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Research Article

Anti-Aging and Skin-Improving Effects of Saussurea Involucrata Stem Cell Extract: Cellular Mechanisms and Clinical Validation

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Abstract

Skin aging manifests as dryness, laxity, pigmentation, and reduced elasticity, compromises both appearance and barrier function. Natural plant extracts, such as Saussurea involucrata (snow lotus), have gained attention for their potent bioactive compounds and anti-aging potential, providing safe alternatives to synthetic ingredients. This study aimed to evaluate the anti-aging effects and skin-improving properties of snow lotus stem cell extract liquid (Cell Young®) through cellular and clinical investigations. Cellular studies assessed immune capacity, collagen secretion, and melanin inhibition in human skin fibroblasts and melanoma cells. Clinical trials included 40 subjects who consumed snow lotus drinks or a placebo daily for eight weeks in a double-blind design. The results showed that snow lotus stem cells extract liquid increased immune cytokines (IL-1β, IL-6, IL-8, TNF-α) and longevity-related genes (FOXO), enhanced keratin barrier function (TGM1), inhibited melanin production (MITF), suppressed collagen-degrading enzymes (MMP9), increased collagen secretion, and promoted wound healing. Human trials further validated their efficacy, showing increased expression of Sirtuin 1(SIRT1) and Fork head Box O3 (FOXO3), improved skin elasticity, after 60 days of snow lotus drink consumption. These findings highlight their potential for cosmetic and functional applications.

Keywords: Immune; Skin Aging; Snow Lotus; Stem Cell

Introduction

Skin aging is a multifaceted biological process driven by a combination of intrinsic (endogenous) and extrinsic (environmental) factors [1]. Skin health and appearance are key indicators of overall well-being and perceived human health. Skin aging not only affects aesthetic appearance but also weakens the skin barrier, leading to moisture loss and reduced resilience [2]. Thus, anti-aging skincare strategies have focused on multiple aspects of skin health, including moisturizing repair, brightening, enhancing elasticity, and delaying aging. Moisturizing repair maintains skin hydration and stabilizes the skin barrier; brightening inhibits melanin production, creating an even and radiant complexion; and enhancing elasticity supports collagen levels, reducing wrinkles and sagging [3]. These strategies collectively work toward delaying visible signs of aging, helping to preserve youthful and healthy skin. However, many commercial anti-aging products rely heavily on synthetic ingredients to achieve these effects. Although synthetic compounds may offer immediate hydration or brightening benefits, long-term use can sometimes lead to sensitivity, allergic reactions, or other health concerns. Furthermore, the origins and quality of synthetic ingredients can be inconsistent, which may compromise the efficacy and safety of products, particularly for individuals with sensitive skin [4]. These limitations highlight the advantages of natural plant extracts. Plant extracts are often rich in natural antioxidants, polyphenols, carotenoids, and flavonoids, providing effective moisturization, pigmentation reduction, elasticity improvement, and long-term safety due to their biocompatibility and multifunctionality [5].

Saussurea involucrata, commonly known as snow lotus, is a rare plant native to high-altitude regions of Xinjiang, China, known for its resilience to cold and drought and its abundance of bioactive

compounds [6]. Snow Lotus contains various active compounds, including flavonoids (such as quercetin and isorhamnetin), polyphenols, alkaloids, and polysaccharides, all of which have shown potential in anti-aging skincare [7]. Studies showed that the flavonoids and polyphenols in snow lotus effectively combated free radicals, reduced oxidative stress, and prevented skin aging caused by UV radiation and environmental pollutants [8]. Additionally, these compounds were found to inhibit melanin production, contributing to a brighter skin tone. Both cellular and clinical studies highlighted the beneficial effects of snow lotus on skin health [6]. In cellular studies, snow lotus extracts enhanced the antioxidant capacity of human skin cells, reduced oxidative damage, and stimulated collagen production, leading to firmer skin [9]. The study also indicated that snow lotus extract significantly improved skin hydration by reducing transepidermal water loss, thereby supporting moisture retention [10]. In addition, snow lotus stem cells were plant stem cells extracted from the snow lotus plant, characterized by highly concentrated bioactivity, including various plant polyphenols, flavonoids, antioxidants, and other natural compounds [11]. Studies showed that compared to the whole plant, the plant stem cells exhibited higher cellular activity and metabolic potential, effectively promoting cell regeneration, antioxidation, and anti-inflammatory effects [12]. Furthermore, plant stem cells held broad application potential in skin repair, whitening, anti-aging, and cellular restoration, making them suitable for use in cosmetic, health, and functional product development [13].

This study aimed to investigate whether snow lotus stem cells extract liquid possessed anti-aging effects and improved skin conditions.

Materials and Methods

The snow lotus stem cells extract liquid

Snow lotus stem cells extract liquid (Cell Young®) provided by TCI Co., Ltd. The extract liquid was cooled and stored at a temperature below -20°C for subsequent experimental use.

Cell culture

Human skin fibroblasts were obtained from the American Type Culture Collection (ATCC, Manassas, VA, USA) and cultured in Dulbecco's Modified Eagle Medium (DMEM; Gibco, Thermo Fisher Scientific, Waltham, MA, USA) supplemented with 10% fetal bovine serum (FBS), 100 U/mL penicillin, 100 µg/mL streptomycin, and 2 mM l-glutamine (Lonza, Basel, Switzerland). The human immortalized keratinocyte cell line, HaCaT, were maintained in Dulbecco's modified Eagle's medium (DMEM) with 10% fetal bovine serum and 1% antibiotics (10,000 µg/ml streptomycin and 10,000 units/ml penicillin). Peripheral blood mononuclear cells (PBMCs) were isolated from human whole blood using density gradient centrifugation with Ficoll-Paque (GE Healthcare, Chicago, IL, USA). The PBMCs were cultured in RPMI-1640 medium (Gibco, Thermo Fisher Scientific, Waltham, MA, USA) supplemented with 10% fetal bovine serum (FBS), 100 U/mL penicillin, 100 µg/mL streptomycin, and 2 mM l-glutamine (Lonza, Basel, Switzerland). B16F10 mouse melanoma cells (CRL-6475) were purchased from the American Type Culture Collection (ATCC, Manassas, VA, USA). The cells were cultured in DMEM supplemented with 10 % fetal bovine serum (FBS, Gibco, NY, USA). These cells were maintained in a humidified incubator at 37°C with 5% CO_2.

Collagen secretion

Seeding human skin fibroblasts at a density of 2×10^4 cells per well in a 24-well plate for 24 hours. The cells were then treated with the test samples in 500 µL serum-free medium in triplicates (n = 3) and incubated for an additional 48 hours. Collagen secretion into the cell culture medium was quantified using the Sircol™ Collagen Assay Kit, which specifically measures the collagen content secreted by the human skin fibroblasts.

Quantification of gene expressions by real-time PCR

The treated cells were harvested, and total RNA was isolated from cells using an RNA purification kit (Geneaid, Taiwan). DNA-free total RNA was reversely transcribed to cDNA using a Super Script™ Reverse Transcriptase kit (Invitrogen, Life Technologies Co., CA, USA). Quantitative real-time PCR was conducted using an ABI Step One Plus™ Real-Time PCR System (Thermo Fisher Scientific, Inc., CA, USA) and the SYBR Green Master Mix (KAPA Biosystems, MA, USA) for transcript measurements. The reaction mixture was cycled as follows: one cycle at 95 °C for 20 s, followed by 40 cycles of 95 °C (1 s), 60 °C (20 s), and a plate reading was conducted after each cycle. The melting curves of the PCR products were analyzed during the quantitative real-time PCR. The gene-specific primers used in this study are listed in table 1. Real-time PCR reactions were performed using the ABI system. GAPDH was used as the reference gene to normalize relative expression. Data were analyzed using the ABI StepOne™ Software v2.2.3 (Thermo Fisher Scientific, Inc., Carlsbad, CA, USA). All PCR assays were performed in duplicate three times.

Cell migration assay

Briefly, human skin fibroblasts (or another suitable cell type) were seeded into 6-well plates and cultured to 90-100% confluence. A sterile pipette tip was used to create a scratch (wound) across the monolayer. The wells were washed gently with phosphate-buffered saline (PBS) to remove detached cells and debris, and cells were then treated with the test samples in a serum-free medium. The migration of cells into the wound area was monitored and imaged using a phase-contrast microscope.

Clinical trial design

This study included a total of 40 subjects aged 30 years and older, with no restrictions on gender. Exclusion criteria included not meeting the inclusion criteria, pregnancy, or drug allergies. Sub-

jects were recruited through advertisements and online social media platforms. After obtaining approval from the Institutional Review Board (CMUH18-REC2-036), subject recruitment and testing were conducted. The trial was carried out in a double-blind manner, where subjects were randomly assigned to consume either a functional beverage or a placebo beverage. During data recording, subjects were categorized as group A or B to ensure blinding. Both subjects and researchers were unaware of the beverage group assignments. Subjects consumed one bottle of the assigned beverage daily for eight consecutive weeks. Throughout the study, subjects were required to maintain their usual dietary and lifestyle habits, with no changes except for consuming the test product. Skin assessments were conducted on days 0, 30, and 60 of the intervention. Subjects were instructed to abstain from smoking, drinking hot beverages, or consuming caffeinated drinks at least three hours before each measurement. Blood samples were collected in a fasting state by licensed nurses or medical laboratory technicians to ensure accuracy. Skin elasticity was determined using the Cutometer MPA580 (C+K, Germany), applying negative pressure to measure the skin's viscoelastic properties.

Test Sample

The snow lotus drink contained snow lotus stem cell extract liquid (0.3 g/day), citric acid, sucralose, citrus pectin, apple juice, fructose, flavor, and water. The placebo drink contained citric acid, sucralose, citrus pectin, apple juice, fructose, flavor, water. The placebo and snow lotus drink group received one bottle daily and took it continuously for two months. The placebo and snow lotus groups were identical in appearance, packaging, and taste to ensure blinding during the trial.

Statistical analysis

The experimental data used paired t-tests and independent two-sample t-tests for statistical analysis, without applying a specific mean separation method for post-hoc multiple comparisons. . A p-value of less than 0.05 was considered statistically significant.

Results

Snow lotus stem cells extract enhanced immunity and anti-aging effects *in vitro.*

First, it was essential to evaluate whether snow lotus stem cells extract liquid possessed the potential to enhance immune function. Cytokines such as IL-1β, IL-6, IL-8, and TNF-α were critical molecules in regulating inflammatory responses and immune defense, serving as a bridge between innate and adaptive immunity. IL-1β and TNF-α were key regulators of acute inflammation, promoting the release of inflammatory mediators, activating immune cells, and increasing vascular permeability to strengthen immune responses [14]. IL-6 played a dual role in inflammation by stimulating the liver to produce acute-phase proteins during the acute phase response and facilitating the differentiation of T cells and B cells [15]. Meanwhile, IL-8 acted as a vital chemokine, attracting neutrophils to inflammation sites, enhancing their bactericidal and phagocytic functions, and supporting tissue repair through the promotion of angiogenesis [16]. The results indicated that snow lotus stem cells extract liquid significantly enhanced the gene expression of immune-related cytokines, including IL-1β, IL-6, IL-8, and TNF-α. Compared to the mock group, IL-1β had increased by 9-fold, IL-6 by 2-fold, IL-8 by 22-fold, and TNF-α by 12-fold (Figure 1A). Forkhead box O (FOXO) is a gene family closely associated with longevity, cellular stability, and stress responses, belonging to the transcription factor family [17]. FOXO genes regulate various longevity-related mechanisms, including antioxidant responses, DNA repair, autophagy, and energy metabolism. The results showed that snow lotus stem cells extract liquid significantly increased the expression of the longevity gene FOXO (Figure 1B).

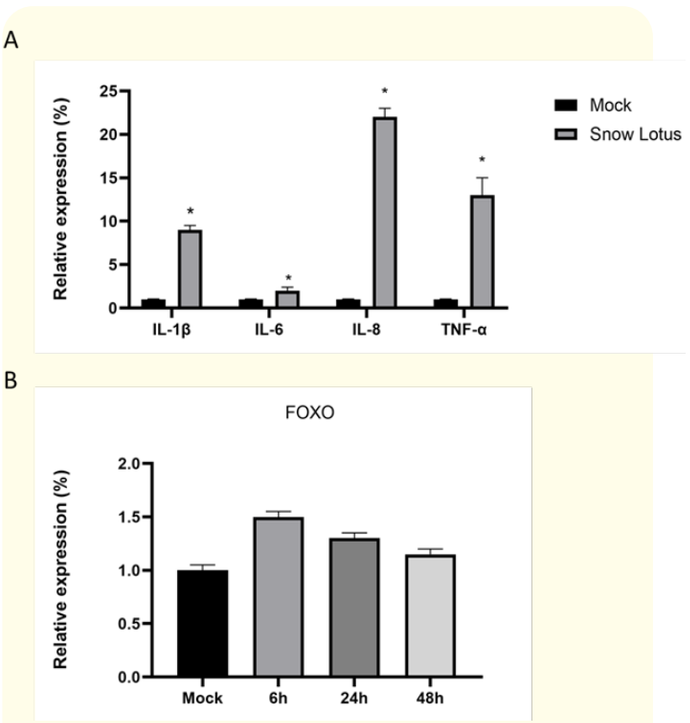

Figure 1: Snow lotus stem cells extract liquid enhanced immune-related cytokine expression and upregulated FOXO gene expression. (A) Relative gene expression levels of immune-related cytokines (IL-1β, IL-6, IL-8, and TNF-α) in PBMCs treated with snow lotus stem cells extract liquid compared to the mock group. *, compared with mock (*p < 0.05). (B) Time-dependent upregulation of FOXO gene expression in PBMCs treated with snow lotus stem cells extract liquid.

Snow lotus stem cells extract improved skin conditions *in vitro*

Next, the evaluation focuses on whether snow lotus stem cells extract liquid can improve skin conditions. TGM1 encodes a cell membrane-bound enzyme known as transglutaminase, which plays a crucial role in reinforcing the skin's keratin barrier [18]. The results showed that snow lotus stem cells extract liquid increased

the expression of the TGM1 gene, with a 33% enhancement compared to the mock group (Figure 2A). The results showed that snow lotus stem cells extract liquid significantly increased melanin inhibition by 13% and 20% compared to kojic acid and snow lotus plant, respectively (Figure 2B). Additionally, snow lotus stem cells extract liquid suppressed MITF gene expression by approximately 30% (Figure 2C), where MITF is a key gene regulating melanin production in melanocytes. Snow lotus stem cells extract liquid suppressed approximately 80% of MMP9 gene expression (Figure 2D). In addition, snow lotus stem cells extract liquid significantly increased collagen secretion by approximately 2.4-fold (Figure 2E) and significantly promoted wound healing by about 5 fold compared to the snow lotus plant (Figure 2F).

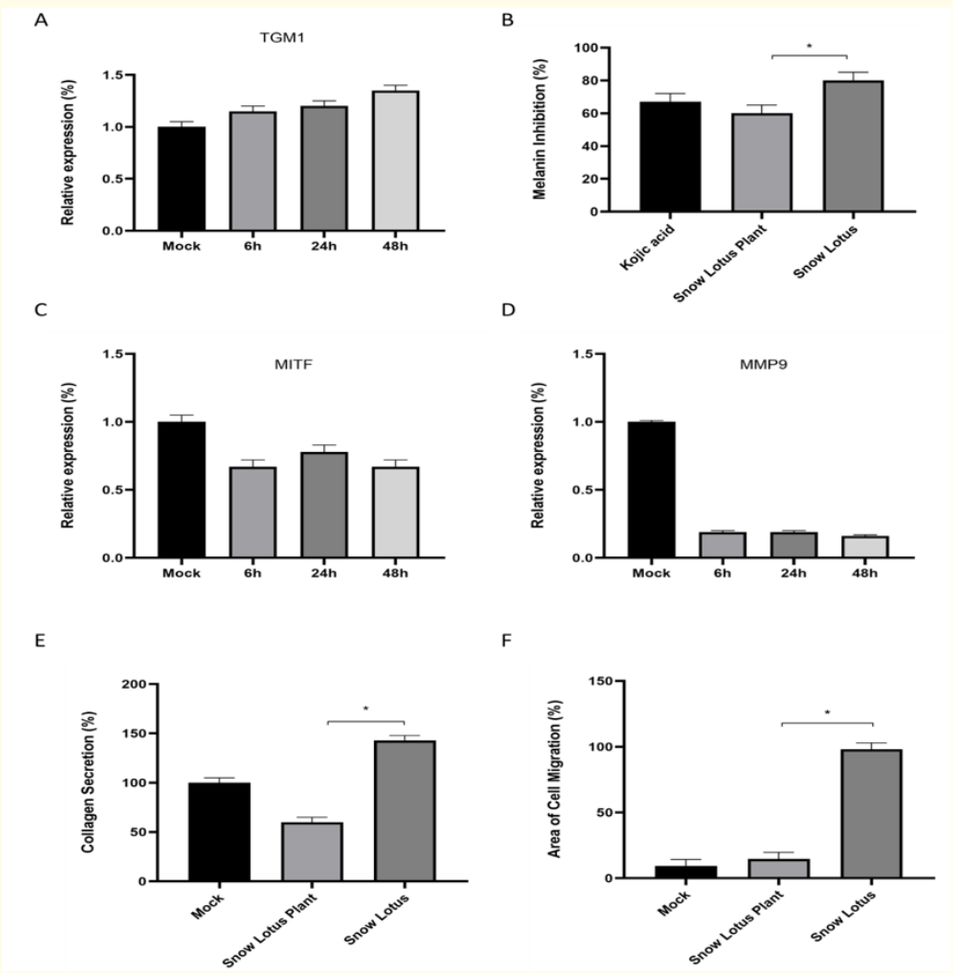

Figure 2: Effects of snow lotus stem cells extract liquid on gene expression, melanin inhibition, collagen secretion, and cell migration. (A) Relative expression of TGM1 in HaCaT treated with snow lotus stem cells extract liquid over time (6, 24, and 48 hours). (B) Melanin inhibition percentage in B16F10 mouse melanoma cells treated with snow lotus stem cells extract liquid compared to kojic acid and snow lotus plant. (C) Relative expression of MITF in B16F10 mouse melanoma cells treated with snow lotus stem cells extract liquid over time. (D) Relative expression of MMP9 in fibroblasts treated with snow lotus stem cells extract liquid over time. (E) Collagen secretion levels in fibroblasts treated with snow lotus stem cells extract liquid compared to the mock group and snow lotus plant. (F) Percentage of cell migration area in fibroblasts treated with snow lotus stem cells extract liquid compared to the mock group and snow lotus plant (*$p < 0.05$).

Snow lotus stem cells extract had anti-aging effects and enhances skin elasticity in human.

The next step was to validate the skin-enhancing effects and anti-aging of snow lotus stem cells extract liquid through human trials. After 60 days of continuous consumption of snow lotus drinks, the expression level of the longevity gene SIRT1 increased by 5.5% compared to the baseline (day 0) (Figure 3A). In addition, the expression level of FOXO3 significantly increased by 8.7% (Figure 3B), and skin elasticity significantly improved by 7.0% compared to baseline (day 0) (Figure 3C).

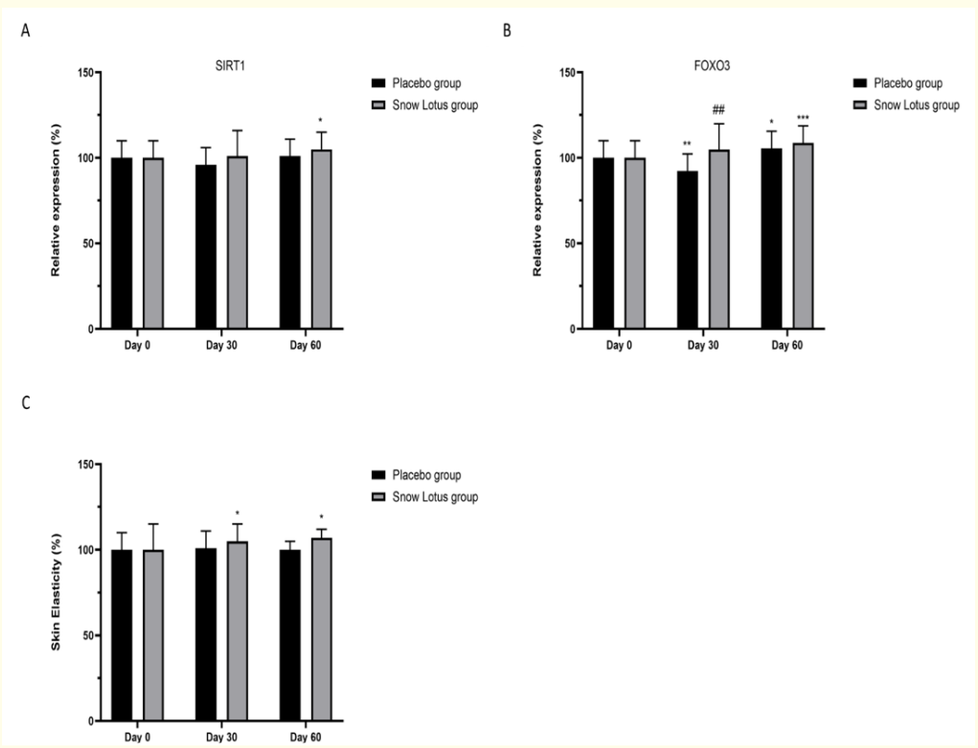

Figure 3: Clinical effects of snow lotus stem cells extract liquid on anti-aging genes and skin elasticity.
The placebo and snow lotus drink group received one bottle daily and took it continuously for two months. (A, B) Relative expression levels of SIRT1, FOXO3 in the placebo and snow lotus group at days 0, 30, and 60. (C) Skin elasticity measured in the placebo group and snow lotus group at days 0, 30, and 60. Compared to Day 0, statistical significance was indicated as *, $p < 0.05$; **, $p < 0.01$; and ***, $p < 0.001$. Compared to the placebo group, statistical significance was indicated as ##, $p < 0.01$.

Gene	Forward Primer (5' → 3')	Reverse Primer (5' → 3')
SIRT1	AGGTTGCGGGAATCCAAAGG	TCCAGCGTGTCAAAGGAGG
FOXO3	TGGACCTGGAAGAGTTCCTG	GCTCAGGTTGTGCTGCTTTC
MMP9	TGTACCGCTATGGTTACACTCG	GGCAGGGACAGTTGCTTCT
MITF	GATGCTGAATGCTGATGCTG	GCTGCTGCTGCTGCTGCTG
TGM1	GCTGCTGCTGCTGCTGCTG	GCTGCTGCTGCTGCTGCTG
FOXO	GCTGCTGCTGCTGCTGCTG	GCTGCTGCTGCTGCTGCTG
IL-1β	ATGATGGCTTATTACAGTGGCAA	GTCGGAGATTCGTAGCTGGA
IL-6	ACTCACCTCTTCAGAACGAATTG	CCATCTTTGGAAGGTTCAGGTTG
IL-8	ACTGAGAGTGATTGAGAGTGGAC	AACCCTCTGCACCCAGTTTTC
TNF-α	CCTCTCTCTAATCAGCCCTCTG	GAGGACCTGGGAGTAGATGAG
GAPDH	GAAGGTGAAGGTCGGAGT	GAAGATGGTGATGGGATTTC

Table 1: Primer sequences.

Discussion

This study showed that snow lotus stem cells extract liquid exhibited notable potential in boosting immunity, enhancing skin health, and delivering anti-aging effects. The regulation of key cytokines and longevity-related genes strengthened immune responses and supported cellular stability. In vitro studies revealed improvements in skin barrier function, reductions in melanin production, and increased collagen secretion and wound healing. Human trials further validated enhancements in skin elasticity and the delay of cellular aging, emphasizing their significance in health and cosmetic applications.

The snow lotus was a rare alpine plant rich in polyphenols, flavonoids, and saponins, which exhibited antioxidant, anti-inflammatory, and wound healing properties [6]. In contrast, snow lotus stem cells were extracted using plant tissue culture technology, making them rich in active metabolites with higher bioavailability and stability [19]. The internal test report showed that the snow lotus stem cell extract was abundant in various active components, with particularly high levels of total flavonoids and total phenolics. The total flavonoid content exceeded 180 ppm, while the total phenolics content also exceeded 180 ppm. In addition, compared to traditional snow lotus extracts, stem cells demonstrated enhanced abilities for cellular repair and regeneration, activating target cells and improving cellular functionality [20]. In terms of skin-enhancing and anti-aging mechanisms, snow lotus primarily operated through antioxidant activity, melanin inhibition, and collagen production pathways. Its antioxidant effects involved polyphenols and flavonoids that scavenged free radicals, reduced oxidative damage, and protected skin cells [21]. The inhibition of melanin production was linked to the downregulation of MITF gene expression, thereby reducing melanin synthesis and improving skin tone uniformity [22]. Snow lotus also promoted collagen secretion, helping to maintain skin elasticity and firmness, which was associated with the activation of the TGF-β signaling pathway [23]. Furthermore, the active components of stem cells stimulated cell proliferation and regeneration, improved the activity of keratinocytes and fibroblasts, and strengthened the skin barrier function [24].

The anti-aging effects of plant-derived stem cells were closely associated with the regulation of longevity genes such as FOXO and SIRT1 [25]. SIRT1 contributes to delaying cellular aging and extending lifespan by regulating gene expression, promoting DNA repair, and reducing oxidative stress [26]. Polyphenols and flavonoids activated FOXO genes, promoting the expression of antioxidant enzymes such as SOD and CAT, which reduced oxidative damage to cells [27]. Simultaneously, these compounds regulated the NAD+-SIRT1 pathway, enhancing DNA repair, autophagy, and antioxidant capacity, thereby delaying cellular aging and maintaining stability [28]. In terms of immune enhancement, polyphenolic compounds from plant-derived stem cells regulated the NF-κB and JAK/STAT signaling pathways, which promoted the expression of cytokines such as IL-1β, IL-6, IL-8, and TNF-α [29]. These cytokines increased immune cell activity, initiated inflammatory responses, attracted neutrophils to inflammation sites, and improved antigen presentation efficiency while mitigating chronic inflammation associated with aging. The skin-enhancing mechanisms of plant-derived stem cells were mediated through the regulation of active compounds across multiple pathways [30]. Polyphenols and flavonoids inhibited the expression of the MITF gene, which regulated tyrosinase activity involved in melanin synthesis, thereby reducing melanin production and improving skin tone and brightness [31]. Active polysaccharides from the stem cells activated the TGF-β/Smad signaling pathway, enhancing fibroblast activity to promote collagen and elastin synthesis, which improved skin elasticity and firmness [32]. Furthermore, polyphenolic compounds stimulated keratinocyte proliferation and regulated the VEGF (vascular endothelial growth factor) pathway to promote angiogenesis [33]. These effects contributed to improved tissue repair and wound healing, providing comprehensive maintenance and recovery for skin health.

The plant stem cells contained highly active metabolites that activated the AMPK-SIRT1 pathway, enhancing cellular energy metabolism and regulating gene expression to promote antioxidant activity and DNA repair [34]. Increased SIRT1 activity suppressed the production of MMP-1 and MMP-9, reducing collagen degradation [35]. Additionally, the deacetylation function of SIRT1 enhanced collagen matrix stability, mitigating skin sagging caused by aging. Plant stem cells reduced AKT activity, decreased FOXO3 phosphorylation, and preserved the stability of FOXO3 in its active form, allowing sustained nuclear action [36]. Activated FOXO3 promoted the expression of antioxidant enzymes (such as GPX and SOD), protecting skin cells from free radical damage [37]. This study primarily utilized in vitro models and a small-scale human trial. Additional large-scale clinical trials were deemed necessary to validate the efficacy and safety across diverse demographic groups. Furthermore, a deeper investigation into the mechanistic pathways, including downstream signaling related to cytokine and gene expression regulation, was essential for a more comprehensive understanding.

Conclusion

Snow lotus stem cells extract liquid showed potential in enhancing immunity, improving skin health, and providing anti-aging benefits. They demonstrated effects on immune defense, cellular stability, skin barrier improvement, and elasticity enhancement. Snow lotus stem cells extract liquid hold promise for use in immune-boosting supplements, anti-aging skincare products, and regenerative therapies. With further validation, these stem cells could be formulated into innovative health and cosmetic products targeting immunity, skin health, and anti-aging, providing comprehensive and sustainable solutions for consumers.

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