International Journal of Clinical Medicine, 2026, 17(4), 116-130
https://www.scirp.org/journal/ijcm
ISSN Online: 2158-2882
ISSN Print: 2158-284X

Retrospective Case Series on Clinical and Functional Outcomes in 40 Osteoarthritis Patients Receiving a Nutraceutical Supplement in Real-World Practice

Beniamino Palmieri[1,2], Maria Vadalà[1], Lucia Palmieri[1,2]

[1]Network del Secondo Parere, Modena, Italy
[2]Polyclinic University Hospital of Modena, Modena, Italy
Email: palmieriben21@gmail.com

How to cite this paper: Palmieri, B., Vadalà, M. and Palmieri, L. (2026) Retrospective Case Series on Clinical and Functional Outcomes in 40 Osteoarthritis Patients Receiving a Nutraceutical Supplement in Real-World Practice. *International Journal of Clinical Medicine*, **17**, 116-130.
https://doi.org/10.4236/ijcm.2026.174009

Received: March 12, 2026
Accepted: April 7, 2026
Published: April 10, 2026

Abstract

Background: Degenerative joint diseases are among the leading causes of chronic pain and disability in the adult population. Assessing the effect of therapeutic interventions in real-world clinical settings (Real World Practice) allows for the integration of randomized controlled trial (RCT) data with observational clinical insights. **Objective:** To evaluate, in daily clinical practice, the improvement of joint function and indirect parameters of cartilage quality in patients with degenerative arthropathy monitored over a 2-month period. **Materials and Methods:** A retrospective observational case series study was conducted on 40 patients with symptomatic osteoarthritis (OA). Participants were administered one sachet of a nutraceutical supplement daily for two months. Clinical evaluation occurred at baseline (T0), first follow-up (T1), and second follow-up (T2) using a structured questionnaire covering pain, stiffness, and functional limitation (analogous to VAS and WOMAC scales). **Results:** A progressive reduction in scores for pain, joint stiffness, and difficulty in daily activities was observed. Comparison across follow-up intervals showed significant symptomatic improvement compared to baseline, suggesting a favorable effect on primary osteoarthritis parameters. **Conclusions:** Results suggest that this nutraceutical formulation may improve symptoms associated with primary osteoarthritis. Further controlled studies with larger samples are required to confirm these encouraging findings.

Keywords

Cartilage, Osteoarthritis, Knee, Hip, Hands, Feet, Spine, IMOpro Cartilago®

1. Introduction

Osteoarthritis (OA) is the most common degenerative joint disease globally and a leading cause of chronic pain and disability in adults and older adults. It is characterized by progressive degeneration of articular cartilage, remodelling of subchondral bone, osteophyte formation, and varying degrees of synovial inflammation, resulting in pain, stiffness, and progressive functional limitation of the affected joint. The disease can affect various joint sites, including the spine (spondyloarthrosis), the knee (gonarthrosis), the hip (coxarthrosis), and the small joints of the hands and feet [1] [2]. Osteoarthritis is traditionally classified into primary (idiopathic) and secondary forms. The primary form is the most common variant and is diagnosed in the absence of an identifiable cause, although risk factors such as advanced age, genetic predisposition, female gender, obesity, biomechanical joint alterations, and joint trauma may contribute to the development and progression of the disease. The secondary form, on the other hand, results from predisposing conditions such as trauma, joint malformations, metabolic diseases, or chronic inflammatory diseases [2].

Among the most common locations of primary osteoarthritis are the knee and hip, which are responsible for a significant proportion of musculoskeletal disability in the adult population. Knee OA is a major cause of pain and functional limitation in individuals over the age of 50 and is often associated with biomechanical and metabolic factors, including excess weight and previous joint trauma. Similarly, primary coxarthrosis is a progressive degenerative disease affecting the hip joint and has an estimated prevalence of 3% to 6% in the Caucasian population, with significant social and health implications [3] [4].

Another site frequently affected by primary osteoarthritis is the small joints of the hands and feet, particularly the distal and proximal interphalangeal joints and the trapeziometacarpal joint of the thumb. Osteoarthritis of the hand is a heterogeneous condition with an increasing prevalence with age and a higher incidence in females, especially after menopause. In the elderly population, the radiographic prevalence can reach very high values, reaching up to 80% of subjects [5].

Spondyloarthritis, which affects the apophyseal joints and intervertebral discs of the spine, is a common manifestation of age-related joint degeneration and can be associated with symptoms such as chronic low back pain, stiffness, and reduced spinal mobility. Degenerative changes in the spine, along with osteoarthritis of large weight-bearing joints such as the knee and hip, contribute significantly to the overall burden of musculoskeletal disability in the adult population [1].

Given increasing life expectancy and the aging population, osteoarthritis represents a significant challenge for healthcare systems, with significant clinical, functional, and economic implications. Understanding the pathogenetic mechanisms, risk factors, and clinical characteristics of different joint locations is therefore es-

sential to improve prevention, early diagnosis, and treatment strategies for the disease [1] [6].

Randomized controlled trials are the gold standard for evaluating the effectiveness of treatments, but they often include selected populations and conditions far removed from daily clinical practice [7] [8]. Real-world practice studies, on the other hand, allow us to evaluate the effect of interventions in real-world care settings, providing complementary information on adherence, tolerability, and long-term functional impact [9] [10].

Assessing cartilage improvement in an outpatient setting is complex: quantitative magnetic resonance imaging is expensive and difficult to replicate, while joint ultrasound is a non-invasive, accessible, and reproducible method for serial monitoring of superficial cartilage and synovitis [10] [11].

The aim of this observational case series is to document, in a real-world outpatient setting, the clinical and functional evolution of patients with primary osteoarthritis and to monitor indirect parameters of cartilage quality over time.

2. Materials and Methods

A retrospective observational case series study was conducted at the Second Opinion Network[1] (Via Ciro Bisi 125, Modena, Italy) [12]-[14] to evaluate the effect of a nutraceutical treatment improving symptoms associated with idiopathic osteoarthritis. The retrospective analysis included three clinical assessments: baseline (T0), first follow-up (T1), and second follow-up (T2).

Inclusion criteria: Age between 20 and 90 years, joint pain for at least 6 months, Kellgren-Lawrence grade II-III, ability to walk independently.

Exclusion criteria: Inflammatory arthritis, prior prosthetic surgery, intra-articular injections in the previous 3 months, chronic systemic corticosteroid therapy, severe renal insufficiency, hepatic and cardiovascular insufficiency, and uncontrolled type 2 diabetes.

The retrospective analysis included patients with symptomatic osteoarthritis referred to outpatient clinics. All participants had a clinical diagnosis of primary osteoarthritis based on clinical assessment and reported symptoms.

Therefore, adult subjects who consented to participate in the study and receive the planned treatment were included in the clinical observation. Patients with inflammatory joint diseases, recent knee trauma, recent previous joint surgery, or other clinical conditions that could interfere with symptom assessment or adherence to the treatment protocol were excluded.

[1]The Second Opinion Network, which organized this retrospective study, is a rapid web-based and outpatient consultation system that includes a large number of specialists in Italy and abroad. Any patient suffering from any disease or multimorbidity who has not been adequately satisfied with the diagnosis and/or prescribed treatment can turn to it for treatment or to improve their quality of life. Individual consultations are conducted online (info@medicocuratestesso.com) or face-to-face. The Second Opinion research team develops targeted "problem-solving" therapies, also using galenic prescriptions and evaluating the evidence or consistency of new prevention and treatment hypotheses through volunteer observational studies, as in the study in question.

Forty volunteers between the ages of 25 and 90 with symptomatic idiopathic osteoarthritis were evaluated. They declared that they were not taking any medications and that they were not pregnant (for women) (Table 1, Table 2). The mean age of the study population was 63.83 ± 18.18 (Mean ± SD), with a distribution of 20 men (50%) and 20 women (50%). All patients were informed of the purpose of this retrospective study and therefore signed the informed consent form and agreed to participate.

Table 1. Baseline characteristics of patients enrolled in this observational study.

N.	Sex	Age	Weight (Kg)	Height (cm)	Conditions
#1	M	62	86	179	Coxarthrosis
#2	F	45	51	159	Osteoarthritis hands
#3	M	71	86	181	Coxarthrosis
#4	F	42	50	153	Spondyloarthrosis
#5	M	84	88	161	Gonarthrosis dx
#6	M	59	88	176	Osteoarthritis feet
#7	M	26	83	154	Gonarthrosis dx
#8	F	59	53	150	Osteoarthritis hands
#9	F	87	58	155	Coxarthrosis sx
#10	F	73	78	157	Spondyloarthrosis
#11	F	76	94	173	Gonarthrosis dx
#12	M	88	85	164	Gonarthrosis dx
#13	M	49	95	183	Gonarthrosis dx
#14	F	78	61	156	Osteoarthritis hands
#15	M	63	73	179	Coxarthrosis dx
#16	F	25	50	164	Osteoarthritis hands
#17	M	77	95	169	Coxarthrosis dx
#18	F	44	62	160	Spondyloarthrosis
#19	F	82	68	155	Spondyloarthrosis
#20	M	88	79	171	Gonarthrosis sx
#21	M	74	86	178	Osteoarthritis feet
#22	F	51	57	161	Gonarthrosis sx
#23	F	75	86	167	Coxarthrosis dx
#24	F	48	57	162	Osteoarthritis hands

Continued

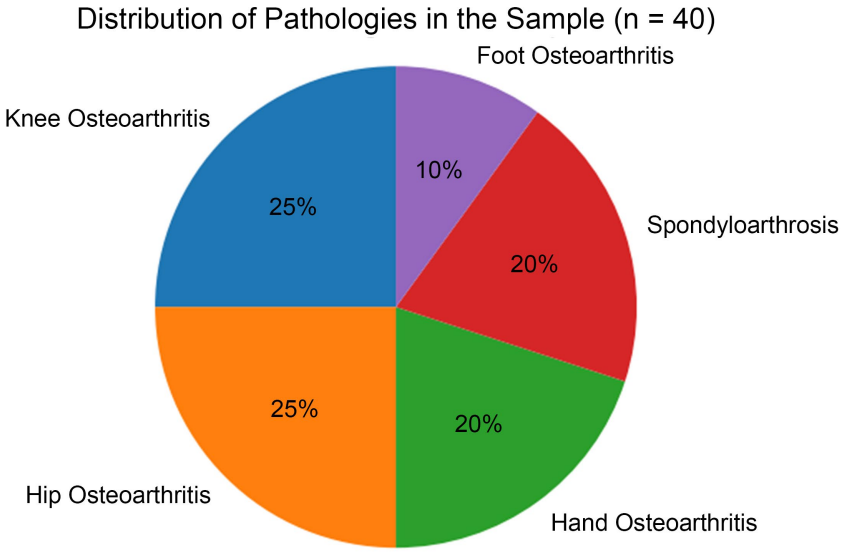
#25	M	71	87	168	Coxarthrosis sx
#26	M	49	64	181	Spondyloarthrosis
#27	F	82	69	151	Coxarthrosis dx
#28	M	76	83	167	Osteoarthritis feet
#29	F	89	73	151	Osteoarthritis hands
#30	F	54	58	174	Spondyloarthrosis
#31	M	67	89	178	Coxarthrosis dx
#32	F	49	78	182	Gonarthrosis dx
#33	M	77	95	161	Gonarthrosis dx
#34	M	36	79	185	Spondyloarthrosis
#35	M	80	72	162	Osteoarthritis feet
#36	M	29	82	187	Gonarthrosis dx
#37	F	54	57	160	Osteoarthritis hands
#38	M	73	84	163	Spondyloarthrosis
#39	F	83	62	149	Coxarthrosis sx
#40	F	58	65	161	Osteoarthritis hands

Table 2. Summary of baseline characteristics of the population enrolled in this observational study.

Variable	Value
Sex (M/F)	20/20
Age (anni)	63.83 ± 18.18
Weight (kg)	74.15 ± 14.16
Height (cm)	166.18 ± 10.95
BMI (kg/m^2)	26.86 ± 4.65

All 40 consecutively enrolled patients who had approached the Second Opinion Network for a treatment proposal that could improve their quality of life, previously inadequately addressed by previous treatments (20 women, 20 men; mean age 63.83 ± 18.18 years) were admitted to the observation based on a clinical, functional, and radiographic diagnosis of primary osteoarthritis according to the criteria of the American College of Rheumatology (**Figure 1**).

All patients signed informed consent for the processing of anonymized clinical data. The study was conducted in accordance with the principles of the Declaration of Helsinki.



Conditions	Number of Subjects (n)	Percentage
Gonarthrosis	10	25%
Coxarthrosis	10	25%
Osteoarthritis hands	8	20%
Spondyloarthrosis	8	20%
Osteoarthritis feet	4	10%
Total	40	100%

Figure 1. Percentage distribution of pathologies in the sample (n = 40).

Each patient included in the retrospective took the nutraceutical IMOpro® CARTILAGO[2]. The treatment protocol required one sachet per day, diluted in a glass of water, for a total period of two months. Patients were advised and monitored to adhere to the indicated dosage regimen for the entire duration of the study, and not to take steroids or common NSAIDs in case of recurrence of symptoms without prior consent from the medical monitor who was responsible for monitoring the dosage and duration of intake. The formulation includes several structural and bioactive components involved in cartilage and connective tissue metabolism, including collagen peptides, glucosamine sulfate, chondroitin sulfate, methylsulfonylmethane (MSM), and sodium hyaluronate. These substances are frequently used individually or in combination in the conservative management of osteoarthritis due to their potential role in maintaining the integrity of the cartilage extracellular matrix and supporting joint function. The formula is also enriched with plant extracts and micronutrients with antioxidant and anti-inflammatory properties, including Boswellia serrata, acerola (a natural source of vita-

[2]IMOpro® CARTILAGO is a nutraceutical supplement developed by IMO S.p.A. (Italy), available in packs containing 15 single-dose sachets of 7.5 g of powder to be dissolved in water. The product is formulated as a multi-component nutraceutical preparation intended to support joint function and cartilage metabolism.

min C), and hesperidin, combined with trace elements such as zinc, manganese, magnesium, and copper, involved in the enzymatic processes that regulate connective tissue metabolism. In particular, vitamin C contributes to normal collagen formation and the physiological active performance of cartilage and bones, while manganese and copper participate in the coenzyme processes of connective tissue homeostasis and protection from oxidative stress. Furthermore, glucosamine and chondroitin sulfate are widely confirmed in the evidence-based scientific literature as structural components of articular cartilage, resulting in their frequent use as "symptomatic slow-acting drugs for osteoarthritis" [15] in the conservative treatment of osteoarthritis. Similarly, hydrolyzed collagen and hyaluronic acid, as bioavailable substrates, have been associated with potentially beneficial effects on joint function and pain symptoms in patients with degenerative joint disease. In this observation, each patient took one sachet of the product per day, dissolved in a glass of water, for a total period of two months, according to the dosage schedule indicated by the manufacturer.

Symptoms and joint function were assessed using a self-assessment questionnaire structured in three sections, administered to patients at the three time points specified in the protocol (T0, T1, and T2). The questionnaire investigated symptoms reported in the 48 hours preceding completion and was divided as follows: 1) Section A—Pain: patients were asked to indicate the intensity of pain attributable to osteoarthritis perceived in the knee in the previous 48 hours; 2) Section B—Joint Stiffness: participants rated the presence and intensity of joint stiffness, distinct from pain, attributable to knee osteoarthritis in the last 48 hours; and 3) Section C—Physical Functioning: this section assessed the difficulty patients encountered in carrying out common physical activities of daily living due to symptoms associated with knee osteoarthritis. The questionnaire structure reflected domains commonly used in the clinical assessment of knee OA, similar to those provided by validated tools such as the WOMAC Index [16] [17]. Each domain consists of 24 items rated on a [0 - 5-points] scale, with higher scores indicating greater symptom severity. Domain scores were summed to obtain a total score ranging from [0 - 120]. The questionnaire was inspired by instruments commonly used in osteoarthritis assessment, particularly the WOMAC Index, but was not formally validated. The cohort of subjects observed with osteoarthritis of the knee, hip, hand, foot, and spine was evaluated by X-ray and MRI. The current questionnaire wording and interpretation are mainly knee-specific, so either restrict the analysis to one joint site or present site-specific outcome wording and results.

3. Statistical Analysis

Statistical analysis was performed using GraphPad Prism 7 (GraphPad Software Inc., San Diego, CA, USA). The P value considered significant was $P < 0.05$. Variables related to the three domains assessed (pain, joint stiffness, and physical function) were analysed by comparing the values recorded at the different time points of the study (T0, T1, and T2). Data were expressed as mean ± standard

deviation for quantitative variables. Differences between the different assessment time points were analysed using appropriate statistical tests for paired data to assess any change in symptoms over the course of treatment.

4. Results

All patients completed the prescribed therapeutic indications, taking the nutraceutical treatment for the entire duration of the observational study without any drop-outs. The product's palatability, in particular, did not affect intake and was generally appreciated.

Four of them took NSAIDs or steroids for a period of no more than 3 days, with prior authorization and medical monitoring due to acute environmental exposure to bad weather, prolonged supramaximal exertion, and intercurrent trauma. In all the others, especially after the second week of treatment, pain, especially in the morning, was tolerable with the supplementation alone. The primary outcome of this observational study was the assessment of changes in symptoms associated with the individual disease, with particular reference to: 1) joint pain intensity, 2) joint stiffness, and 3) functional limitation in daily activities. These parameters were monitored at the three time points established by the protocol (T0, T1, and T2) using a self-assessment questionnaire structured according to the domains commonly used in the clinical assessment of primary osteoarthritis, similar to those provided by the WOMAC Index.

Regarding pain assessment, analysis of pain domain scores showed a progressive reduction in pain symptoms over the observation period. The mean pain score decreased from 6.8 ± 1.4 at baseline (T0) to 4.9 ± 1.3 at the first follow-up (T1) and to 3.2 ± 1.2 at the second follow-up (T2), showing a statistically significant reduction compared to baseline ($p < 0.05$).

Similarly, joint stiffness scores also showed improvement over the course of treatment. The mean stiffness score decreased from 5.9 ± 1.6 at T0 to 4.1 ± 1.4 at T1, reaching 2.8 ± 1.3 at T2, indicating a progressive improvement in symptoms.

Regarding physical function, the assessment of functional limitation in daily activities showed an improvement in patients' functional capacity over the course of this observational study. The mean score for difficulty in performing daily physical activities showed a significant reduction between baseline and subsequent assessments, suggesting improved knee joint function (**Table 3**, **Figure 2**).

Overall, the results obtained indicate a clinically relevant improvement in the main symptoms associated with osteoarthritis, including pain, stiffness, and functional limitation. No significant adverse events were observed.

We also considered it appropriate to evaluate the maximum isometric muscle strength of patients, particularly those with hand osteoarthritis and gonarthrosis and coxarthrosis, i.e., the development of tension by the muscle at a constant length in response to an isotonic contraction, using an "FH-500" digital dynamometer (Rupac Srl, Milan, Italy) before and after treatment (T0 and T2). Each patient was asked to contract their muscles as strongly as possible for 6 seconds

and then immediately relax them [18]. We performed four measurements per participant (elbow extension, hip abduction, knee extension, and ankle dorsiflexion) repeated three times at 1-minute intervals, on both the right and left sides of the body, in order to record the mean of the values, expressed in Newtons (N). The measurements were performed in a standardized manner by the same observer to reduce inter-operator variability (**Figure 3**, **Figure 4**, **Table 4**).

The assessment of maximum isometric muscle strength, measured using an FH-500 digital dynamometer at baseline (T0) and at the end of treatment (T2), showed an increase in mean strength values for all measurements.

Specifically, mean elbow extension muscle strength increased from 182.4 ± 36.7 N at T0 to 214.8 ± 39.2 N at T2, with an average increase of 17.8%. Improvement was also observed in hip abduction, with mean values increasing from 265.1 ± 41.5 N at T0 to 301.6 ± 44.8 N at T2 (+13.8%).

Table 3. Trend of the main clinical symptoms at the three time points envisaged by the protocol (T0, T1, and T2). Parameters relating to joint pain intensity, joint stiffness, and functional limitation in daily activities were assessed using a self-assessment questionnaire structured according to the domains commonly used in the clinical assessment of primary osteoarthritis, similar to the WOMAC Index. Values are expressed as mean ± standard deviation (SD).

Evaluated parameter	T0 (Baseline) Average ± DS	T1 Average ± DS	T2 Average ± DS
Intensity of joint pain	6.8 ± 1.4	4.9 ± 1.3	3.2 ± 1.2
Joint stiffness	5.9 ± 1.6	4.1 ± 1.4	2.8 ± 1.3
Functional limitation in daily activities	6.5 ± 1.5	4.7 ± 1.4	3.3 ± 1.3

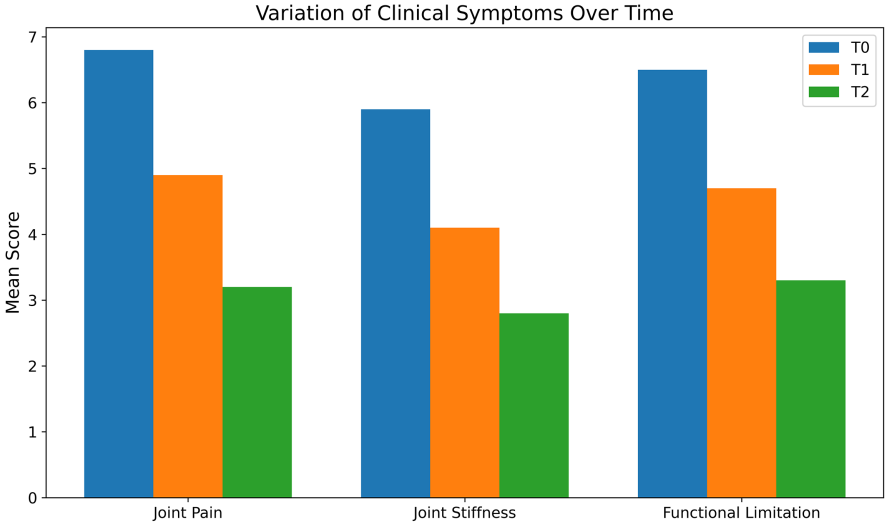


Figure 2. Trend of mean scores for joint pain, joint stiffness, and functional limitation in daily activities at the three assessment points (T0, T1, and T2). The scores show a progressive reduction in symptoms over the course of this observation.

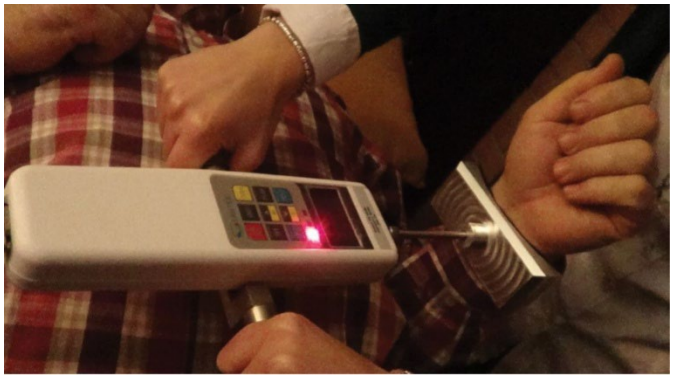


Figure 3. Left elbow extension.

Figure 4. Dorsiflexion of the right ankle.

Table 4. Variation of maximum isometric muscle strength between T0 and T2.

Measurement	T0 (N) Average ± DS	T2 (N) Average ± DS	Improvement %
Elbow extension	182.4 ± 36.7	214.8 ± 39.2	+17.8%
Hip abduction	265.1 ± 41.5	301.6 ± 44.8	+13.8%
Knee extension	298.7 ± 46.3	336.9 ± 49.1	+12.8%
Ankle dorsiflexion	121.6 ± 28.4	142.5 ± 30.1	+17.2%

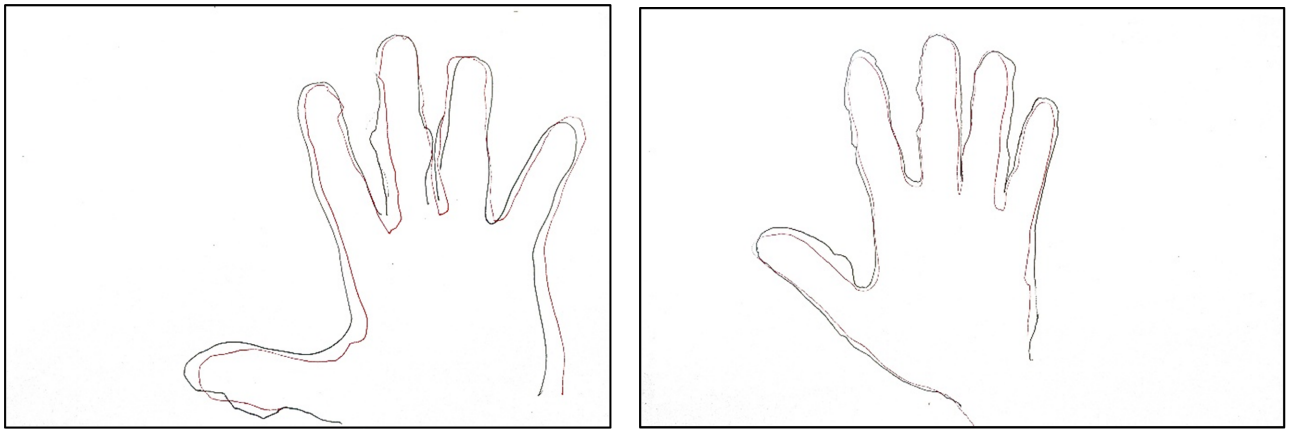
Similarly, mean knee extension force increased from 298.7 ± 46.3 N at T0 to 336.9 ± 49.1 N at T2, corresponding to a 12.8% increase. Ankle dorsiflexion also showed improvement, with mean values increasing from 121.6 ± 28.4 N at T0 to 142.5 ± 30.1 N at T2, corresponding to a 17.2% increase.

Improved muscle strength was particularly evident in patients with hand osteoarthritis, in whom increased elbow extension strength was associated with improved upper limb function. In patients with coxarthrosis and gonarthrosis, however, increased hip abduction and knee extension strength indicated improved lower limb stability and functional capacity.

Overall, the results suggest that the treatment resulted in a significant increase in maximum isometric muscle strength, resulting in improved patients' functional

capacity. This improvement was observed bilaterally, on both the right and left sides of the body.

To detect objective improvement in the metacarpophalangeal and interphalangeal joints, we developed our own original before-and-after comparison system, called alginate-hand-fingerprint. This system is based on the comparison of two imprints (one at time 0 and the other at the end of the trial) produced by standard hand pressure, the soles of which are previously coated with copying ink on a 4 mm thick alginate-covered surface. By comparing these imprints, it is possible to detect changes in volume, shape, and deformity of the arthritic hand, with the possibility of highlighting joint contractures during flexion that will not be inked in the imprint itself. A second, simpler but no less effective method is hand profile (RE-tracing), which involves tracing the patient's hand on the same sheet of paper using a pen. The imprint is outlined in different colours (black at time 0 and red at time 2) and is performed under standard pressure conditions by the experimenter. This test is very useful for evaluating the improvement of edema and joint swelling before and after and can be considered complementary to the first (Figure 5).



(a) (b)

Figure 5. Images of the hand profile test—RE-tracing of two patients with osteoarthritis of the hands: (a) T0 = black colour, T2: red colour, patient: BG, Sex: F, Age 48. (b) T0 = black colour, T2: red colour, patient: LA, Sex: F, Age 89.

In our study, 8 patients with hand osteoarthritis were assessed using the hand profile-RE-tracing method at baseline (T0) and at the end of treatment (T2). Comparison of the tracings obtained at the two time points, created on the same sheet of paper by tracing the patient's hand with different colours (black at T0 and red at T2), highlighted morphological changes in the metacarpophalangeal and interphalangeal joints. In particular, a reduction in the profile of joint swelling and periarticular oedema was observed in several patients, evidenced by a lesser expansion of the joint contour in the tracing taken at the end of treatment. In some cases, the comparison between the two profiles also showed greater regularity of the digital contour, suggesting an improvement in joint mobility and a reduction in functional deformities associated with the arthritic process. Overlapping the tracings allowed these changes to be visually appreciated, enabling an

immediate qualitative assessment of the clinical evolution of the arthritic hand. Overall, most patients showed an improvement in hand profile, with reduced joint swelling and better definition of the anatomical contours of the fingers at time T2 compared to the baseline assessment. No patients showed any significant worsening of the morphological picture. The hand profile-RE-tracing method has proven to be a simple, reproducible, and easy-to-use clinical tool for visually documenting the morphological changes of hands affected by osteoarthritis over the course of treatment (**Figure 5**).

5. Discussion

The study highlights how a structured outpatient treatment program is associated with significant clinical improvement in patients with symptomatic osteoarthritis. Pain reduction and functional improvement are consistent with the literature on conservative multimodal interventions. We believe that the quality and purity of the raw materials used, and the successful stoichiometric integration of the various active ingredients are crucial to the success of the supplement studied in our study. These ingredients can achieve a significant level of symptomatic benefits, requiring only sporadic and very short-term use.

The correlation between clinical improvement and indirect ultrasound changes is particularly significant: the reduction of periarticular tissue oedema and synovial effusion suggests a decrease in local inflammatory activity, while the stabilization of cartilage thickness may indicate a slowing of the degenerative process.

RWE studies allow us to observe therapeutic efficacy in heterogeneous populations, often excluded from randomized trials, such as elderly patients or patients with multiple comorbidities. In this context, treatment adherence and patient education are key factors.

Osteoarthritis is a leading cause of chronic pain and disability in adults and older adults, significantly impacting patients' quality of life and healthcare systems. Among the most frequently involved joints, the knee is one of the most affected, with a prevalence increasing with age and the increase in metabolic and biomechanical risk factors. The results of this study suggest that taking the nutraceutical in question for a two-month period is associated with an improvement in the main symptoms of primary osteoarthritis, evidenced by reduced scores for pain, joint stiffness, and functional limitation.

In recent years, interest in nutraceutical treatments for osteoarthritis has increased considerably. Several studies have shown that specific nutritional compounds can contribute to the modulation of joint inflammatory processes, improved joint function, and reduced pain symptoms in patients with osteoarthritis [19]-[22].

Clinical assessment tools used in osteoarthritis studies, such as the WOMAC Index, allow for standardized measurement of the main symptomatic domains of the disease, including pain, stiffness, and functional limitation. The results observed in this study are consistent with what is reported in the literature regarding

symptom improvement in patients undergoing conservative and nutraceutical treatments. However, the present study has some limitations, including the relatively small sample size and the lack of a control group.

Therefore, further controlled clinical studies with larger samples are needed to confirm the observed results and further clarify the role of nutraceuticals in the management of knee osteoarthritis.

6. Conclusion

Outpatient clinical monitoring in real-world practice has documented significant improvements in pain and joint function, associated with indirect signs of cartilage stabilization, following 60-day therapy with the nutraceutical supplement. These results support the usefulness of personalized conservative programs and joint ultrasound as a repeatable and sustainable follow-up tool in clinical practice. Further randomized, controlled studies are needed to evaluate the promising effect of this nutraceutical supplement.

Acknowledgements

We would like to express our sincere gratitude to Dr. Luigi Alberto Marrari for his collaboration and for providing the essential supporting literature for this study.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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