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Clinical effectiveness and tolerability of UC-II, sodium hyaluronate, and curcumin in osteoarthritis of the knee – CAPE Study: A multicentre, Prospective, real-world evidence study

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Abstract
Background: Osteoarthritis (OA) is a degenerative joint disease that results in the breakdown of cartilage, causing pain, stiffness, and decreased range of motion in the affected joints. It is a common form of arthritis, particularly in older adults. Undenatured type II collagen (UC-II) is a nutritional supplement which has been found to be effective in treating OA.
Objective: To determine the efficacy and safety of UC-II, sodium hyaluronate, and curcumin in treating knee OA.
Materials and Methods: 813 patients with knee OA were enrolled in the study. Subjects received a capsule containing 40 mg UC-II, 80 mg sodium hyaluronate and 200 mg curcumin once daily for three months. The Western Ontario and McMaster Osteoarthritis Index (WOMAC) evaluated pain, joint stiffness, and physical functions. A Visual Analog Scale (VAS) was used to assess the severity of the initial pain. Moreover, clinical symptom scores and patient and physician global assessments were evaluated. The patients were assessed before the treatment and three months after the initiation of the treatment.
Results: The WOMAC scores for pain, stiffness, and function, as well as the VAS score, were significantly improved (P< 0.05) in subjects after three months compared to the baseline. There was a 73.51% improvement in the total WOMAC scores and a 69.92% improvement in the VAS scores. There was a significant reduction in clinical symptoms, and global assessments of treatment by patients and physicians based on overall efficacy were favourable after the three-month treatment.
Conclusion: The study showed that UC-II, sodium hyaluronate and curcumin in combination effectively improve the symptoms of OA and should be positively considered for the symptomatic management of OA.

Keywords: UC-II, collagen peptides, osteoarthritis, sodium hyaluronate, curcumin

Introduction
Osteoarthritis (OA) is a type of joint disease that causes the cartilage degradation - the protective tissue that covers the bones in a joint. Cartilage is a smooth, slippery tissue that allows easy movement and helps absorb shock. In OA, the cartilage becomes damaged and loses its elasticity, leading to inflammation, pain, and stiffness [1]. Osteoarthritis becomes more common with age, and after age 50, more women than men are affected. In mild to moderate OA, pain and stiffness dominate the other symptoms [2]. Treatment should therefore focus on reducing pain and stiffness and maintaining and improving functional capacities. Furthermore, prevention of the progression of joint damage and improvement of quality of life are long-term goals. Oral treatments for patients with mild to moderate OA pain include paracetamol, diclofenac, and other NSAIDs. NSAIDs are effective in OA patients [3]. Although these drugs effectively reduce pain associated with OA, they do not reverse the disease, and they have considerable side effects associated with using these drugs [4].

UC-II, a newly discovered unique nutraceutical ingredient, has drawn significant attention in the management of OA. Undenatured type II collagen UC-II is made from chicken sternum cartilage [5]. Earlier research has demonstrated that undenatured type II collagen in its natural state is effective in managing Rheumatoid Arthritis (RA), and early human and animal studies have indicated its efficacy in treating OA. Animal studies have shown that UC-II stimulates specific regulatory T cells (Tregs) in the gut. These Tregs respond to stimulation by migrating to and gathering in areas of inflammation, where they control local immune responses in a specific, targeted manner [6, 7]. The UC-II supplementation slightly improved cartilage microstructure, degeneration, and surface organisation in OA. UC-II suppresses inflammatory factors related to the NF-κB signalling pathway and inflammatory mediators such as COX-2 and PGE2. UC-II decreases levels of IRF-7 and MCP-1 in OA due to its ability to modulate the immune system. Furthermore, UC-II supplementation effectively lowers the activation of the NF-κB dependent MMP3 pathway and RANKL [8, 9].

Hyaluronic acid (also known as hyaluronan or sodium hyaluronate) is found in synovial fluid and the extracellular matrix of cartilage, which provides synovial fluid's viscoelastic and lubricating properties. When given orally, it has been shown to demonstrate anti-inflammatory action and improve symptoms of knee OA in the same manner as glucosamine [10, 11]. Another potent anti-inflammatory and antioxidant agent that has strong evidence in the treatment of OA is curcumin. In clinical studies, curcumin, an NF-κB suppressor, effectively reduces pain, physical function, and quality of life among OA patients. The effects of curcumin on OA can be attributed to its ability to prevent apoptosis of chondrocytes due to inflammation predominantly and oxidative stress to a lesser extent [12, 13]. Given these observations and results, the present study aims to assess the effectiveness of a combination of UC-II, sodium hyaluronate, and curcumin in subjects with knee OA.

Methods

Study Design

The CAPE study was designed as a multicentre, Prospective, real-world evidence study involving volunteers with OA of the knee. The Suraksha Institutional Ethics Committee approved the study protocol and related materials in compliance with ICMR (Indian Council of Medical Research), New Drugs and Clinical Trials Rules, 2019, ICH GCP, and the declaration of Helsinki. Before the start of the study, written consent was obtained from all participants.

Setting and participants

813 Patients aged between 19 to 75 years with the clinical diagnosis of osteoarthritis of the knee based on the American College of Rheumatology (ACR) criteria and at least moderate pain in the knee (rated at five or greater by the subject on a visual analog scale) during the most painful knee movement during the last month and inadequately controlled with NSAIDs were recruited for the study. Patients with uncontrolled diabetes, hypertension, hepatic disorder, pregnant & lactating women, and acute joint trauma of the knee were excluded from the study.

Study intervention

During the study, the enrolled subjects were instructed to orally take the capsule containing undenatured collagen type II – 40 mg, sodium hyaluronate – 80 mg and curcumin – 200 mg once daily for three months. Universal NutriScience Pvt Ltd, Mumbai, marketed the formulation. Patients were advised not to consume other ayurvedic, herbal, and homoeopathic treatments during the study period. The record of concomitant medication was maintained during the study.

Outcome measures

The primary objective was to evaluate the OA symptoms, Western Ontario and McMaster Universities (WOMAC) score, and pain during the study. Pain on palpation, limited mobility, joint crepitus, oedema, and redness were all graded on a 4-point scale (0 = not at all, 1 = mild, 2 = moderate, 3 = severe). The WOMAC osteoarthritis index was used to quantify the severity of osteoarthritis symptoms, with a higher WOMAC score indicating more severe symptoms. The subjects rated their discomfort on a 10-mm visual analog scale (VAS). The WOMAC, pain, and OA symptoms were evaluated on days 0, 30, 60, and 90. On day 90, the patient's global and physician's global assessments were evaluated.

Statistical Analysis

A primary database was created in validated Microsoft Excel spreadsheets while processing registration forms received from the study sites. The data were analysed using Wilcoxon Signed Rank Test. P-values < 0.05 were considered statistically significant. The final manuscript described and substantiated all deviations from the final version of the statistical analysis plan.

Results

Patient demographics

A total of 813 patients were enrolled during the study based on inclusion and exclusion criteria, comprising 408 (50.2%) males and 405 (49.8%) females. The mean age of subjects was 56.47 years. All the subjects selected during the study received one capsule daily for three months. Intake of concomitant medication was observed in 168 patients (20.7%).

WOMAC Score

There was a significant improvement ($P< 0.05$) in the WOMAC scores for pain, stiffness, difficulty, and total WOMAC score at the end of three months (day 90) when compared to baseline (day 0). At the baseline, the mean WOMAC score for pain was 14.34 ± 3.90, which improved significantly to 3.78 ± 3.16 ($P< 0.05$) after three months, and the percent improvement for pain was 73.64%. The mean WOMAC score for stiffness was 5.13 ± 2.13 at the baseline, which improved significantly to 1.18 ± 1.25 ($P< 0.05$) after three months, and the percent improvement for stiffness was 76.99%. The mean WOMAC score for difficulty was 45.49 ± 13.82 at the baseline, which improved significantly to 12.17 ± 9.28 ($P< 0.05$) after three months, with a percent improvement of 73.24%. At the baseline, the mean WOMAC combined (total) score was 64.86 ± 17.91, whereas it significantly improved to 17.18 ± 12.82 ($P< 0.05$) after three months, with a percent improvement of 73.51% as depicted in Figure 1 and table 1.

Clinical Symptom Scores

Symptoms of OA, such as pain on palpation, limitation of mobility, joint crepitus, swelling and redness, improved significantly ($p< 0.05$) in the patients after the three-month treatment. There was a significant reduction in pain on palpitation (79.10%), limitation of mobility (77.05%), joint

crepitus (73.54%), swelling (86.43%), and redness (84.78%), as shown in figure 2 and table 1.

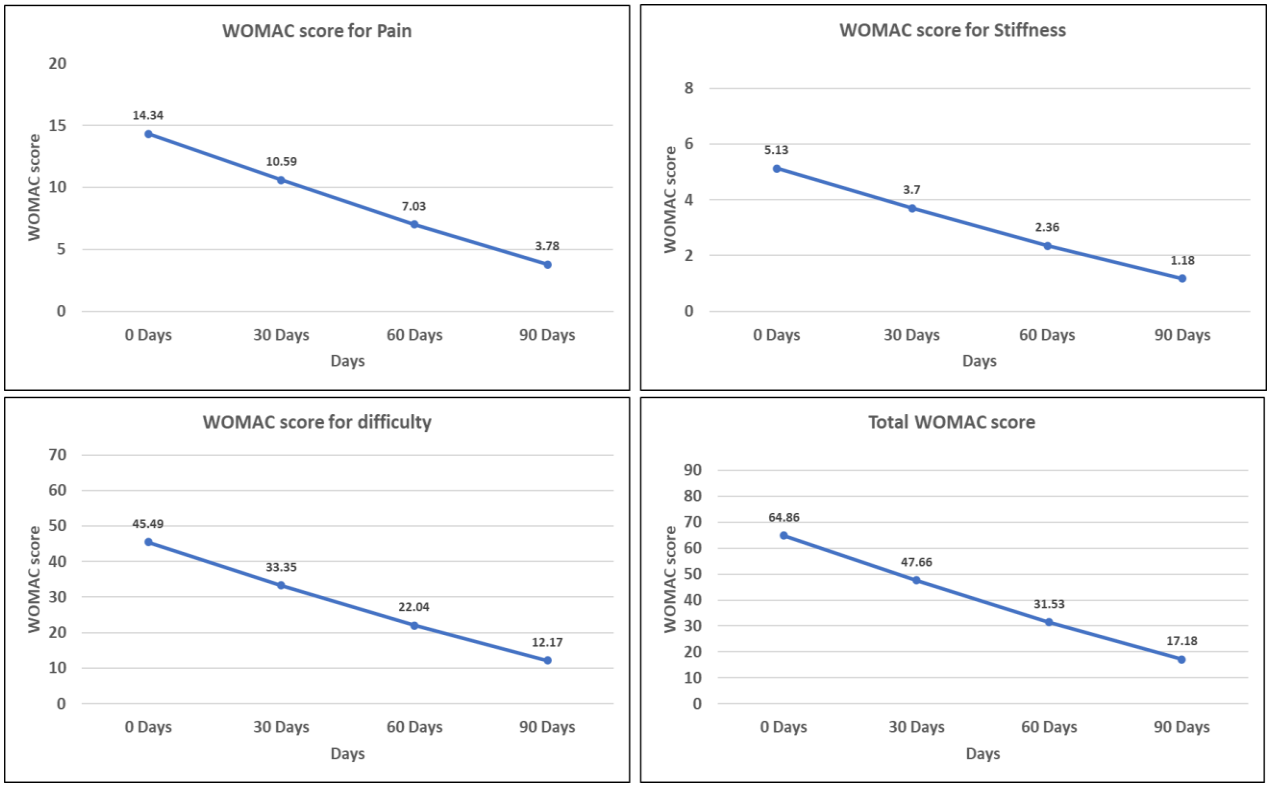


Fig 1: Change in WOMAC scores during the treatment

VAS score

There was a significant improvement ($p< 0.05$) in the VAS scores for pain at the end of three months (day 90) when compared to baseline (day 0). At the baseline, the mean VAS score was 8.16 ± 2.14, which improved significantly to 2.45 ± 1.47 ($p< 0.05$) after three months, with a percent improvement of 69.92%, as depicted in figure 3 and table 1.

Table 1: Outcome measures at baseline and after 90 days of treatment

Parameters	Day 0	Day 90	% Improvement
Pain on Palpitation	2.77 ± 0.58	0.57 ± 0.69	79.10%
Limitation of Mobility	2.56 ± 0.64	0.58 ± 0.62	77.05%
Joint Crepitus	2.41 ± 0.81	0.63 ± 1.05	73.54%
Swelling	2.31 ± 0.85	0.31 ± 0.57	86.43%
Redness	1.41 ± 1.19	0.21 ± 0.45	84.78%
Total WOMAC score	64.86 + 17.91	17.18 ± 12.82	73.51%
VAS score	8.16 ± 2.14	2.45 ± 1.47	69.92%

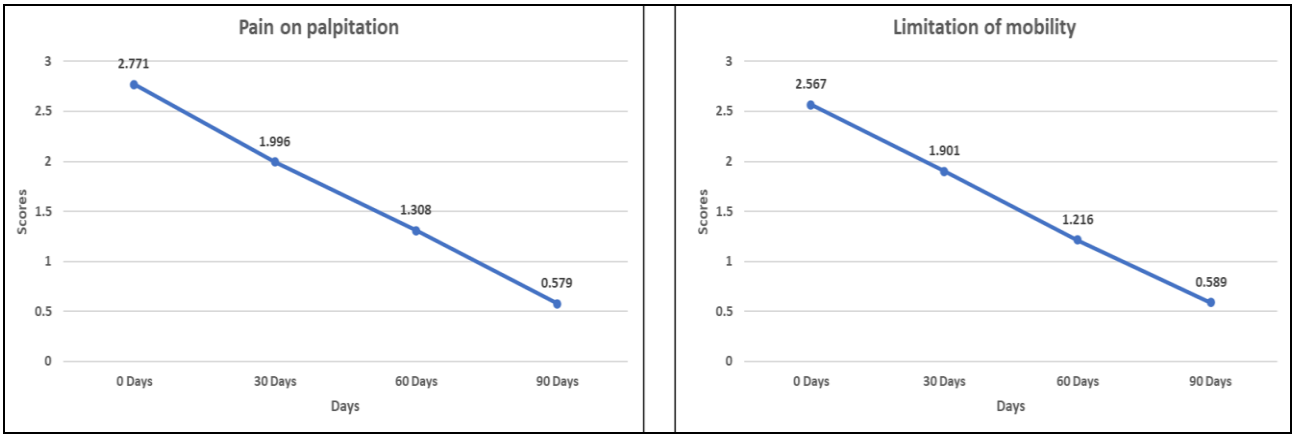
Moreover, global assessments of treatment by patients and physicians based on overall efficacy were favourable after the three-month treatment. A more significant proportion of patients (65.19%), whereas 66.30% of physicians, rated the treatment very satisfactory (Table 2).

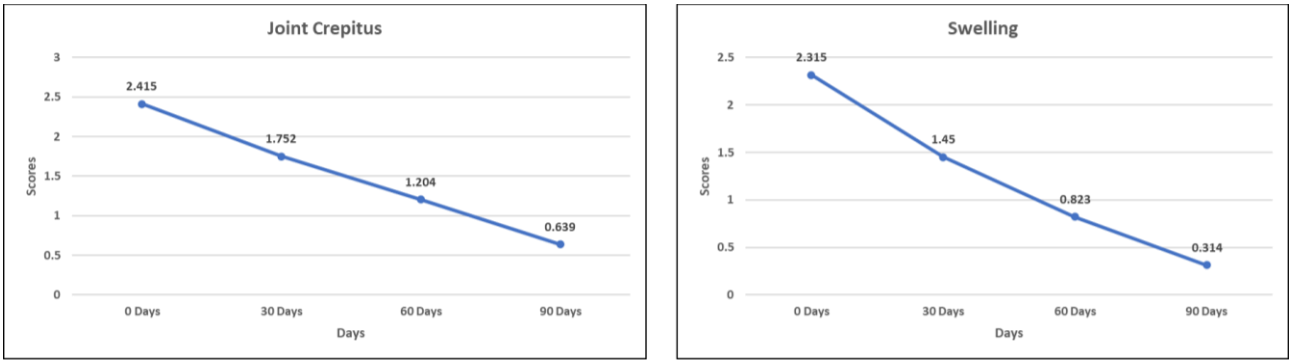
Table 2: Global assessment by physicians and patients after three-month treatment.

Global Assessment Rating	Physician's global assessment	Patient's global assessment
Very satisfactory	66.30%	65.19%
Moderately satisfactory	31.61%	32.23%
Minimally satisfactory	1.72%	2.21%
Not satisfactory	0.37%	0.37%

Safety

There were no significant adverse events observed in the patients during the study.





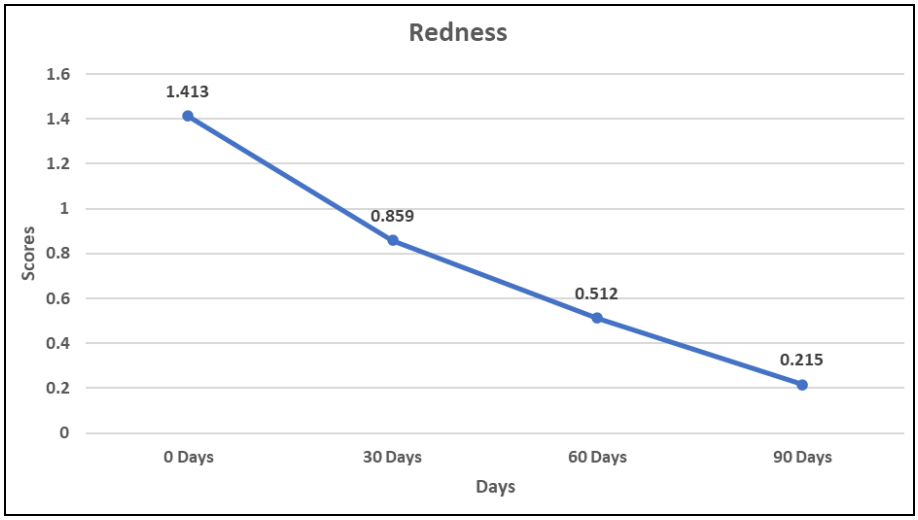


Fig 2: Change in clinical assessment scores of OA symptoms.

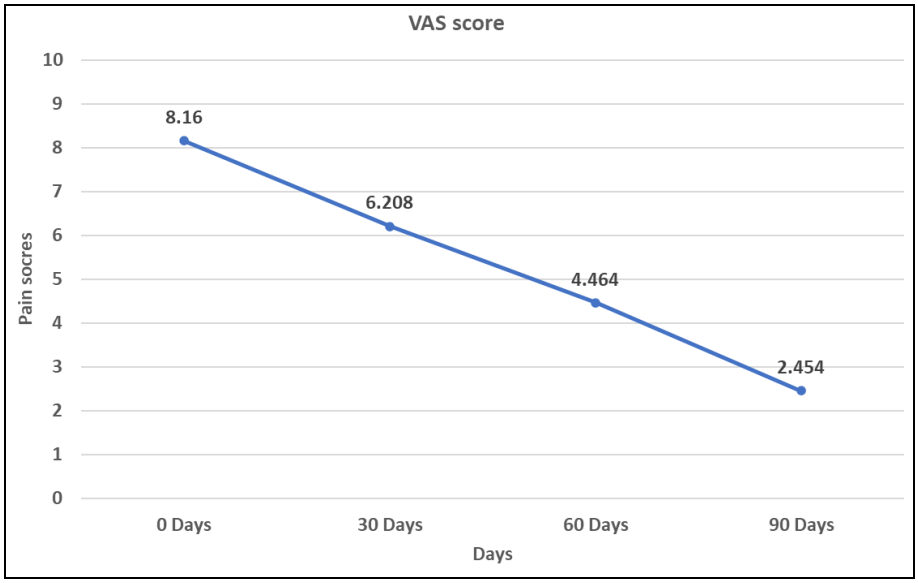


Fig 3: Change in VAS scores during the treatment.

Discussion

OA is the most widespread arthritis, often resulting in substantial disability and decreased quality of life [14]. This multicentre, prospective, real-world evidence study investigated the effectiveness of UC-II, sodium hyaluronate and curcumin for three months in the treatment of OA. There was a significant improvement in the WOMAC scores, clinical symptoms, VAS scores for pain, and the patient's global and physician's global assessments. The results obtained in the current study align with similar published studies in OA patients treated with UC-II, hyaluronic acid and curcumin. Earlier studies have shown that UC-II can effectively treat RA, and preliminary human and animal trials have indicated its potential in treating OA. A study by Crowley *et al*. demonstrated that 40 mg of UC-II reduced the WOMAC score by 33%, with a similar reduction in the VAS scores by 40% after three months. Moreover, the UC-II-treated subjects significantly enhanced their daily activities and quality of life [5]. Another multicenter randomised, double-blind, placebo-controlled study conducted by Lugo *et al*. showed a significant reduction in the overall WOMAC scores (P=0.002), including significant changes for all three WOMAC subscales, pain (P=0.0003), stiffness (P=0.004), and physical function (P=0.007), as well as a significant

decrease in VAS scores (P=0.002) for the group receiving 40 mg UC-II after six months [15].

Furthermore, UC-II collagen has been shown to protect against joint damage in animal models of experimentally-induced OA and RA. A study conducted by Kalman *et al*. demonstrated that subjects who received 80 mg hyaluronic acid orally for eight weeks showed statistically significant improvements in WOMAC pain (P=0.012), stiffness (P=0.092), physical function subscales (P=0.018) and total symptoms (P=0.694) in OA of the knee [16]. Curcumin at various doses has effectively improved WOMAC subscales, total scores, VAS scores, and clinical symptoms (joint tenderness, crepitation, effusion, and limitation to movement) in patients with OA [13] Type II collagen extracts contain the amino acids in human cartilage structure. These amino acids are also necessary for synthesising and repairing connective tissue in the body [17]. The combination of UC-II, sodium hyaluronate, and curcumin helps reduce the destruction of collagen within the body, acts as a chondroprotective and provides anti-inflammatory action, which helps improve pain, stiffness, and function of the knee affected with OA.

Conclusion

In conclusion, the CAPE study showed that UC-II, sodium hyaluronate and curcumin in combination effectively improve the symptoms of OA, including pain, stiffness and physical function in OA of the knee, and was well-tolerated. Supplementation with this therapy showed improvement in daily activities, suggesting an improvement in the overall quality of life in the patients with OA. Based on the data presented herein, this combination should be positively considered for the symptomatic management of OA.

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Conflict of interest: The authors declare no conflict of interest.

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References

1. Bijlsma JWJ, Berenbaum F, Lafeber FPJG. Osteoarthritis: an update with relevance for clinical practice. Lancet [Internet]. 2011 [cited 2023 Jan 28];377(9783):2115-26. Available from: https://pubmed.ncbi.nlm.nih.gov/21684382/
2. Zhang Y, Jordan JM. Epidemiology of Osteoarthritis. Clin Geriatr Med [Internet]. 2010 Aug [Cited 2023 Jan 28];26(3):355. Available from: PMC/articles/PMC2920533/
3. Courtney P, Doherty M. Key questions concerning paracetamol and NSAIDs for osteoarthritis. Ann Rheum Dis [Internet]. 2002 Sep 1 [cited 2023 Jan 28];61(9):767–73. Available from: https://ard.bmj.com/content/61/9/767
4. Yu SP, Hunter DJ. Managing osteoarthritis. Aust Prescr [Internet]. 2015 Aug 1 [cited 2023 Jan 28];38(4):115. Available from: PMC/articles/PMC4653978/
5. Crowley DC, Lau FC, Sharma P, Evans M, Guthrie N, Bagchi M, *et al*. Safety and efficacy of undenatured type II collagen in the treatment of osteoarthritis of the knee: a clinical trial. Int J Med Sci [Internet]. 2009 Oct 9 [cited 2023 Jan 27];6(6):312-21. Available from: https://pubmed.ncbi.nlm.nih.gov/19847319/
6. Bagi CM, Berryman ER, Teo S, Lane NE. Oral administration of undenatured native chicken type II collagen (UC-II) diminished deterioration of articular cartilage in a rat model of osteoarthritis (OA). Osteoarthritis Cartilage. 2017 Dec 1;25(12):2080-90.
7. Asnagli H, Martire D, Belmonte N, Quentin J, Bastian H, Boucard-Jourdin M, *et al*. Type 1 regulatory T cells specific for collagen type II as an efficient cell-based therapy in arthritis. Arthritis Res Ther [Internet]. 2014 May 22 [Cited 2023 Jan 27];16(3):1-12. Available from: https://arthritis-research.biomedcentral.com/articles/10.1186/ar4567
8. Orhan C, Juturu V, Sahin E, Tuzcu M, Ozercan IH, Durmus AS, *et al*. Undenatured Type II Collagen Ameliorates Inflammatory Responses and Articular Cartilage Damage in the Rat Model of Osteoarthritis. Front Vet Sci. 2021 Mar 4;8:86.
9. Tong T, Zhao W, Wu YQ, Chang Y, Wang QT, Zhang LL, *et al*. Chicken type II collagen induced immune balance of main subtype of helper T cells in mesenteric lymph node lymphocytes in rats with collagen-induced arthritis. Inflamm Res [Internet]. 2010 May [cited 2023 Jan 27];59(5):369-77. Available from: https://pubmed.ncbi.nlm.nih.gov/19862478/
10. Punzi L, Schiavon F, Cavasin F, Ramonda R, Gambari PF, Todesco S. The influence of intra-articular hyaluronic acid on PGE2 and cAMP of synovial fluid. Clin Exp Rheumatol [Internet]. 1989 May 1 [cited 2023 Jan 27];7(3):247–50. Available from: https://europepmc.org/article/med/2547540
11. Tashiro T, Seino S, Sato T, Matsuoka R, Masuda Y, Fukui N. Oral administration of polymer hyaluronic acid alleviates symptoms of knee osteoarthritis: A double-blind, placebo-controlled study over a 12-month period. The Scientific World Journal; c2012.
12. Henrotin Y, Priem F, Mobasheri A. Curcumin: A new paradigm and therapeutic opportunity for the treatment of osteoarthritis: Curcumin for osteoarthritis management. Springerplus [Internet]. 2013 Feb 18 [cited 2023 Jan 27];2(1):1–9. Available from: https://link.springer.com/articles/10.1186/2193-1801-2-56
13. Chin KY. The spice for joint inflammation: anti-inflammatory role of curcumin in treating osteoarthritis. Drug Des Devel Ther [Internet]. 2016 Sep 20 [cited 2023 Jan 27];10:3029. Available from: PMC/articles/PMC5036591/
14. Heidari B. Knee osteoarthritis prevalence, risk factors, pathogenesis and features: Part I. Caspian J Intern Med [Internet]. 2011 Mar [Cited 2023 Jan 28];2(2):205. Available from: PMC/articles/PMC3766936/
15. Lugo JP, Saiyed ZM, Lane NE. Efficacy and tolerability of an undenatured type II collagen supplement in modulating knee osteoarthritis symptoms: a multicenter randomized, double-blind, placebo-controlled study. Nutr J [Internet]. 2016 Jan 29 [cited 2023 Jan 27];15(1). Available from: https://pubmed.ncbi.nlm.nih.gov/26822714/
16. Kalman DS, Heimer M, Valdeon A, Schwartz H, Sheldon E. Effect of a natural extract of chicken combs with a high content of hyaluronic acid (Hyal-Joint®) on pain relief and quality of life in subjects with knee osteoarthritis: A pilot randomized double-blind placebo-

controlled trial. Nutr J [Internet]. 2008 Jan 21 [cited 2023 Jan 27];7(1):1-9. Available from: https://nutritionj.biomedcentral.com/articles/10.1186/1475-2891-7-3
17. Wu M, Cronin K, Crane JS. Biochemistry, Collagen Synthesis. StatPearls [Internet]. 2022 Sep 12 [Cited 2023 Jan 28]; Available from: https://www.ncbi.nlm.nih.gov/books/NBK507709

Appendix

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