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Effectiveness of a Cucumber Extract Supplement on Articular Pain in Patients with Knee Osteoarthritis: A Randomized Double-Blind Controlled Clinical Trial

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Abstract: This 8-week randomized double-blind placebo-controlled study aimed to assess the effectiveness of supplementation with an extract of *Cucumis sativus* L. (20 mg/day) on pain and other variables in patients with knee osteoarthritis (OA) over 40 years. The change in pain intensity using a 1–10 cm visual analog scale (VAS) was the primary endpoint. Fifty-five patients (mean age 50.6 ± 8.6 years) were included (experimental group, n = 29; placebo, n = 26). VAS scores for pain decreased significantly in both study groups, but decreases were higher in the experimental group (between-group $p = 0.013$). Improvements in pain, stiffness, and physical function according to the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) were also significantly higher in the experimental group. The Timed Up and Go test result also decreased significantly in the experimental group. An improvement in muscle function was associated with significant increases in isokinetic and isometric dynamometry variables, particularly for isometric $60^{\circ}\cdot s^{-1}$ and $180^{\circ}\cdot s^{-1}$ knee flexion exercises in the experimental group. Plasma levels of interleukin-1-beta (IL-1β) and matrix metalloproteinase-3 (MMP-3) also decreased significantly in the experimental group. Based on the beneficial effects of cucumber on symptomatology and inflammatory and cartilage degradation biomarkers in knee OA, cucumber extract supplementation may a useful natural approach to maintain healthy joints.

Keywords: *Cucumis sativus* L.; knee osteoarthritis; joint pain; randomized trial; muscle function; interleukin (IL)-1β; matrix metalloproteinase 3

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1. Introduction

Osteoarthritis (OA) is the most common form of arthritis and is among the most prevalent chronic diseases [1,2], with articular pain as the cardinal symptom, which results in functional disability, limitations of daily living activities and detrimental effects on quality of life, particularly in patients with long-standing persistent pain and stiffness [3,4]. It has been estimated that 7% of the worldwide population is affected by OA (<500 million people), accounting for 2% of the total years lived with disability (YLDs) [5]. In a comprehensive review of population-based studies, knee OA showed a pooled global prevalence of 22.9% in subjects aged 40 years and older [6]. Symptomatic knee OA occurs in 13% of women and 10% of men of 60 years of age or older [7], and as the population ages and obesity trends continue, the number of adults with OA will increase in the forthcoming years [8].

To date, no curative treatments for patients with OA are available and the main objectives of the current options are to achieve pain control and improvement or maintenance of joint mobility. In many patients, however, the optimal therapeutic strategy is based on the combination of non-pharmacological and pharmacological treatments, taking into account

the intensity of pain and disability, the degree and location of structural damage and individual risk factors, such as age, obesity, physical activity and comorbid diseases [9]. Briefly, medications used in OA can be classified into drugs with symptomatic and/or disease-modifying action. Symptomatic-based drugs include fast-acting drugs such as analgesics, non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids, and slower-acting drugs such as glucosamine and chondroitin sulfate, as well as intra-articular hyaluronic acid, which are also called symptomatic slow-acting drugs for osteoarthritis (SYSADOA) or disease-modifying anti-osteoarthrosis drugs. Evidence-based recommendations to guide clinicians in choosing among the available pharmacological treatments according to considerations based on effectiveness, adverse effects and cost-effectiveness for OA affecting different joints have been summarized by the American College of Rheumatology/Arthritis Foundation [10], the European Alliance of Associations for Rheumatology (EULAR) [11], the National Institute for Health and Care Excellence (NICE) [12] and the Osteoarthritis Research International (OARSI) expert consensus group [13].

Despite the availability of a range of effective medications, adequate pain relief is not achieved for many patients due to contraindications or drug intolerance, side effects and the limited effectiveness of therapy [14–17]. In the Global OA Patient Perception Survey (GOAPPS), with 1512 surveys completed in six countries, a lack of satisfaction with the current treatment for OA was registered in 43% of patients [18]. In the data of 2001 subjects who self-reported having OA, collected in a widespread survey in the UK, varying levels of persistent pain were reported by 71% of them, despite the use of prescribed drugs [19]. In a retrospective study carried out in Spain based on the data of 29,886 OA patients with moderate-to-severe pain, more than half had unsatisfactory pain control [20].

Because of these limitations in the treatment of OA, there has been increasing interest in options offered by nutraceuticals or functional foods isolated or purified from affordable and natural food sources [21–23]. Dietary supplementation with nutraceuticals is based on a wide range of molecules with different actions, including antioxidant, anti-inflammatory and analgesic properties, to reduce joint stiffness and pain, as well as to exhibit chondroprotective effects [23]. Several studies and reviews have evaluated the benefits of natural products and derivatives in OA, including anthocyanins and polyphenols from pomegranate juice [24], phenolic compounds (from olive trees) [25], avocado and soybean unsaponifiables (ASU) [22,23,26,27], acetyl-keto-β-boswellic acid (AKBA) (from *Boswellia serrata*) [28], topical capsaicin (from chili peppers) [29], epigallocatechin 3-gallate (abundant in green tea) [30], gingerols [31], curcumin (from Curcuma longa species) [32,33] and cucumber (from the *Cucurbitacea* family) [34].

Cucumber (*Cucumis sativus* L.), which probably originated in India, is a widely popular cultivated plant and is extensively used in traditional medicine. The active components of cucumber extracts include amino acid derivatives such as L-citrulline and iminosugars, possessing anti-inflammatory activity and improving cartilage nutrition [35–40]. Moreover, it has been suggested that flavonoids and tannins in the phytochemical composition of aqueous fluid cucumber extracts may be responsible for their free radical scavenging and analgesic effects [41]. In animal models, ethanol extracts of cucumber seeds at 100–200 mg/kg showed analgesic and anti-inflammatory actions similar to aspirin and ibuprofen [42]. The cucumber peel and cucumber plant have also medicinal value, with antioxidant and antimicrobial properties, as well as hepatoprotective and hypoglycemic effects after decoction of the fruit and the plant [43–45]. The therapeutic value of different parts of *Cucumis sativus* have been especially explored in different skin formulations for cosmetic applications, such as antioxidant, antiaging and anti-wrinkle products [34]. However, data on the analgesic efficacy of cucumber in patients with arthrosis are scarce. In a randomized controlled study of the effectiveness of a cucumber extract (Q-Actin™) (20 mg/day) against glucosamine-chondroitin (1350 mg twice a day) in 122 patients with moderate OA treated for 6 months, the cucumber product provided a statistically significant improvement in knee pain, physical function and stiffness during the treatment period as compared with glucosamine-chondroitin [46].

The present randomized double-blind controlled trial in patients with OA of the knee was designed to provide evidence of the effectiveness of oral cucumber supplementation on a set of clinical, functional and biochemical variables that, as a whole, have not been previously evaluated. Biochemical variables included biomarkers of inflammation and matrix cartilage degradation, which were selected to determine whether the study product could modify the inflammatory profiles of patients with OA and cartilage metabolism. It was hypothesized that oral supplementation with a natural cucumber extract for 8 weeks could be associated with improvements in pain, physical and muscle function and biomarkers of inflammation and matrix cartilage degradation as compared with a placebo.

2. Materials and Methods

2.1. Design of the Study and Patients

A randomized, double-blind, single-center, placebo-controlled, parallel-arm study was conducted at the Department of Health Sciences of the Catholic University of San Antonio de Murcia (UCAM), in Murcia, Spain. The study began in 12 January 2021 and finished in 19 July 2021. The main objective was to assess the effectiveness of daily use of an oral cucumber extract for 8 weeks on OA knee pain in subjects over 40 years of age. Changes in body composition, functional mobility, knee strength, quality of life and inflammatory and cartilage degradation biomarkers were the secondary objectives.

Recruitment of participants was based on advertising the study through mass media and social networks available at UCAM. Eligible participants were men and women, older than 40 years, diagnosed with knee OA categorized into functional class I-III according to the modified criteria of the American College of Rheumatology (ACR) [47] and with persistent knee pain (>3 using a 1–10 cm visual analog scale (VAS)). Exclusion criteria were subjects treated with OA medications, including non-steroidal anti-inflammatory drugs (NSAIDs), opioids or immunosuppressants, as well as current treatment with glucosamine, chondroitin sulfate, intra-articular hyaluronic acid injections or any supplement for healthy joints; the presence of chronic musculoskeletal inflammatory disorders (rheumatoid arthritis, gout, pseudogout, Paget's disease, etc.), chronic diseases or terminal illness; body mass index (BMI) > 32 kg/m^2; alcohol consumption; known allergy to cucumber; pregnant or breast-feeding women; and investigator's judgement of ineligibility.

The study protocol was approved by the Ethics Committee of Universidad Católica San Antonio de Murcia (code CE032004, approval date 27 March 2020) (Murcia, Spain) and was registered at ClinicalTrials.gov (NCT04607759). All participants provided written informed consent.

2.2. Intervention and Study Procedures

Participants were randomized with a computer program (Epidat 4.1) and were distributed according to a simple randomization procedure to the active or experimental treatment group (cucumber extract supplement) or to the control group (placebo supplementation). An independent investigator performed the randomization process. Neither patients nor investigators were aware of whether the assigned study arm corresponded to the active treatment or placebo.

The active product was an extract of *Cucumis sativus* L. (CuberUp®, Euromed S.A., Mollet del Vallès, Barcelona, Spain), the composition of which included 80% *Cucumis sativus* L., 18% maltodextrin and 2% anhydrous colloidal silica excipient. The percentage of maltodextrin and the excipient only represented 20% of each capsule, and these components were necessary to prevent the agglomeration of the product and to increase the bioavailability. The part of the cucumber used was the whole cucumber fruit, and the varieties and maturation stage were those used applied in extensive cucumber food production. The methodology for obtaining the natural extract was based on an eco-friendly ultrapure continuous water extraction method and refinement by a proprietary tangential flow filtration process (Pure-Hydro Process®). This procedure gave a total concentration of amino

derivatives expressed as L-Citrulline of not less than 50%, the concentration of the extract being 80% of the total. The nutritional value of the cucumber is shown in Table 1.

Table 1. Nutritional value of the cucumber.

Component	Value	Unit
Energy	50 (12)	kJ (Kcal)
Total lipids	0.1	g
Total protein	0.7	g
Water	95.7	g
Carbohydrates		
Total fiber	0.8	g
Carbohydrates	2	g
Vitamins		
Vitamin A	2	µg
Vitamin D	0	µg
Vitamin D	0.09	mg
Folic acid	13	µg
Riboflavin	0.02	mg
Niacin	0.23	mg
Thiamine	0.02	mg
Vitamin B12	0	µg
Vitamin B6	0.04	mg
Minerals		
Calcium	19	mg
Iron	0.3	mg
Potassium	150	mg
Magnesium	12	mg
Sodium	3	mg
Phosphorus	23	mg
Iodure	0.3	µg
Selenium	0.8	µg
Zinc	0.1	mg

Subjects randomized to the experimental arm were instructed to take two capsules a day (10 mg per capsule) at the time of breakfast for 8 consecutive weeks (60 days). Participants assigned to the placebo (control) arm ingested the capsules in the same pattern as the experimental group. The capsules, based on maltodextrin, were identical in appearance. All subjects were instructed regarding the importance of maintaining their eating habits, particularly to consume the same amount of foods containing flavonoids (coffee, tea, chocolate, nuts, etc.). In addition, they were not allowed to consume cucumber throughout the study. A diary card (24-h dietary recall) was provided to collect data for a period of 3 days (two weekdays and one weekend) at the beginning and at the end of the intervention. Dietary data were analyzed with the Dietsource® (v3.0) software package. Moreover, if a new treatment was started, it had to be reported to the principal investigator. Any analgesic or other medications taken during the study period had to be recorded on the diary card.

Participants were assessed twice, at baseline (visit 1) and after product consumption for 60 days (visit 2). At the baseline visit, a signed informed consent form was collected, the satisfaction of the inclusion criteria was confirmed, and all subjects were provided with the corresponding study product. The intensity of knee pain, quality of life, balance and mobility test, muscle function test, body composition and inflammatory and cartilage degradation plasma biomarkers were evaluated at visits 1 and 2. In addition to the study visits, patients received an intermediate telephone call to check the consumption of the product, diet, changes in the intensity of pain and other information of interest. Weekly reminders through WhatsApp messages were also provided. Capsules were returned at the final visit and adherence (consumption of at least 80% of capsules) was assessed by counting the returned study product. Based on 80% adherence, 12 capsules in total could be returned, which corresponded to 6 out of 60 days of consumption. At the final visit, tolerance of the study products was checked.

2.3. Study Variables

Clinical variables were gender, age, height, weight, BMI and knee pain intensity, assessing using a 1–10 cm VAS (0 = no pain, 10 = worst pain ever), with mild, moderate and severe pain categorized as scores >4, between 4 and 6 and >6, respectively. VAS scores were measured at visits 1 and 2, as well as every morning on getting out of bed and in reference to the intensity of pain experienced on the previous day. Daily VAS scores were recorded in a personalized notebook for each patient and were then analyzed at weekly intervals.

The Western Ontario McMaster Universities Arthritis Index (WOMAC) was used to assess pain, stiffness and function in patients with OA. The subscales of pain, stiffness and function have 5, 2 and 17 items, respectively. The test was completed by the volunteer subjects taking into account pain, stiffness and knee functionality in the past 48 h. The test questions are scored on a scale of 0–4 (from 0 = none to 4 = extreme). Higher WOMAC scores are indicative of worse pain, stiffness and functional limitations. A Spanish validated version of the WOMAC index was administered [48].

Body composition was analyzed by bioelectrical impedance analysis (BIA) on a whole-body BIA analyzer: Tanita BC-420MA (Tanita Corporation, Tokyo, Japan). Variables analyzed included weight (kg), fat mass (kg), percentage of fat mass and muscle mass (kg).

The subject's mobility and balance was evaluated using the Timed Up and Go test (TUG). Briefly, subjects are seated properly in a chair with their arms resting (not on the armrest) and are instructed to stand up, walk 3 m, make a turn around the chair and sit down. The recorded time on the stopwatch is the subject's TUG score. Two tests were per-formed, with a resting time of 30 s. The average recorded time of the two tests was the final score. A TUG score $\geq$ 13.5 s is predictive of a risk of falls, whereas a score < 13.5 s suggests better functional performance [49].

The muscle function of the leg with knee pain was measured by isokinetic and isometric dynamometry. These tests were carried out with the Biodex System 3 isokinetic dynamometer (Biodex Medical Systems, Shirley, New York, NY, USA). The measurement protocol included a 5-min warm-up on a cycloergometer (W45, 70–75 rpm).

The dynamometry was performed in a seated position with 90° hip flexion and the knee module aligned with the axis of the knee movement. The pad that exerted resistance during movement was adjusted to the central part of the tibia. The range of motion was set to 0°–90°, taking the maximal active knee extension as the initial value. Subjects were instructed to perform 5 repetitions of maximal knee flexion and knee extension (concentric/concentric) at 60° and $180° \cdot s^{-1}$. Warm-up included 2 sets of repetitions. The variables measured were the isokinetic value of relative peak torque (expressed in Newton meters [Nm]/body mass [Kg]), total work (TW) measured in joules (J), average power measured in watts (W) and total work per repetition maximum (total word for 1RM) measured in J. In isometric dynamometry (at 90°), the force exerted by the subject when attempting to perform full extension of the knee was measured. The force had to be maintained for 5 s, while the lever did not allow leg movement. A total of 3 repetitions

were performed, with a rest period of 40 s between each repetition. The variables measured were maximum isometric torque (Nm) and mean maximum isometric torque (Nm).

After a 12 h fast, at visits 1 and 2, peripheral blood samples were drawn for standard laboratory tests to measure biomarkers of inflammation and matrix cartilage degradation, including interleukin-1 beta (IL-1β), matrix metalloproteinase-3 (MMP-3) or stromelysin-1 and cartilage oligomeric matrix protein (COMP). Plasma levels of IL-1β were measured using a commercial kit (Human IL-1 beta ELISA Kit, ref: E-EL-H0149, Elabscience Biotechnology Inc., Houston, TX, USA), with results expressed as pg/mL. Plasma levels of MMP-3 were measured using a commercial kit (MPP-3 ELISA Kit, ref: E-EL-1446, Elabscience) with results expressed as ng/mL, and plasma levels of COMP using a commercial kit (Cartilage Oligomeric Matrix Protein ELISA Kit, ref: E-EL-H0654, Elabscience) with results expressed as ng/mL. Laboratory tests for safety assessment included a hemogram and standard liver and renal function tests, such as alanine and aspartate aminotransferases, lactate dehydrogenase, gamma-glutamyl transpeptidase, blood urea nitrogen and serum creatinine.

2.4. Study Endpoints

The change in knee pain intensity evaluated by VAS after 8 months of dietary supplementation with a cucumber extract was the primary study endpoint. It was hypothesized that in patients with pain due to OA, the use of 20 mg daily of a natural extract of *Cucumis sativus* for 8 weeks would be associated with a higher analgesic effect as compared with the placebo. Secondary endpoints included changes in quality of life, functional mobility, the isokinetic and isometric muscle strength of the affected leg, body composition and plasma levels of biomarkers of inflammation and cartilage degradation matrix.

2.5. Statistical Analysis

Calculation of the sample size was based on the VAS pain score as the primary study outcome, with a standard deviation of 1.8 reported in a similar population of patients with joint and connective tissue disruption [50]. Then, with precision of 1.25 with a 5% alpha risk and 80% statistical power, 26 subjects in each group were needed, increasing to 29 subjects per group considering a 10% loss to follow-up. Statistical analysis was performed by protocol (PP) corresponding to the participants who completed the study.

The normal distribution of variables was tested by the Kolmogorov–Smirnoff test and homoscedasticity by Levene's test. Categorical variables are expressed as frequencies and percentages, and quantitative variables as mean ± standard deviation (SD). Categorical variables were analyzed with the chi-square test (χ^2) or Fisher's exact test, and quantitative variables with the Student *t* test. Changes in variables in each of the study groups were analyzed with analysis of variance (ANOVA) for repeated measures with two study factors: within-subject factor (baseline and 8 weeks) and between-subject factor (intervention: experimental product and placebo). The Turkey or Bonferroni correction was applied for post-hoc analyses. A p value < 0.05 was accepted as statistically significant. SPSS version 25.0 (IBM Corp., Armonk, NY, USA) was used for the analysis of data.

3. Results

3.1. Characteristics of the Study Population

Ninety-two volunteer subjects were initially selected, but the inclusion criteria were not met in 29, and five subjects refused to take part in the study, so that a total of 34 subjects were excluded. Of the remaining 58 subjects included in the study, 30 were assigned to the experimental group and 28 to the placebo. Thereafter, and over the course of the study, three subjects (experimental group 1, placebo group 1) were lost to follow-up due to inability to attend the final visit (e.g., change in residence). Therefore, the final study population included 55 subjects (29 in the experimental group, 26 in the placebo group), 26 men and 29 women, with a mean age of 50.6 ± 8.6 years. The distribution of the participants is shown in Figure 1.

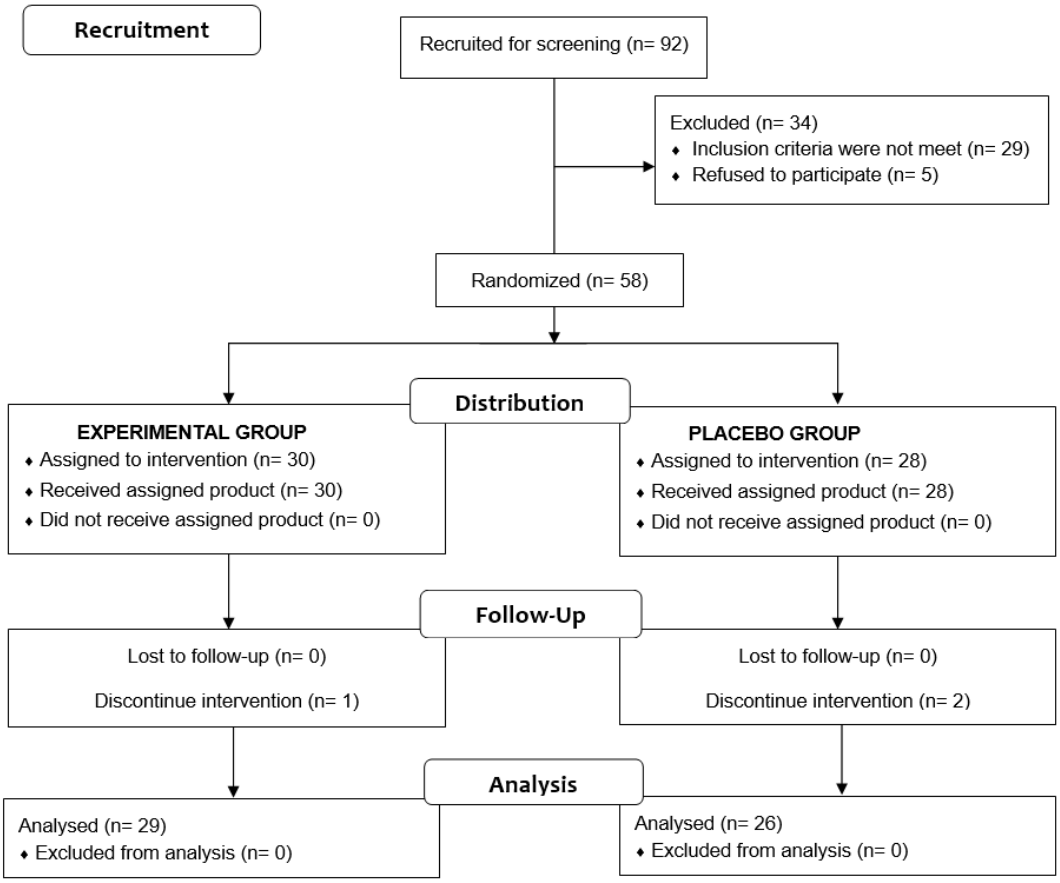

Figure 1. Flow chart of the study population.

At baseline, significant differences between the two study groups were not found (Table 2). Moreover, patients who completed the study and those who did not were also similar, with no statistically significant differences.

Table 2. Characteristics of participants at baseline.

Variables	Total Subjects (n = 55)	Cucumber Extract (n = 29)	Placebo (n = 26)	*p* Value
Age, years	50.6 ± 8.6	51.4 ± 8.5	50.0 ± 8.7	0.543
Weight, kg	76.1 ± 13.6	76.4 ± 13.7	75.7 ± 13.4	0.845
Height, cm	169.2 ± 8.7	169.2 ± 8.7	169.2 ± 8.7	
BMI, kg/m^2	26.5 ± 3.6	26.7 ± 3.7	26.3 ± 3.6	0.737
VAS score	5.2 ± 1.7	5.5 ± 1.5	5.2 ± 1.7	0.576

Data expressed as mean ± standard deviation (SD); BMI: body mass index; VAS: visual analog scale for intensity of knee pain.

3.2. Changes in the Intensity of Knee Pain

As shown in Table 3, the intensity of knee pain decreased significantly at the end of the study as compared with baseline in both study groups, but pain decreases were significantly higher in the experimental group ($p = 0.013$). Similar findings were observed in the decreases in pain intensity throughout the weeks of the study, with statistically significant differences in the within-group comparisons and overall between-group comparisons, although VAS scores were significantly lower in the experimental group than in the placebo group from the fourth week until the end of the study.

Table 3. Changes in VAS scores for intensity of knee pain in the study groups.

VAS Score	Cucumber Extract (n = 29)	Placebo (n = 26)	Between-Group p Value
Baseline	5.5 ± 1.5	5.2 ± 1.7	0.013
End of study	1.7 ± 1.2	2.9 ± 2.6	
Study weeks			
Week 1	3.7 ± 2.1	4.2 ± 2.5	0.001
Week 2	3.2 ± 2.1	3.9 ± 2.5	
Week 3	2.8 ± 2.0	3.8 ± 2.7	
Week 4	2.3 ± 1.5	3.5 ± 2.7	
Week 5	1.7 ± 1.4 *	3.4 ± 2.7 *	
Week 6	1.7 ± 1.4 *	3.3 ± 2.7 *	
Week 7	1.8 ± 1.3 *	2.9 ± 2.4 *	
Week 8	1.7 ± 1.2 *	2.9 ± 2.6 *	

Data expressed as mean ± standard deviation (SD); VAS: visual analog scale; * $p < 0.05$ indicates significant differences when compared with baseline.

3.3. Quality of Life Assessed by the WOMAC Index

In the experimental group, the overall WOMAC score decreased from 32.7 ± 13.6 at baseline to 19.3 ± 11.7 at the end of the study (p = 0.001), and in the placebo group from 31.4 ± 12.1 to 24.7 ± 13.4 (p = 0.004). There were between-group differences in favor of the experimental group (Table 4). In the subscale of pain, statistically significant differences were found in the within-group comparison in the two study groups, whereas in the subscale of stiffness, the within-group comparison was statistically significant for the experimental group only, and between-group comparisons were also significant in favor of the experimental group. Physical function improved significantly in both study groups, but improvements were higher in the experimental group (Table 3).

Table 4. Changes in WOMAC scores in the study groups.

WOMAC Score	Baseline	End of Study	Within-Group p Value	Between-Group p Value
Overall				
Cucumber extract (n = 29)	32.7 ± 13.6	19.3 ± 11.7	0.001	0.038
Placebo (n = 26)	31.4 ± 12.1	24.7 ± 13.4	0.004	
Pain				
Cucumber extract (n = 29)	7.4 ± 3.4	4.0 ± 2.2	0.001	0.114
Placebo (n = 26)	6.9 ± 3.0	5.2 ± 2.8	0.021	
Stiffness				
Cucumber extract (n = 29)	3.1 ± 1.9	1.7 ± 1.5	0.001	0.034
Placebo (n = 26)	2.6 ± 1.4	2.2 ± 1.3	0.207	
Physical function				
Cucumber extract (n = 29)	22.2 ± 10.3	13.6 ± 9.3	0.001	0.089
Placebo (n = 26)	21.9 ± 9.2	17.0 ± 10.4	0.003	

Data expressed as mean ± standard deviation (SD); WOMAC: Western Ontario McMaster Universities Arthritis.

3.4. Function Tests

3.4.1. Timed Up and Go (TUG)

The TUG decreased significantly in the experimental group, from a mean of 6.10 ± 1.4 s at baseline to 5.58 ± 1.0 s at the end of the study (p = 0.001), whereas differences in the placebo group were not significant (6.07 ± 1.2 vs. 6.13 ± 1.3 s, p = 0.702). Between-group differences were statistically significant in favor of the experimental group (p = 0.008).

3.4.2. Knee Isokinetic and Isometric Dynamometry

Table 5 shows data obtained in the isokinetic and isometric dynamometry studies. In the isokinetic dynamometry, functional limitation of the affected knee improved in subjects assigned to the experimental group, in which statistically significant increases in all variables at $60°\cdot s^{-1}$ and $180°\cdot s^{-1}$ knee flexion at the final visit in comparison with baseline were observed. In contrast, in the placebo group, none of the changes in isokinetic variables were significant. Between-group significant differences were found for all variables at $60°\cdot s^{-1}$ and average power at $180°\cdot s^{-1}$ knee extension in favor of the experimental group.

Table 5. Changes in muscle function of knee isokinetic and isometric dynamometry after 8 weeks of food supplementation with a cucumber extract or placebo.

Variables	Experimental Group (n = 29)			Placebo Group (n = 26)			Between-Group p Value
	Baseline	End of Study	Within-Group p Value	Baseline	End of Study	Within-Group p Value	
Isokinetic dynamometry							
At $60°\cdot s^{-1}$ knee extension							
Peak torque, Nm	119.0 ± 48.1	118.6 ± 48.7	0.942	108.4 ± 40.8	107.5 ± 41.1	0.849	0.930
Relative peak torque, Nm/Kg	1.6 ± 0.8	1.6 ± 0.8	0.943	1.5 ± 0.6	1.5 ± 0.6	0.862	0.938
Total work, J	516.6 ± 212.5	493.0 ± 192.3	0.164	484.7 ± 196.7	485.6 ± 188.9	0.960	0.319
Total work for 1RM, J	112.1± 45.4	106.9 ± 41.2	0.167	105.2 ± 41.1	105.4 ± 40.3	0.960	0.322
Average power, W	72.5 ± 28.1	75.6 ± 32.8	0.157	65.6 ± 26.2	64.7 ± 25.3	0.703	0.211
At $60°\cdot s^{-1}$ knee flexion							
Peak torque, Nm	60.0 ± 25.0	66.4 ± 26.3	**0.007**	57.9 ± 22.4	56.5 ± 22.7	0.542	**0.021**
Relative peak torque, Nm/Kg	0.8 ± 0.4	0.9 ± 0.4	**0.004**	0.8 ± 0.3	0.8 ± 0.3	0.633	**0.018**
Total work, J	297.3 ± 137.4	340.8 ± 156.7	**0.001**	294.9 ± 137.1	291.7 ± 138.0	0.779	**0.004**
Total work for 1RM, J	67.0 ± 29.7	76.5 ± 32.7	**0.001**	64.6 ± 28.5	64.7 ± 27.7	0.979	**0.004**
Average power, W	39.9 ± 19.2	46.9 ± 22.6	**0.001**	37.1 ± 17.0	36.7 ± 18.4	0.825	**0.008**
At $180°\cdot s^{-1}$ knee extension							
Peak torque, Nm	78.4 ± 40.2	79.4 ± 33.7	0.720	65.0 ± 24.3	66.8 ± 26.1	0.547	0.848
Relative peak torque, Nm/Kg	1.1 ± 0.7	1.1 ± 0.6	0.835	0.9 ± 0.3	0.9 ± 0.4	0.330	0.572
Total work, J	375.1 ± 193.5	370.5 ± 180.7	0.782	338.9 ± 164.0	317.8 ± 129.8	0.231	0.494
Total work for 1RM, J	82.0 ± 33.5	83.8 ± 35.0	0.568	71.6 ± 28.4	72.0 ± 27.9	0.925	0.746
Average power, W	118.9 ± 58.7	129.3 ± 64.2	**0.008**	102.5 ± 46.1	100.8 ± 44.9	0.655	**0.031**
At $180°\cdot s^{-1}$ knee flexion							
Peak torque, Nm	45.2 ± 19.1	50.0 ± 22.2	**0.006**	40.7 ± 20.8	40.8 ± 20.0	0.930	0.061
Relative peak torque, Nm/Kg	0.6 ± 0.3	0.7 ± 0.4	**0.002**	0.5 ± 0.3	0.6 ± 0.3	0.750	0.055
Total work, J	194.7 ± 143.8	224.2 ± 143.2	**0.004**	138.7 ± 110.0	145.0 ± 114.8	0.557	0.109
Total work for 1RM, J	44.2 ± 29.7	50.7 ± 30.4	**0.011**	32.9 ± 23.3	33.1 ± 23.7	0.934	0.085
Average power, W	61.5 ± 43.4	70.7 ± 41.9	**0.002**	38.7 ± 32.5	40.6 ± 33.6	0.539	0.087
Isometric dynamometry							
At 90° knee position							
Peak torque, Nm	144.7 ± 71.7	171.9 ± 81.8	**0.001**	145.4 ± 61.1	145.0 ± 61.4	0.946	**0.002**
Relative peak torque, Nm/Kg	2.0 ± 1.2	2.4 ± 1.4	**0.001**	1.9 ± 0.9	2.0 ± 0.8	0.942	**0.002**
Average peak torque, Nm	142.5 ± 56.2	162.0 ± 75.8	**0.001**	138.2 ± 58.3	139.2 ± 59.2	0.859	**0.022**

Data expressed as mean ± standard deviation (SD).

In the isometric dynamometry, both peak torque and average peak torque improved significantly in the experimental group only, with statistically significant differences in the between-group comparison.

3.5. Body Composition

At baseline, variables in the two study groups were similar. Significant changes in weight, fat mass, percentage of fat mass and muscle mass were not found, either in the experimental or in the placebo group (Table 6).

Table 6. Changes in body composition after supplementation with cucumber extract or placebo for 8 weeks.

Variables	Baseline	End of Study	Within-Group *p* Value	Between-Group *p* Value
Weight, kg				
Cucumber extract (n = 29)	76.4 ± 13.7	76.0 ± 13.4	0.200	0.753
Placebo (n = 26)	75.7 ± 13.4	75.1 ± 12.7	0.102	
Fat mass, kg				
Cucumber extract (n = 29)	23.4 ± 7.2	22.7 ± 7.5	0.083	0.929
Placebo (n = 26)	21.6 ± 7.9	20.8 ± 7.6	0.078	
Fat mass, %				
Cucumber extract (n = 29)	30.7 ± 8.0	29.8 ± 8.4	0.107	0.835
Placebo (n = 26)	28.4 ± 8.3	27.7 ± 8.5	0.212	
Muscle mass, kg				
Cucumber extract (n = 29)	50.3 ± 11.3	50.6 ± 10.8	0.529	0.215
Placebo (n = 26)	51.5 ± 10.3	51.0 ± 10.7	0.264	

Data expressed as mean ± standard deviation (SD).

3.6. Biomarkers of Inflammation and Cartilage Degradation

As shown in Figures 2 and 3, plasma levels of IL-1β and MMP-3 decreased significantly in patients assigned to supplementation with cucumber extract when final levels were compared with baseline ($p = 0.05$ and $p = 0.001$, respectively). Changes in the placebo group were not statistically significant. In both IL-1β and MMP-3 biomarkers, within-group differences were significant in favor of the experimental group. However, changes in plasma levels of COMP were not observed (Table 7).

Table 7. Changes in plasma biomarkers after 8 weeks of supplementation with cucumber extract or placebo.

Variables	Baseline	End of Study	Within-Group *p* Value	Between-Group *p* Value
IL-1β, pg/mL				
Cucumber extract (n = 29)	1.8 ± 0.9	1.3 ± 0.6	0.050	0.044
Placebo (n = 26)	2.1 ± 2.3	2.4 ± 2.3	0.305	
MMP-3, ng/mL				
Cucumber extract (n = 29)	80.6 ± 25.3	70.1 ± 25.0	0.001	0.018
Placebo (n = 26)	77.2 ± 22.5	75.5 ± 20.8	0.532	
COMP, ng/mL				
Cucumber extract (n = 29)	28.2 ± 17.9	31.0 ± 18.7	0.493	0.896
Placebo (n = 26)	27.6 ± 12.7	29.6 ± 20.0	0.638	

Data expressed as mean ± standard deviation (SD).

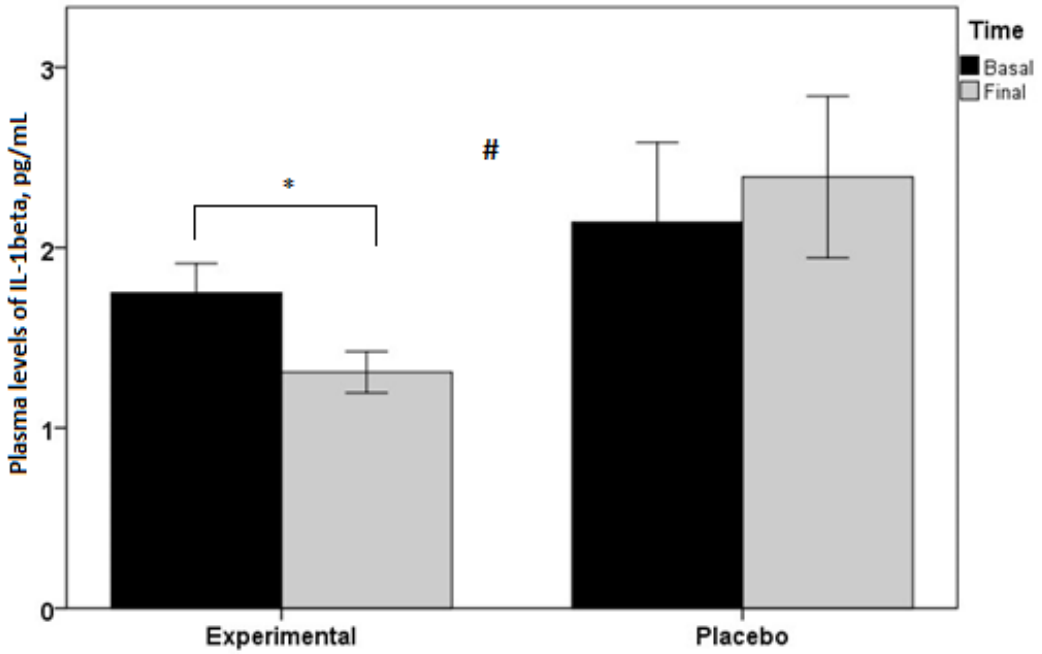

Figure 2. Changes in plasma levels of IL-1β in the experimental (cucumber extract) and placebo groups at the final visit vs. baseline (bars = ±1 standard error); * $p < 0.05$; # $p = 0.044$.

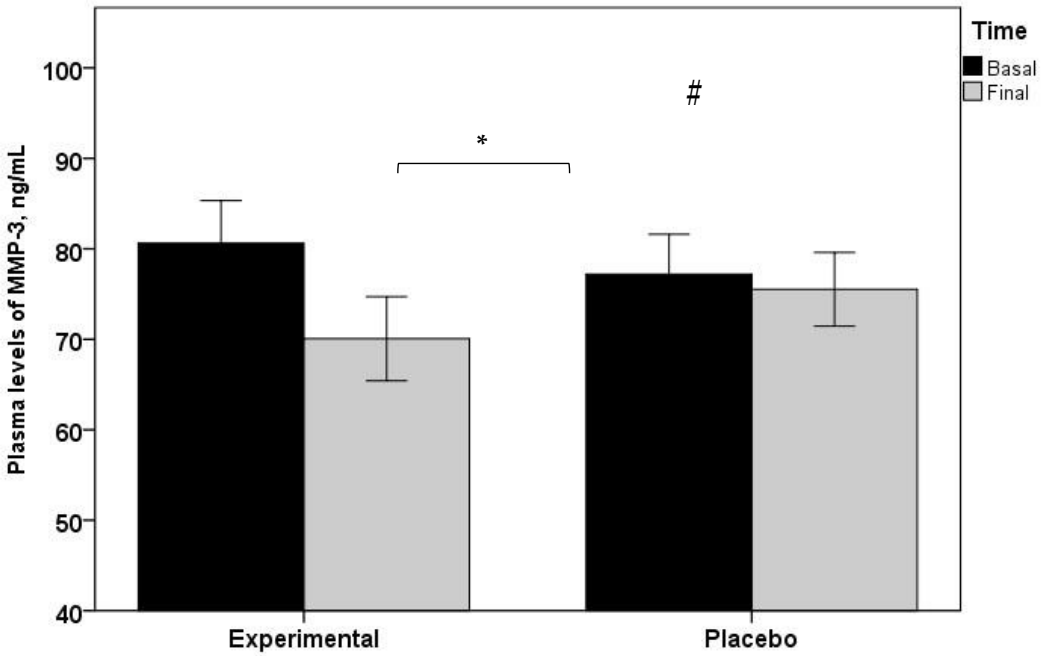

Figure 3. Changes in plasma levels of matrix metalloproteinase 3 (MMP-3) in the experimental (cucumber extract) and placebo groups at the final visit vs. baseline (bars = ±1 standard error); * $p = 0.001$; # $p = 0.018$.

3.7. Dietary Composition, Concomitant Medication and Safety Data

Differences in the micronutrient and macronutrient compositions of the subjects' individual diets were not registered. Changes in concomitant analgesic medication, which was taken by 10% and 6.9% of subjects in the experimental and placebo groups, respectively, at the beginning of the study, were not recorded. All participants who completed the study complied with the consumption of more than 80% of the capsules. Both groups showed good tolerance to the products, with only nine adverse effects in nine patients (seven in

the experimental group and three in the placebo group). All adverse effects were mild in intensity and included gastrointestinal discomfort, diarrhea, rash and back pain. None of these adverse events could be attributed to the consumption of the product. The results of the safety tests were within normal ranges.

4. Discussion

The present findings of a randomized controlled clinical trial confirm the analgesic effectiveness of dietary supplementation based on a natural extract of *Cucumis sativus* administered at 20 mg daily for 8 weeks in patients with articular pain due to knee OA. Pain intensity, assessed by VAS scores at the final visit as compared with baseline, as well as by weekly changes in VAS scores throughout the study period, demonstrated the superiority of *Cucumis sativus* in comparison with a placebo to reduce the intensity of pain significantly. All patients had moderate pain intensity at the beginning of the study, which decreased to mild pain at the final visit in the two study groups, although VAS scores were significantly lower in the experimental group. Although cucumber-treated patients were not pain-free, a mean score of 1.7 indicates very little pain. In fact, subjects assigned to the experimental group experienced a very marked change in VAS pain scores, from 5.5 at baseline to 1.7 at the end of the study, which represents a 69.9% decrease as compared with VAS scores changing from 5.2 to 2.8 in the placebo group, with a 46.1% decrease. In the setting of knee OA, marked pain relief is a clinically relevant finding. Frequent switching between non-pharmacological and pharmacological alternatives, treatment discontinuation, cycling within the healthcare system and limited benefits in the long-term effectiveness of currently available medications are some of the challenges associated with existing pain management options in patients with knee OA [19,51]. Moreover, total joint replacement is not feasible for patients with contraindications for surgery or in the presence of risk factors, such as younger age or comorbidities [52], as well as risk factors for major complications, particularly periprosthetic joint infection, after total joint surgeries [53].

Improvements observed in the VAS scores for pain intensity in the experimental group were also reflected in the overall score of the WOMAC questionnaire, as well as in the pain, stiffness and physical function subscales. Although decreases in the overall WOMAC score and in the subscales of pain and physical function were also observed among patients treated with the placebo, the magnitude of improvement was greater in the experimental group. This observation indicates the beneficial effect of dietary cucumber supplementation on quality of life. Pain and functional restrictions due to knee OA negatively impact daily living activities, social life and psychological well-being, reducing the quality of life of patients [54]. In addition, treatment satisfaction rates are related to the severity of pain, with lower pain, greater pain reduction post-medication and meeting pain management expectations as predictive factors of higher satisfaction [55,56]. In our study, however, satisfaction with dietary supplementation was not evaluated.

In a previous 6-month randomized controlled study carried out by Nash et al. [46], involving supplementation with a proprietary aqueous extract of *Cucumis sativa*, at 10 mg twice a day, the percentage of change in the WOMAC score after 60 days of supplementation was 40.1%, as compared with 21.2% in controls treated with glucosamine-chondroitin (1350 mg twice daily). Similar decreases were observed in our study, with changes in the WOMAC score of 41% in the experimental group and 21.3% in the placebo group. However, decreases in the VAS score for pain intensity were 31.4% in the supplementation group and 19.8% in the glucosamine-chondroitin group, which are notably lower than 69.9% and 46.1%, respectively, found in our study.

Interestingly, the consumption of the cucumber supplement for 8 weeks improved joint function, as shown by the results of dynamometry testing and the TUG test. An improvement in muscle function was associated with significant increases in isokinetic and isometric dynamometry variables, particularly with isokinetic $60^{\circ}\cdot s^{-1}$ and $180^{\circ}\cdot s^{-1}$ knee flexion exercises. Muscle rehabilitation programs in patients with OA are especially designed to improve muscle function, which can be translated into improved functional performance [57]. However,

important and sustained improvements in muscle strength are the benefits achieved with exercise interventions in people with knee OA [58]. Independently of the high content of minerals and vitamins, as well as the antioxidant activity of *Cucumis sativus*, the mechanisms by which cucumber supplementation showed a beneficial effect on muscle function are still unknown and merit further research.

This product contains 5% citrulline. Citrulline is a potent endogenous precursor of arginine [36], the role of which is involved in the positive regulation of the bioavailability of arginine. Nitric oxide (NO) is a free radical synthesized by arginine by a family of NO synthase (NOS) enzymes. NO synthesis is regulated by the activation of NOS isoforms (inducible NOS (iNOS), endothelial NOS (eNOS) and neuronal NOS (nNOS)). NO generated by iNOS is a potent pro-inflammatory mediator, whereas NO generated by eNOS is involved in the control of cardiovascular homeostasis [37]. Increased NO by stimulation of the synthesis of iNOS by chondrocytes is involved in the pathophysiology of OA. Immunofluorescence studies of iNOS expression in different cell populations in synovial membrane biopsies of patients with knee OA showed that, during early OA, iNOS is mostly located in macrophages, whereas, in advanced OA, iNOS is also expressed in leukocytes [38]. An increase in citrulline/arginine would be able to inhibit the inflammatory-related reactions produced by iNOS, also producing an increase in the amount of eNOS with vasodilation and resulting in better cartilage nutrition [39]. This could lead to a decrease in the whole evolutionary–degradative and inflammatory process of the joint, which could lead to an improvement in the clinical symptoms [40,59].

In line with the anti-inflammatory activity of cucumbers, we found a significant decrease in the plasma levels of IL-1β in the experimental group only. IL-1β is a key pro-inflammatory cytokine involved in the cytokine cascade in pain and inflammatory processes [60,61]. Moreover, a significant reduction in plasma levels of MMP-3 in the experimental group was observed, whereas, in the placebo group, values of MMP-3 at baseline and at the end of the study were similar. Matrix metalloproteinases (MMPs) are a class of enzymes involved in the degradation of extracellular matrix molecules, and MMP-3 is considered to be of importance in the degradation of articular cartilage. In a study in patients with hip, knee and hand OA, treatment with NSAIDs was associated with a significant reduction in MMP-3 levels [62]. Increased plasma levels of MMP-3 have been reported in patients with knee OA and generalized OA as compared with normal subjects [63]. Moreover, increased levels of plasma and synovial fluid MMP-3 have been detected in patients with hip and knee OA, suggesting that MMP-3 could be used as a potential biomarker of knee OA [64]. The cucumber extract used in this study was associated with an improvement in biomarkers of inflammation as a manifestation of reduced cartilage degradation in knee OA.

Some limitations of the study should be considered when interpreting the present results, particularly the reduced sample size and the treatment period, which was restricted to 8 weeks, as well as the reliance on endpoints (subjective and biomarkers) that could be influenced by other confounding factors. In this respect, the inclusion of imaging endpoints in future studies would provide further support to our findings. Dietary intake during the study was a variable that was not controlled, despite the strong recommendation to maintain dietary habits throughout the period of supplementation.

5. Conclusions

In the present randomized controlled study, the use of oral supplementation with 20 mg/day of a natural cucumber extract for 8 weeks in adults older than 40 years of age with knee OA provided significant relief of joint pain and improvements in quality of life, mobility and muscle function. Other effects of cucumber supplementation were a significant decrease in inflammatory and cartilage degradation biomarkers. Further studies are required to assess the benefits of cucumber supplementation in the setting of knee OA, but the present findings in patients who met ACR diagnostic criteria for knee OA may support the usefulness of cucumber extract dietary supplementation in incipient OA,

as well as to maintain and improve joint health, alleviating minor joint discomfort and preserving joint mobility. Further randomized controlled studies are necessary to confirm the present findings.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Study data are available from the principal investigator (J.F. López-Román) upon request.

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