Clinical Rheumatology
https://doi.org/10.1007/s10067-025-07621-7

ORIGINAL ARTICLE

Extra Virgin Olive Oil alleviates articular cartilage damage and reduces ox-LDL and oxidative stress in monosodium iodoacetate-induced osteoarthritis in rats

Cemil Erturk[1] · Sabri Kerem Diril[1] · Gülay Yuzbasioglu Ozturk[2] · Ahmet Gulcubuk[2] · Duygu Sultan Oran[3] · Ozge Erdogan Bamac[2] · Nilgun Isiksacan[4]

Received: 14 February 2025 / Revised: 26 June 2025 / Accepted: 3 July 2025
© The Author(s), under exclusive licence to International League of Associations for Rheumatology (ILAR) 2025

Abstract

Objective This study aimed to evaluate the therapeutic effects of extra virgin olive oil (EVOO), known for its antioxidant and cytoprotective properties, in a monosodium iodoacetate (MIA)-induced rat model of osteoarthritis (OA).

Methods Twenty-one male Wistar rats were randomly divided into three groups: Control, OA, and EVOO-treated. OA was induced via intra-articular injection of MIA. The EVOO Group received a diet supplemented with EVOO for 21 days post-induction. Histopathological, immunohistochemical, biochemical, and radiological analyses were performed to evaluate cartilage damage, inflammation, apoptosis and oxidative stress.

Results Histopathological evaluation revealed moderate cartilage destruction and synovitis in the OA Group, which were reduced in the EVOO-treated Group. Safranin-O staining confirmed higher proteoglycan preservation with EVOO supplementation. Immunohistochemistry demonstrated low intensity of oxidized low-density lipoprotein (ox-LDL) in the EVOO-treated Group compared to the OA Group. TUNEL staining indicated a significant reduction in chondrocyte apoptosis in EVOO-fed rats. Biochemically, ox-LDL and other oxidative stress markers, including total oxidative status (TOS) and oxidative stress index (OSI), were significantly reduced in the EVOO Group compared to the OA Group ($p < 0.05$). In contrast, the antioxidant capacity (TAC) level was significantly higher in the EVOO Group ($p < 0.05$). A positive correlation was observed between ox-LDL and TOS ($p = 0.005$).

Conclusions Our findings suggest that EVOO may contribute to cartilage preservation and reduce synovitis in rats with MIA-induced OA. Additionally, EVOO exhibits significant antioxidant effects by reducing ox-LDL and oxidative stress markers and enhancing antioxidant capacity. These results may highlight EVOO as a potential adjuvant therapy for managing OA.

Key Points

- *This study evaluates the therapeutic effects of extra virgin olive oil (EVOO) in a monosodium iodoacetate (MIA)-induced rat model of osteoarthritis (OA).*
- *EVOO supplementation reduced cartilage destruction, synovitis, and chondrocyte apoptosis, while preserving proteoglycan content in the cartilage matrix, as demonstrated by histopathological and immunohistochemical findings.*
- *Significant reductions in oxidized low-density lipoprotein (ox-LDL) and other oxidative stress markers, including total oxidative status (TOS), and oxidative stress index (OSI), were observed in EVOO-fed rats, as confirmed by biochemical analyses.*
- *EVOO shows potential as an adjuvant therapy for managing osteoarthritis due to its antioxidant and cartilage-protective properties.*

Keywords EVOO · MIA · Osteoarthritis · Oxidative stress · Ox-LDL

Introduction

Osteoarthritis (OA) is a degenerative and systemic disease that significantly impacts public health, causing widespread disability and substantial economic burden due to the challenges and costs of treatment [1]. Among the joints in the body, knee OA is the most frequently affected [2]. OA is characterized by inflammation and degeneration of joint cartilage, with morphological changes also occurring in the subchondral bone and synovial membrane [3]. Although the etiopathogenesis of OA is not yet fully

Extended author information available on the last page of the article

Published online: 28 August 2025

understood, mechanical, biochemical, and genetic factors are known to play pivotal roles [4, 5]. To better understand the disease's pathogenesis and explore potential treatments, various animal models have been used to experimentally mimic human OA [6].

Recently, functional food supplements with potent antioxidant and anti-inflammatory properties have gained attention for their role in preventing and treating OA by inhibiting reactive oxygen species (ROS) production and reducing inflammation [7, 8]. Epidemiological studies on the consumption of functional foods have highlighted the antioxidant, anti-inflammatory, immunomodulatory, antiproliferative, and antiapoptotic benefits of extra virgin olive oil (EVOO), particularly in Mediterranean countries [9–11]. Emerging evidence suggests that a diet rich in EVOO exerts neuroprotective, anti-aging, and antiatherogenic effects by regulating key cellular signaling pathways, largely attributed to its phenolic compounds [12–15]. Among these, simple phenols, lignans, and secoiridoids in the phenolic fraction are considered the primary antioxidants in EVOO [16]. Additionally, olive oil phenols have been recognized as anticarcinogenic and chemopreventive agents due to their ability to modulate cell death [17].

Several studies have shown a strong correlation between knee OA and lipid metabolism [18–20]. Oxidized low-density lipoprotein (ox-LDL) is a modified form of LDL under conditions of oxidative stress and is known to possess pro-inflammatory properties. It is recognized by macrophages, leading to increased production of inflammatory cytokines that contribute significantly to the pathogenesis of OA [20]. Moreover, ox-LDL exacerbates joint inflammation, promotes chondrocyte damage, and contributes to synovial tissue deterioration [21–23]. Due to its involvement in these processes, ox-LDL is considered. Therefore, it is considered both a potential biomarker and a promising therapeutic target in OA. Our previous research demonstrated that ox-LDL contributes to knee OA through oxidative stress mechanisms [24]. Some studies have shown that EVOO can inhibit ox-LDL production [12, 13]. Despite this, the therapeutic effects of EVOO consumption in knee OA remain insufficiently explored. Current scientific research suggests that EVOO may help reduce OA symptoms; however, existing studies are limited, often small in scale, and predominantly based on animal models [25–29]. Moreover, most previous EVOO-OA studies lack comprehensive, integrative assessments combining both histological and biochemical parameters. In particular, the role of ox-LDL remains largely underexplored in this context [9, 25, 26, 28].

In this study, we hypothesized that EVOO consumption could reduce ox-LDL levels and oxidative stress, thereby providing therapeutic benefits in a rat model of monosodium iodoacetate (MIA)-induced OA. To evaluate this hypothesis, we conducted a comparative experimental study that included histopathological, immunohistochemical, biochemical, and radiological examinations of the knee joints. In addition to measuring ox-LDL levels, we also assessed oxidative stress parameters, including total antioxidant capacity (TAC), total oxidant status (TOS), and the oxidative stress index (OSI).

Materials and Methods

A total of 21 male Wistar Hannover rats (5–6 months old) with an average weight of 300–350 g constituted the material of the study. Approval for the experimental study was obtained from the Local Ethics Committee for Animal Experiments of Bagcilar Training and Research Hospital (project 83, board/2018–40 dated 23.11.2018). The animals were housed in polycarbonate conventional Type 4 cages (PLEXX, The Netherlands) with access to tap water and food ad libitum [30]. A veterinarian monitored the animals daily to assess their general health and well-being. Body weight was recorded weekly, and no animal exhibited a weight loss greater than 10% during the study period. Animals were housed in standard cages with consistent cage mates to minimise social stress. All cages were cleaned twice weekly by the same technician to ensure hygienic conditions under standardised procedures. Environmental enrichment was not applied, as it had not been implemented at any stage of the animals' lives and was therefore excluded from the experimental protocol. The study was conducted by the ARRIVE 2.0 guidelines for animal research reporting [31]. Compliance with these guidelines ensures transparent and comprehensive reporting, allowing readers and reviewers to critically evaluate the methodological quality and reproducibility of the study.

Animals were randomly assigned to three groups ($n=7$ per group) using a sealed-envelope method to ensure unbiased allocation [32]: OA Group, EVOO-treated Group, and Control Group (Table 1). A power analysis was performed for the ideal number of rats for each group. Based on the one-way analysis of variance (ANOVA) test with a sample size of 7 per group, the effect size of the study was determined as 1.90 and the power analysis of the study was determined as 97% (alpha = 0.05).

To establish the OA model, a single intra-articular injection of MIA was administered, following previously described methods [33, 34]. All surgical procedures were performed in a single session. After preparation, anesthesia was administered intraperitoneally using 90 mg/kg of ketamine HCl and 10 mg/kg of xylazine HCl to all animals [35]. Then the left knee was flexed to 90°, and the patellar ligament was palpated beneath the patella for injection

Table 1 Experimental groups

Experimental groups	
EVOO Group ($n=7$)	OA established + EVOO diet
OA Group ($n=7$)	OA established + isocaloric diet
Control Group ($n=7$)	OA not formed (sham) + isocaloric diet

targeting. MIA (Sigma-Aldrich, Saint Louis, MO, USA) was prepared at a concentration of 10 mg/ml in the sterile injectable saline [36]. Following anesthesia, each rat in OA Group and EVOO-treated Group received an intra-articular injection of 0.025 ml (equivalent to 0.25 mg MIA) of the MIA solution into the left knee joint. The injection was administered through the infrapatellar ligament at a knee flexion using a 27-gauge, 0.5-inch needle. Rats in the Control Group received the same volume (0.025 ml) of physiological saline in the same manner.

Nutrition

All groups were fed with a standardized high-fat, isocaloric diet consisting of 40% carbohydrates, 30% protein, and 30% fats, as previously described [26]. The feed, prepared in the laboratory (Arden Research & Experimentation, Ankara), contained a balanced mix of neutral, saturated, and unsaturated fatty acids. In EVOO-treated Group, the diet was supplemented with EVOO rich in oleic acid. The EVOO used in this study was a cold-pressed product with high phenolic content ($72 \pm 6.3\%$), sourced commercially from the 2021–2022 production season (Semercioğlu Zeytincilik, Balıkesir, Türkiye). In line with earlier studies [37], the standardized diet was initiated one week before OA induction and continued for 21 days after MIA-induced OA. On day 21, the animals were sacrificed under high-dose anesthesia. Intracardiac blood samples were collected, radiographs of the rats were taken, and their knee joints were dissected for gross and histopathological evaluations.

Histopathology

Following euthanasia, the hind limbs were disarticulated at the hip joint, fixed in 4% buffered formalin for 24 h, and decalcified in osteodec solution (Bio-Optica, Catalog No: BO-05-03005Q) for one week. After overnight washing, the specimens were sagittally sectioned and routinely processed. Specimens were embedded in paraffin and sectioned for histopathological and immunohistochemical examination. For histopathological evaluation, four tissue sections, each with 5 µm thickness, were obtained at 80 µm intervals. The sections were stained with Hematoxylin and Eosin (H&E) and Safranin O–Fast Green for routine histopathological evaluation. Scoring was performed using the semiquantitative modified Mankin scoring system [38]. The final score was calculated as the average of the values obtained for each parameter.

Evaluation of the synovial pathology was based on two parameters: synovial epithelial thickness and cell density in the synovial stroma. Synovial epithelial thickness was scored on a scale of 0 to 3 (0 = 1–2 rows of cells; 1 = 2–4 rows of cells; 2 = 4–9 rows of cells; 3 = 10 or more rows of cells). Similarly, cell density in the synovial stroma was scored on a scale of 0 to 3 (0 = normal cellularity; 1 = slightly increased cellularity; 2 = moderately increased cellularity; 3 = highly increased cellularity). Synovitis scores were obtained from four quadrants (medial tibia, medial femur, lateral tibia, and lateral femur). For each parameter, scores from the quadrants were averaged separately. The final synovitis score (0–6 scale) was calculated as the sum of the averages of the two mentioned parameters [39].

Immunohistochemistry (IHC) was used to detect ox-LDL antibodies in joint tissues. Sections were dewaxed in xylene and subjected to antigen retrieval by boiling in citrate buffer (pH 6) in a microwave oven (750 W) for 20 min. Endogenous peroxidase activity was blocked by incubation in 0.3% H_2O_2 in methanol for 15 min. The sections were then blocked with normal blocking serum for 5 min. After blocking, the sections were incubated overnight at 4 °C with rabbit anti-mouse ox-LDL polyclonal antibody (bs-1698R, Bioss, USA; 1:100 dilution). To amplify the primary antibody signal, the sections were incubated with a biotinylated secondary antibody (TP-125-HL, Thermo Scientific, USA) for 10 min at room temperature. The immunoreaction was visualized using 3,3'-diaminobenzidine tetrahydrochloride (DAB) from the Lab Vision UltraVision Detection System (TA-125-HD). The sections were counterstained with Mayer's hematoxylin and mounted. Immunoreactivity was evaluated using the immunoreactive score (IRS) system as previously described [40]. The IRS is calculated by multiplying two parameters: staining intensity (SI) and the percentage of immunopositive cells, both assessed under light microscopy at 20 x magnification. SI was graded on a scale from 0 to 4 as follows: 0 = no staining, 1 = weak, 2 = moderate, 3 = strong, 4 = very strong. The percentage of immunopositive cells was determined by counting the number of positive cells out of 100, and categorised as: 0 = 0%, 1 = < 10%, 2 = 10–50%, 3 = 51–80%, 4 = > 80%. The final IRS score ranged from 0 to 16 and was obtained by multiplying the SI and percentage scores. Negative controls were included by omitting the primary antibody to verify staining specificity.

The apoptotic index was determined using the ApopTag peroxidase in situ Apoptosis Detection Kit (deoxynucleotidyl

terminal transferase, TUNEL, Merck Milipore, catalog no: S7100). Brown-stained nuclei were considered positive, while blue-stained nuclei were considered negative, regardless of staining intensity. For each sample, six randomly selected fields were examined manually at 20 × magnification under a light microscope. In each field, 100 cells were counted, and the apoptotic index was calculated as the ratio of stained to unstained cell nuclei. For each photomicrograph, the proportion of positive cells relative to the total cell count was calculated, and the mean value was obtained for each sample. Results were expressed as percentages [41]. All evaluations were performed in a blinded manner by two independent pathologists.

Biochemistry

The first tube was prepared with K3 EDTA, while the other tubes did not contain anticoagulants. All tubes were gently inverted 3–4 times to ensure thorough mixing. The last two tubes were centrifuged at 3,000 rpm for 10 min to separate the serum, then stored at − 80 °C till the following analysis.

Total Oxidative Status and Total Antioxidant Capacity

TOS and TAC were measured using the methods described by Erel [42, 43]. TOS measurements were based on the principle that oxidants in the sample oxidize the ferrous iron ion-chelate complex to ferric ion. The ferric ion forms a colored complex with chromogen in an acidic environment, and the color intensity, measured spectrophotometrically, is proportional to the total oxidant molecules in the sample. Hydrogen peroxide was used for assay calibration, with results expressed as micromolar hydrogen peroxide equivalents per liter (μmol H_2O_2 equiv/L) (Relassay, Mega Tip, Gaziantep, Türkiye).

TAC measurements relied on the ability of antioxidants in the sample to reduce the dark blue-green ABTS (2,2′-Azino-bis (3-ethylbenzothiazoline-6-sulfonic acid) diammonium salt) radical to a colorless reduced form. Test calibration is based on the principle of reduction of the antioxidants in the sample, which is a vitamin E analogue. It was performed with a stable antioxidant standard solution called Trolox Equivalent (Relassay, Mega Tip, Gaziantep, Türkiye) [42, 43].

Oxidative Stress Index

OSI, representing the percentage of oxidative stress, was calculated as the ratio of TOS to TAC [42, 43]. For this calculation, the TAC unit was converted to μmol/L, and OSI was determined using the formula:

$$OSI\ (arbitrary\ unit) : TOS\ (\mu mol\ H202\ equiv/L)/TAC\ (\mu mol\ Trolox\ equiv/L) \times 10$$

Measurement of Ox-LDL

Ox-LDL concentrations were determined using a sandwich enzyme-linked immunosorbent assay (ELISA) (Immundiagnostic, Cat. No: 201–12-1543) [44]. The ELISA procedure was carried out in accordance with the manufacturer's instructions.

Radiological Parameters

Radiological evaluation was conducted immediately after euthanasia and before the onset of rigor mortis. A dental radiography periapical film unit was used to capture knee radiographs. The knees were positioned in full extension with the ankle in a dorsoplantar position. Radiographs were analyzed for changes in joint space, subchondral sclerosis, and osteophyte formation. The Kellgren & Lawrence scale was used to evaluate OA, with scores ranging from 0 to 4, as follows:

- 0 = No signs of OA
- 1 = Minimal osteophyte of questionable significance
- 2 = Definite osteophyte with preserved joint space
- 3 = Moderate osteophyte with narrowing joint space
- 4 = Significant joint space narrowing with subchondral sclerosis [45].

Statistical Analysis

Statistical analyses were performed using SPSS version 21.0 software (SPSS Inc., IBM, Armonk, NY, USA). ANOVA test was applied to assess differences, with significance thresholds set at $p < 0.05$ and $p < 0.01$. A Pearson's test was used for correlation analysis. Duncan's multiple range test was used to determine significant differences between means at a significance level of $p < 0.05$.

Results

Histopathological findings

Cartilage tissue from the Control Group displayed a normal histological structure, with a smooth femoral and tibial cartilage surface and uniformly distributed chondrocytes (Fig. 1A). In contrast, cartilage sections from the OA Group, stained with H&E, revealed moderate osteoarthritic changes, including articular surface irregularities, fissures in the superficial zone, mild hypocellularity, reduced proteoglycan levels, and thickened subchondral bone (Fig. 1B). In the EVOO-treated Group, osteoarthritic changes such as fissure formation on the articular surface and clustering of chondrocytes (2–4 cells per cluster) were still present, but the severity of these histopathologic findings was reduced compared to the OA Group (Fig. 1C). Safranin-O staining compared to Control Group (Fig. 2A), showed reduction in proteoglycan content in OA Group (Fig. 2B), while EVOO-treated Group exhibited only a modest reduction in proteoglycan levels (Fig. 2C).

No histopathological signs of synovitis were observed in the Control Group (Fig. 3A). Synovitis scores were lower in the EVOO-treated Group compared to the OA Group, with a marked reduction in synovial edema and inflammatory cell infiltration in the EVOO-treated Group (Fig. 3B). In the OA Group, the synovial membrane exhibited prominent edema and inflammatory cell infiltration, predominantly composed of macrophages and mononuclear cells (Fig. 3C and D). Overall, Mankin scores were significantly higher in the OA Group (10.71 ± 0.52), supporting the presence of OA, while EVOO-treated Group showed a statistically significant reduction in histopathologic scores (3.86 ± 0.50) compared to the OA Group ($p = 0.001$) (Table 2).

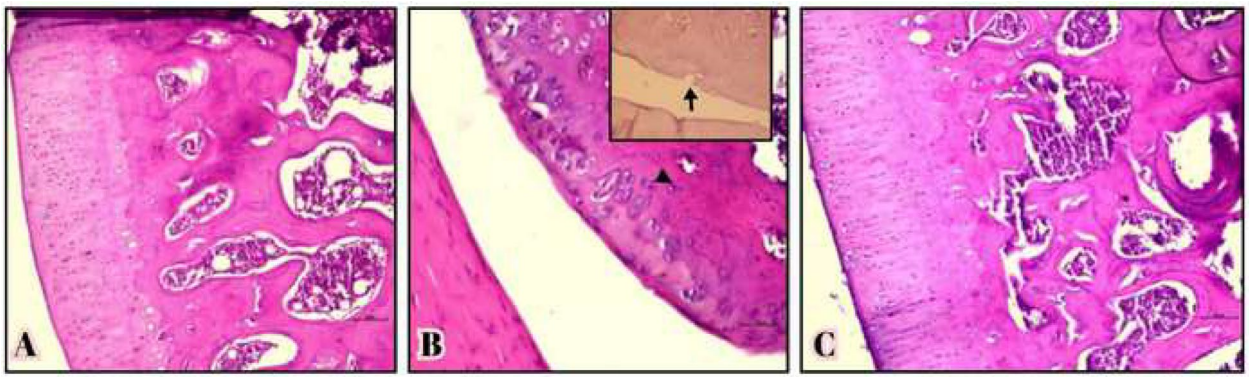


Fig. 1 Histologic micrographs of the articular cartilage in the femoratibial joints. H&E. **A** Control Group. The cartilage surface is smooth, with no irregularities and, chondrocytes are evenly distributed within the lacunae (Bar = 90 µm). **B** OA Group. The knee joint shows irregularities on the articular surface, chondrocytes arranged in clusters (arrow) (Bar = 50 µm). Inset: Irregularities are evident in the upper zone, along with a deep vertical fissure (Bar = 100 µm). **C** EVOO-treated Group. The articular cartilage shows an almost normal appereance (Bar = 90 µm)



Fig. 2 Safranin-0 staining of the cartilage matrix. Safranin-O Light Green Stain. **A** Control Group. The cartilage matrix is intensely stained with Safranin-O. **B** OA Group. A reduction in staining intensity is observed indicating a decreased proteoglycan content. **C** EVOO-treated Group. Staining intensity is markedly increased compared to the OA Group (Bar = 90 µm)

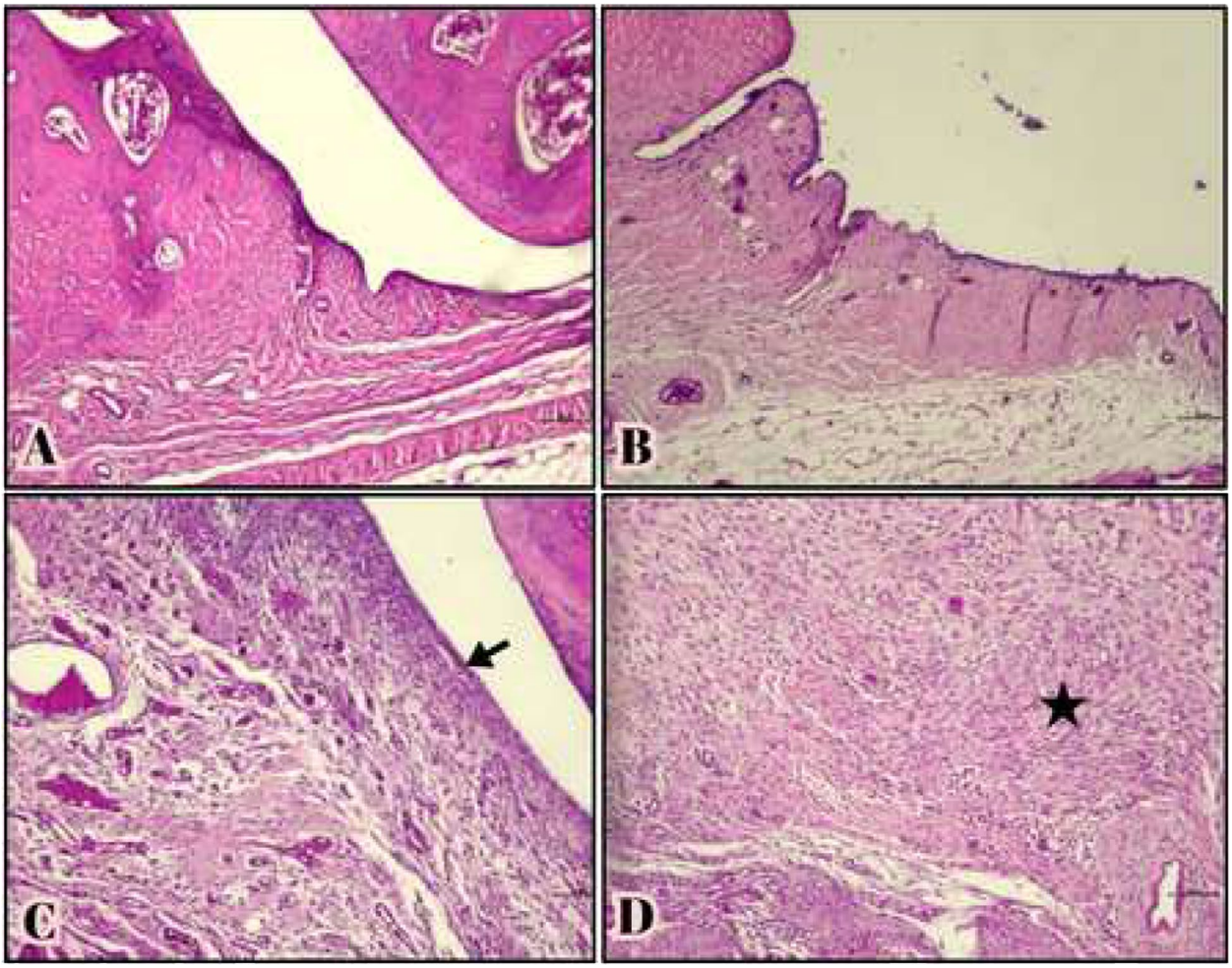


Fig. 3 Histologic micrographs of the synovial membrane. H&E. **A** Control Group. No inflammatory cell infiltration is observed. **B** EVOO-treated Group. Minimal inflammatory cell infiltration is observed in the synovium (**C** and **D**) OA Group. Activation of synovial lining epithelial cells (arrow), inflammatory infiltration consisting mainly of mononuclear cells (star) fibrosis and neovascularization are evident. (Bar = 90 µm)

Table 2 Modified Mankin scores of groups

Parameters	OA Group Mean ± SD	EVOO Group Mean ± SD	Control Group Mean ± SD	*P*-value
Mankin Score	10.71 ± 0.52^{a}	3.86 ± 0.50^{b}	$0.14 \pm 0{,}14^{c}$	0.001

a, b, c: The significance level is p<0.001. *Measurements are given as the mean ± SD. The significance level is $p < 0.0.5$

Immunohistochemical findings

No ox-LDL immunoreactivity was detected in the Control Group (Figs. 4A and 5A). In the OA Group, ox-LDL immunostaining was strong to very strong (IRS scores: + 3 to + 4), accompanied by a significantly elevated immunoreactive score (IRS: 11.29 ± 2.29). In contrast, the EVOO-treated group exhibited moderate to strong staining intensity (IRS scores: + 2 to + 3) with a markedly reduced IRS (5.00 ± 1.00). These findings were consistently observed in both the articular cartilage (Fig. 4B and C) and the synovial epithelial cells (Fig. 5B and C) of the OA and EVOO-treated groups.

The overall IRS was significantly higher in the OA Group (11.29 ± 2.29) compared to both the Control (0 ± 0) and EVOO-treated (5.00 ± 1.00) groups (Fig. 6A), with statistical significance ($p = 0.001$).

TUNEL findings

TUNEL staining in the Control group revealed only a few positively labeled cells, indicating minimal apoptosis (Fig. 7A). In contrast, the OA group exhibited a marked increase in TUNEL-positive cells compared to both

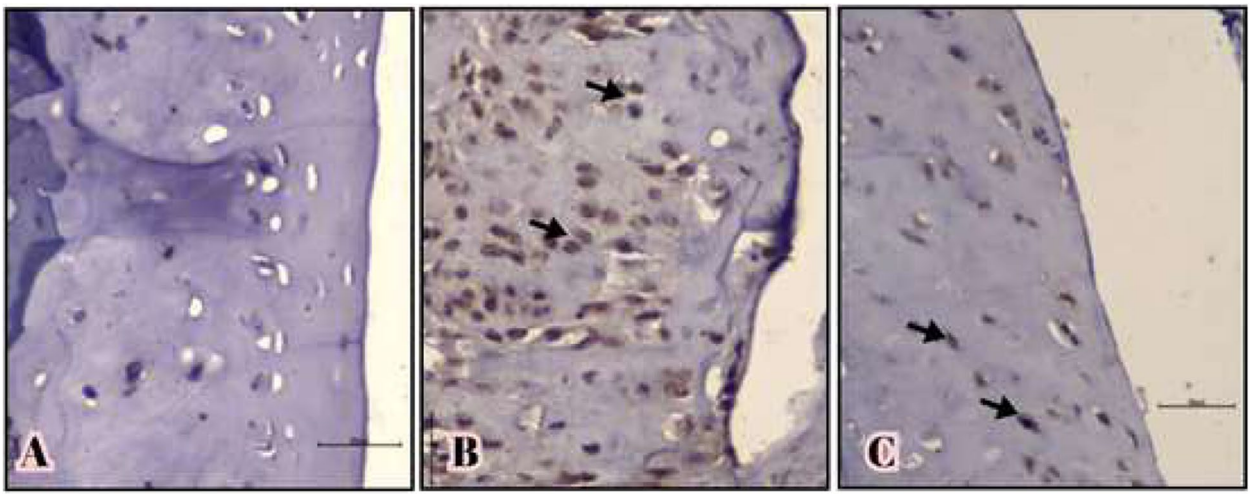


Fig. 4 Immunohistochemical labeling of anti-ox-LDL antibody in articular cartilage cells and synovial epithelium, respectively. **A** Control Group**.** No positive immunoreactivity for ox-LDL is observed either in the articular cartilage (Bar = 90 μm) or the synovial epithelium (Bar = 70 μm). **B** OA Group. A significant increase in ox-LDL expression is observed in both the articular cartilage and synovial epithelial cells. **C** EVOO-treated Group. Decrease in the number of positively stained chondrocytes compared to OA group, suggest that EVOO reduces oxidative stress in OA

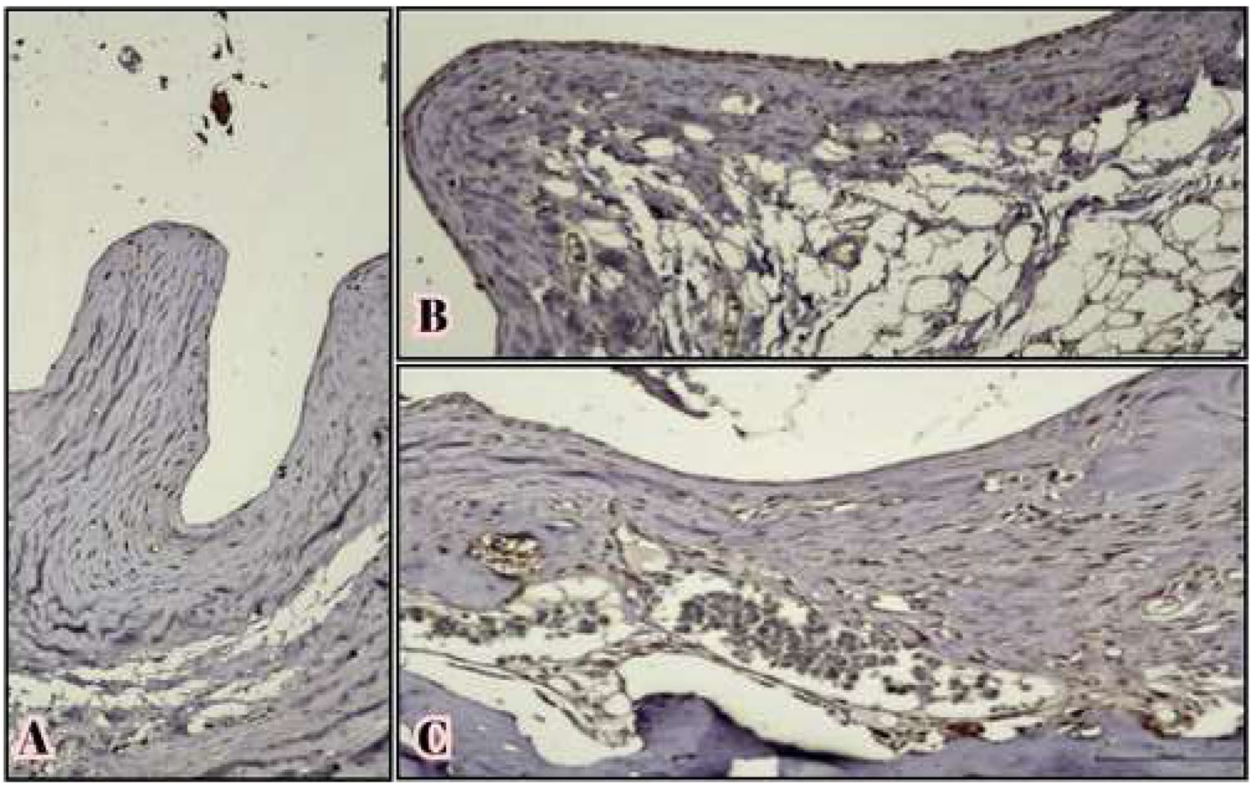


Fig. 5 Immunohistochemical labeling of anti-ox-LDL antibody in articular cartilage cells and synovial epithelium, respectively. **A** Control Group. No positive immunoreactivity for ox-LDL is observed either in the articular cartilage (Bar = 90 μm) or the synovial epithelium (Bar = 70 μm). **B** OA Group. A significant increase in ox-LDL expression is observed in both the articular cartilage and synovial epithelial cells. **C** EVOO-treated Group. Decrease in the number of positively stained chondrocytes compared to OA group, suggest that EVOO reduces oxidative stress in OA

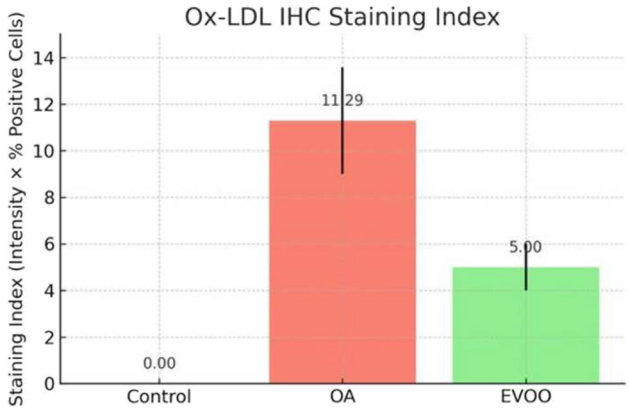


Fig. 6 Immunostaining index for oxidized low-density lipoprotein (Ox-LDL) in the control, osteoarthritis (OA), and extra virgin olive oil (EVOO)- treated groups

the Control and EVOO-treated groups (Fig. 7B and C). The apoptotic index was significantly higher in the OA group (Control: 2.86 ± 0.37; OA: 32.60 ± 1.82; EVOO: 19.16 ± 1.68; $p = 0.001$), confirming the pro-apoptotic effect ofOA and the partial protective role of EVOO supplementation.

Biochemical findings

Besides ox-LDL (OA: 26.63 ± 1.27, EVOO: 20.98 ± 0.92, $p = 0.007$), the other oxidant parameters, including TOS (OA: 2.60 ± 0.52, EVOO: 0.46 ± 0.05, $p = 0.008$) and OSI (OA: 1.83 ± 0.43, EVOO: 0.13 ± 0.02, $p = 0.001$), were significantly lower in the EVOO Group compared to the OA Group. Conversely, TAC levels (EVOO: 0.36 ± 0.02, OA: 0.15 ± 0.02, $p = 0.001$) were significantly higher in the EVOO Group (Table 3).

Correlation analysis between ox-LDL and oxidative stress markers revealed a significant positive correlation of ox-LDL with TOS (r = 0.586, $p = 0.005$) and OSI (r = 0.635, $p = 0.002$). In contrast, ox-LDL was inversely correlated with serum TAC (r = –0.704, $p = 0.001$) in a bivariate analysis. The correlation between ox-LDL and TOS is shown in Fig. 8.

Radiographic and macroscopic findings

No signs of OA was observed in the left knee X-ray radiographs or macroscopic examinations of all the three groups.

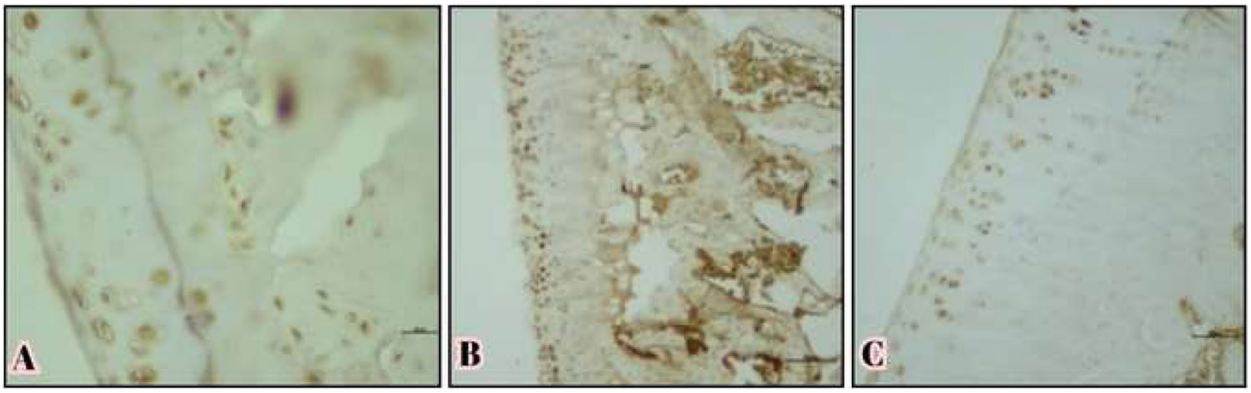


Fig. 7 TUNEL staining of the articular cartilage. **A** Control Group. Only a small number of positively stained cells are observed (Bar = 20 µm). **B** OA Group. A significant increase in the number of positively stained cells is observed (Bar = 50 µm) compared to the control group. **C** EVOO-treated Group. The number of positively stained chondrocytes was lower, compared to OA group. (Bar = 90 µm). Positive reactions are indicated by brown nuclei in the chondrocytes

Table 3 Oxidative stress parameters of groups

	EVOO Group	OA Group	Control Group	*p*-value
Ox-LDL (mmol/L)	20,98 ± 0.92	26,63 ± 1.27	25,31 ± 0.58	0.007
TOS (µmol H2O2equiv/L)	0,46 ± 0.05	2,60 ± 0.52	1,32 ± 0.32	0.008
OSI (Arbitrary unit)	0,13 ± 0.02	1,83 ± 0.43	0,99 ± 0.31	0.001
TAC (mmol Trolox equiv/L)	0,36 ± 0.02	0,15 ± 0.02	0,15 ± 0.02	0.001

Ox-LDL oxided low-density lipoprotein, *TOS* total oxidant status, *OSI* oxidative stress index, *TAC* total antioxidant capacity, *SD* standart deviation

*Measurements are given as the mean ± SD. The significance level is $p < 0.05$

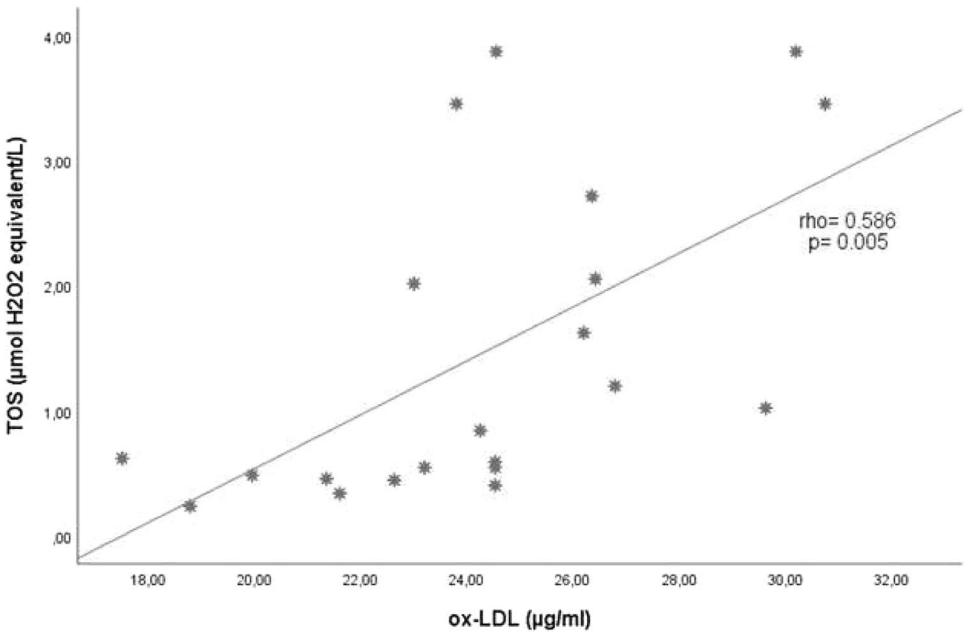


Fig. 8 The correlation of total oxidant status (TOS) with ox-LDL levels

Discussion

The two most significant findings of the present study were the reduced levels of inflammation and apoptosis and decreased serum ox-LDL and oxidative stress markers, in EVOO-fed MIA rats compared to untreated MIA rats.

In this study, we observed a remarkable recovery in the knee joint of EVOO-fed MIA rats compared to untreated rats. Histopathologic evaluation revealed extensive damage in the articular cartilages, synovium and extracellular matrix of untreated rats, consistent with MIA-induced OA. The MIA model, a well-established chemical method for inducing OA, disrupts cartilage integrity by inhibiting glyceraldehyde-3-phosphate dehydrogenase activity and generating ROS. This leads to synovitis, cartilage erosion, and matrix degradation, mimicking the pathophysiology of human OA [46]. Our findings confirm that MIA injection induces significant cartilage degradation and surface irregularities. Notably, EVOO supplementation effectively mitigated these degenerative changes. Although a few studies have reported cartilage-protective effects of EVOO in a collagen type II-induced (CIA) rheumatoid arthritis (RA) model [27, 47–49], this model represents an autoimmune/inflammatory disease rather than pure degenerative joint pathology. CIA models are typically established by subcutaneous administration of collagen type II in genetically susceptible mice (e.g., DBA/1 strain), often accompanied by systemic inflammation and cytokine evaluation [50]. In contrast, our study utilized a monosodium iodoacetate (MIA)-induced OA model in rats, which allows for more detailed histopathologic evaluation due to their larger joint structures and facilitates colleciton collection of sufficient blood and tissue samples for biochemical analysis [51]. Furthermore, unlike studies that focus solely on isolated EVOO-derived phenolic compounds, our study employed an EVOO-enriched diet, reflecting more realistic dietary supplementation. To our knowledge, this is the first study to demonstrate both histopathological improvement and significant reduction in oxidative stress markers, particularly ox-LDL, in rats fed with EVOO-enriched diet within an MIA-induced OA model. In a study conducted by Risollo et al. [47] in 2014, oleocanthal, a polyphenol derived from EVOO, was shown to reduce inflammation and oxidative stress in CIA mouse model. This effect was attributed to decreased levels of inflammatory cytokines (TNF-α, IL-1β, IL-17) and matrix metalloproteinase-3 (MMP-3). Similarly, a recent study published in 2024 demonstrated that oleacein prevented joint inflammation and cartilage damage in a CIA model by reducing pro-inflammatory cytokines (IL-6, IL-1β, TNF-α, IL-17) and suppressing the expression of COX-2 and iNOS enzymes [48].

Another study investigating the effects of EVOO was conducted using an anterior cruciate ligament transection (ACLT)-induced OA model, commonly employed in tissue engineering and cartilage repair research. The ACLT model induces a slowly progressive form of OA over 4 to 12 weeks. In this study, the combination of an EVOO-enriched diet with regular physical activity reduced cartilage damage, decreased IL-6 expression, and increased lubricin levels [27]. In a different approach, a study published in 2022 examined the effects of MOMAST® GR25, a polyphenolic complex derived from EVOO, in a rat model of OA induced by MIA injection into the tibio-tarsal joint [49]. This complex, obtained from the Coratina olive variety, significantly

reduced pain behaviours, as evidenced by decreased licking and biting time in the formalin test. In vivo, compared to controls, rats treated with this complex showed a significant reduction in both licking/biting time in the formalin test. Furthermore, treatment lowered prostaglandin (PG) E2 and 8-iso-PGF2 levels in isolated colon, liver, and heart tissues. However, the exact composition and concentration of the polyphenolic components in MOMAST® GR25 were not clearly defined, warranting caution in attributing these effects solely to EVOO.

Safranin O staining further confirmed our histopathologic findings, showing significantly reduced staining in untreated rats compared to the EVOO-treated and Control Groups. As Safranin O intensity reflects proteoglycan content in cartilage, its reduction indicates extracellular matrix disruption [52]. Previous studies have demonstrated similar MIA-induced cartilage matrix degradation and glycosaminoglycan depletion, aligning with our results [36, 46]. Nitric oxide (NO), a ROS product, exacerbates cartilage damage by inducing apoptosis and inflammation in chondrocytes. Scotece et al. [11] demonstrated that oleocanthal significantly reduced NO production and NOS2 expression in lipopolysaccharide-stimulated human OA chondrocytes.

In the study, we observed high TUNEL positive staining cells in the untreated MIA rats compared to the EVOO fed MIA rats and Control Groups. TUNEL staining detects the DNA breaks formed when DNA fragmentation occurs in the last phase of apoptosis [40]. MIA disrupts the glycolytic energy metabolism in cells and causes chondrocyte death, leading to inflammation and cartilage damage [34, 36, 46]. In a recent study, the mechanisms for the effect of oleocanthal on apoptosis was demonstrated [53]. Several studies suggest that consumption of the EVOO and its phenolic compounds reduces the incidence of certain pathologies related to oxidative stress, chronic inflammation and immune system diseases [11–16, 54].

Immunohistochemical evaluation indicated strong ox-LDL intensity in untreated MIA rats compared to EVOO-fed and Control Groups. Ox-LDL, produced during oxidative stress, acts as a pro-apoptotic and pro-inflammatory agent, contributing to joint damage [55]. These findings suggest that ox-LDL is a valuable early marker to detect tissue destruction due to oxidative stress in the early period.

Serum analysis revealed significantly lower TOS and OSI in EVOO-fed rats compared to untreated MIA rats in our study. This reduction is likely attributable to the antioxidant properties of EVOO, which counteract MIA-induced systemic oxidative stress [36, 46]. EVOO's phenolic compounds are known to exhibit antioxidant, anti-inflammatory, and immunomodulatory effects [10–12, 26]. Rumeu et al. [56] similarly reported reduced oxidative stress markers following EVOO consumption in hyperlipidemic individuals. Additionally, our findings of increased TAC in EVOO-fed rats further support EVOO's protective role.

Serum ox-LDL levels were also significantly lower in EVOO-fed rats. As an early product of lipid peroxidation and marker of oxidative stress, ox-LDL is closely linked to lipid metabolism [24]. EVOO's antioxidant compounds likely contribute to these effects, consistent with previous reports [10–14].

Radiographic analysis revealed no visible OA signs in any group, likely due to the relatively low MIA dose (0.25 mg) used to induce moderate OA. Higher doses, such as the 1 mg dose used by Guzman et al. [37], typically produce more severe pathological changes.

Clinical Implications

This study demonstrates that EVOO supplementation reduces tissue damage and oxidative stress in MIA-induced OA. The findings suggest that EVOO, with its antioxidant properties, may serve as a promising therapeutic option for OA. By inhibiting oxidative processes, EVOO could be incorporated as an adjuvant antioxidant therapy to manage OA.

Limitations

Notable limitations should be acknowledged in this study. First, the sample size was relatively small due to ethical considerations aimed at minimizing animal use. Second, the lack of synovial fluid analysis restricted our ability to use additional biomarkers that might have strengthened our findings. Finally, EVOO is a complex mixture containing various phenolic compounds, which makes it difficult to identify the specific substance responsible for the observed effects in this experimental study.

Conclusion

In the MIA-induced OA model, immunohistochemistry revealed that EVOO-fed rats exhibited less cartilage damage and reduced synovitis. Biochemical analysis showed lower levels of ox-LDL and oxidative stress markers compared to untreated rats. These findings may highlight EVOO's potential as an adjuvant therapy for OA. This study is the first to report both histopathological improvements and reduced oxidative stress markers, especially ox-LDL, in rats subjected to an MIA-induced OA model and supplemented with an EVOO-enriched diet. While promising, further research is necessary to confirm these findings and explore the potential therapeutic applicaitons of EVOO in human OA.

Author Contributions Writing, editing: C.E. and Ö.E.T.; Analysis and interpretation of data: C.E., S.K.D., G.Y.Ö. and D.S.O.; Literature

review: C.E, A.G.; Data processing and statistic: S.K.D., G.Y.Ö. and N.I.; Critical review and supervision: C.E. and A.G.

Funding This project was funded by the Health Sciences University Türkiye Scientific Research Coordination Committee (Number: 2021/010). The authors did not receive any outside funding or grants in support of their research, or during the preparation of this work.

Compliance with ethical standards

Disclosures None.

References

1. Leifer VP, Katz JN, Losina E (2022) The burden of OA-health services and economics. Osteoarthritis Cartilage 30:10–16. https://doi.org/10.1016/j.joca.2021.05.007
2. Allen KD, Thoma LM, Golightly YM (2022) Epidemiology of osteoarthritis. Osteoarthritis Cartilage 30:184–195. https://doi.org/10.1016/j.joca.2021.04.020
3. Altay MA, Ertürk C, Bilge A, Yaptı M, Levent A, Aksoy N (2015) Evaluation of prolidase activity and oxidative status in patients with knee osteoarthritis: relationships with radiographic severity and clinical parameters. Rheumatol Int 35:1725–1731. https://doi.org/10.1007/s00296-015-3290-5
4. Brandt KD, Dieppe P, Radin EL (2008) Etiopathogenesis of osteoarthritis. Rheum Dis Clin North Am 34:531–559. https://doi.org/10.1016/j.rdc.2008.05.011
5. Fathollahi A, Aslani S, Jamshidi A, Mahmoudi M (2019) Epigenetics in osteoarthritis: novel spotlight. J Cell Physiol. https://doi.org/10.1002/jcp.28020
6. de Visser HM, Weinans H, Coeleveld K, van Rijen MH, Lafeber FP, Mastbergen SC (2017) Groove model of tibia-femoral osteoarthritis in the rat. J Orthop Res 35:496–505. https://doi.org/10.1002/jor.23299
7. Mathieu S, Soubrier M, Peirs C, Monfoulet LE, Boirie Y, Tournadre A (2022) A meta-analysis of the impact of nutritional supplementation on osteoarthritis symptoms. Nutrients 1607. https://doi.org/10.3390/nu14081607
8. Maouche A, Boumediene K, Baugé C (2024) Bioactive compounds in osteoarthritis: molecular mechanisms and therapeutic roles. Int J Mol Sci 11656. https://doi.org/10.3390/ijms252111656
9. Rosillo MA, Sánchez-Hidalgo M, Sánchez-Fidalgo S, Aparicio-Soto M, Villegas I, Alarcón-de-la-Lastra C (2016) Dietary extra-virgin olive oil prevents inflammatory response and cartilage matrix degradation in murine collagen-induced arthritis. Eur J Nutr 55:315–325. https://doi.org/10.1007/s00394-015-0850-0
10. Derakhshandeh-Rishehri SM, Kazemi A, Shim SR, Lotfi M, Mohabati S, Nouri M et al (2023) Effect of olive oil phenols on oxidative stress biomarkers: A systematic review and dose-response meta-analysis of randomized clinical trials. Food Sci Nutr 13(11):2393–2402. https://doi.org/10.1002/fsn3.3251
11. Scotece M, Conde J, Abella V, López V, Francisco V, Ruiz C et al (2018) Oleocanthal inhibits catabolic and inflammatory mediators in LPS-activated human primary osteoarthritis (OA) chondrocytes through MAPKs/NF-κB pathways. Cell Physiol Biochem 49:2414–2426. https://doi.org/10.1159/000493840
12. Flynn MM, Tierney A, Itsiopoulos C (2023) Is Extra Virgin Olive Oil the Critical Ingredient Driving the Health Benefits of a Mediterranean Diet? A Narrative Review. Nutrients 27(15):2916. https://doi.org/10.3390/nu15132916
13. Hernáez Á, Remaley AT, Farràs M, Fernández-Castillejo S, Subirana I, Schröder H et al (2015) Olive oil polyphenols decrease LDL concentrations and LDL atherogenicity in men in a randomized controlled trial. J Nutr 145:1692–1697. https://doi.org/10.3945/jn.115.211557
14. Schwingshackl L, Krause M, Schmucker C, Hoffmann G, Rücker G, Meerpohl JJ (2019) Impact of different types of olive oil on cardiovascular risk factors: a systematic review and network meta-analysis. Nutr Metab Cardiovasc Dis 29:1030–1039. https://doi.org/10.1016/j.numecd.2019.07.001
15. Chin KY, Pang KL (2017) Therapeutic Effects of Olive and Its Derivatives on Osteoarthritis: From Bench to Bedside. Nutrients 26 9(10):1060. https://doi.org/10.3390/nu9101060.
16. Servili M, Sordini B, Esposto S, Urbani S, Veneziani G, Di Maio I et al (2013) Biological Activities of Phenolic Compounds of Extra Virgin Olive Oil. Antioxidants (Basel) 20(3):1–23. https://doi.org/10.3390/antiox3010001
17. Cárdeno A, Sánchez-Hidalgo M, Alarcón-de-la-Lastra C (2013) An up-date of olive oil phenols in inflammation and cancer: molecular mechanisms and clinical implications. Curr Med Chem 20:4758–4776. https://doi.org/10.2174/09298673113209990159
18. Ertürk C, Altay MA, Selek S, Koçyiğit A (2012) Paraoxonase-1 activity and oxidative status in patients with knee osteoarthritis and their relationship with radiological and clinical parameters. Scand J Clin Lab Invest 72:433–439. https://doi.org/10.3109/00365513.2012.687116
19. Ertürk C, Altay MA, Sert C, Levent A, Yaptı M, Yüce K (2015) The body composition of patients with knee osteoarthritis: relationship with clinical parameters and radiographic severity. Aging Clin Exp Res 27:673–679. https://doi.org/10.1007/s40520-015-0325-4
20. Papathanasiou I, Anastasopoulou L, Tsezou A (2021) Cholesterol metabolism related genes in osteoarthritis. Bone 152:116076. https://doi.org/10.1016/j.bone.2021.116076
21. Hashimoto K, Akagi M (2020) The role of oxidation of low-density lipids in pathogenesis of osteoarthritis: a narrative review. J Int Med Res 48(6):300060520931609. https://doi.org/10.1177/0300060520931609
22. Lee JS, Kim YH, Jhun J, Na HS, Um IG, Choi JW et al (2024) Oxidized LDL accelerates cartilage destruction and inflammatory chondrocyte death in osteoarthritis by disrupting the TFEB-Regulated Autophagy-Lysosome Pathway. Immune Netw 12;24(3):e15. https://doi.org/10.4110/in.2024.24.e15
23. Morici L, Allémann E, Jordan O, Nikolić I (2025) Promising LOX proteins for cartilage-targeting osteoarthritis therapy. Pharmacol Res 212:107627. https://doi.org/10.1016/j.phrs.2025.107627
24. Ertürk C, Altay MA, Bilge A, Çelik H (2017) Is there a relationship between serum ox-LDL, oxidative stress, and PON1 in knee osteoarthritis? Clin Rheumatol 36:2775–2780. https://doi.org/10.1007/s10067-017-3732-4
25. Bitler CM, Matt K, Irving M, Hook G, Yusen J, EaLyar F et al (2007) Olive extract supplement decreases pain and improves daily activities in adults with osteoarthritis and decreases plasma homocysteine in those with rheumatoid arthritis. Nutr Res 27(8):470–477. https://doi.org/10.1016/j.nutres.2007.06.003
26. Musumeci G, Trovato FM, Pichler K, Weinberg AM, Loreto C, Castrogiovanni P (2013) Extra-virgin olive oil diet and mild physical activity prevent cartilage degeneration in an osteoarthritis model: an in vivo and in vitro study on lubricin expression. J Nutr Biochem 24:2064–2075. https://doi.org/10.1016/j.jnutbio.2013.07.007
27. Szychlinska MA, Castrogiovanni P, Trovato FM, Nsir H, Zarrouk M, Lo Furno D et al (2019) Physical activity and Mediterranean diet based on olive tree phenolic compounds from two different geographical areas have protective effects on early osteoarthritis,

muscle atrophy and hepatic steatosis. Eur J Nutr 58(2):565–581. https://doi.org/10.1007/s00394-018-1632-2
28. NúñezCarro C, Blanco-Blanco M, Paniagua-Barro S, Gómez H, Goyanes N, Gaspar Gaspar MG et al (2024) AB0335 Diet enrichment with extra virgin olive oil influences postural symmetry and epigenetic regulation in an osteoarthritis murine model. Ann Rheum Dis 83:1411–1412. https://doi.org/10.1136/annrheumdis-2024-eular.5279
29. Roshani M, Delfan B, Yarahmadi S, Saki M, Birjandi M (2025) Impact of olive leaf extract on pain management and functional improvement in elderly patients with knee osteoarthritis: a randomized controlled trial. EXPLORE 21(2):103136. https://doi.org/10.1016/j.explore.2025.103136
30. Sarıtaş TB, Ertürk C, Büyükdoğan H, Yıldırım B, Gündüz N, Selek Ş (2024) Effects of N-acetylcysteine on sciatic nerve healing: a histopathological, functional, and biochemical study of the rat sciatic nerve. Jt Dis Relat Surg 35:618–627. https://doi.org/10.52312/jdrs.2024.1784
31. Percie du Sert N, Hurst V, Ahluwalia A, Alam S, Avey MT, Baker M, et al (2020) The ARRIVE guidelines 2.0: Updated guidelines for reporting animal research. PLoS Biol. 18(7):e3000410. https://doi.org/10.1371/journal.pbio.3000410
32. Kilkenny C, Browne WJ, Cuthill IC, Emerson M, Altman DG (2010) Improving bioscience research reporting: the ARRIVE guidelines for reporting animal research. PLoS Biol 8(6):e1000412. https://doi.org/10.1371/journal.pbio.1000412
33. Fernihough J, Gentry C, Malcangio M, Fox A, Rediske J, Pellas T et al (2004) Pain related behaviour in two models of osteoarthritis in the rat knee. Pain 112:83–93. https://doi.org/10.1016/j.pain.2004.08.004
34. Takahashi I, Matsuzaki T, Hoso M (2017) Long-term histopathological developments in knee-joint components in a rat model of osteoarthritis induced by monosodium iodoacetate. J Phys Ther Sci 29:590–597. https://doi.org/10.1589/jpts.29.590
35. Yildirim B, Erturk C, Buyukdogan H, Saritas TB, Yildirim Erdogan N, Ertem F (2025) Effect of N-acetylcysteine on fracture healing in rat femoral diaphysis: a histopathological, radiological, and biomechanical analysis. Jt Dis Relat Surg 36:1–10. https://doi.org/10.52312/jdrs.2025.1975
36. Janusz MJ, Hookfin EB, Heitmeyer SA, Woessner JF, Freemont AJ, Hoyland JA et al (2001) Moderation of iodoacetate-induced experimental osteoarthritis in rats by matrix metalloproteinase inhibitors. Osteoarthritis Cartilage 9:751–760. https://doi.org/10.1053/joca.2001.0472
37. Guzman RE, Evans MG, Bove S, Morenko B, Kilgore K (2003) Mono-iodoacetate-induced histologic changes in subchondral bone and articular cartilage of rat femorotibial joints: an animal model of osteoarthritis. Toxicol Pathol 31:619–624. https://doi.org/10.1080/01926230390241800
38. Takahashi I, Matsuzaki T, Kuroki H, Hoso M (2019) Joint unloading inhibits articular cartilage degeneration in knee joints of a monosodium iodoacetate-induced rat model of osteoarthritis. Osteoarthritis Cartilage 27:1084–1093. https://doi.org/10.1016/j.joca.2019.03.001
39. Zhang Z, Leong DJ, Xu L, He Z, Wang A, Navati M et al (2016) Curcumin slows osteoarthritis progression and relieves osteoarthritis-associated pain symptoms in a post-traumatic osteoarthritis mouse model. Arthritis Res Ther 3(18):128. https://doi.org/10.1186/s13075-016-1025-y
40. Musumeci G, Loreto C, Carnazza ML, Martinez G (2011) Characterization of apoptosis in articular cartilage derived from the knee joints of patients with osteoarthritis. Knee Surg Sports Traumatol Arthrosc 19:307–313. https://doi.org/10.1007/s00167-010-1215-0
41. Yigit F, Gurel-Gurevin E, Isbilen-Basok B, Esener OB, Bilal T, Keser O et al (2016) Protective effect of *Spirulina platensis* against cell damage and apoptosis in hepatic tissue caused by high fat diet. Biotech Histochem 91:182–194. https://doi.org/10.3109/10520295.2015.1114142
42. Erel O (2004) A novel automated method to measure total antioxidant response against potent free radical reactions. Clin Biochem 37:112–119. https://doi.org/10.1016/j.clinbiochem.2003.10.014
43. Erel O (2005) A new automated colorimetric method for measuring total oxidant status. Clin Biochem 38:1103–1111. https://doi.org/10.1016/j.clinbiochem.2005.08.008
44. Kurban S, Mehmetoglu I (2010) Effects of acetylsalicylic acid on serum paraoxonase activity, Ox-LDL, coenzyme Q10 and other oxidative stress markers in healthy volunteers. Clin Biochem 43:287–290. https://doi.org/10.1016/j.clinbiochem.2009.10.054
45. Morais SV, Czeczko NG, Malafaia O, Filho RJM, Garcia JB, Miguel MT et al (2016) Osteoarthritis model induced by intra-articular monosodium iodoacetate in rats knee. Acta Cir Bras 31:765–773. https://doi.org/10.1590/S0102-865020160110000010
46. Jiang L, Li L, Geng C, Gong D, Jiang L, Ishikawa N et al (2013) Monosodium iodoacetate induces apoptosis via the mitochondrial pathway involving ROS production and caspase activation in rat chondrocytes in vitro. J Orthop Res 31:364–369. https://doi.org/10.1002/jor.22250
47. Rosillo MÁ, Alcaraz MJ, Sánchez-Hidalgo M, Fernández-Bolaños JG, Alarcón-de-la-Lastra C, Ferrándiz ML (2014) Anti-inflammatory and joint protective effects of extra-virgin olive-oil polyphenol extract in experimental arthritis. J Nutr Biochem 25(12):1275–1281. https://doi.org/10.1016/j.jnutbio.2014.07.006
48. Rosillo MÁ, Villegas I, Vázquez-Román V, Fernández-Santos JM, Ortega-Vidal J, Salido S et al (2024) Dietary oleacein, a secoiridoid from extra virgin olive oil, prevents collagen-induced arthritis in mice. Food Funct 15(2):838–852. https://doi.org/10.1039/d3fo04240e
49. Recinella L, Micheli L, Chiavaroli A, Libero ML, Orlando G, Menghini L et al (2022) Anti-inflammatory effects induced by a polyphenolic granular complex from olive (*Olea europaea*, mainly *Cultivar coratina*): results from in vivo and ex vivo studies in a model of inflammation and MIA-induced osteoarthritis. Nutrients 14(7):1487. https://doi.org/10.3390/nu14071487
50. Williams RO (2004) Collagen-induced arthritis as a model for rheumatoid arthritis. Methods Mol Med 98:207–216. https://doi.org/10.1385/1-59259-771-8:207
51. Büyükdoğan H, Ertürk C, Eren E, Öztürk Ç, Yıldırım B, Sarıtaş TB, Demirkol M (2025) The impact of N-acetylcysteine on early periods of tendon healing: histopathologic, immunohistochemical, and biomechanical analysis in a rat model. Connect Tissue Res 22:1–14. https://doi.org/10.1080/03008207.2025.2479501
52. Chubinskaya S, Cotter EJ, Frank RM, Hakimiyan AA, Yanke AB, Cole BJ (2021) Biologic characteristics of shoulder articular cartilage in comparison to knee and ankle articular cartilage from individual donors. Cartilage 12:456–467. https://doi.org/10.1177/1947603519847740
53. Fogli S, Arena C, Carpi S, Polini B, Bertini S, Digiacomo M et al (2016) Cytotoxic activity of oleocanthal isolated from virgin olive oil on human melanoma cells. Nutr Cancer 68:873–877. https://doi.org/10.1080/01635581.2016.1180407
54. Casas R, Estruch R, Sacanella E (2018) The protective effects of extra virgin olive oil on immune-mediated inflammatory responses. Endocr Metab Immune Disord Drug Targets 18:23–35. https://doi.org/10.2174/1871530317666171114115632

55. Son DH, Ha HS, Park HM, Kim HY, Lee YJ (2022) New markers in metabolic syndrome. Adv Clin Chem 110:37–71. https://doi.org/10.1016/bs.acc.2022.06.002
56. Romeu M, Rubió L, Sánchez-Martos V, Castañer O, de la Torre R, Valls RM et al (2016) Virgin Olive Oil Enriched with Its Own Phenols or Complemented with Thyme Phenols Improves DNA Protection against Oxidation and Antioxidant Enzyme Activity in Hyperlipidemic Subjects. J Agric Food Chem 9(64):1879–1888. https://doi.org/10.1021/acs.jafc.5b04915

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Springer Nature or its licensor (e.g. a society or other partner) holds exclusive rights to this article under a publishing agreement with the author(s) or other rightsholder(s); author self-archiving of the accepted manuscript version of this article is solely governed by the terms of such publishing agreement and applicable law.

Authors and Affiliations

Cemil Erturk[1] · Sabri Kerem Diril[1] · Gülay Yuzbasioglu Ozturk[2] · Ahmet Gulcubuk[2] · Duygu Sultan Oran[3] · Ozge Erdogan Bamac[2] · Nilgun Isiksacan[4]

✉ Cemil Erturk
erturkc@yahoo.com

Sabri Kerem Diril
sabrikeremdiril@gmail.com

Gülay Yuzbasioglu Ozturk
gulayoz@iuc.edu.tr

Ahmet Gulcubuk
gulcu@iuc.edu.tr

Duygu Sultan Oran
duygusultan.oran@deu.edu.tr

Ozge Erdogan Bamac
oerdogan@iuc.edu.tr

Nilgun Isiksacan
nisiksacan@gmail.com

1 Department of Orthopedics and Traumatology, University of Health Sciences, Kanuni Sultan Süleyman Training and Research Hospital, Istanbul, Türkiye

2 Department of Pathology, Faculty of Veterinary Medicine, Istanbul University-Cerrahpasa, Istanbul, Türkiye

3 Department of Physiology, Faculty of Veterinary Medicine, Dokuz Eylül University, Izmir, Türkiye

4 Department of Clinical Biochemistry, University of Health Sciences, Bakırköy Sadi Konuk Training and Research Hospital, Istanbul, Türkiye