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Research Paper

Fermented *Clostridium butyricum* GKB7 Inhibits Osteoarthritis Induced by Anterior Cruciate Ligament Transection in a Preclinical Model

Wei-Cheng Chen[1,2], Li-Chai Chen[3], You-Shan Tsai[4], Yen-Po Chen[4], Yen-Lien Chen[4], Chin-Chu Chen[5], Yen-You Lin[6], Tzu-Ching Chang[7], Chen-Ming Su[8]✉, Chih-Hsin Tang[7,9,10]✉

1. Department of Medicine, MacKay Medical University, New Taipei, Taiwan.
2. Division of Sports Medicine & Surgery, Department of Orthopedic Surgery, MacKay Memorial Hospital, Taipei, Taiwan.
3. Department of Pharmacy, Tajen University, Pingtung, Taiwan.
4. Biotech Research Institute, Grape King Bio Ltd., Taoyuan City, Taiwan.
5. Institute of Food Science and Technology, National Taiwan University, Taipei City, Taiwan.
6. Translational Medicine Center, Shin Kong Wu Ho-Su Memorial Hospital, Taipei, Taiwan.
7. Department of Pharmacology, School of Medicine, China Medical University, Taichung, Taiwan.
8. Department of Sports Medicine, College of Health Care, China Medical University, Taichung, Taiwan.
9. Chinese Medicine Research Center, China Medical University, Taichung, Taiwan.
10. Department of Medical Laboratory Science and Biotechnology, College of Medical and Health Science, Asia University, Taichung, Taiwan.

✉ Corresponding authors: Chih-Hsin Tang, PhD; Email: chtang@mail.cmu.edu.tw. Chen-Ming Su, PhD; Email: cmsu@mail.cmu.edu.tw.

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Abstract

Aging-related osteoarthritis (OA) affects joints and causes functional impairment. Probiotics are recognized safe for consumption and numerous exhibit beneficial bioactivity for human health conditions. *Clostridium butyricum*, frequently found in the environment and reported to colonize the stomachs of adults and newborns, exhibits anti-inflammatory properties. This study investigated whether fermented *Clostridium butyricum* GKB7 is effective at preventing the advancement of OA. Fermented GKB7 reduces bone pain and the development of OA associated with anterior cruciate ligament transaction. Through the reduction of pro-inflammatory cytokines IL-1β and TNF-α, as well as the chondrolytic factors MMP-3, MMP-13, and ADAMTS5, fermented GKB7 inhibited the degradation of aggrecan and COL2A1. Bone loss and cartilage degradation were blocked as a result of this activity. According to our findings, fermented GKB7 enhances the prevention of OA development.

Keywords: osteoarthritis; fermented GKB7; probiotics

Introduction

Osteoarthritis (OA) is one of the most prevalent degenerative conditions, which have become some of the most frequent health problems due to medical advancements and increased life expectancy. According to the Global Burden of Disease study, OA affected over 528 million people worldwide, and over a ten-year period, its prevalence increased [1, 2]. Pathological characteristics of OA include inflammation of the synovial region, cartilage deterioration, and subchondral bone sclerosis. These characteristics cause joint discomfort and stiffness and are frequently irreversible at the time of diagnosis [3, 4]. There is currently no known cure for OA, and the only available treatments are to reduce discomfort or halt the disease's progression.

Joint discomfort, structural damage, and the release of synovial fluid—all of which are critical in fostering inflammation and tissue deterioration in OA—are closely associated with chronic inflammation of the synovial tissues [5-7]. Proinflammatory cytokines such as TNF-α and IL-1β, as well as synovium-related factors including MMP-3, MMP-13, and ADAMTS5, are significantly correlated with the severity of knee OA and may be associated

with its progression [8-11]. Aggrecan and collagen II are among the components of the cartilage matrix that break down as a result of increased levels of inflammatory mediators and degradative agents [12, 13]. Relevant research suggests that strategies that reduce inflammation may be used to treat OA [5, 14].

Because probiotics are deemed harmless for consumption and many have beneficial functional activity for human ailments, they have become popular targets for research and development in the treatment of OA [15]. *Clostridium butyricum*, an anaerobic bacillus recognized for its production of butyric acid, is commonly found in the environment and has been documented to colonize about 10–20% of the stomachs of both adults and newborns [16]. Non-pathogenic strains of *Clostridium butyricum* are utilized as probiotic supplements for the treatment or prevention of gastrointestinal infections and various other conditions, such as metabolic diseases, bowel disease, multiple sclerosis, and neurodegenerative diseases [16-19]. In our earlier work, we documented that *Clostridium butyricum* GKB7 mitigates the progression of OA by blocking inflammatory cytokine generation associated with it [20]. Both live and dead GKB7 exhibit anti-inflammatory functions [21]. This study investigated whether fermented GKB7 is effective at preventing the advancement of OA. In this study, we discovered that fermented GKB7 prevent the onset of OA triggered by anterior cruciate ligament transection (ACLT) *in vivo*.

Materials and Methods

Materials

Abcam (Cambridge, UK) provided the aggrecan (ab3778) antibody. Santa Cruz Biotechnology (Dallas, TX, USA) provided the MMP-3 (SC-21732) and MMP-13 (SC-30073) antibodies. We purchased TNF-α (A11534), COL2A1 (A1560), and ADAMTS5 (A2836) antibodies from ABclonal, Inc. (Woburn, MA, USA). R&D Systems, Inc. (Minneapolis, MN, USA) provided the IL-1β (MAB601) antibody.

Preparation of fermented GKB7

The *Clostridium butyricum* GKB7 strain was obtained from fecal samples of healthy individuals in Taiwan, as detailed in our earlier report [20]. The fermented GKB7 was prepared according to our previous report [22].

ACLT animal model

We purchased eight-week-old male Sprague Dawley (SD) rats weighing between 300 and 350 g from the National Laboratory Animal Center in Taipei, Taiwan. They were divided into three groups at random: ACLT alone, ACLT plus fermented GKB7 (100 mg/kg), and sham surgery (controls). The process outlined in our previous documents was followed for performing the ACLT operations [23, 24].

The weight-bearing incapacitance test was examined weekly to evaluate spontaneous discomfort after ACLT, based on differences in dynamic weight bearing between the resting right and left hind limbs, in accordance with our previous protocols [25, 26].

μ-CT measurements

The rats were sacrificed after six weeks of treatment. Following our previous techniques, their undamaged right knee joints were scanned using a SkyScan 2211 μ-CT scanner (Bruker; Kontich, Belgium) and processed using CTAn software [25, 27].

Histological analysis

Hematoxylin and eosin (H&E) and Safranin-O/Fast Green stains were used to investigate histological alterations in OA tissue under an optical microscope, as previously reported [28, 29]. Tissues from knee joints were decalcified using 10% EDTA after being fixed in 4% formaldehyde. Ethanol dehydration came next. After being embedded in paraffin blocks, the specimens were cut into sections that were 5 μm thick for histological staining. The structural alterations in the cartilage of the central weight-bearing region of the medial tibial plateau were assessed using the Osteoarthritis Research Society International (OARSI) histopathological assessment system [30, 31]. This system uses staging and grading scores to show the severity of OA and the depth of lesions, respectively.

Immunohistochemistry (IHC) staining

The Leica Novolink Polymer Detection system (Leica Biosystems Inc., IL, USA) was used for the immunohistochemical examination, as described in reference [32, 33]. After a brief application of 3% hydrogen peroxide, tissue slices were treated with 3% BSA. After applying primary antibodies to the sections, they were stained with diaminobenzidine substrate and incubated with a secondary antibody coupled with peroxidase for an hour.

Statistical analysis

Statistical analyses for quantified results were conducted using GraphPad Prism 5.0 software. Data are presented as the mean ± standard deviation (S.D.). The paired sample t-test and One-way ANOVA followed by Bonferroni post hoc testing was used to compare results from two groups and from more than two groups, respectively. Statistical significance was determined by a p-value of less than 0.05 in all cases.

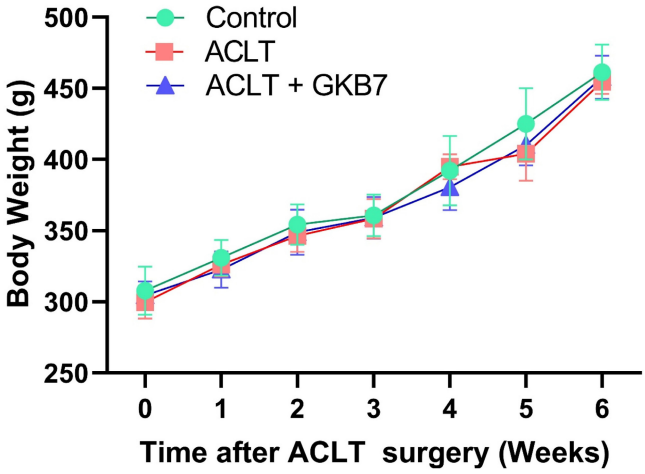

Figure 1. Increase in body weight throughout the experimental phase. Throughout the course of the experiment, body weight was measured.

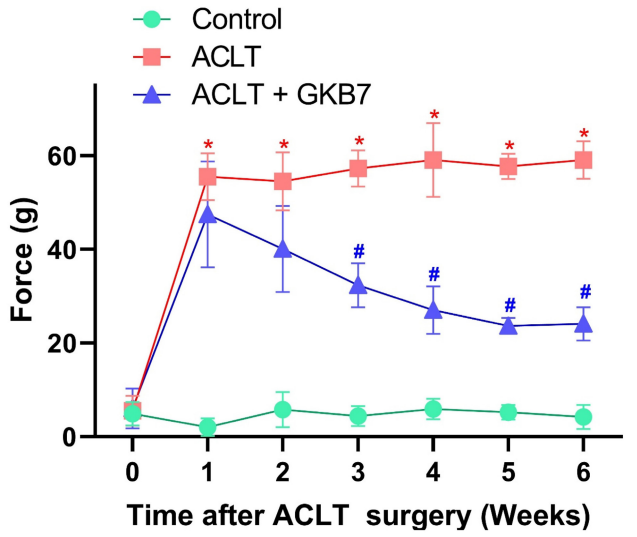

Figure 2. Fermented GKB7 decelerates ACLT-induced bone pain. Every week, weight-bearing behavioral testing was conducted to assess deficits in weight-bearing forces. * $p<0.05$ compared with the control group; # $p<0.05$ compared with the ACLT-only group.

Results

Fermented GKB7 do not affect the body weight growth curve

We investigated the preventive benefits of fermented GKB7 using a rat model of ACLT-induced knee arthritis. To look into the underlying mechanisms, assessments of pain behavior and histological investigations were performed. The rats' body weights were recorded the day before surgery, and this procedure was repeated every week until the rodents were put to death. All groups gradually increased in body weight during the course of the trial, and there were no discernible differences between the groups (Figure 1). According to our research, fermented GKB7 has no harmful negative effects on body weight.

Fermented GKB7 diminishes OA pain

The rats' pain behavior was examined using the static weight-bearing incapacitance test. All groups showed a significant unequal weight-bearing posture during the first week following surgery (Figure 2). Throughout the experiment, this significant imbalance became more pronounced in the ACLT animals. However, there were notable improvements in pain-related behavior in the ACLT+ fermented GKB7 group (Figure 2). These findings imply that fermented GKB7 successfully reduces pain associated with OA.

Fermented GKB7 protects against ACLT-triggered osseous and cartilage damage in an ACLT-triggered OA model

Changes in trabecular microarchitecture were assessed by μ-CT six weeks following ACLT surgery. Significant bone deterioration was seen in ACLT rats as compared to controls, demonstrating the OA lesion brought on by ACLT surgery (Figure 3). Bone mineral density (BMD), bone mineral content (BMC), bone volume/tissue volume ratio (BV/TV), bone surface to tissue volume ratio (BS/TV), trabecular thickness (Tb.Th), trabecular number (Tb.N), and trabecular separation (Tb.Sp) all decreased in ACLT rats, according to quantitative evaluation (Figure 3). Additionally, rats treated with fermented GKB7 showed significant improvements in bone microstructure when compared to the ACLT group (Figure 3).

In the ACLT knee groups, histological evaluation using H&E and Safranin-O/Fast Green staining revealed articular cartilage degeneration and synovial lining hyperplasia (Figure 4 and 5). The ACLT+fermented GKB7 group had less pathological changes in cartilage tissue and less synovial tissue hyperplasia than the ACLT group, according to the quantification of inflammation, OARSI scores, and cartilage scores (Figure 4 and 5).

Fermented GKB7 suppress proinflammatory cytokine production and cartilage degradation

The IHC analysis revealed a significant increase in TNF-α and IL-1β production in the ACLT group's synovial tissue, indicating an increase in inflammatory activity. This rise was considerably reduced in the ACLT+fermented GKB7 group, as shown in Figure 6. Further evaluation of cartilage metabolism was carried out using IHC labeling of MMP-3, MMP-13, ADAMTS5, aggrecan, and type II collagen alpha1 chain (COL2A1), which is the foundation for articular cartilage. The

ACLT+fermented GKB7 group showed higher levels of aggrecan and COL2A1 and lower levels of MMP-3, MMP-13, and ADAMTS5 in comparison to the ACLT group (Figure 7).

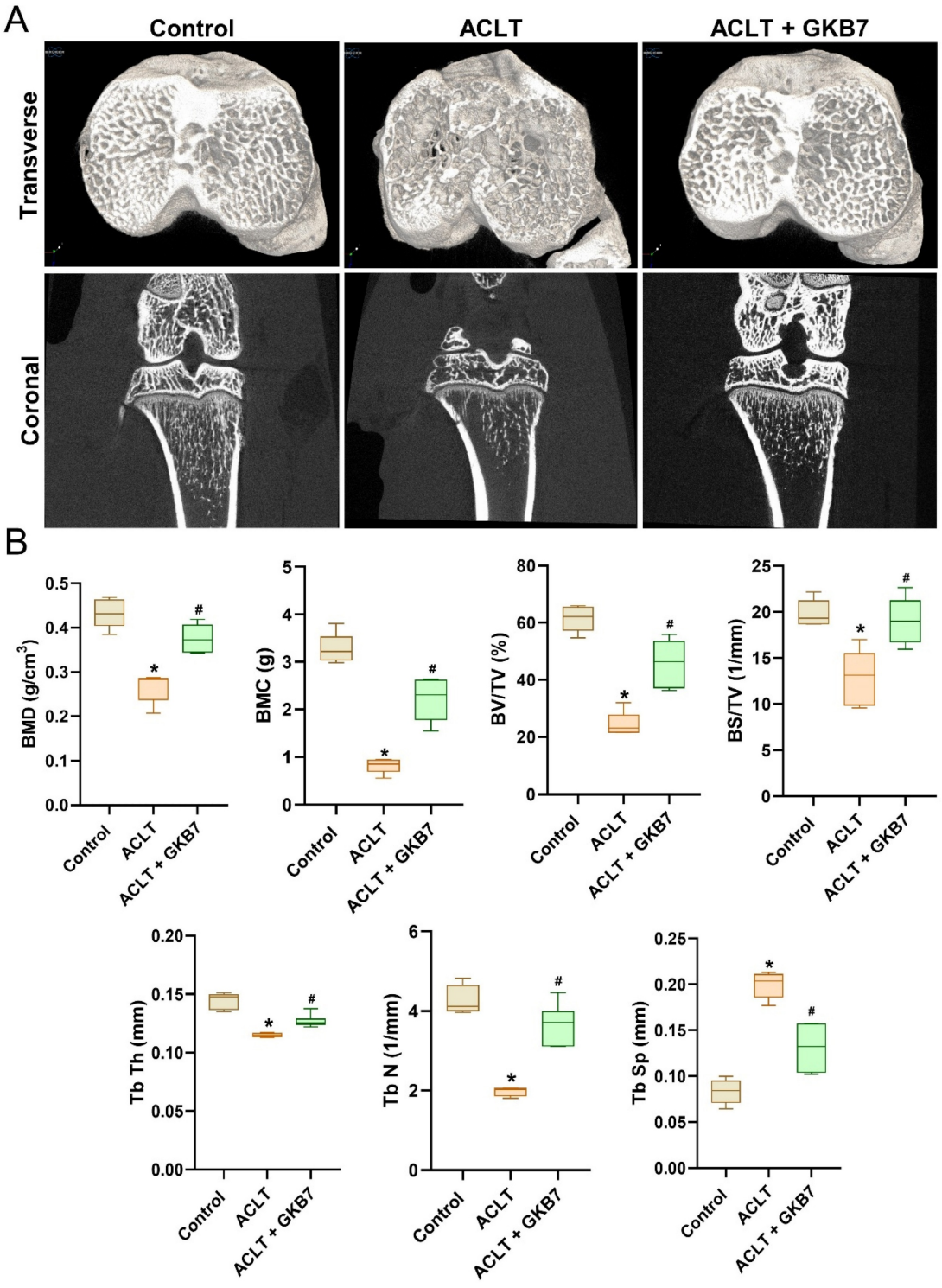

Figure 3. Fermented GKB7 ameliorates osseous damage in the ACLT-induced OA knee joint. (A) Representative micro-CT images from knee subchondral bone. (B) Quantitative analyses of BMD, BMC, BV/TV, BS/TV, Tb.Th, Tb.N, and Tb.Sp. * $p<0.05$ compared with the control group; # $p<0.05$ compared with the ACLT-only group.

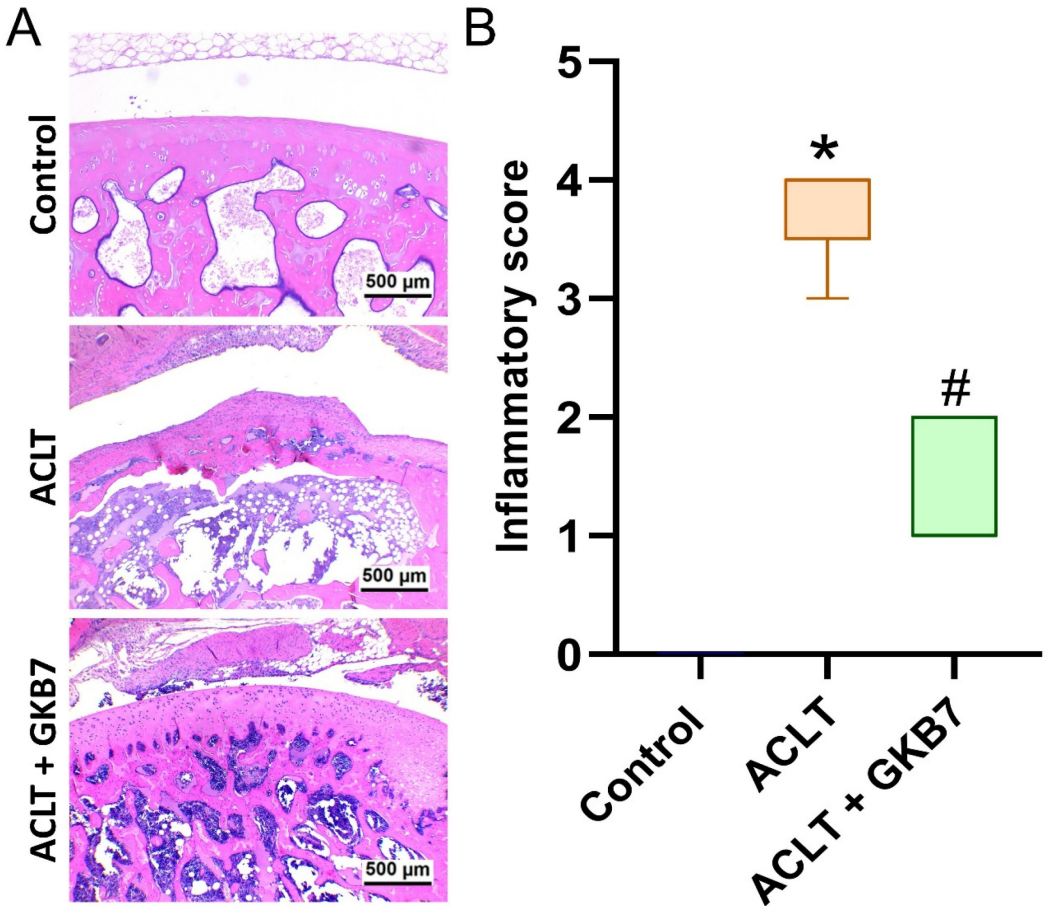

Figure 4. Fermented GKB7 blocks ACLT-induced synovial inflammation and cartilage degradation. (A) Histological sections from knees stained with H&E. (B) Quantitative analyses of synovium scores. Scale bar = 500 μm. * p<0.05 compared with the control group; # p<0.05 compared with the ACLT-only group.

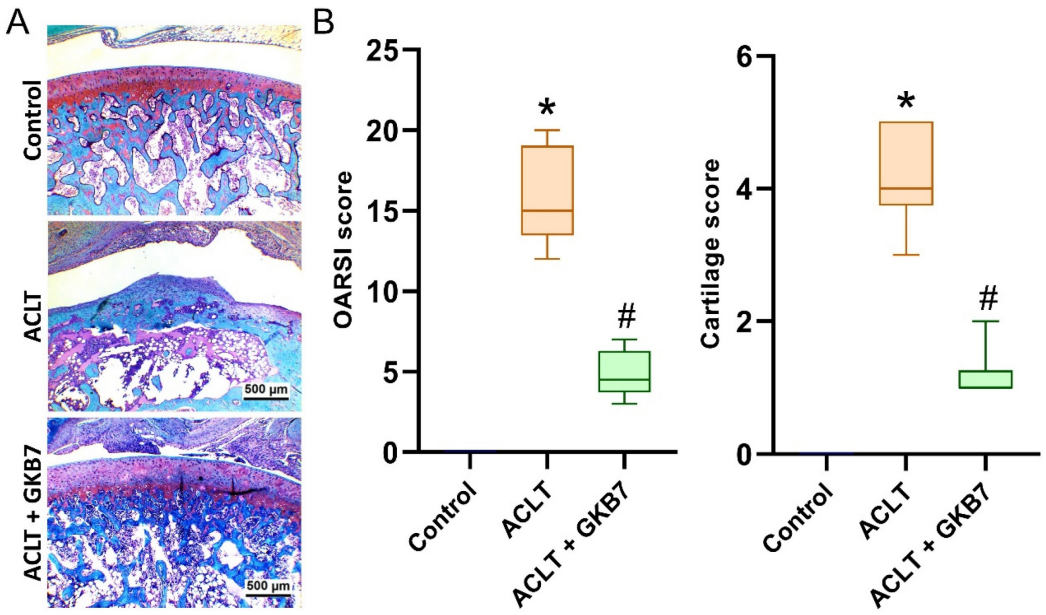

Figure 5. Fermented GKB7 blocks ACLT-induced cartilage breakdown. (A) Histological sections from knees stained with Safranin-O. (B) Quantitative analyses of OARSI and cartilage scores. Scale bar = 500 μm. * p<0.05 compared with the control group; # p<0.05 compared with the ACLT-only group.

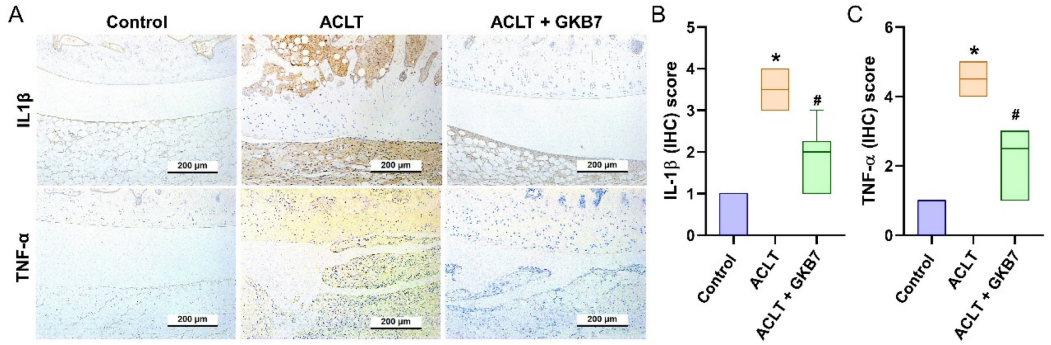

Figure 6. Fermented GKB7 diminishes the induction of IL-1β and TNF-α in ACLT-induced OA articular cartilage. Immuno-histochemistry analysis and scoring of IL-1β (A, B) and TNF-α (A, C) in rat knee joint cartilage. Scale bar = 200 μm. * $p<0.05$ compared with the control group; # $p<0.05$ compared with the ACLT-only group.

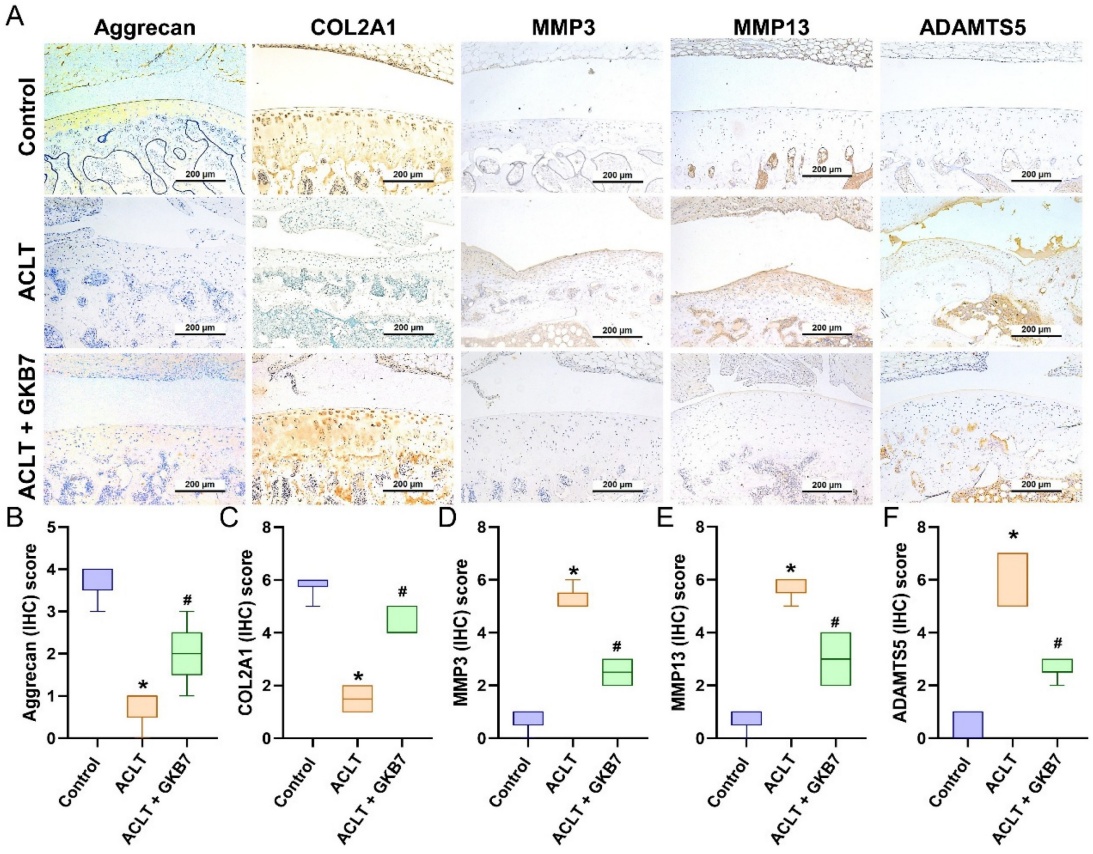

Figure 7. Fermented GKB7 reserves the expression of aggrecan and COL2A1 accompanying with suppression of MMP-3, MMP-13 and ADAMTS5 in ACLT-induced OA articular cartilage. (A) Immuno-histochemistry analysis MMP3, MMP-13, ADAMTS5, aggrecan and COL2A1 in rat knee joint cartilage. (B-F) Scoring of the immunosignals of MMP3, MMP-13, ADAMTS5, aggrecan and COL2A1. Scale bar = 200 μm. * $p<0.05$ compared with the control group; # $p<0.05$ compared with the ACLT-only group.

Discussion

A variety of probiotic strains applied as supplements have demonstrated therapeutic functions for human ailments, including arthritis, respiratory and gastrointestinal issues [34, 35]. Both preclinical and clinical reports reveal that probiotics may alleviate OA-related pain in individuals by positively modulating gut microbiota and reducing inflammation through different mechanisms for the treatment of OA [36]. Furthermore, preclinical trials indicate that probiotics can hinder cartilage breakdown and the advancement of OA models [37]. *Lactobacillus plantarum* is said to reduce the rise in bone erosion and cartilage degradation induced by ACLT [15]. Combination of the probiotic strains *Lactiplantibacillus plantarum* and *Lacticaseibacillus paracasei* notably reduced cartilage erosion at the medial femoral condyle in a mouse model with medical meniscus destabilization [37]. Probiotics such as *Clostridium butyricum* have been employed to treat or avert a range of conditions, including necrotic

enteritis, diabetes, ulcerative colitis, bowel disorder, liver injury, dementia, pouchitis, and antibiotic-induced diarrhea [38, 39]. We previously found that live and dead GKB7 exhibits anti-inflammatory and chondroprotective functions in an OA model [21]. Here, our investigation further revealed that fermented GKB7 reduces OA-related pain and progression in an ACLT-promoted OA model. Fermented GKB7 inhibits inflammatory cytokine expression and cartilage degradation *in vivo*. Fermented GKB7 also serves as a potential supplement for OA management.

OA is a chronic inflammatory disease that affects cartilage degradation, synovial inflammation, and pain behavior [2, 40]. Inflammatory cytokines, such as TNF-α and IL-1β, play a major role in the progression of OA, causing joint pain, increased inflammatory reactions, and abnormalities in chondrocyte metabolism [14, 41]. Additionally, clinical data from previous investigations showed that OA patients have markedly higher serum and synovial tissue levels of TNF-α and IL-1β [23, 42]. IL-1β and TNF-α are important targets for finding successful OA treatment approaches during pre-clinical trials. Our ACLT-induced OA model demonstrated that ACLT surgery replicates clinical features, resulting in increased TNF-α and IL-1β production in synovial tissue and cartilage. The administration of fermented GKB7 clearly resulted in a downregulation of TNF-α and IL-1β production in synovial and cartilage tissues, suggesting that fermented GKB7's anti-OA properties stem from its ability to prevent the synthesis of TNF-α and IL-1β.

Collagen and the proteoglycan aggrecan make up the majority of cartilage's gel-like matrix. Proteoglycans draw water portions to form a gel that preserves the cartilage's robust and inflated properties, while COL2, the main component of the matrix, builds a fibrous network foundation [43]. Chondrocytes are supported in maintaining stability and a balanced metabolism by the cartilage matrix [44]. When chondrocytes are unable to maintain metabolic homeostasis within the cartilage matrix, cartilage-related diseases like joint inflammation and articular degradation arise [45, 46]. Here, we discovered that ACLT increased the synthesis of the chondrolytic factors MMP-3, MMP-13, and ADAMTS5 while decreasing the expression of aggrecan and COL2A1. By reducing the expression of chondrolytic factors, fermented GKB7 restores chondroprotective qualities and slows the progression of OA.

The limitations of the current study should be acknowledged. Although we provided evidence that fermented GKB7 prevents ACLT-induced OA progression, we did not elucidate the underlying mechanisms of action of fermented GKB7. Future studies should investigate these mechanisms in greater detail using *in vitro* cell culture systems.

To sum up, our findings demonstrate that fermented GKB7 reduces bone pain and the development of OA related with ACLT. Through the reduction of pro-inflammatory cytokines IL-1β and TNF-α, as well as the chondrolytic factors MMP-3, MMP-13, and ADAMTS5, fermented GKB7 inhibited the degradation of aggrecan and COL2A1. This action resulted in a blockade of cartilage breakdown and bone loss. The fermented GKB7 improves the prevention of OA progression.

Acknowledgments

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Competing Interests

The authors have declared that no competing interest exists.

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