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Study on the unique rare ginsenoside formulation in combination with Moxidil for anti-hair loss

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Abstract

Minoxidil is the leading choice for anti-hair loss treatment across the globe. However, it can induce side effects such as scalp inflammation and unwanted facial hair growth. In this case, a safer therapy method is needed. In this study, we introduced a promising alternative to Minoxidil: rare ginsenoside compositions, with similar effects in improving blood circulation and providing essential nutrients to the hair follicles to stimulate new hair growth. Additionally, we innovatively developed a targeted nano-drug delivery system that using rare ginsenosides as the shell of nanoliposomes for anti-hair loss. To assess the efficacy and safety of the rare ginsenoside formulation and Minoxidil, we conducted clinical evaluations with 100 patients with hair loss at a tertiary hospital. Through macro photography and dermatoscopy, we observed marked improvements in hair density and scalp health across all treatment groups after 12 weeks. Impressively, we found similar effectiveness of the rare ginsenoside formulation and Minoxidil when used individually. The combination treatment of the rare ginsenoside formulation and Minoxidil outperformed Minoxidil alone by reducing 80% side effects, indicating ginsenoside offers a more favorable safety profile. The innovative formulation of rare ginsenosides liposome demonstrated a better transdermal absorption compared to traditional liposomes with cholesterol, by facilitating easier penetration through the skin and hair follicles. We have also developed foaming agents in mixture of rare ginsenoside and Minoxidil to prevent unwanted facial hair growth caused by liquid flowing. These results indicate rare ginsenosides are a promising component in hair and scalp care.

Keywords Anti-aging, Hair growth, Scalp

1. Introduction

Hair loss affects about 2% of the global population and is influenced by various factors

including hormone levels, genetic predisposition, oxidative stress, the loss of extracellular matrix proteins in hair follicles, medications, and inflammation. These factors can interact with each other to varying degrees, impacting the hair loss process. This can lead to a shortening of the growth phase of hair, a lengthening of the resting phase, and even damage to the hair follicle, resulting in atrophy.

Applying topical medications for skin absorption is a crucial method for combating hair loss. However, the stratum corneum of the skin acts as a barrier, preventing the effective penetration of active ingredients. This barrier significantly hinders the local delivery of these active ingredients to the skin. Therefore, it is essential to develop a delivery system that enhances the penetration of active ingredients into the stratum corneum, effectively targets the hair follicle, and improves the delivery of ingredients to the hair follicles. Liposomes can enhance the penetration of active ingredients into the skin through several mechanisms, including hydration, direct penetration, fusion, and the pathway of follicular sebaceous glands.

Ginsenoside has a molecular structure similar to cholesterol, allowing it to replace cholesterol and interact with phospholipids in liposomes [1]. When used as a carrier, ginsenoside can create temporary gaps upon contact with cell membranes, facilitating the absorption of active ingredients, and the integrity of the cell membranes can be restored in a relatively short time [2]. Ginsenosides are extracted from the *Panax ginseng*, known for their numerous health benefits. Extensive researches support their potential to promote hair growth. Ginsenosides are mild and non-irritating, and they can help address hair loss through various mechanisms and pathways. By inhibiting the activity of 5 α -reductase, ginsenosides can significantly reduce the production of dihydrotestosterone (DHT), a key factor in hair loss [3,4]. As androgen receptor inhibitors, ginsenosides competitively inhibit the binding of DHT to androgen receptor, negatively regulating downstream pathways associated with hair loss. Ginsenosides can also activate the glucocorticoid receptor to maintain the microenvironment of hair follicle stem cells, promoting hair regeneration [5]. They stimulate the production of vascular endothelial growth factor, dilate blood vessels, enhance the activity of alkaline phosphatase, promote the proliferation of dermal papilla cells, and nourish and revitalize hair follicles. Moreover, ginsenosides enhance collagen synthesis, provide anti-inflammatory and soothing effects, regulate the scalp's circadian rhythm, and reduce emotional stress [6], thereby improving the microenvironment of the scalp and addressing hair loss at its source. Therefore, we propose the use of ginsenosides as carriers to encapsulate active ingredients and prepare ginsenoside liposomes, which can enhance the transdermal absorption of active ingredients, specifically target and increase their penetration into hair follicles, and synergize with other active ingredients to exert both the intrinsic activities of ginsenosides and the functional benefits of the formulation.

Currently, common methods for anti-hair loss include topical Minoxidil application, oral finasteride administration, and laser therapy. The 2940 nm non-ablative fractional erbium-doped glass laser can effectively induce the wound-healing response in the normal scalp surrounding lesions, stimulating the production of growth factors such as fibroblast growth factor and vascular endothelial growth factor to promote hair regeneration. Additionally, fractional lasers can enhance the penetration of topical medications. Although topical Minoxidil is widely used, it is associated with certain adverse effects, such as allergic contact dermatitis, erythema, and pruritus, leading to poor patient tolerance of hair loss treatment. Studies have shown that Minoxidil is less effective in patients with follicular inflammation and may even exacerbate hair loss in some cases. Consequently, there is an urgent demand for safer alternative therapies that can prevent hair loss with minimal side effects. We have conducted clinical trials to evaluate the efficacy and safety of a rare ginsenoside essence (GS, primarily containing rare ginsenosides, Copper Tripeptide-1, Ectoin, and Palmitoyl Tetrapeptide-7), aiming to provide a more effective

and safer reference regimen for the treatment of androgenetic alopecia.

Minoxidil is currently available in three main formulations on the market: liquid (tincture), foam, and gel. The foam formulation of Minoxidil is relatively expensive, while the gel formulation has a sticky texture. Therefore, the liquid Minoxidil tincture remains the primary choice for consumers. However, when applying Minoxidil tincture, it tends to flow to areas where hair growth is not desired, such as the forehead and cheeks, potentially leading to hypertrichosis. To address this issue, we have developed a foaming agent composed of amphiphilic ginsenosides, PEG-10 Dimethicone, and polyalcohol. By using a foaming pressure pump bottle, you can transform a small amount of foaming material mixed with Minoxidil tincture into foam. This method provides good foam stability, preventing the Minoxidil tincture from flowing too quickly. It also helps to avoid unwanted hair growth in areas where it is not desired.

Rare ginsenosides have demonstrated excellent efficacy in anti-hair loss, along with good tolerance and safety. It can be utilized as a carrier for active ingredients, enhancing the transdermal absorption of these substances and improving their penetration into hair follicles. Additionally, rare ginsenosides can work synergistically with other active ingredients. When used in conjunction with Minoxidil, it can enhance treatment effectiveness while also reducing the adverse reactions. In addition, rare ginsenosides can be incorporated into Minoxidil to create a foam, which helps prevent the Minoxidil tincture from flowing too rapidly. This helps avoid unintended hair growth in areas where it is not desired. Therefore, rare ginsenosides show promising potential for use in products aimed at preventing hair loss and improving scalp health.

2. Materials and Methods

2.1 Transdermal absorption of ginsenoside liposomes

To trace the penetration performance of liposomes, we prepared FITC-COL17-loaded ginsenoside liposomes and Nile Red-loaded ginsenoside liposomes. FITC is a water-soluble green fluorescent ingredient, while Nile Red is a insoluble red fluorescent ingredient. We added saline and a magnetic stir bar to the receptor chamber of a Franz diffusion cell. Appropriately sized sections of excised porcine skin (which closely resembles human skin in terms of stratum corneum, epidermal thickness, and hair follicle density) were secured between the receptor and donor chambers of the Franz diffusion cell, with the stratum corneum facing upwards towards the donor chamber. Additional receptor solution was added to ensure intimate contact between the skin and the solution. The diffusion cell was then placed in a transdermal diffusion apparatus. One milliliter of liposomes was added to the donor chamber (all operations were performed under light-protected conditions). The transdermal diffusion apparatus was activated, set to a rotation speed of 350 rpm, and maintained at a constant temperature of $(32 \pm 1)^\circ\text{C}$ in a water bath. After 24 hours of in vitro diffusion, the skin was immediately removed and embedded in OTC embedding medium. The skin tissue was then sectioned longitudinally into 16 μm -thick slices using a cryostat. The slices were stained with DAPI (4',6-diamidino-2-phenylindole, a nuclear fluorescent dye for cell localization, emitting blue fluorescence) and mounted. Fluorescence microscopy was used to observe and photograph the longitudinal sections of the skin, allowing for the comparison of fluorescence intensity differences and the depth of fluorescence penetration into the skin among different groups.

2.2 In vivo clinical evaluation of the efficacy and safety of the rare ginsenosides essence

We conducted a 12-week in vivo clinical study on rare ginsenosides essence at a hospital. All participants in the study were individuals diagnosed with androgenetic alopecia, excluding those with allergies to Minoxidil. All participants provided informed consent before enrollment. The study included 100 participants who were randomly assigned ($n=20$): 1) Topical application of Minoxidil tincture alone (5% concentration); 2) Topical application of rare ginsenosides

essence alone (the main components are protopanaxatriol rare ginsenosides, Copper Tripeptide-1, Ectoin, and Palmitoyl Tetrapeptide-7, with ginsenosides being the primary active ingredient for hair loss prevention); 3) Combined topical application of Minoxidil and rare ginsenosides essence; 4) Combined treatment of topical Minoxidil with 2940 nm fractional laser therapy; 5) Combined treatment of topical rare ginsenosides essence with 2940 nm fractional laser therapy. The treatments were applied twice daily (morning and evening), with 2940 nm laser treatments conducted every two weeks at the dermatology outpatient clinic. Hair density was evaluated by taking photographs of the hair before treatment and at weeks 4, 8, and 12 post-treatment. Trichoscopy was used to observe the scalp, and the scalp color score was assigned to assess scalp health. The scoring criteria were as follows: 0 - orange-red; 1 - red; 2 - pink; 3 - localized blood vessels visible; 4 - normal skin color. After completing treatment, participants were asked about any adverse reactions, such as an oily scalp, itching, or increased dandruff.

2.3 Ginsenoside-mediated foaming of Minoxidil

A foaming material containing ginsenosides (Propanediol, ginsenosides, and a surfactant) was prepared according to the specified formula and mixed with Minoxidil. Using a foam pump dispenser, the samples were converted into foam. Ten pumps of foam were placed in a 100 mL graduated cylinder and gently shaken to allow the foam to settle. The initial foam volume was observed, and the 80% liquefaction time (defoaming time, defined as the time taken for the foam volume to decrease from 10 mL to 8 mL after all 10 pumps of foam had fully liquefied) was recorded.

3. Results

3.1 Transdermal absorption of ginsenoside liposomes

As shown in Figure 1a, a small amount of unencapsulated macromolecule XVII collagen (COL17, water-soluble ingredient) entered the skin tissue through the skin appendage (hair follicle) route. It can be seen from Figure 1c, the weak fluorescence of the free sample and the little distribution in the deeper skin tissues indicated that Nile Red (insoluble ingredient) mostly failed to penetrate through the stratum corneum barrier. Compared with common cholesterol liposomes (C-LPs), ginsenoside liposomes (GS-LPs) had a wider area of fluorescence distribution in deep skin tissues, stronger fluorescence intensity ($p < 0.0001$), and aggregated in the hair follicles, suggesting that rare ginsenoside liposomes can significantly enhance the transdermal permeation and absorption of actives, and can be targeted to the hair follicles to permeate the accumulation. The above results indicate that rare ginsenoside liposomes can significantly enhance the percutaneous permeation and absorption of water-soluble/insoluble active ingredients, and can be targeted to the hair follicle for permeation and accumulation, and their permeation ability is significantly better than that of unencapsulated actives and common cholesterol liposomes.

3.2 In vivo clinical evaluation of the efficacy and safety of the rare ginsenosides essence

It can be seen from the photo that after the treatment, the patient's hair density has increased (Figure 2). Under dermoscopy, it was observed that the condition of scalp inflammation had improved, the diameter of the hair shaft had increased, and the number of hairs had risen (Figure 3-a). Over time, the scalp color scores of patients in each treatment group improved, indicating a reduction in scalp inflammation. Furthermore, there were no statistically significant differences in outcomes among the groups at the same time point. Each treatment method contributed to enhancing scalp health (Figure 3-b), with the rare ginsenoside essence group showing particularly favorable results. Since the 2940 nm fractional laser treatment had little effect on the treatment outcome, only the Minoxidil, rare ginsenosides essence, and the combination of Minoxidil with rare ginsenosides essence were subsequently analyzed in focus.

Using the median as a measure offers a more accurate representation of the conditions experienced by the majority of participants. As shown in Figure 3-d, the median for the rare ginsenoside essence, and the combination of Minoxidil with rare ginsenosides essence was slightly higher, suggesting potentially superior efficacy compared to Minoxidil alone.

We then performed a statistical analysis of the degree of improvement in the scalp color score results to compare the differences between the groups. At 4 weeks, Minoxidil demonstrated better short-term efficacy (Figure 3-e). By 12 weeks, the change in scalp color scores using rare ginsenoside essence was significantly greater than that using Minoxidil ($p < 0.01$). These findings indicate that long-term use of rare ginsenoside essence can achieve comparable results to Minoxidil, and significantly enhance scalp health. Additionally, adverse reactions (e.g., scalp pruritus, dermatitis, and increased dandruff) were analyzed. The adverse reaction rates of using rare ginsenoside essence and the combination of Minoxidil with rare ginsenoside essence were much lower than those of Minoxidil (Figure 3-f), indicating that the use of ginsenoside essence is safer.

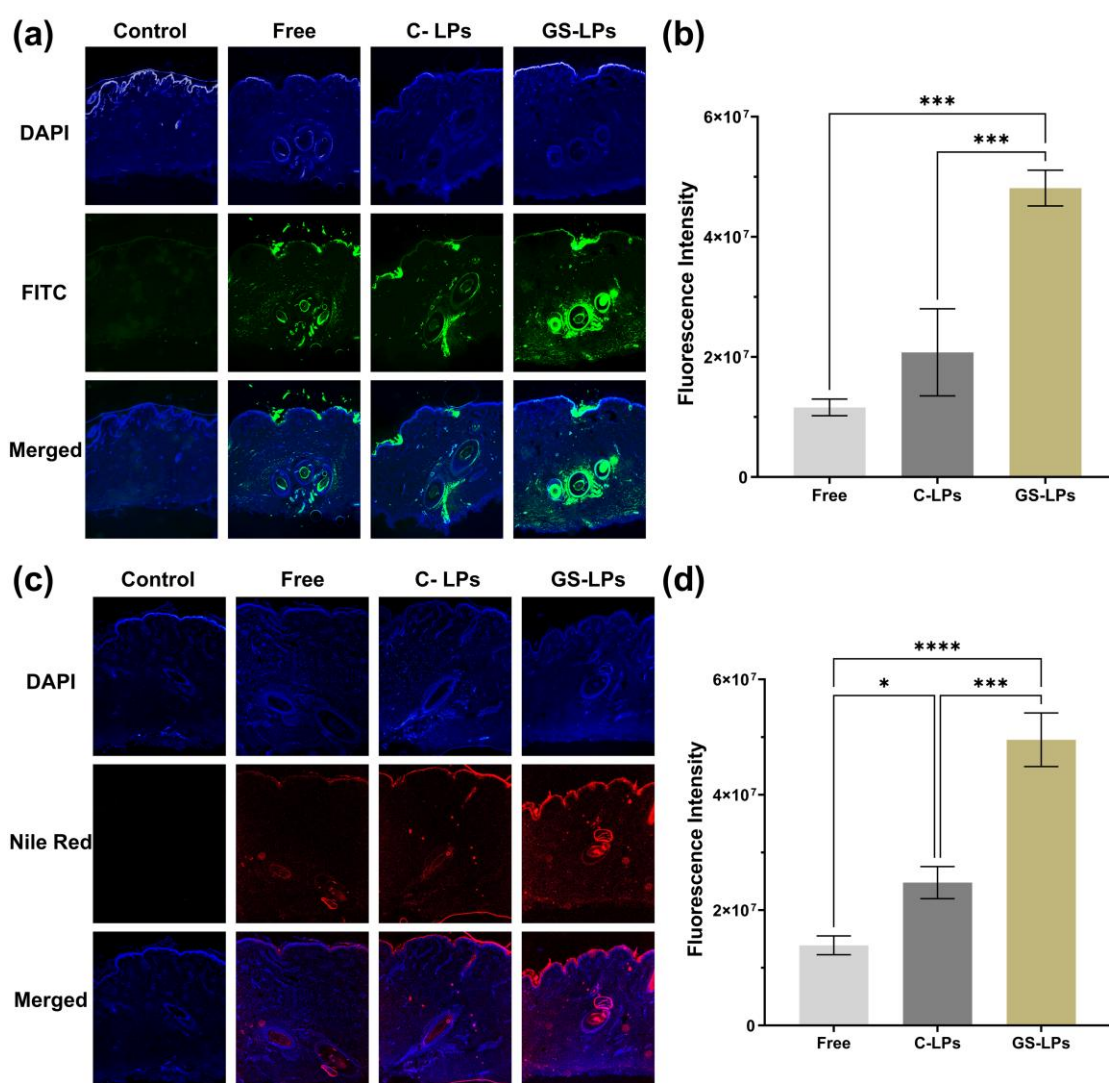


Figure 1. (a) Transdermal absorption fluorescence image of FITC-COL17 (water-soluble ingredient); (b) Analysis of transdermal absorption fluorescence intensity of FITC-COL17; (c) Transdermal absorption fluorescence images of Nile Red (insoluble ingredient); (d) Analysis of transdermal absorption fluorescence intensity of Nile Red, $n = 3$, * $p < 0.05$, *** $p < 0.001$, **** $p < 0.0001$

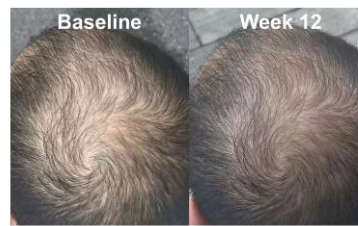


Figure 2. The comparison of photos before and 12 weeks after the combined use of topical Minoxidil and rare ginsenosides essence

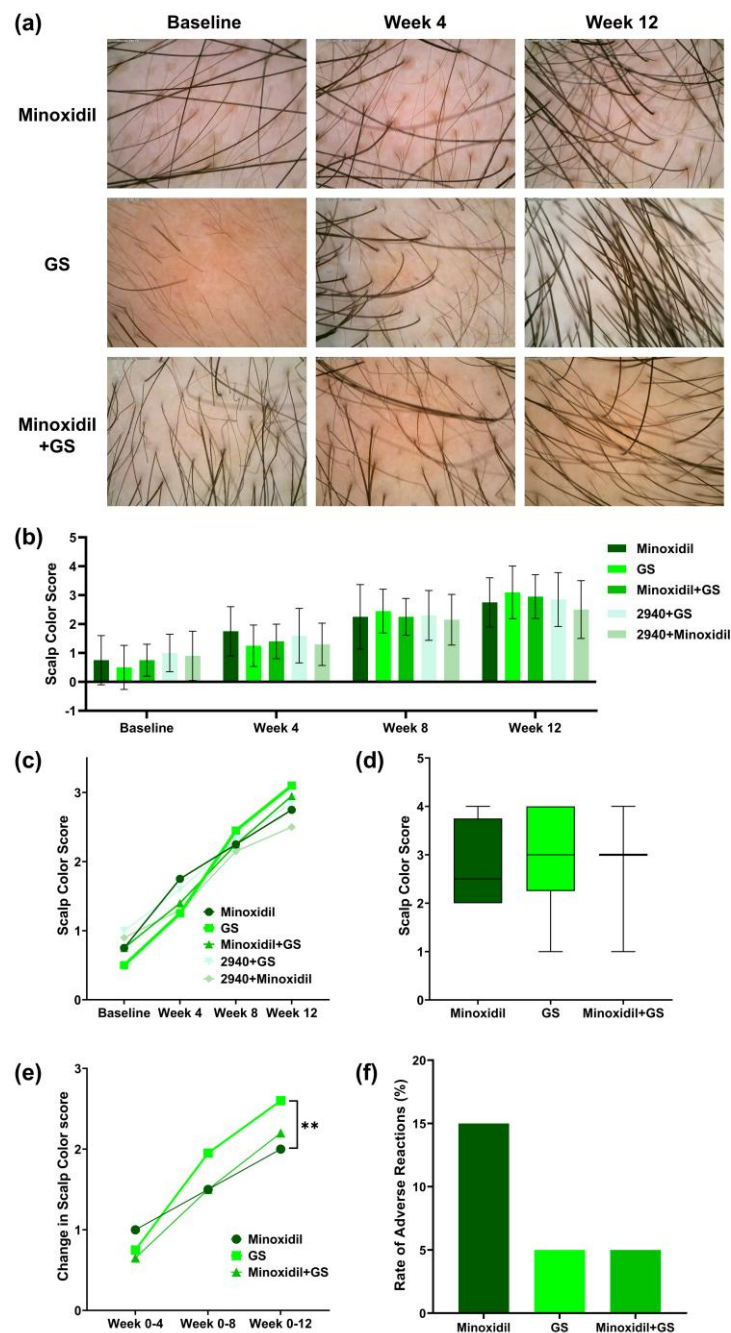


Figure 3. (a) Dermoscopic photos; (b) Scalp color scores at different time points (c) Scalp color scores before and after treatment (d) Distribution of scalp color scores after 12 weeks of treatment (e) Changes in scalp color scores before and after treatment (** $p < 0.01$) (f) Rate of adverse reactions

3.3 Ginsenoside-mediated foaming of Minoxidil

The foam formulation compositions were prepared as outlined in Table 1. A comparison of Sample 1 and Sample 2 indicates that ginsenoside exhibits both foaming and foam-stabilizing properties. Additionally, comparisons among Samples 2 to Sample 6 suggest that when ginsenoside is combined with PEG-10 Dimethicone, it provides excellent foaming and foam-stabilizing performance for Minoxidil.

Table 1. The effects of ginsenosides combined with various surfactants on the foaming properties of Minoxidil

| Sample | Composition | % | Initial Foam Volume (mL) | Liquefaction Time (min) |
|--------|------------------------|------|--------------------------|-------------------------|
| 1 | Propanediol | 6 | 40 | 8 |
| | PEG-10 Dimethicone | 4 | | |
| | Ginsenoside | 0 | | |
| | Minoxidil | 90 | | |
| 2 | Propanediol | 7.5 | 44 | 11 |
| | PEG-10 Dimethicone | 1.25 | | |
| | Ginsenoside | 1.25 | | |
| | Minoxidil | 90 | | |
| 3 | Propanediol | 5.45 | 13 | 2 |
| | Sodium Laureth Sulfate | 3.64 | | |
| | Ginsenoside | 0.91 | | |
| | Minoxidil | 90 | | |
| 4 | Propanediol | 5.45 | 12 | 2 |
| | Polysorbate-20 | 3.64 | | |
| | Ginsenoside | 0.91 | | |
| | Minoxidil | 90 | | |
| 5 | Propanediol | 5.45 | 14 | 2 |
| | Lauryl Hydroxysultaine | 3.64 | | |
| | Ginsenoside | 0.91 | | |
| | Minoxidil | 90 | | |
| 6 | Propanediol | 5.45 | 13 | 2 |
| | Coco-Glucoside | 3.64 | | |
| | Ginsenoside | 0.91 | | |
| | Minoxidil | 90 | | |

4. Discussion

There are numerous causes of hair loss, and the effectiveness of using a single active ingredient is often limited. Ginsenoside liposomes can encapsulate both water-soluble and insoluble active ingredients. Ginsenoside liposomes not only enhance the stability of the active ingredients but also improve their transdermal absorption. Additionally, ginsenoside itself is known for its ability to promote hair growth and its anti-inflammatory and soothing properties. When combined with various active ingredients, rare ginsenosides can create a synergistic effect that

enhances penetration and target hair follicles, making it a promising option in the treatment of anti-hair loss, acne, and folliculitis.

Analysis of the results from in vivo clinical studies reveals differences in the efficacy and safety of various treatments. Minoxidil demonstrated better short-term efficacy at 4 weeks. However, it also had a relatively high incidence of adverse reactions, which could impact patients' compliance with the treatment and their overall satisfaction. In contrast, the long-term use of rare ginsenosides essence, as well as the combination of Minoxidil and rare ginsenosides essence, yielded similar therapeutic effects to Minoxidil. Importantly, the use of rare ginsenosides essence was associated with a lower rate of adverse effects and exhibited better tolerability and safety.

The rare ginsenosides essence presents a valuable treatment option for individuals who prefer herbal. However, this clinical research study has some limitations. The sample may not adequately represent different ethnicities, and the small sample size could impact the generalizability of the results. Additionally, the 12-week duration of the study might not be sufficient to fully evaluate long-term efficacy and safety. On a positive note, rare ginsenosides essence demonstrate a favorable safety profile and tolerability. Future clinical applications should explore combining Minoxidil with rare ginsenosides essence. It is also hoped that these preliminary findings will be confirmed through larger and longer-term clinical trials.

We developed a foaming material that contains amphiphilic rare ginsenosides and PEG-10 Dimethicone. By using a foaming pressure pump bottle, you can transform a small amount of foaming material mixed with Minoxidil tincture into foam. This method provides good foam stability, preventing the Minoxidil tincture from flowing too quickly. It also helps to avoid unwanted hair growth in areas where it is not desired.

5. Conclusion

Rare ginsenosides have demonstrated excellent efficacy in anti-hair loss, along with good tolerance and safety. It can be utilized as a carrier for active ingredients, enhancing the transdermal absorption of these substances and improving their penetration into hair follicles. Additionally, rare ginsenosides can work synergistically with other active ingredients. When used in conjunction with Minoxidil, it can enhance treatment effectiveness while also reducing the adverse reactions. In addition, rare ginsenosides can be incorporated into Minoxidil to create a foam, which helps prevent the Minoxidil tincture from flowing too rapidly. This helps avoid unintended hair growth in areas where it is not desired. Therefore, rare ginsenosides show promising potential for use in products aimed at preventing hair loss and improving scalp health.

Conflict of Interest Statement

The authors declare no conflict of interest.

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