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여드름 치료를 위한 대마씨 추출물의 추출 방법별 효능평가

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Comparative Efficacy of Hemp Seed Extracts Produced by Different Extraction Methods for Acne Treatment

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ABSTRACT

Background: Derived from industrial hemp, Hemp seeds (*Cannabis sativa* L.) have shown potential as a treatment for acne, particularly when used in conjunction with botanical extracts such as green tea and essential oils. However, limited research has investigated the influence of different extraction methods on biological activity. In this study, we aimed to evaluate differences in the antimicrobial, antioxidant, and anti-inflammatory properties of hemp seed extracts obtained using various extraction techniques.
Methods and Results: To assess the effectiveness of hemp seed extracts in acne treatment, we examined their antimicrobial, antioxidant, and anti-inflammatory activities, and their cytotoxicity. Three types of extract were tested, namely, 95% ethanol (HSE-1), 50% ethanol (HSE-2), and hot water (HSE-3). All the extracts exhibited significant biological activity and minimal cytotoxicity. Among them, HSE-1 demonstrated the highest efficacy, showing 37.90% inhibition of *C. acnes* growth, 77.15% antioxidant activity, and 19.7% reduction in nitric oxide (NO) production.
Conclusions: The findings provide a novel comparative evaluation of hemp seed extracts and highlight the significant impact of the extraction methods on their bioactivity. Among the tested extracts, the 95% ethanol extract had the most potent antimicrobial, antioxidant, and anti-inflammatory effects, supporting its potential use in topical formulations for acne and other inflammatory skin conditions. Future studies should focus on isolating key bioactive compounds and optimizing formulation strategies to enhance the bioavailability and therapeutic efficacy of HS-based treatments.

Key Words: *Cannabis sativa,* Acne, Antioxidant, Anti-inflammatory, Extraction Method

INTRODUCTION

Acne vulgaris, commonly referred to as acne, is a prevalent inflammatory skin condition that affects millions of individuals worldwide (Kurokawa *et al*., 2009). Recent epidemiological data indicate that approximately 85% of adolescents and young adults experience acne, with varying degrees of severity across different age groups (Zaenglein *et al*., 2016).

The pathogenesis of acne involves multiple factors, including excessive sebum production, follicular hyperkeratinization, inflammation, and the proliferation of *Cutibacterium acnes* (formerly *Propionibacterium acnes*) (Yamasaki and Gallo, 2008; Pellati *et al*., 2018; Vasam *et al*., 2023; Reynolds *et al*., 2024).

Although conventional treatments—such as benzoyl peroxide, salicylic acid, and antibiotics—are widely used, they often lead to adverse effects like skin dryness, irritation, and the potential development of antibiotic resistance (Thiboutot *et al*., 2006). Consequently, these limitations have propelled the search for safer and more sustainable remedies (Dodov and Kulevanova, 2009).

Hemp seed (*Cannabis sativa* L.) is increasingly recognized for its therapeutic potential, owing to its nutrient-rich profile of

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essential fatty acids, proteins, vitamins, and minerals (Leizer *et al*., 2000; Callaway, 2004). Historically applied in the food and health industries, hemp seed is now being examined for its dermatological benefits (Zaenglein *et al*., 2016). Notably, hemp seed contains cannabinoids such as cannabidiol, which have demonstrated anti-inflammatory, antioxidant, and antimicrobial properties (Fischedick, 2017; Baswan *et al*., 2020; Ferreira *et al*., 2024). These attributes position hemp seed extract as a promising candidate for acne therapy.

However, while previous studies have confirmed its potential efficacy, research comparing the effects of different extraction methods on the biological activity of hemp seed extract remains limited. Extraction techniques and solvents are known to significantly influence the yield and potency of bioactive compounds, as demonstrated in recent studies exploring various extraction conditions (Lazarjani *et al*., 2021; Rožanc *et al*., 2021; Tzimas *et al*., 2024).

Therefore, this study aims to systematically evaluate hemp seed extracts produced using various extraction methods, with a particular focus on their antimicrobial, antioxidant, and anti-inflammatory effects to investigate potential synergistic bioactivity.

MATERIALS AND METHODS

1. Hemp seed extracts preparation

Hemp seeds used in this study were purchased from a commercial supplier, sourced from Canada, packaged in 500 g units, and confirmed to be 100% natural, according to Martins *et al*. (2024).

For the ethanol extracts, 300 g of hemp seeds was mixed with 3 ℓ of 95% ethanol (EtOH) to prepare sample HSE-1, and another 300 g sample was mixed with 3 ℓ of 50% EtOH to prepare sample HSE-2. Both mixtures were stirred at room temperature (25 ± 2℃) for 24 hours.

For the hot-water extract (HSE-3), 300 g of hemp seeds was mixed with 3 ℓ of distilled water and extracted for 4 hours at 90℃. The resulting extracts were filtered through filter paper and concentrated using a rotary evaporator under reduced pressure at 40°C. All dried extracts were then dissolved in 4% dimethyl sulfoxide (DMSO) (Sigma-Aldrich Co. LLC, St. Louis, MO, USA) prior to use in subsequent experiments.

2. Strain and cell culture

C. acnes (KCCM 41747) was obtained from the Korean Culture Center of Microorganisms (KCCM, South Korea). The bacterial strain was cultured in Reinforced Clostridial Medium at 37℃ for 72 hours (Nguyen and Kim, 2020).

Human keratinocytes (HaCaT cells) were maintained in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% fetal bovine serum, penicillin (100 units/㎖), and streptomycin (100 units/㎖) in a 37°C, 5% CO_2 incubator (PHCbi, Tokyo, Japan). The medium was replaced every 3 - 4 days, and cells were subcultured once they reached > 90% confluence (Ruttanapattanakul *et al*., 2021).

3. Antibacterial activity

The antibacterial effect of hemp seed extracts against *C. acnes* was evaluated using a 96-well microplate assay (Appendino *et al*., 2008; Nguyen and Kim, 2020). *C. acnes* cultures were incubated at 37℃ for 3 days, adjusted to 10^8 CFU/㎖, and inoculated into 96-well plates. The test extracts (HSE-1, HSE-2, and HSE-3) were applied at concentrations of 5, 10, 15, 20, and 30 ㎎/㎖, and the plates were incubated for an additional 72 hours.

Bacterial growth inhibition was determined by measuring the optical density at 600 ㎚ (OD_{600}) using a Multiskan™ FC Microplate Photometer (Thermo Fisher Scientific Inc., Waltham, MA, USA). A lower OD_{600} value indicated a stronger antibacterial effect.

4. Antioxidant effect

The DPPH (2,2-diphenyl-1-picrylhydrazyl) radical scavenging assay was employed to assess the antioxidant capacity of the hemp seed extracts (Sharma and Bhat, 2009).

Extracts were prepared at concentrations of 5, 10, 15, 20, and 30 ㎎/㎖, then mixed with the DPPH solution. L-ascorbic acid was used as the positive control. After a 30-minute reaction at 30℃, the absorbance was measured at 517 ㎚ using a Multiskan™ FC Microplate Photometer (Thermo Fisher Scientific Inc., Waltham, MA, USA). The radical scavenging activity (antioxidant activity, %) was calculated using the following formula (not provided in detail here):

$$\text{Antioxidant activity (\%)} = \left(1 - \frac{\text{Absorbance of sample}}{\text{Absorbance of control}}\right) \times 100$$

5. Cytotoxicity effect

Cytotoxicity of the hemp seed extracts on HaCaT cells was evaluated using the MTT assay (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl-tetrazolium bromide), adapted from Ruttanapattanakul *et al*. (2021). HaCaT cells were seeded in a 96-well microplate

at a density of 5×10^4 cells/well and pre-incubated for 24 hours. The cells were then treated with the extracts at concentrations of 100, 200, and 400 ㎍/㎖ for 24 hours.

Subsequently, the medium was removed, and 50 ㎕ of MTT solution (5 ㎎/㎖ in PBS) was added to each well, followed by incubation for 4 hours. The resulting formazan crystals were dissolved in 150 ㎕ of DMSO, and absorbance was measured at 570 ㎚ using an ELISA Microplate Reader (BioTek Instruments, Winooski, VT, USA) (Oláh *et al*., 2014). Cell viability (%) was calculated relative to untreated control cells and expressed as means ± SD (n = 3).

6. Anti-inflammatory effect

The anti-inflammatory effect of the hemp seed extracts was assessed by measuring nitric oxide (NO) production in HaCaT cells (Yang *et al*., 2020). HaCaT cells were seeded in a 96-well plate at 5×10^4 cells/well and incubated for 24 hours (Friedman *et al*., 2016). After pre-treatment with 100, 200, and 400 ㎍/㎖ of the extracts for 2 hours, cells were stimulated with 1.0 ㎍/㎖ lipopolysaccharide (LPS) and cultured for an additional 24 hours.

The cell supernatant (100 ㎕) was mixed with 100 ㎕ of Griess reagent, incubated for 10 minutes at room temperature, and the absorbance was measured at 540 ㎚ using a microplate reader. NO concentration was determined by comparing the absorbance values to a standard curve prepared with sodium nitrite ($NaNO_2$).

7. Statistical analysis

All experiments were performed in triplicate (n=3), and data are presented as means ± SD. Normality was assessed using the Shapiro-Wilk test ($p > 0.05$), and comparisons among groups were conducted using one-way analysis of variance (ANOVA) with Tukey's post-hoc test or independent two-sample *t*-tests when appropriate. All statistical analyses were performed using SPSS (version 28.0; IBM Corp., Armonk, NY, USA).

RESULTS AND DISCUSSION

1. Antibacterial activity

The antibacterial potential of the hemp seed extracts (HSE-1, HSE-2, and HSE-3) was evaluated against *C. acnes*. The bacterial cultures were incubated for three days in the presence of each extract at concentrations of 5, 10, 15, 20, and 30 ㎎/㎖. Optical density was then measured at 600 ㎚ to determine the extent of bacterial growth inhibition (Table 1).

Table 1. Antibacterial activity (%) of hemp seed extracts (HSE-1, HSE-2, and HSE-3) against *C. acnes*.

Concentration (㎎/㎖)	HSE-1 (%)	HSE-2 (%)	HSE-3 (%)
5	2.36	6.28	0.00
10	9.47	11.81	3.14
15	16.58	17.34	7.13
20	23.69	22.87	11.12
30	37.90	33.93	19.10

Notes: Data are expressed as inhibition rates (%) based on the reduction in bacterial growth (OD measured at 600 ㎚). Bacterial growth inhibition was assessed after 3 days of treatment with different extract concentrations (5, 10, 15, 20, and 30 ㎎/㎖), and the percentage inhibition was calculated based on OD_{600} measurements. Data are presented as means ± SD (n = 3).

All three extracts demonstrated concentration-dependent antibacterial activity. Notably, HSE-1 exhibited the strongest inhibitory effect, achieving 37.90% inhibition at 30 ㎎/㎖, compared to 33.93% for HSE-2 and 19.10% for HSE-3. These findings indicate that HSE-1 possesses significantly higher antibacterial efficacy than the other two extracts, underscoring its potential as a potent antibacterial agent for acne treatment.

2. Antioxidant effect

The antioxidant activity of hemp seed extracts is a critical factor in assessing their potential for acne management. In the present study, each extract (HSE-1, HSE-2, and HSE-3) was tested at concentrations of 5, 10, 15, 20, and 30 ㎎/㎖ using the DPPH radical scavenging assay. Samples were incubated with the DPPH solution at 30°C for 30 minutes, and absorbance was subsequently measured. L-ascorbic acid was used as the positive control.

As shown in Table 2, all extracts demonstrated a concentration-dependent increase in DPPH radical scavenging activity. Among the three, HSE-1 exhibited the highest scavenging activity, reaching 77.15% at 30 ㎎/㎖, followed by HSE-3 (73.12%) and HSE-2 (68.36%).

These findings underscore the strong antioxidant potential of HSE-1 relative to the other extracts, suggesting that hemp seed extracts—particularly HSE-1—may serve as effective natural antioxidants, with potential applications for mitigating oxidative stress in skin conditions such as acne.

3. Cell viability

The potential cytotoxicity of hemp seed extracts (HSE-1,

Table 2. Antioxidant activity (% DPPH radical scavenging) of hemp seed extracts (HSE-1, HSE-2, and HSE-3).

Concentration (㎎/㎖)	L-ascorbic acid (%)	HSE-1 (%)	HSE-2 (%)	HSE-3 (%)
5	40.12	18.07	17.12	10.88
10	55.45	26.16	30.72	19.93
15	68.89	38.19	34.83	31.16
20	80.33	55.59	49.84	50.22
30	95.10	77.15	68.36	73.12

Notes: The DPPH radical scavenging activity of hemp seed extracts (HSE-1, HSE-2, and HSE-3) was measured at five concentrations (5, 10, 15, 20, and 30 ㎎/㎖) and expressed as a percentage. L-ascorbic acid was used as the positive control. Data are presented as means ± SD (n = 3).

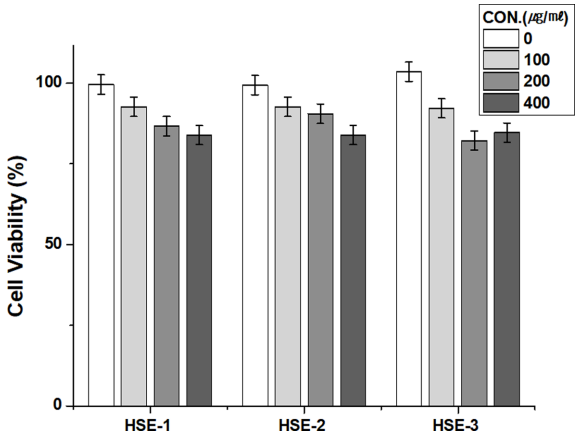

Fig. 1. Cell viability of HaCaT cells treated with hemp seed extracts (HSE-1, HSE-2, and HSE-3), assessed using the MTT assay. Cells were treated with varying concentrations (0, 100, 200, and 400 ㎍/㎖), and viability was expressed as a percentage relative to untreated controls. Data are shown as means ± SD (n = 3).

HSE-2, and HSE-3) was assessed by evaluating the viability of HaCaT cells using the MTT assay. HaCaT cells were treated with each extract at concentrations of 100, 200, and 400 ㎍/㎖ and cultured for 24 hours. As shown in Fig. 1, the cell viability remained at 92.64% following treatment with 100 ㎍/㎖ of HSE-1 (HSE-2: 92.64%, HSE-3: 92.18%), 86.66% at 200 ㎍/㎖ (HSE-2: 90.49%, HSE-3: 82.21%), and above 89.9% at 400 ㎍/㎖ (HSE-2: 83.9%, HSE-3: 84.66%).

These results indicate that, under the tested conditions, none of the hemp seed extracts exhibited significant cytotoxic effects on HaCaT cells, suggesting their potential suitability for topical applications, such as acne management.

4. Anti-inflammatory effect

The anti-inflammatory potential of hemp seed extracts (HSE-1, HSE-2 and HSE-3) was evaluated by measuring nitric oxide (NO) production in HaCaT cells. Cells were pre-treated with each extract at concentrations of 100, 200, and 400 ㎍/㎖ for 2 hours, followed by stimulation with 1.0 ㎍/㎖ lipopolysaccharide (LPS) to induce an inflammatory response. After a 24-hour incubation, NO levels were quantified as shown in Fig. 2.

Exposure to LPS alone resulted in an NO concentration of 38.54 μM, whereas co-treatment with the extracts significantly

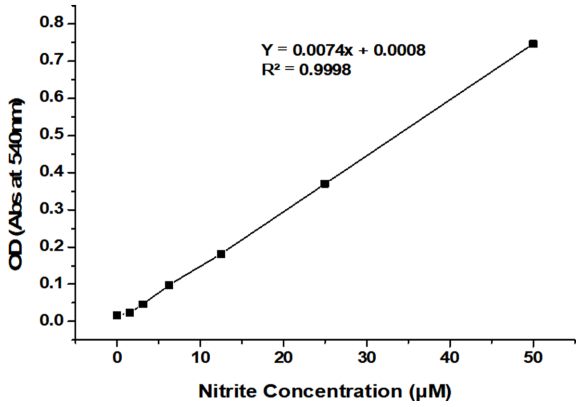

Fig. 2. Standard curve used for the quantification of nitric oxide (NO) production. Sodium nitrite was used to generate a standard curve, and absorbance (OD) was measured at 540 ㎚. A linear regression equation (y = 0.0074x + 0.0008, R^2 = 0.9998) was obtained and used to calculate nitrite concentrations in the experimental samples.

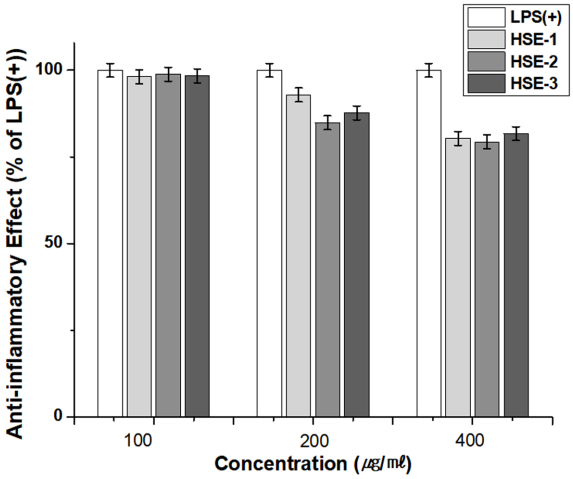

Fig. 3. Nitric oxide (NO) production in HaCaT cells pre-treated with hemp seed extracts (HSE-1, HSE-2, and HSE-3) at concentrations of 100, 200, and 400 ㎍/㎖, followed by stimulation with lipopolysaccharide (LPS, 1.0 ㎍/㎖). NO levels were quantified, and anti-inflammatory activity was expressed relative to the LPS-treated control group, which was set at 100%. Control groups without LPS stimulation were included for comparison. Data are presented as means ± SD (n = 3).

reduced NO levels in a concentration-dependent manner. For HSE-1, NO production decreased to 37.82 μM, 35.81 μM, and 30.97 μM at concentrations of 100, 200, and 400 ㎍/㎖, respectively. Compared to the LPS-only control group, these reductions correspond to NO inhibition rates of approximately 1.9%, 7.1%, and 19.7%, respectively. HSE-2 and HSE-3 similarly exhibited dose-dependent decreases in NO production, although HSE-1 showed the most pronounced inhibitory effect (Fig. 3).

These findings suggest that all the tested hemp seed extracts possess anti-inflammatory potential, with HSE-1 demonstrating the strongest inhibitory effect on NO production. Considering the pivotal role of NO as a pro-inflammatory mediator, the ability of hemp seed extracts—particularly HSE-1—to significantly suppress NO generation highlights their potential as therapeutic agents for managing inflammation-related skin conditions such as acne.

This study comprehensively evaluated the antimicrobial, antioxidant, anti-inflammatory, and cytotoxic properties of three hemp seed extracts (HSE-1, HSE-2, and HSE-3) to assess their potential as natural agents for acne treatment. All extracts exhibited concentration-dependent antibacterial activity against *C. acnes*, with HSE-1 (95% ethanol extract) demonstrating the strongest effect, inhibiting bacterial growth by 37.9% at 30 ㎎/㎖. Similarly, HSE-1 displayed the highest antioxidant capacity, achieving 77.15% radical scavenging activity in the DPPH assay at the same concentration, outperforming HSE-2 and HSE-3.

Cell viability assays using HaCaT keratinocytes revealed that all extracts exhibited low cytotoxicity. Notably, HSE-1 maintained over 80% cell viability at concentrations up to 400 ㎍/㎖, indicating favorable biocompatibility. Additionally, HSE-1 significantly suppressed NO production in LPS-stimulated HaCaT cells, with inhibition rates of approximately 1.9%, 7.1%, and 19.7% at 100, 200, and 400 ㎍/㎖, respectively.

Previous studies have emphasized that extraction methods and solvents critically affect the yield and bioactivity of hemp-derived compounds. For example, extraction techniques can markedly influence the antioxidant activity and cytotoxic potential of the final product. While solvents such as methanol may yield higher cannabinoid concentrations, ethanol is preferred in cosmetic applications due to its safety profile and regulatory approval (Lazarjani *et al*., 2021; Rožanc *et al*., 2021; Tzimas *et al*., 2024). These findings highlight the need to optimize extraction conditions to preserve and enhance bioactive compound content.

Unlike earlier studies that evaluated single extraction methods in isolation, this study conducted a direct comparison of multiple extraction techniques. This comparative approach allowed the identification of the most effective extract for acne-related skin applications. Among the tested samples, HSE-1 emerged as the most promising candidate, combining robust antimicrobial, antioxidant, and anti-inflammatory properties with low cytotoxicity.

Collectively, these results underscore HSE-1's potential as a safe and multifunctional ingredient for acne management. Future studies should aim to isolate and characterize the key active compounds and develop optimized formulations to improve dermal absorption and overall bioavailability. Additionally, investigating its efficacy in other inflammatory skin disorders, such as atopic dermatitis and psoriasis, could expand the therapeutic applications of this promising botanical extract in both functional cosmetics and clinical dermatology.

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