

Promoting Effect of a Mixture of 8 Herbal Extracts (SPELA 707) on Hair Growth

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In Korean folk medicine, several herbs, *Glycyrrhizae Radix*, *Persicae Semen*, *Salviae Radix*, *Angelicae Gigantis Radix*, *Zanthoxyli Fructus*, *Ginseng Radix Alba*, *Cnidii Rhizoma*, and *Carthami Flos*, are known to enhance blood circulation and have wound healing or anti-inflammatory effects. These pharmacological actions prompted us to investigate whether these herbs might stimulate hair growth. Thus, using a mixture of their extracts called SPELA 707, we investigated their effects and found that SPELA 707 possessed significant hair cycle converting activity from the telogen phase to the anagen phase in C3H mice. Furthermore, we found that SPELA 707 enhanced the hair density in subjects with hair loss and also promoted the conversion of hair into the anagen phase in subjects with androgenetic alopecia. In addition, hair growth promotion effect of SPELA 707 occurred through inhibition of steroid 5 α -reductase activity, which is known to block hair growth. Taken together, these results suggest that SPELA 707 has a potential to be used for the treatment of hair loss.

Key Words: Hair growth, Androgenetic alopecia, C3H mouse, Phototrichogram, Steroid 5 α -reductase

INTRODUCTION

Hair loss, regardless of its type, is a common and distressing phenomenon. Recently, there has been increasing number of people suffering from hair loss or thinning. Thus, it is very important to develop new therapeutic materials to prevent hair loss and to enhance hair growth. Since ancient times, many chemicals have been tried to cure baldness, however, only two drugs so far have been approved for hair loss treatment by the Food and Drug Administration (FDA, U.S.A); i.e., minoxidil and finasteride. Minoxidil was originally synthesized as a potassium channel opener and was further developed as an anti-hypertensive. However, it was also found to stimulate the growth of hair follicle cells *in vitro* (Tannigaki-Obana et al, 1992), and to have hair cycle converting activity *in vivo* (Uno et al, 1985). Nevertheless, its exact mechanism has not been clearly elucidated. Finasteride is a type II 5 α -reductase inhibitor, and it was initially used for curing prostatic hypertrophy (Dallob et al, 1994; Gormley, 1995) and later found to stimulate hair growth (McClellan and Markham, 1999; Whiting, 2001). In spite of its prominent hair growing effect, its use is limited because of potential side effects, especially in women (Price VH, 1999).

Attempts have been focused to discover effective materials for hair loss treatment. For instance, procyanthocyanidins extracted from grape seeds were reported to induce hair

growth (Takahashi et al, 1998), and extract of *Sophora flavescens* has been reported to promote hair growth (Roh et al, 2002).

In Korea folk medicine, several herbs, including *Glycyrrhizae Radix*, *Persicae Semen*, *Salviae Radix*, *Angelicae Gigantis Radix*, *Zanthoxyli Fructus*, *Ginseng Radix Alba*, *Cnidii Rhizoma*, and *Carthami Flos*, are known to have pharmacological activities: *Glycyrrhizae Radix*, anti-inflammatory activity (Amagaya et al, 1984); *Persicae Semen*, vasodilatory effect and anti-allergic activity (Kim, 2001); *Salviae Radix*, vasodilatory (Nagai et al, 1996) and wound healing effects (Shi et al, 2000); *Angelicae Gigantis Radix*, anti-inflammatory (Hu et al, 1991), vasodilatory and blood circulation enhancing effects (Kim et al, 2000); *Zanthoxyli Fructus*, anti-bacterial activity (Kim, 2001); *Ginseng Radix Alba*, cell regeneration effect (Takeda et al, 1982; Yonezawa et al, 1985; Jiang & Qian, 1995); *Cnidii Rhizoma*, vasodilatory and blood circulation enhancing effects (Kim, 2001); and *Carthami Flos*, analgesic and blood circulation enhancing effects (Kim et al, 2000). Because of their pharmacological actions, we speculated a possibility that a mixture of these herbs might stimulate hair growth. Therefore, in the present study we examined the effect of a mixture of herbal extracts called SPELA 707 (commercial name by SPELA Co. Ltd., Korea) on hair growth in both C3H mice and human subjects. Thus, we analyzed quantitatively the rate of hair growth to evaluate the efficacy of SPELA 707. We also examined the effect of SPELA 707 on steroid 5 α -reductase which

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ABBREVIATIONS: DHT, dihydrotestosterone; PTG, phototrichogram.

catalyzes the conversion of testosterone into more potent androgen, dihydrotestosterone (DHT). This enzymatic reaction has been suggested to be associated with diseases such as benign prostatic hyperplasia (BPH), prostatic carcinoma, androgenetic alopecia, and hirsutism in women (Bingham and Shaw, 1973; Kuttann et al, 1977; Wilson, 1980). We report herein that SPELA 707 had a hair cycle converting activity and its effect on the hair growth promotion occurred partly by inhibiting steroid 5 α -reductase. The results, therefore, suggest a potential of SPELA 707 for curing androgenetic alopecia.

METHODS

Preparation of SPELA 707

SPELA 707 (SPELA Co. Ltd., Korea) is composed of eight herbs, namely *Glycyrrhizae Radix*, *Persicae Semen*, *Salviae Radix*, *Angelicae gigantis Radix*, *Zanthoxyli Fructus*, *Ginseng Radix Alba*, *Cnidii Rhizoma*, and *Carthami Flos*. *Angelicae gigantis Radix* and *Cnidii Rhizoma* were extracted by distilled water (D.W), *Glycyrrhizae Radix*, *Salviae Radix*, *Zanthoxyli Fructus*, *Ginseng Radix Alba*, and *Carthami Flos* by 100% ethanol and persic oil. Water, ethanol, and oil extracts were mixed at a ratio of 30 : 30 : 30 (by vol.), and the total volume was adjusted to 100 by adding 10 vol. of water.

Assessment of hair growth using a global photography

One hundred and eighty eight volunteers with hair loss, who were in good health and between ages of 7 and 60 years old, participated in this test. Clinical experiments were performed in accordance with the Guidelines for Clinical Experiments issued by the Ethics Committee of Seoul National University. A global photograph of a subject with hair loss was used to record the subject's state (Douglas, 1996): The subject was advised to maintain the same hair style and color, and a stereotatic camera precisely aligned the subject's head and allowed consistent pictures for precise judgment of hair density. SPELA 707 was applied to the hair loss area twice a day for 0.5 to 2 years, and hair growth was observed and photographed every 4 weeks.

Test for hair-growing activity to induce anagen phase in mice

Using 8-week old male C3H/HeSlc mice (Jung-Ang Lab Animal, Inc., Korea), the hair-growing activity to induce the anagen phase was performed, as previously described (Hattori & Ogawa, 1983). Animal experiments were performed in accordance with the Guidelines for Animal Experiments issued by the Ethics Committee of Seoul National University. These mice had follicles synchronized in the telogen stage (Hattori and Ogawa, 1983; Maurer et al, 1997), and the hair on the back of each mouse was shaved with an electric clipper so as not to injure or stimulate the skin. Mice without visible scratches were randomly selected and separated into 3 groups (n=12). One hundred microliters of 30% ethanol as control, SPELA 707, and 3% minoxidil (Hyundaipharm Co. Ltd., Korea) were topically applied to the shaved area once a day for 20 days. Hair regrowth was examined and photographed on the 21 days after shaving.

Quantification of hair growth using a phototrichogram method

Phototrichogram (PTG) was used for the study of hair cycles (Saitoh et al, 1970). With this technique, the hairs are clipped and the area is landmarked. After 2 or 3 days a photograph is taken again, to show the number of actively growing (anagen) hair in relation to the non-growing (telogen) hair. This procedure is repeated after several months to monitor the effect of treatment. Two photographs of the same area were taken at different times, and superimposed. Each hair was marked and numbered. Its status was determined over the course time; each hair was examined whether it is the anagen, initial/final anagen, or telogen phase. By this way, each hair can be identified, and its growth can be monitored over the course of time.

Thirty-one male volunteers between the ages of 30 and 60 years old with androgenetic alopecia, who were in good health, participated in this test. Volunteers were divided into two groups: 7 subjects were placed in the control group, and 24 subjects in the SPELA 707 treatment group. A 1 cm² area of the scalp on the vertex was delineated, and the hair within this area was shaved. This area was marked by a micro-tattoo, and then SPELA 707 was applied to the shaved area twice a day for 2 to 11 months. PTG was recorded every 4 or 6 week.

Assay of rat prostatic 5 α -reductase

Preparation of rat prostatic homogenates and steroid 5 α -reductase assay were carried out according to the method previously described (Liang et al, 1985) with slight modifications. Briefly, male Sprague-Dawley rats (8 weeks old, Dae-Han Lab Animal Center, Korea) were sacrificed with ethyl ether. The ventral prostates were removed, and homogenized rapidly in 4 times volumes of ice-cold homogenizing buffer (0.32 M sucrose, 0.1 mM dithiothreitol and 20 mM sodium phosphate buffer, pH 6.5) with a Dounce homogenizer (Wheaton) at 4°C. The amount of protein was determined by the bicinchoninic acid method using bovine serum albumin as standard (Smith et al, 1985). Homogenates were stored at -70°C until use. The steroid 5 α -reductase activity assay was carried out in a final volume of 500 μ l containing 1 mM dithiothreitol, 40 mM sodium phosphate buffer (pH 6.5), 50 μ M NADPH, 2.2 nM [1, 2, 6, 7-³H] testosterone (2.6~3.9 TBq/mmol, Amersham Pharmacia Biotech) and prostatic homogenate (800 μ g of protein) in the presence of 10 μ l each of 30% ethanol, SPELA 707 or 2 mg/ml finasteride (Propecia, commercial name by Merck, Korea). The reaction mixture was incubated for 30 min at 37°C, and the reaction was stopped by adding 1 ml of ice-cold ethyl acetate. The ethyl acetate phase was then transferred to another tube and evaporated to dryness. The residue obtained was dissolved in ethyl acetate and spotted on a thin-layer chromatography plastic sheet (Kieselgel 60 F₂₅₄, Merck) and then developed in ethyl acetate/cyclohexane (1 : 1, v : v). The areas corresponding to radiolabelled testosterone and dihydrotestosterone were cut out and soaked in scintillation cocktail, and radioactivity was measured using a scintillation counter (Packard).

RESULTS

SPELA 707 enhances the hair growth in subjects with hair loss

As a preliminary examination in this study, we examined whether SPELA 707 promoted hair growth in men with hair loss, using a global photography method. As shown in Fig. 1, the subjects were treated with SPELA 707 for short (0.5~1 year) or long terms (1~2 years). A total of 188 subjects participated in this test. SPELA 707 exhibited a positive response; in other words, increased hair growth in 58% of those subjects. Representative cases of positive response are presented in Fig. 1 with photograph taken at time 0 and at the last day of SPELA 707 application, and these results demonstrate that SPELA 707 increased hair density.

SPELA 707 stimulates anagen phase induction in C3H mice

To investigate whether anagen phase induction was stimulated by SPELA 707, we evaluated hair-growing activity in C3H mouse. C3H mouse dorsal hair is known to have a time-synchronized hair growth cycle (Hattori and Ogawa, 1983). The old dorsal hairs were from 2.5 to 3.5

weeks old or 5 to 14 weeks old; hairs from 0 to 2 weeks or 4 to 4.5 weeks were in the anagen phase. The telogen phase can easily be recognized by the presence of pink skin, and the anagen phase by gray skin. SPELA 707 and minoxidil were topically applied to mice of between 8 to 10 weeks old during the second telogen phase, and hair-covered area was evaluated 21 days later. As shown in Fig. 2, the control group showed little hair growth. On the other hand, most of the shaved area of the mice treated with 3% minoxidil was covered with hair. C3H mice treated with SPELA 707 showed extensive hair growth after 21 days, and this growth was very close to that achieved by minoxidil. Moreover, no inflammation or stimulation was observed in any of the groups. Therefore, these results demonstrate that SPELA 707 possesses marked hair-growth promoting activity and that it induces the anagen phase in C3H mice in vivo without any visible side effects.

SPELA 707 accelerates the conversion of hair to anagen phase

Next, we assessed whether SPELA 707 increased anagen hair in men with androgenetic alopecia using a phototrichogram technique (Fig. 3A), and the results are summarized Table 1. Number of hair and the anagen to total hair ratio decreased by 13.9% and 5.5% in the control

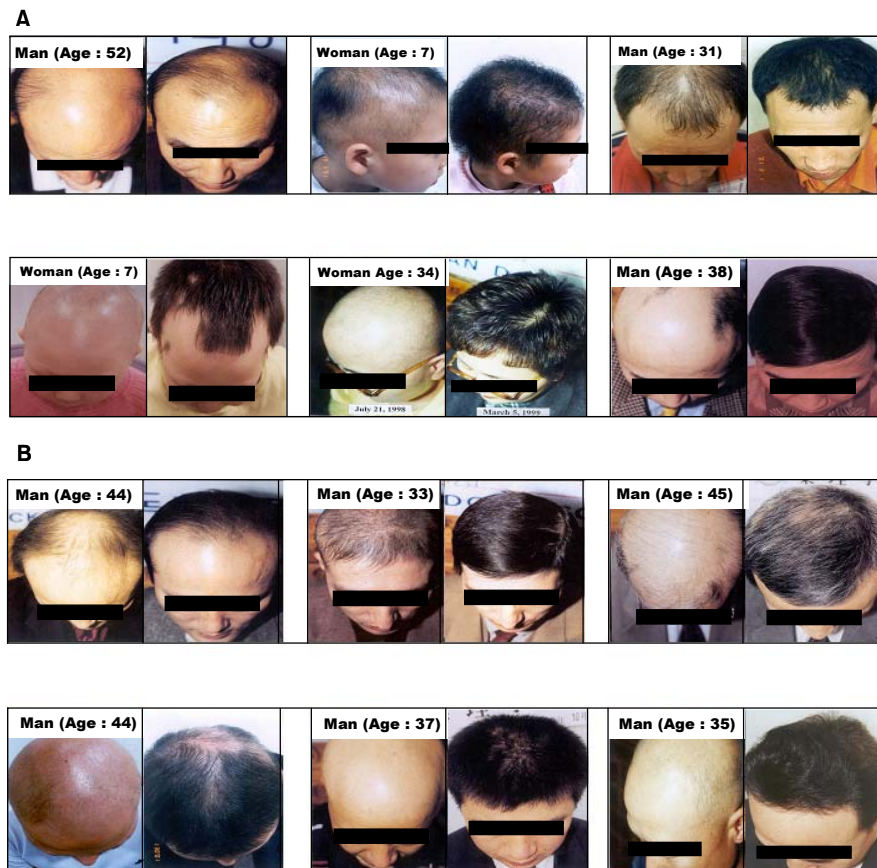


Fig. 1. SPELA 707 enhanced the hair growth in subjects with hair loss. Subjects of various ages, suffering from hair loss, were treated with SPELA 707 for 6 months to 1 year (A), and for 1 to 2 years (B). Representative 12 cases are presented. The photographs of hair loss area were taken before and after SPELA 707 application.

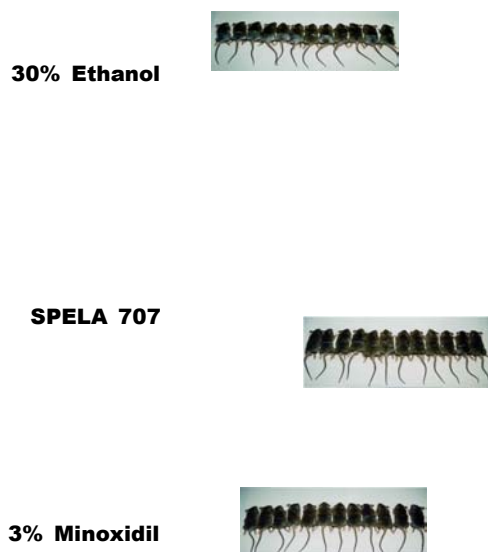


Fig. 2. SPELA 707 induced the anagen phase in C3H mice. Photographs of mice were taken after topical application of 30% ethanol as control, SPELA 707, and 3% minoxidil for 21 days. These agents were applied to shaved area of 8-week old C3H mice at 100 μ l/day.

group, while the respective values in the SPELA 707 group increased by 28.8% and 21.4%. At day 154, the SPELA 707 group had an improvement in number of hair and the anagen to total hair ratio by 42.7% and 26.9%, compared with control. In addition, 95.8% of the subjects (23 out of 24) in the SPELA 707 group obtained the positive response, whereas 85.7% of the subjects (1 out of 7) in the control group obtained the negative response. Thus demonstrating that SPELA 707 increased number of hair and the anagen to total hair ratio. The result also showed that SPELA 707 promoted the conversion of hair follicles into the anagen phase in the subjects with androgenetic alopecia.

SPELA 707 inhibits steroid 5 α -reductase activity

We examined whether SPELA 707 had an inhibitory activity on steroid 5 α -reductase. Steroid 5 α -reductase in the nuclear membrane fraction of prostate time-dependently converted testosterone into DHT, and maximal activity was observed at pH around 6.5 with 2 nM testosterone. Therefore, we examined whether SPELA 707 dose-dependently inhibited steroid 5 α -reductase in the presence of 2 nM testosterone at pH 6.5. As shown in Fig. 4A, SPELA 707 inhibited the steroid 5 α -reductase activity in a dose-dependent manner, and abolished almost 100% activities. The inhibitory activity of SPELA 707 was similar to that of Propecia.

We next determined which fraction of SPELA 707 contained active components. As shown in Fig. 4B, ethanol and oil fractions inhibited the steroid 5 α -reductase activity to the extent similar to that by SPELA 707; water fraction by 7.5%. Thus, these results demonstrate that SPELA 707

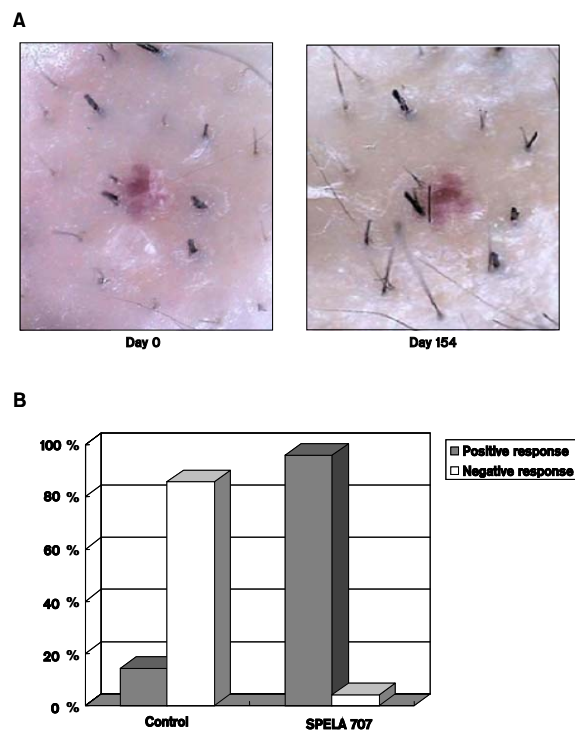


Fig. 3. SPELA 707 increased the total number of hair. The number of the anagen hair at a site was increased by SPELA 707 treatment. (A) Photographs were taken at day 0 and 145 after the initiation of SPELA 707 treatment. (B) Each hair was numbered, and its status was determined over the course time; each hair was examined whether it is the anagen (●), initial/final anagen (•), or telogen (○) phase.

inhibited steroid 5 α -reductase activity in vitro, and that the active components appeared to exist in the ethanol and oil fractions.

DISCUSSION

This study demonstrated that SPELA 707 possesses hair-cycle converting activity in a murine model, and that its activity is similar to that of minoxidil. Moreover, SPELA 707 was also found to promote conversion of hair into the anagen phase in men with androgenetic alopecia, and the hair growth effect of SPELA 707 occurred through inhibition of steroid 5 α -reductase activity.

SPELA 707 is a mixture of eight herbal drugs extracts, namely *Glycyrrhizae Radix*, *Persicae Semen*, *Salviae Radix*, *Angelicae Gigantis Radix*, *Zanthoxyli Fructus*, *Ginseng Radix Alba*, *Cnidii Rhizoma*, and *Carthami Flos*. It has been reported that these herbs possess vasodilatory, wound healing, anti-inflammatory, cell regeneration, anti-bacterial, anti-allergic or analgesic effects. Because of their pharmacological actions, we speculated that these herbs might promote hair growth, and we now demonstrated that SPELA 707 possesses hair-cycle converting activity in C3H mice *in vivo*, which was similar to the effect of minoxidil. Furthermore, SPELA 707 increased total hair count by increasing the number of anagen hair. These phototrichogram measurements provided direct evidence

Table 1. Summary of the hair growth promoting effect of SPELA 707: results of phototrichographic observations

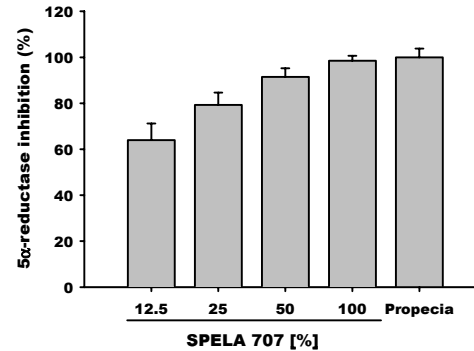
Control				
No. of subjects: 7 (man)				
Average age: 42				
Items	Days			
	0	154		
No. of follicles	17.7	17.7	No change	
No. of hairs	26.7	23.0	13.9% decrease	
Anagen/ total hairs (%)	70.9	65.4	5.5% decrease	
Response of each subjects	Total: 7, positive: 1, negative: 6		85.7% decrease	
SPELA 707 Group				
No. of subjects: 24 (man)				
Average age: 42				
Items	Days			
	0	154		
No. of follicles	19.0	19.0	No change	
No. of hairs	23.3	30.0	28.8% increase	
Anagen/ total hairs (%)	58.0	79.4	21.4% increase	
Response of each subjects	Total: 24, positive: 23, negative: 1		95.8% increase	
Control vs SPELA 707 Group				
Items	Group	Control	SPELA 707 Group	Group difference
No. of hairs		-13.9%	28.8%	42.7%
Anagen/total hairs (%)		-5.5%	21.4%	26.9%

that SPELA 707 promoted the conversion of hair follicles into the anagen phase in men with androgenetic alopecia. Furthermore, these positive changes indicate that SPELA 707 brought about favorable effects on hair quality (increase in density, thickness, length, growth rate, and/or growth duration), which eventually contribute to the visible improvement.

The role of steroid 5 α -reductase in the regulation of hair growth is well recognized (Schweikert et al, 1974). It has been reported that metabolism of testosterone in hair is different depending on their androgen sensitivity within body sites, and the steroid 5 α -reductase in the hair plays a central role in the conversion of testosterone to dihydrotestosterone (Hoffmann, 2001). Thus, the steroid 5 α -reductase is considered to be one of the most important targets for developing drugs for treatment of hair loss. In this regard, it is noteworthy that SPELA 707 has an inhibitory effect on the steroid 5 α -reductase activity. This result is consistent with the increase in the anagen hair and reduction in the telogen hair count in subjects with androgenetic alopecia.

In conclusion, we have demonstrated that SPELA 707 has a potent hair growth promoting effect, and that its effect occurs partly through the inhibition of steroid 5 α -reductase. We suggest that SPELA 707 would be a good candidate for curing hair loss. We are now in a process to identify the active ingredients in SPELA 707 and further improve their efficacy. In addition, we are trying to

A



B

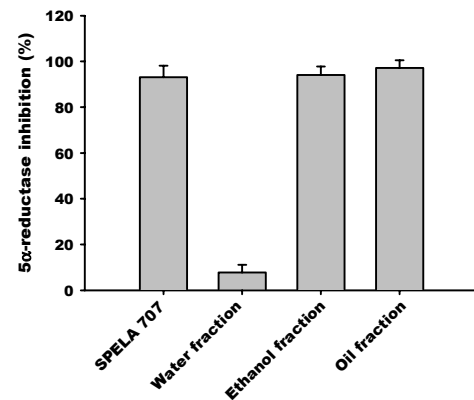


Fig. 4. SPELA 707 inhibited steroid 5 α -reductase activity, and the active components of SPELA 707 existed in the ethanol and oil fractions. (A) Steroid 5 α -reductase inhibition was measured using prostatic homogenate of Sprague-Dawley rat, as described in Methods. After enzyme reaction finished, steroids were extracted, separated on TLC plastic sheet, and then developed in ethyl acetate/cyclohexane. Inhibition ratio in the conversion of testosterone to dihydrotestosterone (DHT) was calculated and expressed as a percentage of control. (B) The inhibitory effect on 5 α -reductase activity by fractions prepared from SPELA 707 was compared. Each column represents the mean S.E. of three experiments.

elucidate its mechanism in the regulation of hair growth.

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