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Hair Growth-Promoting Effects of Rosehip (*Rosa canina* L.) Seed Oil in C57BL/6 Mice

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ABSTRACT: Rosehip (*Rosa canina* L.) seeds, a by-product of the food processing industry, contain various bioactive compounds that have potential cosmetic and pharmacological applications. Rosehip seed oil (RHSO) has been shown to exert therapeutic effects in skin disorders, but its role in promoting hair growth remains unknown. In this study, we aimed to elucidate the hair growth-promoting activity of RHSO and the related mechanisms of action. The depleted dorsal skin of telogenic C57BL/6 mice was topically treated with RHSO for 21 days, and the extent of hair regrowth was assessed. The results indicated that RHSO stimulated hair growth by inducing the early transition of hair follicles from telogen to anagen phase. Histological analysis revealed significant increases in hair follicle density, hair bulb size, and skin thickness. RHSO treatment also upregulated the expression of hair growth-associated genes, including β-catenin, phospho-glycogen synthase kinase-3 beta, Sonic hedgehog, smoothened, cyclin D1, cyclin E, and insulin like growth factor 1. These findings suggest that RHSO stimulates hair growth and may show promise as a preventive and/or therapeutic agent for hair loss.

Keywords: alopecia, hair follicle, hair growth, rosehip seed oil

INTRODUCTION

Hair serves both biological and aesthetic functions, contributing significantly to human overall well-being. The hair cycle consists of growth (anagen), transition (catagen), and rest (telogen) phases and is a dynamic process that ensures the continual replacement of old hairs with new ones (Cotsarelis and Millar, 2001). Hair follicles are small dynamic structures that reside within the skin and play a pivotal role in the process of hair growth. Hair growth initiates in the anagen phase of the hair cycle when specialized cells within the hair follicles divide, multiply, and differentiate, ultimately forming the hair shaft that eventually emerges from the skin's surface (Schneider et al., 2009; Lin et al., 2022). The rate and quality of hair growth are affected by various factors, which include genetics, hormones, diet, and stress (Houschyar et al., 2020). Nourishing the hair follicles with essential nutrients and maintaining a healthy scalp are key to promoting robust and vibrant hair growth. Therefore, understanding the hair cycle and hair follicle development are fundamental in promoting hair growth and preventing hair loss.

Hair loss is a prevalent issue that affects both men and women, which can significantly influence self esteem and confidence (Kim et al., 2014). Hair loss can be attributed to multiple factors, including genetics, hormonal imbalances, stress, diet, and certain medications. These factors can cause the shrinkage of hair follicles, leading to thinner and shorter hair shafts, ultimately resulting in balding or thinning areas (Cotsarelis and Millar, 2001; Truong and Jeong, 2021). Identifying the underlying cause and employing hair restoration procedures are effective strategies for the treatment of hair loss and promoting regrowth. In addition, early intervention and a holistic approach to hair care are essential in managing and potentially reversing hair loss.

Natural products are often abundant in vitamins, minerals, and antioxidants that nourish hair follicles, strengthen hair shafts, and support healthy hair growth (Premanand et al., 2020; Park and Lee, 2021). Rosehip seed oil (RHSO), derived from the seeds of wild rose shrubs, exerts a multitude of biological functions that have contributed to its reputation in skincare and health (Mármol et al., 2017; Ayati et al., 2018; Belkhelladi and Bougrine, 2023). RHSO is renowned for its high content of essential unsaturated fatty acids, which help to maintain the skin's barrier functions, promoting moisture retention and reducing transepidermal water loss (Ilyasoğlu, 2014; Lin et

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al., 2017). In addition, RHSO's vitamin components, particularly vitamin A and vitamin C, contribute to skin rejuvenation and collagen synthesis, resulting in the reduction of fine lines and wrinkles (Phetcharat et al., 2015; Valerón-Almazán et al., 2015; Lei et al., 2019). Moreover, the antioxidant and anti-inflammatory properties of RHSO provide an essential defense against environmental insults and prevent various skin conditions (Mármol et al., 2017). Although several studies have demonstrated the potential of RHSO in enhancing skin health, its role in promoting hair growth has not yet been investigated. Therefore, in this study, we aimed to elucidate the hair growth promoting capability of RHSO in a C57BL/6 mouse model. Based on the findings of previous studies, we hypothesized that RHSO has the potential to promote hair growth.

MATERIALS AND METHODS

Materials

Formalin, hematoxylin, and eosin were acquired from Sigma Aldrich. Anti-β-catenin, lymphoid enhancer binding factor 1 (Lef-1), cyclin E, insulin-like growth factor 1 (IGF-1), vascular endothelial growth factor (VEGF), transforming growth factor beta (TGF-β), Sonic hedgehog (Shh), smoothened (Smo), and anti-mouse antibodies were purchased from Santa Cruz Biotechnology. Anti-cyclin D1, phospho-glycogen synthase kinase-3 beta (p-GSK-3β), and anti-rabbit antibodies were purchased from Cell Signaling Technology. All other reagents used in this study were procured from commercially available sources and were of the highest quality.

Preparation of RHSO

Dried rosehip seeds were ground into small particles (<400 μm) and then extracted twice with *n*-hexane (24 h/time). After filtration, the filtrates were pooled, and the solvent was removed using an evaporation system under reduced pressure. RHSO was collected into an amber vial and stored at −20°C. The yield of RHSO was approximately 10%.

Animal and experimental design

Seven-week-old male C57BL/6 mice (18～20 g bodyweight) were procured from Hyochang Science. The mice were individually housed in plastic cages and maintained under standard laboratory conditions (12/12 h dark/light cycle and 50±5% humidity) with free access to food and distilled water. The experimental procedures adhered strictly to the Institutional Animal Care and Use Guidelines of Inje University (No. 2017-009). Following a 1-week acclimation period, dorsal hair removal was carried out using an electric clipper and Veet depilatory cream (Oxy Reckitt Benckiser). Treatment was commenced the day following hair depilation. In brief, mice were randomly assigned to three groups: control, RHSO, and minoxidil (MNX, positive control). Mice in the control group received a polyethylene glycol-ethanol-H_2O solution (50:20:30). Mice in the RHSO and MNX groups were topically applied with 10% RHSO and 5% MNX, respectively, once daily for 21 days. Dorsal hair growth progress was monitored through photographic records taken on days 0, 7, 14, 17, and 21. Hair growth efficacy was assessed using a scoring scale: 0 (0%), 1 (0～20%), 2 (20～40%), 3 (40～60%), 4 (60～80%), and 5 (80～100%). On days 14 and 21, mice were sacrificed, and skin specimens were snap-frozen in liquid nitrogen and stored at −80°C until further use in the subsequent experiments.

Histological analysis

Skin tissues were immediately fixed in 10% neutral buffered formalin at room temperature and subsequently embedded in paraffin. Five-micrometer longitudinal sections were stained with hematoxylin and eosin, and digital photomicrographs were captured using a digital camera (PAXcam). Various parameters, including hair follicle density, hair bulb size, and skin thickness, were determined.

Western blot analysis

Total protein from each skin specimen was extracted using RIPA Buffer (Cell Signaling Technology) following the manufacturer's instructions. The protein content was quantified using a Pierce BCA Protein Assay Kit (Thermo Fisher Scientific). Equal amounts of protein were separated on SDS-PAGE gels and subsequently electro-blotted onto Immobilon-P polyvinylidene fluoride membrane (Millipore) using a semi-dry transfer system (Bio-Rad). The membranes were blocked with 5% skim milk and then incubated with the appropriate primary antibodies overnight at 4°C. After washing, the membranes were hybridized with horseradish peroxidase-conjugated secondary antibodies for 3 h. The protein blots were visualized using an enhanced chemiluminescence Western blotting reagent (Santa Cruz Biotechnology).

Statistical analysis

Data were expressed as the mean±standard deviation. Statistical significance between the control and treatment groups was determined by Student's *t*-test. *P*-values of <0.05 were considered statically significant.

RESULTS AND DISCUSSION

Effect of RHSO on hair growth in telogenic C57BL/6 mouse model

Hair is synthesized by the hair follicles, small regenerative organs. Normally, each mature hair follicle undergoes repetitive cycles of growth (anagen), brief regression (catagen), and rest (telogen) phases throughout adult life (Schneider et al., 2009; Al-Nuaimi et al., 2010). A normal human hair cycle is generally several years, while the mouse hair cycle is only a few weeks (Müller-Röver et al., 2001). However, the hair cycle of mice is analogous to that of humans. C57BL/6 mice are widely used to screen hair growth-promoting agents because their skin pigmentation is time-synchronized with their hair growth cycle: the skin appears pink in the telogen phase and transitions to black/gray in the anagen phase (Zhang et al., 2016; Akanda et al., 2017).

In this study, to evaluate the hair growth-promoting activity of RHSO, the telogenic dorsal skins of mice were topically applied with 10% RHSO once a day for 21 days. In comparison with the control group, RHSO treatment stimulated hair growth and induced premature transition of hair follicles from the telogen to anagen phase (Fig. 1A). Indeed, both the RHSO and MNX groups exhibited gray skin within 7~10 days and visible hair shafts began to appear by day 14 of treatment, while in the control group, hair shafts were only faintly visible. By day 17, the hair regrowth of mice in the RHSO group was remarkable and comparable to that in the MNX group. The hair growth scores in the RHSO group were similar to those in MNX group (Fig. 1B). The hair growth score for RHSO-treated mice was considerably higher than that of the control mice and equivalent to that of the MNX-treated mice after 17 days of treatment. These findings imply that RHSO treatment activates early progression into the anagen phase of hair cycle and shortens the time required for hair growth initiation.

Effect of RHSO on the development and structure of hair follicles

Hair loss is characterized by changes in the hair cycle and the morphology of the hair follicles. These changes include hair follicle miniaturization, a shortened anagen phase, and promotion of the progression of hair follicles to catagen and telogen phases. Consequently, these alterations cause hair thinning and hair loss after several hair cycles (Cotsarelis and Millar, 2001). Therefore, inducing telogen-to-anagen transition, retaining the anagen phase, and reversing follicular miniaturization are effective ap-

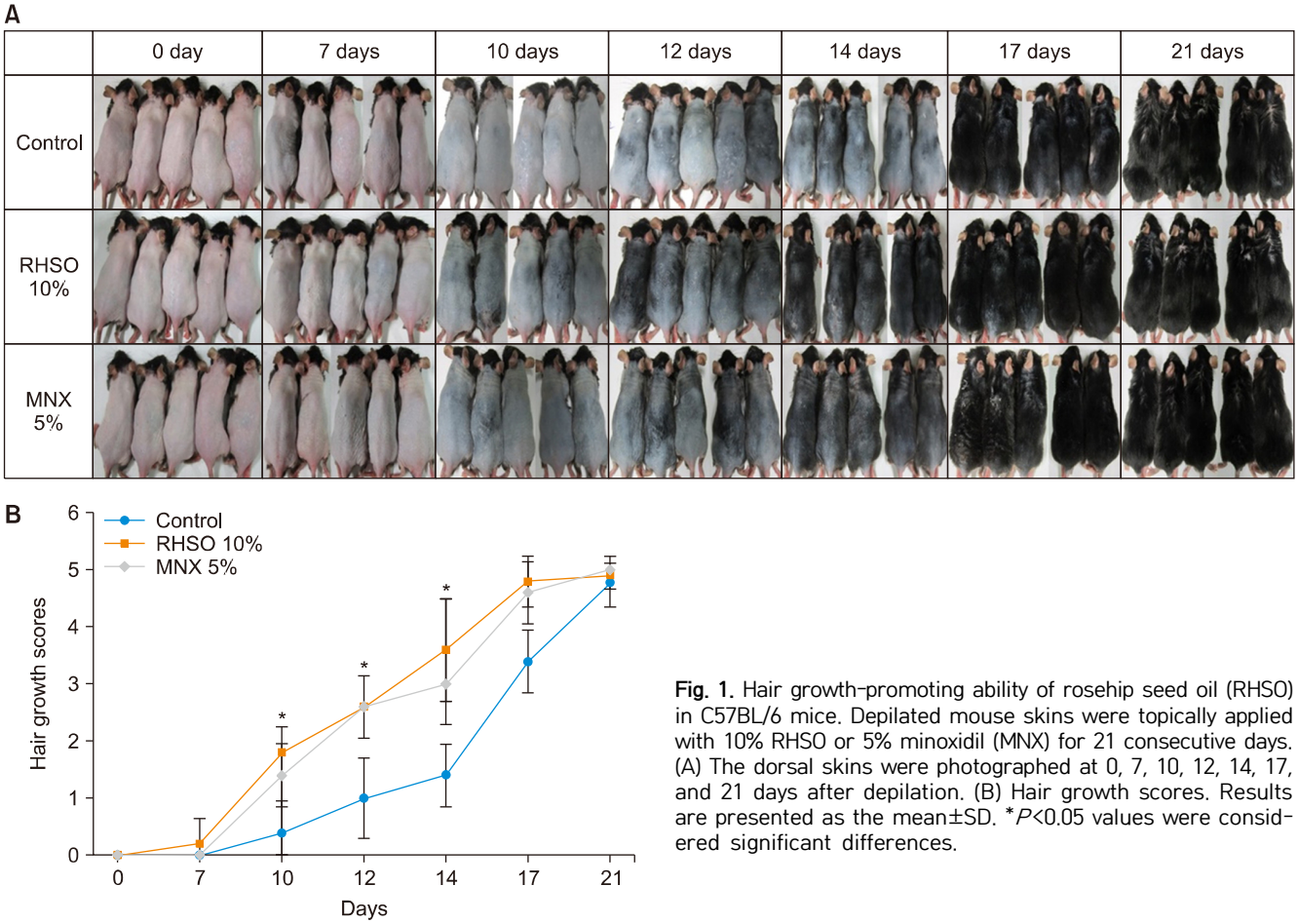

Fig. 1. Hair growth-promoting ability of rosehip seed oil (RHSO) in C57BL/6 mice. Depilated mouse skins were topically applied with 10% RHSO or 5% minoxidil (MNX) for 21 consecutive days. (A) The dorsal skins were photographed at 0, 7, 10, 12, 14, 17, and 21 days after depilation. (B) Hair growth scores. Results are presented as the mean±SD. *P<0.05 values were considered significant differences.

proaches for maintaining heathy hair growth.

The development and structure of hair follicles are markers for the transformation of hair follicles from telogen to anagen phase. At day 14, remarkably visible hair growth was observed in the RHSO-treated mice compared to the control-treated mice. Histological analysis of skin tissues was performed to compare the development of the hair follicles in each group (Fig. 2A). The histophotometric data indicated that topical treatment with RHSO induced earlier telogen-to-anagen transition in the hair follicles compared to control-treated follicles. In RHSO-treated mice, most hair follicles developed fully, with hair roots approaching the subcutaneous tissue, and exhibited growth of the inner and outer root sheaths, with hair shafts erupting out of the epidermis. Furthermore, most hair follicles in the RHSO and MNX groups progressed to the anagen V~VI phase, while the majority of hair follicles in the control mice were in anagen phases III~IV at day 14. Additionally, RHSO treatment led to a substantial increase in the density of hair follicles, the size of hair bulb, and skin thickness compared to the control group (Fig. 2B~2D). Taken together, these results indicate that RHSO promotes the premature transition of hair follicles into the anagen phase of the hair cycle and nourishes the development of hair follicles, thereby augmenting hair regrowth.

Effect of RHSO on expression of genes associated with hair growth

The Wnt/β-catenin and Shh signaling pathways play a pivotal role in regulating follicle development, operating in a coordinated manner to orchestrate the hair cycle and hair growth (Millar, 2002). Therefore, we explored the impact of RHSO on the expression of Wnt/β-catenin pathway-associated genes. RHSO treatment resulted in the upregulation of β-catenin and p-GSK3β expression, compared to the control treatment (Fig. 3A and 3B). However, RHSO failed to induce Lef-1 expression in the dorsal skin (Fig. 3C). Furthermore, RHSO strongly activated the Shh signaling pathway by enhancing the levels of Shh and Smo protein in mouse skin (Fig. 3D and 3E). Consequently, Wnt/β-catenin and Shh target genes, including cyclin D1 and cyclin E were upregulated by the topical application of RHSO (Fig. 3F and 3G).

Wnt/β-catenin signaling is instrumental in commencing the anagen (growth) phase by stimulating the proliferation of hair follicle stem cells and progenitor cells while maintaining the integrity of the follicles (Millar et al., 1999). Meanwhile, the Shh pathway plays a pivotal role in hair follicle development and cycling. During the anagen phase, the activation of Shh signaling contributes to the growth and differentiation of hair follicle cells (St-Jacques et al., 1998; Yu et al., 2019). These two pathways collaborate to support robust hair growth in the anagen phase, while their inhibition is associated with the progression of hair follicles to catagen (regression) and telogen (rest) phases (Millar, 2002). Indeed, previous studies have indicated that epidermal expression of stabilized β-catenin in transgenic mice induced hair follicle development (Lo Celso et al., 2004; Zhang et al., 2008), while β-catenin knockout resulted in a considerable reduction in hair matrix stem cell proliferation and the abolishment of hair follicle regeneration, causing hair loss (Huelsken et al., 2001; Choi et al., 2013). Similarly, Shh overexpression was shown to augment the number of hair follicles in the anagen phase and stimulate hair regrowth in a

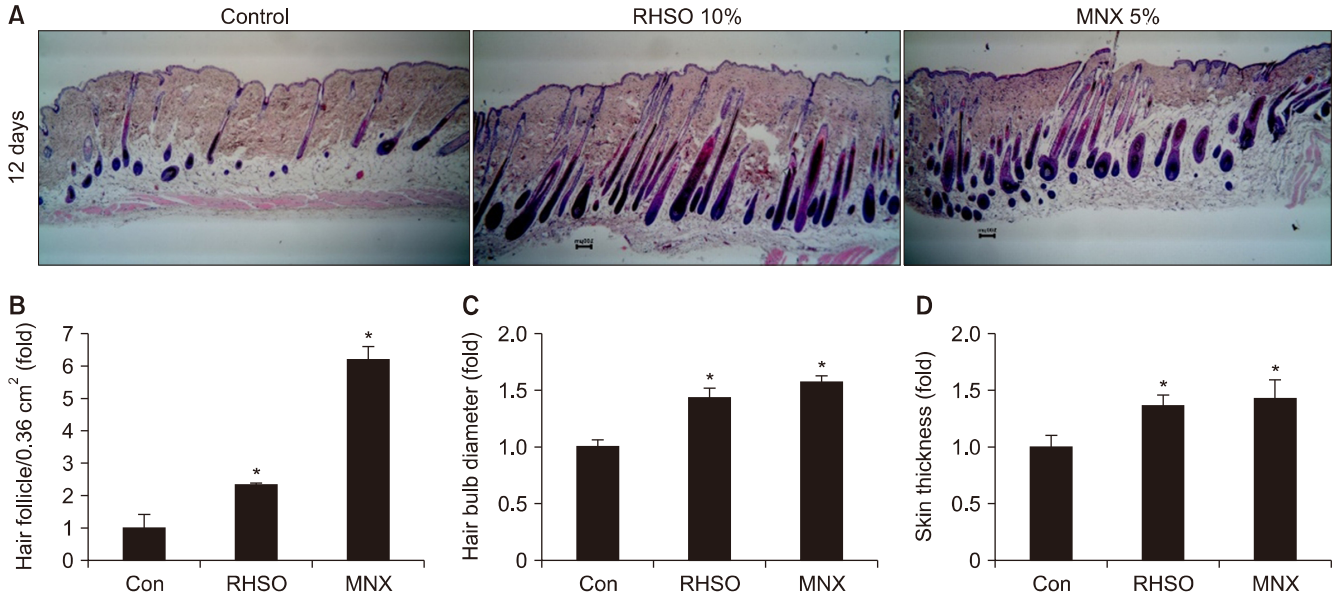

Fig. 2. Effect of rosehip seed oil (RHSO) on the development and structure of hair follicles. (A) Representative hematoxylin and eosin staining images (magnification ×200). (B) Hair follicle density. (C) Hair bulb diameter. (D) Skin thickness. Results are presented as the mean±SD. *P<0.05 values were considered significant differences. MNX, minoxidil.

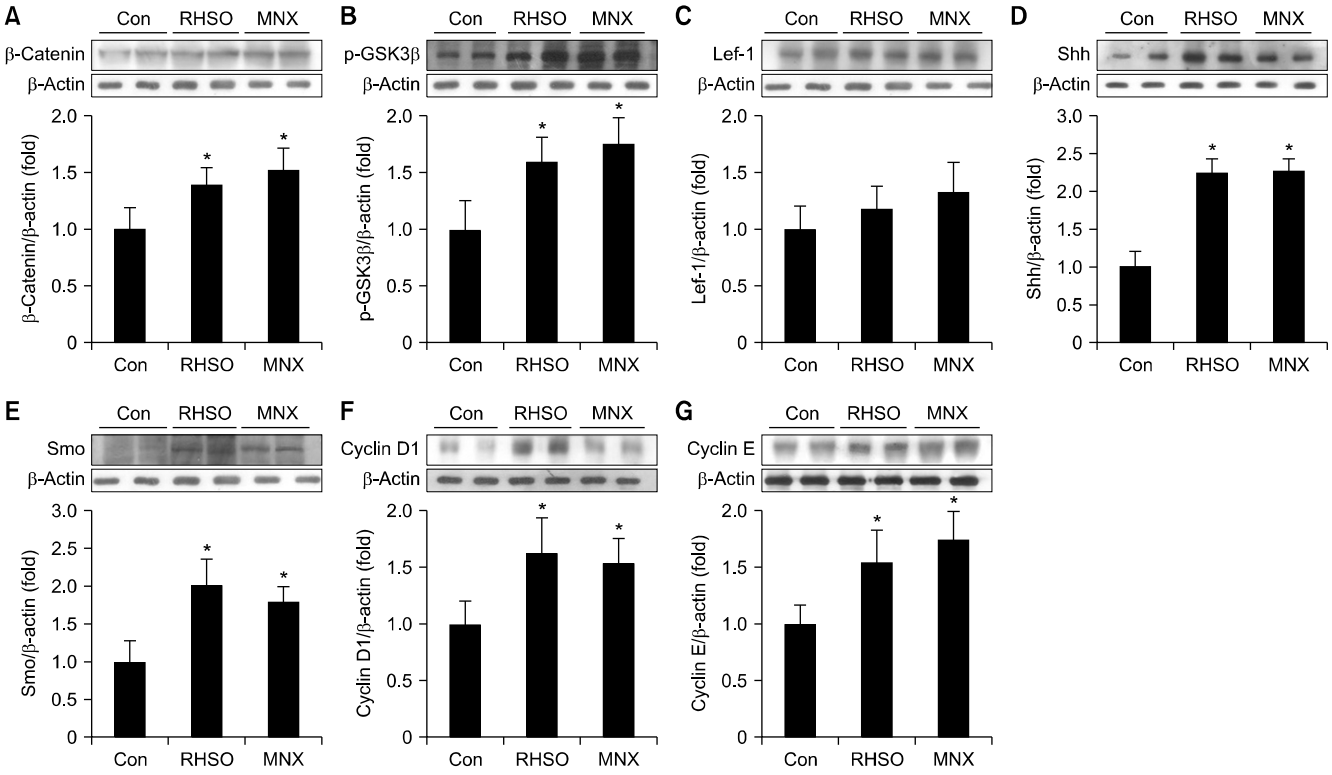

Fig. 3. Effect of rosehip seed oil (RHSO) on the Wnt/β-catenin and Sonic hedgehog (Shh) pathways in C57BL/6 mouse skin. The expressions of β-catenin (A), phospho-glycogen synthase kinase-3 beta (p-GSK-3β) (B), lymphoid enhancer-binding factor 1 (Lef-1) (C), Shh (D), smoothened (Smo) (E), cyclin D1 (F), and cyclin E (G) in mouse skin tissue. Results are presented as the mean±SD. **P*<0.05 values were considered significant differences. MNX, minoxidil.

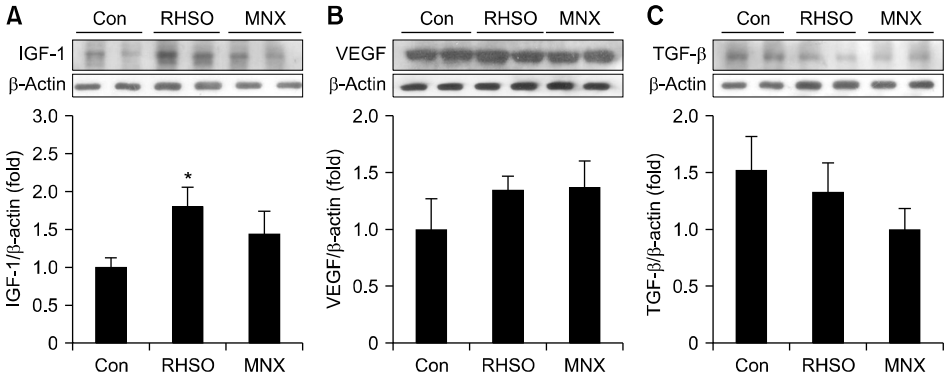

Fig. 4. Effect of rosehip seed oil (RHSO) on the expression of growth factors in C57BL/6 mouse skin. The expressions of insulin-like growth factor 1 (IGF-1) (A), vascular endothelial growth factor (VEGF) (B), and transforming growth factor beta (TGF-β) (C) in mouse skin tissue. Results are presented as the mean± SD. **P*<0.05 values are considered significant differences. MNX, minoxidil.

mouse model of chemotherapy-induced alopecia (Sato et al., 2001). Conversely, the blockage of Shh signaling leads to the development of abnormal hair follicles due to reduced proliferation of dermal papilla cells (St-Jacques et al., 1998; Oro and Higgins, 2003). In addition, the target genes regulated by the Wnt/β-catenin and Shh signaling pathways, such as cyclin D1 and cyclin E, trigger cell cycle progression from G0/1 to S phase, thereby facilitating cell proliferation (Golias et al., 2004).

Numerous growth factors, hormones, and cytokines also play integral roles in the complex process of hair growth (Danilenko et al., 1996). Generally, growth factors such as IGF-1, VEGF, fibroblast growth factor, and keratinocyte growth factors stimulate the proliferation of hair cells, maintain the development of hair follicles, and enhance hair growth and hair shaft elongation. In contrast, other growth factors, such as TGF-β, fibroblast growth factor 5, and prostaglandin D2, can inhibit hair growth (Herman and Herman, 2016; Park and Lee, 2021; Song et al., 2021). The results of the current study indicated that topical application of RHSO enhanced the level of IGF-1 in mouse skins (Fig. 4A). Interestingly, the inductive effect of RHSO on IGF-1 expression was more profound than that of MNX. Although there were no significant differences, RHSO partially changed the expression of the VEGF and TGF-β proteins in mouse skins (Fig. 4B and 4C).

IGF-1 is a fundamental 70 amino-acid peptide that is naturally present in hair follicles. A previous study demonstrated that dermal papilla cells isolated from balding

scalps exhibited lower levels of IGF-1 compared to non-balding scalps (Trüeb, 2018). Through binding to its receptor, IGF-1 can induce the growth, proliferation, and differentiation of matrix hair cells as well as keratinocytes, and thereby promotes follicular development and, consequently, hair growth (Weger and Schlake, 2005; Li et al., 2014). The absence of IGF-1 retains hair follicles in the telogen phase and delays progression to the subsequent anagen phase (Weger and Schlake, 2005). Raspberry ketone has also been suggested to stimulate hair regrowth in both mouse models and human volunteers with alopecia, possibly by increasing the IGF-1 level (Harada et al., 2008). Furthermore, IGF-1 has been shown to reduce the expression of TGF-β, a negative regulator of hair follicle growth (Li et al., 2014).

In conclusion, this study provides novel insights into the hair growth-promoting potential of RHSO. Topical application of RHSO effectively stimulated the transition of hair follicles from the resting (telogen) phase to the active growth (anagen) phase, leading to enhanced hair regrowth in a telogenic mouse model. These positive effects were associated with the activation of key signaling pathways, specifically the Wnt/β catenin and Shh pathways, which are crucial for initiating and prolonging the anagen phase. Additionally, RHSO was found to elevate the IGF-1 level in the skin, further contributing to hair growth. These compelling findings suggest that RHSO holds potential as an agent for the prevention and/or treatment of hair loss, offering promising prospects for those seeking effective solutions to maintain and enhance hair health.

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AUTHOR DISCLOSURE STATEMENT

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Concept and design: VLT, WSJ. Analysis and interpretation: VLT. Data collection: VLT. Writing the article: VLT. Critical revision of the article: WSJ. Final approval of the article: all authors. Statistical analysis: VLT. Obtained funding: WSJ. Overall responsibility: WSJ.

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