IFSCC 2025 full paper (IFSCC2025-660)

"Synergistic effects of a novel ascorbic acid-carnosine conjugates and its composition on skin protection and whitening for next generation skincare"

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1. Introduction

Skin aging is a natural physiological process, accompanied by problems such as collagen loss, elastic fiber breakage, and weakened barrier function, resulting in wrinkles, relaxation, and dryness. Anti-aging can not only improve the appearance, but also maintain the skin barrier function, reduce the damage to the dermis caused by external stimuli (such as ultraviolet rays, and pollutants), and reduce the risk of sensitivity, inflammation, and skin diseases. Ultraviolet (UVA / UVB) is the main external cause of skin aging (more than 80%). When the skin is stimulated, the skin barrier function is weakened, the lipid synthesis in the stratum corneum is reduced, and the transepidermal water loss (TEWL) is increased, making the skin more susceptible to external stimuli (ultraviolet, pollution, etc.) invasion. Thereby increasing damage. In addition, UV-induced DNA damage causes DNA repair capacity to decline, and accumulated gene mutations may further cause pigment abnormalities and aging. For example, the efficiency of melanin metabolism is reduced. Aging leads to slower regeneration of keratinocytes, blocked transport and shedding of melanin granules, and easy formation of stains (such as senile plaques and chloasma). When free radical scavenging is insufficient, it stimulates tyrosinase activity, promotes melanin synthesis, and aggravates inflammatory pigmentation. In addition, abnormal melanin production can also aggravate skin aging, such as accelerated wrinkle formation and uneven skin color. At the same time, after the skin barrier is damaged, external stimuli increase, induce oxidative stress and inflammatory response, interfere with melanin metabolism, and promote pigmentation; conversely, pigmentation can also affect the integrity of the skin barrier and reduce its defensive ability. Therefore, Skin aging and melanin production interact and reinforce each other, forming a vicious cycle. The key to whitening lies in multi-dimensional approaches: (1) Inhibit melanin production from the source: Numerous studies have shown that many plant extracts and chemically synthesized substances can inhibit the activity of tyrosinase. (2) Hinder melanin transportation: For example, niacinamide can inhibit the transfer of melanin from melanocytes to keratinocytes.

(3) Accelerate melanin metabolism: Chemical exfoliants promote the shedding of the stratum corneum, and antioxidant components such as vitamin C and its derivatives enhance metabolism. (4) Repair the structure and function of aging skin and enhance the skin's self-protection ability: Ingredients such as collagen and hyaluronic acid can replenish the nutrients lost by the skin, increase skin elasticity and moisture content, improve the skin barrier function, reduce damage to the skin caused by factors such as ultraviolet rays, decrease the activity of melanocytes, and indirectly achieve a whitening effect.

To address a series of skin problems such as skin aging, pigmentation, and damaged skin barrier, skincare product formulations no longer focus solely on single-efficacy testing. While ensuring skin safety, they can pay attention to the synergy of multiple functions to safeguard skin health from multiple dimensions. This study explores the synergistic effects of a rationally designed novel ascorbic acid-carnosine conjugate (EAC-L-Carnosine) in combination with nonapeptide-1 and collagen peptide on skin repair, aging, and whitening. We demonstrate the composition’s superior antioxidant antisenescence and whitening efficacy. Additionally, through network pharmacology analysis, the mechanism of action of the formulation on skin problems was further clarified, providing insights into the synergistic activity of the compound.

2. Materials and Methods

2.1 Sample Preparation and Materials

The formulation used in this study was composed of EAC-L-Carnosine, nonapeptide-1, and collagen peptide. EAC-L-Carnosine and nonapeptide-1 were derived from chemical synthesis, and collagen peptides were derived from microbial fermentation processes. These components were tested after mixing with 10ppm EAC-L-Carnosine, 20ppm nonapeptide-1, and 20ppm collagen peptides.

2.2 In Vitro Skin Model Testing

2.2.1 B16F10 Cell Line Testing

The B16F10 cell line was used to evaluate the effect of the formulation on α-MSH-induced pigmentation. The cells were exposed to α-MSH (0.1μM) to induce melanin secretion, and the whitening effect was evaluated by adding the formulation.

- Tyrosinase activity assay: The effect of α-MSH irradiation on tyrosinase activity of B16F10 cells was detected.
- Melanin content assay: The effect of α-MSH irradiation on tyrosinase activity of B16F10 cells was detected.

2.2.2 HaCaT Cell Line Testing

The HaCaT cell line was used to assess the formulation’s impact on oxidative stress. The cells were exposed to H_2O_2 (200 μM) to induce oxidative damage, and the formulation was added to evaluate its protective effects. The following assays were performed:

- ROS (reactive oxygen species) Assay: To measure the production of reactive oxygen species (ROS) induced by H_2O_2 exposure.

2.2.3 HFF-1 Cell Line Testing

The HFF-1 cell line was used to evaluate the effect of the preparation on UVA-induced cell senescence and damage. The cells were exposed to UVA radiation (40 mJ/cm^2/30 J/cm^2) to induce cell senescence, and the formulation was added to evaluate its anti-aging effect. The following tests were performed:

- Collagen I and Collagen III assay: The effects of UVA irradiation on the secretion of Collagen I and Collagen III in HFF-1 cells were detected.

• ATP (adenosine triphosphate) and NAD+ (nicotinamide adenine dinucleotide): The effects of UVA irradiation on the secretion of ATP and NAD+ in HFF-1 cells were detected.

2.3 Network Pharmacology Analysis

Network pharmacology was used to study the molecular mechanism of the formulation. The specific scheme is as follows:

• Molecular structure acquisition and target prediction: Peptidomics was used to identify 100 peptides from collagen peptide complexes. The 2D structure of EAC-L-Carnosine was drawn by ChemDraw and the smile format was obtained. The smile format of nonapeptide-1 was obtained from pubchemistry. Convert 100 collagen peptides into smile format using the PepSMI database. Swiss Target Prediction and Super-PRED databases are used to predict potential molecular targets.

• Targets acquisition related to skin problems: The related target factors were obtained by inputting “skin barrier”, “skin inflammation and oxidative stress”, and “skin melanin synthesis” in the GeneCards database, and the top 500 targets were selected for later use. Subsequently, the small molecule targets were intersected with them, and finally, the targets related to skin problems were obtained.

• Key targets acquisition: The above targets were imported into the String online website to select Homo sapiens with a comprehensive score of ⩾ 0.9, exclude proteins without interaction, and generate a protein-protein interaction (PPI) network. The medians of betweenness centrality, closeness centrality, and degree centrality were analyzed using the CytoNCA plug-in in Cytoscape 3.8 software. Targets above the median of degree, betweenness, and proximity were selected as key targets, and the PPI network was visualized.

• Kyoto Encyclopedia of Genes and Genomes (KEGG) and Gene Ontology (GO) enrichment analysis: Metascape was used to analyze the mechanism of action of core targets, focusing on whitening, barrier repair, and oxidative stress pathways. From these data, the potential mechanism of the formulation for skin problems was explored.

3. Results

3.1 Compared with carnosine and 3-o-ethyl ascorbic acid (EAC), EAC-L-Carnosine has stronger whitening activity

First, we evaluated the whitening activity of EAC-L-Carnosine. EAC-L-Carnosine is composed of an EAC by replacing the hydrogen next to the carnosine bond. Among them, the -CH_3 connected to C-O-C and the hydroxyl group connected to -C = C- of EAC are combined to form an ether bond, which makes EAC-L-Carnosine more stable and less likely to break. In addition, through molecular docking, it was found that EAC-L-Carnosine L had stronger binding force with NRF2 than monomer. This indicates that EAC-L-Carnosine may have stronger antioxidant capacity. Antioxidation plays an important role in regulating melanin production, which directly or indirectly affects the process of melanin production by maintaining the body's redox balance. Therefore, EAC-L-Carnosine may also have stronger whitening activity.

To evaluate the efficacy of EAC-L-Carnosine in skin whitening, B16F10 cell model was used in this experiment. B16F10 cells were treated with 0.1 μM α-MSH to construct a skin melanin deposition model, and EAC-L-Carnosine, Carnosine, and EAC were added at a concentration of 24.25 μM for 48 h. Subsequently, the whitening activity of the preparation was evaluated by measuring tyrosinase activity and melanin secretion.

For tyrosinase activity, tyrosinase activity in B16F10 cells increased after α-MSH intervention. Compared with the α-MSH group, the preparation at 24.25 μM concentration significantly reduced tyrosinase activity. Among them, the inhibition rate of EAC-L-Carnosine was 20.0 %, which was comparable to that of carnosine and better than EAC.

Similarly, α-MSH exposure led to a significant rise in melanin production in B16F10 cells. While both carnosine and EAC exhibited inhibitory effects on melanin production, EAC-L-Carnosine demonstrated a remarkable 19.1% reduction in relative melanin production. These findings suggest that EAC-L-Carnosine inhibits melanin-related proteins and shows potential as a whitening agent.

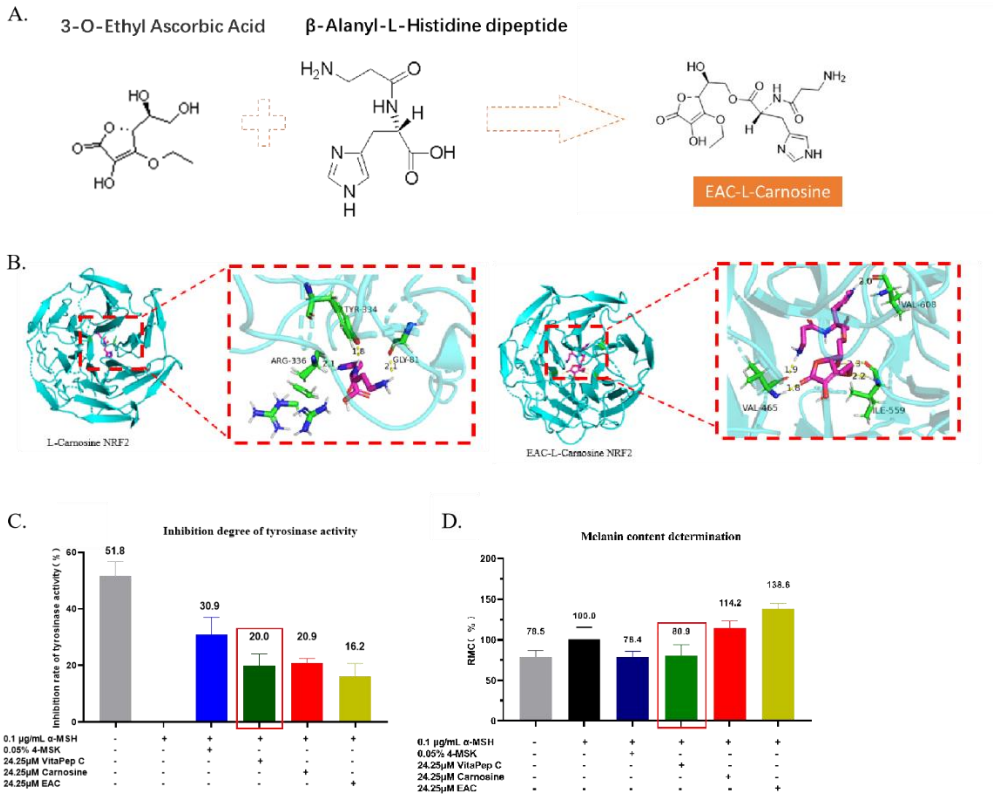

Figure 1. The structure of a rationally designed novel ascorbic acid-carnosine conjugate (EAC-L-Carnosine) and its efficacy for skin protection and whitening. (A) The structure of EAC-L-Carnosine (VitaPep C); (B Molecular docking 3D structure of carnosine with EAC-L-Carnosine and NRF2; (C) The effects of Carnosine, EAC-L-Carnosine, and EAC on tyrosinase activity in α-MSH-induced B16F10; (D) The effects of Carnosine, EAC-L-Carnosine, and EAC on α-MSH-induced melanin production in B16F10.

3.2 The effect of formulation intervention on B16 whitening and HaCaT antioxidant activity.

While EAC-L-Carnosine (VitaPep C) offers internal whitening benefits, nonapeptide-1 acts as an external signal to inhibit MSH-induced melanin formation, and collagen peptides enhance skin metabolism and elasticity for a more complete effect. When combined, the synergistic results surpass those of individual ingredients.

To further boost EAC-L-Carnosine's whitening effects, we combined it with nonapeptide-1, an MC1R inhibitor, and collagen peptides, which support skin metabolism and elasticity. Tests on the B16F10 melanin production model showed that the formulation outperformed individual components in inhibiting tyrosinase activity and melanin production. Specifically, the formulation achieved inhibition rates of 63.02% for tyrosinase activity and 43.69% for melanin production compared to single-ingredient counterparts.

Subsequently, the antioxidant effect of EAC-L-Carnosin, nonapeptide-1, Collagen Type 21, and the formulation was evaluated using the H_2O_2-induced HaCaT oxidative damage model.

The results showed that compared with the Control group, the ROS in the model group was significantly increased. After sample intervention, ROS was significantly reduced and the formulation group had a better ability to inhibit ROS production. This indicates that the formulation has excellent antioxidant capacity and can effectively reduce H_2O_2-induced ROS accumulation in HaCaT.

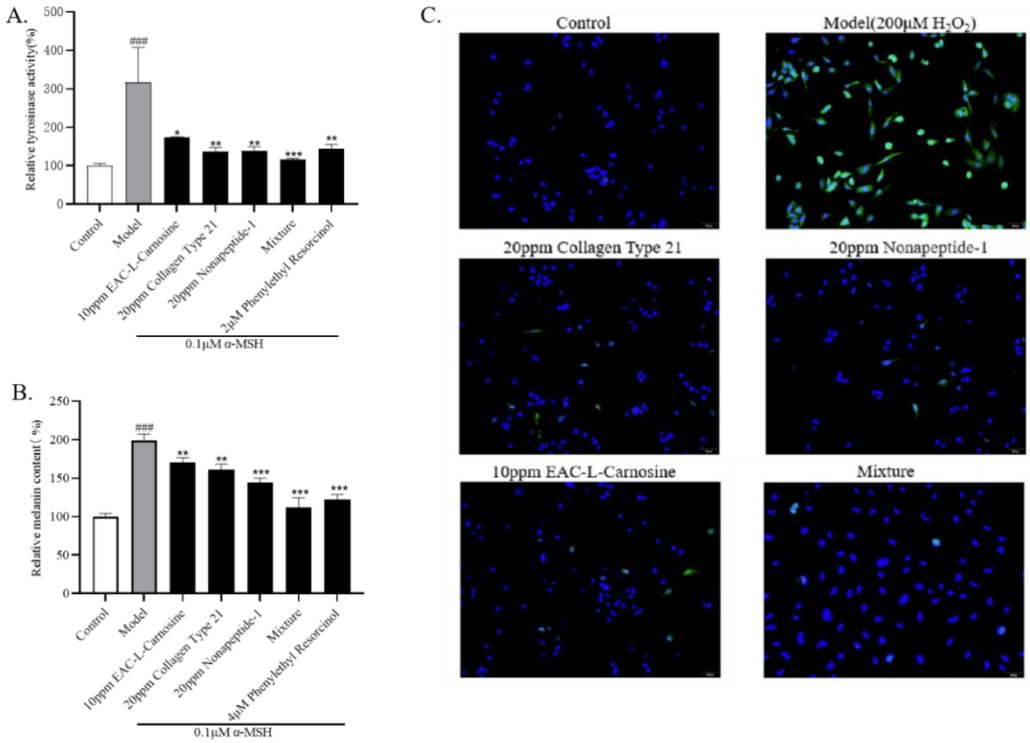

Figure 2. The effect of the formulation on the whitening effect of B16F10 induced by α-MSH and the production of ROS in HaCaT after H_2O_2 stimulation. (A-B) The effects of 10 ppm EAC-L-Carnosine, 20 ppm Collagen Type 21, nonapeptide-1, and formulation (containing 10 ppm EAC-L-Carnosine, 20 ppm Collagen Type 21 and 20 ppm nonapeptide-1) on tyrosinase activity and melanin content in B16F20 after α-MSH induction; (C) The effects of 10 ppm EAC-L-Carnosine, 20 ppm Collagen Type 21, nonapeptide-1, and formulation (containing 10 ppm EAC-L-Carnosine, 20 ppm Collagen Type 21 and 20 ppm nonapeptide-1) on ROS release in HaCaT after H_2O_2 stimulation.

3.3 The contents of collagen I, collagen III, ATP, and NAD$^+$ in HFF-1 treated with the formulation increased significantly.

Beyond whitening, the formulation's impact on energy-related anti-aging indicators was assessed. As individuals age, physiological changes such as slower epidermal turnover, altered melanocyte function, and a weaker skin barrier lead to increased pigmentation. Thus, combating aging is vital for maintaining skin health and mitigating pigmentation.

To comprehensively evaluate the biological activity of the samples in inhibiting skin aging, a series of in vitro experiments were carried out using HFF-1. Cell senescence was induced by UVA irradiation (40 mJ/cm^2), and then the effects of single component and formula components on the contents of type I and III collagen, ATP, and NAD+ were evaluated to evaluate the anti-aging effect of the preparation.

Compared with the control group, the content of type I and III collagen in the model group decreased significantly after 40mJ/cm^2 UVA treatment. After sample intervention, the content of type I and III collagen increased significantly. In addition, the formulation group had the strongest promotion effect, and the up-regulation rates of type I and III collagen were 682.47%

and 2332.29%, respectively. These data indicate that the formulation is more effective in reducing UVA-induced loss of type I and III collagen in HFF-1 than a single component.

In addition, the ability of the samples to inhibit UVA-induced cell senescence was evaluated by measuring ATP and NAD+ contents. Compared with the model group, the content of NAD+ increased to a certain extent after sample intervention. Among them, the NAD+ content in the formulation intervention group was the highest, and the NAD+ up-regulation rate was 71.26%, which was about 3 times higher than that in the single-component intervention group. Meanwhile, the ATP content in HFF-1 was also significantly increased after formulation intervention. These experiments show that the formulation can delay cell senescence by increasing NAD+ content and improving mitochondrial function.

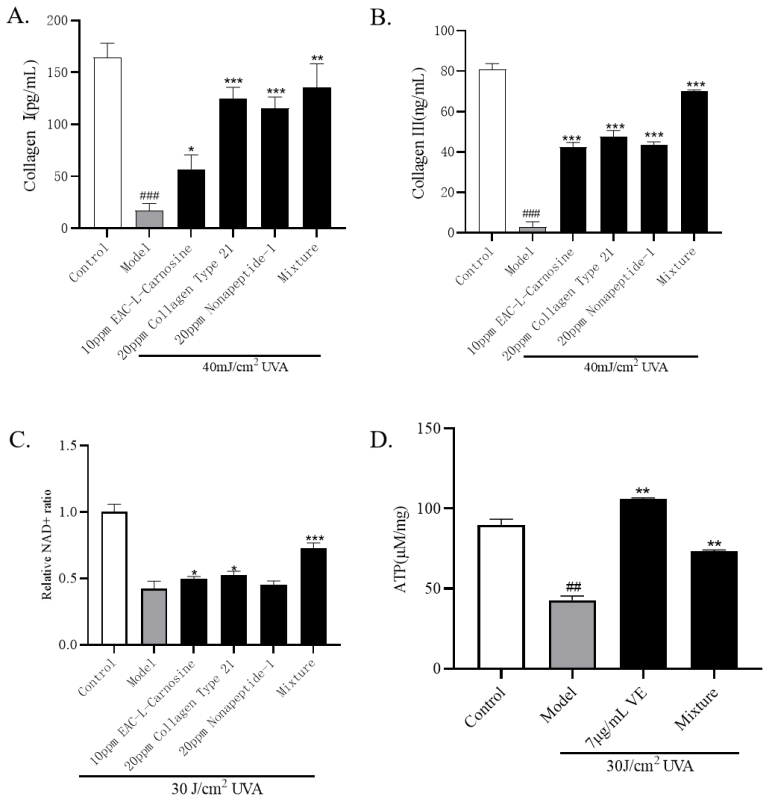

Figure 3. The effects of formulation on the content of type I and III collagen, NAD+, and ATP in HFF-1 cells induced by UVA. (A-B) The effects of 10ppm EAC-L-Carnosine, 20ppm Collagen Type 21, nonapeptide-1, and formulation (containing 10ppm EAC-L-Carnosine, 20ppm Collagen Type 21 and 20ppm nonapeptide-1) on the content of type I and III collagen in HFF-1 after UVA irradiation; (C) The effects of 10ppm EAC-L-Carnosine, 20ppm Collagen Type 21, nonapeptide-1, and formulation (containing 10ppm EAC-L-Carnosine, 20ppm Collagen Type 21 and 20ppm nonapeptide-1) on the content of NAD+ in HFF-1 after UVA irradiation; (D) The effects of formulation (containing 10ppm EAC-L-Carnosine, 20ppm Collagen Type 21, and 20ppm nonapeptide-1) on the content of NAD+ in HFF-1 after UVA irradiation.

3.3 Network Pharmacology Analysis

The network pharmacology method was used to reveal the potential mechanism of EAC-L-Carnosine, nonapeptide-1, and Collagen Type 21 formulation to exert their skin barrier repair, anti-inflammatory, and whitening effects.

Firstly, 100 collagen type 21 peptide sequences were identified by peptidomics. Target prediction was then performed using the Swiss Target Prediction and Super-PRED databases. The predicted targets were compared with the skin problem-related targets obtained by

Genecards, and 135 targets were finally obtained. Then, the protein-protein interaction (PPI) network was constructed through the STRING database, and the combination of 135 unique targets was analyzed to identify the key target proteins involved in regulating skin physiology. Cytoscape 3.8 was used for visual analysis, and central indicators such as degree, betweenness, and tightness were calculated. Finally, 15 core targets (including MAPK1, AKT1, PIK3CA, PIK3CD, PIK3R1, AKT3) that play a key role in regulating skin barrier integrity and repair pathways were identified. Further, GO enrichment analysis of these core targets revealed that they were significantly involved in a variety of biological processes (BP), molecular functions (MF), and cellular components (CC). It is worth noting that the core targets are mainly related to key biological processes such as cell response to stimulation, enzyme-linked receptor protein signaling pathway, response to peptide hormones, and response to growth factors. In addition, these targets are also involved in molecular functions such as nitric oxide synthase regulator activity, protein kinase activity, and protein kinase binding. At the same time, these targets are involved in the regulation of cellular components such as phosphatidylinositol 3-kinase complex, cell leading edge, and plasma membrane microdomains. In addition, KEGG pathway analysis identified 128 signaling pathways, including 64 pathways related to human diseases, 39 pathways related to organismal systems, 8 pathways related to cellular processes, and 18 pathways related to environmental information processing. Excluding human disease-related pathways, the top 30 signaling pathways were ranked according to P values, mainly involving key processes such as pigmentation, collagen degradation, cell proliferation, and inflammatory response. TLR, TNF, JAK-STAT, and PI3K-Akt signaling pathways are associated with inflammatory regulation and cell proliferation. This shows that the EAC-L-Carnosine, nonapeptide-1, and Collagen Type 21 formulation can regulate the cell's stimulation of the external environment through multiple channels to cope with a variety of skin problems.

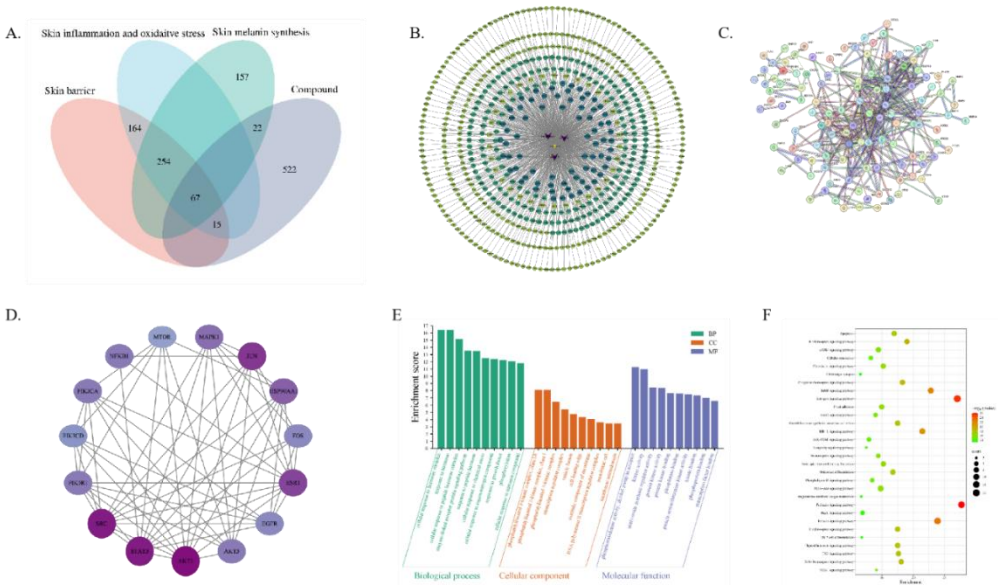

Figure 4. Network pharmacology analysis of key targets and pathways for skin barrier repair, anti-inflammatory and whitening of EAC-L-Carnosine, nonapeptide-1, and Collagen Type 21 formulation(A) The Venn diagram showed that there was a target overlap between the predicted formulation target and the GeneCards-derived “skin barrier”, “skin inflammation and oxidative stress”, and “skin melanin synthesis” genes; (B) Component target correspondence diagram; (C) The protein-protein interaction (PPI) network of 135 targets was constructed using STRING (score ⩾ 0.9). The node represents the protein, and the thickness of the edge represents the confidence level; (D) CytoNCA was used to identify core targets, in which 15

highly central nodes were identified based on the Betweenness, Closeness, and Degree indicators. The node size and color intensity reflection value size; (E) GO enrichment analysis (top 10 items for each BP, MF, and CC). (F) KEGG signaling pathway enrichment analysis (excluding human disease-related, top 30 signaling pathways).

4. Discussion

4.1 Synergistic formulation of EAC-L-Carnosine,nonapeptide-1, and Collagen Type 21 and its efficacy

This study confirms that the combination of EAC-L-Carnosine, nonapeptide-1, and Collagen Type 21 effectively enhances the skin barrier, reduces oxidative stress, delays skin aging, and inhibits melanin production.

In the α-MSH-induced melanogenesis pathway, tyrosinase gene expression is controlled by MITF, yet its catalytic activity is the rate-limiting step in melanin synthesis. Even without changes in gene expression levels, inhibiting enzyme activity can significantly reduce melanin production. In vitro experiments showed that the formulation of EAC-L-Carnosine, nonapeptide-1, and Collagen Type 21 could inhibit melanin synthesis from the source by inhibiting tyrosinase activity, and the effect was better than 2~4 μM phenethyl resorcinol. Studies have shown that phenylethyl resorcinol can act on the transient receptor potential (TRP) channel family, triggering the depolarization of sensory neurons, thereby generating a stimulating sensation. The formulation of EAC-L-Carnosine, nonapeptide-1, and Collagen Type 21 can become promising core functional components in whitening skin care products due to their good whitening effect and low irritation. Considering the relationship among skin aging, melanin production, and skin barrier damage, subsequent experimental designs have confirmed that this formulation not only has a whitening effect but also can mitigate oxidative stress and prevent aging.

Reactive oxygen species (ROS) are closely linked to melanin production. Moderate ROS levels can activate signaling pathways like mitogen-activated protein kinase, enhancing tyrosinase activity and promoting melanin synthesis. Excessive ROS, however, causes oxidative stress, damaging biomacromolecules in skin cells, triggering inflammatory responses, and disrupting the skin barrier. In this study, H_2O_2 intervention significantly increased ROS levels in HaCaT cells. Subsequent addition of the formulation inhibited ROS release, indicating its potential to combat oxidative stress and repair damaged barriers.

Collagen loss and structural damage are key signs of aging. Factors like UV radiation, oxidative stress, and glycation accelerate collagen degradation, leading to reduced, fractured, and disordered collagen fibers in the dermis. This results in wrinkles, laxity, and decreased elasticity. In HFF-1 in vitro tests, the EAC-L-Carnosine, nonapeptide-1, and Collagen Type 21 formulation significantly enhanced UVA-induced cellular secretion of collagen I and III, outperforming single components. This highlights their synergistic effects. Additionally, NAD+, a key coenzyme in cellular energy metabolism and DNA repair, declines with age, potentially affecting Sirtuin protein activity and influencing cellular aging and inflammation. NAD+ is a substrate of PARP, directly involved in UV-induced DNA damage repair. NAD+ also participates in glucose breakdown as an electron carrier. After generating NADH, it enters the mitochondrial electron transport chain and produces ATP through oxidative phosphorylation. ATP, the cellular energy transfer 'currency,' powers skin cell proliferation, repair, barrier function, and collagen synthesis. This study shows that the formulation can enhance cellular energy metabolism and DNA repair, and boost antioxidant capacity by increasing NAD+ and ATP levels, thereby regulating aging.

Network pharmacology analysis reveals that the formulation regulates multiple signaling pathways to repair the skin barrier, whiten the skin, and reduce inflammation. These pathways

influence skin physiology and pathology by regulating cellular processes like proliferation, differentiation, apoptosis, and migration, as well as inflammatory factor production. Skin barrier repair and inflammatory responses are closely interconnected. When the skin barrier is compromised, pathogens and irritants can penetrate, activating inflammatory pathways like TLR and TNF, triggering inflammation that further damages the barrier, creating a vicious cycle. Signaling pathways involved in barrier repair can also impact inflammation by regulating inflammatory cell function and factor expression. For example, the focal adhesion pathway can inhibit inflammatory cell migration and activation, reducing inflammation and supporting barrier repair. Whitening and inflammatory responses are also correlated. Inflammation can cause skin pigmentation, such as post-inflammatory hyperpigmentation (PIH), where inflammatory factors like TNF-α and IL-6 stimulate melanocyte activity and melanin synthesis. Whitening-related pathways can reduce pigmentation by regulating inflammatory factor expression and alleviating inflammation. Inflammation can also indirectly affect whitening by impacting skin microcirculation and metabolism. These results indicate that this formulation can act in multiple dimensions to regulate aspects such as skin melanin production, skin barrier function, oxidative stress, and inflammation.

In summary, the formulation's inhibitory effects on skin aging, oxidative stress, barrier damage, and melanin production have been confirmed, laying a solid foundation for its application in skincare and medical aesthetics. The results hold significant scientific and industrial potential. In the realm of skincare, it's crucial to adopt a comprehensive approach, personalize routines, use cosmetics rationally, and adjust lifestyle while focusing on ingredient safety and efficacy. This study shows that the formulation offers a safe, effective, and all-encompassing solution for improving skin issues and maintaining skin health and beauty. Future research can further explore its in vivo role and potential applications in cosmetics and medical aesthetics.

5. Conclusion

This study shows that the synergistic combination of EAC-L-Carnosine, nonapeptide-1, and Collagen Type 21 provides an effective solution for preventing skin aging, reducing oxidative stress, and inhibiting skin pigmentation. In vitro cell results showed that it had a significant effect on inhibiting skin aging, oxidative stress, and melanin production. The results of network pharmacology showed that the preparation maintained skin health through multi-channel regulation.

In the process of skincare, attention should be paid to comprehensive care, personalized skin care, scientific and rational use of cosmetics, combined with lifestyle adjustment, and attention to the safety and effectiveness of ingredients. The results of this study indicate that this formulation can be used as a safe, effective, and comprehensive method to better improve skin problems and maintain skin health and beauty. In the future, we can continue to explore the role of the formulation in the body, and further clarify the application potential of the formulation in cosmetics, medical beauty, and other fields.

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