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Research Article

Protective Effects of Rutinoside on Oxidative Induced Articular Cartilage Damage and Catabolic Activity in Rat Chondrocyte

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ABSTRACT

Objective: This study aimed to look into the therapeutic potential of rutinoside in reducing articular cartilage degeneration in a rat model of osteoarthritis generated by monosodium iodoacetate (MIA). **Methods**: We formed three groups of male Wistar rats: the OA, rutinoside, and control groups. Monosodium iodoacetate (3.0 mg) was injected intra-articularly into the knee joint to cause osteoarthritis. For four weeks, oral administration of rutinoside at 100 mg/kg/day was given to the groups that were given the treatment. Histological examination, immunohistochemistry, and biochemical tests were used to assess the level of articular cartilage injury, oxidative damage, catabolic activity, and biomarker expression. **Results**: The results showed that treatments with rutinoside significantly reduced the damage to articular cartilage in rats with MIA-induced osteoarthritis. Compared to the osteoarthritis group, the rutinoside-treated groups showed enhanced cartilage structure, proteoglycan content, and chondrocyte organization. Immunohistochemistry revealed reduced NF κ B, IL-1 β, and MMP-13 expressions in the rutinoside-treated groups, indicating suppressed inflammatory and catabolic activity in chondrocytes. Additionally, rutinoside treatment increased SOD activity and decreased MDA levels, which showed less oxidative damage to the joint. A substantial drop in CTX-II levels was found by biochemical research, indicating less type II collagen breakdown. **Conclusion**: According to a study, rutinoside effectively reduces oxidative damage and catabolic activity in chondrocytes, which can lead to decreased articular cartilage loss in a rat model of MIA-induced osteoarthritis. The study also found that rutinoside can control critical biomarkers such as NF κ B, IL-1 β, SOD, MDA, MMP-13, and CTX-II, highlighting its potential as a treatment for osteoarthritis. These findings provide valuable insights into using natural chemicals as a promising treatment for OA and suggest that rutinoside could potentially modulate the critical interplay between oxidative stress, inflammation, and chondrocyte catabolism in osteoarthritis. However, further research is required to understand the underlying molecular mechanisms and evaluate rutinoside's translational potential for OA therapy.

Keywords: Rutinoside, Osteoarthritis, Oxidative stress, Inflammation.

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INTRODUCTION

Osteoarthritis (OA) is a chronic joint condition that affects millions of individuals worldwide and is one of the most common. This disorder mainly affects weight-bearing joints such as the hips, knees, and spine, resulting in discomfort, reduced mobility, and diminished usefulness. The progressive breakdown of joint cartilage, subchondral bone remodeling, and synovial inflammation that define OA impact the quality of life of those who suffer from it. The causes of OA are multifaceted and complicated, involving genetic, environmental, and biomechanical factors. During the progression of OA, several factors work together to degrade cartilage and impair joint function, including oxidative stress, inflammation, and catabolic activity within chondrocytes.[1-3]

The microenvironment of the joint is undergoing oxidative stress due to an imbalance between reactive oxygen species (ROS) production and cellular antioxidant defense mechanisms. While ROS is necessary for normal cellular activities, excessive generation overwhelms antioxidant defenses, resulting in oxidative damage. An increasing amount of data shows that oxidative stress is essential in the development and progression of OA, impacting chondrocyte activity, cartilage matrix integrity, and overall joint homeostasis. Inflammation, like oxidative stress, has also become a significant component of OA pathogenesis. The release of pro-inflammatory cytokines, chemokines, and matrix-degrading enzymes is promoted by synovial inflammation and immune cell infiltration, ultimately leading to tissue destruction and remodeling. Furthermore, inflammation promotes oxidative stress by activating pro-oxidant enzymes and inhibiting antioxidant pathways, resulting in a self-perpetuating loop that aggravates joint damage.[4,5]

Rutinoside, a compound naturally present in various fruits and plants, has demonstrated remarkable therapeutic promise in treating several illnesses because of its antioxidant and anti-inflammatory effects. Prior research has shown its capacity to neutralize ROS and control inflammatory pathways to protect cells from oxidative stress and reduce inflammatory responses. Rutinoside's precise impact on articular cartilage degradation and its underlying processes in the setting of osteoarthritis, however, have yet to be well studied.[6,7]

The study aimed to investigate rutinoside's therapeutic effects for treating articular cartilage degeneration in rats with osteoarthritis induced by monosodium iodoacetate (MIA). The study focused on analyzing how rutinoside affected oxidative damage and catabolic activity in chondrocytes, as

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well as the expressions of essential biomarkers such as nuclear factor kappa B (NFκB), IL-1β, superoxide dismutase (SOD), malondialdehyde (MDA), MMP-13, and the C-terminal telopeptide of type II collagen (CTX-II). An in-depth understanding of these variables could provide valuable insights into how rutinoside can treat osteoarthritis. Administering rutinoside could reduce articular cartilage deterioration by suppressing chondrocatabolic activity, reducing oxidative damage, and altering the expression of essential biomarkers associated with inflammation and cartilage degradation. The study has promising results, which could pave the way for new methods of managing osteoarthritis and enhancing joint function.

MATERIALS AND METHOD

Animals

This study used 18 male Wistar rats. The rats were housed in standard laboratory cages with controlled temperature and lighting conditions, ensuring a consistent environment for the experiment. Maintaining a 12-hour light-dark cycle is essential for regulating the rats' circadian rhythms. The rats were provided standard food and unlimited water access throughout the trial. This standardizes their diet and hydration, reducing potential confounding variables that could affect the results. The mention of the Research Ethics Committee of the Faculty of Medicine at the University of Indonesia Jember signifies that this study adheres to ethical standards and guidelines for animal research. This committee plays a crucial role in ensuring the welfare and ethical treatment of animals in research, which is vital for maintaining the integrity of scientific investigations. Overall, this experiment's setup and ethical considerations create a controlled and ethical environment for the study of these Wistar rats, making the results more reliable and generalizable.

Experimental design

Eighteen Wistar rats were divided randomly into three groups, each consisting of six rats. This randomization helps ensure that the groups are comparable and reduces bias. The first group was the control group (C). Rats in this group received a saline injection in their left knee. Saline injections are typically used as a placebo or control to compare the effects of experimental treatments. The second group is the OA Group (OA), which received 3 mg of monosodium iodoacetate (MIA) in 50 µl of normal saline in their left knee. Monosodium iodoacetate is a chemical commonly used to induce osteoarthritis-like symptoms in animal models. This group is likely intended to study the effects of MIA-induced osteoarthritis. The third group is the Rut Group (Rut), which received 3 mg of MIA in their left knee, similar to the OA group, but they also received 100 mg/kg of rutinoside daily for 28 days. Rutinoside is a flavonoid compound in various plants and may have potential therapeutic effects. This group seems to investigate the impact of rutinoside in mitigating the effects of MIA-induced osteoarthritis. At the end of the study, blood samples were collected from the rats and analyzed biochemically. Furthermore, the researchers removed the knee joints from the rats and prepared them for histological analysis. This histological analysis would involve examining the joint tissues under a microscope to assess the structural changes and damage caused by the experimental treatments.

Biochemical analysis

Following the experiment, we implemented specific post-experiment procedures to evaluate the effects of different treatments on the rats. The animals were fasted for one night after the experiment. Fasting in this context likely aimed to standardize the baseline for blood sample analysis, ensuring that the results are not influenced by recent food consumption. After fasting, blood samples were taken from the rats. This step is crucial for assessing various blood markers to understand the physiological changes due to the experimental treatments. The collected blood samples were allowed to clot at room temperature for 30 minutes. After clotting, the samples were centrifuged at 2000 rpm for 15 minutes. This process separates the blood into liquid (serum) and solid components (clots). The serum contains various biomolecules that can be analyzed. The serum obtained from the blood samples was extracted and stored at -80°C until analysis. Keeping the serum at very low temperatures helps preserve the integrity of the samples and prevents degradation of the biomolecules within. To measure specific markers in the blood, the researchers used rat enzyme-linked immunosorbent assay (ELISA) kits. In this study, we assessed the levels of two markers: interleukin-1 (IL-1) and the cross-linked C-telopeptide of type II collagen (CTX-II). The ELISA kits for IL-1 and CTX-II were used as directed by the manufacturer. Following the manufacturer's instructions is essential to ensure the accuracy and reliability of the assay results.

Immunohistochemical analyses

We maintained the knee joint in a 10% formalin solution for 24 hours. Formalin is a common fixative used in histology to preserve tissue samples and prevent their decay. After formalin fixation, the joint was decalcified in a 20% ethylenediaminetetraacetic acid (EDTA) solution. This step is essential for removing calcium deposits that might interfere with the histological examination. The decalcified joint was embedded in paraffin. Paraffin embedding is a standard method to prepare tissue samples for sectioning and histological analysis. The paraffin-embedded joint was then sectioned into 5-micron-thick slices. These thin slices allow for a detailed examination of the tissue structure. The tissue slices were deparaffinized and rehydrated through a graded series of ethanol concentrations (100%, 90%, and 70%). This process prepares the tissue for staining and immunohistochemical procedures. The tissue slices were stained with hematoxylin and eosin (H&E). H&E staining is a standard method to visualize tissue structures under a microscope. Hematoxylin stains cell nuclei blue, while eosin stains the cytoplasm and extracellular matrix pink. The modified Mankin histological score and the OARSI (Osteoarthritis Research Society International) assessment were used to evaluate the pathological deterioration of the articular cartilage. These scoring systems help quantify and classify the severity of cartilage damage.

For immunohistochemical analysis, the paraffin slices were deparaffinized and rehydrated in ethanol. Antigen retrieval was performed using a citric acid solution. This step helps to expose the target antigens for antibody binding. The tissue sections were incubated with a primary antibody overnight at 4°C. This antibody likely targets a specific protein or antigen of interest in the tissue. After primary antibody incubation, the tissue sections were treated with a secondary biotinylated antibody (in this case, goat anti-mouse IgG), which binds to the primary antibody. We applied a streptavidin-peroxidase mixture to the sections for 10 minutes. Subsequently, 3,3-diaminobenzidine tetrahydrochloride (DAB) was used to visualize the binding of the secondary antibody. The sections were washed in phosphate-buffered saline, counterstained with hematoxylin, and mounted. Counterstaining helps provide contrast and allows for the visualization of specific immunohistochemical reactions. These histological and immunohistochemical procedures are essential for assessing tissue structure, cellular components, and the presence of particular proteins or antigens, contributing to a comprehensive analysis of the joint tissue and the effects of the experimental treatments.

Statistical Analysis

GraphPad Prism is a popular software used for data analysis and graphing. The program presents results in the form of mean and standard deviation (SD), which are commonly used in statistical analysis. The significance level is set at 0.05, indicating that the results are statistically significant.

RESULT

Biochemical parameters

The OA group, which received monosodium iodoacetate (MIA) to induce osteoarthritis-like symptoms in their left knee, had significantly higher serum levels of IL-1β compared to the control group (p<0.001) (Figure 1). This indicates that the MIA treatment effectively induced an inflammatory response, as IL-1β is a pro-inflammatory cytokine often associated with inflammation and tissue damage. In contrast, the rutinoside group, which received both MIA and rutinoside treatment, showed a significant decrease in serum IL-1β levels compared to the OA group (p<0.05). This suggests that rutinoside treatment had an inhibitory effect on the elevation of IL-1β, potentially mitigating the inflammatory response associated with osteoarthritis induction.

Blood CTX-II levels, a marker associated with cartilage degradation, were significantly increased in the OA group compared to the control group (p<0.001) (Figure 1). This indicates that the MIA-induced osteoarthritis led to the degradation of type II collagen in the articular cartilage. The rutinoside treatment group exhibited a significant decrease in serum CTX-II levels compared to the OA group (p<0.05). This suggests that rutinoside may protect articular cartilage, reducing CTX-II levels and indicating less cartilage degradation.

These findings indicate that the MIA-induced osteoarthritis model effectively increased pro-inflammatory cytokine levels (IL-1β) and promoted cartilage degradation (CTX-II). However, the rutinoside treatment appeared to have a beneficial effect by reducing the levels of both IL-1β and CTX-II. This suggests that rutinoside may have potential anti-inflammatory and cartilage-protective properties, which could be valuable in osteoarthritis research and treatment.

Immunohistochemistry

MIA Induction and Inflammation

MIA induction, used to create an osteoarthritis-like condition, significantly increased the expression of several key markers associated with inflammation and oxidative stress. These include MDA (malondialdehyde), MMP-13 (matrix metalloproteinase-13), and NFκB (nuclear factor kappa B) (p<0.001) (Figure 2). Elevated levels of these markers often indicate an inflammatory response in tissues. Notably, rutinoside treatment led to a significant decrease in the expression of MDA, MMP-13, and NFκB (p<0.001). This suggests that rutinoside attenuated the inflammation and oxidative stress associated with MIA-induced osteoarthritis.

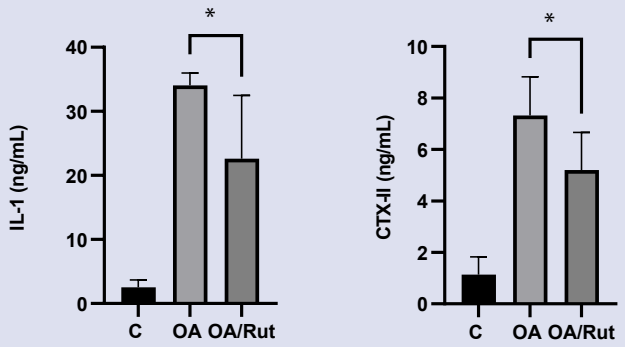

Figure 1: Effect of Rutinoside on Serum level of IL-1β and CTX-II. MIA injection increased IL-1β and CTX-II significantly compared to the Control group, and serum IL-1β and CTX-II decreased in the Rut group compared to the OA group. *p<0.05, C: Control, OA: Osteoarthritis, Rut: Osteoarthritis with rutinoside treated.

SOD Expression and Antioxidant Defense

In comparison to the control group, the osteoarthritic (OA) rats showed considerably lower expression of SOD (superoxide dismutase) in both articular cartilage and subchondral bone (p<0.001). SOD is an important antioxidant enzyme responsible for neutralizing reactive oxygen species (ROS) and protecting tissues from oxidative damage. Rutinoside treatment, when compared to the OA group, significantly increased the expression of SOD in both the articular cartilage and subchondral bone (p<0.001). This indicates that rutinoside treatment enhanced the antioxidant defense mechanisms in the joint tissues, which can be beneficial in reducing oxidative stress and preserving joint health.

The findings suggest that MIA induction increased inflammation and oxidative stress markers in the knee joint. At the same time, rutinoside treatment had a significant mitigating effect on these markers. Furthermore, the reduction in SOD expression in osteoarthritic rats was reversed by rutinoside treatment, indicating an improvement in the antioxidant defense system. These results support the notion that rutinoside may have a protective and anti-inflammatory role in osteoarthritis, which is promising for potential therapeutic applications in managing this condition.

The modified Mankin scoring system is a widely used method to assess structural damage in cartilage. It uses a scale from 0 to 13, with higher scores indicating more severe cartilage damage. The study reports that when compared to the OA (osteoarthritis) group, the groups treated with rutinoside exhibited significantly lower modified Mankin scores (p<0.05) (Figure 3). This finding suggests that rutinoside treatment resulted in less structural damage in the cartilage compared to the untreated OA group. The OARSI grading system, developed by the Osteoarthritis Research Society International, is another standard tool for assessing cartilage abnormalities. It uses grades ranging from 1 to 6, with 1 indicating normal cartilage and 6 indicating complete cartilage loss. The study reports that similar to the modified Mankin scoring system when compared to the OA group, the groups treated with rutinoside showed significantly lower OARSI scores (p<0.05). This indicates that rutinoside treatment was associated with less severe cellular abnormalities and cartilage degradation, as evidenced by the lower OARSI grades. These findings strongly suggest that rutinoside treatment positively reduced structural damage and cellular abnormalities in the context of osteoarthritis. The significantly lower scores in both the modified Mankin and OARSI systems indicate that rutinoside may be an effective intervention in mitigating the progression of osteoarthritis and preserving the integrity of articular cartilage. This is promising for potential therapeutic approaches in the management of osteoarthritis.

DISCUSSION

Our study aimed to explore the potential therapeutic benefits of rutinoside in preventing articular cartilage degradation in a rat model of osteoarthritis induced by MIA. We conducted a comprehensive analysis of the impact of rutinoside on oxidative damage, catabolic activity in chondrocytes, and critical biomarkers such as nuclear factor kappa B (NFκB), interleukin-1 (IL-1β), superoxide dismutase (SOD), malondialdehyde (MDA), matrix metalloproteinase-13 (MMP-13), and the C-terminal telopeptide of type II collagen (CTX-II). Our results show that rutinoside therapy significantly reduces articular cartilage degradation in rats with MIA-induced osteoarthritis. The histological research demonstrates that the group that received rutinoside treatment had better cartilage structure, proteoglycan content, and chondrocyte organization than the osteoarthritis group. Based on our findings, it is safe to assume that rutinoside has chondroprotective properties that help maintain the structural integrity of the cartilage matrix, thus preventing cartilage breakdown.[8,9]

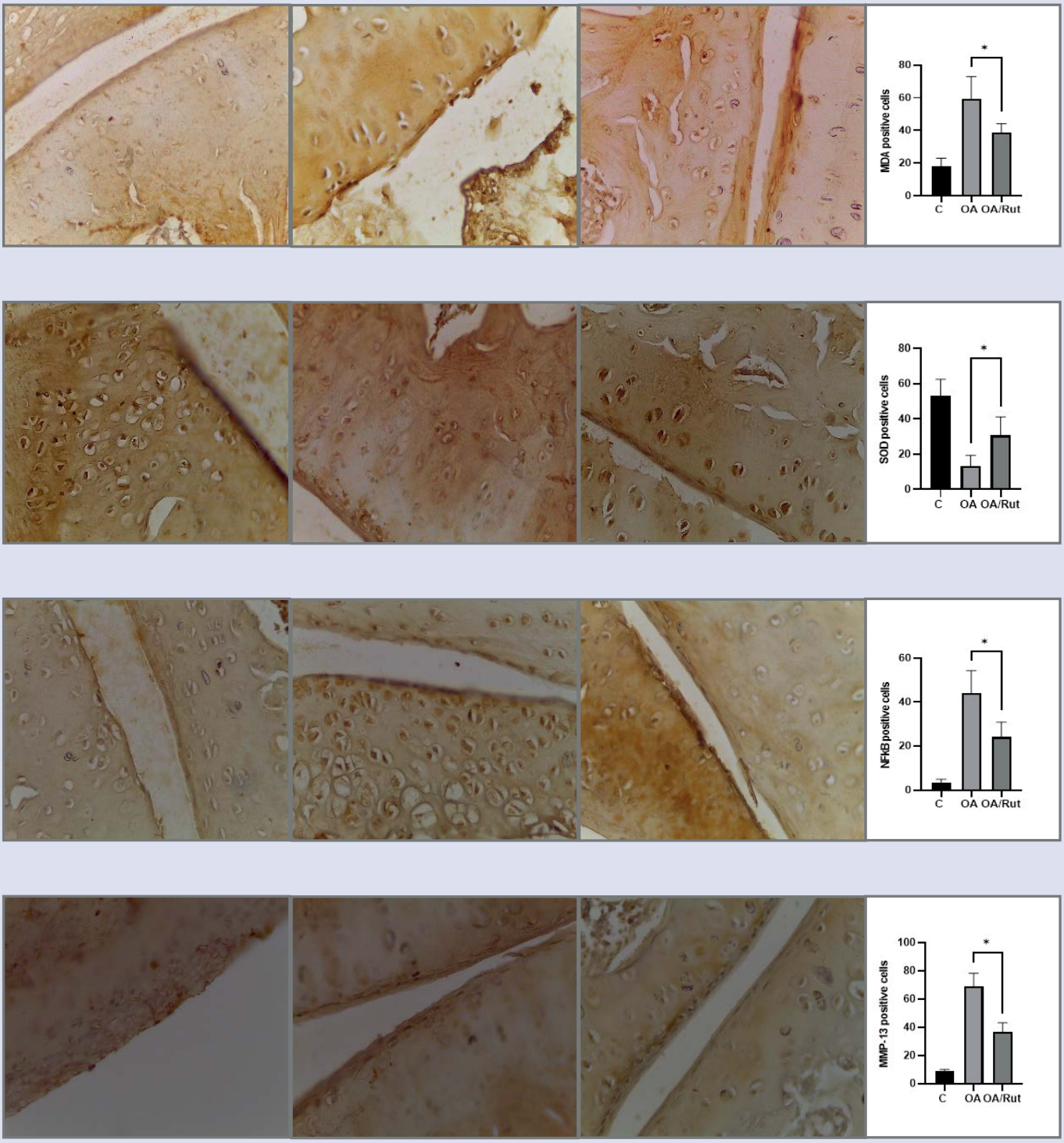

Figure 2: Representative MDA, SOD, NFκB, and MMP-13 staining of rat knee joints of different groups: MIA injection up-regulated expression of MDA, NFκB, and MMP-13. This increase was significantly decreased in Rut groups. On the other hand, SOD expression decreased in the OA group and significantly increased in the Rut-treated group. C: Control, OA: Osteoarthritis, OA/Rut: Osteoarthritis with rutinoside treated.

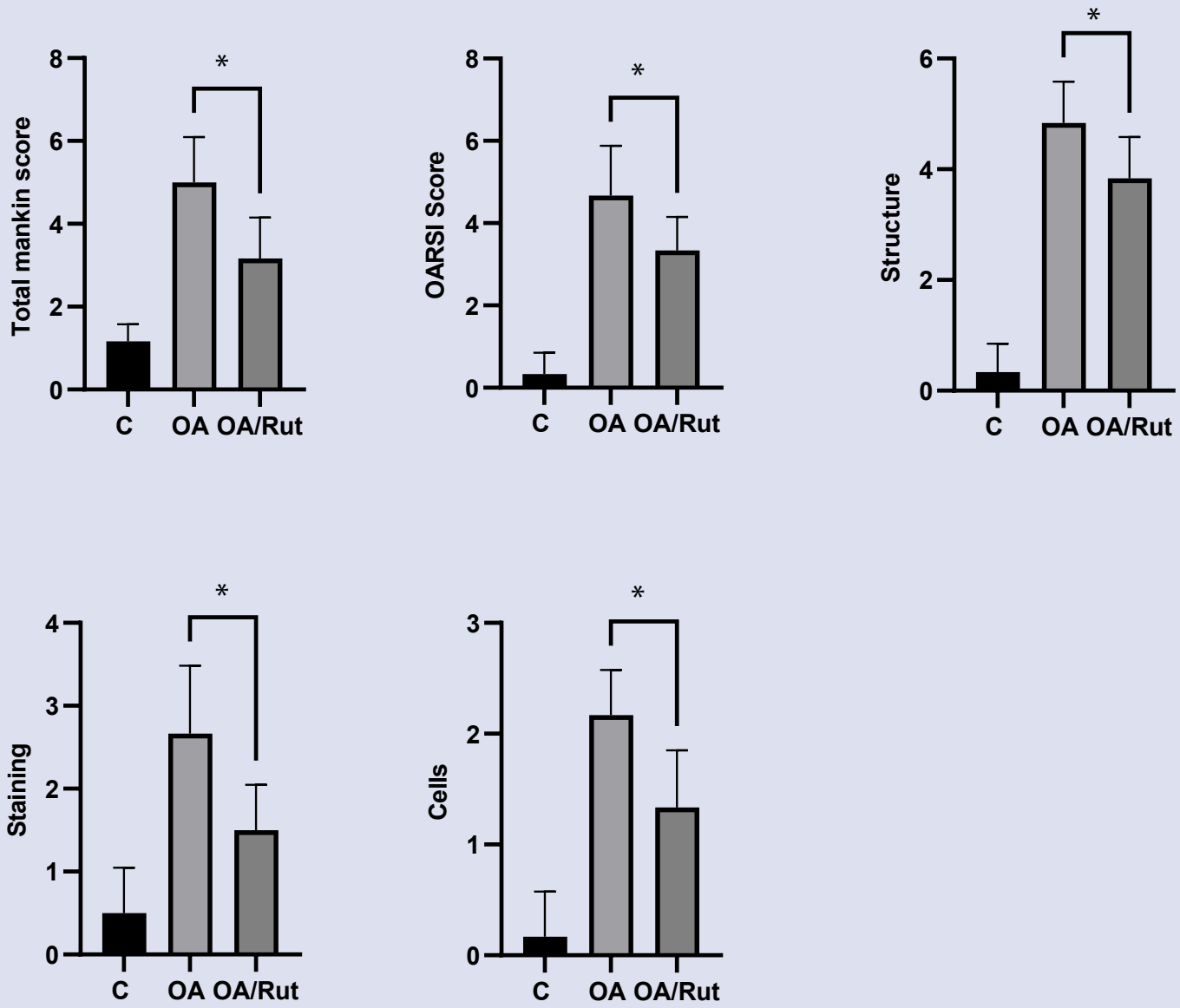

Figure 3: Mankin score and OARSI grading. * $p<0.05$, C: Control, OA: Osteoarthritis, OA/Rut: Osteoarthritis with rutinoside treated.

The study demonstrated that rutinoside may have potential therapeutic benefits for osteoarthritis by reducing articular cartilage destruction in rats with MIA-induced osteoarthritis. Reducing oxidative damage and catabolic activity in chondrocytes may be attributed to their anti-inflammatory and antioxidative characteristics and their regulation of critical biomarkers implicated in cartilage breakdown. Further research is required to investigate rutinoside's ideal dose, long-term effects, and potential therapeutic uses.[10,11]

Inflammation is a critical factor in developing osteoarthritis (OA), with interleukin-1β (IL-1β) being a key mediator of the inflammatory process. According to our study, rutinoside treatment led to a significant decrease in IL-1β levels. IL-1β is known to activate nuclear factor kappa B (NFκB), a transcription factor that plays a vital role in regulating pro-inflammatory genes. Therefore, the fact that rutinoside suppresses NFκB activation suggests that it has a potential anti-inflammatory mechanism. This is particularly important because chronic inflammation is closely linked to cartilage degradation and the production of matrix metalloproteinase-13 (MMP-13), a collagen-degrading enzyme. These results suggest that rutinoside has anti-inflammatory properties, which may help to reduce inflammatory responses within the joint and thus counteract cartilage degeneration. As a result, rutinoside may have promising implications for preserving articular cartilage in OA.[12,13]

Osteoarthritis is characterized by cartilage degradation, which results in the loss of type II collagen. The findings suggest that rutinoside may have a protective effect against type II collagen degradation, as demonstrated by a decrease in the levels of the type II collagen degradation marker (CTX-II). This protective effect is most likely owing to MMP-13 downregulation and IL-1β inhibition, both of which are important in collagen breakdown. MMPs, notably MMP-13, are crucial enzymes implicated in cartilage degradation in osteoarthritis, and MMP-13 expression was much lower in the rutinoside-treated groups than in the osteoarthritis group. This indicates that rutinoside may limit chondrocyte catabolism and prevent excessive breakdown of the extracellular matrix, thereby preserving cartilage integrity.[14]

In addition, we measured type II collagen C-terminal telopeptide (CTX-II) levels to evaluate type II collagen degradation, a characteristic of osteoarthritic cartilage disintegration. The rutinoside-treated groups showed significantly lower CTX-II levels, indicating a reduction in collagen degradation. This further supports rutinoside's chondroprotective properties, as it helps to maintain cartilage integrity and slow the progression of osteoarthritis.[15-17]

Our findings suggest that rutinoside can potentially reduce articular cartilage damage in rats with osteoarthritis induced by MIA. This reduction is achieved by reducing oxidative damage and catabolic activity in chondrocytes. Rutinoside exhibits anti-inflammatory and antioxidative properties and regulates critical biomarkers involved in cartilage breakdown. This indicates that it can be a promising therapeutic drug for osteoarthritis. However, more research is needed to determine its long-term effects, ideal dosage, and potential therapeutic applications.

CONCLUSION

Rutinoside reduces chondrocyte catabolism and oxidative damage in osteoarthritis by regulating key markers such as IL-1, CTX-II, MDA, SOD, NFκB, and MMP-13.

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DISCLOSURE

The authors have stated that they do not have any conflicts of interest concerning this study.

AUTHORS' CONTRIBUTIONS

All authors participated in data analysis, article preparation, and paper revision and agreed to accept responsibility for all parts of this study.

ETHICAL CONSIDERATION

This research was approved by the ethical committee of Jember University's Faculty of Medicine with certificate number 1554/H25.1.11/KE/2021.

DATA AVAILABILITY

All data underlying the results are available in the article and no additional source data are required.

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