

Antioxidant and Anti-Inflammatory Effects of Turmeric Fermentation Liquid in Knee Osteoarthritis

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Background: *Curcuma longa* L. (turmeric) is a widely used medicinal plant with potent antioxidant and anti-inflammatory properties. It has been traditionally employed to manage inflammatory diseases such as osteoarthritis. This study explored the therapeutic potential of turmeric fermentation liquid (TF) in reducing oxidative stress, inflammation, and cartilage degradation in a monosodium iodoacetate-induced rat model of knee osteoarthritis (KOA).

Methods: Fresh turmeric was washed, sliced, and fermented using *Lactobacillus* strains under controlled conditions to enhance its bioavailability and produce TF. Male Wistar rats were divided into four groups: Control, MIA, MIA+glucosamine hydrochloride, and MIA+TF. TF was administered orally for four weeks, and its effects were assessed through ELISA, histological staining, and immunohistochemistry to measure oxidative stress markers, inflammatory cytokines, and cartilage integrity.

Results: TF enhanced antioxidant capacity and significantly reduced lipid peroxidation. It suppressed pro-inflammatory cytokines (TNF- α , IL-1 β) and increased anti-inflammatory IL-10 levels. Histological analysis revealed cartilage preservation, reduced proteoglycan loss, and decreased synovitis severity. Safranin O staining confirmed higher proteoglycan retention in TF-treated cartilage, while immunohistochemistry showed reduced IL-6 and IL-1 β expression. Furthermore, TF improved synovial fluid quality and decreased chondrocyte apoptosis, resulting in better joint mobility and reduced pain behavior in KOA rats.

Conclusion: Turmeric fermentation liquid exhibits potential as a natural therapy for KOA by addressing oxidative stress and inflammation. The fermentation process enhances bioavailability, providing a novel approach for preserving joint health and function. Further clinical studies are needed to confirm its efficacy and safety in humans.

Plain Language Summary:

Why was the study done? Knee osteoarthritis is a common joint disease that causes pain and stiffness. While turmeric is a traditional remedy for inflammation, its natural compounds are hard for the body to absorb. This study investigated if fermenting turmeric could create a liquid supplement that is more effective at relieving osteoarthritis symptoms.

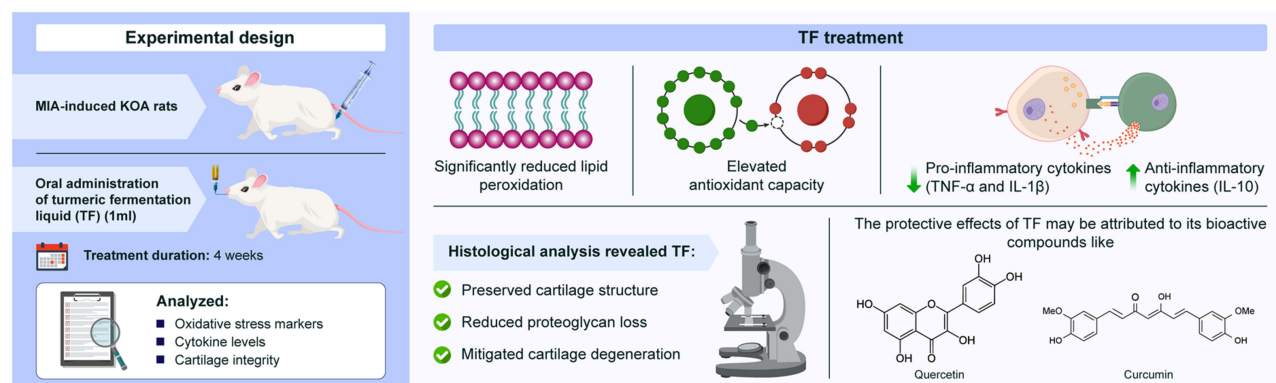
What did the researchers do and find? Researchers gave a specially prepared turmeric fermentation liquid to rats with induced knee osteoarthritis for four weeks. They found that the liquid helped reduce markers of inflammation and cellular damage in the rats' knee joints. The treatment also appeared to protect the joint cartilage from breaking down, which was associated with improved joint health.

What do these results mean? These findings suggest that fermenting turmeric may enhance its natural anti-inflammatory and antioxidant properties, offering a promising approach for managing osteoarthritis. The turmeric fermentation liquid shows potential as a natural supplement to support joint health and alleviate symptoms associated with knee osteoarthritis. However, this is an animal study, and more research, including human clinical trials, is necessary to confirm these benefits and ensure safety.

Keywords: osteoarthritis, turmeric fermentation liquid, knee osteoarthritis, antioxidant therapy, anti-inflammatory treatment, cytokine modulation, cartilage preservation, oxidative stress



Graphical Abstract



Introduction

Osteoarthritis¹ is characterized by the progressive destruction of articular cartilage and development of chronic pain, contributing to a significant socioeconomic burden.^{2,3} The disease is multifactorial, with mechanical joint failure and loss of joint function as the expected outcomes.⁴ OA is characterized by the progressive destruction of articular cartilage and the development of chronic pain, contributing to a significant socioeconomic burden. Inflammation plays a critical role in OA pathogenesis, with pro-inflammatory cytokines like IL-1 β and TNF- α initiating a cycle of catabolic and degradative events in cartilage, primarily mediated by metalloproteinases that degrade the extracellular matrix.^{4,5} Synovial macrophage activation further contributes to these inflammatory processes and promotes disease progression.⁶ Additionally, oxidative stress resulting from an imbalance between reactive oxygen species (ROS) and antioxidants accelerates chondrosenescence and apoptosis, leading to further cartilage damage.⁷ Currently, the management of OA is broadly categorized into conservative and surgical therapies. Conservative treatments include pharmacological interventions (such as nonsteroidal anti-inflammatory drugs (NSAIDs) and analgesics), physical therapy, and intra-articular injections (eg, corticosteroids or hyaluronic acid). Among these, herbal medicines like *Curcuma longa* (turmeric) are gaining attention as complementary and alternative therapies. Surgical options are typically reserved for severe cases and may include joint replacement surgery.⁸

Curcuma longa L. has been widely documented in traditional medicine systems, particularly Ayurveda and traditional Chinese medicine, for its therapeutic applications in inflammatory diseases, including OA.⁹ In Ayurveda, *Curcuma longa* L. is traditionally prescribed for “Sandhivata”, a condition characterized by joint pain, stiffness, and inflammation, which aligns with the clinical manifestations of OA.¹⁰ The Charaka Samhita and Sushruta Samhita, two authoritative Ayurvedic texts, document the use of *Curcuma longa* L. in treating joint disorders.¹¹ In traditional Chinese medicine, turmeric is classified as a herb that “invigorates blood circulation and dispels stasis”, traditionally used for joint pain and mobility disorders, as recorded in Bencao Gangmu (Compendium of Materia Medica).¹² Modern pharmacological studies have demonstrated that curcumin, the active component of turmeric, exhibits potent anti-inflammatory and antioxidant properties, helping to reduce pain and inflammation in patients with arthritis.⁹ Furthermore, systematic reviews and meta-analyses of randomized controlled trials have highlighted the potential benefits of turmeric extracts in alleviating osteoarthritis symptoms, particularly in pain reduction and functional improvement.¹³ In addition, Curcumin, the primary bioactive compound in the traditional Chinese medicine turmeric, is a natural substance with significant potential for clinical applications.¹⁴ It is widely utilized in traditional Chinese medicine to treat osteoarthritis, including knee osteoarthritis (KOA).^{9,15} Moreover, turmeric contains curcuminoids, including curcumin, demethoxycurcumin, and bisdemethoxycurcumin, which are known for their potent antioxidant and anti-inflammatory properties.^{16,17} These compounds have been shown to reduce oxidative

stress and inflammation, the two key factors in OA pathogenesis.¹⁸ Another class of compounds in turmeric, turmeronols, has demonstrated anti-inflammatory effects by inhibiting the NF- κ B signaling pathway, which is crucial for the production of inflammatory mediators.¹⁹ The ethanolic extract of *Curcuma longa* has also been found to activate the Nrf2/HO-1 signaling pathway, contributing to its anti-inflammatory effects by reducing the expression of pro-inflammatory mediators.²⁰ However, one of the primary challenges associated with curcumin is its low bioavailability due to poor water solubility, which has led to strategies aimed at enhancing its bioavailability, such as developing curcumin analogs. Despite these advances, studies on turmeric fermentation liquid (TF) and its effects on OA remain limited and warrant further investigation. We hypothesized that TF exerts protective effects against KOA by reducing oxidative stress and downregulating pro-inflammatory cytokines within the knee joint. This study aimed to evaluate the therapeutic potential of TF in a rat model of KOA by examining its effects on oxidative stress, inflammatory cytokine expression, and cartilage preservation. Our findings provide new insights into the therapeutic potential of TF as a novel treatment strategy for osteoarthritis, focusing mainly on its antioxidant and anti-inflammatory mechanisms.

Materials and Methods

Ethical Statement

This study was conducted in accordance with the ARRIVE guidelines 2.0 for reporting animal research. All animal procedures were approved by the Institutional Animal Care and Use Committee (IACUC) at the Kaohsiung Veterans General Hospital (Approval No. IACUC-2212-2312-22,149). This research also adheres to the principles of ethical animal research outlined in the Basel Declaration and follows the ethical guidelines established by the International Council for Laboratory Animal Science (ICLAS).

Materials

A voucher specimen (No. 118962) has been deposited in the Herbarium of Taiwan Forestry Research Institute, Taipei, Taiwan. Wild turmeric was purchased from the Health Plant Production and Marketing Group No. 7 in Taitung, Taiwan. Turmeric fermentation liquid (TF) was obtained from SCT BioMed Company Limited (Kaohsiung, Taiwan). The turmeric of the botanical name *Curcuma longa* L. has been verified with The World Flora Online (<http://www.worldfloraonline.org>, <http://www.worldfloraonline.org/taxon/wfo-0000365771>, accessed on: 14 Feb 2025). Monosodium iodoacetate (MIA; Cat. No. I2512) and Glutamic Acid hydrochloride (GH; Cat. No. HY-N0733) were purchased from Sigma-Aldrich (St. Louis, MO, USA). The Supplementary Materials and Methods 1 provide comprehensive details on the preparation of the turmeric substrate (with main compounds identified by HPLC), activation and cultivation of *Lactobacillus*, optimization of fermentation parameters (including turmeric concentration, temperature, and stirring speed), and the monitoring of fermentation quality and active ingredient content.

Preparation and Characterization of Turmeric Fermentation Liquid (TF)

Fresh *Curcuma longa* L., organically cultivated in Taitung, Taiwan, was used as the substrate. The turmeric was washed, sliced, and sterilized. The fermentation was initiated by inoculating the substrate with *Lactobacillus* strains previously isolated from fresh turmeric, including *Lactobacillus brevis* (BCRC No. 12187), at a concentration of 6.0 log CFU/mL. The fermentation was carried out for 48 hours at 37°C with a stirring speed of 100 rpm, conditions that were optimized for maximal *Lactobacillus* viability. The final turmeric fermentation liquid (TF) was collected for subsequent analysis and animal experiments.

The concentrations of key bioactive compounds in the TF were quantified. Total phenolic content was determined using a Folin-Ciocalteu phenol reagent, with gallic acid as the standard. Flavonoid content was analyzed using an Al (NO₃)₃ and CH₃COOK reagent-based colorimetric method, with quercetin as the standard. The curcumin content was specifically quantified using High-Performance Liquid Chromatography (HPLC) with a Diamonsil C18 column. The

mobile phase consisted of acetonitrile and 5% acetic acid (75:25, v/v) at a flow rate of 1.0 mL/min, and detection was performed at 420 nm. Curcumin ($\geq 99.5\%$ purity) was used as the standard for quantification.

Animal Care and Experimental Design

55 male Wistar rats, aged 5 weeks, were obtained from Lasco BioMed. The animals were housed in Kaohsiung Veterans General Hospital's (Kaohsiung, Taiwan) animal room. These animals were fed regular rat chow (Purina; St. Louis, MO, USA) and had free access to ordinary tap water throughout the experiments. The rats were randomly divided into four groups: Control, MIA, MIA+GH, and MIA+TF. Control group: intra-articular injection of 0.9% NaCl (20 μ L) and no treatment. MIA group: Intra-articular injection of 3 mg/mL monosodium iodoacetate¹⁶ (20 μ L) to induce knee osteoarthritis (KOA).²¹ MIA + GH group: Intra-articular injection of MIA followed by daily oral administration of 6 mg glucosamine hydrochloride²² (500 μ L/ddH₂O) for 4 weeks.²³ MIA+TF group: Intra-articular injection of MIA followed by daily oral administration of 150 μ g/mL turmeric fermentation liquid (TF) for 4 weeks.^{24,25} For intra-articular injections of MIA, animals were anesthetized with isoflurane (4–5% for induction, 1–3% for maintenance) delivered via inhalation to minimize pain and distress during the procedure.

The animals were housed in the animal room of Kaohsiung Veterans General Hospital (Kaohsiung, Taiwan) in individually ventilated cages (IVCs) with 3–4 rats per cage. The room was maintained at a controlled temperature ($22 \pm 2^\circ\text{C}$), humidity ($55 \pm 10\%$), and a 12-hour light/dark cycle. The animals were provided with standard rat chow (Purina; St. Louis, MO, USA) and had free access to autoclaved tap water. Environmental enrichment was provided in the form of nesting material. Animals were monitored daily for any signs of pain, distress, or adverse events, such as changes in posture, grooming, or activity levels. Humane endpoints were established, and any animal showing severe signs of suffering, such as significant weight loss ($>20\%$), inability to access food or water, or persistent signs of pain, would have been euthanized. No adverse events were observed during the study.

Sample Collection

At the end of the experimental period (4 weeks after treatment initiation), animals were euthanized following a two-step protocol in accordance with the American Veterinary Medical Association (AVMA) Guidelines for the Euthanasia of Animals (2020 Edition). First, rats were anesthetized with isoflurane (4–5% for induction) delivered via inhalation. Once the absence of pedal reflex confirmed deep anesthesia, animals were then euthanized by exposure to 100% carbon dioxide (CO₂) at a high flow rate to ensure rapid and humane death. Confirmation of death was verified by the absence of heartbeat, respiratory movements, and corneal reflex before tissue collection. Blood samples (2 mL) were collected from the heart via cardiac puncture immediately after euthanasia confirmation. The samples were centrifuged at 3000 rpm at 4°C to obtain serum. Knee joints were collected for histological and immunohistochemical analyses, and surrounding muscles and fascia were collected for Western blot analysis.

ELISA Assay

Serum samples were collected and analyzed for oxidative stress markers and inflammatory cytokines using commercial ELISA kits. The total antioxidant capacity was measured using an Antioxidant Assay Kit (No. 709001, Cayman Chemical, MI, USA) according to the manufacturer's instructions. Lipid peroxidation (LPO) levels were assessed using a Lipid Peroxide Assay Kit (E-BC-K176-M; Elabscience, Texas, USA) to quantify oxidative damage. Serum concentrations of IL-1 β , TNF- α , and IL-6 were determined using enzyme-linked immunosorbent assay (ELISA) kits (Abclonal, MA, USA). All assays were performed in duplicate and the data were analyzed according to the manufacturer's protocol.

Western Blotting Assay

Tissues from the surrounding muscles and fascia of the knee joint were collected and subjected to Western blotting to assess the expression of inflammatory cytokines. Proteins were extracted from the tissues using RIPA lysis buffer and quantified using a BCA protein assay. Equal amounts of protein were separated by SDS-PAGE and transferred to polyvinylidene difluoride (PVDF) membranes. The membranes were blocked with 5% non-fat milk and incubated

overnight at 4°C with the following primary antibodies: IL-6 (1:3000; GTX110527, GeneTex, Hsinchu City, Taiwan), IL-10 (1:5000; GTX632359, GeneTex), TNF- α (1:1000; GTX110520, GeneTex), IL-1 β (1:2000; GTX636887, GeneTex), and GAPDH (1:10000; No. 60004-1-Ig, Proteintech, IL, USA). After washing, membranes were incubated with HRP-conjugated secondary antibodies for 1 hour at room temperature. Protein bands were visualized using an enhanced chemiluminescence system and quantified using image analysis software.²⁶ GAPDH was used as a loading control.

Tissue Fixation and Decalcification

After the animals were sacrificed, knee joint tissues were harvested and immediately fixed in 10% neutral-buffered formalin for 48 hours at room temperature. This step ensured the preservation of the tissue structure and proteins for further analysis. The Fixed tissues were then transferred to ethylenediaminetetraacetic acid (EDTA) solution for 3–4 weeks to decalcify the bone tissue. A 10% solution of EDTA in distilled water was adjusted to a pH of 7.4 using NaOH to facilitate decalcification while preserving tissue integrity. The decalcification process was monitored weekly to ensure complete removal of calcium deposits. After decalcification, the tissues were washed in PBS to remove any residual EDTA and then dehydrated using a series of graded alcohols (70%, 80%, 95%, and 100%) to remove water from the tissues. Following dehydration, tissues were cleared in xylene and embedded in paraffin. Embedding tissues in paraffin allows the creation of thin sections suitable for histological analysis.

Sectioning and Staining

Paraffin-embedded tissues were sectioned to a thickness of 5 μ m using a microtome. The sections were carefully placed on glass slides and oven-dried to ensure adequate adherence. Hematoxylin and Eosin Staining, including hematoxylin, was used to stain the cell nuclei blue, providing a clear visualization of cellular structures. Eosin stained the cytoplasm, extracellular matrix, and other tissue components pink, highlighting tissue morphology, inflammation, and cellular degeneration in the knee joints. Safranin O specifically stains proteoglycans in the cartilage, turning them orange-red. This helps evaluate the extent of cartilage degradation in osteoarthritis models, as a loss of proteoglycan content correlates with disease progression.

Immunohistochemical Staining

Immunohistochemistry (IHC) was performed to assess the localization and expression levels of specific inflammatory cytokines in knee joint tissues. After deparaffinization and rehydration, the tissue sections were subjected to antigen retrieval to unmask epitopes that may have been altered during fixation. This was done by heating the slides in a sodium citrate buffer (pH 6.0) in a heat plate 85°C for 30 minutes. To prevent non-specific binding, the sections were incubated with 5% bovine serum albumin for 30 minutes at room temperature. The sections were incubated overnight at 4°C with specific primary antibodies targeting IL-6 (1:500; ARG56625, Arigo, Taipei, Taiwan) and IL-1 β (1:500; ARG66285, Arigo). After washing with PBS, the sections were incubated with a biotinylated secondary antibody (1:500; anti-rabbit or anti-mouse IgG) for 30–60 minutes at room temperature. The antigen-antibody complexes were visualized using 3,3'-diaminobenzidine (DAB) substrate, which produces a brown precipitate at the site of antigen localization, making it possible to identify areas of IL-6 and IL-1 β expression. The sections were counterstained with hematoxylin to visualize nuclei. Finally, the slides were dehydrated, cleared in xylene, and mounted on coverslips using synthetic resin. Images were captured using a light microscope to evaluate the expression of IL-6 and IL-1 β in the synovium and cartilage of knee joints. For histological analysis (H&E and Safranin O staining), the degree of cartilage degeneration and proteoglycan loss was evaluated using a semi-quantitative scoring system. The staining intensity and tissue morphology were compared between the groups. Immunohistochemical staining was quantified by calculating the percentage of positive cells or staining intensity using image analysis software (ImageJ). The expression levels of IL-6 and IL-1 β were compared between the MIA, MIA+GH, and MIA+TF groups to assess the anti-inflammatory effects of the turmeric fermentation liquid.

Statistical Analysis

Data from each group are presented as mean $\pm$ standard deviation, except for the immunohistochemical staining results, which are presented as mean $\pm$ standard error of the mean. Differences between groups were analyzed using one-way analysis of variance (ANOVA) followed by Tukey's post-hoc test. Differences were considered statistically significant at * $p < 0.05$, ** $p < 0.01$.

Results

Quantification of Bioactive Components in Turmeric Fermentation Liquid (TF)

The fermentation process was optimized to enhance the concentration of bioactive compounds in the turmeric fermentation liquid (TF). The final TF product was analyzed for its key chemical constituents. As shown in Figure 1, the total phenolic content was quantified to be 320 ± 40 $\mu\text{g/mL}$, and the total flavonoid content was 1600 ± 200 $\mu\text{g/mL}$. Furthermore, HPLC analysis confirmed the presence of curcumin at a concentration of 130 ± 15 $\mu\text{g/mL}$. These results demonstrate that the fermentation process yielded a liquid rich in key antioxidant and anti-inflammatory compounds derived from turmeric.

Effects of Turmeric Fermentation Liquid on Oxidative Stress and Inflammatory Markers

To evaluate the effects of turmeric fermentation liquid on oxidative stress and inflammation in an osteoarthritis rat model, we measured antioxidant levels, lipid peroxidation (LPO), and inflammatory cytokines (Figure 2A). As illustrated in Figure 2B, the antioxidant capacity was significantly enhanced in the MIA+TF group compared to that in the MIA group ($p < 0.05$), suggesting that turmeric fermentation liquid could effectively scavenge free radicals and mitigate oxidative stress in arthritic joints. Consistent with the increased antioxidant capacity, LPO levels were significantly reduced in the MIA+TF group compared with in those the MIA group ($p < 0.05$) (Figure 2C). This finding further supports the protective role of turmeric fermentation liquid against OA-induced lipid peroxidation. The expression levels of pro-inflammatory cytokines, including IL-1 β and TNF- α , were significantly elevated in the MIA group compared to the control group ($p < 0.05$) (Figure 2D and E). However, there was no significant difference in the expression of IL-6 between the groups (Figure 2F). Treatment with turmeric fermentation liquid significantly attenuated the expression of these cytokines, suggesting its potent anti-inflammatory effects in osteoarthritis.

Effects of Turmeric Fermentation Liquid on Inflammatory Cytokine Expression

To further investigate the anti-inflammatory effects of turmeric fermentation liquid, we examined the protein expression levels of various inflammatory cytokines in the knee joint tissues. As shown in Figure 3A, the expression of IL-6 was significantly higher in the MIA group than in the control group, indicating a robust inflammatory response in the osteoarthritic joints. Interestingly, treatment with turmeric fermentation liquid effectively attenuated the expression of IL-6 and significantly increased the expression of the anti-inflammatory cytokine IL-10 (Figure 3B). Additionally, turmeric

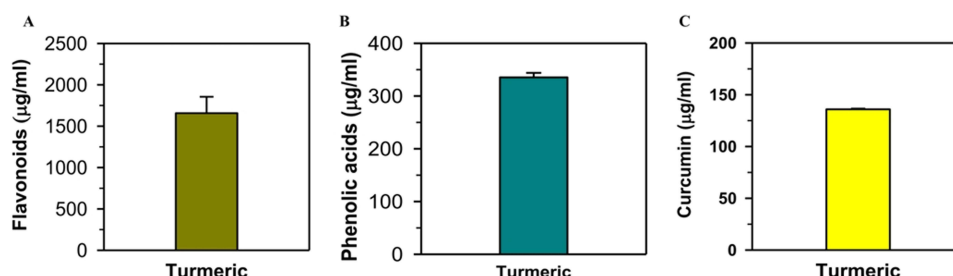


Figure 1 Quantification of active components in the turmeric matrix. (A). Flavonoid content ($\mu\text{g/mL}$) determined using quercetin as the standard. (B). Using gallic acid as the standard, total phenolic acid content ($\mu\text{g/mL}$) was determined. (C). Curcumin content ($\mu\text{g/mL}$) was analyzed using High-Performance Liquid Chromatography (HPLC) with $\geq 99.5\%$ curcumin as the standard.

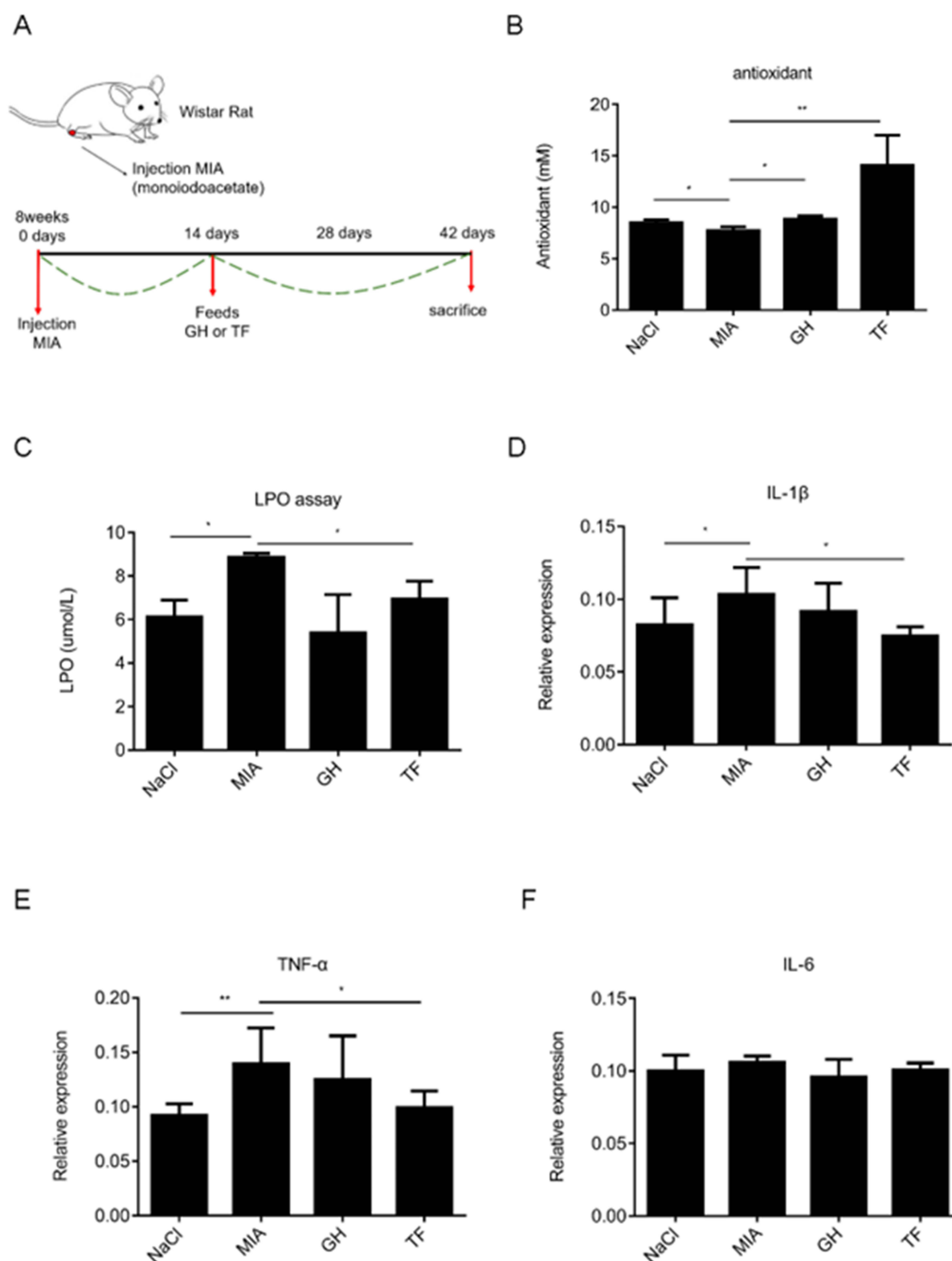


Figure 2 Effects of turmeric fermentation liquid on oxidative stress and inflammation in osteoarthritis rat model. **(A)** Experimental timeline. Rats were injected with monosodium iodoacetate¹⁶ to induce osteoarthritis. After 14 days, the animals were treated with either glucosamine²² or turmeric fermentation liquid (TF) for four weeks before sacrifice. **(B)** Antioxidant capacity of rat serum. **(C)** Lipid peroxidation (LPO) levels in rat serum. **(D, E, F)** protein expression levels of IL-6, TNF-α, and IL-1b in the knee joint, as determined by quantitative ELISA. Data are presented as the mean ± SD (n = 5/group). *p < 0.05, **p < 0.01 compared with the MIA group.

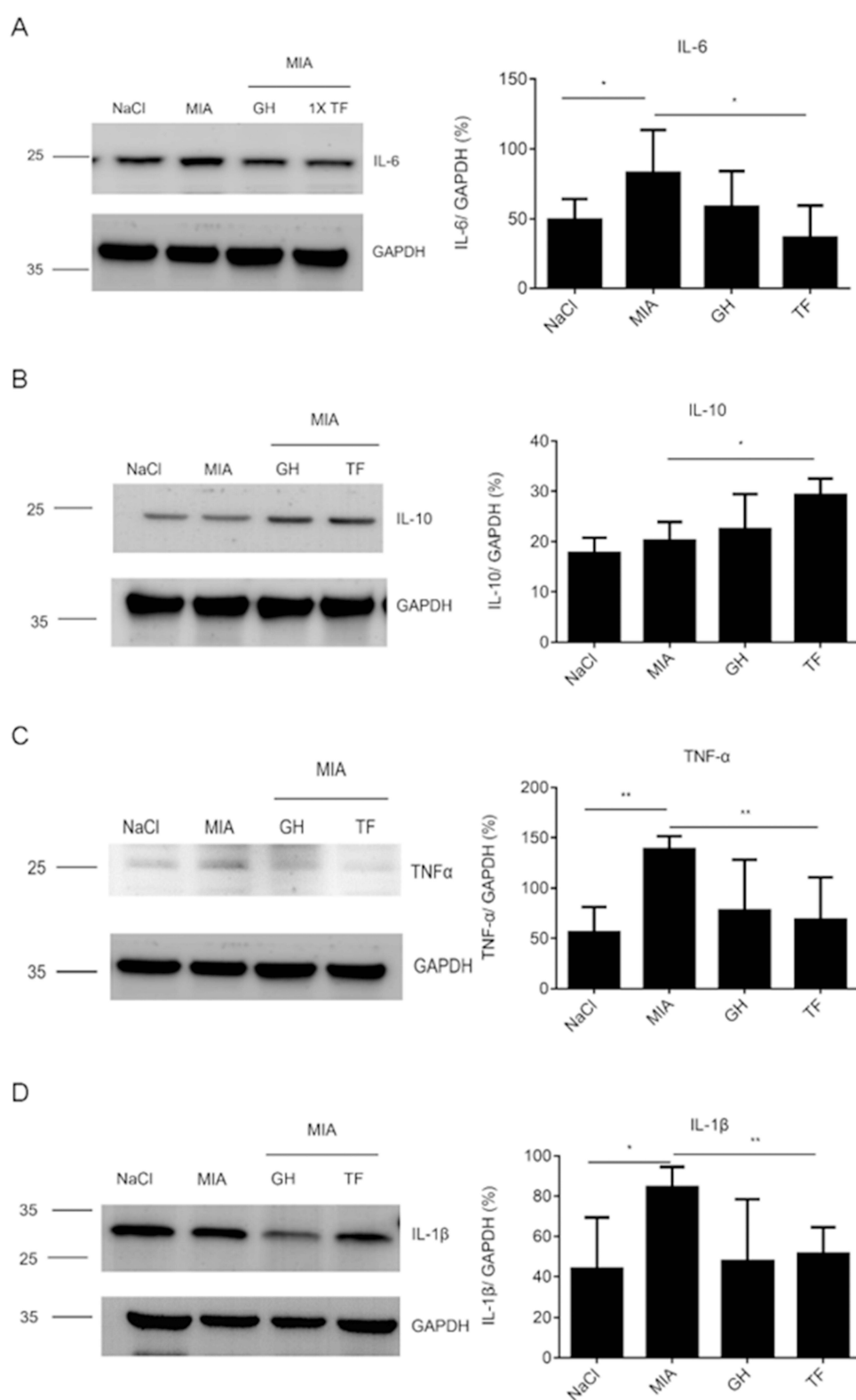


Figure 3 Effects of turmeric fermentation liquid on inflammatory cytokine expression in osteoarthritis rat model. Western blot analysis of IL-6 (**A**), IL-10 (**B**), TNF- α (**C**), and IL-1 β (**D**) protein expression in the surrounding muscles and fascia of knee joint tissues. GAPDH was used as a loading control. Data are presented as the mean $\pm$ SD ($n = 5/\text{group}$). * $p < 0.05$, ** $p < 0.01$ compared with the MIA group.

fermentation liquid treatment effectively attenuated the expression of TNF- α and IL-1 β (Figure 3C and D). These findings suggest that turmeric fermentation liquid exerts its anti-inflammatory effects by suppressing the production of pro-inflammatory cytokines, such as TNF- α and IL-1 β , and enhancing the expression of the anti-inflammatory cytokine IL-10.

Histological Analysis of Articular Cartilage

Histological analysis was performed to further evaluate the protective effects of turmeric fermentation liquid on the articular cartilage. H&E staining (Figure 4A) revealed that the MIA group exhibited severe cartilage degeneration, characterized by the loss of chondrocytes, reduced proteoglycan content, and increased cellularity in the synovium. In contrast, treatment with turmeric fermentation liquid significantly attenuated these histological changes, suggesting its protective effects on the cartilage. Safranin O staining (Figure 4B) confirmed the preservation of proteoglycans in the articular cartilage of the MIA+TF group, indicating that the turmeric fermentation liquid could effectively prevent cartilage degradation.

Immunohistochemical Analysis of Inflammatory Cytokine Localization

To further investigate the localization of inflammatory cytokines, immunohistochemical staining was performed to assess the expression of IL-6 and IL-1 β in knee joint tissues. As shown in Figure 5A and B, the expression of IL-6 was significantly increased in the synovium and cartilage of the MIA group compared to that in the control group, indicating a

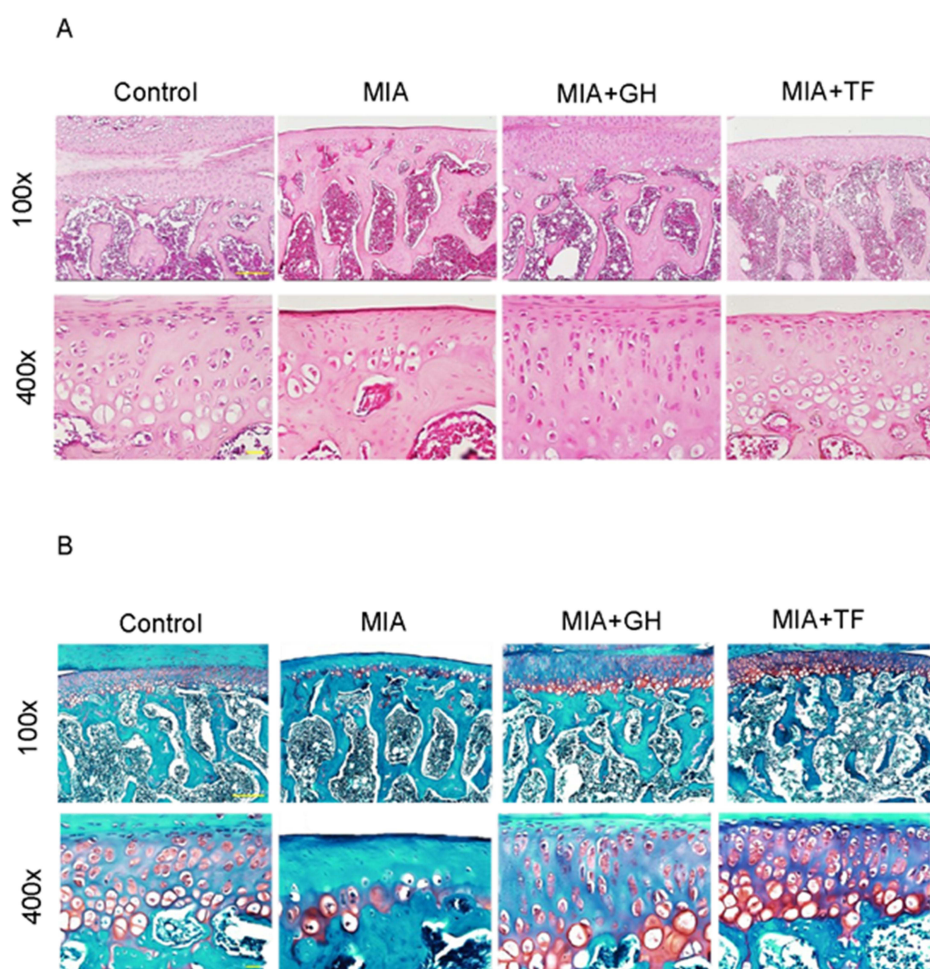


Figure 4 Histological analysis of knee joints. Representative H&E-stained (A) and Safranin O-stained (B) sections of knee joints from control, MIA, MIA+GH, and MIA+TF groups. Scale bar = 100x (100 μ m); 400x (20 μ m).

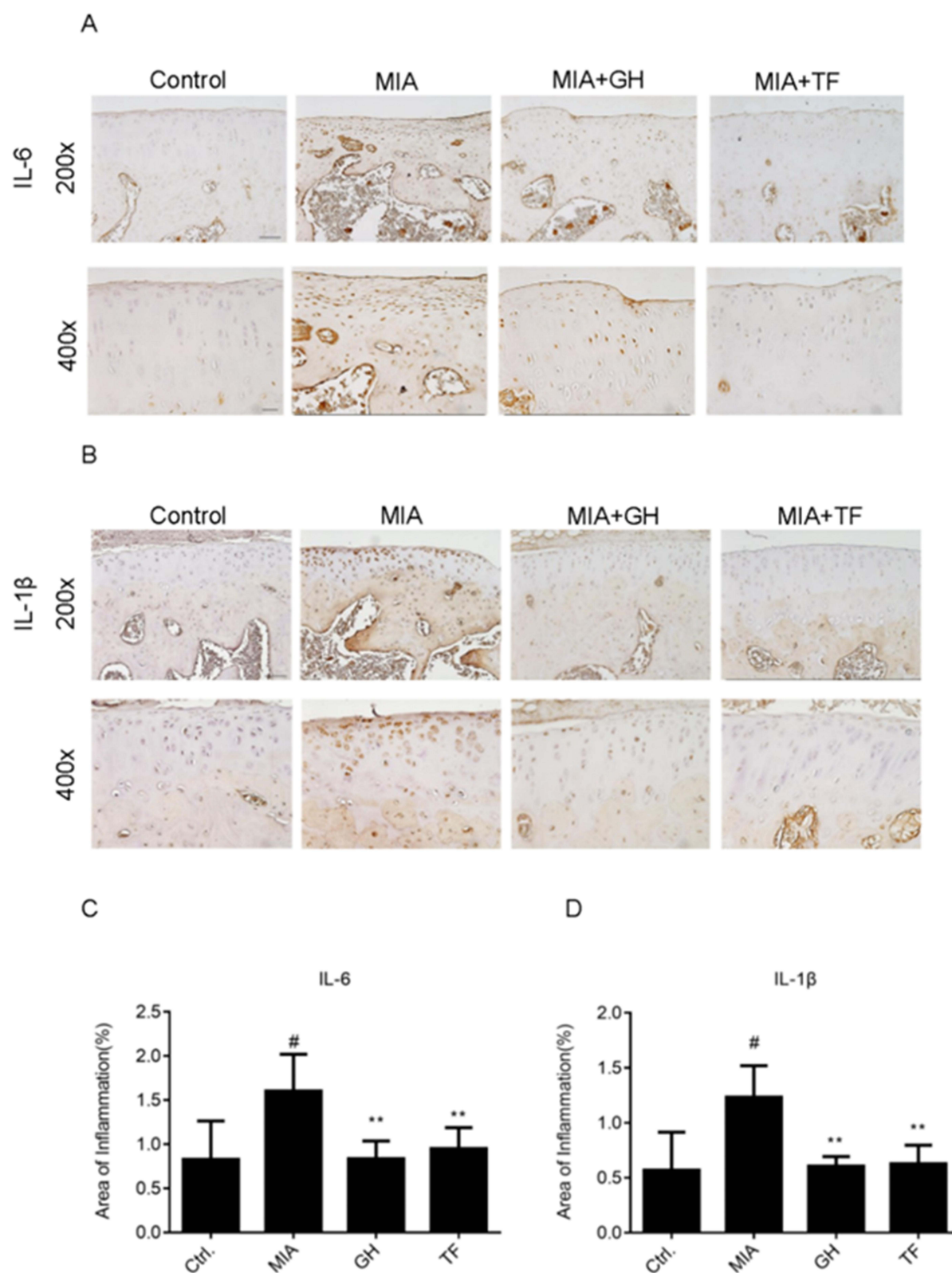


Figure 5 Immunohistochemical staining of IL-6 and IL-1 β in knee joints. Representative images of **(A)** IL-6 immunostaining in knee joints of the control, MIA, MIA+GH, and MIA+TF groups. **(B)** Quantitative analysis of IL-6 positive staining area. **(C)** IL-1 β immunostaining in knee joints of the control, MIA, MIA+GH, and MIA+TF groups. **(D)** Quantitative analysis of IL-1 β positive staining area. Scale bar = 200x (50 μ m); 400x (20 μ m). Data are presented as the mean $\pm$ SD (n = 5/group). #p < 0.05, compared with the control group; **p < 0.01, compared with the MIA group.

robust inflammatory response in the osteoarthritic joints. Treatment with turmeric fermentation liquid significantly attenuated the expression of IL-6, suggesting its anti-inflammatory effect. Similarly, IL-1 β expression increased dramatically in the MIA group (Figure 5C and D). Treatment with turmeric fermentation liquid effectively reduced the expression of IL-1 β . These findings further confirmed that turmeric fermentation liquid can effectively suppress the production of pro-inflammatory cytokines in osteoarthritis.

Discussion

Our study demonstrated that turmeric fermentation liquid (TF) has significant protective effects in a monosodium iodoacetate¹⁶-induced knee osteoarthritis (KOA) rat model. Specifically, TF treatment enhanced antioxidant capacity, evidenced by reduced lipid peroxidation (LPO) levels, and significantly reduced the expression of pro-inflammatory cytokines, such as TNF- α and IL-1 β , while upregulating the anti-inflammatory cytokine IL-10. Histological analysis revealed that TF effectively preserved the cartilage integrity, prevented proteoglycan loss, and mitigated cartilage degeneration. These results highlight the dual role of TF in reducing oxidative stress and inflammation, both of which are key contributors to KOA progression.

In OA, oxidative stress results from a redox imbalance, producing excessive ROS. This imbalance is worsened by the failure of endogenous antioxidant defense systems, such as superoxide dismutase, which play a critical role in regulating ROS levels within cartilage.²⁷ Overproduction of ROS results in mitochondrial dysfunction, chondrocyte apoptosis, and degradation of the extracellular matrix, which includes glycosaminoglycan and type II collagen.^{28,29} ROS are critical mediators of OA progression and contribute to chondrocyte senescence. Increased levels of senescence markers, such as γ -H2AX and p21, and decreased glycosaminoglycan production following oxidative stress exposure evidence this.³⁰ Inflammatory stresses, such as those induced by IL-1 β and TNF- α , further exacerbate ROS production, leading to increased expression of senescence-associated secretory phenotype factors and degradation of the cartilage matrix.³⁰ Our study indicated that the antioxidant properties of TF help mitigate ROS-mediated cartilage damage, as evidenced by decreased LPO levels, which is a known contributor to KOA progression. This finding is consistent with previous studies on curcumin, a major bioactive component of turmeric, which has been shown to activate the Nrf2/HO-1 signaling pathway, leading to enhanced cellular antioxidant defenses.²⁰ By reducing oxidative stress, TF may slow the degenerative processes in OA joints, offering a potential therapeutic avenue that addresses one of the root causes of cartilage degradation.

TNF- α plays a crucial role in the inflammatory cascade, promoting cartilage and bone resorption and producing other pro-inflammatory cytokines like IL-1 β .³¹ Anti-TNF- α treatments have been shown to significantly reduce the severity of arthritis and reverse structural damage in animal models, highlighting the potential of targeting TNF- α for OA management.³² The combination of TNF- α and IL-1 β contributes to matrix degradation in the articular cartilage, emphasizing the importance of therapies that can modulate these cytokines.³³ On the other hand, IL-6 is another critical cytokine involved in OA, with its expression being elevated in inflammatory conditions. TF treatment has been shown to reduce IL-6 levels, further supporting its broad anti-inflammatory effects.³⁴ The downregulation of IL-6 by TNF- α -blocking agents, such as infliximab, has been associated with reduced bone loss and improved bone mineral density, suggesting a beneficial impact on OA progression.³⁴ Similarly, our study observed a reduction in pro-inflammatory cytokines (TNF- α and IL-1 β) and an increase in IL-10 levels, indicating that TF has potent anti-inflammatory effects. Given that these cytokines are key drivers of the inflammatory cascade in OA, TF's ability to modulate their expression could disrupt the cycle of inflammation and tissue degradation that characterizes the disease.¹⁹ This dual antioxidant and anti-inflammatory action makes TF a promising candidate for OA therapy, potentially offering a more comprehensive approach than treatments targeting only one aspect of the disease. Histological analysis revealed that TF-treated cartilage exhibits reduced structural damage and a higher density of proteoglycans, essential for cartilage resilience and function.²² The preservation of proteoglycans, as observed through Safranin O staining, indicates that TF helps maintain the extracellular matrix of the cartilage. This preservation is essential for protecting the cartilage from oxidative stress, which can exacerbate cartilage degeneration.³⁵ Histological analysis of cartilage treated with TF showed less degeneration than untreated cartilage, suggesting that TF's antioxidant properties of TF play a role in reducing oxidative

damage.³⁵ Additionally, while TF shows promise in preserving cartilage, further research is needed to fully understand its long-term effects and potential therapeutic applications in human osteoarthritis.

Turmeric fermentation liquid (TF), which contains bioactive compounds such as flavonoids (eg, quercetin) and curcumin, likely exerts its anti-inflammatory and antioxidant effects through several key mechanisms. Quercetin inhibits NF- κ B activation in various cell types. For instance, in HepG2 cells, quercetin reduced NF- κ B DNA-binding activity induced by hydrogen peroxide, thereby preventing oxidative DNA damage.³⁶ Similarly, in glomerular cells, quercetin suppresses IL-1 β -induced NF- κ B activation, leading to decreased expression of monocyte chemoattractant protein-1 (MCP-1).³⁷ Quercetin mitigates oxidative stress by modulating ROS levels, which in turn reduces NF- κ B activation. This was observed in lung epithelial cells, where quercetin decreased ROS levels and suppressed nuclear translocation of NF- κ B, leading to reduced expression of TNF- α , IL-1, and IL-6.³⁸ Quercetin also affects the NLRP3 inflammasome pathway, which is involved in the inflammatory response. It inhibits the activation of this pathway, thereby reducing the production of pro-inflammatory cytokines, such as IL-1 β .^{39,40} Similarly, Curcumin has been well documented for its ability to suppress NF- κ B activation. In osteoarthritis models, curcumin reduced NF- κ B-driven gene expression, which is associated with inflammation and cartilage degradation.⁴¹ Both quercetin and curcumin exhibit complementary actions in modulating inflammatory pathways. While quercetin primarily targets the NF- κ B and ROS pathways, curcumin also enhances antioxidant defenses and inhibits additional pathways like the NLRP3 inflammasome, making them effective in various inflammatory conditions.⁴² Quercetin and curcumin effectively reduce inflammation through multiple mechanisms, but the complexity of inflammatory pathways suggests that a broader therapeutic approach, such as using TF, may be more effective in managing KOA.

Curcumin activates defense genes and increases the activity of antioxidant enzymes such as superoxide dismutase (SOD) and catalase.²¹ This is evident in studies where curcumin administration led to increased antioxidant defense mechanisms and reduced oxidative stress and inflammation in various models, including spinal cord ischemia-reperfusion injury and diabetic retinopathy.^{43,44} Curcumin effectively reduced oxidative damage by decreasing lipid peroxidation and oxidative DNA damage. In renal injury models, curcumin and its derivative tetrahydrocurcumin significantly inhibited the formation of lipid peroxidation products and oxidative DNA damage markers.⁴⁵ Curcumin induces the expression of heme oxygenase-1 (HO-1) and other Phase II detoxification enzymes, providing neuroprotection against oxidative stress. This upregulation enhances cellular resistance to oxidative damage, as has been demonstrated in neuronal studies.⁴⁶ Quercetin's antioxidant properties are attributed mainly to its ability to chelate metal ions and inhibit lipid peroxidation. This is reflected in studies where quercetin treatment reduced lipid peroxide (LPO) levels, thereby protecting cells from oxidative damage.³⁸ Quercetin also modulates inflammatory pathways by suppressing the production of ROS and inhibiting nuclear translocation of nuclear factor kappa B (NF- κ B). This results in the decreased expression of inflammatory cytokines, further reducing oxidative stress and inflammation.³⁸ Although curcumin and quercetin exhibit promising antioxidant properties, it is important to consider the bioavailability and pharmacokinetics of these compounds. For instance, curcumin is known for its poor bioavailability, which can limit its therapeutic efficacy. Strategies to enhance the absorption and stability of these compounds could improve their clinical utility. Additionally, while preclinical studies provide valuable insights, well-designed clinical trials are necessary to fully understand the effects and potential applications of curcumin and quercetin in human health.⁴⁵ The mechanisms underlying the protective effects of TF can be attributed to several factors. First, the fermentation process may enhance the bioavailability of curcuminoids and other bioactive compounds, allowing for more effective ROS scavenging and inhibition of the inflammatory pathways. Fermentation may also produce metabolites that enhance the anti-inflammatory and antioxidant properties of turmeric. Additionally, TF's ability to modulate cytokine expression (eg, increasing IL-10 while decreasing TNF- α and IL-1 β) suggests that it reduces inflammation and promotes a more balanced immune response, which could be crucial for the long-term management of KOA.

Although the findings of this study are promising, some limitations warrant consideration. First, we tested only a single dose of TF (150 μ g/mL). Although this dose was selected based on preliminary in vitro cytotoxicity and efficacy screening, a full dose-response study is needed to determine the optimal therapeutic window. Second, the 4-week treatment period is relatively short for a chronic disease like OA and may not be sufficient to evaluate long-term regenerative effects. Future studies with longer follow-up periods are warranted. Third, our study relied on biochemical

and histological markers and did not include functional or behavioral assessments, such as weight-bearing or gait analysis, which would provide a more comprehensive evaluation of pain and mobility. Finally, while we included glucosamine hydrochloride as a positive control, a comparison with clinically used anti-inflammatory drugs like NSAIDs would provide a better context for the therapeutic potential of TF. Future studies should address these limitations.

Conclusion

In this study, TF may mitigate osteoarthritis progression by suppressing inflammatory cytokine production and enhancing antioxidant defenses, primarily through the synergistic actions of quercetin and curcumin. These findings suggest that TF could serve as a promising therapeutic strategy for KOA, offering a natural alternative to conventional treatments by targeting both the oxidative and inflammatory pathways involved in disease progression. Further research is required to validate these results in clinical settings and explore TF's full potential in KOA management.

Abbreviations

KOA, Knee osteoarthritis; OA, Osteoarthritis; TF, Turmeric fermentation liquid; MIA, Monosodium iodoacetate; GH, Glucosamine hydrochloride; ROS, Reactive oxygen species; LPO, Lipid peroxidation; IL, Interleukin; IL-1 β , Interleukin-1 beta; IL-6, Interleukin-6; IL-10, Interleukin-10; TNF- α , Tumor necrosis factor-alpha; H&E, Hematoxylin and eosin; EDTA, Ethylenediaminetetraacetic acid; IHC, Immunohistochemistry; DAB, 3,3'-diaminobenzidine; NF- κ B, Nuclear factor kappa-light-chain-enhancer of activated B cells; NLRP3, NOD-, LRR- and pyrin domain-containing protein 3; Nrf2, Nuclear factor erythroid 2-related factor 2; HO-1, Heme oxygenase-1; SOD, Superoxide dismutase; CAT, Catalase; GAPDH, Glyceraldehyde-3-phosphate dehydrogenase.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The author(s) report no conflicts of interest in this work.

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