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RESEARCH PAPER

Camellia japonica seed extract promotes hair growth by preventing dermal papilla cell senescence and activating hair follicle stem cells

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Abstract

Camellia japonica has various beneficial effects on the skin and hair; hence, it is widely used for hair care. However, the cellular mechanism(s) underlying these effects remains elusive. In this study, we aimed to confirm the efficacy of *C. japonica* seed extract (CJSE) in promoting hair growth and determine the action mechanism. CJSE was prepared using *Camellia* seed cake, and the components were analyzed through high-performance liquid chromatography. CJSE and its main components, camelliasaponins B1 and B2, significantly promoted the proliferation of human hair follicle dermal papilla cells and hair elongation in cultured human hair follicles. They also prevented cellular senescence and DNA damage caused by a hair loss-inducing factor, dihydrotestosterone (DHT), via the p16 ^{INK4a}-pRb pathway in human hair follicle dermal papilla cells. Moreover, CJSE restored the activities of human hair follicle stem cells (HFSCs) repressed by a DHT-treated dermal papilla cell-conditioned medium. It also directly activated human HFSCs by downregulating p21 expression. A clinical trial involving patients with pattern hair loss showed a significant increase in total hair count in the CJSE-treated group after 24 weeks. CJSE stimulates hair growth by preventing premature senescence of human hair follicle dermal papilla cells and upregulating the activation of human HFSCs. These results suggest that CJSE can be used as a novel functional ingredient for preventing male and female pattern hair loss.

Keywords *Camellia japonica* · Cell culture · Chemical analysis · Hair growth

1 Introduction

Alopecia is a disorder characterized by abnormal hair loss and thinning in a defined pattern [1]. Various inducers, including dihydrotestosterone (DHT) and environmental factors such as ultraviolet irradiation, oxidative stress, and stress hormones, stimulate alopecia. When a stimulus triggers DNA damage in human dermal papilla cells (hDPCs), the cell cycle is interrupted in response to premature senescence. DHT has been shown to accelerate premature senescence in hDPCs, leading to the expression of senescence-associated beta-galactosidase (SA β-gal), p16^{INK4a}, and the DNA damage marker γ-H_2AX [1–4]. The intricate interplay between hair follicle stem cells (HFSCs) and hDPCs, known as epithelial–mesenchymal interaction, regulates the developmental morphogenesis and growth of hair follicles [5–8]. HFSCs are a type of adult stem cells that can differentiate into various cell types within the hair follicles to produce and maintain a hair shaft by interacting with hDPCs. HFSCs can be inactivated by various factors, including androgens [9], radiation, and reactive oxygen species [10–12], which can induce hair loss. Recent studies have reported that p21 is an important factor for proliferative quiescence in HFSCs and acts as a cell cycle inhibitor [13, 14]. Although dermal papilla cell senescence and HFSC inactivation are crucial factors in hair loss, no effective therapeutic drugs have been identified to promote their recovery.

Camellia japonica L. (Theaceae) is a perennial shrub found in China, Taiwan, Korea, and Japan. Camellia oil, extracted from *C. japonica* seeds, has a high oleic acid content (85–90%) and is widely used in cosmetics and food.

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However, after oil extraction, the cakes are discarded as waste. *C. japonica* seed cakes contain various biologically active compounds [15]. *Camellia oleifera* seed cake extracts reportedly promotes hair growth [16, 17]. However, the effects and underlying cellular mechanism(s) of *C. japonica* seed extract (CJSE) on hair growth remain to be elucidated. Therefore, in this study, we aimed to evaluate the hair growth efficacy and elucidate the molecular mechanism of *C. japonica* seed cake extract using hDPCs, HFSCs, and human hair follicles (hHFs) and conducting a clinical trial.

2 Materials and methods

Detailed experimental methods are presented in the Online Resources (Supplementary Materials and Methods).

2.1 Sample preparation and analysis

CJSE was prepared by extracting the seed cake of *C. japonica* obtained from Jeju Island. We obtained *C. japonica* seed saponin fraction after several filtration steps, followed by solvent and column separation steps. Camelliasaponins in *C. japonica* seed saponin fractions were analyzed using high-performance liquid chromatography (HPLC) with diode array detection and evaporative light scattering detection with a C18 column (250 mm × 4.6 mm I.D., 5 µm, Luna C18(2); Phenomenex). The mobile phase comprised acetonitrile and 0.01% aqueous trifluoroacetic acid. The powdered saponin fraction was dissolved in 50% aqueous ethanol to prepare 10% CJSE solution for use in in vitro experiments. The detailed extraction procedure and HPLC analysis conditions are described in the Online Resources (Supplementary Materials and Methods).

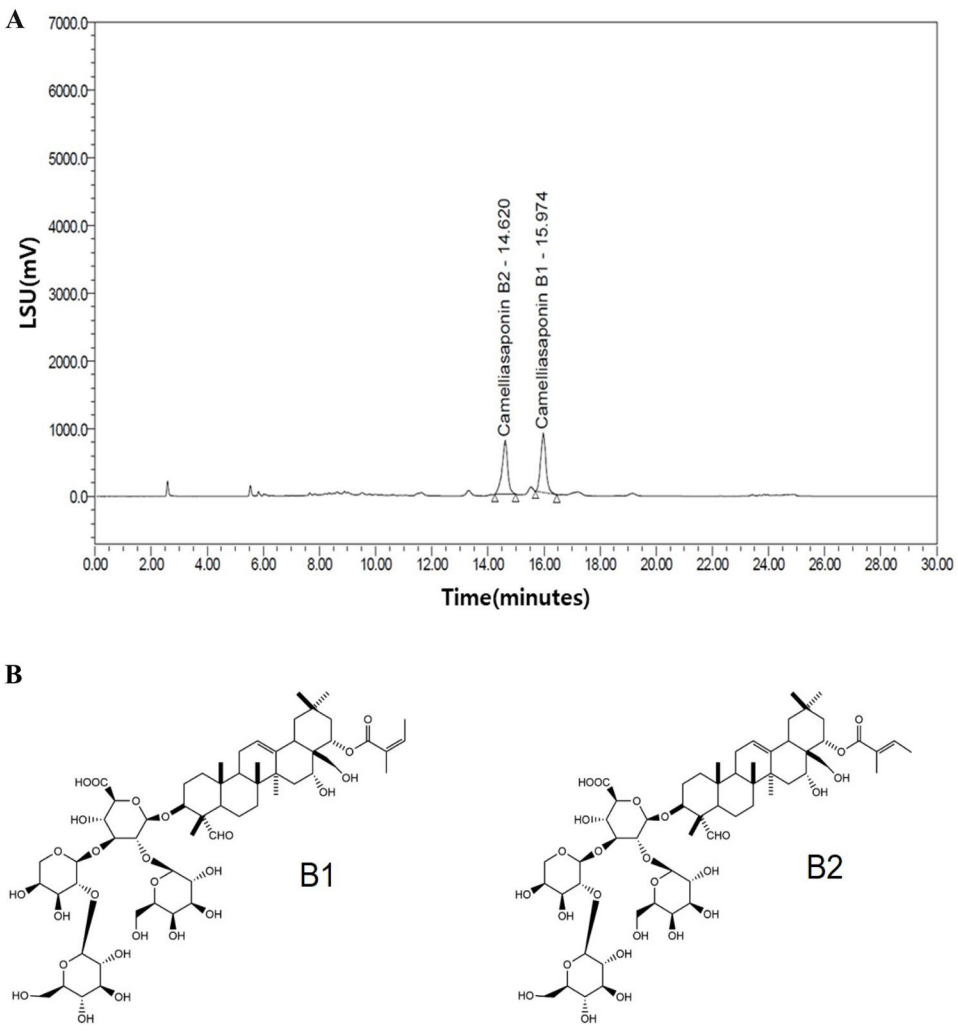


Fig. 1 Main components of *Camellia japonica* seed crude extract. **A** Chromatogram of the saponin fraction of *C. japonica* seed crude extract analyzed using HPLC. **B** Structure of camelliasaponins B1 and B2. The molecular structure of the two saponins is $C_{58}H_{90}O_2$, and their molecular weight is 1,203.3 g/mol. HPLC: high-performance liquid chromatography

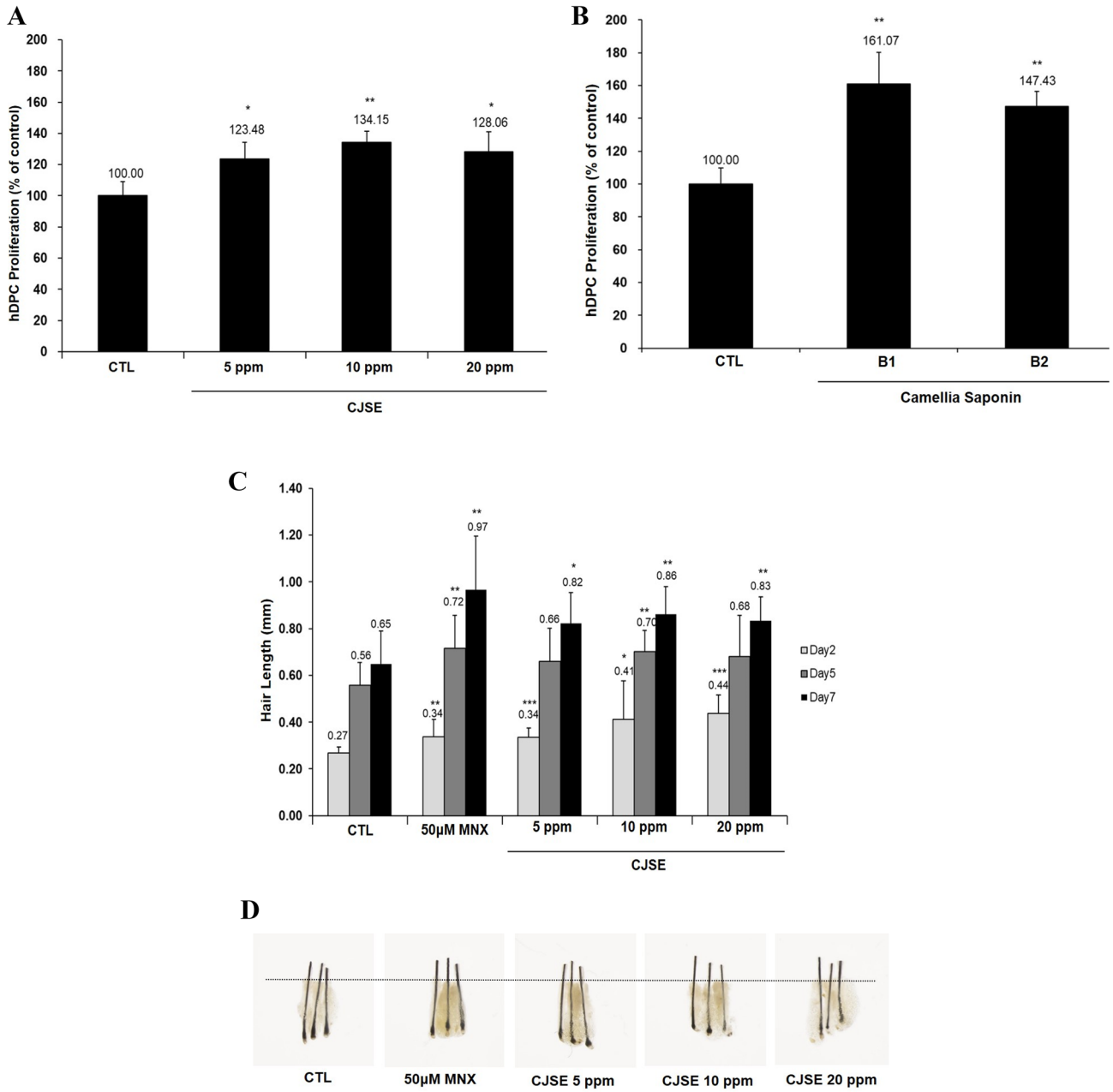
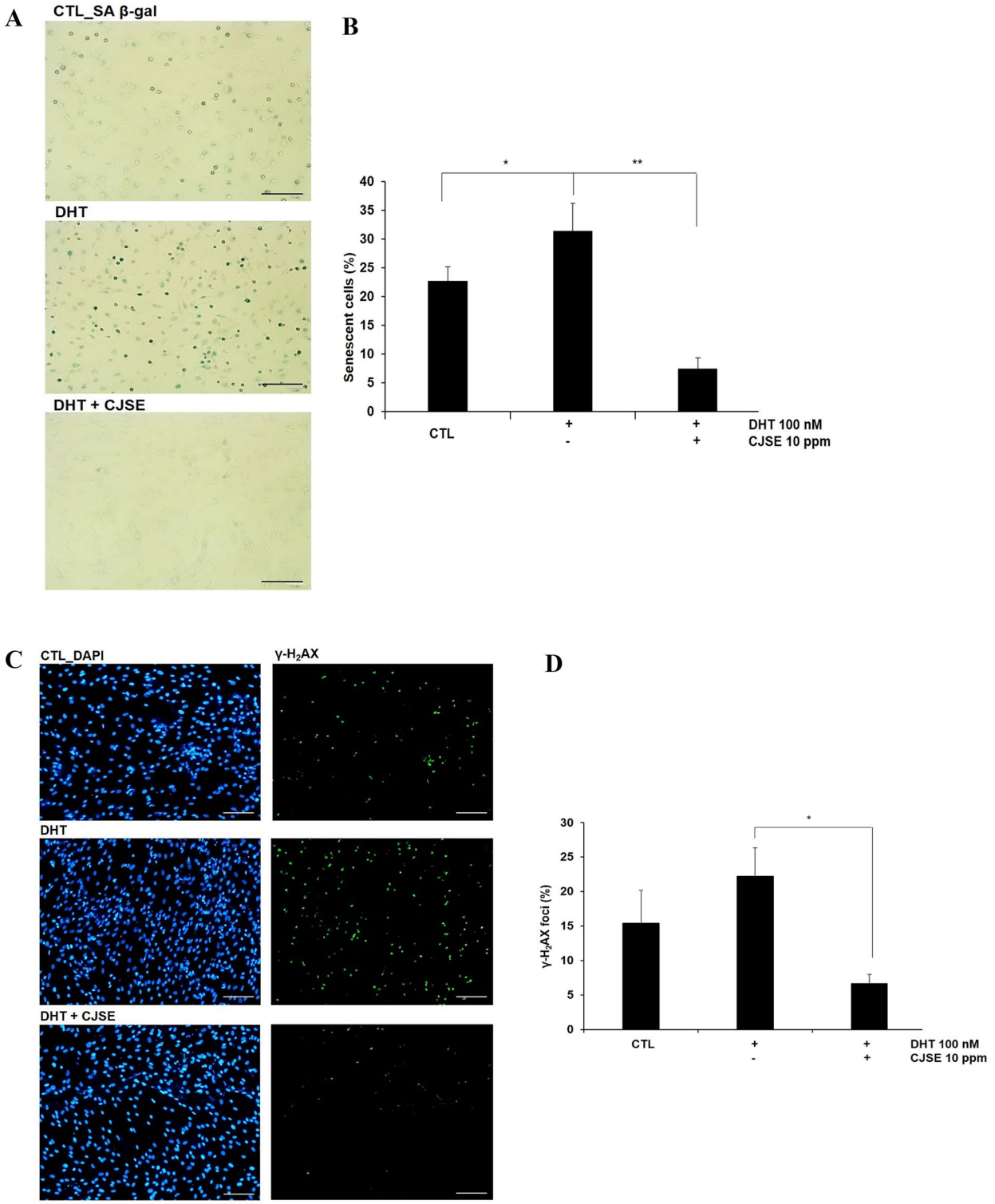


Fig. 2 *Camellia japonica* seed extract (CJSE) increased the proliferation of dermal papilla cells and the length of human hair follicles. **A** Cell counting kit-8 (CCK-8) assay results of human dermal papilla cells (hDPCs) treated with CJSE at different doses. Data are represented as the mean ± standard deviation of three experimental replicates. **B** CCK-8 assay results of hDPCs treated with 0.1 ppm camelliasaponins B1 and B2. Data are represented as the mean ± standard deviation of three experimental replicates. **C** Length of human hair follicles treated with CJSE increased dose-dependently compared with that of the control. Minoxidil (MNX) used as the positive control (p values: $*p<0.05$ vs. CTL, $**p<0.01$ vs. CTL, $***p<0.001$ vs. CTL; CTL: non-treated group; graph bars: average; error bars: standard deviation; three experimental replicates). **D** Three representative images of the human hair follicles correlate to the hair length graph

2.2 In vitro and ex vivo studies

hDPCs were obtained from Kyoungbook University, and human HFSCs were purchased from Celprogen. The proliferation-inducing effect of CJSE on hDPCs was measured using the Cell Counting Kit-8 assay for 72 h. hDPC senescence level was determined using an SA β-gal staining kit (Cell Signaling Technology), and DNA damage in hDPCs was evaluated using a γ-H_2AX staining kit (Invitrogen). Gene and protein expression of senescence



pathway markers, $p16^{INK4a}$ and pRb (phospho-Rb), was examined using real-time polymerase chain reaction (PCR) and western blotting. The HFSC-activating effect of CJSE was determined by measuring the HFSC differentiation level using a fluorescence-activated cell sorter (FACS) after staining with CD200 (MRC OX-104; BIORAD) and ITGA6 (Pharmingen clone GoH3; BD Biosciences) antibodies. p21 expression level in HFSCs was measured using an enzyme-linked immunosorbent assay (ELISA) kit (LS Bio ELISA Kit). hHFs were obtained from patients undergoing hair follicle transplant surgery after approval from the Dankook University Hospital Medical Ethics Committee (Cheonan,

◂**Fig. 3** *Camellia japonica* seed extract (CJSE) inhibited dihydrotestosterone (DHT)-induced senescence and DNA damage of dermal papilla cells, as determined using senescence-associated beta-galactosidase (SA β-gal) and γ-H_2AX staining. **A** Human dermal papilla cells (hDPCs) were treated with 100 nM DHT and 10 ppm CJSE for 24 h. The cells were then stained using an SA β-gal staining kit. Scale bar: 1 mm. Three experimental replicates were performed, with representative images presented. **B** The percentage of SA β-gal activity was calculated from three spots randomly selected in each group (SA β-gal-stained cells/all counted cells). **C** hDPCs were treated with 100 nM DHT and 10 ppm CJSE for 72 h. To assess the double-strand breaks of DNA, γ-H_2AX staining was performed using fluorescence-based immunocytochemistry. Blue and green indicate DAPI and γ-H_2AX staining, respectively. Scale bar: 200 μm. Three experimental replicates were performed, with representative images presented. **D** The mean number of foci was calculated using the same SA β-gal staining method (*p* values: $*p<0.05$ vs. CTL, $**p<0.01$ vs. CTL,; CTL: non-treated group; graph bars: average; error bars: standard deviation)

Korea; DKUH-2021-12-005). The hHFs were incubated in William's E medium following Philpott's method, and hair elongation was measured using a stereomicroscope (Olympus). The detailed experimental procedure is presented in the Online Resources (Supplementary Materials and Methods).

2.3 Clinical study

Fifty male and female patients with androgenetic alopecia who had not used topical or systemic medications affecting hair growth in the past 6 months were enrolled in this study. Finally, 24 and 23 individuals in the treatment and control groups, respectively, completed the study. The Institutional Review Board approved the study protocol (DKUH 2019-11-004, ClinicalTrials.gov number_PRE20240815-001), and all study participants provided informed consent. The assessed area of the scalp was semi-permanently tattooed before the treatment. CJSE (2%) and vehicle solutions were applied to the scalp once a day for 24 weeks. Total hair counts, including terminal and vellus hair, were determined using a phototrichogram (VEOS® Canfield; 4 Wood Hollow) at 0, 8, 16, and 24 weeks. Two clinical photos were taken at baseline and after 8, 16, and 24 weeks of treatment with a DSLR camera (Canon EOS). Detailed experimental methods are presented in the Online Resources (Supplementary Materials and Methods).

2.4 Statistical analysis

Experimental results are presented as mean ± standard deviation. The data were analyzed using Student's *t*-test or repeated measures analysis with IBM SPSS Statistics for Windows, versions 22.0 and 25.0 (IBM Corp.). Results with two-tailed p values < 0.05 were considered statistically significant.

3 Results

3.1 Analysis of camelliasaponin content in CJSE

Several studies have revealed that the main compounds in the seeds of *C. japonica* are oleanane-type saponins [18, 19]. Additionally, we recently reported nine novel saponins, camoreosides A-I, isolated from *C. japonica* seeds [20]. The composition of the saponin fraction of *C. japonica* seed crude extract was profiled using HPLC analysis. The saponin fraction comprised two main saponins (camelliasaponins B1 and B2). The HPLC chromatogram of each saponin is shown in Fig. 1A, and the structures of the two major saponins are depicted in Fig. 1B. The content of camelliasaponins B1 and B2 in the saponin fraction was 47% and 25% (w/w), respectively.

3.2 hDPC proliferation and hHF organ culture

The effects of CJSE and the two major camelliasaponins on hDPC proliferation were evaluated. Hair follicle growth results from organized mechanisms and signals inducing dermal papilla cell proliferation [21, 22]. As shown in Fig. 2A, CJSE promoted hDPC proliferation compared to the control. Particularly, 10 ppm CJSE showed a significantly higher effect than the control, at 134.15%. Camelliasaponins B1 and B2, found in CJSE, significantly increased hDPC proliferation compared to the control, improving the level of hDPC proliferation to 161.07% (Fig. 2B). To evaluate the effect of CJSE on hHF elongation, we assessed hair growth using cultured occipital hHFs. The dissected hHFs were treated with 5, 10, and 20 ppm CJSE, and hair elongation was measured on days 2, 5, and 7. As shown in Fig. 2C and D, CJSE significantly increased hair growth at all concentrations compared to the control.

3.3 Examination of premature senescence and DNA damage in hDPCs

The senescence phenotype in hDPCs treated with a hair loss-inducing factor, DHT, was examined using an SA β-gal staining kit. As shown in Fig. 3A, the SA β-gal activity in the DHT treatment group increased compared with that in the control group. Additionally, DHT and 10 ppm CJSE co-treated hDPCs showed significantly decreased SA β-gal activity compared to DHT-treated cells (Fig. 3B). According to previous studies, premature senescence of hDPCs is highly related to DNA damage [23, 24]. To evaluate whether γ-H_2AX, a marker of double-stranded DNA breaks in hDPCs, was affected by DHT, hDPCs were cultured under DHT treatment and stained with γ-H_2AX antibody. As shown in Fig. 3C, DHT-treated

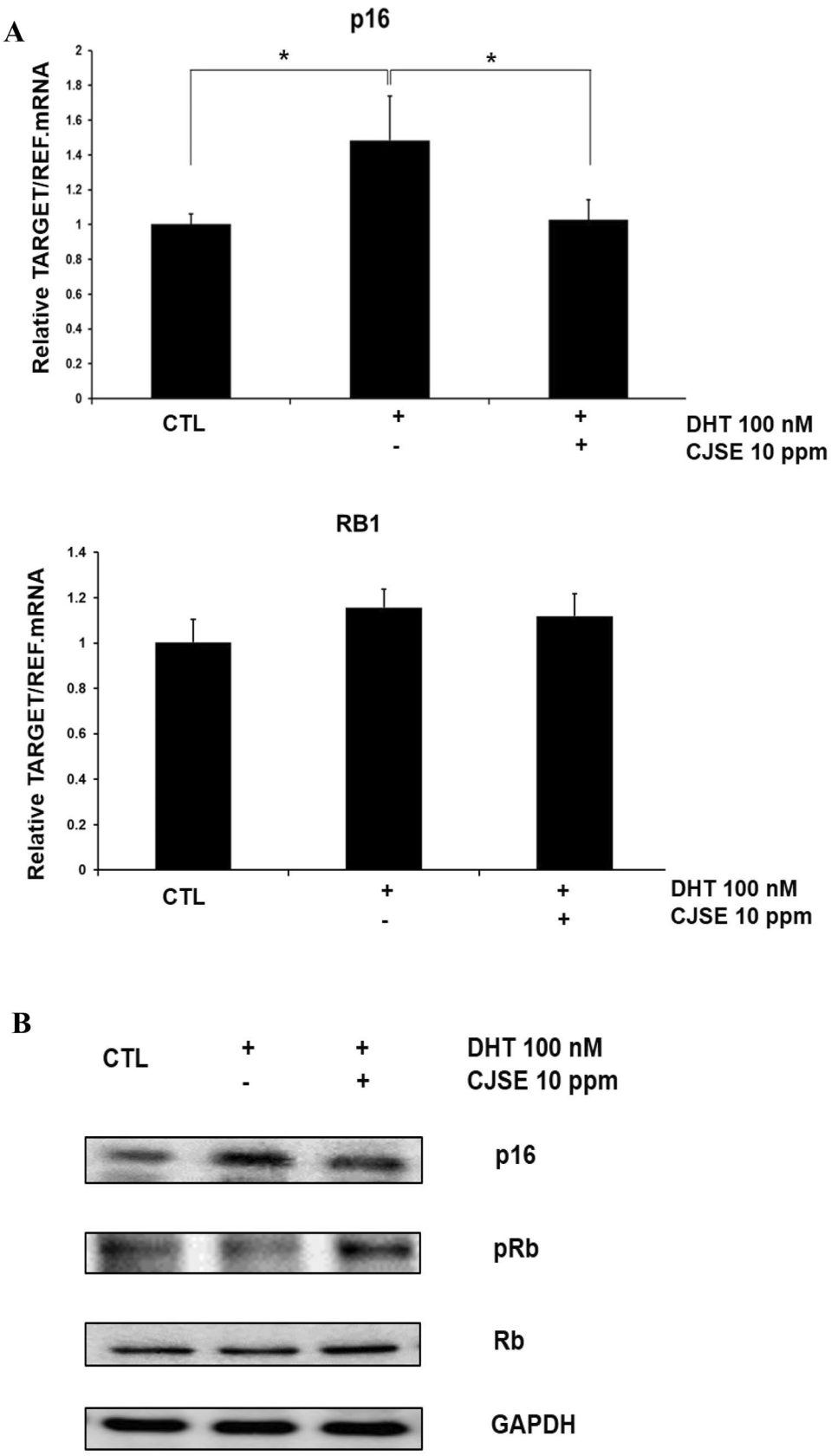


Fig. 4 Effect of *Camellia japonica* seed extract (CJSE) on dihydrotestosterone (DHT)-induced p16-pRb pathway related to senescence of dermal papilla cells. **A** Human dermal papilla cells (hDPCs) were treated with 100 nM DHT and 10 ppm CJSE for 48 h. *p16* expression was downregulated in the CJSE-treated group compared with that in the DHT-induced group. However, *RB1* expression was not altered (*$p < 0.05$ vs. CTL, CTL: untreated group). Data presented as the mean ± standard deviation of three experimental replicates. **B** hDPCs were treated with 100 nM DHT and 10 ppm CJSE for 72 h. p16 ^{INK4a} expression was downregulated and pRb expression was upregulated in the CJSE-treated group compared with those in the DHT-induced group. Three experimental replicates were performed, with representative images presented

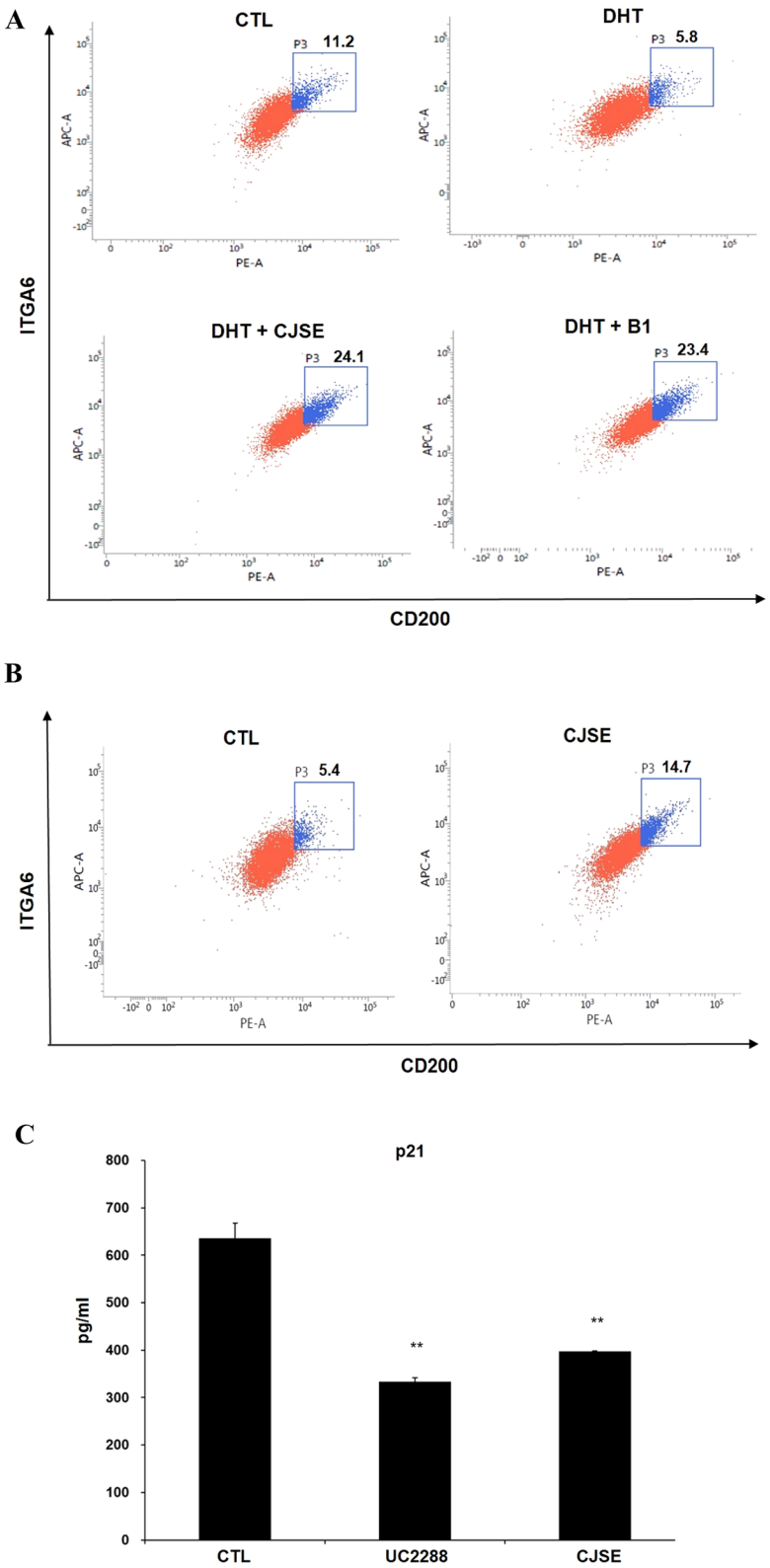


Fig. 5 Effect of *Camellia japonica* seed extract (CJSE) on the activation of HFSCs. **A** Hair follicle stem cells (HFSCs) were treated with human dermal papilla cells (hDPCs) conditioned medium, which was treated with 100 nM dihydrotestosterone (DHT), 10 ppm CJSE, and 0.1 ppm camelliasaponin B1 for 24 h and evaluated using double-color FACS analysis with CD200 and IGA6 antibodies. Numerical values represent the percentage of cells in the gated population for all cells plotted in each group. Three experimental replicates were performed, with representative images presented. **B** HFSCs were treated with 10 ppm CJSE for 24 h and evaluated using double-color FACS analysis with CD200 and IGA6 antibodies. Three experimental replicates were performed, with representative images presented. (C) HFSCs were treated with 10 ppm CJSE for 24 h, and p21 expression was evaluated. p21 inhibitor, UC2288 (Abcam), was used as a negative control at 250 nM concentration (*p* values:, $^{**}p < 0.01$ vs. CTL, CTL: non-treated group; graph bars: average; error bars: standard deviation; three experimental replicates)

hDPCs exhibited significantly increased γ-H_2AX staining. These results confirm that DHT is a crucial factor in hDPC senescence. Furthermore, hDPCs co-treated with DHT and 10 ppm CJSE showed decreased γ-H_2AX level compared to DHT-treated cells. The quantitative analysis of these results showed an increase in the percentage of γ-H_2AX-stained cells after DHT stimulation and a decrease after CJSE treatment (Fig. 3D).

Table 1 Comparison of hair density change between the test and control groups

Hair density change (number/cm^2)	8 weeks	16 weeks	24 weeks
CJSE group	8.655 ± 12.099	8.476 ± 22.451	14.982 ± 21.744
Vehicle group	4.422 ± 8.183	− 0.609 ± 8.616	− 2.323 ± 8.407
p value	0.166	0.263	< 0.001*

Values are presented as mean ± standard deviation. CJSE: *Camellia japonica* seed extract. **p* value: statistically significant probability (comparison to the vehicle group), Mann–Whitney *U*-test

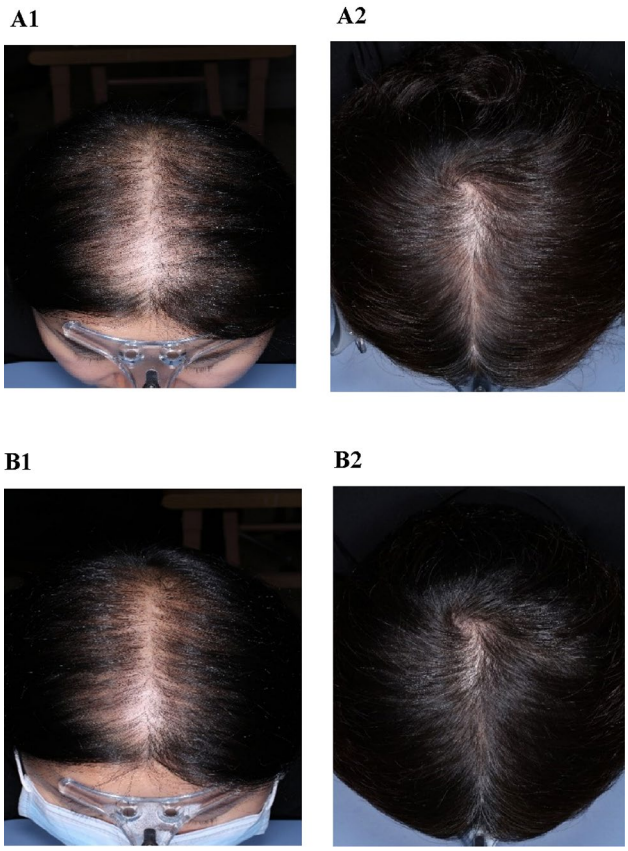


Fig. 6 Representative image of the *Camellia japonica* seed extract-treated group before and after 24-week treatment. **A1** Pre-treatment_Female, **A2** Pre-treatment_Male, **B1** 24-week post-treatment_Female, **B2** 24-week post-treatment_Male

3.4 Senescence-associated p16-pRb pathway in hDPCs

To investigate the potential of CJSE to inhibit premature senescence, we conducted a q-PCR analysis of senescence pathway markers, including $p16^{INK4a}$–pRb (phospho-Rb, pRb). When DNA damage occurs, cells can pass through the p53-p21 and/or $p16^{INK4a}$-pRb pathways to reset cell cycle progression and repair the damaged DNA [25, 26]. During this phase, the p16 level increases, accompanied by a reduction in the phosphorylation of Rb. As shown in Fig. 4A, $p16^{INK4a}$ expression was significantly upregulated in hDPCs treated with 100 nM DHT compared with that in the control group; however, no change was found in RB1 expression. Co-treatment of hDPCs with DHT and CJSE resulted in the downregulation of $p16^{INK4a}$ expression; however, no significant difference was observed in RB1 expression. Additionally, we conducted western blotting to analyze the expression of $p16^{INK4a}$ and pRb. As shown in Fig. 4B, $p16^{INK4a}$ expression was upregulated in DHT-treated hDPCs and downregulated in DHT–CJSE co-treated hDPCs. In contrast, the expression of pRb was downregulated in DHT-treated hDPCs and upregulated in DHT–CJSE co-treated hDPCs. This finding indicates that CJSE can prevent premature senescence of hDPCs by suppressing p16 expression and increasing Rb phosphorylation without affecting Rb gene expression.

3.5 Activation of HFSCs and inhibition of p21 expression

To investigate the effect of CJSE on the activation of HFSCs, we assessed the expression levels of the stem cell differentiation markers CD200 and ITGA6 using FACS analysis. First, we investigated whether the senescence-preventing effect of CJSE in hDPCs affects HFSC activity. We found that the proportions of CD200- and ITGA6-positive populations were reduced by DHT-treated hDPC-conditioned medium (CM), and their expression was restored after co-treatment with CJSE-treated hDPC-CM. Additionally, the main component camelliasaponin B1 upregulated the expression of the stem cell differentiation markers to a level similar to that induced by CJSE (Fig. 5A). We then assessed whether CJSE can directly affect the activation of HFSCs. As shown in Fig. 5B, CJSE treatment significantly increased the activated HFSC population compared to the control. According to recent studies, p21 is an important factor for proliferative quiescence in HFSCs and acts as a cell cycle inhibitor [13, 14]. Therefore, we measured p21 expression level using ELISA to evaluate the effect of CJSE on p21 expression in HFSCs. As shown in Fig. 5C, CJSE significantly reduced p21 expression in HFSCs compared to the control. We used UC2288, a well-known p21 inhibitor [27]. These results suggest that CJSE can enhance HFSC activity by preventing senescence of hDPCs and inhibiting p21 expression in HFSCs.

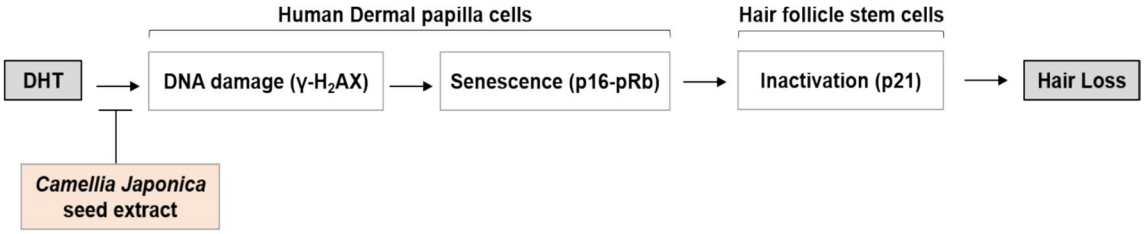


Fig. 7 Dihydrotestosterone (DHT) causes DNA damage to the dermal papilla cells of hair follicles, accelerating senescence. As a result, the inactivity of hair follicle stem cells leads to hair loss. *Camellia japonica* seed extract promotes hair growth by preventing dermal papilla cell senescence and activating hair follicle stem cells

3.6 Clinical study

In this study, 47 male and female participants aged 18–54 years, diagnosed with pattern hair loss according to the BASP, Norwood–Hamilton, and Ludwig classifications, successfully completed the study. Of these, 24 participants (11 male and 13 female participants) used the topical scalp tonic containing 2% CJSE, and the other 23 (10 male and 13 female participants) used the vehicle solution once a day for 24 weeks.

The number of hairs cm^{-2} at weeks 0, 8, 16, and 24 was 189.262 ± 47.750, 197.917 ± 55.974, 197.738 ± 61.937, and 204.244 ± 62.448, respectively, in the CJSE group, and 181.168 ± 30.467, 185.590 ± 34.667, 180.559 ± 34.433, and 178.845 ± 29.200, respectively, in the vehicle group. The hair count of the CJSE group continued to increase significantly, whereas that of the vehicle group decreased during the study period. The hair count change (number cm^{-2}) of the CJSE-treated group at week 24 was 14.982 ± 21.744, whereas that of the vehicle group was -2.323 ± 8.407. A significant difference was observed between the groups ($p < 0.001$; Table 1). The representative photos of male and female participants in the CJSE-treated group showed a significant improvement in hair density (Fig. 6). During the study, no severe adverse skin reactions were reported or observed.

3.7 Overview of the mechanism of hair loss and role of *Camellia Japonica* seed extract

The figure (Fig. 7) summarizes the proposed mechanism of hair loss involving human dermal papilla cells and hair follicle stem cells. Dihydrotestosterone (DHT) induces DNA damage (γ-H_2AX), leading to cellular senescence (p16-pRB) in dermal papilla cells. This senescence subsequently inactivates hair follicle stem cells via p21 signaling, resulting in hair loss. This diagram also illustrates the protective effect of Camellia Japonica seed extract, which inhibits this pathway and may help prevent hair loss.

4 Discussion

Camellia has a long history of use in hair care, and previous studies have investigated the effects of *Camellia* seed extract on hair growth [16, 17]. However, there are only a few studies on *C. japonica* and camelliasaponins. The seeds of *C. japonica* contain oleanane-type saponins as the main components [18, 19]. The representative plant saponin ginsenoside has been extensively studied for its effect on hair growth [28, 29]. We hypothesized that saponins of *C. japonica* have a hair growth-promoting effect similar to that of ginsenoside. The main components of the saponin-rich fraction of CJSE analyzed in this study were camelliasaponins B1 and B2. We proved that CJSE and camelliasaponins have significant hair growth-promoting effects in hDPCs and hHF organ culture. Subsequently, we evaluated the anti-senescence and HFSC-activation effects of CJSE to establish its cellular mechanism.

Recent studies have indicated that hDPCs of patients with alopecia have more senescent morphology than those of normal people [1, 2]. Additionally, DHT generated by 5 alpha-reductase is considered an inducer of androgen signaling in hDPCs and a suppressor of HFSC activation [9]. Controlling the androgen effect on hair follicles is important in alopecia to mitigate the acceleration of DPC senescence and HFSC inactivation. In this study, we found that DHT induced senescence in hDPCs by promoting DNA damage. CJSE alleviated the premature senescence of DHT-treated hDPCs by regulating the p16 ^{INK4a}-pRb pathway and notably inducing the hyper-phosphorylation of Rb. p16 ^{INK4a} expression increases and Rb phosphorylation decreases during the process of cellular senescence [25, 26, 30]. We found that CJSE can prevent hDPC senescence by downregulating p16 ^{INK4a} expression and upregulating Rb phosphorylation significantly.

The interaction between HFSCs and their surrounding cells is important for hair follicle regeneration [31, 32]. In particular, hDPCs produce various growth factors that stimulate epithelial bulge cell proliferation and anagen phase induction [33]. In this study, we used hDPC-CM to evaluate the effect of CJSE on HFSC activation through the

interaction between hDPCs and HFSCs. DHT-treated hDPC-CM reduced HFSC differentiation, and CJSE and camelliasaponin B1 co-treated hDPC-CM restored HFSC activation. This finding suggests that the senescence of hDPCs induced by DHT could suppress HFSC activation, and CJSE can restore HFSC activity by its anti-senescence action on hDPCs. Additionally, we found that direct treatment of CJSE without hDPC-CM promoted HFSC differentiation. Recent studies have revealed that p21 not only represses the proliferation of HFSCs [14] but also exhibits significantly upregulated expression in HFSCs of aged mice displaying telogen retention [13]. CJSE treatment significantly reduced p21 expression in HFSCs compared with that in the control. These results suggest that CJSE restores HFSC activity directly by suppressing p21 expression.

Most plant-based hair loss treatments have been proposed to exert their effects by maintaining the anagen phase of hair follicles [34]. Among these, camellia saponin has emerged as a useful anti-hair loss agent, as it facilitates the transition of hair follicles from the telogen to the anagen phase through interactions between dermal papilla cells and HFSCs. Additional research into the molecular processes that occur during interactions between hDPCs and HFSCs is required to more clearly elucidate the action of CJSE on hair growth.

To confirm the efficacy of CJSE in promoting hair growth, we conducted a 6-month clinical trial with 47 male and female individuals with androgenetic hair loss. The CJSE-treated group showed a significant change in hair counts at 24 weeks compared with those at 0 weeks and those in the vehicle-treated group. The clinical results suggested that CJSE treatment enhanced new hair growth, whereas the vehicle showed decreased hair density. The representative photos of the CJSE group shown in Fig. 6 support the results of this clinical study.

5 Conclusions

In this study, we demonstrated the effectiveness of CJSE in promoting hair growth through both in vitro experiments and a clinical trial. CJSE enhanced hair growth by preventing premature senescence of hDPCs via p16 ^{INK4a}-pRb pathway regulation and HFSC activation. The clinical trial results showed that CJSE effectively promoted hair growth in individuals with androgenetic hair loss. Therefore, CJSE may serve as a promising hair growth-promoting agent for treating androgenic or senescent alopecia.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12257-025-00210-0.

Author contributions Conceptualization: MJH and SHS; methodology: MJH and SHS; investigation: MJH and SP; resources: SHK, BCP, and GBN; writing—original draft preparation: MJH and JK; writing—review and editing: SNK and WSP; visualization: MJH; supervision: SNK and WSP; project administration: SNK and HJK.

Data availability All data are available in the main text or the supplementary information.

Declarations

Conflict of interest The authors declare no conflict of interest.

Ethical approval The study protocol was approved by the Institutional Review Board (DKUH 2019–11-004). The trial was conducted in accordance with the ethical principles based on the Declaration of Helsinki and the Good Clinical Practice guidelines of the International Conference on Harmonization, and local regulatory requirements.

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