Introduction

Skin homeostasis is the foundation of skin health and beauty, and many factors can lead to the imbalance of skin homeostasis, which leads to dry skin, redness, greasy skin, breakouts and other conditions. Therefore, maintaining skin homeostasis is the basis of cosmetic efficacy in the development of cosmetics, but there is a lack of corresponding evaluation methods. At present, some efficacy claims related to skin homeostasis, such as moisturizing and repairing, are only evaluated from a certain aspect of the skin, which is not completely consistent with the overall concept of homeostasis. With the development of omics technologies especially cutaneous lipidomics, cutaneous microbiome and proteomics technologies, which are based on the systematic concept to systematically analyze the lipidomics, microbiome and proteome that affect the skin. Based on a variety of omics research techniques, combined with steady-state correlation target analysis, more comprehensive and in-depth analysis can be conducted, which is a potential emerging evaluation method for skin homeostasis maintenance. In this paper, the future development direction of the evaluation method of homeostasis maintenance is forecasted, which provides a theoretical basis for the development of cosmetics for maintaining skin homeostasis.

Skin Homeostasis and Related Efficacy Claims

Skin homeostasis is a stable state of the skin, which covers the normal metabolism of the skin, including the growth, apoptosis
and functional operation of various cells in the skin, and is a homeostasis of the "neuro–immune–endocrine" system. The skin barrier is a prerequisite for maintaining a stable environment in the body, ensuring that the skin is protected from sun damage, mechanical injury, pathogens and chemical stress as the first line of defense (Wang et al., 2022). At the same time, the skin is not a simple barrier, but is involved in maintaining internal homeostasis through multidirectional communication between the central nervous system, endocrine and immune systems, which share the language of neuropeptides, cytokines, hormones and other effector molecules and recognize the neuro–immune–endocrine system(Brazzini et al., 2003). In terms of nervous system, the skin nervous system receives foreign stimulation signals mainly through sensory nerves and nervous system cells, releasing nutrients and neuropeptides, and skin nervous system cells can release different types of neurotransmitters: In terms of immunity, the skin is protected not only by physical barriers, but also by immune cells and molecules, which also cause inflammation (Jin et al., 2022): In terms of the endocrine system, the skin is able to receive and secrete most hormones and has a skin function equivalent to the hypothalamic–pituitary–adrenal (HPA) axis. Therefore, skin homeostasis is a “system” concept. The homeostasis of the skin is mainly due to the disorder of the body’s neuro–immune–endocrine system, resulting in dryness, redness, acne, aging, sensitivity and other skin problems under the stimulation of internal and external environment. Currently, cosmetic claims for maintaining skin homeostasis include soothing, repairing, moisturizing, oil-control, and Sunscreen. Soothing products mainly work to rebuild and repair the skin barrier. Moisturizing products are mainly for people who are stimulated by factors such as dry environmental climate, ultraviolet radiation and psychological pressure, resulting in weakened barrier function and unbalanced homeostasis, which further leads to dry skin (Shen et al., 2018). Oil–control by regulating sebum secretion, Excessive secretion of lipid in the skin will destroy skin homeostasis, resulting in skin dullness, acne and other skin problems (Li et al., 2018a). Sunscreen also plays an important role in maintaining skin homeostasis by preventing photoaging (You et al., 2021). Table 1 briefly lists the assessment methods proposed in this study for maintaining skin homeostasis.

Relevant evaluation methods are available

1. **In vivo methods**

   In vivo mainly consists of subjective evaluation and objective instrument analysis. Subject self–assessment is the most commonly used subjective evaluation, mostly in the form of face–to–face inquiry or questionnaire (Liu et al., 2021). Visual assessment can be used to evaluate soothing and moisturizing effects, to evaluate soothing effects by skin erythema, and to quantitatively evaluate dry skin based on relevant parameters such as dander size and skin roughness (Abdlaty & Fang, 2021). Objective instrumental analysis includes image–based and image–based assessments of significant differences in dielectric constants between water and other substances. The former compares the facial skin roughness, wrinkle depth, skin color ($L^*a^*b^*$), skin brightness (ITa°) and other indicators before and

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after using a specific product, and analyzes and characterizes the skin state (Pérard, 1998; Gianeti & Maia Campos, 2014). The latter measures cuticle (SC) hydration and transepidermal water loss (TEWL) to assess the skin barrier (Lyu et al., 2022). Subject self-assessment, visual assessment and other evaluation methods are highly subjective, and some difficult assessments need to be standardized according to the general scoring scheme. At present, there is no method to evaluate steady-state in vivo method, but it is only related to steady-state in a certain aspect, so it is not comprehensive.

2. In vitro methods

In vitro experiments, a variety of methods are usually used, including physics, chemistry, cell biology, and 3D skin construction. Physicochemical method is to evaluate the function of the product by testing its own physical properties and specific chemical composition (Yin & Zhao, 2018). Biochemical method is the use of physical and chemical technical means to test and analyze the characteristic indicators that affect the efficacy and the content of important biological molecules (Dunaway et al., 2018). Cell biological method can obtain a lot of information of microscopic cell biological indicators, and supplement and improve the in vitro and in vivo tests. The safety and efficacy of skin cosmetics are usually evaluated by various types of epidermal cells (human or mouse melanoma cells, fibroblasts, keratinocytes, etc.) grown in vitro (Guo & Wang, 2018). The 3D skin model uses the biocompatible matrix conditions, the human source of dermal fibroblasts, epidermal keratinocytes and other injected on its surface and cultured, so as to build a 3D skin with a similar structure and function of human skin (Jiang & Santos, 2018). Including epidermal model, whole skin model and melanin skin model (Ma et al., 2020). It can be used in the evaluation of cosmetic efficacy for safety testing (Fu et al., 2020; Brathwaite et al., 2022; Sanches et al., 2020), as well as for efficacy testing, including skin barrier, anti-inflammatory and transdermal absorption (Li et al., 2018b). The in vitro method has low cost and avoids animal and human experiments, but there are still big differences between the in vitro method and the real human situation of the product, so the reliability of the results needs to be further proved.

1. Evaluation methods based on steady-state correlation targets

Target-based evaluation is a multi-level, multi-angle analysis method, usually using high-throughput screening techniques and computer simulation techniques, such as molecular docking simulation, bioinformatics, network pharmacology and data mining (Yu et al., 2022). By integrating and mining cross-information, we can predict the action targets and pathways of the active ingredients, analyze the action mechanism and biological effects of the ingredients, and use the collected information to design and optimize the formulation.

Skin homeostasis is the overall stable state of the "nervous system-immune-endocrine" system. When the skin is subjected to external stimulation, if the skin barrier function is weakened, the Ca\(^{2+}\) of the ER will be released from the class C fibers to the nerve endings, and the peptide of the calcitonin gene will be produced after entering the neurons, and then cause a series of neurogenic inflammatory reactions. The interaction of decreased function of epidermal nerve endings, increased nerve fiber density, and enhanced sensory nerve reflexes can lead to cutaneous sensory nerve dysfunction, which in turn is closely related to transient receptor potential (TRP) family activation (Wang & Pan, 2018; Xiso et al., 2023; Crocco et al., 2021; Rokni et al., 2021). In immune-related experiments, the method to evaluate the body's ability to avoid sores is to conduct quantitative or qualitative tests on four indicators: cellular immunity, humoral immunity, mononuclear macrophages function and natural killer cell (NK) cell activity. Cellular immunity is to detect the number and functional status of immune cells, such as IL-2, IL-4, IFN-γ and other cytokines (Grøne, 2002); Humoral immunity often detects substances such as IgE, IgM, IgA, etc., Monocyte-macrophage function testing substances are interleukins (ILs), tumor necrosis factor (TNF-α), etc (Ma et al., 2021a): Natural killer (NK) cell activity assay Killing index or percentage of NK cells (Fan et al., 2023), Yang et al. (2022) used a network pharmacology approach to explore the mechanism of action of antler velvet antler active ingredients in immunomodulation, and obtained 33 active ingredient-immunity action targets, involving biological processes mainly inflammatory response, protein synthesis, cancer pathway, NF-κB signaling pathway and so on, Yan et al. (2022) analyzed the targets of effective compounds of rosehip based on network pharmacology, and found 154 targets that can exert antioxidant, anti-inflammatory, and immunomodulatory
functions. Using high-resolution mass spectrometry to identify the main efficacy components of Colla Corii Asini, Tiehang et al. showed that it has the efficacy value to be developed as a cosmetic raw material and has the basic safety that is necessary to be used as a cosmetic raw material (Hang et al., 2020). The evaluation based on homeostasis-related targets is based on the results of existing studies and has some scientific value and guidance.

2. Skin lipidome

Skin lipids are the most important substances in skin metabolism and account for a significant proportion of skin metabolites (Elpa et al., 2021). It has an important role in skin barrier, immunity and endocrinology. It is mainly composed of sebaceous gland lipids and intercellular lipids, 75% to 90% of the lipids in the skin are secreted by the sebaceous glands, and the epidermis is the most active part of the body in lipid metabolism, with 10% to 25% of the lipids synthesised by the epidermis (Xue et al., 2020). Skin lipids are a combination of lipids of keratinocyte, sebocyte and microbiological origin that influence the state of the skin through various mechanisms with physicochemical, biochemical and microecological functions (Wei, 2020). Skin lipids are mainly composed of ceramides (50 per cent), cholesterol and its esters (37 per cent), cholesterol sulphate (2–5 per cent) and non-esterified fatty acids (10–15 per cent), which play an important role in the function of the skin barrier (Uche et al., 2019). Normalisation of ceramide subclass composition, increase in CER and FFA chain lengths and decrease in monounsaturated fatty acid and unsaturated CER levels improve skin barrier function (Niehues et al., 2018). Long-chain CERs are highly involved in the maintenance of barrier function, Fatty acids are involved in the barrier function of the skin and the maintenance of acidic pH, and are necessary for the antibacterial and antifungal function of the skin (Drakou et al., 2021).

Understanding lipid–skin barrier integrity relationships through in situ, in vitro and 3D reconstructed epidermal models, Different types of lipid mixture models have elucidated the role of specific lipids in barrier function, especially intercellular lipids, CHOLs, CERs and FFAs are essential for maintaining epidermal barrier homeostasis. These models have been used to assess the efficacy of various natural and synthetic lipid mixtures in optimising barrier health, CER is used as a key ingredient in moisturisers and other products to restore the skin barrier (Barresi et al., 2021). However, further systematic research is needed to determine the correct combination of essential skin lipids and the appropriate delivery system, and it is important to determine the benefits of these lipid–containing formulations for skin barrier damage caused by everyday skin stressors, Luo et al. (2022) used cellular experiments to study the repairing effect of composite ceramide nanocarriers on the skin barrier, and the results indicate that they have good prospects for application in the field of moisturising and anti-inflammatory cosmetics, Jacques et al. (2023) analyzed the stratum corneum of a reconstructed human epidermal model using high-throughput lipidomics techniques, and emollient creams may be beneficial for skin lesions by altering SC lipids, balancing CER levels and ratios, and improving barrier function.

Evaluation methods based on skin lipidomics can, on the one hand, go through the skin lipid metabolites to better understand the skin physiology and the role of active ingredients; on the other hand, the high throughput of lipidomics can obtain more accurate data, improve the quality and efficiency of cosmetic evaluation, and increase the reliability of cosmetic evaluation. Evaluation methods based on skin lipidomics can, on the one hand, go through the skin lipid metabolites to better understand the skin physiology and the role of active ingredients; on the other hand, the high throughput of lipidomics can obtain more accurate data, improve the quality and efficiency of cosmetic evaluation, and increase the reliability of cosmetic evaluation. By analyzing different lipid compositions, it is possible to evaluate skin homeostasis not only in terms of maintaining the skin barrier function, but also to infer the homeostasis of microorganisms on the surface of the skin through the analysis of lipid compositions, and to comprehensively evaluate the homeostasis of the skin.

3. Skin microbiome

The surface of human skin is colonised by a wide range of commensal microorganisms, including bacteria, fungi, viruses, archaea and mites, which together form the skin microbiota (SM), contributing to skin integrity and homeostasis. Many of the beneficial effects induced by SM are exerted by microbial metabolites. Examples include bacteriocins, biofilms, antimicrobial peptides and indoles that inhibit many moulds and yeasts (di Lorenzo et al., 2021). Escherichia coli KUB-36 metabolites and single–chain fatty acids inhibit the expression of inflammatory cytokines IL-1β, IL-6, IL-8, and TNF-α, while inducing the expression of the anti–inflammatory cytokine IL-10, which affects the lipopoly saccharide–induced inflammatory response in THP-1 macrophages (Fu, 2021; Liu et al., 2013). The interaction between microorganisms on the skin surface, the host and the external environment forms the skin microecological environment (Xue et al., 2020). A disruption of
the epidermal microecological balance can lead to pathological (seborrhoeic dermatitis, acne, psoriasis) or non-pathological (sensitive, dry skin, etc.) lesions. Thus, the skin microbiome is also an important aspect of skin homeostasis.

The microbiome in the skin has been evaluated comprehensively or locally, using the species and relative abundance of the skin colonisation flora as indicators. Such microbiome analyses are often combined with analyses of common physiological parameters, such as moisture content, skin redness, elasticity, sebum content, etc., and are only used for correlation analyses (Fournière et al., 2020). Recently, Aline M’etris et al. (Métris et al., 2021) proposed a 3-layer framework to qualitatively assess the potential impact of skin microbiota perturbations on consumer health. Different techniques from classical culture to the use of histology and modelling to identify hazards, define endpoints and describe dose–response, Marito et al. (2020) found that the PEG–8 lauric acid fermentation product of Streptococcus epidermidis had an inhibitory effect on Propionibacterium acnes, and that the development of resistance could be avoided by reducing the required dose of antibiotics and maintaining skin microbiome homeostasis. Lactobacillus plantarum fermentation lysate can be used as a control of skin microecological balance and has potential application in cosmetics (Fan et al., 2022). Microorganisms affect not only the immune function of the organism to some extent, but also the composition and amount of lipids on the skin surface. Therefore, the evaluation of skin homeostasis based on the skin microbiome is inevitably a direction of methodological development.

4. Skin proteasome

Proteomics is the systematic study of the expression of proteins present in cells, tissues, organs or organisms in pathological or physiological states at specific moments in the life cycle (Xu et al., 2023). Skin barrier, immune, and endocrine–related proteins have been emphasised. AQP s are a class of membrane–integrated proteins that rapidly transport water (Guo & Wang, 2018). In keratinocytes, AQP–3 (aquaporin–3) is mainly involved in the absorption and secretion of intracellular substances, which is important for maintaining skin elasticity and repairing damage: The function of filaggrin (FLG) is to link keratin fibres together, thus maintaining the morphology of keratin–forming cells and forming the keratin envelope: Caspase–14 (cysteine aspartate–specific protease–14) is involved in the final differentiation process of keratin–forming cells and helps silk proteins to form a complete stratum corneum. Keratinocyte (KC) can produce a variety of cytokines, such as IL–1, IL–6, IL–8, TNF–α, etc., but also produce a large number of mucopolysaccharides and cytokeratins, etc., which is also the target cell of a variety of cytokines, and plays an important role in maintaining the physiological balance of the skin, exerting the skin’s immunity, and maintaining the skin’s osmotic effect and barrier function (Ma et al., 2021b). Yan et al. (2023) applied the anti-inflammatory efficacy of HaCaT cells by detecting the expression of inflammatory factors IL–6, TNF–α and COX–2. The results showed that the fermentation broth of Xanthopanax has a great potential to be used in cosmetics as an efficacious raw material for anti-aging, anti-inflammatory and antioxidant applications, Guo et al. (2023) assessed the potential application of recombinant Ganoderma lucidum protein (rFIP–glu) as a bioactive ingredient in cosmetics, then the protein was evaluated for its free radical scavenging ability and its effect on the in vitro viability of human immortalised keratinocytes and mouse B16–F10 melanoma cells, and then on the melanin synthesis of the B16 cells, SDS–PAGE and protein blotting analysis of the results showed successful expression of rFIP–glu, Liu et al. (2023) established a cellular model of UVB irradiation–induced inflammation to determine the effects of Panax notoginseng flower (PNFS) on inflammatory factors and its relationship with the antibacterial peptide LL–37 expression. Enzyme–linked immunosorbent assay (ELISA) and protein blotting analysis were used to detect inflammatory factors and a novel peptide LL1 production. Finally, liquid chromatography–tandem mass spectrometry was used to quantify the main active ingredients in PNF. The results suggest that they have the potential to be used in cosmetics to reduce the occurrence of skin inflammation.

High–throughput mass spectrometry methods based on proteomics can accurately determine the composition and content of proteins in the skin, analyse the interaction relationships, and then evaluate the skin homeostasis in terms of immunity and barrier from a proteomics perspective.

Conclusion

Skin stabilisation is a more complex concept, and existing cosmetic efficacy claims related to it mainly include moisturisation, repair, soothing, oil control and sun protection, etc., and its efficacy evaluation methods are mainly classified
into *in vivo* and *in vitro* methods. The *in vivo* method consists of the subjective evaluation method and the objective instrumental analysis method, and the subjective evaluation method is more subjective, so the two methods are usually used in combination for evaluation. All of these methods evaluate the skin from one aspect, but as the skin is a complex system of "nervous system—immune—endocrine", it is difficult for a single method to evaluate the skin’s homeostasis in a comprehensive way.

With the development of systems biology, a variety of omics technologies are emerging, and their application in the field of skin science is gradually playing a more and more important role. In the process of skin metabolism, lipids account for the largest proportion and skin microbiome interactions are closely related to skin cells. Therefore, skin lipidomics and skin microbiome technologies have been paid more and more attention in the study of skin and cosmetics. The former studies the types, content and structure of all lipids that make up the skin and their role in the maintenance of skin homeostasis, while the latter studies the types, abundance and metabolism of microorganisms that live symbiotic with the skin and how they affect the overall state of the skin. The omics technology based on systems biology is more consistent with the definition and connotation of skin homeostasis. With the deepening of the research, more accurate targets will be gradually discovered, and the evaluation of skin homeostasis will become more and more accurate.

**Author’s contribution**

QS consulted relevant literature, edited manuscripts and revised manuscripts. YJ gave advice for the article and revised the manuscript, LZ and BY have made great contributions to the concept of skin homeostasis and design of the article. QJ and ZW participated in the discussion and research of homeostatic pathway, and made substantial contributions to the content of the article.

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Application of Omics Techniques in Skin Homeostasis Evaluation

국문초록

오믹스 기술을 이용한 피부 항상성 평가

소천천1, 직뢰뢰2, 요빙1, 초천1, 왕자적1, 가염1

1북경공상대학 화학 및 재료공정학원 중국공업화장품중점실험실, 북경, 중국
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최근 몇 년 동안 화장품 업계에서는 피부 항상성에 대한 관심이 더욱 높아지고 있다. 많은 요인들이 피부 항상성을 손상시키고 피부 건강과 미용에 영향을 미친다. 따라서 피부 항상성을 유지하는 것이 미용 효능의 기반이다. 하지만 이에 상응하는 평가 방법이 현재로서는 부족한 실정이다. 현재, 보습, 회복 등 피부 항상성과 관련된 일부 효능은 피부의 특성 측면에서만 평가되며, 항상성의 전반적인 개념과 완전히 일치하지 않는다. 피부에 영향을 미치는 리피도믹스, 마이크로바이옴, 프로테오믹스를 체계적으로 분석하는 체계적 개념을 바탕으로 오믹스 기술, 특히 피부 리피도믹스, 피부 마이크로바이옴, 프로테오믹스 기술이 개발되고 있습니다. 다양한 오믹스 연구 기법을 바탕으로 정상상태의 상관관계 표적 분석과 결합하면 보다 포괄적이고 섬세한 분석이 가능하며, 이를 피부 항상성 유지에 대한 잠재적인 평가 방법으로 떠오르고 있다. 본 총설에서는 피부 항상성 유지를 위한 화장품 개발에 이론적 기초를 제공하는 항상성 유지 평가 방법의 향후 발전 방향을 예측하고자 한다.

핵심어: 피부 항상성, 효능평가, 지질체학, 미생물, 신기술
中文摘要

组学技术在皮肤内稳态研究与评价中的应用

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近些年来，皮肤稳态受到化妆品行业的重视。许多因素会破坏皮肤稳态而影响皮肤健康和美丽，因此，维持皮肤稳态是化妆品功效的基础，但缺乏相应的评价方法。目前有一些功效宣称与皮肤稳态相关，比如保湿、修护等仅是从皮肤某一方面来评价，这与稳态的整体概念并不完全一致。随着组学技术的发展，尤其是皮肤脂质组学、皮肤微生物组学以及蛋白质组学技术，它们是建立在系统观念上，对影响皮肤的脂质组、微生物组及蛋白质组进行系统分析。基于多种组学研究技术，结合稳态相关靶点分析，可以更全面、更深入地进行分析，是具有潜力的皮肤稳态新兴评价方法。本文对维稳评价方法未来的发展方向进行了展望，为开发维持皮肤稳态的化妆品提供了理论依据。

关键词: 皮肤稳态，功效评价，脂质组学，微生物，新兴技术