Anti-osteoclastogenic effects of *Coriandrum sativum* L. via the NF-κB and ERK-mediated NFATc1 signaling pathways

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Abstract. *Coriandrum sativum* L. (CSL) is an aromatic plant that belongs to the Apiaceae family. The present study aimed to determine the effects of the ethanol extract of the aerial part of CSL on osteoclast formation *in vitro* and *in vivo*, and the underlying molecular mechanism of its anti-osteoclastogenic effect. The levels of osteoclast formation and bone resorption were evaluated by tartrate-resistant acid phosphatase staining and bone resorption pit assays. The expression levels of osteoclast-related molecules were analyzed by reverse transcription-quantitative PCR and western blotting. The ethanol extract of CSL suppressed osteoclast formation in a mouse co-culture system. In osteoblasts, CSL exerted a minor effect on the mRNA ratio of receptor activator of nuclear factor-κB (NF-κB) ligand (RANKL) to osteoprotegerin, suggesting a direct effect of CSL on osteoclast precursors. Notably, CSL inhibited RANKL-induced osteoclast differentiation and bone resorption activity in bone marrow-derived macrophage cultures. Mechanistically, CSL abolished RANKL-induced NF-κB and extracellular signal-regulated kinase (ERK) MAPK activation, which effectively impaired the induction of c-Fos and nuclear factor of activated T cells (NFATc1). Finally, the ethanol extract of CSL prevented osteoclast formation in a lipopolysaccharide-induced calvarial bone loss model *in vivo*. The findings of the present study suggested that CSL may suppress osteoclast differentiation and function by downregulating the NF-κB and ERK/c-Fos/NFATc1 signaling pathways. Thus, CSL could be explored as a potential candidate for the prevention and treatment of osteolytic diseases.

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Abbreviations: BMM, bone marrow-derived macrophage; M-CSF, macrophage colony-stimulating factor; RANKL, receptor activator of NF-κB ligand; OPG, osteoprotegerin; TRAP, tartrate-resistant acid phosphatase; ERK, extracellular signal-regulated kinase

Key words: Coriandrum sativum L., osteoclast, NFATc1, c-Fos genes, NF-κB, ERK MAPK

Introduction

Excessive bone destruction often occurs in bone-related diseases, such as osteoporosis, rheumatoid arthritis, and osteomyelitis (1). Osteoclasts are the only cells that can degrade old bones (2). Thus, osteoclasts are considered to be clinically important. Many researchers have attempted to identify new drugs that target osteoclasts for the treatment of bone loss (3).

Osteoclasts are multinucleated monocyte/macrophage lineage cells (4). The downstream signaling pathways of macrophage colony-stimulating factor (M-CSF) and receptor activator of NF-κB ligand (RANKL) are essential for osteoclastic differentiation (5). Upon RANKL stimulation in osteoclast precursors, the recruitment of cytoplasmic TNF receptor-associated factors (TRAFs) triggers the activation of downstream signaling pathways, such as nuclear factor κB (NF-κB) and MAPKs [p38, c-Jun N-terminal kinase, and extracellular signal-regulated kinase (ERK)] (6,7). These signaling cascades induce the activation of transcription factors, such as c-Fos and nuclear factor of activated T cells (NFATc1) (8-10). NFATc1 is the master transcription factor for osteoclastogenesis and is involved in the induction of osteoclast-specific marker genes (11,12).

Coriandrum sativum L. (CSL) is an aromatic herb that belongs to the Apiaceae family (13). The fresh leaves of CSL are known as cilantro and have been employed as medicine (14). Although CSL has long been used as a traditional remedy to treat digestive problems, hyperglycemia, and other disorders (13,14), its regulatory effect on bone metabolism has not been investigated. Therefore, we aimed to determine the effect of the ethanol extract of the aerial part (stem and leaf) of CSL on osteoclast differentiation *in vitro* and *in vivo*.

Materials and methods

Reagents. The ethanol extract of CSL (reference no. 154) was provided by the National Institute of Horticultural and Herbal Science (Jeollabuk-do, Korea). Briefly, the aerial portion of CSL was extracted with 99.99% ethyl alcohol at 85˚C using an accelerated solvent extractor. The extract was subsequently filtered and concentrated using a rotary evaporator (JP-SD1000, Eyela, Tokyo Rikikatai, Japan). The final extract

was dissolved in dimethyl sulfoxide (Sigma-Aldrich) and then diluted in phosphate buffered saline (PBS). Antibodies against ERK, phospho-ERK, p38, phosphor-p38, IκB, β-actin, GAPDH and c-Fos were obtained from Cell Signaling Technology. The antibody against NFATc1 was purchased from Santa Cruz Biotechnology. All other reagents were purchased from Sigma-Aldrich.

Co-culture system. All animal experiments were performed in accordance with the NIH Guide for the Care and Use of Laboratory Animals and the Association for Assessment and Accreditation of Laboratory Animal Care of Sookmyung Women's University. For cell harvest, mice were sacrificed by CO_2 (50% vol/min) asphyxiation followed by cervical dislocation. Primary calvarial osteoblasts were extracted from the calvariae of neonatal ICR mice (Samtako Inc.), as previously described (15). Bone marrow cells were extracted from the long bones of 4- to 6-week-old ICR male mice. To examine osteoclast differentiation, mouse bone marrow cells ($1x10^5$ cells) were co-cultured with calvarial osteoblasts ($5x10^3$ cells) and 1,25-dihydroxyvitamin D_3 ($1,25-(OH)_2D_3$, 10 nM) in the presence or absence of the ethanol extract of CSL in 96-well culture plates (Corning). After six days of culture, the cells were fixed and then stained with tartrate-resistant acid phosphatase (TRAP) staining solution [0.01% naphthol AS-MX phosphate (Sigma-Aldrich) and 0.06% Fast Red Violet LB Salt (Sigma-Aldrich) in 50 mM sodium tartrate dehydrate and 45 mM sodium acetate, at pH 5.0]. TRAP-positive ($TRAP^+$) multinucleated cells (>3 nuclei/cell) were counted as mature osteoclasts.

Bone marrow-derived macrophage (BMM) culture system. Mice were sacrificed by CO_2 (50% vol/min) asphyxiation followed by cervical dislocation. Bone marrow cells were extracted from the long bones of 8- to 10-week-old ICR mice (Samtako Inc., Osan, Korea). Bone marrow cells were cultured for three days in the presence of M-CSF (30 ng/ml; PeproTech Inc.) to generate BMMs. To assess osteoclast differentiation, BMMs were treated with the ethanol extract of CSL, M-CSF (30 ng/ml), and RANKL (100 ng/ml; PeproTech Inc.). After four days, the cells were fixed and stained using TRAP.

Cell cytotoxicity assay. Cell viability was determined using the MTT assay. BMMs ($1x10^4$ cells/well) were seeded in a 96-well plate and incubated with M-CSF (30 ng/ml, R&D) and the ethanol extract of CSL in α-MEM for 48 h. Thereafter, the MTT solution was added, and culture was allowed to proceed in the dark. After 5 h, solubilization buffer (10% SDS in 0.01 M HCl) was added and the cells were cultured overnight. The viability of the BMMs was determined by measuring the optical density at 570 nm.

RNA extraction and polymerase chain reaction (PCR) assay. Total RNA was purified using Easy-Blue (iNtRON Biotechnology Inc.). cDNA was synthesized from 5 μg of RNA using the Revert Aid™ first-strand cDNA synthesis kit (iNtRON Biotechnology Inc., Korea) and amplified reverse transcription-quantitative PCR (RT-qPCR) or RT-PCR. The primers for the osteoclastogenic genes were as follows: *RANKL*: 5'-CCAAGATCTCTAACATGACG-3' (forward), 5'-CACCATCAGCTGAAGATAGT-3' (reverse); *OPG*: 5'-ACGGACAGCTGGCACACCAG-3' (forward), 5'-CTCACACACTCGGTTGTGGG-3' (reverse); calcitonin receptor (*CTR*): 5'-TTTCAAGAACCTTAGCTGCCAGAG-3' (forward), 5'-CAAGGCACGGACAATGTTGAGAAG-3' (reverse); cathepsin K (*CTK*): 5'-CTTCCAATACGTGCAGCAGA-3' (forward), 5'-ACGCACCAATATCTTGCACC-3' (reverse); *GAPDH*: 5'-AACGGATTTGGTCGTATTGGG-3' (forward), 5'-CAGGGGTGCTAAGCAGTTGG-3' (reverse); and *β-actin*, 5'-TTTGATGTCACGCACGATTTCC-3' (forward), 5'-TGTGATGGTGGGAATGGGTCAG-3' (reverse). RT-qPCR analysis was performed using SYBR® Green PCR Master Mix (Applied Biosystems) according to the manufacturer's instructions. Thermocycling was performed using a 7500 Real-time PCR System (Applied Biosystems) with the following cycling conditions: initial hold, 95˚C for 10 min; followed by 40 cycles of denaturation at 95˚C for 15 sec, annealing at 58˚C, and extension at 60˚C for 1 min. An index mRNA level was assessed using a threshold cycle value and normalized against glyceraldehyde 3-phosphate dehydrogenase (GAPDH) expression. The RT-PCR conditions for CTR, cathepsin K, and β-actin were as follows: an initial denaturation at 94˚C for 3 min, followed by 28 cycles (CTR) or 22 cycles (cathepsin K, β-actin) of denaturation at 94˚C for 30 sec, annealing at 58˚C for 45 sec, and extension at 72˚C for 60 sec; and a final extension at 72˚C for 10 min.

Western blot analysis. Total cell lysates were separated by SDS-PAGE and transferred onto Immobilon-P membranes (Millipore). The membranes were blocked with BSA in PBS-Tween (PBS-T); immunostained with anti-phospho-ERK (1:1,000), anti-ERK (1:1,000), anti-phospho p38 (1:1,000), anti-p38 (1:1,000), anti-IκB (1:1,000), anti-NFATc1 (1:200), anti-c-Fos (1:1,000), and anti-β-actin (1:4,000); and incubated with a horseradish peroxidase-conjugated secondary antibody (1:5,000). The membranes were developed using an advanced chemiluminescence detection kit (Amersham Biosciences).

Bone resorption assay. BMMs were differentiated on dentine slices in the presence of M-CSF (30 ng/ml) and RANKL (100 ng/ml) for four days and then treated with the ethanol extract of CSL for two days. The dentine slices were stained with toluidine blue (1 μg/ml) (J.T. Baker). The number of resorption pits on the dentine slices was counted.

Osteoclast formation in vivo. Mice were housed in specific pathogen-free (SPF) conditions under a 12 h light/dark cycle. Mice were provided *ad libitum* access to food and water. The experiments are terminated if the mice reach the humane end points; weight loss ≥10% compared with control group and severe necrosis at the injection site. ICR mice (12-week-old) were injected s.c. with vehicle (PBS) or lipopolysaccharide (LPS, 0.5 mg) over the calvarial bone. Mice were also administered daily i.p. injections of the ethanol extract of CSL (50 mg/kg) (dissolved in DMSO and corn oil) or vehicle beginning on day 1. On day 6, mice were euthanized by CO_2 (50% vol/min) asphyxiation followed by cervical dislocation. Whole calvaria was extracted and fixed with 4% paraformaldehyde for 24 h and then stained with TRAP. Image analysis was performed using ImageJ software (version 1.32; National Institutes of Health) according to the manufacturer's protocol.

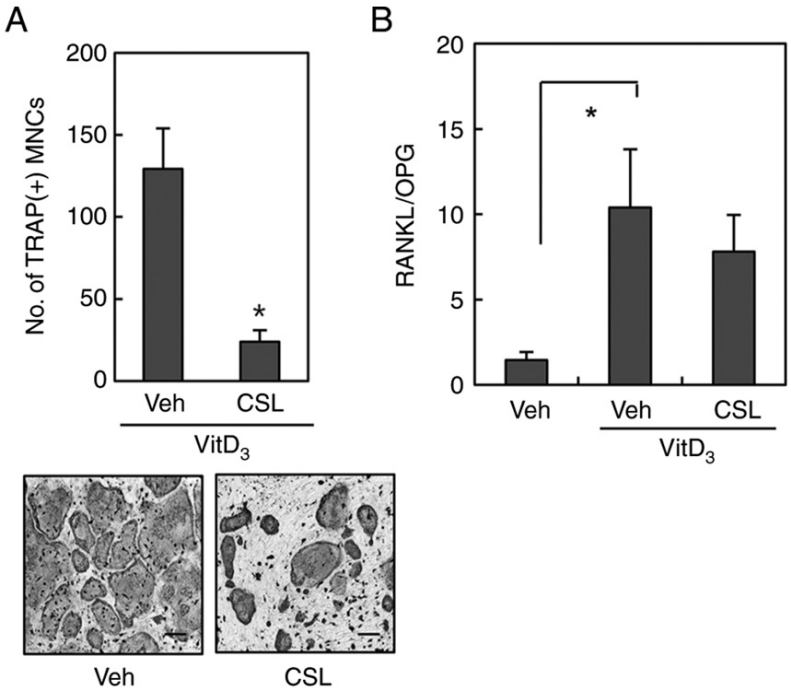

Figure 1. CSL suppresses osteoclast formation in a co-culture system. (A) Mouse bone marrow cells and primary osteoblasts were co-cultured with either Veh or the ethanol extract of CSL (10 μg/ml) in the presence of 1α,25-$(OH)_2D_3$ (10 nM) for six days. After TRAP staining, $TRAP^+$ MNCs containing three or more nuclei were counted as osteoclasts. Scale bar, 200 μm. (B) Mouse primary osteoblasts were pretreated with the ethanol extract of CSL (10 μg/ml) for 30 min and then cultured with VitD3 for 24 h. The mRNA expression level was determined using reverse transcription-quantitative polymerase chain reaction. Data are expressed as the mean ± SD of at least three independent experiments. *P<0.05 vs. Veh. CSL, *Coriandrum sativum* L.; TRAP, tartrate-resistant acid phosphatase; Veh, vehicle; VitD3, 1α,25-$(OH)_2D_3$; OPG, osteoprotegerin; MNCs, multinucleated osteoclasts.

Statistical analysis. Data are presented as mean ± standard deviation (SD) of three independent experiments and were analyzed with Prism 6 software (GraphPad Inc.). Comparisons between two and multiple groups were performed with the unpaired Student's t-test and one-way analysis of variance (ANOVA) with a post-hoc Tukey test, respectively. P<0.05 was considered to indicate a statistically significant difference.

Results

CSL inhibits osteoclast differentiation and bone resorption. First, we determined whether the ethanol extract of CSL modulates osteoclast differentiation using a mouse co-culture system. In co-cultures of mouse bone marrow cells and osteoblasts, the presence of $1,25(OH)_2D_3$ induced mature TRAP-positive ($TRAP^+$) multinucleated osteoclasts (MNCs). However, the differentiation of these MNCs was substantially inhibited by treatment with the ethanol extract of CSL (10 μg/ml) (Fig. 1A). Osteoblasts express both RANKL and osteoprotegerin (OPG), and the ratio of RANKL to OPG is known to be critical for osteoclast differentiation (16,17). As the ethanol extract of CSL exerted an inhibitory effect on osteoclast formation in the co-culture system, we further investigated whether the addition of CSL could alter the ratio of RANKL to OPG in osteoblasts. As shown in Fig. 1B, RT-qPCR revealed that treatment with $1,25(OH)_2D_3$ increased the mRNA expression ratio of RANKL to OPG, which was slightly altered by the addition of CSL. These findings suggest that the ethanol extract of CSL does not modulate the ratio of RANKL and OPG mRNAs in osteoblasts.

As the expression level of RANKL/OPG was not associated with the inhibitory effect of CSL on osteoclast formation, we proceeded to determine the effects of CSL on osteoclastogenesis using primary mouse bone marrow cells. Bone marrow cells were cultured with M-CSF to generate BMMs, and further cultured with M-CSF and RANKL for differentiation into osteoclasts. TRAP staining revealed that the ethanol extract of CSL significantly decreased the number $TRAP^+$-MNCs in a dose-dependent manner (Fig. 2A). Further, the MTT assay showed that the maximum concentration of CSL (10 μg/ml) exerted minor effects on cell viability, suggesting that the anti-osteoclastogenic effect of CSL was not attributable to cellular toxicity (Fig. 2B).

The expression levels of several marker genes are upregulated during osteoclast differentiation (11,12). Thus, we further evaluated the suppressive effect of CSL on osteoclastogenesis by measuring the mRNA expression levels of osteoclast marker genes, such as *calcitonin receptor* and *cathepsin K*. As shown in Fig. 2C, the presence of CSL clearly suppressed the mRNA expression level of *calcitonin receptor* and *cathepsin K* induced by treatment with RANKL and M-CSF, thereby confirming the anti-osteoclastogenic effect of CSL.

The main function of active osteoclasts is bone resorption. As CSL exhibited an anti-osteoclastogenic effect in a plastic plate, we determined whether the addition of CSL inhibits the bone-resorbing activity of osteoclasts using dentine slices. Resorption pits were generated in BMMs in the presence of RANKL and M-CSF. However, the addition of CSL significantly decreased the number of pits (Fig. 2D). Altogether,

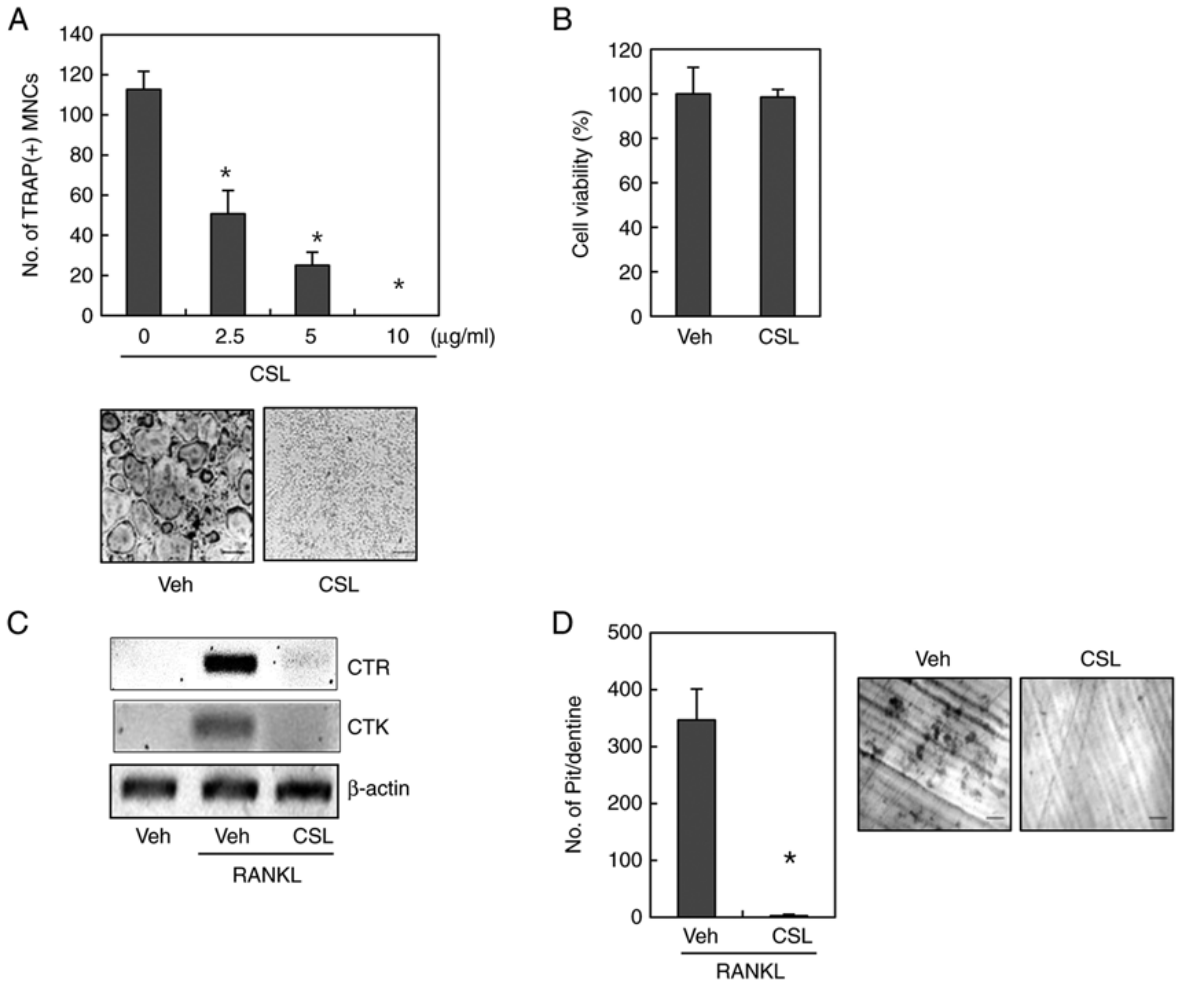

Figure 2. CSL suppresses RANKL-induced osteoclast formation and bone resorption. (A) BMMs were incubated with RANKL (100 ng/ml) and M-CSF (30 ng/ml) in the presence of the indicated concentration of the ethanol extract of CSL for four days. After TRAP staining, TRAP$^+$ MNCs were counted. (B) BMMs were cultured with M-CSF (30 ng/ml) with or without the ethanol extract of CSL (10 μg/ml) for 48 h; thereafter, an MTT assay was performed. (C) In BMM cultures, the mRNA expression level was determined using reverse transcription-polymerase chain reaction. (D) BMMs were incubated on dentine slices with M-CSF (30 ng/ml) and RANKL (100 ng/ml) for four days followed by the ethanol extract of CSL (10 μg/ml) for an additional two days. The number of resorption pits were counted. Scale bar, 200 μm. Data are expressed as mean ± SD of at least three independent experiments. *P<0.05 vs. 0 μg/ml (A) or Veh (D). CSL, *Coriandrum sativum* L.; RANKL, receptor activator of NF-κB ligand; BMMs, bone marrow-derived macrophages; M-CSF, macrophage colony-stimulating factor; TRAP, tartrate-resistant acid phosphatase; Veh, vehicle; MNCs, multinucleated osteoclasts; CTR, calcitonin receptor; CTK, cathepsin K.

these results suggests that the ethanol extract of CSL inhibits the formation of bone-resorbing osteoclasts.

CSL downregulates the RANKL-induced expression of NFATc1 and c-Fos possibly via the NF-kB and ERK MAPK pathway. As CSL has been suggested to inhibit RANKL-induced osteoclast differentiation, we explored the molecular mechanism of CSL using BMMs. Osteoclast differentiation by RANKL is primarily regulated by the master transcriptional regulator, NFATc1. c-Fos is the most well-known positive regulator of NFATc1 (8,10). Thus, we initially investigated the effects of CSL on the expression levels of NFATc1 and c-Fos. Treatment with RANKL stimulated the induction of NFATc1 and c-Fos expression in BMMs, which was completely abolished by the addition of CSL (Fig. 3A and B). These findings indicate that the ethanol extract of CSL may inhibit osteoclast differentiation by downregulating c-Fos and NFATc1 expression.

Several signaling pathways are involved in RANKL-induced osteoclast formation. When the involvement of the ERK and p38 MAPK pathways in the anti-osteoclastogenic effect of CSL was examined, pretreatment with CSL was found to suppress RANKL-induced activation of ERK, but not p38 (Fig. 3C). The involvement of the NF-κB signaling pathways was also assessed by measuring the degradation level of IκB. As reported previously (18), RANKL stimulates the degradation of IκB, which implies the activation of NF-κB. Pretreatment with CSL also suppressed RANKL-induced degradation of IκB (Fig. 3C). We additionally confirmed that the inhibitor of ERK or NF-kB pathway suppressed RANKL-stimulated NFATc1 and c-Fos expression (Fig. 3D). Taken together, these results suggest that the ethanol extract of CSL suppresses RANKL-induced expression of NFATc1 and c-Fos via the NF-κB and ERK MAPK pathways.

CSL suppresses LPS-induced osteoclast formation in vivo. As the anti-osteoclastogenic effect of CSL was observed *in vitro*, we finally examined the effect of CLS on osteoclast formation *in vivo* using a mouse model of bone destruction (19).

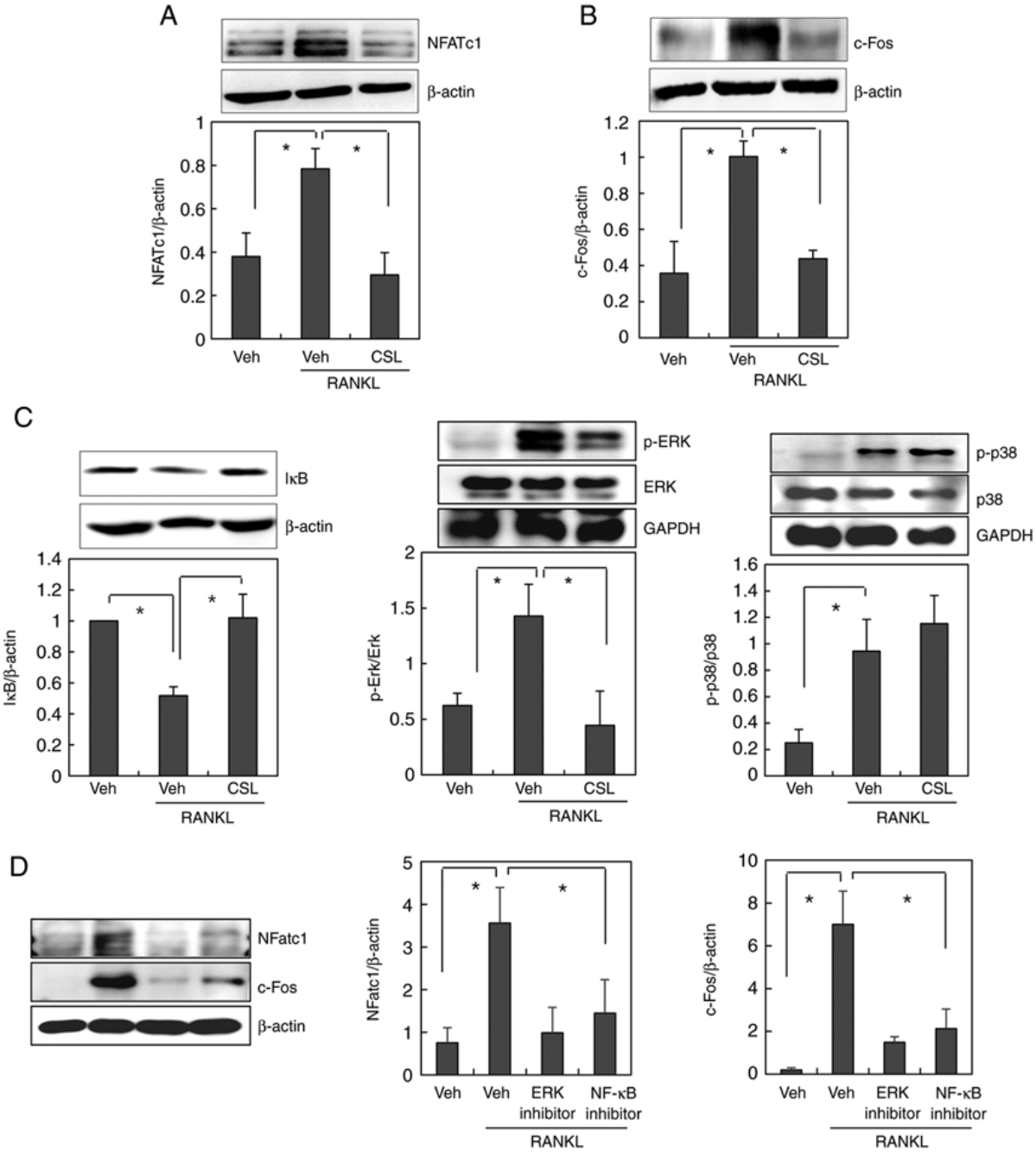

Figure 3. CSL inhibits the RANKL-induced expression of c-Fos and NFATc1 via NF-κB and ERK MAPK activation. (A-C) BMMs were preincubated with or without the ethanol extract of CSL (10 μg/ml) for 30 min, and then treated with 100 ng/ml of RANKL for 24 h (for NFATc1 and c-Fos) or 15 min (for IκB, p-ERK and p-p38). The cell lysates were then subjected to western blot analysis using (A) NFATc1, (B) c-Fos, (C) IκB, p-ERK, or p-p38 antibodies. (D) BMMs were incubated with or without ERK inhibitor (U-0126, 10 μM) or NF-κB inhibitor (Bay 11-7082, 10 μM) before RANKL treatment. The cell lysates were then subjected to western blot analysis. Data are expressed as mean ± SD of at least three independent experiments. *P<0.05. CSL, *Coriandrum sativum* L.; RANKL, receptor activator of NF-κB ligand; BMMs, bone marrow-derived macrophages; Veh, vehicle; NFATc1, nuclear factor of activated T cells; p-, phosphorylated; ERK, extracellular signal-regulated kinase; NF-κB, nuclear factor-κB.

Briefly, LPS was injected into the calvarial bones of mice with or without the ethanol extract of CSL. TRAP staining of whole calvariae revealed that the injection of LPS significantly increased the number of osteoclasts (Fig. 4). Systemic administration of the ethanol extract of CSL markedly decreased LPS-induced osteoclast formation *in vivo*, thereby aligning with the effects observed *in vitro*. Altogether, these results suggest that LPS-induced osteoclast formation was effectively prevented by the ethanol extract of CSL *in vivo*.

Discussion

Metabolic bone disorders are often caused by excessive bone destruction by hyper-activated osteoclasts. Several plants have been traditionally used to treat bone loss (20-22); however, little is known regarding the effects of CSL on bone metabolism. In this study, CSL was demonstrated to effectively suppress osteoclast differentiation and bone resorption activity. Among the signaling pathways involved in osteoclast formation, the

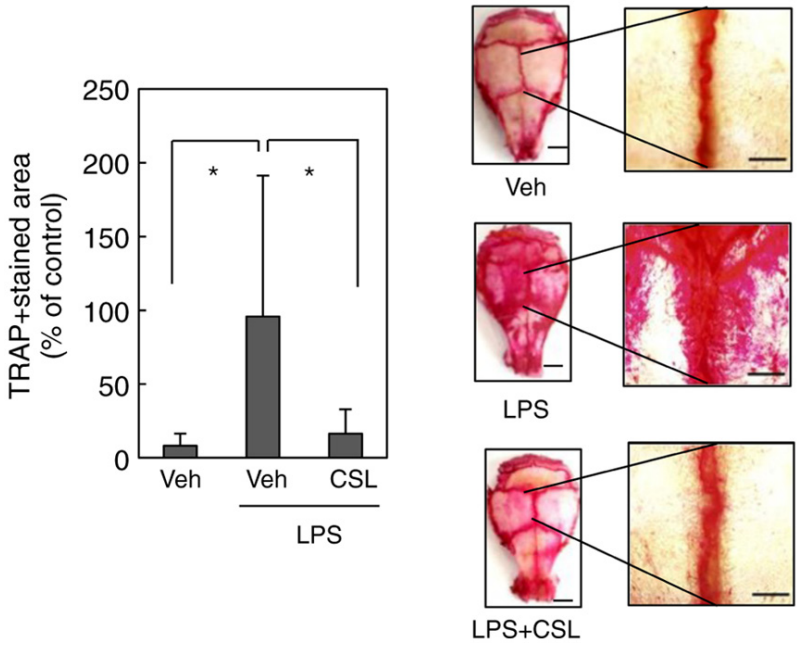

Figure 4. CSL inhibits LPS-induced osteoclast formation *in vivo*. Mice were injected s.c. with LPS (0.5 mg) over the calvarial bone. Mice were also administered daily i.p. injections of the ethanol extract of CSL (50 mg/kg) or Veh for 5 days. The calvariae of mice administered vehicle, LPS, or LPS combined with CSL were subjected to TRAP staining. The TRAP-stained area was measured using ImageJ Software. Data are expressed as mean ± SD of at least three independent experiments. *P<0.05. Scale bar, 2 mm (left) or 200 μm (right). CSL, *Coriandrum sativum* L.; LPS, lipopolysaccharide; TRAP, tartrate-resistant acid phosphatase; Veh, vehicle.

addition of CSL abolished the activation of the NF-κB and ERK MAPK pathways. CSL also inhibited RANKL-induced NFATc1 expression. As NFATc1 is the master transcription factor for osteoclast differentiation, CSL is suggested to modulate osteoclast formation by downregulating the activation of NF-κB and ERK MAPK and its downstream NFATc1 signaling pathways.

In this study, CSL was found to inhibit osteoclast formation in co-cultures of mouse primary osteoblasts and bone marrow cells. CSL was found to have minor effects on the mRNA expression ratio of RANKL to OPG in osteoblasts treated with 1α,25-$(OH)_2D_3$. These findings suggest that CSL inhibits osteoclast formation by acting directly on osteoclast precursors. The effect of CSL on bone-forming activity in osteoblasts needs further verification.

Numerous reports have revealed the therapeutic value of the aerial parts of *C. sativum*. These values include antioxidant and free radical scavenging activities and metal-chelating and anti-bacterial effects (23,24). Previously, the anti-inflammatory effect of *C. sativum* was suggested (25). The aerial part of *C. sativum* was found to inhibit LPS-induced iNOS, COX-2, and IL-1β expression via the MAPK and NF-κB pathways in RAW264.7 macrophage cells. As LPS stimulates osteoclast formation in RAW264.7 macrophage cells (26), *C. sativum* may use this mechanism to suppress osteoclast formation. The precise molecular mechanism of the inhibitory effect of CSL on osteoclastogenesis requires further investigation.

According to the previous study, luteolin, vicenin, ferulic acid, and arbutin were suggested as the main components in the aerial part of *C. sativum* (27). Furthermore, rutin was identified as a major component of *C. sativum* with anti-inflammatory properties (25). Luteolin, ferulic acid, arbutin, and rutin have been reported to prevent bone loss by inhibiting osteoclast differentiation and function (28-31). As the whole extract of *C. sativum* has been used as a traditional oriental medicine, we investigated the effect of the crude extract of CSL. However, our study on the isolation of component of CSL with biological activities remain limited. A further study is needed to isolate and validate the components of CSL that prevent osteoclast-related bone diseases. It would be also of worth to verify the synergistic or counteractive interaction between the components of CSL with anti-osteoclastogenic effect.

In conclusion, we reveal that the ethanol extract of CSL modulates RANKL-induced osteoclast differentiation. This inhibitory activity of CSL, at least in part, occurs through NF-κB and ERK MAPK-mediated NFATc1 expression. As many effective drugs originate from plants, CSL could be a good candidate for the development of new therapeutics targeting osteoclasts to prevent various bone diseases.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

This work was designed by JSS, HYL and MY. Experiments were performed by JSS and HYL. Data collection, analysis and interpretation were performed by JS, HL and MY. MY drafted and revised the manuscript. JSS, HYL and MY confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The animal study protocol was approved by the Institutional Review Board of Sookmyung Women's University (approval no. SMWU-IACUC-2109-013).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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