Bitter is better: new way to sooth sensitive skin

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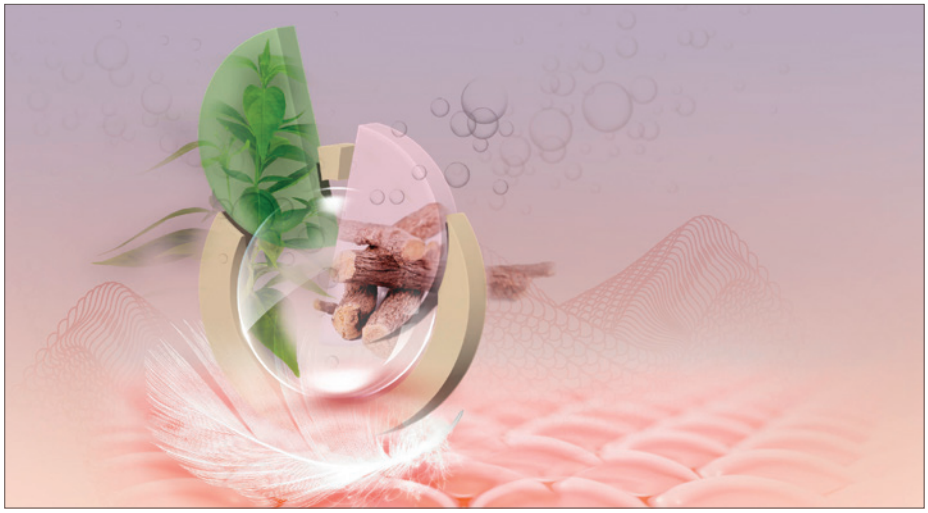

ABSTRACT

Good medicine tastes bitter, said Confucius.[1] Indeed, many active pharmaceutical ingredients taste bitter, manifesting the cross-cultural believe that the bitterness of medicine is correlated with beneficial pharmacological activity. Bitter taste receptors have recently been discovered in skin. Their activation triggers the synthesis of skin barrier lipids,[2-6] making them novel targets for the treatment of sensitive skin. Amaretine® (hereafter called the bittersweet complex) builds on this new knowledge by combining bitter with sweet components: bitter andrographolide from *Andrographis paniculata* leaves and sweet glycyrrhetinic acid from *Glycyrrhiza glabra* roots activate the skin's bitter receptors and reduce inflammatory responses.[7,8] Both active components are enclosed in a liposomal carrier system for optimal dermal delivery, to synergistically comfort sensitive skin. The bittersweet complex performs excellently in consumer surveys, where people with sensitive skin report a reduction in redness, itching, stinging, or burning sensations after treatment. This action was further confirmed in clinical studies, as well as in placebo controlled *in vivo* and *in vitro* studies. Finally, we could show that improving symptoms of sensitive skin measurably improves the quality of life of affected people.

Skin sensitivity and its symptoms like redness, itching, stinging, or burning sensations, are now a top concern among consumers globally. Around 60% of the population report having some degree of skin sensitivity,[9] with many experiencing a negative impact on their quality of life.[10]

Increasing awareness of skin sensitivity is changing the beauty industry. According to a Mintel database search, the number of beauty and personal care products with sensitive skin claims has increased by 37% since 2018. Sensitive skin claims are used across several categories and product formats; the top category with the greatest number of sensitive skin product launches (January to December 2022) is 'skin care' (56%), with their subcategories 'face/neck care' (41%), 'body care' (16%), 'face cleansers' (15%) and 'sun care' (9%).

Characteristics of sensitive skin

Sensitive skin is typically described as skin with regular occurrences of unpleasant sensations, such as heat, stinging, burning, itching, or tingling, but also as skin with visible changes, like redness, dryness, scaling, bumps, or hives, all caused by forms of stimulation that wouldn't normally create this type of reaction.[9]

Sensitive skin does not appear the same way for everyone. Its severity can range from moderate discomfort to severe reactions. Its frequency can fluctuate from occasional flare-ups to more persistent, daily sensitivity. Its underlying cause can range from genetic predisposition to physical, environmental, or chemical stimuli, or even overuse of cosmetics. Despite this great variety, all types of sensitive skin share these three key characteristics.

- **A compromised epidermal barrier.** A key characteristic of sensitive skin is a compromised lipid barrier, causing disturbed skin functions, such as increased trans-epidermal water loss, dryness, or scaling. Further, a weakened stratum corneum barrier is more permeable to environmental irritants.
- **Redness and inflammation.** Redness, flushing, irritation are common symptoms of sensitive skin arising from inflammatory processes, all characterized by the production and release of inflammatory cytokines, chemokines, and interleukins.
- **Sensory discomfort.** Subjective, uncomfortable, sensory effects typically occur with sensitive skin. Itching, burning, stinging, or tightness are consistently present. Nerves are more responsive and have lower thresholds to environmental, physical, and chemical factors, provoking unpleasant skin sensations.

Bitter taste receptors in skin – novel cosmetic targets

The database of bitter substances lists more than 1,000 compounds,[11] mostly originating from plants. Plants produce bitter-tasting substances as protection to deter herbivorous animals. Indeed, some bitter substances are poisonous, and their ingestion must be avoided, whereas others have health benefits. For example, andrographolide, derived from the bitter-tasting herb *Andrographis paniculata*, is used in Ayurvedic medicine as bitter tonic.

The recognition of bitter substances in the oral cavity is mediated by bitter taste receptors belonging to the taste 2 family (TAS2R) of G-protein coupled receptors. We humans have 25 different bitter taste receptors, each specific for a different set of bitter substances. The activation of bitter taste receptors on taste receptor cells triggers an intracellular signal cascade that finally produces the sensation of bitterness.[12]

Apart from sensing taste, bitter taste receptors have more physiological roles: Bitter taste receptors also exist in extra-oral tissues, for example in our digestive tract, where epithelial cells recognize bitter nutrients, or

in our lungs, where bitter substances induce bronchial relaxation. Yet bitter taste receptors also exist in heart, or in adipose tissue where they modulate adipogenesis, or activate the immune system.[12]

Interesting from a cosmetic perspective is the fact that bitter taste receptors also exist in skin. Recent research identified bitter taste receptors in keratinocytes. Here, they trigger the synthesis of skin barrier lipids and proteins or induce anti-inflammatory processes.[13] This makes bitter taste receptors novel cosmetic targets to treat sensitive skin.

Andrographis paniculata - an activator of bitter taste receptors in skin

Andrographolide is an extremely bitter-tasting substance isolated from the stems and leaves of *Andrographis paniculata* – also known as 'King of Bitters'. It is a diterpene that selectively binds and activates human bitter taste receptors of the TAS2R family in skin keratinocytes.[13] Receptor activation induces a signal cascade that leads to enhanced production of skin barrier lipids and reduces inflammatory markers, linking bitter andrographolide to skin physiology and making it a potential active substance to target sensitive skin (Figure 1).

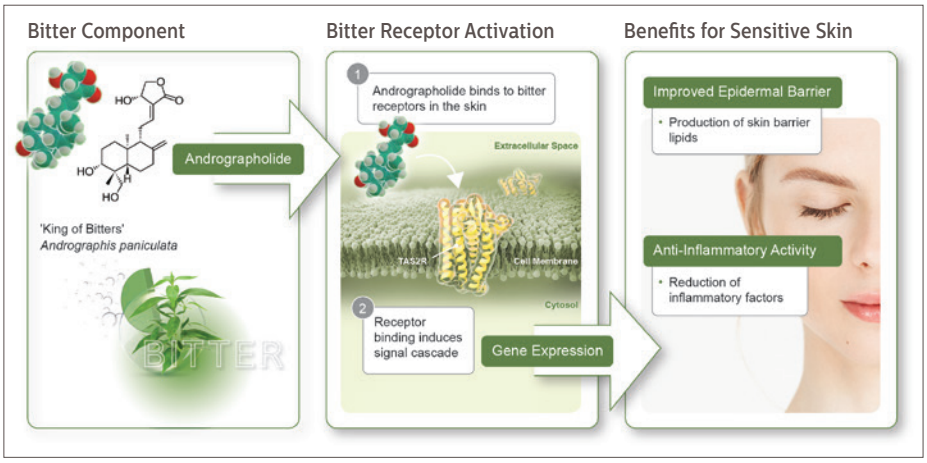

Figure 1: Bitter compound andrographolide is a natural activator of bitter taste receptors. Bitter receptors are integral membrane proteins that are used by cells to convert extracellular chemical signals into intracellular responses. The signaling cascade starts by docking a bitter molecule to the receptor. The activated receptor activates a G-protein, which finally triggers the influx of Ca++ ions. In keratinocytes, the influx of Ca++ induces the production of skin barrier lipids

Sweet tasting licorice root – a source of natural anti-inflammatory compounds

To date, the most effective and widely prescribed compounds to combat inflammation are glucocorticoid derivatives, for example cortisol. They exhibit anti-inflammatory effects by suppressing the expression of pro-inflammatory genes and by inhibiting the production of inflammatory cytokines. Therefore, topical corticosteroid creams and ointments are the main form of therapy to control acute flares of atopic dermatitis.

The growing trend of natural cosmetics demands for plant-derived solutions as attractive alternatives for the treatment of sensitive skin or atopic dermatitis. One good example is licorice, the root of *Glycyrrhiza glabra*, which contains the active compound glycyrrhizin – one of the sweetest substances found in nature. It has 30–50 times the sweetness of sucrose.

Glycyrrhizin is a triterpene glycoside and its hydrolysate, glycyrrhetinic acid (GA), has a structure close to mineral-corticoids and glucocorticoids. For its anti-inflammatory action, GA and licorice root extract have been successfully tested in the treatment of atopic dermatitis and pruritus.[7-8] The rise of natural cosmetics makes plant-derived glycyrrhetinic acid from *Glycyrrhiza glabra*, as well as andrographolide from *Andrographis paniculata*, very attractive alternatives for the treatment of sensitive skin.

The novel approach: first system of bitter and sweet for sensitive skin

The bittersweet complex, for the first time, combines bitter and sweet actives for the treatment of sensitive skin: Firstly, andrographolide, as activator of bitter taste receptors, triggers the production of skin barrier lipids. Secondly, glycyrrhetinic acid from sweet tasting licorice root, suppresses inflammation and stress reactions. This complementary action makes the bittersweet complex unique.

The bittersweet complex restores bitter taste receptor levels in atopic skin

The study's objective was to show that skin keratinocytes contain bitter taste receptors and to demonstrate that bittersweet complex restores a deregulated expression of bitter taste receptors in atopic skin. In the experiment, a 3D model of reconstituted human epidermis with atopic skin alterations was treated with bittersweet complex and compared to normal skin.[14] The expression of bitter taste receptors was monitored by immunofluorescence microscopy using specific antibodies.

The study revealed that bitter taste receptor TAS2R50 is expressed in human epidermis confirming earlier results.[3] Furthermore, the expression level of TAS2R50 (intensity of fluorescence signal) is significantly reduced in the atopic skin model but could be restored by the bittersweet complex (Figure 2).

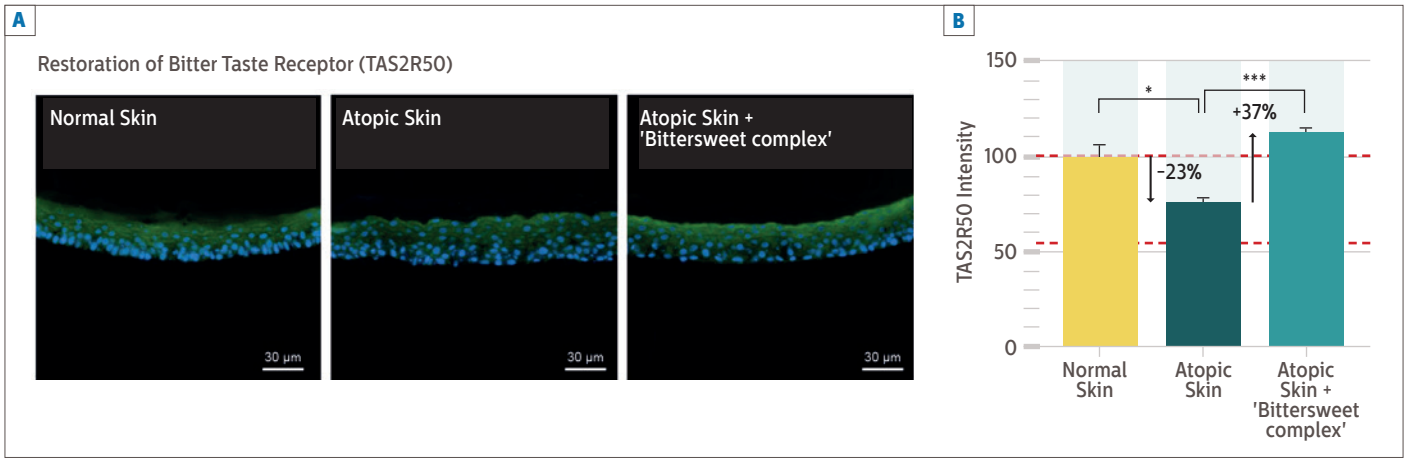

Figure 2: The expression of bitter receptors in a human skin model is restored by bittersweet complex. (A) Immunofluorescence images of reconstituted human epidermis 'Normal Skin Model', 'Atopic Skin Model' or upon addition of the bittersweet complex. The green staining refers to labelling of TAS2R50 with specific antibodies. The signal is proportional to the amount of expressed bitter taste receptors. The blue signal highlights the cell nuclei. (B) TAS2R50 fluorescence intensity expressed in percent relative to normal skin. N = 3; Mean + SEM. Student's t-test. * = $p < 0.05$, *** = $p < 0.001$

Bittersweet complex reverses an imbalanced gene expression in atopic skin

The study's objective was to show that bittersweet complex can reverse imbalanced gene expression in atopic skin, when focusing on genes associated with barrier function, inflammation, lipid metabolism, and hypersensitivity.

In the experiment, a 3D skin model of atopic skin was subjected to bittersweet complex, and a transcriptomic analysis was performed on 93 epidermal gene targets, all related to atopic dermatitis and sensitive skin.[14] Changes in gene expression were monitored by real-time quantitative polymerase chain reaction (RT-qPCR) using TaqMan Low Density Arrays and compared to a model of normal skin.

Of the 93 genes screened, 27 are presented here. These genes showed significant differences in gene expression in the atopic skin model (beige dots), of up to 2,000-fold compared to the normal skin model (grey dots). The addition of 0.01% bittersweet complex to the culture medium inversely modulated their expression (green dots), shifting it back to levels of healthy skin. Thus, the bittersweet complex is active and functional *in vitro*.

On a gene expression level, it reverses alterations seen in atopic skin, with a broad impact on genes that restore epidermal integrity, reduce inflammation, and alleviate sensory discomfort. The bittersweet complex therefore addresses the major symptoms of sensitive skin, including barrier function, inflammatory response, skin lipid metabolism, and hypersensitivity (Figure 3).

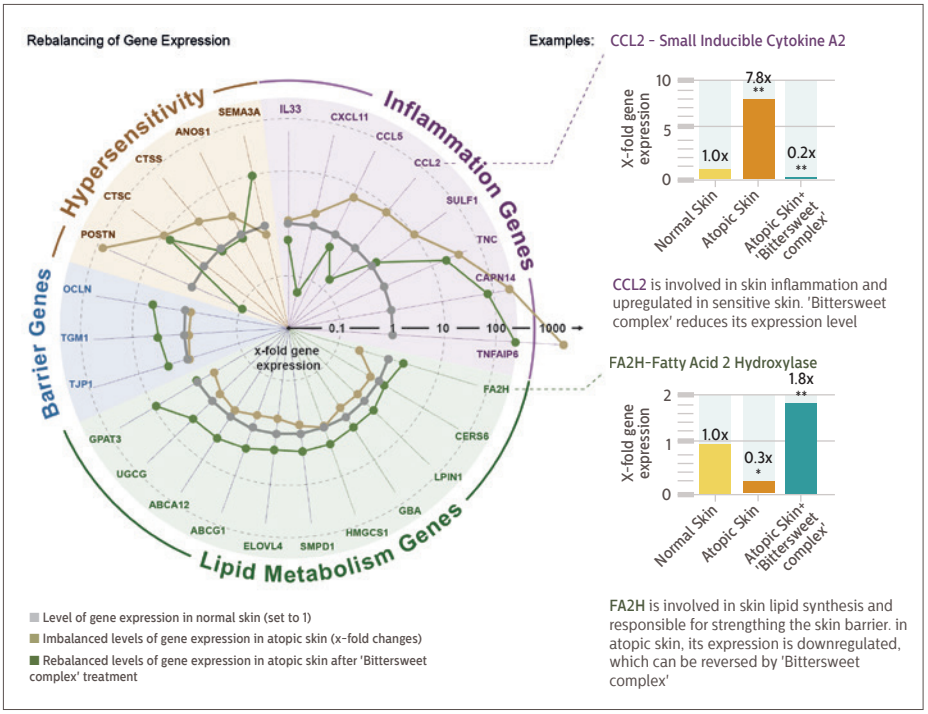

Figure 3: The bittersweet complex rebalances sensitive skin-related gene expression. The radar plot shows gene expressions in normal skin (gray dots) as baseline level: fold-change = 1. Gene expression after induction of atopic dermatitis (beige dots), and gene expression in atopic skin + bittersweet complex (green dots). Genes are grouped according to function in skin (for in depth information of individual genes see [www.genenames.org]. N = 3; Mean. Student's t-test, atopic skin vs. normal skin; atopic skin + bittersweet complex vs. atopic skin; * = $p < 0.05$; ** = $p < 0.01$)

Bittersweet complex regenerates the skin barrier and protects from irritation

This study measured the capacity of the bittersweet complex to regenerate a compromised epidermal barrier and its capacity to protect skin from irritation. In a placebo-controlled, double blinded study, a reduced epidermal barrier and skin irritation were induced by treating the inner arms of healthy volunteers with an aggressive detergent (SDS = sodium dodecyl sulphate). Regeneration of barrier function was monitored by following trans-epidermal water loss (TEWL). Protection from irritation was monitored by measuring skin redness with a colorimeter.

The study concluded that the addition of bittersweet complex to a simple base formulation is effective, acting quickly on major symptoms of sensitive skin. The bittersweet complex regenerates barrier function and protects skin from irritation (Figure 4).

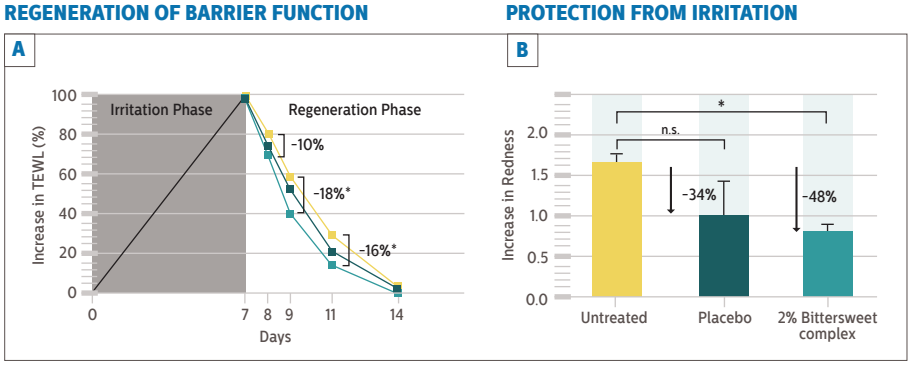

Figure 4: The bittersweet complex regenerates the skin barrier and protects from irritation. (A) 20 volunteers washed their inner arms with SDS for 7 days, thereby disrupting the skin barrier (increased TEWL in irritation phase). To evaluate the regenerative properties of bittersweet complex upon irritation, the skin was treated with a test cream containing 2% bittersweet complex or a placebo, and regeneration of TEWL was monitored for another 7 days. With the bittersweet complex, regeneration was faster and stronger. (B) To evaluate the preventive and protective properties of bittersweet complex against irritation, the volunteers applied the test creams one hour before SDS washing. After 7 days, the skin became irritated (increased redness), which was prevented to a great extent by the bittersweet complex. N = 20; Mean + SEM. Student's t-test versus untreated; * = $p < 0.05$

The bittersweet complex eases symptoms of sensitive skin & improves the quality of life

In a clinical study, a base cream formulation with bittersweet complex was tested for its ability to ease sensitive skin symptoms like dryness, redness, and itching. The study also investigated whether improvements in sensitive skin symptoms do have an impact on the quality of life of affected people.

The study included only volunteers with sensitive skin. Each volunteer identified its own individual problem zone (size and location of sensitive skin) and applied a cream with 2% bittersweet complex to the selected area, twice daily over the next 14 days.

Improvements in sensitive skin symptoms were objectively measured using grading scales. Subjective evaluations of product efficiency and changes in quality of life were rated by answering a questionnaire. The clinical study revealed that treatment with a bittersweet complex cream on self-selected areas improved symptoms of sensitive skin – this effect is confirmed by a clinical assessment and self-observation (questionnaire) (Figure 5).

Furthermore, improvements in sensitive skin parameters correlate well with quality-of-life sensations, emphasizing that sensitive skin problems are not confined to physical symptoms of skin health or skin esthetics alone, but also impact the mental status and overall wellbeing of an individual. The effectiveness of the bittersweet complex is based on cumulative data from face, body, hands, and arms – this highlights the broad range of possible skin care applications for the bittersweet complex (Figure 6).

Conclusion

With the bittersweet complex, Lipoid Kosmetik presents the first active ingredient combining bitter and sweet active components that synergistically address the symptoms of sensitive skin. The bittersweet complex is a 100% natural, COSMOS-approved, all-encompassing approach for the treatment of sensitive skin. **PC**

References

1. Wong KC, Hangchow L. Chinese medical sayings and proverbs. *Chinese Medical Journal.* 1926;150-153
2. Wölfle U, Schempp CM. Bitterstoffe – von der traditionellen Verwendung bis zum Einsatz an der Haut. Zeitschrift für Phytotherapie 2018;39(05):210-215
3. Reszka E, Nowakowska-Świrta E, Kupczyk M, Dudek W, Świerczyńska-Machura D, Wittczak T *et al.* Expression of bitter taste receptors in the human skin *in vitro*. *J. Clinic. Res. Bioeth.* 2015;6:2
4. Meyerhof W, Batram C, Kuhn C, Brockhoff A, Chudoba E, Bufe B, Appendino G, Behrens M. The molecular receptive ranges of human TAS2R bitter taste receptors. *Chem. Senses.* 2010;35:157–170
5. Wölfle U, Elsholz FA, Kersten A, Haarhaus B, Müller WE, Schempp CM. Expression and functional activity of the bitter taste receptors TAS2R1 and TAS2R38 in human keratinocytes. *Skin Pharmacol. Physiol.* 2015;28:137–146
6. Wölfle U, Haarhaus B, Seiwerth J, Cawelius A, Schwabe K, Quirin KW, Schempp CM. The herbal bitter drug gentiana lutea modulates lipid synthesis in human keratinocytes *in vitro* and *in vivo*. *Int. J. Mol.* Sci. 2017;18:1814
7. Kowalska A, Kalinowska-Liset U. 18b-glycyrrhetinic acid its core biological properties and dermatological applications. *International Journal of Cosmetic Science.* 2019;41:325–331
8. Saeedi M, Morteza-Semnani K, Ghoreishi MR. The treatment of atopic dermatitis with licorice gel. *Journal of Dermatological Treatment.* 2003;14:1–3
9. Farage MA. The prevalence of sensitive skin. *Frontiers in Medicine.* 2019; 6:98.
10. Georgieva F, Velevska J, Kalinova T, Brostilova V. The impact of sensitive skin on the quality of life. *Scripta Scientifica Medica.* 2019;51(2):30-34.
11. The Hebrew University of Jerusalem, Institute of Biochemistry, Food Science and Nutrition, Faculty of Agriculture. Bitter DB. Available from: http://bitterdb.agri.huji.ac.il/bitterdb/
12. Tuzim K, Korolczuk A. An update on extra-oral bitter taste receptors. *J. Transl. Med.* 2021;19:440
13. Behrens M, Brockhoff A, Batram C, Kuhn C, Appendino G, Meyerhof W. The human bitter taste receptor hTAS2R50 is activated by the two natural bitter terpenoids andrographolide and amarogentin. *J. Agric. Food Chem.* 2009;57:9860–9866
14. Hubaux R, Bastin C, Salmon M. On the relevance of an in vitro reconstructed human epidermis model for drug screening in atopic dermatitis. *Experimental Dermatology.* 2018;27:1403–1407

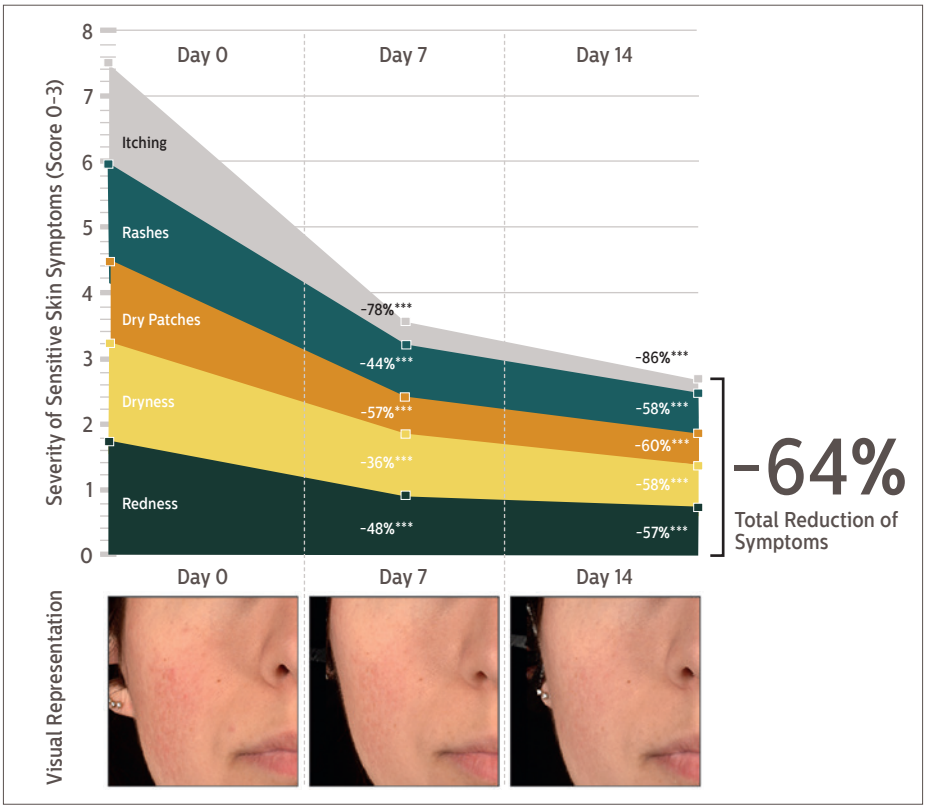

Figure 5: The bittersweet complex reduces symptoms of sensitive skin. 24 volunteers with sensitive skin applied a test cream containing 2% bittersweet complex for 14 days. Changes in sensitive skin parameters, including itching, rashes, dry patches, dryness, and redness, were evaluated by a clinical expert before treatment (D0), after one week (D7), and after two weeks (D14) of treatment. The evaluation used pre-established scales ranging from 0 (no symptoms), 1 (low symptoms), 2 (moderate symptoms), to 3 (severe symptoms). The graph shows an additive representation of sensitive skin parameters over time of treatment. Overall, sensitive skin symptoms decreased by 64% after 14 days. N = 24. Mean. Student's t-test versus baseline (D0). *** = $p < 0.001$

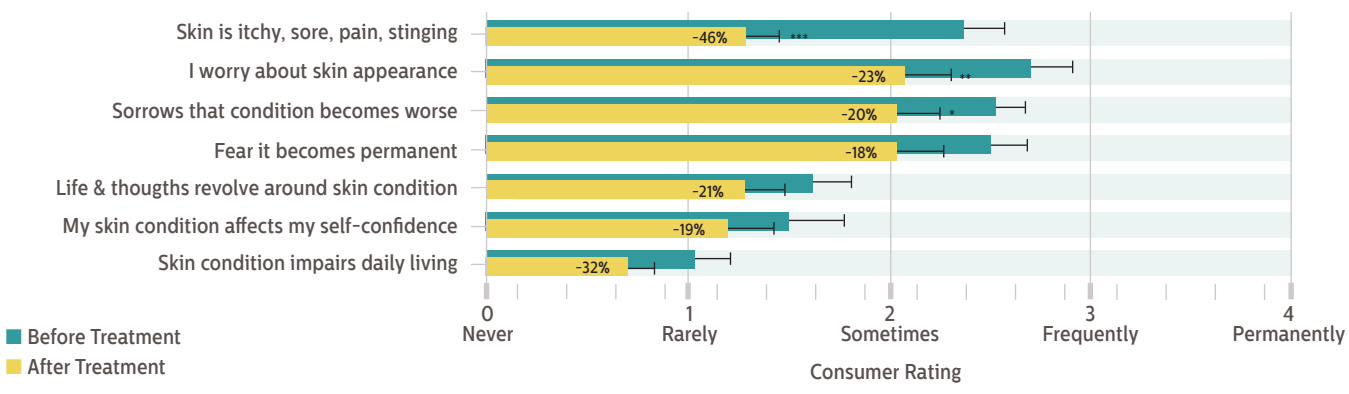

Figure 6: A test cream with bittersweet complex improves the quality of life of consumers with sensitive skin. In a consumer study, 24 volunteers with sensitive skin applied a test cream containing 2% bittersweet complex for 14 days. Volunteers rated multiple quality-of-life statements before (D0) and after two weeks of treatment (D14), on a scale from 0 to 4 (0 = 'never', 1 = 'rarely', 2 = 'sometimes', 3 = 'frequently', 4 = 'permanently'). Average score + SEM. Changes in scores (before vs. after treatment) are represented in percent changes. N = 24. Student's t-test versus before treatment. * = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$