IFSCC 2025 full paper (IFSCC2025-367)

"A Chinese traditional medicine inspired and computational desinged novel Octappeptide for Enhancing Skin Radiance and well-agingby targeting Renin-Angiotensin System and regulating interacullular comminication"

Junxiang Li [1,2,*], Wenyu Ding [1], Siyu Zhu[1], Cheng Zheng [1], Jingyong Zhu [1], Yao Li [1], Sining Kang[1] and Xuhui Li [2]

[1]Harvest Biotech (Zhejiang) Co., Ltd., Zhejiang, China
[2]AGECODE R&D Center, Yangtze Delta Region Institute of Tsinghua University, Zhejiang, China
*lijunxiang@acrdc.cn

Abstract

In traditional Chinese medicine (TCM), the interplay between 'Qi' (vital energy) and 'Color' (external manifestation) is integral to health and skin vitality. The Renin-Angiotensin System (RAS), a pivotal regulator of cellular communication, parallels TCM principles by influencing skin health and aging. A novel Octappeptide (named acGA8-2), targets the AT1R receptor within the RAS, inspired by the Chinese medicine *Salvia miltiorrhiza*, which regulates qi and blood, and optimized by computer structural rationalization, to address skin dullness and aging. Laboratory and clinical trials demonstrated its efficacy in enhancing skin vitality, reducing inflammation, inhibiting melanogenesis, and promoting collagen synthesis. This innovative approach represents a significant advancement in precision skincare, particularly for Eastern skin types.

1. Introduction

Traditional Chinese Medicine (TCM) has long recognized the intricate relationship between "Qi" (vital energy) and "Color" (external manifestation), emphasizing that the vitality of the skin is a reflection of the body's overall health[1]. TCM practitioners have historically used various herbs and treatments to regulate "Qi" and improve skin conditions. For instance, *Salvia miltiorrhiza* has been used to regulate blood circulation and enhance skin vitality[2]. Modern science has also identified parallels between TCM principles and the physiological mechanisms governing skin health, particularly the role of the Renin-Angiotensin System (RAS) in cellular communication and skin aging.

The RAS is involved in various physiological processes, including blood pressure regulation, inflammation, and oxidative stress[3]. Angiotensin II (Ang II), a key component of the RAS, binds to the Angiotensin II Type 1 Receptor (AT1R), triggering a cascade of reactions that can lead to skin aging, pigmentation, and inflammation. Targeting the RAS, particularly the

AT1R receptor, has emerged as a promising strategy for developing anti-aging and skin-enhancing treatments.

Advancements in computational biology and AI have revolutionized the development of bioactive peptides. By leveraging AI algorithms, researchers can mine vast databases of natural compounds and optimize their structures to achieve desired biological activities. This approach allows for the rapid identification and optimization of peptides with high affinity for specific targets, such as the AT1R receptor. The integration of TCM principles with computational biology has led to the development of innovative skincare solutions tailored to the unique needs of Eastern skin types.

2. Materials and Methods

2.1 design of acGA-8-2 and Molecular Docking

Based on the database of Chinese traditional plant actives that are beneficial for skin tone adjustment, AI algorithm was applied to mine 66 peptides with sequence similarity to Ang II, and based on structure simulation optimization, acGA-8-2 was obtained (Figure 1 (a)).

Molecular docking studies were conducted to evaluate the peptide's affinity for the AT1R, revealing a higher binding affinity compared to the natural ligand Angiotensin II.

2.2 Modified Chick Embryo Chorioallantoic Membrane (CAM) Test

To assess the ability of acGA-8-2 to promote metabolic circulation, the chick embryo chorioallantoic membrane (CAM) test method was employed. Chick embryos were induced with 10 μM ANG II, and then treated with 10 ppm acGA-8-2. The changes in the diameter of the blood vessels in the chick embryos were observed.

2.3 Whitening Efficacy Test

To investigate the whitening efficacy of acGA-8-2, B16 cells were induced with 10 μM ANG II and treated with 2/5/10 ppm acGA-8-2. The melanin content and tyrosinase activity were measured.

2.4 Soothing Efficacy Test

To investigate the soothing efficacy of acGA-8-2, HFF-1 cells were induced with 10 μM ANG II and treated with 2/5/10 ppm acGA-8-2. The levels of TNF-α, IL-6, and NF-κB were measured.

2.5 Anti-wrinkle Efficacy Test

To investigate the anti-wrinkle efficacy of acGA-8-2, HFF-1 cells were induced with 10 μM ANG II and treated with 2/5/10 ppm acGA-8-2. The levels of NAD+, AMPK, and COL I were measured.

2.6 Clinical Efficacy Test

Thirty volunteers with dull skin, pigmentation, poor skin firmness, and sensitive skin were recruited, with an average age of 43.4±8.2 years. A split-face randomized control group was set up, and participants were required to use the respective products twice daily, consisting of a placebo group and test group. The test group used a lotion containing 15 ppm acGA-8-2. Measurements of crow's feet, nasolabial folds, under-eye fine lines, skin elasticity, skin firmness, skin anisotropy, skin radiance, roughness, pigmented area, erythema area, L* value, ITA° value, and MI value were taken on day 3, day 14, and day 28.

3. Results

3.1 The innovative peptide acGA-8-2 has a higher affinity for AT1R than ANG Ⅱ.

Molecular docking simulations were performed to assess the interaction between acGA8-2 and the AT1R receptor. The results indicated that acGA8-2 exhibited a binding affinity of -11.62 kCal/mol (Figure 1 (b)), significantly higher than that of Angiotensin II (-9.48 kCal/mol). This superior binding affinity suggests that acGA8-2 can effectively modulate the RAS, potentially leading to improved skin health and reduced aging effects.

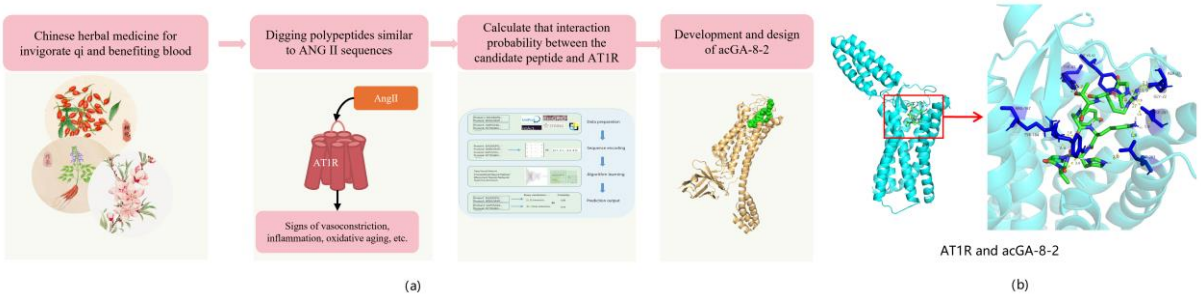

Figure 1. (a) Design of acGA-8-2. Development flowchart for acGA-8-2 . The development of acGA-8-2 is inspired by traditional Chinese medicine plants for improving qi and blood, and the innovative peptide molecule is obtained by AI computational biology method. (b) Molecular Docking. The binding energy of AT1R and acGA-8-2 is -11.62 kCal/mol.

3.2 acGA-8-2 inhibits ANG-induced vasoconstriction.

After the induction of vasoconstriction by ANG II, the addition of a sample containing 10 ppm acGA-8-2 can cause vasodilation, as shown in Figure 2, the enhancement rates of diameter of blood vessels was 18.18%.

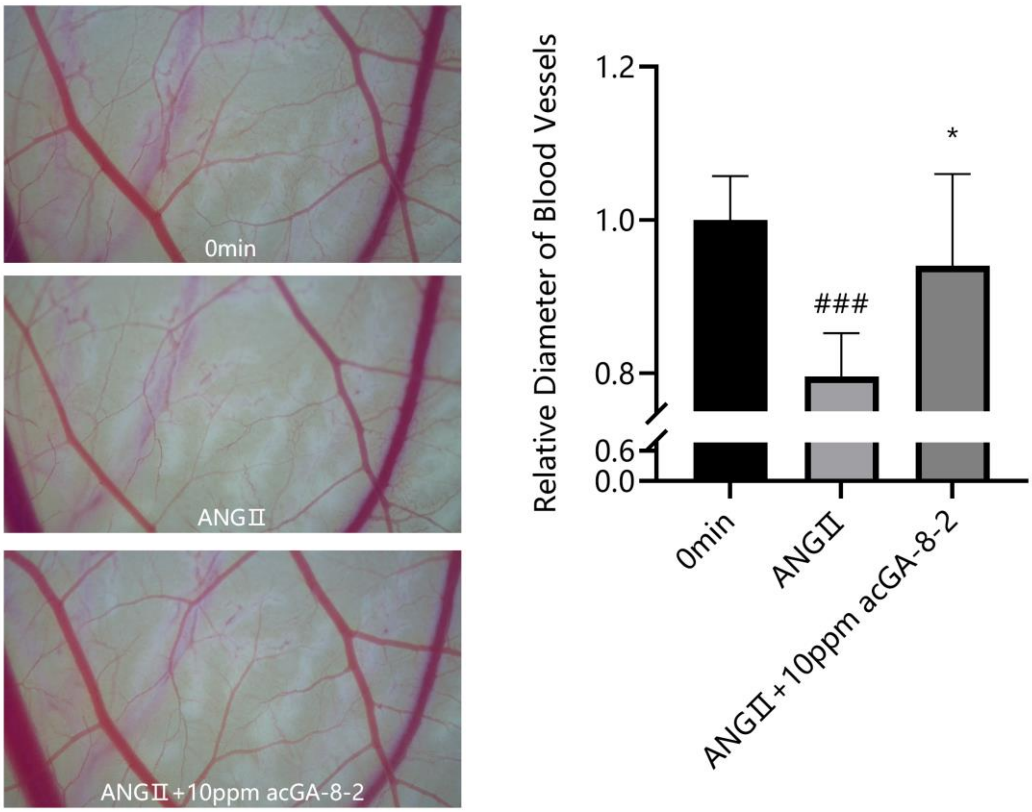

Figure 2. Utilizing the chick embryo chorioallantoic membrane assay to demonstrate the vasodilatory effect of acGA-8-2 on blood vessels. Compared with the blank control group, ###p<0.001. Compared with the ANG Ⅱ group, *p<0.05.

3.3 acGA-8-2 possesses whitening, soothing, and anti-wrinkle effects.

In the experiment, different types of skin cells were modeled using ANG II to induce cell damage. Afterward, 2/5/10 ppm acGA-8-2 was added to assess the whitening, soothing, anti-wrinkle, and cell energy promotion effects of acGA-8-2.

As shown in Figures 3(a) and 3(b), ANG II can induce a significant increase in melanin content and tyrosinase activity in B16 cells. When 2/5/10 ppm acGA-8-2 was added, the melanin content and tyrosinase activity were significantly reduced, demonstrating the whitening effect of acGA-8-2. The inhibition rates of melanin content by 2/5/10 ppm acGA-8-2 were 9.49%, 15.82%, and 16.46% respectively; the inhibition rates of tyrosinase activity were 12.59%, 24.71%, and 30.10% respectively.

As shown in Figures 3 (c) and 3 (d), ANG II can induce significant secretion of inflammatory factors by RAW264.7 cells. When 2/5/10 ppm acGA-8-2 was added, the levels of inflammatory factors were significantly reduced. The inhibition rates of TNF-α by 2/5/10 ppm acGA-8-2 were 20.34%, 36.44%, and 51.88% respectively; the inhibition rates of IL-6 were 15.98%, 41.86%, and 44.56% respectively. As shown in Figure 3(e), 5 ppm acGA-8-2 significantly inhibited NF-κB. Thus, proving that acGA-8-2 has soothing effects.

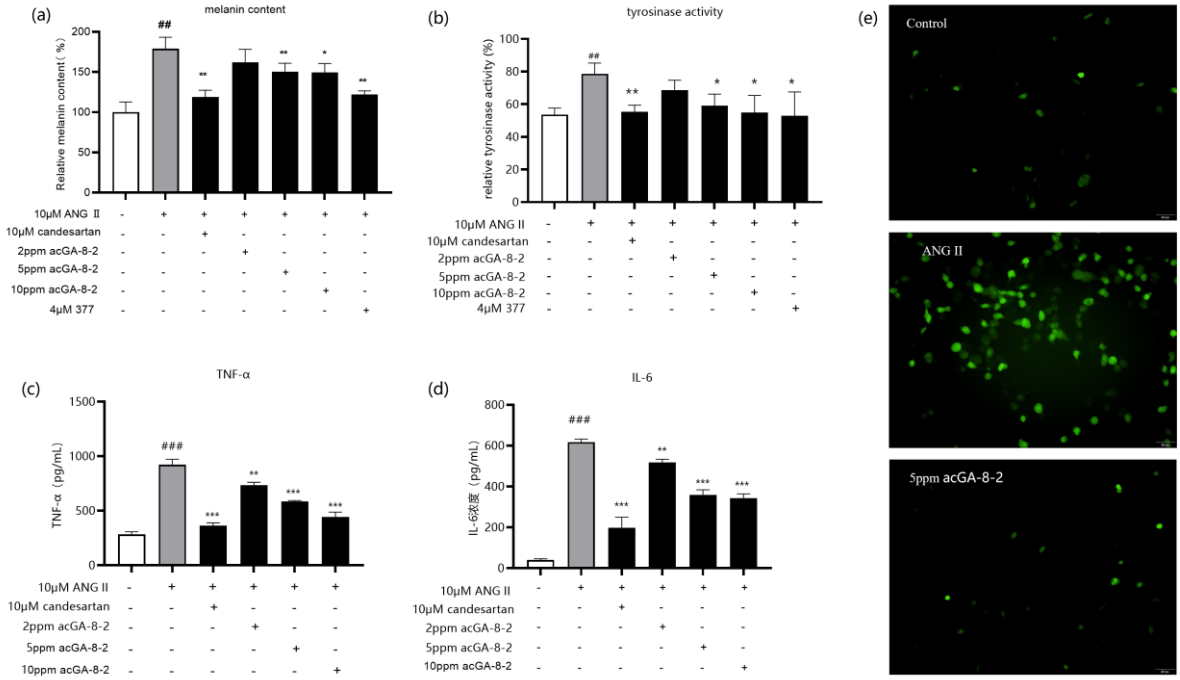

Figure 3. Effects of acGA-8-2. (a) Melanin content. (b) Tyrosinase activity. (c) TNF-α content. (d) IL-6 content. (e) NF-κB fluorescence intensity.Compared with the blank control group, ##p<0.01, ###p<0.001. Compared with the ANG II group, *p<0.05, **p<0.01, ***p<0.001.

As shown in Figure 4 (a), ANG II induced HFF-1 cells, leading to a decrease in fluorescence intensity and a significant reduction in type I collagen. When 5 ppm acGA-8-2 was added, the red fluorescence intensity increased, indicating an increase in the content of type I collagen. As depicted in Figures 4 (b) and 4 (c), ANG II can significantly inhibit the expression of NAD+ and AMPK in HFF-1 cells. Upon the addition of 2/5 ppm acGA-8-2, the expression of NAD+ and AMPK notably increased. The enhancement rates of NAD+ by 2/5 ppm acGA-8-2 were 45.71% and 65.64%, respectively; the enhancement rates of AMPK were 50.93% and 105.63%, respectively. This demonstrates that acGA-8-2 has anti-wrinkle and energy-promoting effects.

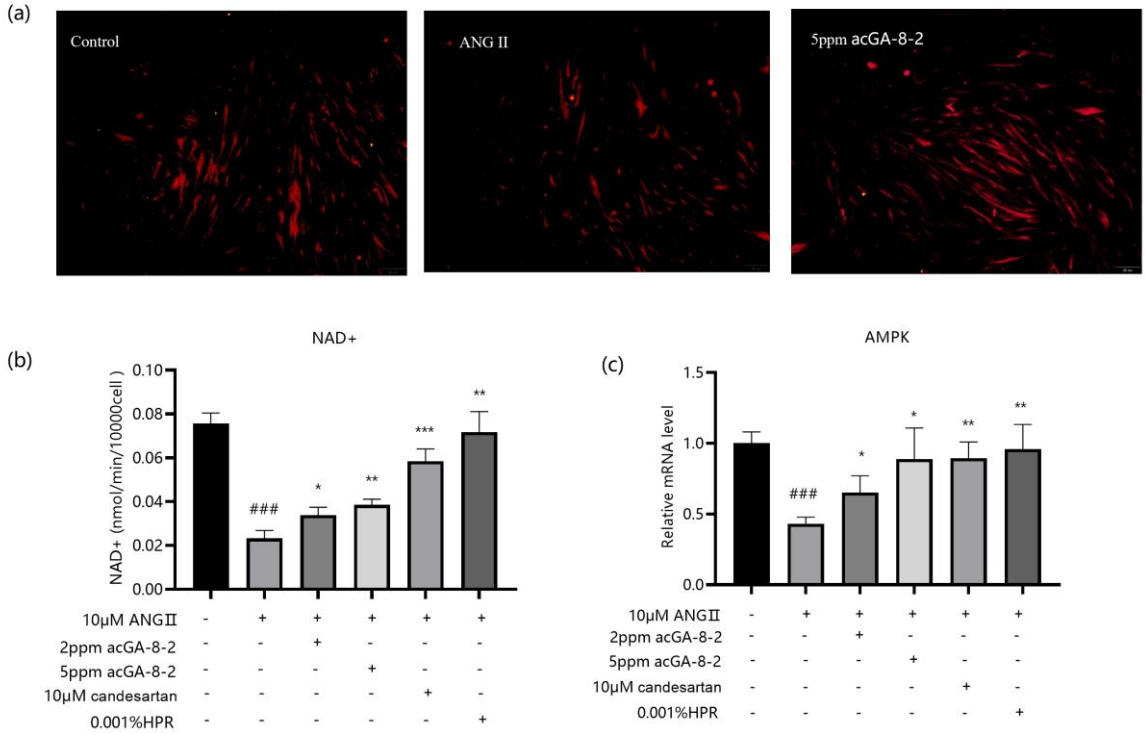

Figure 4. Effects of acGA-8-2. (a) COL1 fluorescence intensity. (b) NAD+ content. (c) AMPK content. Compared with the blank control group, ###p<0.001. Compared with the ANG II group, *p<0.05, **p<0.01, ***p<0.001.

3.4 15 ppm acGA-8-2 has demonstrated excellent whitening, soothing, and anti-wrinkle effects in clinical testing.

Thirty volunteers with dull skin, pigmentation, poor skin firmness, and sensitive skin were recruited, with an average age of 43.4±8.2 years. A split-face randomized control group was set up, and participants were required to use the respective products twice daily, consisting of a placebo group and test group. The test group used a lotion containing 15 ppm acGA-8-2. Measurements of crow's feet, nasolabial folds, under-eye fine lines, skin elasticity, skin firmness, skin anisotropy, skin radiance, roughness, pigmented area, erythema area, L* value, ITA° value, and MI value were taken on day 3, day 14, and day 28. As shown in Figures 5 (a) and 5 (b), they respectively illustrate the reduction effect on wrinkles after using an emulsion containing 15 ppm acGA-8-2 for 3 days, 14 days, and 28 days. Figure 5 (a) represents the fine lines under the eyes, with fewer red lines indicating fewer wrinkles; Figure 5 (b) represents the crow's feet at the corners of the eyes, with lighter colors indicating fewer wrinkles. This proves that acGA-8-2 has anti-wrinkle effects. The results of other indicators are shown in Table 1. Table 1 lists the change rates of each indicator over 28 days (test group), including the maximum individual change rate for each indicator. In addition, the data compared with the placebo group on the 28th day are also listed in the far right column. By comparing with the placebo group, it is demonstrated that acGA-8-2 has whitening, anti-wrinkle, and soothing effects.

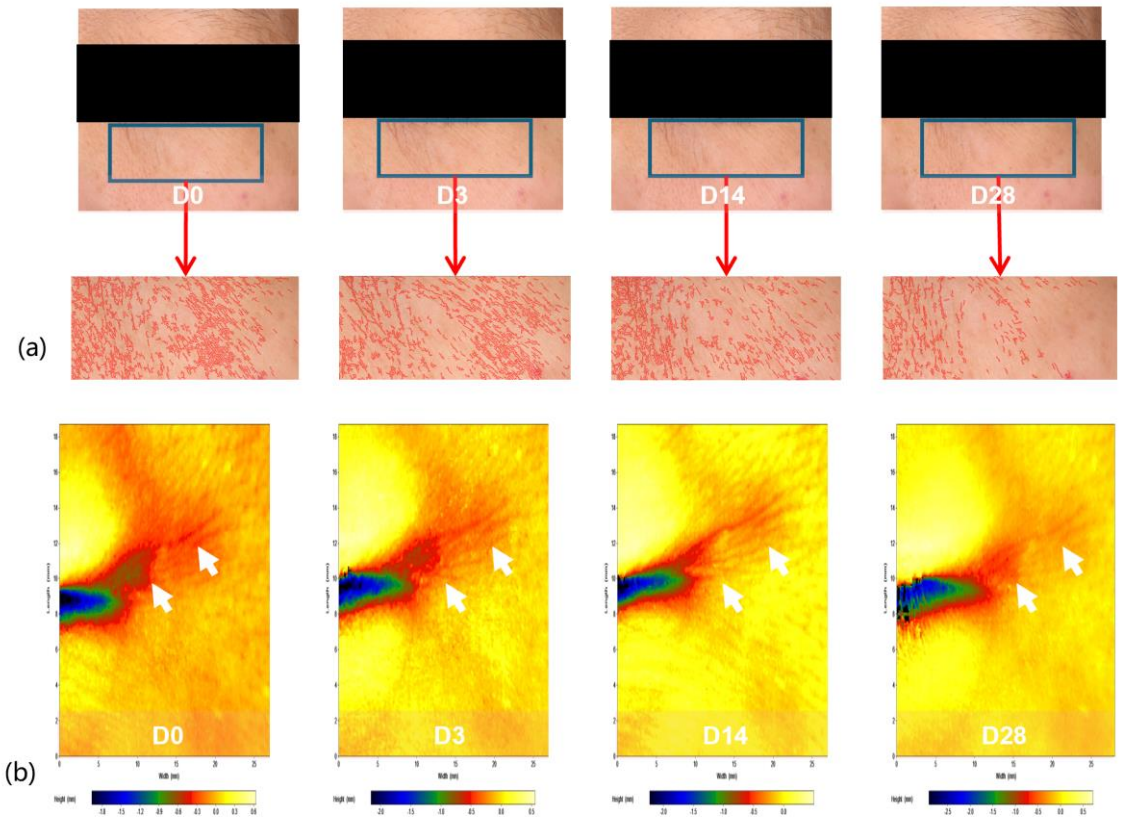

Figure 5. Demonstration of effective cases in clinical testing. (a) Changes in fine lines under the eyes. (b) Changes in crow's feet.

Table 1. Changes in various indicators of clinical efficacy testing

Indicator	With 15 ppm acGA-8-2 improvement rate（D28 vs D0）/ individual maximum improvement rate	With 15 ppm acGA-8-2 vs Placebo group
Crow's Feet number	-54.82% / -76.09%	-16.76%
Crow's feet depth	-18.44% / -89.71%	-17.09%
Crow's feet number	-59.24% / -87.88%	-22.25%
Crow's feet volume	-37.14% / -95.91%	-34.02%
R0	-21.30% / -57.59%	-16.49%
R5	+42.64% / +99.02%	+13.62%
R7	+41.71% / +95.18%	+10.18%
F4	-41.36% / -70.47%	-18.54%
Fine lines under the eyes	-27.51% / -71.74%	-23.74%
L	+2.38% / +9.28%	+0.61%
MI	-6.63% / -55.11%	-14.20%
ITA°	+13.57% / +67.49%	+9.04%
Pigmentation area	-15.79% / -38.16%	-18.87%
Red Zone	-42.36% / -91.93%	-26.43%
Glossiness	+26.60% / +72.49%	+25.24%

4. Discussion

4.1 Design and Efficacy of acGA-8-2

Inspired by traditional Chinese medicinal plants known for their ability to improve skin blood and energy (Qi) status, this study leverages modern AI technologies and integrates the latest findings from Cell on the Hallmarks of aging: An expanding universe[4] to develop acGA-8-2, targeting the AT1R (Angiotensin II Type 1 Receptor) for improving blood and energy (Qi) in the skin.

The in vitro and in vivo test results strongly support that acGA-8-2 can dilate blood vessels constricted by ANG II, thereby promoting metabolic circulation. Additionally, acGA-8-2 demonstrates anti-aging effects by reducing melanin content, inhibiting the expression of inflammatory factors, and enhancing cellular energy. These findings effectively highlight the promising application of AI in the development of active peptide ingredients for cosmetics. The whitening and anti-aging effects of acGA-8-2 offer the cosmetics industry a new target and concept, empowering product innovation in the new era of whitening.

4.1 acGA-8-2 Solves Problems in Various Life Scenarios

Research has found that various life scenarios can activate the renin-angiotensin system (RAS), leading to abnormal intercellular communication, which is one of the twelve hallmarks of aging. Matsuura-Hachiya Y et al. found that[5] UV irradiation increases the expression of ANG II and AT1R in the skin. Hedayatyanfard K et al. found that[6] skin inflammatory responses can activate the RAS system. In addition, Dunn JH et al. found that[7] stress factors can also activate the RAS system. Activation of the RAS system leads to the activation of the ANG II-AT1R signaling pathway, resulting in vasoconstriction, increased melanin production, and the release of inflammatory factors, all of which contribute to skin aging.

5. Conclusion

acGA-8-2 represents a breakthrough in precision skincare by harnessing the power of A.I. to create a peptide that not only enhances skin radiance but also combats the signs of aging. Its multifaceted approach to skin health through the modulation of intercellular communication offers a promising avenue for cosmetic development, catering to the unique needs of Eastern skin types.

6. Reference

[1]. Gu Zhonghua, Wu Fengzhi, Gan Xiulun. Qi and blood as main indicators of traditional Chinese medicine [J].Modern Chinese Clinical Medicine,2021,28(03):34-38.

[2]. XIA Shihui, LI Hongxia, ZHANG Qiyue, LIN Jianhua, ZHANG Yan. Correlation between renin-angiotensin system and central neural system diseases and regulatory effects of traditional Chinese medicine intervention [J].Shanghai J Tradit Chin Mes,2024,58(06):88-94.DOI:10.16305/j.1007-1334.2024.2311093.

[3]. Yi W, Chen F, Zhang H, Tang P, Yuan M, Wen J, Wang S, CA.I. Z. Role of angiotensin II in aging. Front Aging Neurosci. 2022 Dec 2;14:1002138. doi: 10.3389/fnagi.2022.1002138. PMID: 36533172; PMCID: PMC9755866.

[4]. López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. Hallmarks of aging: An expanding universe. Cell. 2023 Jan 19;186(2):243-278. doi: 10.1016/j.cell.2022.11.001.

[5]. Matsuura-Hachiya Y, ArA.I. KY, Ozeki R, Kikuta A, Nishiyama T. Angiotensin-converting enzyme inhibitor (enalapril maleate) accelerates recovery of mouse skin from UVB-induced wrinkles. Biochem Biophys Res Commun. 2013 Dec 6;442(1-2):38-43. doi: 10.1016/j.bbrc.2013.10.162. Epub 2013 Nov 8. PMID: 24216112.

[6]. Hedayatyanfard K, Khalili A, Karim H, Nooraei S, Khosravi E, Haddadi NS, Dehpour AR, Bayat G. Potential use of angiotensin receptor blockers in skin pathologies. Iran J Basic Med Sci. 2023;26(7):732-737. doi: 10.22038/IJBMS.2023.66563.14606.

[7]. Dunn JH, Koo J. Psychological Stress and skin aging: a review of possible mechanisms and potential therapies. Dermatol Online J. 2013 Jun 15;19(6):18561. PMID: 24011311.