JAR Journal of Acupuncture Research

Original Article

pISSN 2586-288X • eISSN 2586-2898
J Acupunct Res 2023;40(1):35-43
https://doi.org/10.13045/jar.2022.00269

Scutellaria baicalensis Extract Alleviates Pain and Inflammation in Animal Models

Haeni Seo
Ho-Sueb Song

Department of Acupuncture & Moxibustion Medicine, College of Korean Medicine, Gachon University, Seongnam, Korea

Background: This study aimed to examine the effect of *Scutellaria baicalensis* extract (SBE) on ameliorating pain response and inflammation in an animal model.
Methods: The effects of SBE on joint inflammation-induced rats and pain writhing response were measured. In rats with monosodium iodoacetate (MIA)-induced knee osteoarthritis (OA), the weight-bearing distribution of the hind legs was measured, the actual joint condition was visually confirmed, and serum cytokines were extracted from whole blood and measured. In addition, the acetic acid-induced pain was measured by the number of abdominal wall contractions and writhing responses.
Results: 1. The weight-bearing distribution of the hind limbs of the SBE group was remarkably improved compared with that of the control group 7 days after MIA treatment, and the SBE 300 group was improved similarly to that of the indomethacin group. 2. Cartilage erosion was significantly recovered in the SBE and indomethacin groups, and the degree of healing of cartilage erosion by SBE was similar to that by indomethacin. 3. The serum levels of cytokines interleukin-1β, tumor necrosis factor-α, and interleukin-6 were significantly decreased in the SBE group compared with that in the control group, and the SBE 300 group had reduced levels of cytokines similar to the indomethacin group. 4. As regards acetic acid-induced writhing response, the number of writhes was significantly reduced in the SBE and ibuprofen groups, and the SBE 600 group had fewer writhes than the ibuprofen group.
Conclusion: SBE significantly improves knee OA and pain and is expected to show similar therapeutic effects to indomethacin and ibuprofen.

Keywords: Baicalein; Inflammation; Knee osteoarthritis; Pain; *Scutellaria baicalensis* extract

Received: October 20, 2022; Revised: November 2, 2022; Accepted: November 11, 2022

Corresponding author: Ho-Sueb Song
Department of Acupuncture & Moxibustion Medicine, College of Korean Medicine, Gachon University, 1342 Seongnam-daero, Sujeong-gu, Seongnam 13120, Korea
E-mail: hssong70@gachon.ac.kr

Copyright © Korean Acupuncture & Moxibustion Medicine Society

This is an Open Access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derives License (https://creativecommons.org/licenses/by-nc-nd/4.0/). For non-commercial purposes, lets others distribute and copy the article, and to include in a collective work (such as an anthology), as long as they credit the author(s) and provided they do not alter or modify the article.

INTRODUCTION

Knee osteoarthritis (OA) is the most representative chronic joint disease and causes more dysfunctions and dependence than any other disease in older people [1]. The knee joint has high mobility and is the biggest synovial joint in the human body; however, it has an unstable structure and mainly undergoes degenerative changes under direct weight [2]. Knee OA refers to histological changes in soft tissues and joints, such as the overproduction of cartilage around and within joints, destruction of articular cartilage, and deformation of joints [3], causing inflammation, pain, swelling, and shortening, and stiffness of muscles. These cause movement disorders and lower the quality of life [4].

Knee OA is diagnosed based on clinical manifestation or a combination of radiology and clinical findings. OA has several classification systems. The European League Against Rheumatism recommends diagnosing knee OA if three symptoms (reduced function, persistent pain, and limited morning stiffness) and three signals (crepitus, restricted range of motion, and bony enlargement) are present [5]. The higher the number of elements present, the more likely that the diagnosis is OA, and when all six symptoms and signals are present, OA is confirmed in radiographs at 99% [6]. In addition, one of the most frequently used clinical categorization criteria was established by the American College of Rheumatology, in which OA diagnosis is based on laboratory criteria, clinical symptoms, and radiographs [7].

As a non-surgical treatment, nonsteroidal anti-inflammatory drugs (NSAIDs) are generally used for the medical care of knee arthritis, and a recent meta-analysis reported that diclofenac 150 mg/day is the most helpful NSAID available to improve both pain and function [8]. However, the excessive use of these drugs may cause cardiovascular and gastrointestinal disorders, requiring caution [9]. Although intra-articular knee injection provides potential pain reduction and function improvement and has a low risk of injury, long-term use is limited, and no studies have proved the objective effect [5].

Scutellaria baicalensis Georgi is a herb widely used in East Asia and has traditionally been used to treat febrile cough, infectious enteritis, and jaundice [10]. According to recent studies, it has various pharmacological activities and neuroprotective, hepatoprotective, anti-inflammatory, antibacterial, antioxidant, and anticancer effects [11]. *S. baicalensis* extract (SBE) contains various polyphenols and flavonoids, among which baicalin is the most representative material indicator. Specifically, baicalin has been investigated to have antitumor, hepatoprotective, antiviral, antioxidant, and antibacterial effects at the cellular level [12,13]. Therefore, this study aimed to investigate whether SBE inhibits knee OA-induced inflammatory substances in rats, restores OA-induced joint damage, improves OA-induced discomfort and pain, and treats analgesic seizures. Following the experiments, results were compared with those of drugs mainly used for knee OA and pain.

MATERIALS AND METHODS

1. Preparation of SBE

The root of *S. baicalensis* George was purchased from Yaksudang Pharmaceutical Co., Ltd. (Seoul, Korea). A voucher specimen (2009150001) was deposited by Professor Donghun Lee, Department of Herbal Pharmacology, College of Korean Medicine, Gachon University. The dried root of *S. baicalensis* was extracted in a reflux apparatus (30% ethanol, 3 hours at 85℃), and the ratio of the extract to the herbal product was 10:1. The extract was filtered and concentrated under reduced pressure and then spray dried to yield a powder. The yield of the extract was 43.4%. Thereafter, the extract was lyophilized under −80℃.

2. High-Performance Liquid Chromatography analysis of SBE

Chromatographic analysis of SBE was performed by High-Performance Liquid Chromatography (HPLC) using a 1100 series HPLC system (Agilent, Santa Clara, CA, USA). A Zorbax EclipseXDB C18 column (4.6 × 250 mm, 5 μm; Agilent) at 30℃ was used for chromatic separation. A 1-mg sample was diluted in 10 mL of 50% methanol and sonicated for 10 minutes. Samples were filtered through a 0.45-μm syringe filter (Waters Corp., Milford, MA, USA). The mobile phase composition was 0.1% formic acid (A) and acetonitrile (B), and the column was eluted as follows: 0–3 minutes, 20%; 3–15 minutes, 20–45%; 15–20 minutes, 45–60%; 20–22 minutes, 60% solvent B with a flow rate of 1.0 mL/min. The outflow was indicated at 276 nm using an injection volume of 10 μL. The analysis was performed in triplicate.

3. Animal treatment

Five-week-old male Sprague-Dawley (SD) rats and 6-week-old male ICR mice were provided by DBL Co., Ltd. (Eumseong, Korea). The animals were acclimatized to standard laboratory conditions (22 ± 2℃, 55 ± 10% humidity, and 12 hours light/dark cycle) for at least 7

days before the experiment. The animals were given feed and water freely. All experimental procedures described above were approved by the Gachon University Center of Animal Care and Use (GIACUC-R2020028).

4. Monosodium iodoacetate injection and diet preparation

SD rats were separated into five groups (n = 9 per group), namely, sham, control, indomethacin, SBE 100 mg/kg, and SBE 300 mg/kg groups. After being anesthetized using 2% isofluorane with O_2 mixture, the rats were injected with 50 μL of 40 mg/mL Monosodium iodoacetate (MIA) (Sigma-Aldrich, St. Louis, MO, USA) intra-articularly into the knee joints to induce OA. The sham and control groups were provided basic diet (American Institute of Nutrition [AIN]-93G), the indomethacin group were provided AIN-93G diet with 0.003% indomethacin (final dose: 3 mg/kg), and each SBE group was provided AIN-93G diet with 0.11% and 0.33% SBE (final dose: 100 and 300 mg/kg). After the induction of OA by MIA, a diet of 18 g per 200 g body weight was provided every day for 24 days.

5. Hind limb's weight-bearing measurement

After inducing OA in SD rats, the weight-bearing of the hind limb was recorded on days 0, 3, 7, 10, 14, 17, 21, and 24 using an incapacitance Meter Tester 600 (IITC Life Science Inc., Woodland Hills, CA, USA), and the strength applied to each limb was averaged over 10 seconds. The percentage of weight distributed in the hind limb of the treated side (right) was calculated using the following equation: weight-bearing ratio (%) = (weight on the right hind limb / weight on the left and right hind limbs) × 100.

6. Serum measurement in the OA-induced model

Whole blood was drawn from the abdominal vein and left for 30 minutes to clot. The samples were centrifuged for 10 minutes at 4,000 rpm, and the separated serum was stored at –70℃. The multiplex assay was conducted with interleukin (IL)-1β, IL-6, and tumor necrosis factor (TNF)-α using the Premixed Multi-Analyte Kit (R&D Systems Inc., Minneapolis, MN, USA) for measurements of cytokines in the serum, and the results were analyzed with the Luminex MAGPIX Analyzer (Luminex Corp., Austin, TX, USA). The experimental procedure of all multiplex assays was performed according to the manufacturer's protocols.

7. Acetic acid-induced writhing response

ICR mice were isolated into four groups (n = 8 per group) and administered with SBE (200 and 600 mg/kg), distilled water (control), and ibuprofen 200 mg/kg (Sigma-Aldrich). Thirty minutes after oral administration, 0.7% acetic acid was injected intraperitoneally at 10 mL/kg, and writhing responses were recorded 10 minutes later. A writhing response was composed of an abdominal wall contraction and a pelvic turn following the swelling of the hind limbs.

8. Statistics

Statistical analysis was conducted using GraphPad Prism 5.0 (GraphPad Software Inc., San Diego, CA, USA) with one-way analysis of variance and Dunnett's post hoc test. The significance was verified at $p < 0.05$, and measurements were indicated as mean ± standard error of the mean.

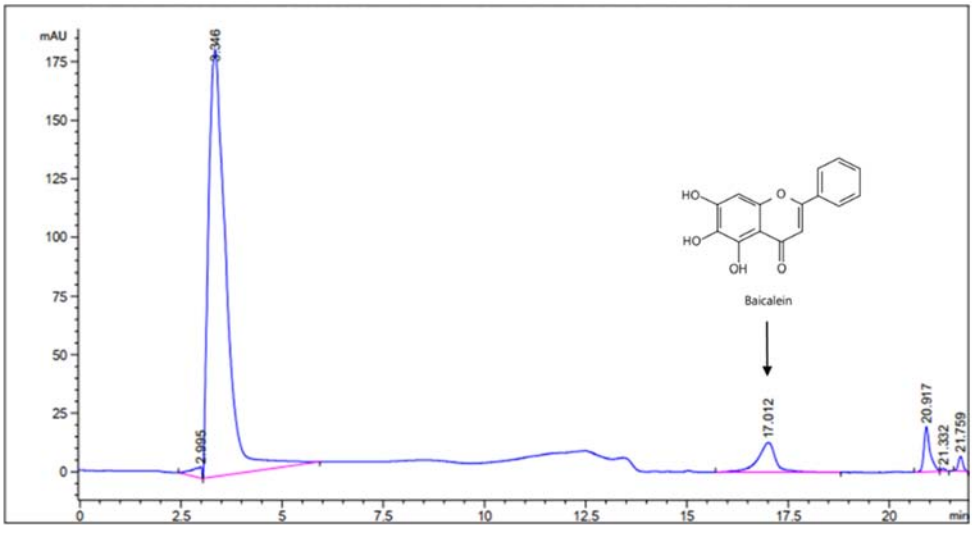

Fig. 1. High-Performance Liquid Chromatography chromatogram of *Scutellaria baicalensis* extract. The X-axis is the retention time (minutes), and the Y-axis is the absorbance unit (mAU).

RESULTS

1. HPLC analysis

In this study, baicalein was obtained, and measured in the SBE with the HPLC-UV method. The SBE contained 0.37 mg/g of baicalein. An HPLC chromatogram of the analysis along with the chemical structure of the component is shown in Fig. 1.

2. Effects on weight-bearing distribution in the MIA model

The hind limb's weight-bearing is an indicator of discomfort, and joint pain is generally used in animal models to evaluate the analgesic effects of herbal medicine in OA. The weight-bearing ratio between the right and left limbs was measured 24 days after OA induction. As shown in Fig. 2A, the weight-bearing distribution in the sham group was unchanged. However, in the control (MIA) group, it remarkably decreased on day 7 and was

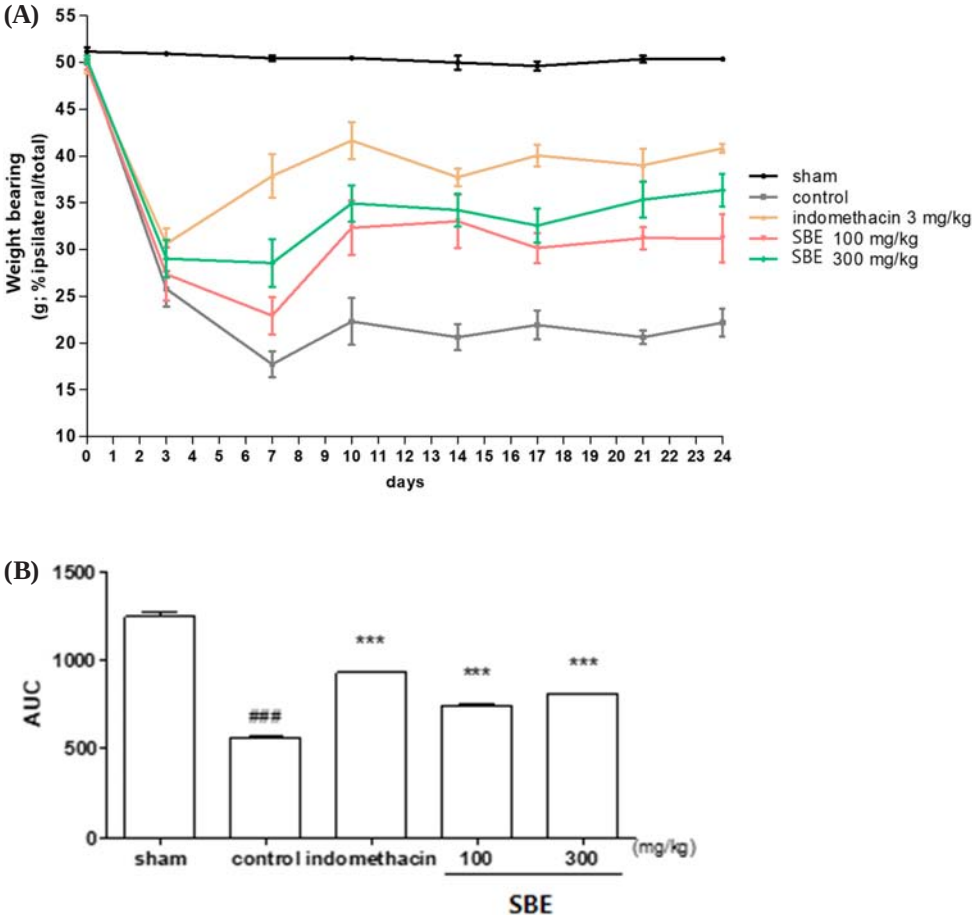

Fig. 2. Effects of *Scutellaria baicalensis* extract (SBE) on the weight-bearing of the hind limb in the monosodium iodoacetate (MIA)-induced osteoarthritis model. (A) Weight-bearing distribution of MIA rats 0–24 days with 100 mg/kg SBE and 300 mg/kg SBE or 3 mg/kg indomethacin and (B) the area under the curve (AUC) were analyzed by an incapacitance meter tester. $^{###}p < 0.001$ vs. sham, $^{***}p < 0.001$ vs. control.

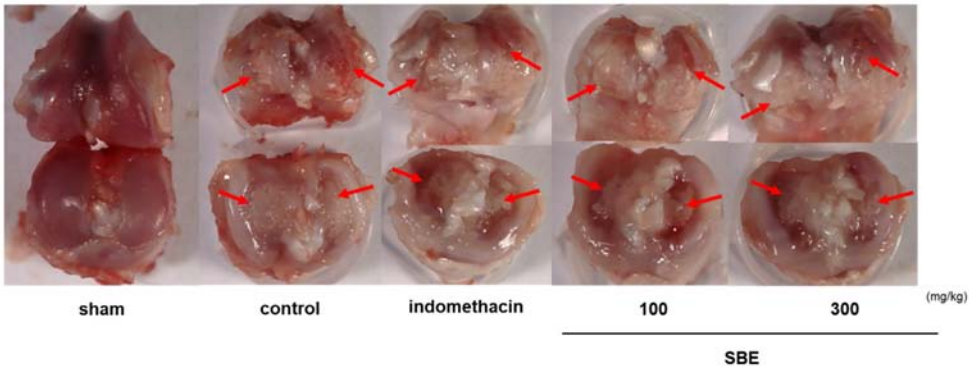

Fig. 3. Knee joint cartilages of monosodium iodoacetate (MIA)-induced osteoarthritis rats. MIA rats were treated with *Scutellaria baicalensis* extract (SBE) 100 mg/kg, SBE 300 mg/kg, and indomethacin (3 mg/kg body weight).

gradually lower than that in the sham group. In the SBE group, the weight-bearing of MIA rats notably increased. Specifically, the weight-bearing increase by SBE 300 was equivalent to that by indomethacin (Fig. 2B).

3. Effects on knee joint damage in the MIA model

The typical image of the knee joints in each experimental group shows that SBE inhibited the cartilage damage induced by MIA. As illustrated in Fig. 3, the joint cartilage of the sham group was shiny and smooth, whereas the cartilage of the control group was less gleamed and irregular with damages in several areas. The MIA-induced cartilage erosion was remarkably recovered in the indomethacin and SBE groups. Remarkably, the recovery of cartilage erosion in the SBE group was similar to that in the indomethacin group.

4. Effects on inflammatory cytokines in MIA-induced rat model

The levels of TNF-α, IL-1β, and IL-6 in the rat serum were recorded after isolating the serum from blood samples collected from each experimental group. Compared with the control group, the SBE group demonstrated a notable dose-dependent decrease in the serum concentrations of TNF-α, IL-1β, and IL-6. Intriguingly, the SBE 300 group had reduced levels of cytokine close to that of the indomethacin group (Fig. 4).

5. Effect on acetic acid-induced writhing responses

The pain-reducing effects of SBE were evaluated by the writhing responses of acetic acid-induced mice. The average number of writhes in the control group for 10 minutes was set to 100. SBE decreased the number of writhes compared with the control. The SBE 600 group had a mean number of writhes of 43.86, which was lower than that of the ibuprofen group (49.65). This result suggests the pain-reducing effects of SBE (Fig. 5).

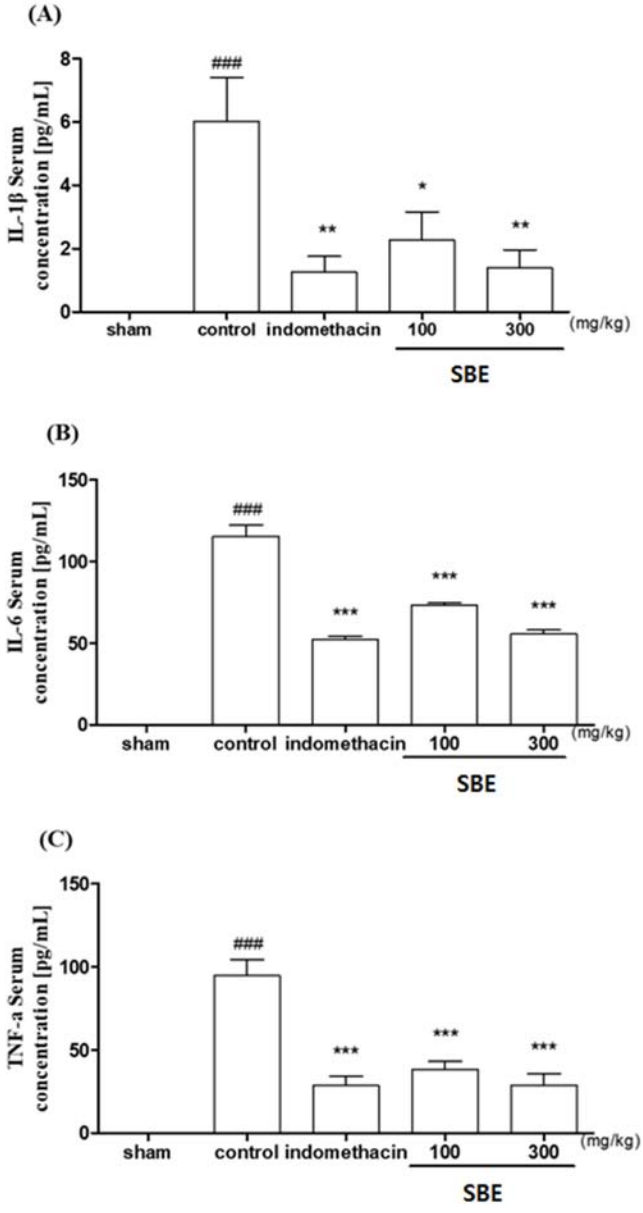

Fig. 4. Serum inflammatory cytokine levels in MIA rats. Rats were treated with 100 mg/kg and 300 mg/kg SBE for 24 days. (A) IL-1β serum levels, (B) IL-6 serum levels, (C) TNF-α serum levels. MIA, monosodium iodoacetate; SBE, *Scutellaria baicalensis* extract; IL, interleukin; TNF, tumor necrosis factor. $^{###}p < 0.001$ vs. sham group, $^{*}p < 0.05$ vs. control group, $^{**}p < 0.01$ vs. control group, $^{***}p < 0.001$ vs. control group by one-way analysis of variance, Dunnett's test.

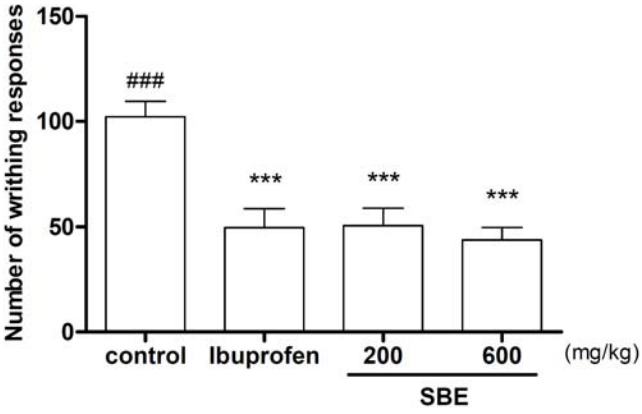

Fig. 5. Number of writhing responses in acetic acid-induced ICR mice. Thirty minutes after oral administration, each mouse was intraperitoneally injected with 0.7% acetic acid before the 10-minutes period. SBE, *Scutellaria baicalensis* extract. Each group had 8 mice: $^{###}p < 0.001$ vs. ibuprofen, $^{***}p < 0.001$ vs. control by the one-way analysis of variance, Dunnett's test.

DISCUSSION

Knee OA management aims to reduce pain, improve function, and significantly improve joint damage. The primary goal of the clinician should be the reduction of risk factors [14]. Because the effectiveness of current therapy is negligible, combination therapy is commonly used for treatment, and safer treatments should be prioritized before considering potentially harmful opioids or NSAIDs. In addition to benefits, adverse event profiles, patient-specific disorders and preferences, intervention local availability, and budgets should be considered [15].

Non-pharmacological methods are the main treatment for knee OA management and should be tried before other treatments and, when necessary, with medications to relieve pain. Non-pharmacological treatments include weight management, exercise, education, and, if necessary, the use of assistive devices [16].

In the initial stage of drug treatment, additional drugs are used in patients who have not responded appropriately to non-pharmaceutical measures or whose symptoms have worsened. Pharmacological treatment should only be used during the symptomatic period, as no drug can improve OA itself. The main drugs used for knee OA include oral and topical NSAIDs, with limited use of duloxetine, topical capsaicin, and intra-articular glucocorticoids [17].

Total joint replacement is the most common surgical treatment, which is very successful in patients with knee OA when conservative treatment and drug therapy fail to provide appropriate pain relief [18]. However, a systematic review of 14 studies found that 9–20% of patients undergoing total hip and knee replacement reported moderate-to-severe long-term pain after surgery [19]. In addition, the patient may experience serious complications, especially in younger patients; thus, reoperation may be necessary [20].

Currently, treatments used in OA in traditional Korean medicine include herbal medicine, acupuncture, moxibustion, and pharmacopuncture. The recently used components of pharmacopuncture include Chinemys reevesii Gary, Cnidium officinale, Angelica, Salvia miltiorrhiza, Homnis placenta, sweet bee venom, etc. [21]. Especially, sweet bee venom acupuncture showed statistically significant results in reducing knee joint pain and improving function in randomized controlled trials [22]. Corni fructus, Achyranthis bidentatae radix, Aconiti radix, Curcuma longa, and Vernonia amygdalina, which are currently reported as the latest traditional Korean medicine treatments for OA, can suppress inflammatory stimulation, and reduce pain symptoms in OA. In addition, traditional Korean medicine treatment restores the function of the damaged joint, significantly increases the treatment effectiveness, and significantly reduces the recurrence rate [23-25].

S. baicalensis Georgi belongs to the genus Lamiaceae and is often used for alleviating fever and detoxification in traditional Korean medicine [11]. Representative flavonoids include compounds such as baicalin, baicalein, and wogonin. Specifically, baicalin, an indicator material, and active ingredient, has antitumor, hepatoprotective, antibacterial, antiviral, antioxidant, reactive oxygen species removal, and anticonvulsant effects [13,14]. Baicalin significantly inhibited IL and NO in LPS-stimulated RAW 264.7 cells [26] and have anti-inflammatory action while suppressing the activations of TNF-a, MAPK, and NF-κB without inducing cytotoxicity [27,28]. In addition, the complex extract of *S. baicalensis*, *Morus alba*, and *Acacia catechu* showed improvement in pain and recovery of damaged cartilage and reduction of C-terminal telopeptide of type II collagen (CTX-II) in urine in MIA-induced knee OA mice [29].

In this study, OA, and pain were induced experimentally using MIA and acetic acid. OA was evaluated through the hind limb's weight-bearing distribution; levels of inflammatory cytokines TNF-α, IL-1β, and IL-6; and actual cartilage dissection, and pain was evaluated through writhing response. Moreover, whether SBE reduces inflammation, pain, and discomfort in the joints was investigated. In addition, the effect of SBE was compared with those of indomethacin and ibuprofen, which are traditionally used drugs, and the difference according to the concentration of SBE was also investigated.

In the MIA-treated group, the right weight-bearing was significantly reduced compared with that of the Siamese group. In the drug and control groups, it decreased similarly until day 3. From day 7, the indomethacin group showed a significant increase in weight-bearing compared with the control group, and in the SBE group, the weight-bearing increased significantly from day 10. On day 24, the last day of evaluation, all experimental groups showed significantly improved results ($p < 0.001$) compared with the control group. The increase in weight-bearing by SBE 300 was similar to that of indomethacin. As a result, SBE was found to improve arthritis-induced pain and discomfort.

As a result of joint dissection, the sham group showed normal results; however, the MIA-treated group was precisely less shiny and irregular with damage in some areas. The MIA-induced erosion was notably recovered in

the SBE and indomethacin groups. Remarkably, the healing of cartilage erosion by SBE 300 resembled that by indomethacin. As a result, SBE was found to help repair cartilage damage in arthritis.

Cytokines in the serum were extracted from the abdominal vein, left for 30 minutes, and then centrifuged at 4,000 rpm for 10 minutes. The SBE group showed a significant reduction in serum TNF-α, IL-1β, and IL-6 concentrations in a dose-dependent manner compared with the control group (IL-1β, $p < 0.05$; TNF-α and IL-6, $p < 0.001$). Interestingly, SBE 300 reduced the cytokine levels similar to the positive control. Thus, SBE was found to have a cytokine-reducing effect.

To confirm the analgesic effect of SBE, acetic acid-induced writhes were assessed. The analgesic effect of SBE was confirmed by comparing the number of writhes. In the control group, the average number of writhes for 10 minutes was 100. The number of writhes was remarkably decreased in the SBE group compared with that in the control group ($p < 0.001$). Specifically, the average number of writhes in mice fed 600 mg of SBE per 1 kg was 43.86, which was lower than 49.65 measured in the ibuprofen group. Thus, SBE showed analgesic effects.

This study was conducted to confirm whether SBE improves OA and pain. Before drug administration, HPLC chromatogram was performed using baicalein as a major component in SBE as an index. SBE contained 0.37 mg/g of baicalein. In previous studies, SBE-related studies have focused on baicalin, baicalein, and wogonin, and among them, baicalein was the most studied. Baicalein has been reported to have antibacterial, antiviral, and antioxidant effects and inhibit inflammatory cytokines [11,13,14,26-29]. Therefore, the present study agrees with previous studies that have investigated whether inflammatory cytokines were suppressed. In addition, the present study investigated the recovery of OA-induced dysfunction and damaged cartilage. The results indicated that SBE inhibited inflammatory cytokines, similar to results of other studies, rehabilitate motor dysfunction caused by OA, and improved damaged cartilage. This is considered the effect of baicalein.

In conclusion, SBE improved pain, and discomfort in an animal model and showed anti-inflammatory effects similar to indomethacin by inhibiting inflammatory cytokines. In addition, it aided in the recovery of damaged joints and had a similar effect to ibuprofen on pain. Therefore, SBE shows potential as a new alternative to the treatment of knee OA and pain.

CONCLUSION

The SBE group had significantly improved hind-limb weight-bearing distribution in the MIA-induced knee OA group compared with the control group. As for the degree of recovery of knee cartilage damage, cartilage erosion was significantly recovered in the SBE and indomethacin groups, and the degree of healing of cartilage erosion by SBE was similar to that by indomethacin. The serum levels of cytokines TNF-α, IL-1β, and IL-6 dose-dependently decreased in the SBE group compared with those in the control group. The SBE 300 group had reduced levels of cytokines similar to the indomethacin group. In the acetic acid-induced writhing test, the number of writhes was significantly reduced in the SBE and ibuprofen groups, and the SBE 600 group had fewer writhes than the ibuprofen group. Therefore, SBE significantly improves knee OA and pain and is expected to show similar therapeutic effects to indomethacin and ibuprofen.

AUTHOR CONTRIBUTIONS

Conceptualization: HS, HSS. Data curation: HS, HSS. Formal analysis: HS, HSS. Investigation: HS, HSS. Methodology: HS, HSS. Project administration: HS, HSS. Resources: HS, HSS. Software: HS, HSS. Supervision: HS, HSS. Validation: HS, HSS. Visualization: HS, HSS. Writing – original draft: HS, HSS. Writing – review & editing: All authors.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

FUNDING

None.

ETHICAL STATEMENT

This study was approved by the Gachon University Center of Animal Care and Use (GIACUC-R2020028).

ORCID

Haeni Seo, https://orcid.org/0000-0003-1092-4357
Ho-Sueb Song, https://orcid.org/0000-0001-5306-8795

REFERENCES

1. Baek K, An Y, Shin MR, Kim MJ, Lee JA, Roh SS. Protective effect of Corni Fructus extracts on MIA-induced animal model of osteoarthritis: effect of Corni Fructus extracts on OA. J Intern Korean Med 2020;41:1-13. doi: 10.22246/jikm.2020.41.1.1
2. Korean Acupuncture & Moxibustion Society Textbook Compilation Committee. Acupuncture medicine. Hanmi Medicine Publish Company; 2016;130-132, 537-552.
3. The Society of Korean Medicine Rehabilitation. Oriental rehabilitation medicine. 2nd ed. Koonja; 2005;84-97.
4. Korean Pharmacopuncture Institute. Pharmacopuncturology. 2nd ed. Elsevier Korea; 2011;181-215.
5. Lespasio MJ, Piuzzi NS, Husni ME, Muschler GF, Guarino A, Mont MA. Knee osteoarthritis: a primer. Perm J 2017;21:16-183. doi: 10.7812/TPP/16-183
6. Zhang W, Doherty M, Peat G, Bierma-Zeinstra MA, Arden NK, Bresnihan B, et al. EULAR evidence-based recommendations for the diagnosis of knee osteoarthritis. Ann Rheum Dis 2010;69: 483-489. doi: 10.1136/ard.2009.113100
7. Wu CW, Morrell MR, Heinze E, Concoff AL, Wollaston SJ, Arnold EL, et al. Validation of American College of Rheumatology classification criteria for knee osteoarthritis using arthroscopically defined cartilage damage scores. Semin Arthritis Rheum 2005; 35:197-201. doi: 10.1016/j.semarthrit.2005.06.002
8. da Costa BR, Reichenbach S, Keller N, Nartey L, Wandel S, Jüni P, et al. Effectiveness of non-steroidal anti-inflammatory drugs for the treatment of pain in knee and hip osteoarthritis: a network meta-analysis. Lancet 2017;390:e21-e33. doi: 10.1016/S0140-6736(17)31744-0
9. Soloman DH, Avorn J. Gastrointestinal complications of nonsteroidal antiinflammatory drugs: prophylactic and therapeutic strategies. Am J Med 1995;99:441-443. doi: 10.1016/s0002-9343(99)80203-4
10. Zhao T, Tang H, Xie L, Zheng Y, Ma Z, Sun Q, et al. Scutellaria baicalensis Georgi. (Lamiaceae): a review of its traditional uses, botany, phytochemistry, pharmacology and toxicology. J Pharm Pharmacol 2019;71:1353-1369. doi: 10.1111/jphp.13129
11. Cheng CS, Chen J, Tan HY, Wang N, Chen Z, Feng Y. Scutellaria baicalensis and cancer treatment: recent progress and perspectives in biomedical and clinical studies. Am J Chin Med 2018;46: 25-54. doi: 10.1142/S0192415X18500027
12. Wang ZL, Wang S, Kuang Y, Hu ZM, Qiao X, Ye M. A comprehensive review on phytochemistry, pharmacology, and flavonoid biosynthesis of Scutellaria baicalensis. Pharm Biol 2018;56:465-484. doi: 10.1080/13880209.2018.1492620
13. Zhao Q, Chen XY, Martin C. *Scutellaria baicalensis*, the golden herb from the garden of Chinese medicinal plants. Sci Bull (Beijing) 2016;61:1391-1398. doi: 10.1007/s11434-016-1136-5
14. Hunter DJ. Focusing osteoarthritis management on modifiable risk factors and future therapeutic prospects. Ther Adv Musculoskelet Dis 2009;1:35-47. doi: 10.1177/1759720X09342132
15. McAlindon TE, Bannuru RR, Sullivan MC, Arden NK, Berenbaum F, Bierma-Zeinstra SM, et al. OARSI guidelines for the non-surgical management of knee osteoarthritis. Osteoarthritis Cartilage 2014;22:363-388. doi: 10.1016/j.joca.2014.01.003
16. Basedow M, Esterman A. Assessing appropriateness of osteoarthritis care using quality indicators: a systematic review. J Eval Clin Pract 2015;21:782-789. doi: 10.1111/jep.12402
17. Derry S, Conaghan P, Da Silva JA, Wiffen PJ, Moore RA. Topical NSAIDs for chronic musculoskeletal pain in adults. Cochrane Database Syst Rev 2016;4:CD007400. doi: 10.1002/14651858.CD007400.pub3
18. Skou ST, Roos EM, Laursen MB, Rathleff MS, Arendt-Nielsen L, Simonsen O, et al. A randomized, controlled trial of total knee replacement. N Engl J Med 2015;373:1597-1606. doi: 10.1056/NEJMoa1505467
19. Beswick AD, Wylde V, Gooberman-Hill R, Blom A, Dieppe P. What proportion of patients report long-term pain after total hip or knee replacement for osteoarthritis? A systematic review of prospective studies in unselected patients. BMJ Open 2012;2: e000435. doi: 10.1136/bmjopen-2011-000435
20. Weinstein AM, Rome BN, Reichmann WM, Collins JE, Burbine SA, Thornhill TS, et al. Estimating the burden of total knee replacement in the United States. J Bone Joint Surg Am 2013;95: 385-392. doi: 10.2106/JBJS.L.00206
21. Lee YJ, Jo HR, Kim SH, Sung WS, Kim EJ. Efficacy and safety of pharmacopuncture and bee venom acupuncture for knee osteoarthritis: a systematic review and meta-analysis. J Korean Med 2020;41:55-83. doi: 10.13048/jkm.20005
22. Conrad VJ, Hazan LL, Latorre AJ, Jakubowska A, Kim CMH. Efficacy and safety of honey bee venom (*Apis mellifera*) dermal injections to treat osteoarthritis knee pain and physical disability: a randomized controlled trial. J Altern Complement Med 2019; 25:845-855. doi: 10.1089/acm.2019.0121
23. Hu J, Zhou J, Wu J, Chen Q, Du W, Fu F, et al. Loganin ameliorates cartilage degeneration and osteoarthritis development in an osteoarthritis mouse model through inhibition of NF-κB activity and pyroptosis in chondrocytes. J Ethnopharmacol 2020; 247:112261. doi: 10.1016/j.jep.2019.112261
24. Wang L, Zhang XF, Zhang X, Guo DY, Duan YW, Wang ZC, et al. Evaluation of the therapeutic effect of traditional Chinese medicine on osteoarthritis: a systematic review and meta-analysis. Pain Res Manag 2020;2020:5712187. doi: 10.1155/2020/

5712187
25. Song W, Chen J, Yang G, Liao J, Shen H, Li S, et al. Research on herbal therapies for osteoarthritis in 2004-2022: a web of science-based cross-sectional bibliometric analysis. Evid Based Complement Alternat Med 2022;2022:6522690. doi: 10.1155/2022/6522690
26. Suh MG, Choi HS, Cho K, Park SS, Kim WJ, Suh HJ, et al. Anti-inflammatory action of herbal medicine comprised of *Scutellaria baicalensis* and *Chrysanthemum morifolium*. Biosci Biotechnol Biochem 2020;84:1799-1809. doi: 10.1080/09168451.2020.1769464
27. Hong GE, Kim JA, Nagappan A, Yumnam S, Lee HJ, Kim EH, et al. Flavonoids identified from Korean Scutellaria baicalensis Georgi inhibit inflammatory signaling by suppressing activation of NF-κB and MAPK in RAW 264.7 cells. Evid Based Complement Alternat Med 2013;2013:912031. doi: 10.1155/2013/912031
28. Lee YE, Park HJ, Park CB, Hwang SM. Anti-inflammatory activity of Scutellaria Baicalensis root extract in lipopolysaccharide-induced RAW 264.7 cells. Korean J Food Sci Technol 2021;53:115-120. doi: 10.9721/KJFST.2021.53.2.115
29. Yimam M, Horm T, Wright L, Jiao P, Hong M, Brownell L, et al. Cartilage protection and analgesic activity of a botanical composition comprised of *Morus alba*, *Scutellaria baicalensis*, and *Acacia catechu*. Evid Based Complement Alternat Med 2017;2017:7059068. doi: 10.1155/2017/7059068