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RESEARCH ARTICLE

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# Undenatured type II collagen for knee osteoarthritis

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**ABSTRACT**

**Introduction:** Knee Osteoarthritis (OA) leads to significant pain and reduced function and affects patients' overall quality of life (QoL). Conservative modalities are the first line of management, resorting to surgery only if they fail. However, these modalities have limitations, and do not address the underlying cause of knee OA. The use of nutraceuticals, including native/undenatured type II collagen (UC-2), has evolved and shown promise in the conservative management of knee OA. This article highlights the mechanism of action, and qualitatively presents the pre-clinical, clinical and on-going scientific literature exploring the safety and efficacy of UC-2 for the management of knee OA.

**Methods:** A search was performed using multiple databases (PubMed, Web of Science, Embase and Scopus) employing terms for UC-2 and Knee OA for articles published in English language, while adhering to Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. All pre-clinical and clinical studies utilizing UC-2 for knee OA were included. Studies not using UC-2 alone or not focusing on the management of knee OA were excluded.

**Results:** Twelve studies (3 pre-clinical studies, 8 clinical studies and 1 study with both pre-clinical and clinical component) met our pre-defined search and inclusion criteria, and were included in this review.

**Discussion:** UC-2 acts *via* a specific immune mediated mechanism, known as oral tolerance, which can lead to reduced inflammation and enhanced cartilage repair in the knee joint. In addition, administration of UC-2 (40 mg daily) is safe and efficacious in the short- and mid-term, reducing inflammation and pain, and improving function, range of motion (ROM) and overall QoL. Nonetheless, more adequately powered, prospective, multi-center, non-randomized and randomized controlled trials with longer follow-up are warranted to establish the long-term efficacy of UC-2 in knee OA patients and justify its routine clinical use.

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## Introduction

Osteoarthritis (OA), the most predominant joint disease impacting millions of individuals worldwide [1], is a degenerative joint disorder generally affecting large weight-bearing joints, including knees [1]. Its etiology entails inflammation of synovial tissue and deterioration of articular cartilage, leading to significant pain and decreased function, thereby affecting an individual's overall quality of life (QoL) [2]. Knee OA is conventionally managed with non-pharmacological modalities such as activity modification, physiotherapy; pharmacological agents such as non-steroidal anti-inflammatory drugs (NSAIDs), viscosupplementation, corticosteroids and opioids; and surgical interventions, after traditional modalities have been ineffective [3]. These treatment modalities have flaws and side-effects, and usually try to decrease pain without targeting the underlying pathophysiology [1–3]. To overcome these limitations, efforts have been made to find alternative treatments that can attenuate joint degradation, improve range of motion (ROM) and alleviate pain.

Lately, there has been a considerable interest in the usage of nutraceuticals including Symptomatic Slow Action Drugs for OA (SYSADOA), for example, glucosamine, chondroitin, etc. and collagen supplementation,

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to avert damage to the articular cartilage and support the healing process subsequent to the inception of OA [4]. This review highlights the mechanism of action and document the pre-clinical and clinical outcomes of native/undenatured type II collagen (UC-2), derived from the cartilage of chicken sternum, for the management of knee OA.

## Mechanism of action

UC-2 has a definite immune mediated mechanism of action (MOA) named oral tolerance [4]. Oral tolerance is an immune process where the body differentiates between harmless antigens such as dietary proteins or commensal microorganisms, and potentially detrimental foreign aggressors [5]. Oral tolerance initiates in the gut-associated lymphoid tissue (GALT). GALT comprises of mesenteric lymph nodes and patches of lymphoid tissue adjoining the small intestine (known as Peyer's patches) [6]. Peyer's patches uptake UC-2 post-consumption and activate the immune cells [6]. In particular, the naïve T-cells are transformed into effector or regulatory T-cells (Treg) that precisely target type II collagen [6]. Tregs migrate through blood circulation, and upon recognition of type II collagen in joint cartilage, they secrete anti-inflammatory cytokines, including transforming growth factor-beta (TGF-β), interleukin 4 (IL-4) and IL-10, while simultaneously decreasing the expression of pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α) [4,5,7,8]. This can help reduce inflammation and augment cartilage repair in the joint (Figure 1) [4]. Importantly, UC-2 preserves active epitopes/glycosylated antigenic regions, which is lacking in denatured type II collagen, essential for interaction with Peyer's patches and induction of oral tolerance [4].

## Search criteria

A search was performed using terms, ('undenatured type II collagen' OR 'native type II collagen') AND ('knee osteoarthritis' OR 'osteoarthritis' OR 'arthritis'), in databases including PubMed, Web of Science, Embase and Scopus for articles published in English to 13 August 2024, while adhering to Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. All pre-clinical and clinical studies utilizing UC-2 for knee OA were included. Studies not using UC-2 alone or not focusing on the management of knee OA were excluded (Figure 2). We carefully read and assessed each included article to minimize any potential bias.

Additionally, we searched ClinicalTrials.gov, Clinical Trials Registry – India (CTRI), and Chinese Clinical Trial Register (ChiCTR) using the above-mentioned search terms to identify registered on-going trials on the use of UC-2 for the management of knee OA.

## Results

### *Pre-clinical studies*

Sahin et al. [9] examined the effect of different doses of UC-2 on monosodium iodoacetate-induced OA in young and old female Wistar albino rats ($N = 70$; 35

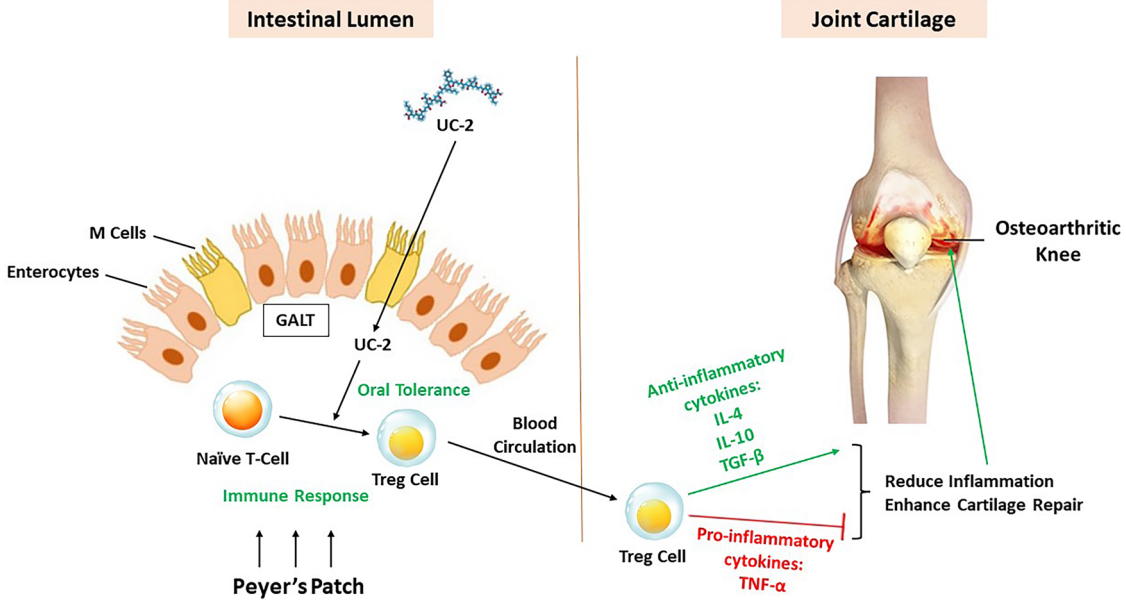


**Figure 1.** Schematic diagram showing the mechanism of action of undenatured type II collagen (UC-2). GALT: gut-associated lymphoid tissue, Treg: regulatory T-cells, IL- interleukin, TGF-β: transforming growth factor-beta, TNF-α: tumor necrosis factor-alpha.

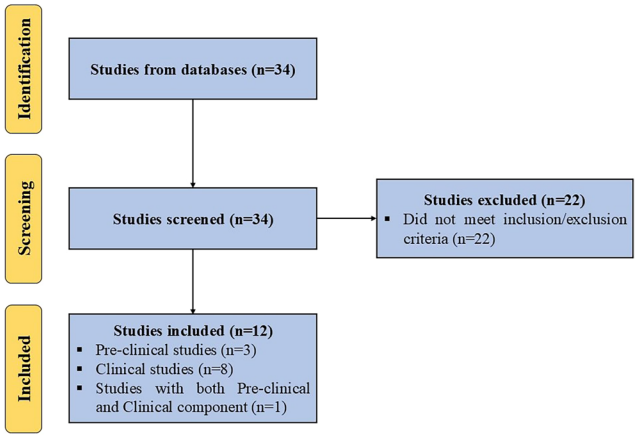


**Figure 2.** A PRISMA flow diagram outlining the record identification and selection process.

young rats – 8 weeks old, 170 ± 20 g; 35 old rats – 8 month old, 340 ± 20 g). Both young and old rats were divided into five groups (with 7 rats per group) – control (saline treated), monosodium iodoacetate (MIA) (single intra-articular injection of MIA), MIA + UC 0.66 (treated with 0.66 mg/kg UC-2), MIA + UC 1.33 (treated with 1.33 mg/kg UC-2), and MIA + UC 2 (treated with 2 mg/kg UC-2). These doses represent human doses of 40, 80 and 120 mg/day, respectively [10]. All gait measurements and Mankin scores were improved in both young and old rats post-administration of UC-2 at 28 days follow-up, with the highest efficacy reported with the 2 mg/kg dose (significantly greater than the 0.66 mg/kg dose). In addition, all doses of UC-2 significantly decreased the Kellgren-Lawrence (KL) score in young rats, while only the two larger doses significantly reduced the KL score compared to the MIA group. Moreover, administration of UC-2 led to a significant decrease in the inflammatory cytokines expression level, including IL-6, IL-1β, PGE2, TNF-α and COMP compared to the MIA group in both young and old rats. The amount of reduction was higher in the 2 mg/kg dose group compared to the 0.66 mg/kg dose. This study demonstrated that all doses of UC-2 can improve MIA-induced OA symptoms, but the higher doses were more effective [9].

Sahin et al. [11] investigated the effects of niacinamide and UC-2, alone and in combination, on inflammation and joint pain behavior of rats with MIA-induced OA. 8-week old male Wistar rats were used with 7 rats per group. Administration of UC-2 led to significant reduction in the levels of inflammatory IL-6, IL-1β, TNF-α, COMP, and CRP compared to the MIA group. UC-2 supplementation also resulted in reduction in the level of malondialdehyde (MDA) and increase in antioxidants level, including catalase (CAT), superoxide dismutase (SOD) and glutathione peroxidase (GPx). Additionally, significant improvements in stride length, paw areas and paw widths were reported in the UC-2 group compared to the MIA group. Moreover, KL score and Mankin scores were significantly improved in the UC-2 supplementation group compared to the MIA group. This study also demonstrated the ability of UC-2 to reduce inflammation and mitigate symptoms of OA in rats.

Rui et al. [12] investigated the preventative and therapeutic effects of UC-2 on OA in aging male C57BL/KsJ-leprdb/leprdb diabetic (db/db) mice. Aging db/db mice were randomly divided into three sub-groups ($n = 15$) – old model group (OM), UC-2 (dose of 6 mg/kg body-weight), and positive control (PC) group (treated with 180 mg chondroitin sulfate (CS) + 225 mg glucosamine hydrochloride (GH). Non-diabetic mice (db/m) and young db/db mice were used as normal control (NC) group ($n = 15$) and young control (YC) group ($n = 15$), respectively. The intervention was administered orally *via* drink for 12 weeks. The UC-2 group demonstrated significant superiority regarding movement trajectories, trajectory area, tremor index, standing time, swing, stride length, step cycle and cadence compared to the OM group. The levels of pro-inflammatory markers, including IL-6, IL-1β, hs-CRP and TNF-α, were significantly lower; anti-inflammatory markers, including IL-10 and IL-4 were significantly higher; MDA was significantly lower, and antioxidants, including GSH-Px and SOD, were significantly higher; and MMP-1,3 and 13 were significantly lesser in the UC-2 treated group compared to the OM group. These results demonstrated the potential of UC-2 in improving oxidative stress, inflammatory responses, pain and motor function in diabetic mice with OA.

Bagi et al. [13] determined the ability of UC-2 to prevent excessive articular damage in a partial medial meniscectomy tear (PMMT)-induced OA model in rats. 4 month old Lewis rats were divided into four groups

**Table 1.** Summary of results of included pre-clinical studies.

| Author [Reference] | Main findings |
|---|---|
| Sahin et al. [9] | Administration of undenatured type II collagen (UC-2) led to improvements in all gait measurements, Mankin and Kellgren-Lawrence (KL) scores, and reduction in the expression level of inflammatory cytokines compared to the control groups. |
| Sahin et al. [11] | Administration of UC-2 led to significant reduction in levels of inflammatory cytokines and malondialdehyde (MDA) levels, increase in antioxidant levels, and improvements in stride length, paw areas and widths, KL and Mankin scores compared to the control group. |
| Rui et al. [12] | Administration of UC-2 led to significant improvement in movement trajectories, trajectory area, tremor index, standing time, swing, stride length, step cycle and cadence. It also resulted in reduction in the levels of pro-inflammatory cytokines and MDA and increase in levels of anti-inflammatory cytokines and antioxidants compared to the control group. |
| Bagi et al. [13] | Administration of UC-2 led to significantly lower expression of cartilage degradation marker, lesser osteophyte formation and damage to articular cartilage, improvement in weight-bearing capacity, greater quantity of cancellous bone at the proximal tibial metaphysis, higher bone volume, bone mineral density and trabecular number, and lower trabecular separation parameter compared to the control/vehicle group. |

(10 rats/group) – UC-2 (0.66 mg/Kg/day; equivalent to 40 mg/day in humans), vehicle (0.5% methyl cellulose), intact control and sham (received sham surgery). UC-2 or vehicle were orally administered for 8 weeks. UC-2 treated animals showed significantly lower expression of cartilage degradation marker, CTX-II, compared to the vehicle group. The weight-bearing capacity was significantly greater in the UC-2 group compared to the vehicle group at the end of the study. Rats in the UC-2 group also exhibited greater quantity of cancellous bone at the proximal tibial metaphysis; higher bone volume, bone mineral density and trabecular number; and lower trabecular separation parameter compared to the vehicle group. Additionally, osteophyte formation and damage to articular cartilage were less severe in the UC-2 group compared to the vehicle group. Administration of a clinically relevant dose immediately after injury can help to improve knee function and prevent excessive articular cartilage deterioration.

The results from aforementioned pre-clinical studies are summarized in Table 1.

## *Clinical studies*

Luo et al. [14], in a randomized, multi-center, double-blind, placebo-controlled, parallel-group study, investigated the safety and efficacy of UC-2 in knee OA patients. The inclusion criteria included age ≥40 to ≤65 years, body mass index (BMI) ≥18.5 to ≤29.9 kg/m$^2$, Visual Analogue Scale (VAS) score ≥60 mm for knee joint pain, radiographic evidence of knee OA, willing to abstain from food containing collagen type II 48 h prior to assessment visit. The exclusion criteria included FBG >125 mg/dL, SBP ≥140 mm Hg and/or DBP ≥90 mmm Hg, Grade I or IV knee OA, history of trauma or fractures or surgery to the index knee, use of corticosteroid or viscosupplementation in the last 3 days, use of oral or systemic analgesics, and other joint pathologies such as rheumatoid arthritis or gout. The primary outcome measure was the Western Ontario and McMaster Universities Arthritis Index (WOMAC) total score assessed at baseline and at 4, 8 and 12 weeks follow-up. The secondary outcome measures included the WOMAC subscales (stiffness, pain and physical function) evaluated at baseline and at 4, 8 and 12 weeks follow-up, and EQ-5D-5L and QoL assessments at baseline and 12 weeks follow-up. 101 participants were enrolled and randomized into 3 groups – placebo ($n$ = 34), GH + CS ($n$ = 33) and UC-2 ($n$ = 34). Both UC-2 and GH + ES groups showed significant improvements in WOMAC total score as well as pain, stiffness and physical function subscale scores compared to the placebo group at follow-up visits, and no significant difference was reported between UC-2 and GH + CS group. In addition, both UC-2 and GH + CS groups significantly improved their QoL compared to the placebo group, while the UC-2 was more effective compared to the GH + CS group. No adverse events were observed throughout the duration of the study. Despite its small cohort size and short follow-up, the results of this study demonstrated that administration of UC-2 is safe, and improved joint health in terms of stiffness, pain and physical function, and overall QoL of knee OA patients.

Sadigursky et al. [15], in a prospective, comparative study tested whether UC-2 relieves pain, improves QoL and joint function of patients aged 60 to 80 years with knee OA. The inclusion criteria included imaging diagnosis of knee OA, acceptance of conservative treatment during the study period, and willingness to not start alternative treatment. The exclusion criteria included history of allergy to study drugs, previous knee infection, secondary inflammatory arthritis, marked angular deformities. 53 patients in the UC-2 (40 mg UC-2 daily) and 52 patients in the control group (without UC-2) were randomized and evaluated for QoL, pain, function, anthropometric data, alignment, ROM and radiographic analysis at 1, 3 and 90 days. The UC-2 treated group showed significant improvements in VAS, WOMAC pain, WOMAC total score and physical function of SF-12 compared to the baseline as well as the control group at

90 days follow-up. The limits of this study include its small sample size and short follow-up duration. Administration of UC-2 helps to relieve pain, improve function and QoL in patients (60-80 years old) suffering from knee OA.

Shiojima et al. [16], in a randomized, double-blind, placebo-controlled, parallel-group clinical study assessed the safety and efficacy of 12 weeks of intake of UC-2 on joint and motor function in 64 healthy female and male Japanese patients. The primary outcome measure included knee passive ROM (measuring joint and motor functions). The secondary outcome measures included VAS for knee discomfort, Japan Knee Osteoarthritis Measure (JKOM) and motor functions (10-m walking and stair-climbing test). 58 participants (placebo = 28; UC-2 = 30) completed the study. For knee passive ROM, the UC-2 group showed significant improvements in the flexion and flexible angle (range) at 4, 8 and 12 weeks of follow-up. In addition, UC-2 also showed significant improvements in VAS, JKOM and motor functions. Administration of UC-2 is safe and effective in improving pain, flexibility, mobility and motor function.

Schön et al. [17], in a randomized, double-blind, placebo-controlled study assessed the effect of UC-2 on knee flexibility in healthy participants experiencing activity-related joint discomfort. The inclusion criteria included healthy males and females aged 20–55 years old, BMI 19–29.9 Kg/m$^2$, performed sports at least 2 times/week, and experienced reversible knee joint discomfort (during or immediately after physical activity) for at least 3 months. The exclusion criteria included knee joint replacement, planned surgery during the duration of the study, any intra-articular injection within 3 months of screening visit, hip, spine or foot injuries. Ninety-six subjects were enrolled in the study and randomized into two groups – placebo or UC-2 (40 mg UC-2). The ROM flexion and extension were measured as outcome measures. The ROM flexion in the UC-2 group was significantly better compared to the placebo control at 8 weeks and continued to increase to the end of the study, at 24 weeks. In addition, the UC-2 treated group showed significant improvement over time for ROM extension to 24 weeks of supplementation, while no differences were observed in the placebo group. Additionally, no study-related adverse or severe adverse events were reported throughout the duration of the study. Administration of UC-2 is safe and improved joint flexibility and extension in healthy participants with activity-related joint discomfort.

Rui et al. [12], in a double-blind, placebo-controlled, randomized controlled trial, investigated the preventive and therapeutic effects of UC-2 on OA in Type II Diabetes Mellitus (T2DM) patients. The inclusion criteria involved patients with a knee pain score of ≥2 for more than 3 months, symptomatic radiographic primary femorotibial knee OA, KL grade II or III in the more symptomatic knee, and minimum joint space width of more than 2.5 mm in the medial compartment. The exclusion criteria included prior surgery of the symptomatic knee, rheumatoid arthritis, BMI ≥35 kg/m$^2$, intra-articular injections within the prior month. The participants were randomized into two groups – UC-2 (administered two 20 mg UC-2 capsules) and placebo control (two empty capsules). The primary outcome measure was the WOMAC pain score. The secondary outcome measures were WOMAC total score, stiffness and function subscale scores, gait kinematics, physical activity, and 6-min walk test (6-MWT). 55 knee OA patients combined with T2DM met the inclusion/exclusion criteria and were enrolled in this 3-month follow-up study ($n$ = 28 in UC-2 group and $n$ = 27 in control). The WOMAC subscale and total scores were significantly decreased post-treatment with UC-2 compared to the baseline as well as the control group. The distance of the 6-MWT was significantly increased, and pain was significantly reduced in the UC-2 group compared to baseline. Additionally, for gait analysis, significant improvements in cadence, speed, knee flexion ROM, knee abduction ROM, and varus at initial contact were significantly improved for UC-2 group compared to both the baseline and the control group. These results demonstrated the potential of UC-2 in improving inflammatory responses, oxidative stress, pain and motor function in T2DM patients with knee OA.

Lugo et al. [18], in a multi-center, randomized, double-blind, placebo-controlled study examined the efficacy and tolerability of UC-2 in knee OA patients. The inclusion criteria included 40-75 years old males and females, BMI of 18–30 kg/m$^2$, moderate-to-severe OA by physical exam and KL grade II or III, knee pain for at least 3 months, a Lequesne Functional Index (LFI) score of 6-10, and VAS score of 40–70 mm seven days post-withdrawal from omitted medications. The exclusion criteria included history of allergic reaction to the rescue drug or products used in the study. 191 subjects were randomized in three groups—UC-2 (40 mg), GH + CS and placebo. The primary outcome measure was the WOMAC score. The secondary outcome measures included LFI, VAS and WOMAC subscales. The subjects were followed for 180 days. The UC-2 treated group showed significant improvements in WOMAC subscales and total scores, VAS score and LFI compared to the placebo at 180 days follow-up. The UC-2 group also showed significant improvements for WOMAC total score, pain and stiffness, VAS score and LFI compared to GH + CS at

180 days follow-up. Safety outcomes were similar for all three groups. The administration of UC-2 resulted in significant decrease in pain and improvement in function and was well-tolerated in knee OA patients.

Lugo et al. [19], in a randomized, double-blind, placebo-controlled study, investigated the tolerability and efficacy of UC-2 in moderating pain and joint function from vigorous exercise in healthy participants. The inclusion criteria included age ≥30 to ≤65 years, BMI ≥18 to ≤35 Kg/m$^2$, no knee joint discomfort at rest, discomfort score of at least 5 (on 11-point Likert scale) within 10 min of starting stepmill protocol. The exclusion criteria included indicators of arthritis, joint disorders, daily use of NSAIDs, autoimmune disorders, daily use of omega-3 supplements, history of hip or knee surgery, intra-articular injection of corticosteroid or viscosupplementation in the last 3 months. 55 subjects met the inclusion/exclusion criteria and were randomized into two groups—UC-2 (40 mg daily, $n=27$) and placebo ($n=28$). Subjects were followed-up at baseline, and at days 7, 30, 60, 90 and 120. They were evaluated for anthropometric measures, knee ROM, 6-MWT, KOOS, stepmill procedure and Stanford exercise scales. The UC-2 treated subjects exhibited significantly higher knee extension compared to the baseline and the placebo group at 120 days follow-up. The UC-2 group also showed a significant increase in the time of start of initial pain in the joint compared to the baseline at 120 days follow-up. In addition, both groups showed significant improvement in joint pain compared to the baseline, with greater reduction in pain in the UC-2 group. No adverse effects related to UC-2 administration were reported throughout the duration of the study. Administration of UC-2 is safe, and led to improved knee joint extension, alleviated joint pain and lengthened the duration of pain free strenuous exertion.

Crowley et al. [20] investigated the safety and efficacy of UC-2 in knee OA patients. The inclusion criteria included females and males 40–75 years old, knee OA on radiographs symptomatic for more than 3 months, moderate OA as indicated by LFI score. The exclusion criteria included history of inflammatory arthropathy, gout, joint fracture, septic arthritis, injury in the knee, scheduled surgery in the next 4 months, severe OA per LFI score, corticosteroid injection(s) in last 3 months, viscosupplementation in last 6 months. The outcome measures included WOMAC, VAS, LFI, knee flexion, time to climb 10 steps and walk 50 m. The patients were followed at baseline and at days 30, 60 and 90. 52 subjects were enrolled in the study and randomized into two groups—UC-2 (40 mg/day, $n=26$) and GH + CS ($n=26$). The UC-2 treated group demonstrated significant improvement in pain and difficulty when walking on flat surface, ascending stairs, and performing heavy domestic duties compared to GH + CS group. In addition, treatment with UC-2 led to significant improvement in WOMAC score compared to baseline at all follow-up time points and was also more effective compared to the GH + CS group. For the VAS score, the UC-2 group was significantly better in terms of resting and night pain, and pain while climbing up and down stairs at 60 and 90 days, respectively, compared to the GH + CS group. UC-2 group also showed a significant decline in total VAS scores at 60 and 90 days follow-up compared to baseline. Additionally, UC-2 treatment showed significant improvement in the LFI score compared to baseline and was more effective compared to the GH + CS group. Safety outcomes were similar for both groups. UC-2 supplementation resulted in improvement in daily activities, thereby improving the overall QoL of knee OA patients.

Santana et al. [21] in a blinded randomized controlled trial investigated the efficacy of UC-2 compared to exercise therapy on function and QoL of women with knee OA. The inclusion criteria included females aged 40–80 years old, diagnosis of symptomatic primary non-inflammatory grades 2–4, no history of prior knee surgery, no treatment of knee OA in the last 6 months, and no history of continuous chronic use of NSAIDs. The exclusion criteria included inability to carry out assessments or follow the exercise protocol, presence of pain or functional limitation in any other segment that was higher than knee pain and missing two sessions in a row. The outcome measures included WOMAC, Tampa scale for kinesiophobia (ETC), ROM, 6-MWT and Timed up and go (TUG) test. The patients were assessed at baseline and at 6 weeks. 39 patients completed the study ($n=13$ per group), and were randomized into three groups: exercise group (EG), medication group (MG) (UC-2) and control group (CG). Both EG and MG groups showed significant improvements in the 6-MWT, TUG test and ROM compared to the CG and at 6 weeks follow-up compared to the baseline; however, no differences were observed between the EG and MG groups. For WOMAC total score, all groups showed significant improvement at 6 weeks follow-up compared to the baseline. For WOMAC pain subscale, both EG and MG showed significant improvement compared to the CG. For WOMAC stiffness subscale, only the EG group showed significant improvement compared to the CG. No inter- or intra-group differences were observed for ETC. Administration of UC-2 led to similar effects as the exercise group in terms of improving function, whereas the exercise group was slightly superior in terms of improving quality of life score.

The results from aforementioned clinical studies are summarized in Table 2.

**Table 2.** Summary of results of included clinical studies.

| Author [Reference] | Main findings |
|---|---|
| Luo et al. [14] | Administration of undenatured type II collagen (UC-2) is safe and led to significant improvements in Western Ontario and McMaster Universities Arthritis Index (WOMAC) total and subscale scores, and quality of life (QoL) compared to the placebo group at 12 weeks follow-up. |
| Sadigursky et al. [15] | Administration of UC-2 led to significant improvements in Visual Analogue Scale (VAS) score, WOMAC total score and physical function of 12-item Short Form survey (SF-12) compared to the baseline and control group at 90 days follow-up. |
| Shiojima et al. [16] | Administration of UC-2 is safe and led to significant improvements in the flexion and flexible angles (passive range of motion (ROM)), VAS, Japan Knee Osteoarthritis Measure (JKOM), and 10-meter walking and stair-climbing test (motor functions) compared to the placebo group at 12 weeks follow-up. |
| Schön et al. [17] | Administration of UC-2 is safe and led to significant improvements in ROM flexion and extension compared to the placebo group at 24 weeks follow-up. |
| Rui et al. [12] | Administration of UC-2 led to significant improvements in WOMAC total and subscale scores, 6-minute walk test (6-MWT), and cadence, speed, knee flexion and abduction, and varus at initial contact compared to the baseline and the control group at 3 months follow-up. |
| Lugo et al. [18] | Administration of UC-2 led to significant improvements in WOMAC total and subscale scores, VAS score and Lequesne Functional Index (LFI) score compared to placebo and glucosamine hydrochloride (GH) + chondroitin sulfate (CS) at 180 days follow-up. |
| Lugo et al. [19] | Administration of UC-2 is safe and led to significantly higher knee extension, increase in time of start of initial pain in the joint, and improvement in joint pain compared to the placebo group at 120 days follow-up. |
| Crowley et al. [20] | Administration of UC-2 is safe and led to significant improvement in pain and difficulty when walking on flat surface, ascending stairs, performing heavy domestic duties, WOMAC score, resting and night pain, pain while climbing up and down stairs, total VAS score, and LFI score compared to the baseline and GH+CS group at 90 days follow-up. |
| Santana et al. [21] | Administration of UC-2 led to significant improvements in 6-MWT, timed up and go test, ROM and WOMAC pain score in both exercise and medication groups compared to the control group and at 6 weeks follow-up compared to the baseline. |

### *On-going clinical studies*

As of August 13, 2024, there are no on-going clinical trials registered on ClinicalTrials.gov, CTRI, or ChiCTR to study the safety and efficacy of UC-2 alone for the management of Knee OA.

## Discussion

This study highlighted the MOA of UC-2. UC-2 acts *via* a definite immune mediated mechanism, named oral tolerance, which ultimately leads to secretion of anti-inflammatory cytokines and simultaneous decrease in expression of pro-inflammatory cytokines, essential to reduce inflammation and enhance cartilage repair in the joint [4–8].

In addition, this review investigated the safety and efficacy of UC-2 for the management of knee OA. Pre-clinical, clinical and on-going studies focusing on the effect of UC-2 on knee OA were included. The pre-clinical studies showed the potential of UC-2 in reducing inflammation and pain, and improving function in different animal models [9,11–13]. Moreover, the results from clinical studies showed that administration of UC-2 is safe and efficacious in regard to decreasing pain, improving function, ROM and overall QoL of the patients with knee OA [12,14–21]. The results from these clinical studies are in accordance with a recently published systematic review and meta-analysis [22]. Briefly, Kumar et al. [22] included 8 randomized controlled trials (RCTs), involving 243 patients (91 males and 152 females), who received UC-2 for knee OA. The mean age ranged from $53.5 \pm 0.99$ to $68.7 \pm 5.3$ years. The BMI ranged from $22.6 \pm 1.8$ to $30.20 \pm 5.27$ kg/m$^2$. The average follow-up duration was 3–6 months. The KL scale grade distribution was 20 patients in grade I, 104 patients in grade II, and 70 patients in grade III. In most trials, patients received a daily dose of 40 mg of UC-2. The results from RCTs demonstrated significant reduction in the VAS score and WOMAC total and subscales in UC-2 group compared to baseline, and GH + CS and placebo/control groups at 3 and/or 6 months follow-up. In addition, walking improvements measured *via* Timed Up and Go (TUG) test and 6-MWT, demonstrated significant improvements for the UC-2 group compared to the baseline. The results of the present investigation and those of Kumar et al. [22] are also in agreement with an earlier systematic review and meta-analysis by Liu et al. [23], which reported statistically significant improvement in pain for the UC-2 group compared to the placebo/control groups at short- and medium-term. Liu et al. [23] also reported statistically significant improvements in physical function and stiffness for the UC-2 group compared to the placebo/control group in the short-term. No on-going clinical trials are registered on any clinical trial protocol registries.

### *Limitations and future studies*

The studies included in the present investigation are not without shortcomings, including small cohort size, short follow-up, and lack of studies comparing the effectiveness of UC-2 to commonly used interventions for the management of knee OA, such as corticosteroids, viscosupplementation, autologous peripheral blood-derived orthobiologics, orthobiologics derived

from autologous sources, and formulations derived from perinatal tissues [1–3,24,25]. In addition, the risk for publication bias remains, as studies with positive outcomes are more likely to be published, possibly resulting in incomplete representation of the overall efficacy of UC-2 for the management of knee OA.

Thus, more adequately powered, prospective, multicenter, non-randomized and randomized controlled trials with longer follow-up are warranted to establish the long-term efficacy of UC-2 in the management of knee OA and justify its regular clinical use. In addition, more studies assessing the effectiveness of UC-2 compared to other commonly used interventions are necessary to aid clinicians in determining the most optimal treatments for managing knee OA.

## Conclusions

In summary, UC-2 acts *via* a definite immune mediated mechanism, named oral tolerance, which can lead to reduced inflammation and some articular cartilage repair in the knee joint. In addition, administration of UC-2 is safe and efficacious in the short- and mid-term, reducing inflammation and pain, and improving function, ROM and overall QoL.

## Ethics approval and consent to participate

Not applicable.

## Consent for publication

Not applicable.

## Authors contributions

AG conceptualized the study and wrote the initial draft. AG and NM revised it critically for intellectual content, approved the final version to be published, and agreed to be accountable for all aspects of the work.

## Disclosure statement

The authors report no conflict of interest.

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## Data availability statement

The data supporting the findings of this study is available from the corresponding author upon reasonable request.

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