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Article

The Effectiveness and Safety of a New Nutraceutical in Patients with Knee Osteoarthritis: A Pilot Study

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Abstract

Background: Nutraceuticals are increasingly used in clinical practice for their anti-inflammatory, antiproliferative, and antioxidant properties. This study aimed to evaluate the safety and efficacy of a fixed nutraceutical combination containing chondroitin sulfate, α-lipoic acid, astaxanthin, lycopene, escin, and omega-3 fatty acids [eicosapentaenoic acid and docosahexaenoic acid] in improving pain and quality of life in patients with chronic knee osteoarthritis (OA). Methods: This observational study included patients with chronic knee OA referred to the ambulatory pain clinic at Dulbecco University Hospital, Catanzaro, Italy. Participants received one tablet daily for three months. Quality of life was assessed using the 36-Item Short Form Health Survey (SF-36), and adverse drug reactions (ADRs) were evaluated using the Naranjo scale. Results: Fifty patients (20 men and 30 women; mean age, 63.6 ± 11.4 years; range, 26–88 years; mean body mass index, 26.9 ± 3.7 kg/m^2) were enrolled. A statistically significant improvement in pain symptoms was observed over time ($p < 0.01$). No ADRs were reported during the study period. Conclusions: The fixed nutraceutical combination improved pain and quality of life in patients with chronic knee osteoarthritis and demonstrated an excellent safety profile.

Keywords: nutraceutical; knee osteoarthritis; safety; pain; quality of life

1. Introduction

Knee osteoarthritis (OA) is a multifactorial disease characterized by articular cartilage degradation, formation of bone osteophytes, subchondral bone sclerosis, and, in advanced stages, the development of subchondral cysts [1]. The most common clinical manifestation of knee OA is persistent or intermittent chronic pain > 3 months, which typically correlates with the extent of joint destruction [2,3].

Since usually drug treatment could be used, e.g., non-steroidal anti-inflammatory drugs (NSAIDs) [4] with or without topical compounds (e.g., corticosteroids or hyaluronic acid) [5–7] their use could be related to the development of adverse drug reactions (ADRs) or drug-interactions [8,9].

Advances in molecular medicine suggest that targeting specific cellular pathways may alter the course of chronic diseases. In this context, compounds with antioxidants and anti-inflammatory properties hold potential as therapeutic agents in the management of various pathological conditions [10–12].

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International guidelines suggest that dietary supplements may represent a first-line treatment option for patients with mild to moderate knee osteoarthritis; however, their safety should be carefully evaluated, especially in patients receiving multiple medications [13].

Several nutrients used in the management of knee OA exhibit anti-inflammatory and antioxidant properties. Among these, chondroitin sulfate and alpha-lipoic acid have been reported to play a significant role in managing this chronic condition. Two systematic reviews have demonstrated the efficacy of glucosamine and chondroitin compared to active controls and placebo [14,15]. Additionally, alpha-lipoic acid has been proposed as a potential therapeutic agent due to its antioxidant activity [16].

Thia pilot study serves as a proof of concept for a fixed combination of chondroitin sulfate, alpha-lipoic acid, astaxanthin, lycopene, escin, omega-3 fatty acids, including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), to evaluate its effects on symptoms of mild to moderate knee pain in patients with knee OA. Effective symptom reduction may significantly improve knee mobility and overall quality of life in these patients.

2. Materials and Methods

2.1. Study Design

In this observational, single-center, open-label study, patients of both sexes with a diagnosis of knee osteoarthritis and referred to the pain room of the Clinical Pharmacology and Pharmacovigilance Unit of the "R Dulbecco" University Hospital of Catanzaro from January 2025 to September 2025, were enrolled. During this period, treatment with the fixed combination of a new nutraceutical (1 tablet daily for 3 months; Diaco Biofarmaceutici, Trieste, Italy) was added to their common therapy. At the beginning of the study, patients were asked not to change their usual dietary habits or any other medications used for their comorbidities.

2.2. Ethical Considerations

To ensure participant privacy, each subject was assigned a numerical identification code generated by a physician who was not involved in the study. All participants were fully informed about the study's purpose and procedures and provided written informed consent prior to enrollment. The study was conducted in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki, with full compliance with Italian privacy regulations. Ethical approval was obtained from the Institutional Ethics Committee (Authorization No. 120/2018; Clinical trial registration: NCT05509075).

2.3. Inclusion and Exclusion Criteria

Patients were enrolled according to the following inclusion criteria:

Age ≥ 18 years, of either sex.

Diagnosis of knee osteoarthritis (OA).

Ability to comply with the study protocol and provision of written informed consent.

Exclusion criteria included:

a) Age < 18 years.

b) Pregnancy or breastfeeding, or women of childbearing potential not using adequate contraception.

c) Known allergy or hypersensitivity to the study treatment or rescue medications.

d) Advanced-stage malignancies.

e) Moderate to severe renal impairment (glomerular filtration rate < 30 mL/min).

f) Severe hepatic or cardiac dysfunction.

g) Severe asthma.

h) History of drug or alcohol abuse.

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i) Any condition or comorbidity that, in the investigator's judgment, could pose a risk to the participant or interfere with the evaluation of efficacy and safety.

j) Participation in another clinical trial or receipt of an investigational drug within 30 days before screening.

2.4. Experimental Protocol

Clinical data were collected at two main time points: at enrollment (T0, prior to treatment initiation) and at the end of the study (T3, three months after T0). All patients presented with chronic pain and were receiving NSAIDs as needed; therefore, baseline data at T0 served as the control condition.

Questionnaires were administered by the study's medical staff. Given the open-label design, patient confidentiality was maintained through the assignment of unique numerical codes by a physician not involved in the study. This ensured privacy while enabling accurate data analysis in compliance with ethical research standards.

At both T0 and T3, detailed medical history was collected, physical examinations were performed, and standardized questionnaires were completed. Pain intensity and functional status were assessed using the Numeric Rating Scale (NRS) and the Knee Injury and Osteoarthritis Outcome Score (KOOS). Throughout the study, any systemic or local adverse drug reactions (ADRs) were monitored and evaluated using the Naranjo scale to determine causality.

Prior to enrolling in this study, all patients had received systemic treatment with NSAIDs, without achieving any clinical improvement. Consequently, the pretreatment period (T0) was used as the control for comparison with follow-up assessments.

2.4.1. Questionnaires

Validated instruments were employed, consistent with previous studies:

36-Item Short Form Health Survey (SF-36): Assesses health-related quality of life across eight domains. Higher scores indicate better perceived health status, whereas lower scores reflect poorer quality of life.^{17,18}

Zung Self-Rating Anxiety Scale (Zung SAS): A 20-item questionnaire assessing anxiety, categorized as normal (0–44), moderate (45–59), or severe (60–80).¹⁹

Zung Self-Rating Depression Scale (Zung SDS): A 20-item instrument measuring depressive symptoms, classified as normal (20–49), mild (50–59), moderate (60–69), or severe (70–80).²⁰

Adverse Drug Reaction Probability Scale (Naranjo Scale): A 10-item tool used to standardize the assessment of ADR causality. Scores classify ADRs as doubtful (≤0), possible (1–4), probable (5–8), or definite (≥9).^{21,22}

Knee Injury and Osteoarthritis Outcome Score (KOOS): Evaluates knee pain, symptoms (e.g., swelling, range of motion), activities of daily living, sport/recreation function, and knee-related quality of life. Scores range from 0 (extreme problems) to 100 (no problems).

2.4.2. Clinical Tests

Clinical assessments were performed according to established protocols:

- **Timed Up and Go (TUG) Test:** Evaluates functional mobility and fall risk by timing how long it takes for a patient to rise from a chair, walk three meters, turn, return, and sit down. Shorter times indicate better mobility, whereas times ≥13.5 seconds indicate increased fall risk.
- **Visual Analogue Scale (VAS):** Measures pain intensity on a 10-cm line, where 0 represents "no pain" and 10 represents "worst imaginable pain." The onset of pain during the TUG test was also recorded.

2.5. Efficacy End Points

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Primary endpoint:

Statistically significant improvement ($p < 0.05$) in KOOS scores at follow-up visits (T1–T3) compared with baseline (T0).

Secondary endpoints:

Statistically significant improvement ($p < 0.05$) in VAS scores at T1–T3 compared with T0.

Statistically significant improvement ($p < 0.05$) in overall SF-36 scores at T1–T3 compared with T0.

Statistically significant changes ($p < 0.05$) in mood disorder scores (Zung SAS and SDS) between T1–T3 and T0.

2.6. Safety End-Points

ADRs related to the nutraceutical treatment were recorded throughout the study using the Naranjo scale. ADRs leading to participant withdrawal were also documented.

2.7. Nutraceutical Formulation

Each tablet contained a fixed combination of chondroitin sulfate, α-lipoic acid, astaxanthin, lycopene, escin, omega-3 fatty acids, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) (Diaco Biofarmaceutici, Trieste, Italy; Table 1).

Table 1. Active compounds and their dosage in each tablet of the new nutraceutical formulation.

Active compound	Dosage (per capsula)
chondroitin sulfate	500 mg
alpha lipoic acid,	400 mg
Astaxanthin	5 mg
Lycopene	7 mg
Escin	15 mg
omega 3	53 mg
eicosapentaenoic acid	212.2 mg
docosahexaenoic acid	10.6 mg

2.8. Statistical Analysis

Continuous variables with a Gaussian distribution were described as mean ± standard deviation (SD), whereas categorical variables were summarized as counts and percentages. The normality of continuous variables was assessed using the Shapiro–Wilk test. Comparisons of continuous variables were performed using the Student's t-test or one-way analysis of variance (ANOVA), as appropriate. Categorical variables were compared using the chi-square test.

Multivariate analyses were adjusted for potential confounders, including age, sex, smoking status, alcohol consumption, physical activity, educational level, body mass index (BMI), comorbidities, and concomitant drug use. Correlations between continuous variables were assessed using Pearson's correlation coefficient.

For repeated measures, the nonparametric Friedman test was used, followed by post hoc pairwise comparisons with the Wilcoxon signed-rank test. Data are presented as mean ± SD unless otherwise specified. Statistical significance was set at $p < 0.05$. All analyses were conducted using SPSS software, version 22.0 (IBM Corp., Armonk, NY, USA).

Because no prior data were available for this novel compound, a formal power calculation could not be performed; therefore, this investigation was designed as a pilot study.

3. Results

3.1. Population

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In this study, we enrolled 50 patients (20 men and 30 women) with a mean age of 63.6 ± 11.4 years (range: 26–88 years) and a mean body mass index (BMI) of 26.9 ± 3.7 kg/m² (Table 2). All patients had a history of knee OA unresponsive to typical or atypical NSAIDs (Table3) and provided written informed consent. Among the study population, 11 patients (22%) reported a history of articular trauma, while the remaining 39 patients (78%) had knee OA attributed to chronic degeneration. No significant differences in age, sex, or BMI were found between these two groups ($p > 0.05$). Additionally, bilateral knee OA was documented in 28 patients (56%), with no significant differences in its prevalence by sex (women: n = 18, 45%; men: n = 10, 50%), age, or BMI. All the enrolled patients completed the course of treatment.

Table 2. Demographic characteristics of the population with knee osteoarthritis (n = 50). Data are expressed as mean ± standard deviation for continuous variables and number (percentage) for categorical variables.

Characteristics	Data	Women	Men
Sex	50	30 (60)	20 (40)
Age (years)	63.6 ± 11.4	63.1 ± 12.1	64.3 ± 10.7
Body max index (kg/m²)	26.9 ±3.7	27.1 ± 3.9	26.3 ± 3.5
Comorbidity			
Diabetes Mellitus Type 2	7 (14)	4 (57.1)	3 (42.9)
Blood Hypertension	30 (60)	17 (56.7)	13 (43.3)
Osteoporosis	6 (12)	3 (50)	3 (50)

Table 3. Typical and atypical non-steroidal anti-inflammatory drugs used before the enrollment. Data are expressed as number (percentage). Student's *t*-test was used for statistical evaluation. **P<0.01.

	Women (*n* = 30)	Men (*n* = 20)
Ibuprofen	8 (26.6)	6 (30)
Ketoprofen	2 (6.7)	2 (10) **
Diclofenac	7 (23.3)	5 (25)
Celecoxib	5 (16.7)**	2 (10)
Etoricoxib	3 (10)	2 (10)
Acetaminophen	5 (16.7)	3 (15)

3.2. Effects on Pain

At baseline (T0), the mean Visual Analogue Scale (VAS) score was 7.5 ± 0.6 (men: 7.7 ± 0.6; women: 7.3 ± 0.8), the mean Knee Injury and Osteoarthritis Outcome Score (KOOS) was 43.8 ± 12.65, and the mean Timed Up and Go (TUG) test time was 4.8 ± 2.2 seconds. All patients exhibited a positive walking test after 3 minutes (Table 4). At T0, Pearson correlation analysis revealed no significant associations between pain intensity and sex, age, or body mass index (BMI) (Table 5).

During the follow-up period (T1–T3), a significant, time-dependent improvement in clinical symptoms was observed ($p < 0.001$; Table 6). Specifically, when patients were stratified by age group (20–60 years and > 60 years), oral treatment with the nutraceutical combination resulted in a statistically significant reduction in VAS scores over time ($p < 0.01$) (Figure 1).

Table 4. Clinical and functional scales change at T1 (1 month) vs T0 (admission) in patients treated with fixed combination of oral nutraceutical. Data are expressed as median (interquartile range). KOOS: Knee Injury and Osteoarthritis Outcome score; VAS: Visual analogue scale.

Score	T0	T1	P
KOOS	41.5 ± 8.7	52.3 ± 9.6	0.000
VAS	7.5 ± 0.6	4.6 ± 1.1	0.000
Six minutes Walking test (meters)	381 ± 125	425 ± 152	0.000

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Timed Up and Go test (sec)	7.3 ± 2.1	6.2 ± 1.8	0.000

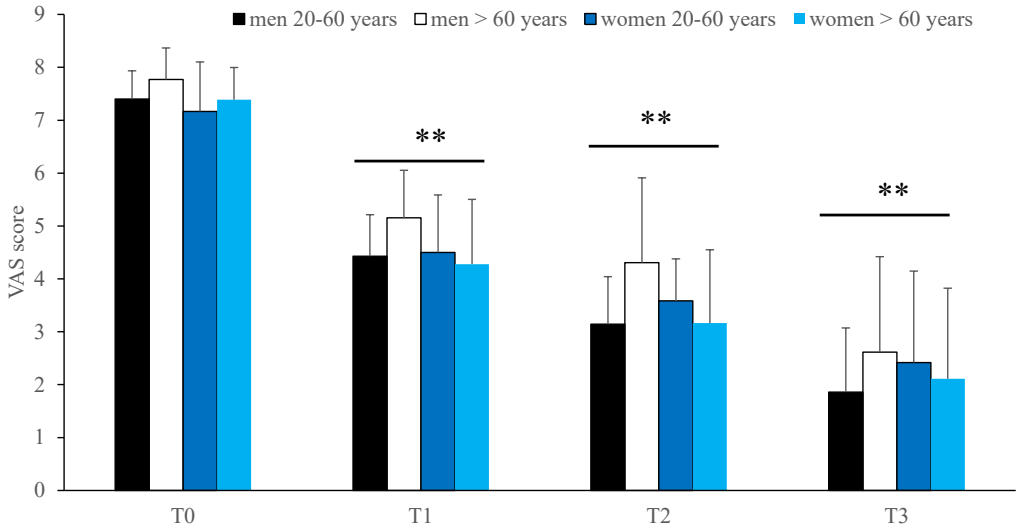

Figure 1. Time dependent effect of nutraceutical treatment (T1: 1 month, T2: 2 months, T3: 3 months, after the beginning of the fixed oral nutrient) on pain perception (evaluated through visual analogue scale, VAS), in enrolled patients with chronic knee OA. **P<0.01 vs T0.

Table 5. Pearson's correlation in enrolled patients respect to sex, age, body mass index (BMI) and pain.

		Age vs BMI	Age vs Pain	BMI vs Pain
Women	Pearson's correlation	0.349	-0.242	-0.277
	Sig	0.074	0.243	-0.200
Men	Pearson's correlation	0.279	0.012	-0.088
	Sig.	0.263	0.962	0.713

Table 6. Clinical and functional data recorded at T2 (2 months) and T3 (3 months) after the admission (T0), in patients treated with fixed combination of oral nutraceutical. Data are expressed as mean ± standard deviation. KOOS: Knee Injury and Osteoarthritis Outcome score; VAS: Visual analogue scale.

Score	T0	T2	P T2 vs T0	T3	P T3 vs T0
KOOS	41.5 ± 8.7	63.1 ± 12.6	0.000	78.37 ± 20.54	0.000
VAS	7.5 ± 0.6	3.6 ± 1.3	0.000	2.4 ± 1.6	0.000
Six minutes Walking test (meters)	381 ± 125	512 ± 136	0.000	585 ± 134	0.000
Timed Up and Go test (sec)	7.3 ± 2.1	5.35 ± 1.8	0.000	4.68 ± 2.1	0.000

3.3. Effects on Quality of Life

At T3 (3 months after the beginning of the nutrients). SF-36 questionnaire score revealed a time-related significant improvement in the quality of life (P < 0.01) (Table 7), without difference respect to age, sex and BMI.

Table 7. Short Form Health Survey (SF) 36 recorded in enrolled patients 3 months (T3) after the admission (T0), in patients treated with fixed combination of oral nutraceutical. Data are expressed as mean ± standard deviation.

SF-36		
T0	T3	P

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Physical functioning	50.65 ± 5.8	70.65 ± 6.64	0.000
Role limitations due to physical health	49.06 ± 10.22	64.78 ± 4.41	0.000
Role limitations due to emotional problems	46.46 ± 7.69	61.84 ± 7.17	0.000
Energy/fatigue	46.74 ± 6.61	53.58 ± 7.42	0.000
Emotional well-being	47.12 ± 5.32	56.21 ± 6.64	0.000
Social functioning	40.5 ± 4.96	64.67 ± 12.04	0.000
Pain	27.23 ± 5.03	58.37 ± 12.08	0.000
General health	32.71 ± 8.82	61.63 ± 11.13	0.000
Health change	33.69 ± 8.41	62.82 ± 12.36	0.000

3.4. Effect on Mood Symptoms

Using both Zung SDS (depression) and Zung SAS (anxiety) scales, at the end of the study (T3, 3 months after the admission) we observed a statistically significant improvement of mood disorders ($P < 0.01$) (Table 8).

Table 8. Zung depression and anxiety scales recorded in enrolled patients 3 months (T3), after the admission (T0), in patients treated with oral nutraceutical. Data are expressed as mean ± standard deviation.

	T0	**T3**	**P**
Depression	58.22 ± 8.75	42.21 ± 7.25	0.000
Anxiety	49.81 ± 9.22	32.10 ± 7.65	0.000

3.5. Safety

No ADRs were documented during the study, and all enrolled patients reported high adherence to the treatment. As of August 2025, approximately three months after the final follow-up, no ADRs or drug interactions have been recorded in the study participants.

4. Discussion

In this study, we evaluated the safety and efficacy of a fixed nutraceutical combination in patients with knee OA. OA is a common, chronic, degenerative joint disease for which pharmacological treatment primarily aims to reduce pain and improve quality of life. Conventional pharmacotherapy typically includes NSAIDs, analgesics (such as acetaminophen or opioids), and symptomatic slow-acting drugs for osteoarthritis (SYSADOAs) [13,23–25].

Wilson et al. [26], previously reported that glucosamine and chondroitin are safe therapeutic options for patients with OA; however, it remains essential to thoroughly evaluate both their efficacy and the overall effectiveness of symptomatic SYSADOAs. Many naturally derived substances are readily available and are often taken without medical supervision, sometimes leading to uncertain benefits or even adverse effects and drug interactions. In our study, a three-month treatment with a fixed combination of several nutrients, including chondroitin sulfate, resulted in significant improvement in clinical symptoms. This nutraceutical combination was selected based on the established analgesic, anti-inflammatory, and antioxidant properties of its components, which are thought to act synergistically [27–32].

Each compound included in the formulation has demonstrated activity relevant to OA management. For example, in an experimental mouse model of OA, Zhan et al. [33], showed that daily intragastric administration of lycopene (5 mg/kg) for 8 weeks attenuated IL-1β-induced chondrocyte inflammation by inhibiting the Nuclear Factor-κB pathway. Additionally, Martinez-Garcia et al. [34], in a recent literature review, highlighted that omega-3 fatty acid consumption is associated with decreased pain and improved joint function and quality of life in OA patients. The omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) exert beneficial

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effects by modulating inflammatory responses, enhancing cartilage repair, and regulating bone metabolism [35].

Furthermore, we previously reported that escin exhibits glucocorticoid-like anti-inflammatory activity [36] as well as antioxidant properties [37], supporting its potential role in the management of OA. Astaxanthin, another component, has demonstrated both anti-inflammatory and antioxidant effects; it has been shown to reduce the expression of matrix metalloproteinases (MMP-1, MMP-3, and MMP-13) in chondrocytes [38] suggesting a possible therapeutic benefit in OA. In addition, astaxanthin possesses hepatoprotective properties, which are particularly relevant in patients undergoing polypharmacy. All patients in our study presented with comorbidities and were receiving multiple medications; nevertheless, no ADRs or drug interactions were observed. This favorable safety profile may be related to the dosages of the active compounds used in the fixed nutraceutical combination. The improvement in quality of life and mood observed among our patients was likely attributable to the significant reduction in pain. Our study has some limitations, including a small sample size, which is typical of a pilot study. Larger, randomized controlled trials are warranted to confirm these preliminary findings.

5. Conclusion

Treatment with this new fixed combination of nutraceuticals improved clinical outcomes and quality of life in patients with knee OA without the development of adverse drug reactions, suggesting its potential as a safe and effective add-on therapy in this population.

Author Contributions: Conceptualization, CV, CP, GDM and LG; Data curation, CV, VR, GM, D.M. and LM; Formal analysis, GM; Investigation, CV, VR, GM, and LM MA-G; Methodology, EC, MCC and LG; Software, GM; Supervision, LG, EC; Writing – original draft, CV, GM; Writing – review & editing, MCC, DM, EC and LG. All authors will be informed about each step of manuscript processing including submission, revision, revision reminder, etc. via emails from our system or assigned Assistant Editor.

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

Data Availability Statement: The original contributions presented in the study are included in the article, further inquiries can be directed at the corresponding author. Data is available if requested.

Conflicts of Interest: The authors declare no conflicts of interest.

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