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Research Article

Therapeutic evaluation of galangin on cartilage protection and analgesic activity in a rat model of osteoarthritis

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ABSTRACT

Background: Osteoarthritis (OA) is a form of arthritis due to degradation of articular cartilage. OA is associated with stiffness, joint pain, and dysfunction, affecting adults worldwide. Galangin is a bioactive flavonoid that exerts several therapeutic and biological activities. Anti-hyperglycemic, anti-inflammatory, anti-cancer, and anti-apoptotic activities of galangin have been reported in several studies. In the present study, rats were divided into normal control, OA (control), galangin 10 mg/kg (low-dose), galangin 100 mg/kg (high-dose), and celecoxib 30 mg/kg (positive control) groups. All doses were administered orally for 14 consecutive days. The urinary type II collagen (μCTX-II) level as well as reactive oxygen species, tumor necrosis factor-alpha, interleukin-1 beta, interleukin-6, superoxide dismutase, catalase, lipid peroxidation, reduced glutathione, and glutathione peroxidase levels were measured. In addition, the CTX-II mRNA and protein expression levels were measured.

Results: Galangin supplementation significantly reduced the μCTX-II level compared with controls. Galangin treatment significantly reduced reactive oxygen species, lipid peroxidation, interleukin-1 beta, interleukin-6, and tumor necrosis factor-alpha levels, but increased catalase, superoxide dismutase, glutathione peroxidase, and reduced glutathione levels. Galangin treatment significantly reduced the CTX-II mRNA and protein expression levels. The low CTX-II level in tissue indicated the inhibition of cartilage degradation.

Conclusions: In summary, supplementation with galangin was effective against OA. The identification of potential therapeutic agents that inhibit inflammation may be useful for the management and prevention of OA.

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1. Introduction

Osteoarthritis (OA) is a form of arthritis due to degradation of articular cartilage [1]. OA is associated with stiffness, joint pain, and dysfunction, affecting adults worldwide [2]. Allen et al. [3] reported that joint injury, genetic factors, and development of abnormal limb are the main causes of OA. Symptoms usually develop gradually and affect the activities of daily living [4]. Researchers have reported that mechanical stress and inflammation (low-grade) induce OA [5]. McAlindon et al. [6] reported that regular exercise and pain medications are helpful for the treatment of OA. Although several advances have been made in drug discovery for the treatment of OA, successful therapies and drugs are not yet available [7]. In the present study, whether symptomatic relief could inhibit the primary etiology that causes the severe articular structure damage in OA was investigated.

Plants, food, and beverages act as potential biological and therapeutic agents in traditional and modern clinical treatments [8]. Natural flavonoids are widely present in several plants and known to exert various therapeutic activities such as anti-cancer, anti-diabetic, anti-hypertensive, and anti-hepatotoxic effects [9,10,11,12,13]. Galangin is a bioactive flavonoid possessing several therapeutic and biological properties [14]. Several researchers

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have reported anti-hyperglycemic, anti-inflammatory, anti-cancer, and anti-apoptotic activities of galangin [15,16,17]. Fang et al. [18] have reported the chemopreventive effect of galangin against hepatocellular carcinoma. Huang et al. [19] have reported the anticancer activity of galangin through p53-dependent pathway in ovarian cancer. Xuan et al. [20] have reported the protective effect of galangin against acute colitis through the modulating gut microbiota and activating autophagy. Aladaileh et al. [14] have reported the therapeutic effect of galangin against oxidative damage and apoptosis in hepatotoxicity induced rats. Researchers have reported the effect of galangin on the mRNA expression and activities of seven CYP450, and DPP-4 inhibitory effect of galangin, and improves glucose uptake in skeletal muscles [21,22]. Patil et al. [23] have reported the effect of galangin loaded galactosylated pluronic F68 polymeric micelles for liver targeting. Yang et al. [24] have reported the inhibitory effect of galangin against MMP-9 expression in SK-N-SH cells. Sulaiman [25] have reported the anti-proliferative effect of galangin in HCT-116 cells. Kale and Namdeo [26] reported the anti-arthritic activity of galangin in arthritis-induced rats. Fu et al. [27] reported the protective effects of galangin against human rheumatoid arthritis *via* downregulation of the NF-κB/NLRP3 pathway. Thus, in the present study, the therapeutic effects of galangin against OA were analyzed in Sprague-Dawley rats.

2. Materials and methods

2.1. Rats

Sprague-Dawley rats (190–210 g) were obtained from the animal house of Shanghai Jiao Tong University Affiliated Sixth People's Hospital (No. 600, YiShan Road, Shanghai 200233, People's Republic of China). All rats were kept in polycarbonate cages under 12-h light/12-h dark and standard atmospheric conditions. All rats had free access to food and water. Each experiment was performed following the guidelines for the care and use of laboratory animals and institutional guidelines.

2.2. Induction of OA

Monoiodoacetate (MIA) was used for the induction of OA. Briefly, the rats were anesthetized with isoflurane and 3 mg/kg of MIA in 50 μL normal saline was injected into the intra-articular pocket of the left femorotibial joint using a 26 G needle. All rats were carefully monitored daily for abnormal swelling and OA was established 7 d after MIA injection [7].

2.3. Experimental groups

The 30 male rats were randomly divided into five groups: normal control (NC), OA (control), galangin 10 mg/kg (low-dose), galangin 100 mg/kg (high-dose), and celecoxib 30 mg/kg (positive control). The doses were administered orally for 14 consecutive days. Each group contained six rats.

2.4. Enzyme-linked immunosorbent assay (ELISA)

The urinary type II collagen (μCTX-II) levels were measured using an enzyme-linked immunosorbent assay (ELISA) kit according to the manufacturer's protocol. Briefly, the rat urine was collected, kept on ice, and diluted at a 1:3 ratio using sample diluent. Then, 100 μL of standards and samples were added to CTX-II antibody pre-coated 96-well plates and incubated for 120 min at room temperature. Next, 100 μL of detection reagent was added to all wells and incubated for 60 min. Then, the solution was discarded, and samples were incubated with blocking solution for 60 min. Next, wells were incubated with substrate for 30 min followed by addition of 50 μL stop solution; absorbance was measured at 450 nm [7].

2.5. Biomarkers

At the end of the treatment, femorotibial joints were carefully dissected, homogenized, centrifuged, and supernatant collected. Reactive oxygen species (ROS), tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and IL-6 levels were measured in the supernatant [28]. In addition, superoxide dismutase (SOD), catalase, lipid peroxidation, reduced glutathione (GSH), and glutathione peroxidase (Gpx) levels were measured in the supernatant [28].

2.6. RT-PCR

Total RNA was extracted from femorotibial joint tissues and converted into cDNA using oligo(dT) primers. The qPCR was used to measure mRNA expression with specific primers for CTX-II (forward: 5-CGGGCRATGGCGCARAC-3; reverse: 5-TGCRCCGGTS GTATTGCC-3). The $2^{-\triangle\triangle}$CT method was used to quantitate the relative expression of CTX-II [29].

2.7. Western blot analysis

The proteins in the femorotibial joint tissue homogenate were separated using SDS-PAGE and then transferred to PVDF membranes. Membranes were treated with CTX-II primary antibodies (ab34712, Abcam, Cambridge, MA, USA) overnight. Then, membranes were washed and treated with horseradish peroxidase (HRP)-IgG (ab97023, Abcam) for 60 min. Finally, the CTX-II protein level was measured using a standard method [30].

2.8. Immunohistochemistry

At the end of the treatment, femorotibial joints were carefully dissected and sliced into thin sections. Then, tissue sections were incubated with CTX-II primary antibodies (ab34712, Abcam) overnight. Next, sections were treated with horseradish peroxidase (HRP)-IgG (ab97023, Abcam) for 60 min. The sections were viewed under a fluorescence microscope [31].

2.9. Statistical analysis

The values are presented as the means ± standard error of the mean. The differences between the control and galangin-treated groups were evaluated using Student's *t*-test and analysis of variance. A *P*-value <0.05 was considered statistically significant.

3. Results

In the present study, the therapeutic effects of galangin on OA were analyzed in Sprague-Dawley rats. The progression of articular cartilage degradation directly correlated with μCTX-II level, a type II collagen. The μCTX-II level drastically increased 79% in OA rats due to degradation of articular cartilage. However, the μCTX-II level was significantly reduced by 5.7% and 35.9% after 14 consecutive days of treatment with 10 mg/kg and 100 mg/kg galangin, respectively (Table 1, $P < 0.05$). The μCTX-II was significantly reduced (39.1%) after 14 consecutive days of treatment with celecoxib, positive control drug (Table 1, $P < 0.05$). The low μCTX-II level indicated the inhibition of cartilage degradation and protective effect of galangin against OA.

Table 1
The urine CTX-II (uCTX-II) normalized to total protein at 14 d.

Group	uCTX-II (ng/l)	Total protein (g/l)	Ratio (CTX-II/protein)
Normal control	362 ± 23	3.41 ± 0.25	106.2
OA	648 ± 27#	6.75 ± 0.46#	96
Galangin (10 mg/kg)	611 ± 21	7.13 ± 0.51	85.7
Galangin (100 mg/kg)	415 ± 29*	7.25 ± 0.34*	57.2
Celecoxib (30 mg/kg)	394 ± 26*	4.41 ± 0.25*	89.3

#$P < 0.05$ *vs.* Normal control; *$P < 0.05$ *vs.* OA.

ROS from osteoblasts, synoviocytes and chondrocytes activates the cartilage degradation due to ruptured joint homeostasis which favors catabolic processes. The intracellular ROS level was expressed as relative fluorescence units (RFUs). Compared with the OA group, the galangin supplementation significantly reduced the ROS level by 9.9% and 40.7% at 10 mg/kg and 100 mg/kg galangin, respectively (Fig. 1, $P < 0.05$). Intracellular ROS level was significantly reduced (47.4%) after 14 consecutive days of treatment with celecoxib (Fig. 1, $P < 0.05$). Pro-inflammatory mediators such as cytokines and lipid mediators from osteoblasts, synoviocytes and chondrocytes activates the cartilage degradation due to ruptured joint homeostasis which favors catabolic processes. Inflammatory markers were significantly increased in OA rats compared with the normal controls. However, the galangin supplementation significantly reduced IL-1β, IL-6, and TNF-α levels after 14 consecutive days of treatment (Fig. 2, $P < 0.05$). In addition, IL-1β, IL-6, and TNF-α levels were reduced after 14 consecutive days of treatment with celecoxib (Fig. 2, $P < 0.05$).

The imbalance and disturbance of pro-oxidant/anti-oxidant leads to oxidative stress, which can be corrected through the addition of appropriate anti-oxidants. Compared with controls, the galangin supplementation increased the catalase, SOD, Gpx, and GSH levels after 14 consecutive days of treatment (Table 2, $P < 0.05$). The celecoxib supplementation also increased catalase, SOD, Gpx and GSH levels after 14 consecutive days of treatment ($P < 0.05$, Table 2). Excessive lipid peroxidation is thought to have an important role in the pathogensis of OA. Lipid peroxidation was significantly increased in the OA rats. However, the galangin supplementation significantly reduced lipid peroxidation to near normal range after 14 consecutive days of treatment (Table 2, $P < 0.05$).

The progression of articular cartilage degradation directly correlated with CTX-II level. The CTX-II mRNA and protein expression levels were measured. The CTX-II mRNA expression was significantly increased by 80% in the OA rats. However, 10 mg/kg and 100 mg/kg galangin supplementation significantly reduced OA in rats by 8.3% and 23.9%, respectively (Fig. 3A, $P < 0.05$). The celecoxib supplementation significantly reduced the CTX-II mRNA expression by 27.8% after 14 consecutive days of treatment (Fig. 3A, $P < 0.05$). CTX-II protein expression was increased by 70% in the OA rats. However, 10 mg/kg and 100 mg/kg galangin supplementation significantly reduced OA in rats by 5.3% and 17.1%, respectively (Fig. 3B-C, $P < 0.05$). The celecoxib supplementation also significantly reduced the CTX-II protein expression by 19.4% after 14 consecutive days of treatment (Fig. 3B-C, $P < 0.05$). Immunohistochemistry results showed the CTX-II protein expression was significantly increased by 65% in the OA rats. However, 10 mg/kg and 100 mg/kg galangin supplementation significantly reduced OA in rats by 7.3% and 18.2%, respectively (Fig. 4A-B, $P < 0.05$). The celecoxib supplementation also significantly reduced the CTX-II protein expression by 17.6% after 14 consecutive days of treatment (Fig. 4A-B, $P < 0.05$). The low CTX-II level in tissue indicates the inhibition of cartilage degradation and protective effect of galangin against OA.

4. Discussion

In the present study, the therapeutic effects of galangin on OA were analyzed in Sprague-Dawley rats. OA is a form of arthritis due to the degradation of articular cartilage [1]. Allen et al. [3] reported that joint injury, genetic factors, and development of abnormal limb are the main causes of OA. The symptoms usually develop gradually and affect the activities of daily living [4]. Researchers have reported that mechanical stress and inflammation (low-grade) induce OA [5]. McAlindon et al. [6] reported that regular exercise and pain medications are helpful for treatment of OA. Although several advances have been made in drug discovery for the treatment of OA, successful therapies and drugs are not yet available [7].

OA model induction was confirmed based on increased CTX-II level and hypersensitivity, as well as histopathology results (data not shown). The results confirmed the significant improvement in pain tolerance and protection of articular cartilage. In addition,

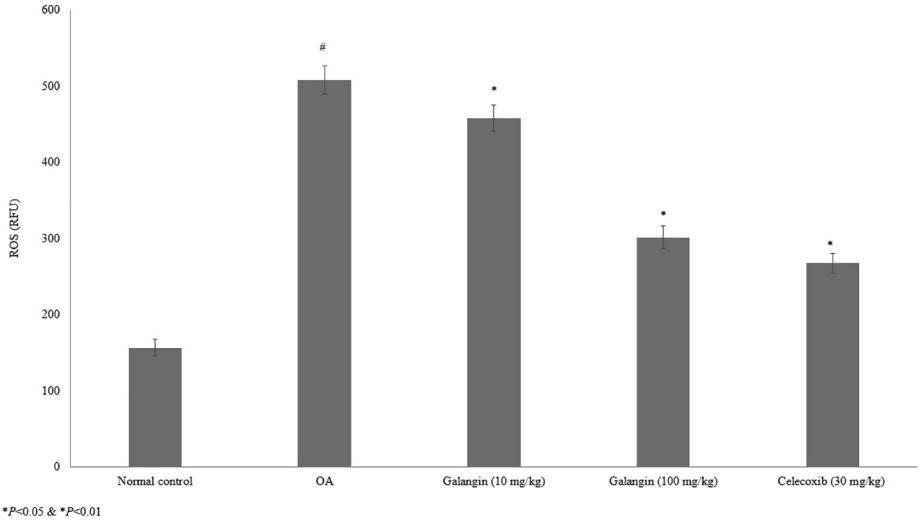

Fig. 1. Protective effects of galangin on intracellular reactive oxygen species (ROS) level in osteoarthritis (OA) rat model. #$P < 0.05$ *vs.* Normal control; *$P < 0.05$ *vs.* Control (OA); $N = 6$.

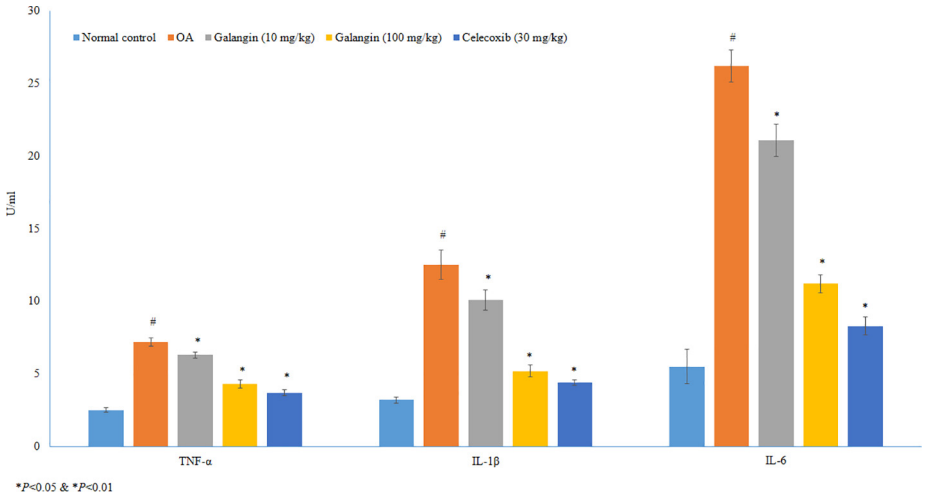

Fig. 2. Protective effects of galangin on tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and IL-6 levels in osteoarthritis (OA) rat model. $^{\#}P < 0.05$ *vs*. Normal control; $^{*}P < 0.05$ *vs*. Control (OA); $N = 6$.

Table 2
Protective effect of galangin on antioxidant markers in monoiodoacetate (MIA) induced OA model rats.

Markers	Normal control	OA	Galangin (10 mg/kg)	Galangin (100 mg/kg)	Celecoxib (30 mg/kg)
Catalase (U/ml)	10.9 ± 0.2	4.2 ± 0.2$^{\#}$	6.1 ± 0.2*	8.5 ± 0.3*	9.3 ± 0.3*
SOD (U/ml)	361.5 ± 13	138 ± 11$^{\#}$	193 ± 15*	272 ± 17*	296 ± 16*
GSH (nmol/ml)	0.55 ± 0.03	0.21 ± 0.01$^{\#}$	0.27 ± 0.04*	0.42 ± 0.05*	0.45 ± 0.05*
Gpx (U/ml)	0.43 ± 0.03	0.24 ± 0.01$^{\#}$	0.32 ± 0.01*	0.38 ± 0.01*	0.41 ± 0.01*
MDA (nmol/ml)	0.58 ± 0.02	1.18 ± 0.1$^{\#}$	0.91 ± 0.03*	0.73 ± 0.05*	0.68 ± 0.05*

$^{\#}P < 0.05$ *vs*. Normal control; $^{*}P < 0.05$ *vs*. OA.

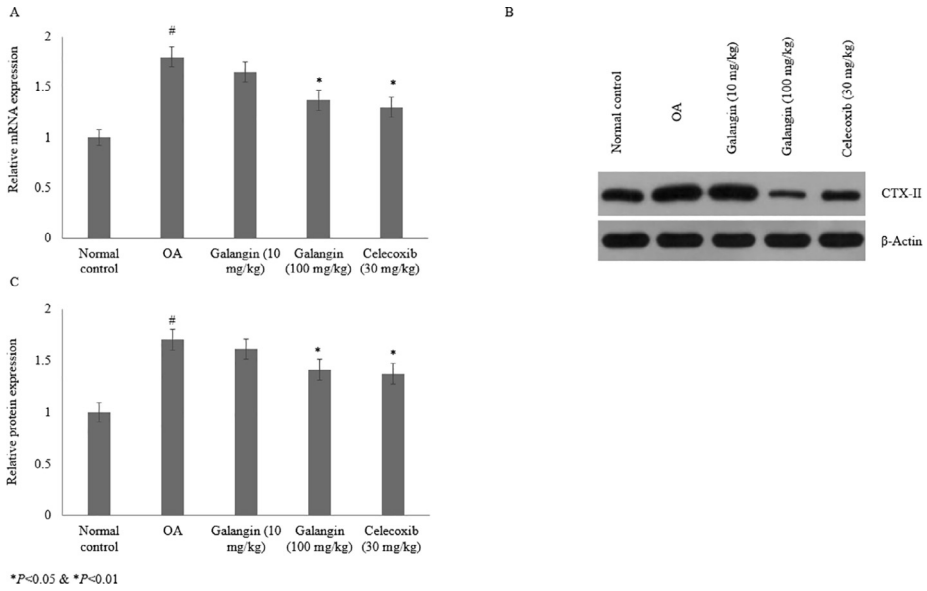

Fig. 3. Protective effects of galangin on CTX-II mRNA and protein expression levels in osteoarthritis (OA) rat model. A. CTX-II mRNA expression. B and C. CTX-II protein expression. $^{\#}P < 0.05$ *vs*. Normal control; $^{*}P < 0.05$ *vs*. Control (OA); $N = 6$.

pain sensitivity was significantly inhibited after galangin treatment. The μCTX-II level was significantly reduced after galangin treatment, indicating galangin exerted protective effects on articular cartilage confirming the merit of galangin as an analgesic and anti-inflammatory product. Castrogiovanni et al. [32] have reported the nutraceutical supplements in the Management and Prevention of OA through the reduction of CTX-II level. Dimitra et al. [33] have reported that the flavonoids reduced CTX-II level in inflammatory arthritis.

Researchers have reported that inflammatory mediators including NF-κB, IL-1β, and IL-6 play key roles in OA [34]. Infiltration macrophages, chronic inflammation, and activated T cells in joint tissues are the major pathological findings in arthritis [35]. Low levels of cellular antioxidants and increased free radical production

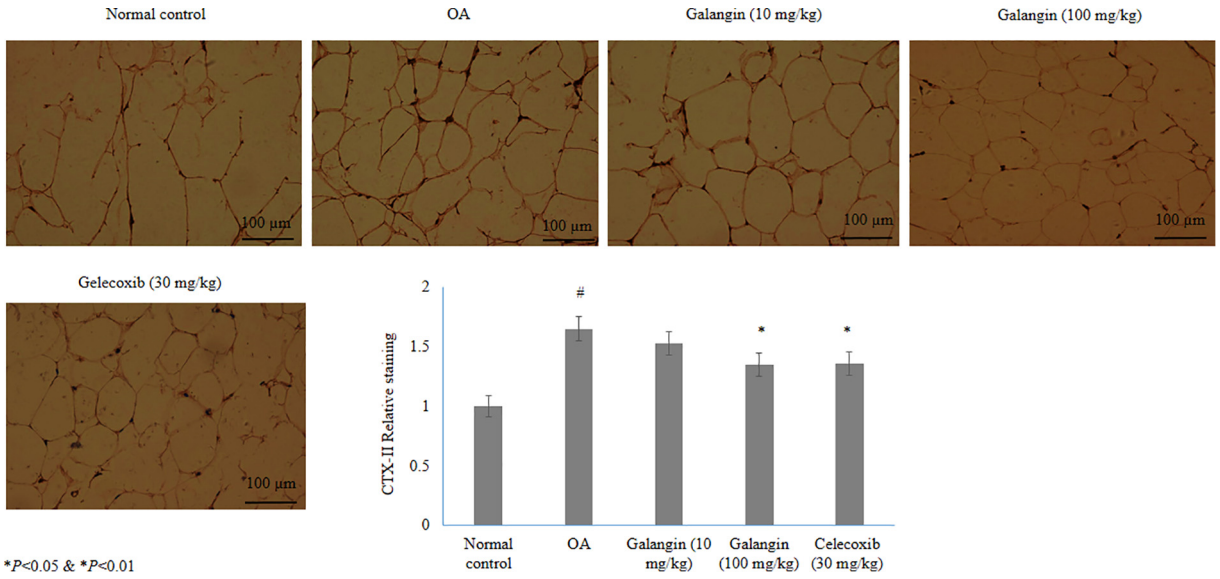

Fig. 4. Protective effects of galangin on CTX-II protein expression in osteoarthritis (OA) rat model based on immunohistochemistry. A. The immunohistochemical images of CTX-II. B. The relative CTX-II protein expression. $^{\#}P < 0.05$ *vs.* Normal control; $^{*}P < 0.05$ *vs.* Control (OA); $N = 6$.

in inflamed areas aggravate arthritis [36]. Oxidation of membrane fatty acids and other chain reactions can lead to cell membrane damage [37]. Gonzalez-Gay et al. [38] reported that IL-1β, IL-6, and TNF-α are arthritis markers. Goldring and Gravallese [39] reported that IL-1 and TNF-α are produced from synovium lining cells and chondrocytes of affected joints. Supplementation with galangin significantly inhibited these inflammatory markers. Leyva-López et al. [40] have reported that the flavonoids are vital modulators of pro-inflammatory cytokines, such as IL-1β, IL-6 and TNF-α. Kaempferol is one of the important flavonoid known to have anti-inflammatory effect via suppressing IL-1β, IL-6 and TNF-α levels in SW982 cells [41].

Researchers reported the MIA-induced rat model of OA is a frequently used standard model to mimic human OA [42]. The induction of OA involves the injection of MIA in the femorotibial joint area, which induces cartilage degradation and pain responses in the ipsilateral limb. Researchers have reported the MIA injection in the femorotibial joint area causes the disruption of chondrocyte glycolysis *via* inhibition of glyceraldehyde-3-phosphatase dehydrogenase, which leads to neovascularization, chondrocyte death, and inflammation [43]. Based on these pathological features, the MIA-induced rat model of OA is very useful for the investigation of anti-inflammatory and analgesic activities. The imbalance and disturbance of pro-oxidant/anti-oxidant leads to oxidative stress, which can be corrected through the addition of appropriate anti-oxidants. In this study, the galangin supplementation increased the catalase, SOD, Gpx, and GSH levels after 14 consecutive days of treatment. Researchers have reported that the kaempferol is known to have anti-oxidant effect via increasing catalase, SOD, Gpx, and GSH levels in SW982 cells [41]. Amal et al. [44] have reported that the galangin improves the anti-oxidant levels in diabetic rats.

Several researchers have reported the anti-hyperglycemic, anti-inflammatory, anti-cancer, and anti-apoptotic activities of galangin [15,16,17]. Kale et al. [26] reported the anti-arthritic activity of galangin in arthritis-induced rats. Fu et al. yy[27] reported the protective effects of galangin against human rheumatoid arthritis *via* downregulation of the NF-κB/NLRP3 pathway. CTX-II in tissue was significantly reduced after galangin treatment, indicating that galangin exerted protective effects on articular cartilage and confirming that galangin is an analgesic and anti-inflammatory product.

5. Conclusions

Galangin supplementation significantly reduced the μCTX-II level compared with controls. Galangin treatment significantly reduced ROS, lipid peroxidation, IL-1β, IL-6, and TNF-α levels, but increased catalase, SOD, Gpx, and GSH levels. Galangin treatment significantly reduced the CTX-II mRNA and protein expression levels. In summary, supplementation with galangin was effective against OA. The identification of potential therapeutic agents that inhibit inflammation may manage and prevent OA.

Ethical statement

The study protocol was approved by the Ethics Committee of Tongji University School of Medicine, with the approval number (2019090/20-21).

Conflict of interest

All authors declare that they have no conflicts of interest.

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