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A 12-Week Multi-Ingredient Joint Health Supplement Alleviates Activity-Related Knee Discomfort and Improves Pain-Limited Load Tolerance in Endurance-Trained Adults: A Pilot Randomized, Double-Blind, Placebo-Controlled Trial

Wentao Gu [1,2,†], Zhenhua Niu [3,†], Qisijing Liu [1,2,†], Haitao Wang [1,2], Miao Yu [1,2], Meiying Xu [1,2], Xuemeng Ji [1,2], Dancai Fan [1,2], Jin Wang [1,2], Yanrong Zhao [3,*] and Shuo Wang [1,2,*]

[1] Tianjin Key Laboratory of Food Science and Health, School of Medicine, Nankai University, Tianjin 300350, China
[2] Research Institute of Public Health, Nankai University, Tianjin 300350, China
[3] Nankai University MACTION Joint Laboratory of Nutrition Research, Tianjin 300350, China
* Correspondence: zhaoyanrong@mengniu.cn (Y.Z.); wangshuo@nankai.edu.cn (S.W.); Tel.: +86-22-8535-8445 (S.W.)
† These authors contributed equally to this work.

Abstract

Background: Activity-related knee discomfort is common in endurance-trained adults. Multi-ingredient supplements targeting complementary biological pathways may support knee comfort and load tolerance in this population, but controlled evidence is limited. Methods: In this randomized, double-blind, placebo- and active-comparator-controlled pilot trial, 60 endurance-trained adults (20 per group) with activity-related knee discomfort received for 12 weeks either a multi-ingredient formula (undenatured type II collagen, curcumin phytosome, and enzymatically hydrolyzed bone powder; Group A), glucosamine hydrochloride plus chondroitin sulfate (Group B), or placebo (Group C). Assessments of functional and patient-reported outcomes were conducted at baseline, week 6, week 12, and 24 h after a post-intervention half-marathon challenge. Outcome measures covered functional pain tolerance, patient-reported pain symptoms, exploratory biomarkers of cartilage turnover, inflammation, and oxidative stress. Results: Group-by-time interactions were significant for SLSD repetitions to pain levels 2 and 5 and for VAS (all $p < 0.0001$). At week 12, Group A exceeded placebo for the SLSD repetitions to pain level 5 (mean difference 30.5 repetitions; 95% CI 8.7 to 52.3; $p = 0.0201$), for SLSD repetitions to pain level 2 (21.4; 8.8 to 34.1; $p = 0.0037$), and for VAS (−1.6; −2.6 to −0.7; $p = 0.0030$), whereas Group B differed from placebo for SLSD pain level 2 and VAS but not for the SLSD pain level 5. No direct comparison between Groups A and B was statistically significant (all adjusted $p > 0.05$). After the half-marathon, only Groups B and C showed significant within-group declines in ROM relative to baseline ($p = 0.0262$ and $p = 0.0147$), whereas Group A did not ($p > 0.99$), although between-group ROM contrasts were not significant. Biomarker changes were exploratory, and no between-group biomarker difference reached significance. Conclusions: In this pilot trial, 12 weeks of multi-ingredient supplementation improved pain-limited knee load tolerance and self-reported knee pain relative to placebo in endurance-trained adults. These results require confirmation in a larger trial.

Keywords: knee discomfort; knee load tolerance; endurance exercise; multi-ingredient supplement; randomized controlled trial

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1. Introduction

Knee discomfort during or after endurance exercise is one of the most common musculoskeletal complaints among recreational and competitive endurance athletes. Unlike radiographic knee osteoarthritis (OA), which is characterized by progressive structural degeneration and persistent resting symptoms, exercise-related knee discomfort in otherwise healthy individuals is typically intermittent, load-dependent, and functionally reversible [1–3]. Despite its transient nature, recurrent load-induced discomfort often leads to reduced training volume, interrupted training consistency, and compensatory movement strategies that further elevate the risk of secondary overuse injury and early-onset joint degeneration [4–6].

Critically, this clinical phenotype has been proposed to occupy a transitional window between physiological adaptation and early joint dysfunction [7]. Current research and clinical practice predominantly focus on symptomatic treatment of established OA, while evidence for early, non-pharmacological interventions targeting pre-clinical activity-related discomfort remains limited. From a functional perspective, the core demand for active populations is not merely pain relief at rest, but enhanced knee load tolerance. In this study, "knee pain-limited load tolerance" is used as an operational working construct—defined as the knee's ability to withstand repetitive high-intensity mechanical loading while keeping pain manageable: (i) tolerating repeated loading before functionally limiting pain (high-threshold pain tolerance), (ii) preserving function and range of motion under acute high-load conditions, and (iii) recovering efficiently after strenuous endurance exertion [2,8–10].

Whether the knee remains resilient under such loading ultimately depends on the balance between the mechanical stress imposed and the joint's endogenous adaptive and recovery capacity. Endurance exercise imposes repetitive cyclic loading, shear stress, and impact forces on the knee joint, triggering transient inflammatory responses, oxidative stress, and accelerated cartilage matrix turnover [11–13]. Physiological loading is essential for maintaining cartilage homeostasis and promoting adaptive remodeling; however, an imbalance between mechanical stress and endogenous recovery capacity disrupts cartilage matrix equilibrium, alters subchondral bone signaling, and heightens nociceptive sensitivity, ultimately manifesting as activity-related discomfort [14,15]. Given this multifactorial pathophysiology, functional assessments that directly challenge load-bearing capacity—such as the single-leg step-down (SLSD) test and post-exercise functional evaluation—are more sensitive than resting measures for detecting early joint impairment and evaluating intervention efficacy in active populations [16,17].

The multifactorial nature of this pathophysiology suggests that single-pathway interventions may be insufficient; accordingly, nutritional intervention has emerged as a promising non-pharmacological strategy for supporting joint health in active populations. Traditional single-agent supplements, such as glucosamine and chondroitin, target cartilage matrix synthesis alone, but clinical evidence for their efficacy in active, OA populations remains heterogeneous and inconsistent [18,19]. This variability underscores the limitations of single-pathway interventions and highlights the potential advantage of multi-ingredient formulations that act on complementary biological mechanisms. A rational multi-target strategy that simultaneously addresses cartilage homeostasis, inflammatory regulation, oxidative defense, and tissue repair may deliver more comprehensive benefits for improving knee pain-limited load tolerance. Three bioactive ingredients with distinct mechanisms form the basis of the multi-ingredient formula evaluated in this study. First, undenatured type II collagen acts via oral immune tolerance, inducing regulatory T-cell responses that attenuate cartilage-specific autoimmune inflammation and support long-term cartilage matrix homeostasis [20,21]. Clinical trials have demonstrated that undenatured type II collagen improves joint comfort, flexibility, and pain-free exertion in both OA patients and healthy

active adults [22,23]. Second, curcumin phytosome (a bioavailability-enhanced curcumin extract) exerts pleiotropic anti-inflammatory and antioxidant effects by modulating NF-κB and Nrf2 signaling pathways, thereby buffering acute exercise-induced inflammatory flares and oxidative stress [24–27]. Third, enzymatically hydrolyzed bone powder serves as a natural source of chondroitin sulfate, a core structural component of the articular cartilage extracellular matrix. It participates in glycosaminoglycan synthesis, maintains cartilage elasticity and mechanical buffering capacity, and supports structural remodeling and repair of connective tissue. Together, these three components target chronic cartilage homeostasis, acute inflammatory and oxidative stress, and structural tissue repair, respectively, with the potential to form a complementary three-pathway framework to enhance knee pain-limited load tolerance.

Accordingly, the present study conducted a 12-week randomized, double-blind, placebo- and active-comparator-controlled pilot trial in endurance-trained adults with activity-related knee discomfort, combined with a post-intervention half-marathon acute loading challenge. The study aimed to test the hypothesis that the multi-ingredient formula would improve pain-limited knee load tolerance and self-reported knee comfort relative to placebo and would show a numerically broader pattern of benefit than the single-pathway active comparator, manifesting as enhanced high-threshold pain tolerance, preserved joint function under acute loading, and favorable modulation of exploratory cartilage turnover, inflammation, and oxidative stress biomarkers.

2. Materials and Methods

2.1. Study Design

This was a 12-week, randomized, double-blind, placebo- and active-comparator-controlled, parallel-group nutritional intervention trial with three arms. Participants were assessed at screening, baseline, week 6, week 12, and 24 h after a half-marathon challenge performed after the 12-week supplementation period. The trial was designed as a pilot to evaluate the effects of joint-health supplementation on knee discomfort in endurance-trained adults and assess feasibility for a future confirmatory trial.

2.2. Participants

Participants were adults aged 18–65 years with a body mass index of 18.5–30 kg/m^2 who reported at least three endurance exercise sessions per week for at least three months. Eligible exercise modalities included running, swimming, and cycling. Reversible knee discomfort was defined as intermittent knee discomfort occurring during or after endurance exercise for at least three months, triggered by load-bearing activity, and resolving at rest (no pain at rest, no nocturnal pain, and no morning stiffness lasting more than 30 min). In addition, participants were required to have a positive SLSD test, operationalized as a Likert pain score of 5 reached within 150 repetitions. The clinical diagnosis, symptom location (anterior, medial, or lateral knee), and symptom characteristics (load-dependent, non-inflammatory) were characterized at screening by medical history and physical examination. Participants were otherwise physically and mentally healthy and had no history, physical examination, or vital-sign abnormality that would interfere with the study. As a pilot trial, no exact sample size was calculated; the sample size of 20 participants per group was determined on feasibility grounds (recruitment capacity and the burden of the half-marathon protocol) and is broadly consistent with previous pilot randomized trials of joint-health supplements in physically active adults [23]. Effect-size estimates from this pilot will inform the sample size of a future confirmatory trial [28].

Exclusion criteria were: diagnosed knee osteoarthritis or clinical features suggestive of osteoarthritis, established on the basis of medical history; inflammatory or autoimmune

joint disease; recent knee surgery, trauma, or injection therapy within three months; acute musculoskeletal injury of the lower limb; severe knee injury history; recent use of non-steroidal anti-inflammatory drugs, glucocorticoids, or joint-health supplements; pregnancy or lactation; allergy to active or placebo ingredients; cardiovascular disease or relevant comorbidities; unwillingness to discontinue joint-specific analgesics; and vegetarianism.

All participants provided written informed consent prior to enrollment. The study was conducted in accordance with the Declaration of Helsinki and approved by the Nankai University Institutional Review Board (NKUIRB2025185, 3 November 2025). Participants were recruited between 7 November 2025 and 31 December 2025. The trial was registered with the Chinese Clinical Trial Registry (identifier ChiCTR2600126913). No changes were made to the registered primary or secondary outcomes or to the analysis plan after enrollment began.

2.3. Randomization and Blinding

Eligible participants were randomized in a 1:1:1 ratio to the three groups. The allocation sequence was generated with SAS 9.4 by an independent statistician who was not involved in participant enrollment or outcome assessment. Allocation was concealed using sequentially numbered, opaque, sealed envelopes. Participants were enrolled by study staff who had no access to the allocation sequence, and treatment assignment was revealed only after enrollment was complete. The active supplements and placebo were provided in sealed packages with similar appearance, size, shape, color and smell. Product blinding was implemented during production, and participants, investigators, and outcome assessors remained unaware of treatment allocation throughout the intervention; outcome assessors did not handle or dispense study products. This blinding strategy was intended to minimize expectation and measurement bias in outcome measures.

2.4. Interventions

Group A received the multi-ingredient joint-health product (MACTION Co. Ltd., Tianjin, China) as oral tablets. The daily dose comprised 250 mg curcumin phytosome (20% curcumin), 800 mg enzymatically hydrolyzed bone powder (≥60% chondroitin sulfate), and 40 mg cartilage powder containing type II collagen protein (≥4% undenatured type II collagen). The excipients were sorbitol and magnesium stearate. Group B received glucosamine hydrochloride 1500 mg/day and chondroitin sulfate 1200 mg/day. Group C received a matched placebo composed of maltodextrin. All interventions were taken orally as one daily dose with meals for 12 weeks. Participants were instructed to maintain their habitual dietary and exercise patterns. The study product was dispensed at each visit, and adherence was monitored by counting returned product and reviewing subject dosing diaries. Adherence was calculated as the percentage of prescribed doses consumed over the 12-week period (consumed doses/prescribed doses × 100%), and adherence of ≥80% was prespecified in the protocol as the compliance threshold. Adverse events were collected at each visit by open-ended questioning and review of subject diaries.

2.5. Outcome Measures

The primary outcome was the change in SLSD repetitions to pain level 5 from baseline to week 12, as this measure reflects high-threshold functional pain tolerance under repetitive knee loading [29]. Secondary outcomes included SLSD repetitions to pain level 2, knee range of motion (ROM), VAS pain, the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC; Likert version, 24 items scored 0–4, total score 0–96, higher scores indicating worse status [30]), and biochemical biomarkers. Exploratory outcomes included acute post-half-marathon changes in functional performance and biomarkers at 24 h post-exercise. Specifically, the SLSD test was performed as per the protocol described by

Juturu et al. [29] and Schön et al. [31]. In brief, participants stepped forward and down from a platform with adjustable height, which was set to the individual shank length divided by 2.3 (e.g., 20 cm for a 46 cm shank). Repetitions were performed at a metronome-paced interval of one step every 3 s, up to a maximum of 150 repetitions in the present trial. Each repetition comprised a forward step-down in which the stepping limb lightly brushed the floor with the heel and then returned to the platform to full knee extension, with the knee aligned over the foot and the trunk upright. Repetitions in which the participant lost balance, used the hands for support, or failed to brush the floor with the heel were not counted, and the test continued until the required number of valid repetitions was reached. Participants performed as many single-leg step-down repetitions as possible until they reported knee pain reaching level 2 (first onset of pain) and level 5 on an 11-point Likert scale, where 0 indicated "no pain" and 10 indicated "worst pain possible"; the number of repetitions to each level was documented. If pain level 5 was not reported by 150 repetitions, the test was terminated at 150 repetitions, and this value was recorded; by design, all enrolled participants reached pain level 5 within 150 repetitions at screening. The leg with the highest pain level after regular physical activity was defined as the target knee and was assessed at all visits. At the initial screening, the SLSD test was used to determine study eligibility, and the test was repeated at baseline and at each study visit. Pain level 2 was thus interpreted as the first clearly noticeable discomfort threshold and pain level 5 as the predetermined moderate pain threshold used to define eligibility and to terminate the test. ROM was measured as active knee flexion in supine with a goniometer by a blinded assessor. VAS pain reflected the average knee pain during physical activity over the past 7 days on a 0–10 scale (0 = no pain, 10 = worst imaginable pain). All participants who completed the 12-week intervention were eligible and expected to run a 21.1 km half-marathon at a self-selected pace. Participants' running history and prior experience with this distance were characterized by self-report at baseline. The completion of the half-marathon distance was verified by data recorded from each participant's sports watch (GPS tracking, recorded distance). Assessments were performed 24 h after finishing.

Biochemical outcomes were grouped into cartilage turnover or joint-tissue injury markers (cartilage oligomeric matrix protein (COMP) and C-terminal telopeptide of type II collagen (CTX-II)), inflammatory markers (high-sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α)), muscle-damage markers (creatine kinase (CK)), and oxidative-stress or antioxidant markers (malondialdehyde (MDA), superoxide dismutase (SOD)). All biochemical outcomes were assessed in serum/plasma and urine samples collected after an overnight fast and stored at −80 °C until analysis. Concentrations were measured with commercially available enzyme-linked immunosorbent assay (ELISA) kits (Shanghai Yuanju Biotechnology Center, Shanghai, China) according to the manufacturers' instructions, with all samples measured in duplicate. Biomarkers were assessed at baseline, week 12, and 24 h after the half-marathon.

The International Physical Activity Questionnaire (IPAQ) was used to monitor physical activity so that changes in knee discomfort could be interpreted in the context of relatively stable activity exposure rather than differential reductions in training load.

2.6. Statistical Analysis

Continuous data are expressed as mean ± standard deviation (SD) when describing the spread of individual observations. For comparisons of group means, data are expressed as mean ± standard error of the mean (SEM) to emphasize the precision of the mean estimates. Functional outcomes (SLSD repetitions to pain levels 2 and 5, ROM, VAS) were assessed at four occasions (baseline, week 6, week 12, and 24 h after the half-marathon); WOMAC at three occasions (baseline, week 6, week 12); and biomarkers at three occasions (baseline,

week 12, 24 h after the half-marathon). Between-group and longitudinal differences were analyzed using linear mixed-effects models with fixed effects for group, time, and group-by-time interaction and a random intercept per participant (implying a compound-symmetry correlation structure among repeated measures), fitted by restricted maximum likelihood. The assumptions underlying the linear mixed models were verified as follows. Normality of residuals was assessed using Q–Q plots. Homoscedasticity was assessed by plotting studentized residuals against fitted values and by Levene's test. When the group-by-time interaction was not significant at $\alpha = 0.10$ (likelihood-ratio comparison of the full and reduced models), the reduced main-effects model was refitted and reported. The primary contrast of interest was the between-group difference at week 12 (Group A vs. placebo and Group A vs. Group B) for the primary outcome; because the groups were balanced at baseline for the outcome, the week-12 between-group contrasts approximate the between-group differences in baseline-to-week-12 change. The week-12 endpoint contrasts and the within-group baseline-to-week-12 changes are reported separately. Between-group contrasts (A vs. B, A vs. C, B vs. C) are model-based (linear mixed model with random intercepts; Kenward–Roger degrees of freedom). Bonferroni correction was applied within each family of comparisons (three group contrasts at each time point; within-group time contrasts per group). Reported *p*-values are the Bonferroni-adjusted values unless stated otherwise. Effect estimates are reported with 95% confidence intervals computed from the model-based estimate and standard error. Missing data were handled within the mixed model under a missing-at-random assumption; the analysis population comprised all randomized participants with at least one post-baseline assessment. Randomization was performed using SAS 9.4, and statistical analyses were performed using R 4.4.0.

3. Results

3.1. Participant Disposition

Participant disposition is shown in Figure 1. A total of 68 participants were initially screened for eligibility, of whom 8 (11.8%) did not meet the inclusion criteria during the preliminary screening. Sixty participants were randomized equally to Group A, Group B, and Group C, with 20 participants in each group at baseline; baseline values of all assessed outcomes are summarized in Supplemental Table S1. All 60 participants were followed through the 12-week intervention. At the post-half-marathon assessment, Group C included 17 participants: three participants did not perform the post-race assessment owing to non-compliance with the study protocol (Figure 1). Intervention adherence was high: mean adherence across randomized participants was 92%, and all participants achieved the prespecified ≥80% compliance criterion.

3.2. Functional Performance and Pain-Tolerance Outcomes

As shown in Figure 2a, for SLSD repetitions to pain level 2, the group-by-time interaction was significant ($F(6, 168.1) = 6.51$, $p < 0.0001$), indicating different trajectories across the four assessment points. Group A increased from 22.8 ± 21.9 repetitions at baseline to 30.3 ± 24.7 at week 6 and 37.6 ± 24.8 at week 12, with a significant week-12 increase from baseline ($p < 0.0001$). Group B increased from 21.3 ± 18.0 at baseline to 31.4 ± 22.5 at week 6 and 33.6 ± 22.8 at week 12 ($p < 0.0001$ vs. baseline). Group C showed minimal change (14.8 ± 16.1 to 16.1 ± 12.4 repetitions). At week 12, Groups A and B both differed significantly from placebo (A vs. C: +21.4 repetitions, 95% CI 8.8 to 34.1, $p = 0.0037$; B vs. C: +17.6, 4.9 to 30.2, $p = 0.0222$), whereas the direct A-vs-B contrast was not significant (+3.9, −8.8 to 16.6, $p > 0.99$). After the half-marathon, both active groups remained above placebo (A vs. C: +23.7, 10.9 to 36.5, $p = 0.0013$; B vs. C: +19.3, 6.5 to 32.1, $p = 0.0107$; A vs. B: +4.4, −8.4 to 17.2, $p > 0.99$) (Supplemental Table S1).

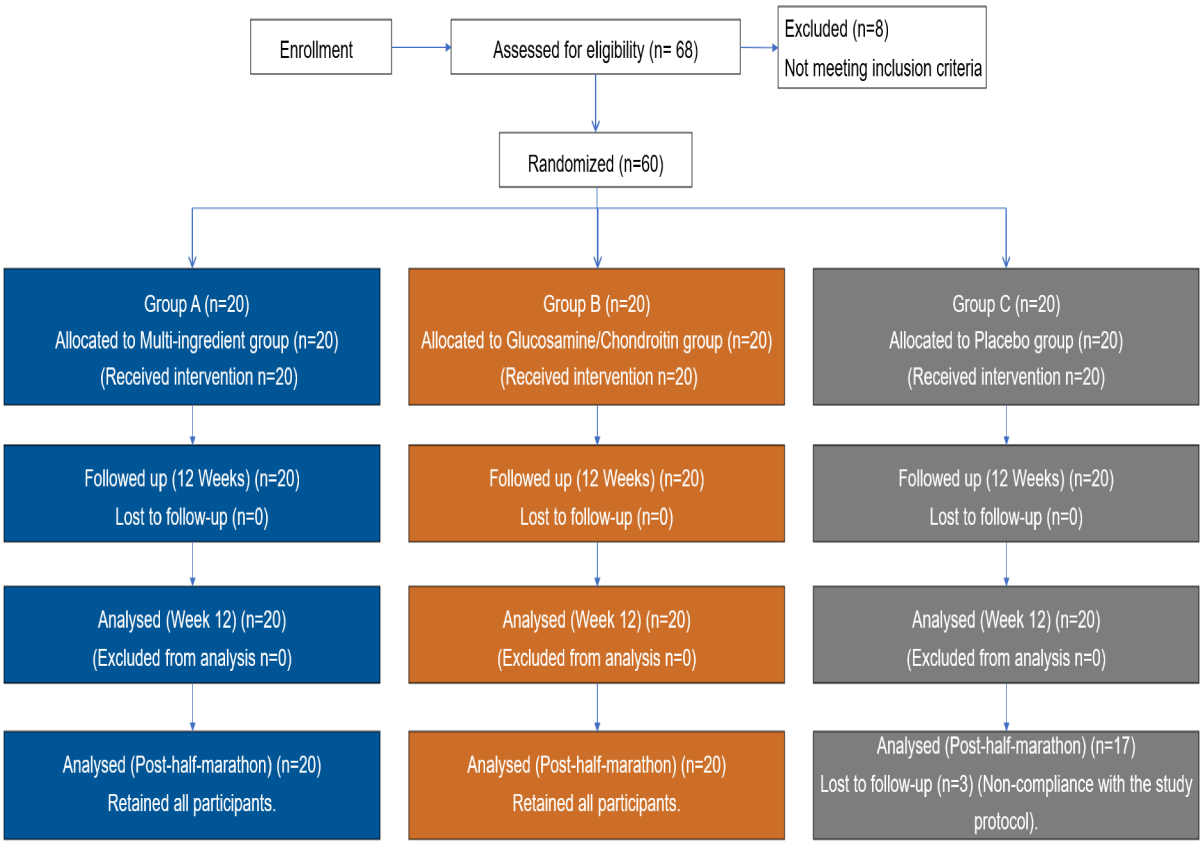


Figure 1. Flow chart of subject recruitment, randomization and follow-up.

As shown in Figure 2b, for SLSD repetitions to pain level 5, the primary outcome, the interaction was also significant ($F(6, 168.1) = 10.86$, $p < 0.0001$). Group A increased from 57.8 ± 36.1 repetitions at baseline to 78.6 ± 35.7 at week 6 and 89.8 ± 34.0 at week 12, a sustained, significant improvement ($p < 0.0001$ vs. baseline). Group B improved from 58.4 ± 32.3 to 71.1 ± 35.5 at week 6 and 75.8 ± 36.9 at week 12 ($p < 0.0001$ vs. baseline), although its later increase was smaller. Placebo remained stable during the chronic phase and declined after the half-marathon. At week 12, only Group A differed significantly from placebo (A vs. C: +30.5 repetitions, 95% CI 8.7 to 52.3, $p = 0.0201$; B vs. C: +16.6, −5.2 to 38.3, $p = 0.4003$), and the direct A-vs-B contrast was not significant (+13.9, −7.8 to 35.7, $p = 0.6144$). The corresponding within-group changes from baseline to week 12 were +32.0 repetitions in Group A ($p < 0.0001$), +17.5 repetitions in Group B ($p < 0.0001$), and +0.7 repetitions in placebo ($p > 0.99$), indicating that the week-12 contrast between Group A and placebo primarily reflected the improvement accumulated in Group A. After the half-marathon, Group A remained significantly above placebo (A vs. C: +36.0, 14.0 to 57.9, $p = 0.0049$), whereas the B-vs-C (+22.3, 0.3 to 44.3, $p = 0.1371$) and A-vs-B (+13.7, −8.1 to 35.4, $p = 0.6437$) contrasts did not reach significance (Supplemental Table S1).

As shown in Figure 2c, knee ROM showed a significant overall group-by-time interaction ($F(6, 168.4) = 2.28$, $p = 0.0383$). During the chronic intervention, no within-group ROM change reached Bonferroni-adjusted significance, although Group A increased from 111.0 ± 6.5 degrees at baseline to 115.0 ± 5.8 degrees at week 12 ($p = 0.0754$), whereas Groups B and C did not change appreciably. From week 12 to 24 h after the half-marathon, all three groups showed a similar, non-significant acute decline (all $p > 0.05$). Relative to baseline, Groups B and C showed significant post-race reductions (−5.0 degrees, $p = 0.0262$; −5.0 degrees, $p = 0.0147$), whereas Group A did not (+1.0 degrees, $p > 0.99$). Between-group contrasts for ROM were not statistically significant at week 12 (A vs. B: +4.1 degrees,

95% CI 0.2 to 7.9, $p = 0.1201$; A vs. C: +2.7, −1.2 to 6.6, $p = 0.5031$) or after the race (A vs. B: +3.9, 0.0 to 7.8, $p = 0.1444$; A vs. C: +3.5, −0.5 to 7.5, $p = 0.2614$) (Supplemental Table S1).

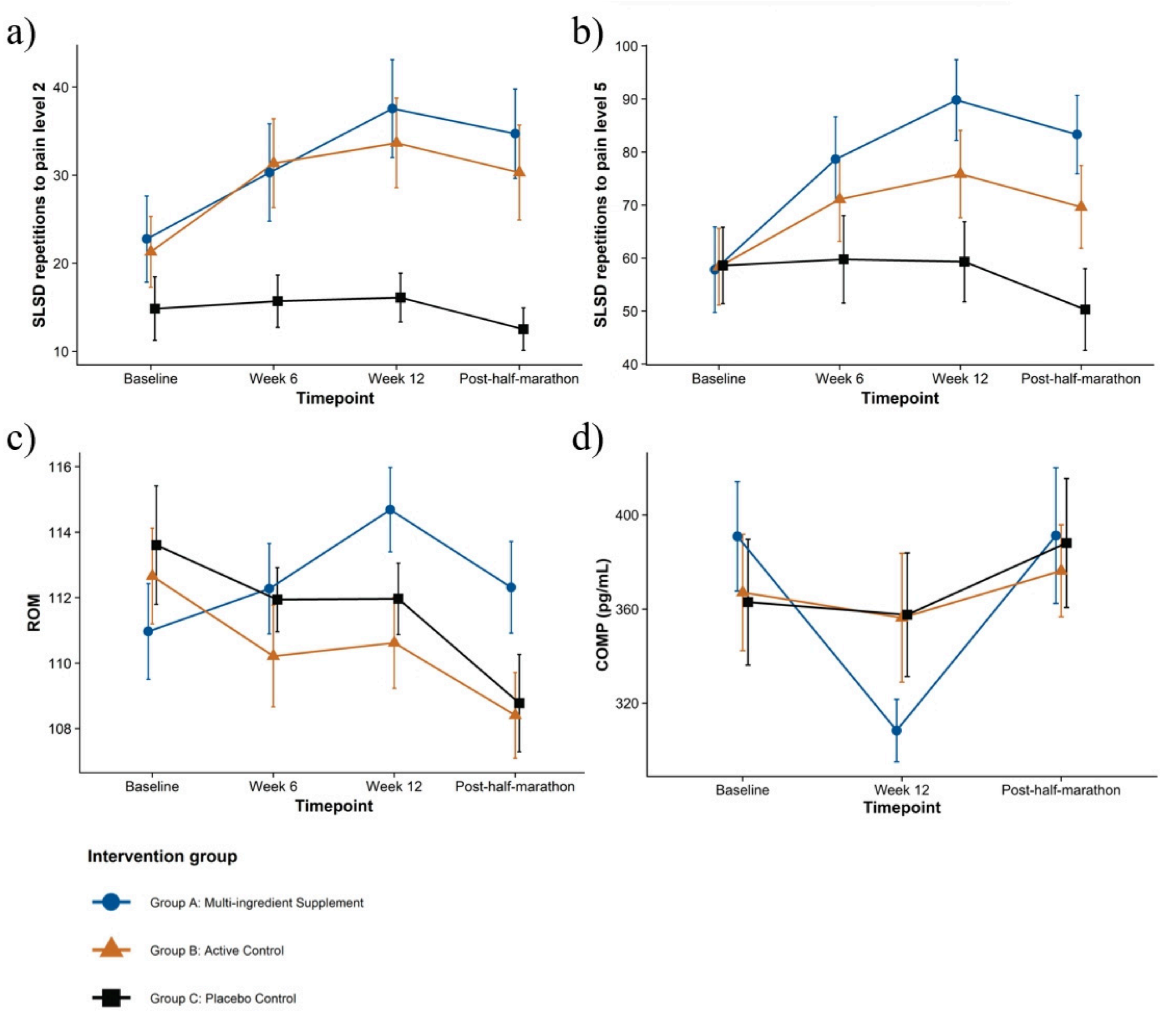


Figure 2. Group means for (**a**) single-leg step-down (SLSD) test repetitions to pain level 2, (**b**) SLSD test repetitions to pain level 5, (**c**) knee range of motion (ROM), and (**d**) COMP. SLSD and ROM were assessed at baseline, week 6, week 12, and 24 h after the half-marathon challenge; COMP was assessed at baseline, week 12, and 24 h after the half-marathon. Data are presented as mean ± SEM.

3.3. Cartilage Turnover and Inflammatory Biomarkers

As shown in Figure 2d, the group-by-time interaction for COMP was not significant ($F(4, 112.5) = 0.97$, $p = 0.4290$), the time effect was not significant ($F(2, 112.5) = 2.83$, $p = 0.0632$), and the group main effect was not significant ($F(2, 56.8) = 0.03$, $p = 0.9669$). In within-group comparisons, Group A showed a significant decrease from 391.0 ± 104.0 pg/mL at baseline to 308.0 ± 59.3 pg/mL at week 12 (−82.5 pg/mL; adjusted $p = 0.0413$), whereas Groups B and C showed smaller, nonsignificant decreases (−10.8 and −5.3 pg/mL, respectively; both adjusted $p > 0.99$). After the half-marathon, Group A returned to baseline levels (391.0 ± 129.0 pg/mL; +82.8 pg/mL vs. week 12, adjusted $p = 0.0403$), whereas the post-race increases in Groups B (+19.9 pg/mL) and C (+29.2 pg/mL) were not significant (adjusted $p > 0.99$). CTX-II is a marker related to type II collagen degradation. Descriptively, CTX-II in Group A declined from 261.0 ± 153.0 ng/mL at baseline to 242.0 ± 172.0 ng/mL at week 12 ($p > 0.99$) and 162.0 ± 117.0 ng/mL after the half-marathon ($p = 0.0308$), whereas Groups B and C showed smaller changes. No between-group biomarker comparison reached significance.

Inflammatory markers showed generally modest changes, and no group-by-time interaction was significant (hs-CRP: $F(4, 111.8) = 0.31$, $p = 0.8690$; IL-6: $F(4, 111.9) = 1.41$, $p = 0.2370$; TNF-α: $F(4, 112.3) = 0.26$, $p = 0.9000$). After the half-marathon, hs-CRP increased descriptively in all groups, with the largest mean increase in Group B; IL-6 increased most visibly in Group B, whereas Group A remained slightly below baseline; TNF-α decreased modestly in Groups A and B from baseline to week 12 and remained below baseline after the race in Group A. Complete values by group and time point are provided in Supplemental Table S1; none of the between-group differences reached significance.

3.4. Oxidative-Stress and Muscle-Damage Biomarkers

As shown in Figure 3a, SOD showed a significant time main effect ($F(2, 112.7) = 4.30$, $p = 0.0158$), whereas the group main effect ($F(2, 56.8) = 0.30$, $p = 0.7430$) and the group-by-time interaction ($F(4, 112.7) = 1.57$, $p = 0.1883$) were not significant. In within-group comparisons, Group A increased significantly from 3.0 ± 1.6 ng/mL at baseline to 4.4 ± 1.6 ng/mL at week 12 (+1.4 ng/mL; adjusted $p = 0.0289$). Group B showed a similar increase (+1.2 ng/mL; adjusted $p = 0.0734$), and placebo did not change (−0.1 ng/mL; adjusted $p > 0.99$). After the half-marathon, SOD decreased from week-12 values in both active groups, although Group A remained above baseline. MDA did not reveal significant intervention-specific patterns (interaction $F(4, 112.4) = 0.97$, $p = 0.4280$) (Supplemental Table S1).

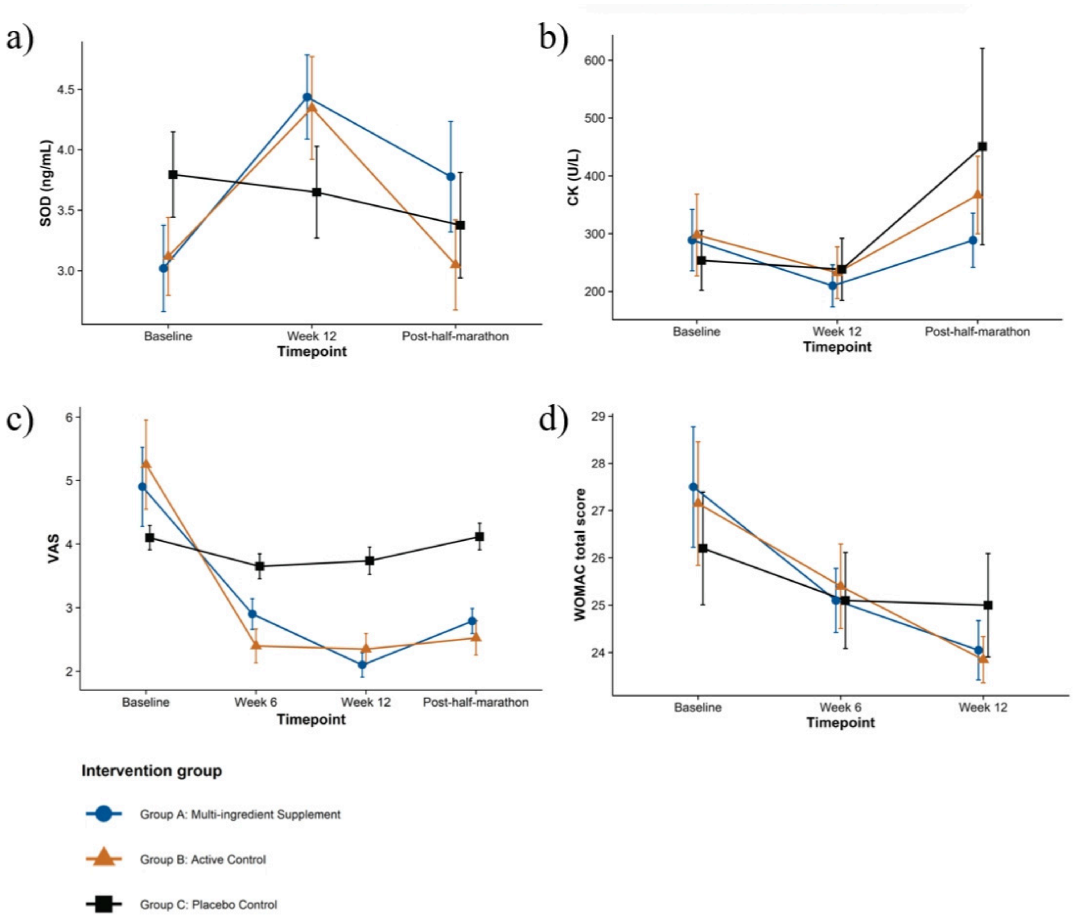


Figure 3. Group means for (**a**) superoxide dismutase (SOD), (**b**) creatine kinase (CK), (**c**) visual analog scale (VAS) pain scores, and (**d**) the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) total score. SOD and CK were assessed at baseline, week 12, and 24 h after the half-marathon challenge; VAS at baseline, week 6, week 12, and 24 h after the half-marathon; WOMAC at baseline, week 6, and week 12. Data are presented as mean ± SEM.

As shown in Figure 3b, CK, a marker of muscle damage or membrane disruption after strenuous exercise, did not change significantly during the chronic intervention (all within-group week-12 changes adjusted $p \geq 0.95$). After the half-marathon, placebo increased significantly from 238.0 ± 241.0 U/L at week 12 to 451.0 ± 701.0 U/L (+217.5 U/L; 95% CI 52.3 to 382.7; adjusted $p = 0.0311$), whereas Groups A (+78.7 U/L; adjusted $p = 0.9653$) and B (+134.3 U/L; adjusted $p = 0.2767$) showed smaller, nonsignificant increases. The group-by-time interaction was not significant ($F(4, 111.8) = 0.82$, $p = 0.5148$), so these patterns are exploratory and do not establish a protective effect of the interventions (Supplemental Table S1).

3.5. Patient-Reported Outcomes and Physical Activity Control

As shown in Figure 3c, VAS pain showed a significant group-by-time interaction ($F(6, 166.3) = 5.76$, $p < 0.0001$). Group A decreased from 4.9 ± 2.8 points at baseline to 2.9 ± 1.1 at week 6 and 2.1 ± 0.9 at week 12, while Group B decreased from 5.3 ± 3.1 to 2.4 ± 1.2 at week 6 and 2.4 ± 1.1 at week 12; placebo changed little (4.1 ± 0.9 to 3.7 ± 0.9). At week 12, both active groups had significantly lower VAS scores than placebo (A vs. C: −1.6 points, 95% CI −2.6 to −0.7, $p = 0.0030$; B vs. C: −1.4, −2.3 to −0.4, $p = 0.0153$), whereas the A-vs-B contrast was not significant (−0.2, −1.2 to 0.7, $p > 0.99$). After the half-marathon, VAS scores remained lower in both active groups than in placebo (A vs. C: −1.3, −2.3 to −0.3, $p = 0.0310$; B vs. C: −1.6, −2.6 to −0.6, $p = 0.0060$; A vs. B: +0.3, −0.7 to 1.2, $p > 0.99$) (Supplemental Table S1).

As shown in Figure 3d, WOMAC total score showed a significant time main effect in the reduced model ($F(2, 117.2) = 9.62$, $p = 0.0001$), but neither the group main effect ($F(2, 57.0) < 0.01$, $p = 0.9962$) nor the group-by-time interaction ($F(4, 113.2) = 0.86$, $p = 0.4901$) was significant. Both active groups showed significant within-group reductions from baseline to week 12 (Group A: −3.5 points, adjusted $p = 0.0041$; Group B: −3.3 points, adjusted $p = 0.0064$), whereas placebo did not (−1.2 points, adjusted $p = 0.9899$). Between-group differences were not statistically significant (Supplemental Table S1).

IPAQ total weekly energy expenditure did not differ significantly among groups over time (group-by-time interaction $F(4, 114.0) = 0.63$, $p = 0.6430$).

4. Discussion

This randomized, double-blind, placebo- and active-comparator-controlled pilot trial suggests that 12 weeks of supplementation with a three-pathway multi-ingredient joint health formula improved pain-limited knee load tolerance and self-reported knee pain relative to placebo in endurance-trained adults. The benefits were most pronounced in load-sensitive functional outcomes and under acute endurance stress; the pattern of results is hypothesis-generating for a future confirmatory trial.

The divergent results between SLSD pain level 2 and pain level 5 carry potential functional implications. Pain level 2 reflects an early discomfort threshold, while pain level 5 represents high-threshold pain tolerance under repetitive loading—a metric conceptually more relevant to training persistence in endurance athletes [32]. Both active groups improved the low-threshold endpoint relative to placebo, whereas only the multi-ingredient formula differed significantly from placebo for the high-threshold endpoint at week 12 and after the half-marathon. However, the direct A-vs-B contrasts did not reach significance (week 12: +13.9 repetitions, 95% CI −7.8 to 35.7, $p = 0.6144$), so the data support a significant advantage over placebo but not over the active comparator. It should also be emphasized that the SLSD endpoint is pain-limited by design: it records the number of repetitions tolerated until a predetermined pain level is reached, so performance depends on symptom perception and may change through pain modulation, pacing, or task familiarity without a

corresponding change in tissue tolerance; the test therefore does not constitute a measure of load-bearing capacity that is independent of pain or of the structural integrity of the knee. The observed Group-A-vs-placebo difference of 30.5 repetitions at week 12 corresponds to a large standardized effect (≈0.9 SD), but we are not aware of an established minimal clinically important difference for repetitions-to-pain, and the clinical importance of this magnitude remains uncertain.

The VAS pain results align with and complement the SLSD findings. Both active groups showed significant reductions in self-reported pain over the 12-week intervention and remained below placebo after the half-marathon. The A-vs-B contrast for VAS was not statistically significant at week 12 (−0.2 points, 95% CI −1.2 to 0.7, $p > 0.99$) or after the race (+0.3, −0.7 to 1.2, $p > 0.99$). Because the trial was not designed as an equivalence or non-inferiority study with a prespecified, clinically justified margin, the absence of a significant difference does not allow for a conclusion that the two interventions have comparable efficacy; the two regimens cannot be distinguished based on subjective pain in this pilot.

The knee ROM findings should be interpreted cautiously. All three groups showed a similar, non-significant acute decline from week 12 to 24 h after the half-marathon (−2.4°, −2.2°, and −3.1° in Groups A, B, and C), so ROM was not "preserved" relative to the immediate pre-race assessment in any group. The relevant observation is that only Groups B and C fell significantly below baseline after the race, whereas Group A did not—a pattern attributable to Group A's non-significant chronic-phase gain. Because the between-group ROM contrasts were not significant, this pattern provides at most preliminary support for a buffering effect. It should be noted that the post-race contrasts reflect group differences in ROM at 24 h after the race, not differences in the race-induced change itself (the between-group differences in the week-12-to-post-race change were not significant); whether the multi-ingredient formula buffers exercise-induced periarticular stress therefore remains a hypothesis for future testing [33].

Notably, WOMAC scores improved within both active groups but showed no significant group-by-time interaction. This discordance with the SLSD and VAS findings is consistent with the literature: the WOMAC was developed and validated for OA populations, and its items focus on daily living function rather than high-load exercise-specific tolerance [30,34]. For active, pre-clinical populations, load-challenge-based functional assessments may be more sensitive to intervention effects. Although IPAQ does not capture knee-specific loading, exercise intensity, or recovery behavior, IPAQ scores were comparable across groups, which is consistent with the interpretation that the observed improvements were not attributable to a selective reduction in overall self-reported training volume.

The biomarker results are exploratory and should be interpreted as hypothesis-generating only. For cartilage turnover markers, Group A showed a significant within-group reduction in COMP after 12 weeks (−82.5 pg/mL, adjusted $p = 0.0413$), with a transient return to baseline after the half-marathon, consistent with the normal physiological response of COMP to mechanical loading [35]. However, the group-by-time interaction was not significant ($p = 0.4290$), so this within-group change cannot be attributed to the intervention with confidence. The descriptive post-race reduction in CTX-II in Group A is likewise supportive at most. For oxidative stress and muscle damage markers, the significant time effect for SOD ($p = 0.0158$) reflected increases in both active groups in circulating SOD concentration measured by ELISA. After the half-marathon, the placebo group showed a significant increase in CK (+217.5 U/L, adjusted $p = 0.0311$), while the active groups showed smaller, nonsignificant increases; the interaction was not significant ($p = 0.5148$), and CK is not specific to periarticular damage. These patterns are biologically plausible but do not establish a protective effect. Inflammatory markers showed modest, non-significant

between-group differences; the relatively stable hs-CRP and IL-6 responses in Group A after acute loading are consistent with the anti-inflammatory properties of curcumin and the immune-modulating effects of undenatured type II collagen, but cannot be taken as evidence of a treatment-specific effect in this pilot. The biological rationale for the multi-ingredient formulation rests on the complementary actions of its three components, which together target chronic homeostasis maintenance, acute stress buffering, and structural tissue repair: undenatured type II collagen acts via oral immune tolerance to modulate cartilage-specific low-grade inflammation [22,23,36]; curcumin targets exercise-induced inflammatory and oxidative stress via NF-κB and Nrf2 pathways [37,38]; and enzymatically hydrolyzed bone powder delivers naturally sourced chondroitin sulfate, a structural substrate of the cartilage extracellular matrix. Preclinical evidence indicates that a formula comprising curcumin, enzymatically hydrolyzed bone powder, and undenatured type II collagen exerts synergistic ameliorative effects on joint inflammation in a rat model and in chondrocyte assays [39]. It must be stressed, however, that the present trial was not designed to identify individual component effects or to demonstrate synergy between them, and it cannot distinguish the contribution of any single ingredient; the preclinical synergy data provide a rationale for the formulation, not evidence of synergy in humans.

This study has several strengths. First, it targets an active, pre-clinical population rather than patients with established OA, addressing an evidence gap in early-phase joint-health support for active populations. Second, the inclusion of both a placebo and an active comparator provides useful benchmarking of the effects observed. Third, the post-intervention half-marathon challenge represents a real-world stress test, moving beyond resting outcomes to evaluate function under conditions relevant to endurance athletes. Finally, the multi-domain assessment battery—combining functional load tests, patient-reported outcomes, and exploratory biomarkers—provides a broad evaluation of knee-related outcomes in this population.

Several limitations should be acknowledged. First, the small pilot sample (20 per group) was chosen on feasibility grounds without exact sample-size calculation, limiting statistical power, particularly for between-group biomarker comparisons and the direct A-vs-B functional comparisons; the effect estimates from this pilot should inform the sample size of a confirmatory trial [28]. Second, the multi-ingredient design does not allow for quantification of individual component effects or confirmation of synergistic interactions, and future confirmatory factorial designs are needed. Third, participants included swimmers and cyclists as well as runners, and running-specific training and experience varied; the half-marathon challenge therefore imposed a heterogeneous stimulus, although it was standardized as an event. Three placebo participants missed the post-race assessment (non-compliance with the study protocol). Fourth, the SLSD endpoint is pain-limited and may be influenced by pain modulation and task familiarity; biomarker results are exploratory and highly variable (e.g., CK), and between-group biomarker differences were not significant.

5. Conclusions

In conclusion, this pilot randomized, double-blind, placebo- and active-comparator-controlled trial provides preliminary evidence that 12 weeks of supplementation with a multi-ingredient formula containing undenatured type II collagen, curcumin phytosome, and enzymatically hydrolyzed bone powder improved pain-limited knee load tolerance and self-reported knee pain relative to placebo in endurance-trained adults. These findings support the need to conduct a larger confirmatory trial evaluating this multi-ingredient strategy for managing activity-related knee discomfort in active populations.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/nu18223785/s1, Table S1: Functional, patient-reported, and biomarker outcomes by group and assessment occasion in the 12-week randomized pilot trial of a multi-ingredient joint-health supplement.

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Abbreviations

The following abbreviations are used in this manuscript:

SLSD	single-leg step-down
VAS	visual analog scale
ROM	range of motion
COMP	cartilage oligomeric matrix protein
SOD	superoxide dismutase
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index
OA	osteoarthritis
CTX-II	C-terminal telopeptide of type II collagen
hs-CRP	high-sensitivity C-reactive protein
IL-6	interleukin-6
TNF-α	tumor necrosis factor-alpha
CK	creatine kinase
MDA	malondialdehyde

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