitivity, irritation and allergy

Properties	Skin sensitivity Skin condition	Skin irritation	Skin allergy
		Skin reaction	
Causes	1 Damaged barrier function 2 Neurobiological dysfunction	1 Sensitive skin 2 Physical/chemical stimuli (acidic substances, organic solvents, surfactants)	1 Poor barrier function/sensitive body constitution 2 Allergens (fat-soluble substance with low molecular weight)
Cells	Keratinocytes, fibroblasts, neurons	Mast cells, basophil granulocyte, non-specific T-cells	Langerhans cells, phagocytes, specific T-cells
Substances	Cells and components related to the structure of corneum	1 Histamine 2 Kininogenase (catalyses the formation of plasmakinin, bradykinin)	1 Cytokine (CK) 2 Interleukin (IL factor)
Manifestations	1 Structural damage to the epidermis 2 Dryness, constriction, erythema	1 Erythema, oedema, desquamation 2 Keratinocytes forming cell vesicles or undergoing amyloidosis	1 Similar to stimulations 2 Systemic illness
Characteristics	1 Poor tolerance to irritants (reduced threshold) 2 More prone to allergic reactions	1 Direct response after contact 2 Local response 3 May be triggered by any substances (critical density)	1 Incubation period (triggered by re-exposure) 2 Complex whole-body response 3 Diseased sites are symmetrical
Links	1 Sensitive skin is prone to irritations and allergies, and can be considered as a reason for them. 2 Skin irritations and allergies are the responses of sensitive skin to exogenous stimuli		

thereby affecting the adhesion, growth, multiplication and division of cells [49]. As such, HA plays an essential role in maintaining the moisture and elasticity of the skin, as well as in tissue healing and vascularization processes [50]. HAase is the specific lyase of HA, and inhibiting its activity would help maintain the quantity and normal function of HA [51]. Further, decrease in HA accounts for the loss of skin moisture, ultimately resulting in a loss of elasticity and the development of wrinkles [52]. Hence, suppression of HAase would in turn result in the retention of skin moisture and maintenance of its barrier function. Moreover, the HAase suppression rate can be used as an indicator to evaluate the anti-sensitive

efficacy of substances, with a higher rate indicating a stronger power (Fig. 3).

RBC haemolysis test system

The RBC experiment was established by the European Centre for the Validation of Alternative Methods (ECVAM) as an alternative to the testing of irritants on animals. The principle is to measure the amount of haemoglobin leakage from red blood cells as a proxy to determine the extent of damage to cell membranes. A larger amount of haemoglobin leakage means a more severe damage [53]. The protective capabilities of active substances over

Table II Anti-allergic and anti-irritant ingredients and their efficacious characteristics

Active substance	Extraction source	Main efficacies	Action mechanism
Hydroxytyrosol	Olives	Strong anti-oxidant [15], protect RBC [16], suppresses inflammations [17], anti-hyperplasia of blood vessels [18]	Cell repair Barrier repair
Procyanidin	Grape seeds	Eliminates free radicals [19], stabilizes cell membranes [20]	
Echium oil	Echium seed	Strong anti-oxidant [21], restores fluidity of cell membranes, promotes cell regeneration	
	Lavender	Eliminates free radicals, promotes cell regeneration [22]	
	Purslane	Eliminates free radicals, retracts and smoothens muscle, prevents drying and ageing	
Echinacoside	Narrow-leaf echinacea purpurea	Anti-oxidation [23], anti-ageing [24], suppresses over-proliferation [25], protects blood vessels [26]	Structural maintenance
Brown algal polysaccharides	Brown algae	Promotes generation of neural acrylamide, anti-oxidation [27], suppresses inflammation [28], promotes healing [29]	
Piscidic acid	Cactus stems	Regulates cell multiplication [30], repairs damages [31], moisture retention and anti-oxidation [32]	
Total glucosides of peony	Chinese herbaceous peony	Regulates cell multiplication [33], anti-ageing [34], suppresses inflammation factors [35]	
Tea polyphenol	Tea leaves	Anti-oxidation [36], regulates cell multiplication [37], suppresses inflammation factors [38]	
Trans-4-tertiary butyl cyclohexanol	Synthetic	Suppresses overexpression of TRPV-1	Nerve sedation
Peony phenolic glycosides	Peony bark	Anti-allergy, anti-inflammation, anti-bacteria	Anti-bacterial activity
Baicalin	Stems and leaves of scutellaria	Removes blemishes and whitens skin, suppresses allergies, sterilization [39, 40]	
Nightshade alkali	Dried green fruits of nightshade	Anti-tumour, increases blood glucose, strengthens the heart, anti-allergy, anti-bacteria	
Stachyose	Legumes	Suppresses hydrolysis of hyaluronic acid, suppresses inflammation [41, 42]	Anti-inflammatory activity
Acyl anthranilic acid	Oats bran	Anti-histamine, anti-allergy, anti-inflammation, anti-oxidant	
Quercetin	Various plants	Anti-oxidation [43], Suppresses inflammation [44], protects blood vessels [45], reduces cell infiltration [46]	
β -Boswellic acid	Boswellia serrata (Salai guggal)	Suppresses 5-lipoxygenase and leucocyte elastase	
Farfara ketone	Farfara leaves	Anti-inflammatory, pain relief, anti-spasm [47]	

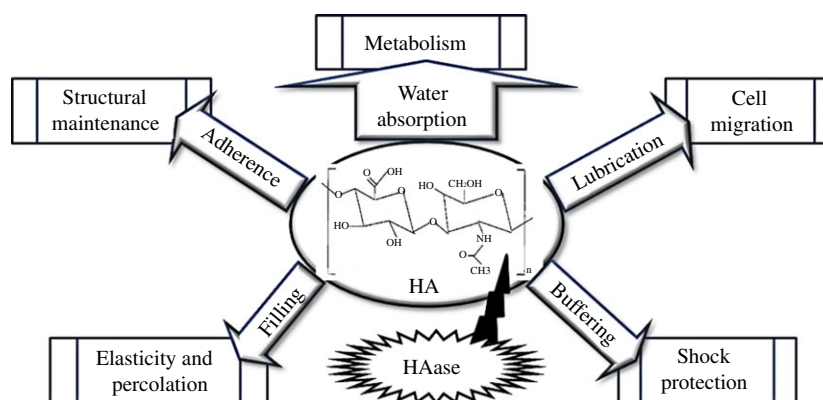
**Figure 3** Role of skin hyaluronic acid (HA) and hyaluronidase (HAase).

Table III Physiological functions of AQP-3, filaggrin, and caspase-14

Name	Physiological function
AQP-3 Aquaporin-3	Involved in cells' absorption and secretion of substances; help maintain elasticity and repair damage [57]
FLG Filaggrin	Connect keratin fibres, form keratin envelopes, and maintain the flat shape of keratinocyte [58]
Caspase-14 Cysteinyl aspartate-specific 3proteinase-14	Participate in the terminal differentiation of keratinocytes and assist FLG to form a complete corneum [59]

cell membranes can be evaluated through an improved RBC experiment.

Elimination of free radicals

Free radicals produced by mitochondria during the electron transfer process can attack cell membranes, proteins and even DNA [54], thereby causing cell ageing and death. Once there are exogenous stimuli, excessive amounts of free radicals are produced. Suppressing the activity of these free radicals can effectively alleviate the degradation of cellular structures and functions, thus maintaining the healthy skin barrier.

Analysis of ceramide content in the corneum

Ceramide (Cer) is also known as N-fatty acyl (nerve) sphingosine. It is an important component of corneum or skin lipid, and its functions include maintaining structural stability of the corneum (adhesiveness), moisture retention and damage repair [55]. Properties and quantity of Cer affects the stability of the skin barrier and occurrence of some skin diseases. After active substances have been applied to the skin, observations are made to determine whether there is ceramide secretion by the keratinocytes or changes in the expression of acidic ceramide. If so, it proves the efficacy of the active substances in supplementing the corneum lipid and restoring the skin barrier.

There are currently systematic tests, including sampling, separation (liquid chromatography, LC) of corneum or skin lipid, and quantitative analysis methods such as electrospray ionization mass spectrometry (ESI-MS), atmospheric pressure chemical ionization mass spectrometry (APCI-MS) and tandem mass spectrometry (MS-MS) [56]. However, these methods have only been used to analyse inherent ceramide contents in corneum, but not the analysis of the impact of exogenous substances on it.

Protein related to skin barrier structure

This topic has not been extensively researched, but is gradually getting widespread attention. In recent years, researches on the way active substances affect the expressions of aquaporin-3 (AQP-3), filaggrin (FLG), and cysteinyl aspartate-specific proteinase-14 (Caspase-14) after exposure to exogenous stimuli have appeared. The main physiological functions of these three proteins are shown in Table III.

Experiments on nerve sedation

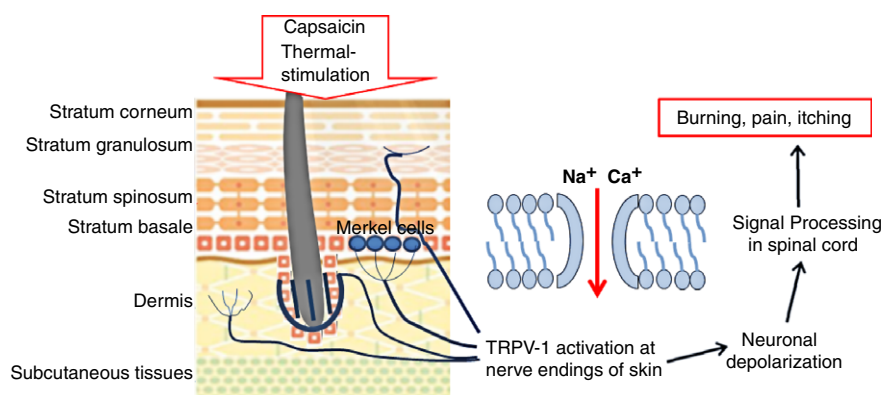
The sensory and autonomic nerve fibres play modulatory functions in processes related to the nutrition and immunity of the skin, thereby contributing to the maintenance of homeostasis and wound healing. Neurogenic inflammation increases blood flow, causing the exudation of plasma proteins and formation of oedema in the skin [60].

Calcitonin gene-related peptide

When exposed to exogenous stimuli, Ca^{2+} flows into the neurons, releasing calcitonin gene-related peptide (CGRP) and causing hemangiectasis. CGRP is an inflammatory prion that activates mast cells, macrophages, fibroblasts, melanocytes, keratinocytes, dendritic cells, and lymphocytes B and T, thereby promoting the development of oedema induced by IL-1 and IL-8 [61]. Fluorescence identification test of CGRP quantity as pre-inflammatory neurotransmitters can be used to evaluate the signal transduction of neurons, thereby showing the nerve sedation effect under stimulation.

Transient receptor potential vanilloid-1

Transient receptor potential vanilloid-1 is expressed in fibroblasts, keratinocytes, melanocytes and mast cells, causing inflammatory pain and slowing down barrier repair [62]. It is activated by stimulations from toxins, acidity, or high temperatures, resulting in

**Figure 4** Relationship between skin Transient receptor potential vanilloid type 1 (TRPV-1) and skin sensitivity.

allergic symptoms such as itchiness, pain or burning sensations [63]. Currently, cosmetic ingredients targeting neurogenic sensitive skin are mainly produced as antagonists of expression or function of TRPV-1. Reduction of the expression of TRPV-1 demonstrates that the substance has anti-sensitive efficacy and can soothe facial discomforts (Fig. 4).

Evaluation of inhibition of inflammation

Evaluation of inflammation inhibition can illustrate samples' ability to suppress the negative effects on skin caused by exogenous substances (irritants or allergens). The ingredients affect the key factors for each phase of skin inflammation, which mainly includes expression and release of various cytokines, number of mast cells and their secretion of histamine, leukotrienes, and other inflammatory substances, as well as the activity of the LC (skin immune-presenting cells).

Study of CD 54/CD86 expressions on THP-1 cells

Given the limitations in their quantity and form, it is difficult to cultivate LC *in vitro*. It is generally accepted that an increase in CD54/CD86 expression on the human acute monocytic leukaemia cell line (THP-1) serves as the equivalent alternative indicator for the activation effect of LC. By comparing the value of the respiratory failure index (RFI) of the CD54/CD86 on THP-1 cells with that of the traditional experiment using guinea pigs and local lymph node assay (LLNA) using mice, and using $\text{RFI} \geq 150$ as the limit to distinguish between allergens and non-allergens, researchers discovered that the accuracy rates for CD86 and CD54 were analysed to be 100% and 85%, respectively, indicating that CD86 is a relatively more sensitive and reliable indicator than CD54 [64].

Study of leukotriene-based 5-lipoxygenase activity

Leukotriene is one of the strongest inflammatory messengers, causing leakages in blood capillaries and white blood cells, resulting in various localized inflammation symptoms including itching, erythema and swelling. 5-lipoxygenase (5-LOX) is the most critical pro-inflammatory enzyme during the generation process of leukotrienes (inflammatory cytokines) through the inflammatory arachidonic acid path. It has already been established that a selective 5-LOX inhibitor exhibited an improved efficacy in arachidonic acid-induced ear oedema [65]. Some cosmetic material companies report that active ingredients in cosmetic products were able to inhibit the generation of leukotrienes through suppression of the key enzyme, thus terminating inflammation expression.

Experimentations on humans and animals

Human experimentations

Human experimentations remain an essential part of the research process for most cosmetic ingredients and products. Stimulation patch tests are usually performed on voluntary subjects aged 18–60 years and satisfied testing requirements. After exposure to the irritant and samples, each subject will give a score based on his/her subjective feeling, which is deemed as the evaluation for the sample's relief efficacy.

In addition, human experimentations are used for evaluating the skin erythema index, moisture content, or other physiological

indices of the skin, as well as skin thickness and structural changes. These tests help to determine the degree of skin sensitivity. When the human body is subjected to these experiments, data that are more intuitive are obtained. Although variation exists because of differences between individuals, as each individual experiences different degrees of skin sensitivity and the manner in which a person's skin reacts to a product will determine whether they continue to use it, we still consider human testing as the most valuable evaluation method.

Animals can also be used as test subjects. The irritant and samples are similarly applied, but the researcher rates and evaluates the efficacy based on the skin damage observed in the animals. Visual inflammatory response can be observed through patch tests, but the results are often very subjective and far from convincing.

Animal experimentations

Animal experimentations were the most widely used evaluation method for anti-allergic efficacy. Beside the stimulation patch test, most tests aim to analyse the suppression of inflammation and allergic responses. Researches in this area are not limited to the skin, but extend to the internal organs and immune system of the organisms. These types of experiments include histology observations, measurements for level of various immune factors, analysis of related gene expressions, as well as detection of the activity levels of various cells (eosinophils, white blood and ventricular hypertrophy) [66–68].

Animal experimentations focused on immune response and the process was relatively cumbersome, so it was not often applied to the research on active ingredients in cosmetic products. The European Parliament and Council of the European Union (EU) reached an agreement in Brussels on 7 November 2002 and decided 'the use of animals for cosmetics toxicity and allergy experiments would be prohibited in the EU from 2009; the use of animals in the safety evaluation of cosmetics would be prohibited from 2013; and all EU members would be gradually prohibited from importing and selling cosmetics that had used animals for experimentation'. Since then, the use of animal experimentations in the cosmetic industry had to be replaced by other methods worldwide. However, the point of sensitive skin is a person's skin reacts to a product, which will determine whether they continue to use it. Therefore, human testing is the most valuable evaluation method.

Conclusion

Climate change, air pollution and the increasing complexity in the materials and types of cosmetics have increased the occurrence of sensitive skin and its possibility of being irritated. Scientists in the cosmetic industry became more concerned about the development of anti-sensitive cosmetics as they had become aware of this phenomenon.

Causes of sensitive skin include skin barrier dysfunction, too strong neural response or the vicious cycle of inflammation, and based on this, we can classify the anti-sensitive activities into three types: barrier repair, nerve sedation and anti-inflammation. Then, a systematic cosmetics sensitive skin-targeted R & D system will be established by filtering and improving *in vitro*, cells, human, as well as animal experimentations according to the classification above. This will help to provide consumers with anti-sensitive cosmetics with clear efficacy and good effect.

However, the causes of sensitive skin, especially neural factors is still not clear, with a lot of cells, factors and their physiological functions to be found; varieties of cultured human skin cells and 3D skin model are not full-used as emerging materials. It will be an important step in the development of cosmetic industry to analyse the causes of sensitive skin and find the appropriate efficacy methods for evaluations of anti-sensitive ingredients.

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