ORIGINAL ARTICLE
Archives of Rheumatology 2026 [epub ahead of print]
DOI: 10.5152/ArchRheumatol.2026.25143

Effects of Luteolin on an MIA-Induced Osteoarthritis Rat Model via Reducing IL-18

ABSTRACT

Background/Aims: Luteolin (LUT), a flavone abundant in *Reseda luteola*, possesses well-documented anticancer, antioxidant, and anti-inflammatory properties. This study aimed to investigate whether LUT attenuates osteoarthritis (OA) progression by suppressing interleukin (IL)-18 expression in a monosodium iodoacetate (MIA)-induced OA rat model.

Materials and Methods: Osteoarthritis was induced by intra-articular injection of MIA. Luteolin and celecoxib (CLX) were administered orally once daily for 2 weeks, beginning 2 weeks after MIA injection (n = 6 per group). Pain-related behaviors were evaluated using weight-bearing and von Frey tests. Structural pathology was assessed using hematoxylin and eosin (H&E), Safranin O, and Toluidine Blue staining, followed by modified Mankin scoring. Interleukin-18 expression was quantified in serum and articular cartilage using immunohistochemistry and quantitative real-time polymerase chain reaction (qRT-PCR).

Results: Luteolin significantly increased the weight-bearing ratio and mechanical withdrawal threshold. Luteolin also showed a trend toward attenuating cartilage damage and reducing modified Mankin scores, although these effects were not statistically significant. In addition, LUT significantly reduced the number of IL-18-positive chondrocytes in cartilage and showed a tendency to decrease IL-18 mRNA expression and serum IL-18 concentrations. These effects were comparable to those observed with CLX treatment.

Conclusion: This study provides preclinical evidence that LUT may exert anti-inflammatory and chondroprotective effects in MIA-induced OA, potentially through modulation of IL-18. These findings support further investigation of LUT as a potential therapeutic candidate for OA.

Keywords: Luteolin, osteoarthritis, interleukin-18, inflammation, cartilage pathology

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Received: September 11, 2025
Revision Requested: November 4, 2025
Last Revision Received: June 1, 2026
Accepted: June 4, 2026
Publication Date: July 3, 2026

Cite this article as: Kim JH, Lee SH, Lee YJ, Song JY, Gil HH, Lee J. Effects of luteolin on an MIA-induced osteoarthritis rat model via reducing IL-18. *ArchRheumatol.* Published online July 03, 2026. doi: 10.5152/ArchRheumatol.2026.25143.

Introduction

Osteoarthritis (OA) is a chronic degenerative joint disease characterized by pain and stiffness resulting from progressive joint deterioration and mechanical stress[1]. The prevalence of OA increases with age and is expected to continue to rise further with the aging population.[2] Osteoarthritis is accompanied by inflammation of the synovial membrane, cartilage breakdown, osteophyte formation, and changes and destruction of subchondral bones.[3] Age-related cartilage degeneration is considered a major cause of OA and may be influenced by various factors, including obesity, sex, and diet.[4] Current OA management primarily focuses on symptom relief rather than disease modification. For example, nonsteroidal anti-inflammatory drugs (NSAIDs) are

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widely used to reduce inflammation and alleviate pain.[5] However, currently available treatments, including commonly prescribed NSAIDs, are limited in their ability to halt or reverse disease progression.[6] Moreover, long-term NSAID use is associated with serious systemic adverse effects, including gastrointestinal toxicity, cardiovascular complications, renal and hepatic toxicity, and potential cartilage damage.[7]

Interleukin-18 (IL-18), a member of the IL-1 cytokine family, is a pro-inflammatory cytokine secreted by various cell types, including chondrocytes, osteoblasts, and macrophages.[8] Upon binding to its receptor, IL-18 promotes articular cartilage degeneration, osteophyte formation, and synovitis by increasing the expression of IL-18 receptor, matrix metalloproteinases (MMPs), and cyclooxygenase-2 (COX-2).[9] Furthermore, IL-18 levels in synovial fluid and serum increase with disease severity.[10] Activation of the mitogen-activated protein kinase (MAPK) and nuclear factor kappa B (NF-κB) signaling pathways enhances COX-2 expression, suppresses proteoglycan production and aggrecan synthesis, and increases MMP expression, thereby contributing to cartilage degeneration.[11] In addition to promoting cartilage destruction, IL-18 stimulates the secretion of pro-inflammatory cytokines through activation of the NF-κB and MAPK pathways, thereby exacerbating inflammation.[12] Therefore, IL-18 is considered a key mediator of OA pathogenesis, and recent studies have explored therapeutic strategies targeting IL-18.

Luteolin (LUT) is a flavone that can be isolated from *Reseda luteola*.[13] Luteolin is abundant in fruits and green vegetables and has demonstrated therapeutic potential in chronic diseases, including alcoholic liver disease,[14] atherosclerosis,[15] and ulcerative colitis.[16] In addition, LUT exerts antitumor effects through inhibition of the nuclear factor erythroid 2–related factor 2 (Nrf2) pathway.[17] Luteolin also exhibits anti-inflammatory activity by regulating the expression of pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), IL-1β, and IL-6. However, studies investigating whether LUT specifically modulates IL-18 expression or activity, a key pathogenic mediator in OA, remain limited.

MAIN POINTS

- *Luteolin (LUT) attenuated pain-related behaviors in monosodium iodoacetate-induced osteoarthritis rats.*
- *Histological analyses indicated that LUT alleviated cartilage damage and reduced modified Mankin scores.*
- *LUT suppressed interleukin-18 (IL-18) expression in both articular cartilage and serum.*
- *These findings suggest that LUT may serve as a potential therapeutic agent for osteoarthritis through IL-18 inhibition.*

Therefore, this study aimed to investigate the therapeutic efficacy of LUT in a rat OA model and elucidate the underlying mechanism, specifically focusing on the suppression of IL-18, a key factor implicated in cartilage degradation and inflammation.

Materials and Methods

Materials

Monosodium iodoacetate (MIA), xylazine, and dimethyl sulfoxide (DMSO) were purchased from Sigma-Aldrich (MO, USA). Zoletil®50 was purchased from Virbac Korea (Seoul, Republic of Korea). Phosphate-buffered saline (PBS) was obtained from WELGENE, Inc. (Daegu, Republic of Korea). Luteolin was purchased from Santa Cruz Biotechnology, Inc. (TX, USA). Celecoxib (CLX) was purchased from Pfizer Korea (Seoul, Republic of Korea). IL-18 and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) primers were purchased from Bioneer (Daejeon, Republic of Korea).

Osteoarthritis Rat Model

Twenty-four male Sprague–Dawley rats were purchased from Young Bio (Gyeonggi-do, Republic of Korea). This study was approved by the the Institutional Animal Care and Use Committee (IACUC) of Chung-Ang University (approval no. 202100210; March 27, 2021). The animals were housed three per cage under controlled environmental conditions (temperature: 22°C; relative humidity: approximately 50%; 12-h light/dark cycle; Dates of study: April 1, 2021-May 6, 2021). The rats were acclimatized for 1 week before experimentation. After acclimatization, animals were randomly assigned to four groups (n = 6 per group): (1) Normal group (PBS injection), (2) MIA group (MIA injection), (3) MIA + LUT group, and (4) MIA + CLX group. Luteolin and CLX were administered by oral gavage for 14 days following MIA injection. Osteoarthritis was induced by intra-articular injection of MIA (60 mg/mL in PBS, 50 μL) into the left knee joint, except in the Normal group, which received PBS (50 μL). Animals in the LUT and CLX groups received LUT (30 mg/kg/day, dissolved in 0.1% DMSO) and CLX (3 mg/kg/day), respectively, for 14 days (Figure 1A). The sample size (n = 6 per group) was determined in accordance with the 3R principles to minimize animal use while ensuring statistical validity.

Weight-Bearing Test

The weight-bearing test was performed before MIA injection and on days 0, 3, 6, 10, and 14 after treatment. Each rat was placed in a 60° inclined plexiglass chamber to measure hind limb weight distribution. The hind limbs were positioned centrally on the sensor, and weight distribution was recorded for approximately 10 seconds using an incapacitance meter (Bioseb, FL, USA). Mean values were calculated.

$$Weight\ bearing\ ratio\ (\%) = \frac{left\ hind\ limb\ weight\ (g)}{total\ hind\ limb\ weight\ (g)} \times 100$$

Measurements of the Paw Withdrawal Threshold

Paw withdrawal threshold (PWT) was assessed using von Frey monofilaments (Bioseb) at baseline and on days 0, 3, 6, 10, and 14. Animals were placed in plexiglass cages (IWOO Scientific Corporation, Seoul, Republic of Korea) for 15 minutes before testing. Mechanical stimuli were applied to the plantar surface of the left hind paw using monofilaments with gradually increasing force. Behavioral responses, including paw withdrawal, licking, or lifting, were recorded by a blinded observer. The threshold force eliciting a response was recorded as the PWT.

Histological Analysis

Following LUT administration, the left knee joints were harvested and fixed in 10% formaldehyde for 48 hours, followed by rinsing in running tap water for 2 hours. Specimens were decalcified in a decalcifying solution (Sigma-Aldrich) for 24 hours. After dehydration in graded ethanol and clearing in xylene, tissues were embedded in paraffin and sectioned sagittally at approximately 5 μm thickness. Sections were stained with hematoxylin and eosin (H&E), Safranin O, and Toluidine Blue.

Evaluation of Articular Damage (Modified Mankin Score)

Cartilage damage was evaluated using H&E and Safranin O staining. Osteoarthritis-related morphological changes were characterized by cartilage erosion and surface irregularity in the MIA group. The severity of cartilage degeneration was assessed using the modified Mankin scoring system, where normal tissue was assigned a score of 0, surface irregularities were assigned a score of 1, pannus formation with surface irregularities was assigned a score of 2, and clefts extending to the transitional zone were assigned a score of 3.[18]

Enzyme-Linked Immunosorbent Assay

At the end of the 2-week treatment period, blood samples were collected from the abdominal vein. Serum was obtained by centrifugation at 1,500 × g for 10 minutes and stored at −80 °C until analysis. Serum IL-18 levels were measured using an enzyme-linked immunosorbent assay (ELISA) kit (Thermo Fisher Scientific, MA, USA) according to the manufacturer's instructions. Optical density was measured at 450 nm using a microplate reader (FlexStation 3, Molecular Devices, USA).

Quantitative Real-Time Polymerase Chain Reaction

Cartilage tissues were immediately frozen in liquid nitrogen and pulverized. Total RNA was extracted using TRIzol reagent (Invitrogen, MA, USA), and RNA concentration was measured using a NanoDrop spectrophotometer (Thermo Fisher Scientific). Complementary DNA (cDNA) synthesis was performed using an iScript cDNA synthesis kit (Bio-Rad, CA, USA). Quantitative real-time polymerase chain reaction (qRT-PCR) was conducted using iQ SYBR Green Supermix (Bio-Rad) and gene-specific primers (Table 1). Relative messenger RNA (mRNA) expression was calculated using Ct (cycle threshold) values.

Immunohistochemistry

Paraffin-embedded sections were incubated at 60℃ for 1 hour, deparaffinized in xylene, and rehydrated through

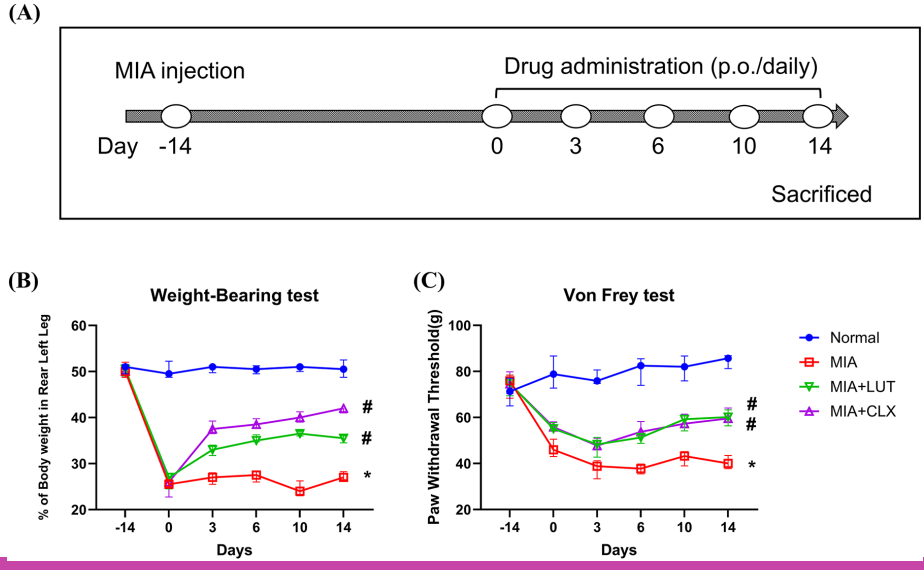

Figure 1. Experimental timeline and effects of LUT on behavioral outcomes in an MIA-induced OA model. (A) Experimental schedule for MIA-induced OA. (B) Weight-bearing analysis was performed using an incapacitance meter to evaluate the proportion of body weight supported by the left hind limb. (C) Mechanical sensitivity of the left hind limb was assessed by measuring the paw withdrawal threshold using von Frey filaments. Data from the Normal, MIA, MIA + LUT, and MIA + CLX groups are presented as line graphs showing the median with IQR (n = 6 per group). Statistical analysis was performed using a linear mixed-effects model (LMM) followed by Tukey's post hoc multiple-comparison test. *vs. Normal group; #vs. MIA group.

graded ethanol to distilled water. Antigen retrieval was performed in 10 mM sodium citrate buffer (pH 6.0, 0.05% Tween-20) using a microwave (95℃, 5 minute), followed by cooling to room temperature. Endogenous peroxidase activity was blocked using 3% hydrogen peroxide. Non-specific binding was blocked with 5% normal goat serum. Sections were incubated overnight at 4℃ with anti-IL-18 antibody (1:100; Cell Signaling Technology, MA, USA). After PBS washes, sections were incubated with a biotinylated secondary antibody (1:200; Thermo Fisher Scientific), followed by the avidin–biotin–peroxidase complex. Signal was developed using 3,3'-diaminobenzidine for 1 minute. Slides were counterstained with hematoxylin, rinsed, dehydrated, and mounted. Images were acquired using a PA53 BIO FS6 microscope (Motic, Hong Kong).

Blinded Assessment

All behavioral and histological analyses were performed by a single trained investigator blinded to group allocation. Samples were coded before analysis, and group identities were revealed only after data acquisition and scoring were completed.

Statistical Analysis

All data are presented as medians with interquartile ranges (IQRs). Statistical analyses were performed using GraphPad Prism 11.0 (GraphPad Software, Inc.; CA, USA). Statistical tests were selected based on the experimental design and data distribution. For longitudinal behavioral data, including weight-bearing and von Frey tests, a linear mixed-effects model (LMM) was used to account for within-subject correlations across repeated measurements, followed by Tukey's post hoc multiple-comparison test. For single-time-point outcomes, including histopathological and molecular data (IL-18), non-parametric tests were applied owing to the non-normal distribution expected in small sample sizes. Group differences were analyzed using the Kruskal–Wallis test, followed by Dunn's post hoc multiple comparisons test. Statistical significance was set at $P < .05$.

Results

Effect of Luteolin on Weight-Bearing Ratio in a Monosodium Iodoacetate–Induced Osteoarthritis Model

Weight-bearing and von Frey tests were performed to evaluate weight distribution and PWT in the MIA-induced OA model. At day 0, all groups except the Normal group exhibited a weight-bearing ratio of less than 30%, whereas the Normal group showed a balanced distribution of approximately 50% ($P < .001$), confirming successful OA induction. Oral administration of LUT and CLX significantly restored the MIA-induced reduction in weight-bearing ratio ($P < .001$) (Figure 1B). At day 0, all groups except the Normal group exhibited a paw withdrawal threshold of less than 60 g, whereas the Normal group showed a threshold of approximately 80 g ($P < .001$). From day 3 onward, the MIA + LUT and MIA + CLX groups showed a significant increase in withdrawal threshold compared with the MIA group ($P < .001$) (Figure 1C). Luteolin and CLX showed significant differences in weight-bearing analysis over time (day 3: $P = .002$; day 6: $P = .011$; day 10: $P < .001$; day 14: $P < .001$), but no significant differences were observed in the von Frey test (day 3: $P = .986$; day 6: $P = .071$; day 10: $P = .995$; day 14: $P = .998$).

Effect of Luteolin on Histological Changes in Articular Cartilage in a Monosodium Iodoacetate–Induced Osteoarthritis Model

To evaluate cartilage structural changes, knee joints were harvested and processed for histological analysis. Cartilage tissues were stained with H&E, Safranin O, and Toluidine Blue (Figure 2A–C). Monosodium iodoacetate-induced OA resulted in marked cartilage degeneration, reflected by a significant reduction in knee diameter ($Z = 2.944$, $P = .0194$; effect size $r = 1.20$) and an increased modified Mankin score ($Z = 4.450$, $P < .0001$; effect size $r = 1.28$). Luteolin showed a non-significant trend toward increased knee diameter ($Z = 1.132$, $P > .9999$; effect size $r = 0.46$) and reduced modified Mankin score ($Z = 1.872$, $P = .3676$; effect size $r = 0.72$ (Figure 2D and E). Similarly, CLX showed a non-significant trend toward increased knee diameter ($Z = 2.038$, $P = .2492$; effect size $r = 0.83$) and reduced modified Mankin score ($Z = 2.495$, $P = .0755$; effect size $r = 0.72$) (Figure 2D and E). No significant differences were observed between the LUT and CLX groups in knee diameter ($Z = 0.906$, $P > .9999$; effect size $r = 0.37$) or Mankin score ($Z = 0.624$, $P > .9999$; effect size $r = 0.18$).

Effects of Luteolin on Interleukin-18 Expression in an Monosodium Iodoacetate-Induced Osteoarthritis Model

Interleukin-18 is a key mediator of joint inflammation and cartilage destruction. Interleukin-18 expression in cartilage and serum was evaluated using immunohistochemistry (IHC), qRT-PCR, and ELISA. The number of IL-18-positive chondrocytes was increased in the MIA group, although this change was not statistically significant ($Z = 0.42$, $P > .9999$; effect size $r = 0.42$). Luteolin significantly reduced IL-18-positive chondrocytes ($Z = 2.737$, $P = .0372$; effect size $r = 1.12$), whereas CLX showed a non-significant reduction ($Z = 2.395$, $P = .0998$; effect size $r = 0.98$) (Figure 3A and 3B). Interleukin-18 mRNA expression in cartilage showed a non-significant increase in the MIA group ($Z = 2.378$, $P = .1045$; effect size $r = 0.97$). Luteolin ($Z = 1.925$, $P = .3255$; effect size $r = 0.79$) and CLX ($Z = 1.812$, $P = .4202$; effect size $r = 0.74$) showed non-significant reductions in IL-18 mRNA expression (Figure 3C). Serum IL-18 levels were significantly elevated in the MIA

Table 1. The Primer Sequences for RT-qPCR

Gene		Sequence (5' → 3')
IL-18	Forward	GCTCCATGCTTTCCGTAATC
	Reverse	TTTCCTGATCCTGGAGGTTG
GAPDH	Forward	TCTCCCTCACAATTCCATCC
	Reverse	GGGTGCAGCGAACTTTATTG

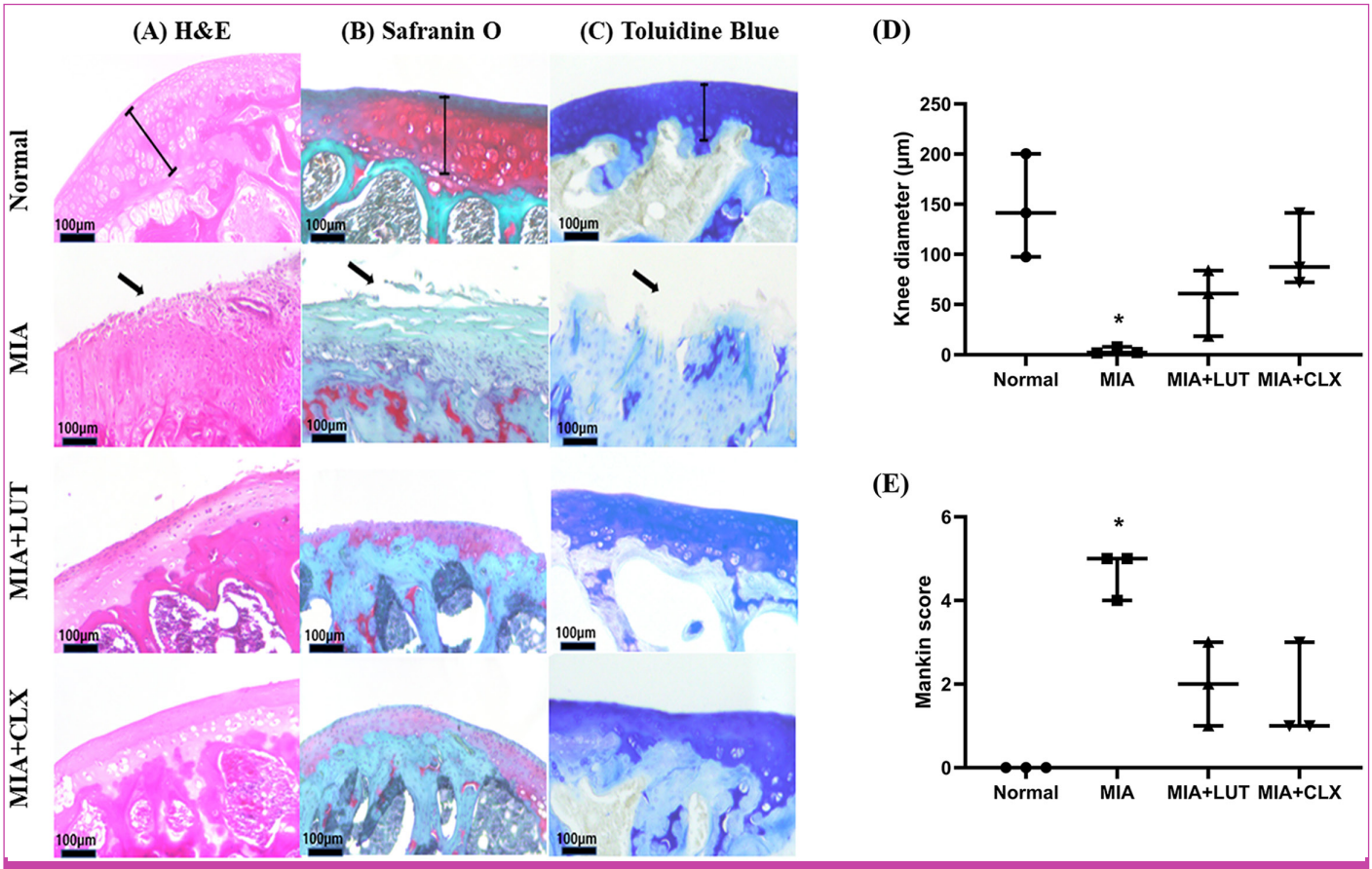

Figure 2. Histological analysis of articular cartilage in an MIA-induced OA model. Cartilage structure in the femoral condyle was evaluated using (A) H&E, (B) Safranin O, and (C) Toluidine Blue staining. Magnification, ×40. Lines and arrows indicate cartilage thickness and cartilage destruction, respectively. Scale bar = 100 μm. Cartilage damage was assessed based on (D) knee joint diameter and (E) modified Mankin score (n = 3 per group). Data are presented as box-and-whisker plots showing the median with IQR. Statistical analysis was performed using the Kruskal–Wallis test followed by Dunn's multiple comparisons test. *vs. Normal group; #vs. MIA group.

group compared with the Normal group ($Z = 4.421$, $P < .0001$; effect size $r = 1.28$). Luteolin ($Z = 2.128$, $P = .1998$; effect size $r = 0.61$) and CLX ($Z = 2.292$, $P = .1314$; effect size $r = .66$) showed non-significant reductions in serum IL-18 levels (Figure 3D). No significant differences were observed between the LUT and CLX groups in IL-18-positive chondrocytes ($Z = 0.3421$, $P > .9999$; effect size $r = 0.14$), IL-18 mRNA expression ($Z = 0.1132$, $P > .9999$; effect size $r = 0.05$), or serum IL-18 levels ($Z = 0.1637$, $P > .9999$; effect size $r = 0.05$).

Discussion

This study investigated the chondroprotective effects and mechanisms of action of LUT compared with CLX in an OA model. The OA pharmacological effects of LUT were first evaluated using behavioral assessments, including the weight-bearing and von Frey tests. Oral administration of LUT and CLX significantly reduced the difference in weight-bearing and increased the threshold for inducing hind paw withdrawal. These findings indicate that MIA-induced pain was alleviated by both LUT and CLX. In the weight-bearing test, CLX showed a significantly greater effect than LUT; however, no significant difference was observed in the von Frey test. Histological analyses, including H&E, Safranin O, and Toluidine Blue, suggested a trend in which LUT attenuated MIA-induced cartilage degeneration. These results indicated that the observed reduction in pain behavior may be partially associated with LUT-mediated attenuation of cartilage damage. Given the observed protective effects on cartilage, cartilage tissue and serum were analyzed to assess IL-18 expression, a key mediator of cartilage degradation. The number of IL-18-positive cells in cartilage showed an increasing trend in the MIA group and was significantly reduced in the LUT group. Assessment of IL-18 mRNA expression in cartilage and IL-18 protein levels in serum revealed similar reductions, although not statistically significant. Overall, these findings suggest that LUT modulation of IL-18 may contribute to the observed trends toward reduced cartilage damage and pain in OA. No significant differences were observed between the LUT and CLX groups in cartilage degeneration or IL-18 expression, suggesting that LUT may provide effects comparable to

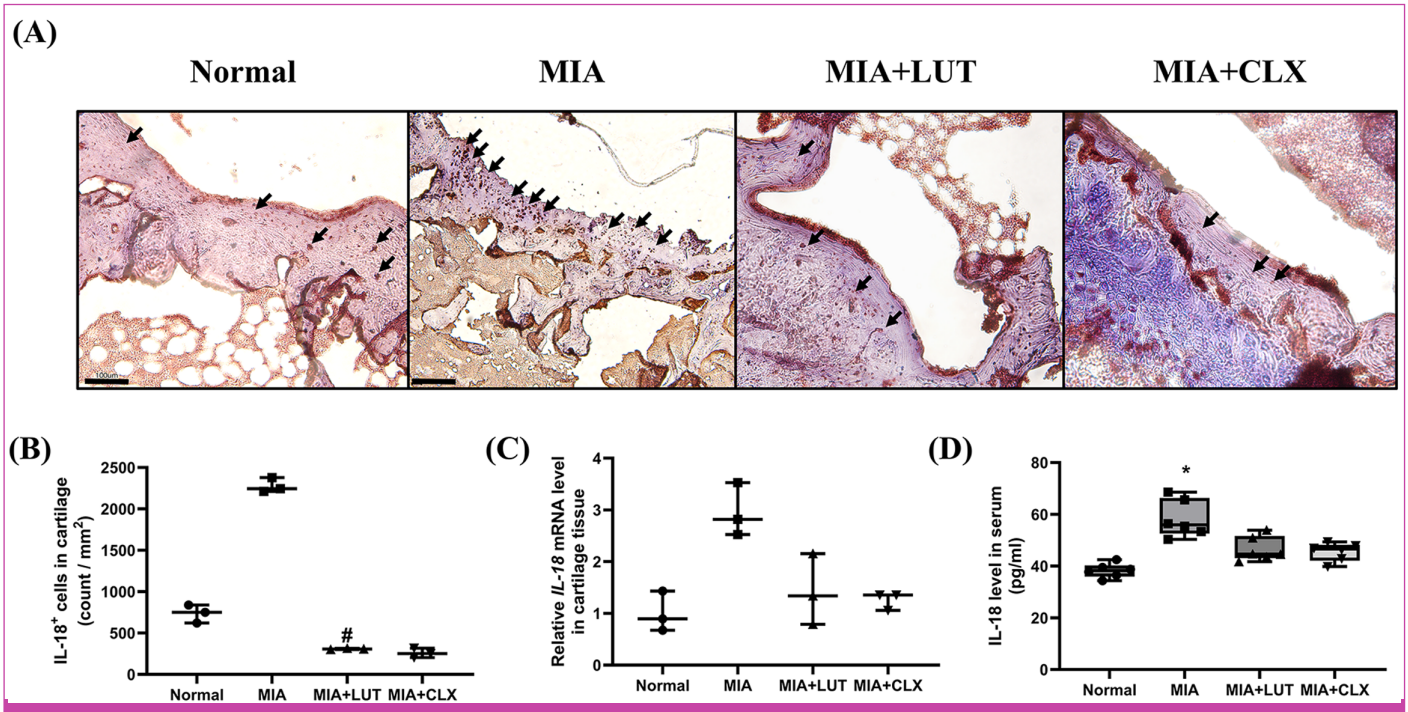

Figure 3. Effects of LUT on IL-18 expression in an MIA-induced OA model. (A) Immunohistochemical staining of IL-18 in cartilage sections. Magnification, ×40. Black arrows indicate IL-18-positive chondrocytes. Scale bar = 100 μm. (B) Quantification of IL-18-positive chondrocytes in cartilage tissue (n = 3 per group). (C) Relative IL-18 mRNA expression in cartilage tissue measured by qRT-PCR (n = 3 per group). (D) Serum IL-18 concentrations measured by ELISA (n = 6 per group). Data are presented as box-and-whisker plots showing the median with IQR. Statistical analysis was performed using the Kruskal–Wallis test followed by Dunn's multiple comparisons test. *vs. Normal group; #vs. MIA group.

those of established NSAIDs in certain anti-inflammatory outcomes. However, these findings should be interpreted with caution, given the exploratory nature of the analyses and the need for further validation.

This study suggests that LUT may mitigate cartilage damage by suppressing IL-18 expression in a mouse model. These therapeutic effects may also be associated with LUT's modulation of multiple signaling pathways. First, LUT inhibits NF-κB activation, a key transcription factor involved in inflammation, thereby reducing the transcription of inflammatory cytokines, including IL-18, and MMPs.[19] Second, LUT suppresses inflammatory signaling by inhibiting phosphorylation of MAPK pathways, including p38 and JNK.[20] Third, LUT reduces oxidative stress by activating Nrf2, a key regulator of antioxidant and cytoprotective responses.[21] Collectively, these mechanisms suggest that LUT may modulate OA progression, potentially through indirect suppression of OA inflammasome-related pathways, including IL-18–mediated signaling.

Although this study provides promising evidence for the anti-osteoarthritic effects of LUT, some limitations should be acknowledged. First, the relatively small sample size (n = 6 per group) may have limited the statistical power to detect subtle differences between treatment groups. Therefore, future studies with larger sample sizes are warranted to improve statistical robustness and confirm these findings. This limitation also indicates that the present study should be considered a pilot investigation. Second, the 14-day treatment duration, while sufficient to assess early inflammatory and structural changes in this OA model, does not reflect the chronic and progressive nature of human OA. Accordingly, longer-term studies, including experiments using human-derived chondrocytes, are needed to evaluate the sustained efficacy, safety, and disease-modifying potential of LUT.

In conclusion, this study demonstrates that LUT may inhibit the progression of MIA-induced OA. In particular, IL-18 modulation appears to be associated with reduced inflammation and attenuation of cartilage degeneration. These findings suggest that LUT has potential as a candidate therapeutic agent for OA.

Data Availability Statement: *The data that support the findings of this study are available on request from the corresponding author.*

Artificial Intelligence Usage Statement: *The authors declared that no Artificial Intelligence Tool was used in the preparation of the manuscript.*

Ethics Committee Approval: *Ethical committee approval was received from the Institutional Animal Care and Use Committee*

(IACUC) of Chung-Ang University (Approval No.: 202100210; Date: March 27, 2021).

Informed Consent: *N/A.*

Peer-review: *Externally peer-reviewed.*

Author Contributions: *Concept – J.H.K., J.Y.L.; Design – J.H.K., J.Y.L.; Supervision – J.Y.L.; Resources – J.Y.L.; Materials – J.H.K., J.Y.S; Data Collection and/or Processing – J.H.K., S.H.L., Y.J.L.; Analysis and/or Interpretation – J.H.K., J.Y.S.; Literature Search – J.Y.S., H.H.G.; Writing – J.H.K., S.H.L., J.Y.S.; Critical Review – J.Y.S.*

Declaration of Interests: *The authors have no conflicts of interest to declare.*

Funding: *The authors declare that this study received no financial support.*

References

1. Di Nicola V. Degenerative osteoarthritis a reversible chronic disease. *Regen Ther*. 2020;15:149-160. [CrossRef]
2. Prieto-Alhambra D, Judge A, Javaid MK, et al. Incidence and risk factors for clinically diagnosed knee, hip and hand osteoarthritis: influences of age, gender and osteoarthritis affecting other joints. *Ann Rheum Dis*. 2014;73(9):1659-1664. [CrossRef]
3. Dieppe PA, Lohmander LS. Pathogenesis and management of pain in osteoarthritis. *Lancet*. 2005;365(9463):965-973. [CrossRef]
4. Palazzo C, Nguyen C, Lefevre-Colau MM, et al. Risk factors and burden of osteoarthritis. *Ann Phys Rehabil Med*. 2016;59(3):134-138. [CrossRef]
5. Härle P, Fleck M. Treatment of osteoarthritis with drugs and other modalities. *Internist*. 2008;49(12):1458-1462. [CrossRef]
6. Hijos-Mallada G, Sostres C, Gomollón F. NSAIDs, gastrointestinal toxicity and inflammatory bowel disease. *Gastroenterol Hepatol*. 2022;45(3):215-222. [CrossRef]
7. Ribeiro H, Rodrigues I, Napoleão L, et al. Non-steroidal anti-inflammatory drugs (NSAIDs), pain and aging: adjusting prescription to patient features. *Biomed Pharmacother*. 2022;150:112958. [CrossRef]
8. Kashiwamura S, Ueda H, Okamura H. Roles of interleukin-18 in tissue destruction and compensatory reactions. *J Immunother*. 2002;25(suppl 1):S4-S11. [CrossRef]
9. Fu ZZ, Liu P, Yang DH, et al. Interleukin-18-induced inflammatory responses in synoviocytes and chondrocytes from osteoarthritic patients. *Int J Mol Med*. 2012;30(4):805-810. [CrossRef]
10. Nozaki Y, Ri J, Sakai K, et al. Inhibition of the IL-18 receptor signaling pathway ameliorates disease in a murine model of rheumatoid arthritis. *Cells*. 2019;9(1):11. [CrossRef]
11. Dai SM, Shan ZZ, Nishioka K, et al. Implication of interleukin 18 in production of matrix metalloproteinases in articular chondrocytes in arthritis: direct effect on chondrocytes may not be pivotal. *Ann Rheum Dis*. 2005;64(5):735-742. [CrossRef]
12. Di Y, Wang Z, Xiao J, et al. ACSL6-activated IL-18R1-NF-κB promotes IL-18-mediated tumor immune evasion and tumor progression. *Sci Adv*. 2024;10(38):eadp0719. [CrossRef]
13. Villela A, van der Klift EJC, Mattheussens ESGM, et al. Fast chromatographic separation for the quantitation of the main flavone dyes in Reseda luteola (weld). *J Chromatogr A*. 2011;1218(47):8544-8550. [CrossRef]
14. Liu GG, Zhang YX, Liu CC, et al. Luteolin alleviates alcoholic liver disease induced by chronic and binge ethanol feeding in mice. *J Nutr*. 2014;144(7):1009-1015. [CrossRef]
15. Ding XJ, Zheng LL, Yang B, et al. Luteolin attenuates atherosclerosis via modulating signal transducer and activator of transcription 3-mediated inflammatory response. *Drug Des Dev Ther*. 2019;13:3899-3911. [CrossRef]
16. Li BL, Du PL, Du Y, et al. Luteolin alleviates inflammation and modulates gut microbiota in ulcerative colitis rats. *Life Sci*. 2021;269:119008. [CrossRef]
17. Chian S, Thapa R, Chi ZX, et al. Luteolin inhibits the Nrf2 signaling pathway and tumor growth in vivo. *Biochem Bioph Res Commun*. 2014;447(4):602-608. [CrossRef]
18. Reed DA, Zhao Y, Han M, et al. Mechanical loading disrupts focal adhesion kinase activation in mandibular fibrochondrocytes during murine temporomandibular joint osteoarthritis. *J Oral Maxillofac Surg*. 2021;79(10):2058.e1-2058.e15. [CrossRef]
19. Xue L, Jin X, Ji T, et al. Luteolin ameliorates DSS-induced colitis in mice via suppressing macrophage activation and chemotaxis. *Int Immunopharmacol*. 2023;124(B):110996. [CrossRef]
20. Gu M, Pang Z. Luteolin inhibits inflammation and M1 macrophage polarization in the treatment of Pseudomonas aeruginosa-induced acute pneumonia through suppressing EGFR/PI3K/AKT/NF-κB and EGFR/ERK/AP-1 signaling pathways. *Phytomedicine*. 2025;141:156663. [CrossRef]
21. Yu H, Huang L, Gui L, et al. Luteolin ameliorates hyperuricemic nephropathy by activating urate excretion and Nrf2/HO-1/NQO1 antioxidant pathways in mice. *Food Sci Nutr*. 2024;12(10):8053-8066. [CrossRef]