

# Feasibility, safety and preliminary efficacy of a new nutritional supplement for fibromyalgia patients: a pilot study

## Abstract

Current treatments for fibromyalgia (a chronic pain disorder) have limited efficacy, posing significant challenges for patients and healthcare providers, and prompting exploration of alternative approaches, such as nutritional supplements. Although limited in the literature, small-scale prospective pilot studies are crucial for assessing the safety and feasibility of these interventions, guiding subsequent research. Here we evaluated the viability and relevance of broader investigations of a new nutritional supplement, combining unique ingredients that are potentially beneficial for addressing the multifaceted nature of fibromyalgia symptoms, based on previous systematic reviews and meta-analyses.

Thirty consecutive fibromyalgia patients received an 8-week intervention with the new nutritional supplement. Patients were assessed at baseline, 4 weeks, and 8 weeks to identify primary outcomes for future larger-scale trials, and evaluate safety, challenges, protocol adjustments, and treatment adherence.

Treatment adherence was satisfactory, with only two patients experiencing mild adverse effects that did not warrant discontinuation. After the 8-week intervention, we observed moderate improvements in functionality and pain levels, but no significant improvements in fatigue, hemogram, biochemical values, sleep quality, or emotional well-being.

Therefore, our results support the safety and tolerability of the new nutritional supplement for fibromyalgia, and indicate the feasibility of an 8-week larger scale trial. A minimum of 43 participants should be recruited in a subsequent trial, with an anticipated 10% dropout rate. Primary outcomes should include functionality, extent of widespread pain, and presence/severity of centralized pain features. Alternative tests should assess fatigue improvement, while changes in blood parameters, sleep, and emotional issues may have lesser significance.

**Keywords:** fibromyalgia, nutraceutical, nutritional supplement, pilot study

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**Abbreviations:** ITT, intention to treat; PP, per protocol; SD, standard deviation; sFIQ, fibromyalgia impact questionnaire; VAS, visual analogue scale; PSQI, pittsburgh sleep quality index; FHAQ, fibromyalgia health assessment questionnaire; SF-36, medical outcomes study-short form 36; HAD, hospital anxiety and depression scale; AST, aspartate aminotransferase test; ALT, alanine aminotransferase test; LDH, lactate dehydrogenase; CPK, creatine phosphokinase

## Introduction

More than one hundred years after its first definition, fibromyalgia syndrome (FM) remains a pervasive, complex, and resistant health challenge that affects individuals worldwide, impairing their quality of life and imposing a substantial burden on healthcare systems.<sup>1</sup> Efforts to improve FM treatment have included explorations of nutritional supplements as potential adjunctive therapies.<sup>2</sup> Considering the limitations and side effects of existing therapeutic options,<sup>3</sup> such supplements might offer potential benefits in terms of pain severity, functional outcomes, and overall patient well-being. Though uncommon in the research literature, pilot studies are highly important as a crucial preliminary step in the investigation of efficacy and safety. The British Medical Council<sup>4</sup> recommends that large-scale clinical trials should be preceded by pilot studies to assess feasibility, minimize

unnecessary risks and efforts from researchers and participants, and guide protocol improvements, when appropriate.<sup>5</sup> Pilot studies can help define the best therapeutic targets and primary outcome measures, and can facilitate the calculation of sample size, to avoid underpower studies or overpowered studies, which waste resources. Finally, the interest of an intervention from the researchers' point of view may significantly differ from the acceptance of the individuals who will receive it. Therefore, it seems advisable to assess in advance whether participants are reasonably interested in that intervention.<sup>6</sup>

For these reasons, we conducted a pilot study of Fibrofix Plus®, a new nutritional supplement for FM, with the aims of examining its potential benefits, safety, and costs. If the results indicate that further testing is warranted, the pilot study will also guide treatment duration, the most appropriate outcome measures, and the likelihood of adverse effects to ensure a safe and well-designed subsequent larger trial.

Fibrofix Plus includes components that might be relevant for FM treatment, according to previous systematic reviews and meta-analyses. For example, supplementation of curcumin might improve inflammation levels in patients with rheumatoid arthritis,<sup>7</sup> and depression and anxiety symptoms in depressed patients.<sup>8</sup> Saffron (*Crocus sativus L.*) also seems to improve depression and anxiety.<sup>9</sup> Moreover, sustained supplementation of folic acid seems to reduce the

incidence of perinatal depressive symptoms.<sup>10</sup> Gamma-aminobutyric acid (GABA) improves osteoarthritis pain in humans,<sup>11</sup> and neuropathic pain in animal models.<sup>12</sup> The efficacy of other components of Fibrofix Plus remains controversial. Chondroitin sulfate has yielded both negative<sup>13</sup> and positive<sup>14</sup> results for pain reduction.<sup>15</sup> To our knowledge, studies have not yet thoroughly examined the efficacy of other components (e.g., manganese) for relevant symptoms of chronic pain disorders.<sup>16</sup>

In the present study, we assessed the feasibility of an 8-week regimen of the Fibrofix Plus nutritional supplement that is allegedly specific for FM. We expected that the administration of Fibrofix Plus would be safe and accepted by most patients. We also expected that preliminary efficacy data would show a preliminary benefit justifying further testing.

## Materials and methods

The research was completed in accordance with the Declaration of Helsinki as revised in 2013, and the study was approved by the Research Ethics Committee of the Hospital Clinic of Barcelona; approval number HCB/2021/1185. All patients signed a written informed consent to participate in the study.

### Participants

This study included 30 participants, based on previous suggestions about the appropriate sample size to understand the feasibility of participant recruitment and the study design.<sup>17</sup> We enrolled 30 consecutive patients who had been referred to the Interdisciplinary Primary Chronic Pain Unit of the Hospital Clinic of Barcelona for specialized confirmation of a suspected diagnosis of FM, according to American College of Rheumatology (ACR) criteria.<sup>18</sup> Patients were included if a diagnosis of FM was confirmed by the rheumatologists of our unit, and if they were older than 18 years, scored  $\geq 4$  on a 0–10 cm visual analog scale (VAS) of fatigue and pain, and were free of psychotropic drugs and narcotic analgesics for at least 4 weeks before entering the study. Paracetamol up to 2 g/day and tramadol 100 mg/8 h were allowed. Patients were excluded if their pain was mainly related to a traumatic injury, they suffered an active chronic inflammatory or autoimmune disease, or they suffered a psychiatric disorder that might interfere with the reliability of results reported, or that required immediate attention (e.g., dementia, suicide risk, unstable psychotic or bipolar disorder, or drug dependence or abuse). Patients were also excluded if they were receiving any other treatment for FM (including alternative therapies), had participated in a clinical trial for FM in the previous 3 months, were applying for disability, were pregnant or breastfeeding, or reported hypersensitivity to the active principles or to any of the excipients of the nutritional supplement.

### Procedure

Patients received one sachet of Fibrofix Plus each day, for 8 weeks. The composition per sachet included collagen-bioactive peptides (4000 mg), chondroitin sulfate (1200 mg), GABA (400 mg), curcuminoids (rhizome of *Curcuma longa* L.) (303 mg), vitamin C (80 mg), copper (1 mg), manganese (1 mg), saffron extract (*Crocus sativus* L. flower) (30 mg), and folic acid (200  $\mu$ g).

To identify primary outcomes of the intervention, which might guide the design of larger-scale trials, patients completed the following assessment protocol at baseline, and at 4 and 8 weeks after starting the intervention.

**Pain and fatigue:** Pain and fatigue were measured using a 10-cm visual analog scale (VAS). The degree of widespread body pain was

quantified using the Widespread Pain Index (WPI), and the presence and severity of symptoms associated with centralized pain were assessed with the Symptom Severity Scale (SSS).<sup>18</sup>

**Functional capacity:** Functionality was measured using the 10-item Spanish version of the Fibromyalgia Impact Questionnaire (s-FIQ).<sup>19</sup> The s-FIQ was complemented with the 8-item Spanish version of the Fibromyalgia Health Assessment Questionnaire (FHAQ).<sup>20</sup>

**Emotional distress:** Emotional distress was assessed using the 14-item Hospital Anxiety and Depression Scale (HADS).<sup>21</sup> The HADS assesses anxiety and depressive symptoms, with lower contamination by somatic symptoms compared to other psychopathology questionnaires.<sup>22</sup>

**Health-related quality of life (HRQOL):** The interference of FM on patients' HRQOL was measured using the Spanish version of the Medical Outcomes Study-Short Form 36 (SF-36).<sup>23</sup>

**Sleep quality.** Sleep disturbances and poor-quality sleep were measured using the Spanish version of the Pittsburgh Sleep Questionnaire Index (PSQI), which has been specifically validated in FM patients.<sup>24</sup>

**Physical parameters:** To assess the changes of common physical parameters after administration of the nutritional supplement, our study included the following blood count measurements: red blood cells ( $\times 10^{12}/L$ ); hematocrit (L/L); hemoglobin (g/dL); erythrocyte indices, including mean corpuscular volume (MCV, fL) and mean corpuscular hemoglobin (MCH, pg); leukocyte number and formula ( $\times 10^9/L$ , %) (neutrophils, lymphocytes, monocytes, eosinophils, and basophils); platelet count ( $\times 10^9/L$ ); and glomerular sedimentation rate (ESR, mm/h). We also measured the following blood biochemistry parameters: glucose (mg/dL), glycosylated hemoglobin (HbA1c, %), alkaline phosphatase ( $\mu$ mol/L), AST and ALT transaminases (U/L), lactate dehydrogenase (LDH, U/L), C-reactive protein (CRP, mg/dL), blood urea nitrogen (BUN, mg/dL), serum creatinine, and creatine phosphokinase (CPK,  $\mu$ mol/L).

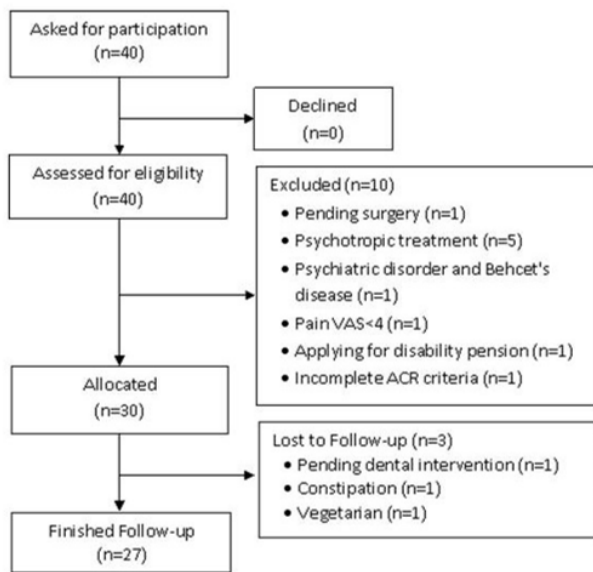
**Treatment adherence:** To assess the participants' active choice to follow a daily regimen of nutritional supplement intake, we calculated the percentage of sachets consumed between visits, and recorded the reasons for non-adherence, when appropriate.

### Statistical analysis

For patients who dropped out from the study, missing values were imputed by assigning the last-observation-carried-forward to the missing value. Descriptive results were analyzed by calculating the mean and standard deviation for quantitative variables, and frequency and percentage for qualitative variables. The means of outcome variables were compared between visits using non-parametric tests for repeated measurements (Friedman or Wilcoxon tests). We also calculated the effects sizes and percentages of participants reaching a minimum clinically important difference (MCID) at the end of the study, for those variables for which it has been defined.

## Results

Forty patients were invited to enter the study, and all agreed and were assessed for eligibility. Ten patients were excluded, and 30 began the intervention. These 30 patients were all women, and had a mean age of 49.33 years (10.99 years). Of these patients, 27 completed the study. Reasons for dropping out of the study included being vegetarian (and thus refusing derivatives of animal origin), constipation, and having to undergo a dental intervention (Figure 1).



**Figure 1** Flow of participants through each stage of the study.

Treatment adherence seemed appropriate. After 8 weeks, 12 participants (40%) had complied with the treatment on 100% of the days, 17 (57%) on over 80% of the days, and one patient complied with treatment on 17% of the days. Most participants cited forgetfulness as the main reason for non-compliance.

Twenty-five participants had to use paracetamol and/or tramadol once or several times during the study. Paracetamol was used on 23 occasions (19 times for pain, including headache; and 4 for infections), tramadol was used 4 times for pain, and tramadol plus paracetamol was used on 23 instances (22 times for pain, and once for urinary tract infection).

Regarding the safety of the food supplement, two participants experienced mild gastrointestinal discomfort and nocturnal polyuria, which did not prevent their continuation in the study.

After 8 weeks of intake of the nutritional supplement, we observed statistically significant improvements of several variables (Table 1). At 4 weeks, we observed improvement of the interference of FM in the participants' functional capacity, according to the sFIQ [effect size, 0.64 (intermediate magnitude)], with 11 patients (36.7%) showing a reduction above the 14% established as the minimal clinically important difference (MCID).<sup>25</sup> At 8 weeks, we also observed improvement according to the FHAQ [effect size, 0.39 (small magnitude)], with 11 participants (36.7%) showing a reduction above the 17% observed in validation studies.<sup>20</sup> Patients also showed improvement of their limitations in carrying out moderate physical activities (small effect size of 0.42), as measured by the SF-36 Physical Function subscale. To our knowledge, no MCID has been defined for the SF-36 subscales in FM patients. Therefore, we decided to apply the 10-point MCID established in a previous study with patients with lupus erythematosus.<sup>26</sup> At the end of the study, 15 participants (50%) exhibited an improvement of their physical function by  $\geq 10$  points.

**Table 1** Clinical variables in fibromyalgia patients after 8 weeks of Fibrofix Plus intake

		ITT population				PP population				
		Mean	SD	Friedman (p)	Wilcoxon signed rank test (p)	Mean	SD	Friedman (p)	Wilcoxon signed rank test (p)	
sFIQ	Baseline	64.79	14.33		4 week - Baseline	0.000	64.76	14.87	4 week - Baseline	0.000
	4 weeks	55.41	16.70	0.000	8 week - 4 week	0.719	54.61	17.32	8 week - 4 week	0.719
	8 weeks	55.57	16.64		8 week - Baseline	0.002	54.80	17.26	8 week - Baseline	0.003
FHAQ	Baseline	1.94	0.48		4 week - Baseline	0.190	1.90	0.48	4 week - Baseline	0.091
	4 weeks	2.03	0.45	0.040	8 week - 4 week	0.018	2.03	0.45	8 week - 4 week	0.018
	8 weeks	2.13	0.43		8 week - Baseline	0.009	2.14	0.43	8 week - Baseline	0.003
Pain VAS	Baseline	7.75	1.15		4 week - Baseline	0.001	7.83	1.15	4 week - Baseline	0.001
	4 weeks	6.62	1.79	0.000	8 week - 4 week	0.593	6.65	1.80	8 week - 4 week	0.593
	8 weeks	6.55	1.65		8 week - Baseline	0.000	6.57	1.64	8 week - Baseline	0.000
Symptoms severity score	Baseline	8.43	1.52		4 week - Baseline	0.000	8.30	1.54	4 week - Baseline	0.000
	4 weeks	6.8	2.02	0.000	8 week - 4 week	0.197	6.59	2.01	8 week - 4 week	0.197
	8 weeks	6.53	1.99		8 week - Baseline	0.000	6.3	1.94	8 week - Baseline	0.000
Widespread pain index	Baseline	10.3	2.12		4 week - Baseline	0.000	10.52	2.08	4 week - Baseline	0.000
	4 weeks	6.4	2.34	0.000	8 week - 4 week	0.169	6.37	2.32	8 week - 4 week	0.169
	8 weeks	5.7	2.31		8 week - Baseline	0.000	5.59	2.26	8 week - Baseline	0.000
Fatigue VAS	Baseline	8.10	1.37		4 week - Baseline	0.177	8.15	1.43	4 week - Baseline	0.177
	4 weeks	7.43	1.79	0.005	8 week - 4 week	0.153	7.41	1.89	8 week - 4 week	0.153
	8 weeks	7.10	1.73		8 week - Baseline	0.005	7.04	1.81	8 week - Baseline	0.005
PSQI	Baseline	13.67	3.52		4 week - Baseline	-	13.85	3.63	4 week - Baseline	-
	4 weeks	12.33	3.94	0.192	8 week - 4 week	-	12.22	3.98	8 week - 4 week	-
	8 weeks	12.1	4.21		8 week - Baseline	-	11.96	4.27	8 week - Baseline	-
SF-36 Physical function	Baseline	38.83	18.74		8 week - Baseline	0.012	37.04	18.09	8 week - Baseline	0.012
	8 weeks	46.83	19.80	-			45.93	19.95		

Table 1 Continued...

		ITT population				PP population			
		Mean	SD	Friedman (p)	Wilcoxon signed rank test (p)	Mean	SD	Friedman (p)	Wilcoxon signed rank test (p)
Role physical	Baseline	37.92	24.67	-	8 week - Baseline 0.089	38.66	25.42	-	8 week - Baseline 0.089
	8 weeks	44.79	22.27	-		46.30	22.42	-	
Bodily pain	Baseline	19.90	17.09	-	8 week - Baseline 0.001	18.30	14.92	-	8 week - Baseline 0.001
	8 weeks	32.13	15.52	-		31.89	13.84	-	
General health	Baseline	31.55	14.60	-	8 week - Baseline 0.023	30.348	14.14	-	8 week - Baseline 0.023
	8 weeks	36.67	16.47	-		36.04	16.60	-	
Vitality	Baseline	21.67	18.04	-	8 week - Baseline 0.066	21.06	18.11	-	8 week - Baseline 0.066
	8 weeks	29.38	23.05	-		29.63	23.68	-	
Social functioning	Baseline	42.92	23.37	-	8 week - Baseline 0.002	42.59	24.33	-	8 week - Baseline 0.002
	8 weeks	57.08	21.45	-		58.33	21.93	-	
Role emotional	Baseline	63.33	29.89	-	8 week - Baseline 0.049	63.89	31.52	-	8 week - Baseline 0.049
	8 weeks	72.22	28.73	-		73.76	29.93	-	
Mental health	Baseline	51.83	25.44	-	8 week - Baseline 0.066	50.37	26.20	-	8 week - Baseline 0.066
	8 weeks	58.17	24.01	-		57.41	24.98	-	
<b>HADS</b>									
Anxiety	Baseline	10.5	4.94	-	8 week - Baseline 0.087	10.63	5.13	-	8 week - Baseline 0.087
	8 weeks	9.87	4.58	-		9.93	4.76	-	
Depression	Baseline	10.03	4.13	-	8 week - Baseline 0.058	10.22	4.30	-	8 week - Baseline 0.058
	8 weeks	9.17	4.50	-		9.26	4.72	-	

ITT, intention to treat; PP, per protocol; SD, standard deviation; sFIQ, fibromyalgia impact questionnaire; VAS, visual analogue scale; PSQI, pittsburgh sleep quality index; FHAQ, fibromyalgia health assessment questionnaire; SF-36, medical outcomes study-short form 36; HAD, hospital anxiety and depression scale

Pain intensity improved at 4 weeks [effect size, 1.04 (large magnitude)], and did not show further improvement at 8 weeks, with 4 participants (13.3%) showing a reduction above the 30% established as the MCID.<sup>27</sup> The Bodily Pain subscale of the SF-36 showed significant improvement at 8 weeks [effect size, 0.72 (intermediate magnitude)], with 16 participants (53.3%) having achieved an improvement of  $\geq 10$  points. The degree of widespread body pain, measured with the WPI, was significantly reduced at 4 weeks [effect size, 2.17 (large magnitude)], with no further reduction at 8 weeks. The presence and severity of symptoms associated with centralized pain, measured using the SSS, was also reduced after 4 weeks of nutritional supplement intake [effect size, 1.25 (large magnitude)]. At the beginning of the study, all participants satisfied the first and mandatory ACR diagnostic criterion for FM:<sup>18</sup> among the 30 participants, 29 reported a WPI score of  $\geq 7$ , while 1 reported a WPI score of 6 and an SSS of 10. At the end of the study, 9 participants reported a WPI of  $\geq 7$ , and 2 reported a WPI of 4–6 and a SSS of  $> 9$ . Therefore, at the end of the study, 19 participants (63.3%) no longer satisfied the ACR FM diagnostic criteria.

It took 8 weeks for fatigue intensity to improve [effect size, 0.73 (intermediate magnitude)]. To our knowledge, an MCID has not been defined for a fatigue VAS in FM. Therefore, we applied a minimum improvement of 2.8 points, as observed in the responder subsample of a previous study about the fatigue VAS content validity.<sup>28</sup>

Only 3 patients (10%) showed this minimal reduction. Similarly, the SF-36 Vitality subscale, which has shown agreement with the Fatigue VAS,<sup>28</sup> did not significantly improve among our patients.

Patients reported small improvements in their subjective perceptions of their health as bad, and in their anticipations of health worsening (SF-36 General Health subscale) (effect size, 0.35), with 13 participants (43.3%) showing an improvement of  $\geq 10$  points. Interference of physical problems with ordinary social activities (SF-36 Social Functioning) was moderately improved at the 8-week assessment [effect size, 0.61 (intermediate magnitude)], with 17 participants (56.7%) showing an improvement of  $\geq 10$  points.

Sleep Quality did not improve after 8 weeks of intake of the nutritional supplement. Additionally, we did not observe significant improvements in limitations due to physical problems (SF-36 Role Physical subscale), limitations due to emotional problems (SF-36 Role Emotional subscale), mental health, or HADS anxiety or depressive symptoms.

As shown in Table 2, non-significant differences were observed in the hemogram. The only exception was a statistically significant decrease in leukocytes between baseline and the 4th week (both values within the normal range), which was not maintained at 8 weeks. Similarly, non-significant differences were observed in biochemical values (Table 3).

**Table 2** Blood test values (hemogram) of fibromyalgia patients before and after 8 weeks of Fibrofix Plus intake

		Hemogram test (ITT. n = 30)				Hemogram test (PP. n = 27)					
		Mean	SD	Friedman (p)	Wilcoxon signed Rank test (p)	Mean	SD	Friedman (p)	Wilcoxon signed Rank test (p)		
Red blood cells (x 10 <sup>12</sup> /L)	Baseline	4.52	0.35		4 weeks - baseline	-	4.54	0.36		4 weeks - baseline	-
	4 weeks	4.49	0.42	0.139	8 weeks - 4 weeks	-	4.52	0.43	0.124	8 weeks - 4 weeks	-
	8 weeks	4.44	0.34		8 weeks - baseline	-	4.47	0.35		8 weeks - baseline	-
Hematocrit (L/L)	Baseline	0.42	0.03		4 weeks - baseline	-	0.42	0.03		4 weeks - baseline	-
	4 weeks	0.42	0.04	0.056	8 weeks - 4 weeks	-	0.42	0.04	0.087	8 weeks - 4 weeks	-
	8 weeks	0.41	0.03		8 weeks - baseline	-	0.42	0.03		8 weeks - baseline	-
Hemoglobin (g/dL)	Baseline	135.93	9.9		4 weeks - baseline	-	136.37	10.24		4 weeks - baseline	-
	4 weeks	134.87	11.2	0.145	8 weeks - 4 weeks	-	135.41	11.58	0.208	8 weeks - 4 weeks	-
	8 weeks	133.3	9.52		8 weeks - baseline	-	133.67	9.85		8 weeks - baseline	-
Mean corpuscular volume (fL)	Baseline	93.1	3.74		4 weeks - baseline	-	93.23	3.77		4 weeks - baseline	-
	4 weeks	92.87	3.52	0.867	8 weeks - 4 weeks	-	92.94	3.55	0.963	8 weeks - 4 weeks	-
	8 weeks	92.99	3.53		8 weeks - baseline	-	93.08	3.56		8 weeks - baseline	-
Mean Corpuscular Hemoglobin (pg)	Baseline	30.12	1.24		4 weeks - baseline	-	30.05	1.22		4 weeks - baseline	-
	4 weeks	30.1	1.34	0.562	8 weeks - 4 weeks	-	30.01	1.32	0.544	8 weeks - 4 weeks	-
	8 weeks	30.04	1.2		8 weeks - baseline	-	29.94	1.15		8 weeks - baseline	-
Leukocyte count (x 10 <sup>9</sup> /L)	Baseline	6.51	1.69		4 weeks - baseline	0.043	6.52	1.7		4 weeks - baseline	0.058
	4 weeks	6.12	1.5	0.047	8 weeks - 4 weeks	0.464	6.19	1.54	0.04	8 weeks - 4 weeks	0.464
	8 weeks	6.09	1.38		8 weeks - baseline	0.052	6.16	1.42		8 weeks - baseline	0.071
Neutrophil (x 10 <sup>9</sup> /L)	Baseline	3.48	1.13		4 weeks - baseline	0.053	3.49	1.19		4 weeks - baseline	-
	4 weeks	3.29	1.13	0.036	8 weeks - 4 weeks	0.406	3.34	1.15	0.052	8 weeks - 4 weeks	-
	8 weeks	3.28	0.95		8 weeks - baseline	0.156	3.33	0.95		8 weeks - baseline	-
Lymphocytes (x 10 <sup>9</sup> /L)	Baseline	2.26	0.69		4 weeks - baseline	-	2.29	0.6		4 weeks - baseline	-
	4 weeks	2.14	0.53	0.144	8 weeks - 4 weeks	-	2.19	0.48	0.127	8 weeks - 4 weeks	-
	8 weeks	2.12	0.6		8 weeks - baseline	-	2.16	0.58		8 weeks - baseline	-
Monocytes (x 10 <sup>9</sup> /L)	Baseline	0.35	0.11		4 weeks - baseline	-	0.36	0.11		4 weeks - baseline	-
	4 weeks	0.35	0.11	0.899	8 weeks - 4 weeks	-	0.35	0.12	0.89	8 weeks - 4 weeks	-
	8 weeks	0.35	0.09		8 weeks - baseline	-	0.35	0.1		8 weeks - baseline	-
Eosinophils (x 10 <sup>9</sup> /L)	Baseline	0.16	0.1		4 weeks - baseline	-	0.16	0.1		4 weeks - baseline	-
	4 weeks	0.21	0.16	0.35	8 weeks - 4 weeks	-	0.21	0.17	0.476	8 weeks - 4 weeks	-
	8 weeks	0.2	0.17		8 weeks - baseline	-	0.2	0.17		8 weeks - baseline	-
Basophils (x 10 <sup>9</sup> /L)	Baseline	0.03	0.05		4 weeks - baseline	-	0.03	0.04		4 weeks - baseline	-
	4 weeks	0.04	0.05	0.627	8 weeks - 4 weeks	-	0.04	0.05	0.627	8 weeks - 4 weeks	-
	8 weeks	0.03	0.05		8 weeks - baseline	-	0.03	0.05		8 weeks - baseline	-
Platelets (x 10 <sup>9</sup> /L)	Baseline	266.93	53.52		4 weeks - baseline	-	269.37	53		4 weeks - baseline	-
	4 weeks	264.57	54.75	0.221	8 weeks - 4 weeks	-	268.7	54.18	0.396	8 weeks - 4 weeks	-
	8 weeks	253.57	61.97		8 weeks - baseline	-	256.48	62.96		8 weeks - baseline	-
Erythrocyte sedimentation rate (mm/h)	Baseline	13.37	11.17		4 week - baseline	-	14	11.61		4 weeks - baseline	-
	4 weeks	16.47	15.38	0.08	8 weeks - 4 weeks	-	16.48	15.73	0.19	8 weeks - 4 weeks	-
	8 weeks	15.77	11.56		8 weeks - baseline	-	15.7	11.53		8 weeks - baseline	-

ITT, intention to treat; PP, per protocol; SD, standard deviation

**Table 3** Blood test values (biochemical) of fibromyalgia patients before and after 8 weeks of Fibrofix Plus intake

		Blood biochemistry (ITT, n = 30)				Blood biochemistry (PP, n = 27)			
		Mean	SD.	Friedman (p)	Wilcoxon signed Rank test (p)	Mean	SD	Friedman (p)	Wilcoxon signed Rank test (p)
Glucose (mg/dl)	Baseline	93.17	17.18		4 weeks - baseline	94.3	17.62		4 weeks - baseline
	4 weeks	94.37	18.66	0.49	8 weeks - 4 weeks	95.63	19.14	0.49	8 weeks - 4 weeks
	8 weeks	96.63	26.13		8 weeks - baseline	98.15	27.06		8 weeks - baseline
Glycosylated hemoglobin (%)	Baseline	5.49	0.63			4 weeks - baseline	5.53		0.63
	4 weeks	5.38	0.66	0.138	8 weeks - 4 weeks	5.43	0.64	0.224	8 weeks - 4 weeks
	8 weeks	5.43	0.68		8 weeks - baseline	5.49	0.66		8 weeks - baseline
AST (GOT) (U/L)	Baseline	20.97	4.1			4 weeks - baseline	20.59		4.04
	4 weeks	21	5.27	0.549	8 weeks - 4 weeks	20.26	4.69	0.415	8 weeks - 4 weeks
	8 weeks	20.6	4.05		8 weeks - baseline	19.81	2.94		8 weeks - baseline
ALT (GPT) (U/L)	Baseline	21.1	11.03			4 weeks - baseline	21		11.33
	4 weeks	21.37	11.51	0.423	8 weeks - 4 weeks	21.15	11.85	0.402	8 weeks - 4 weeks
	8 weeks	19.17	7.22		8 weeks - baseline	18.7	6.99		8 weeks - baseline
Alkaline phosphatase (µKat/L)	Baseline	73.5	26.58			4 weeks - baseline	75.8		26.86
	4 weeks	74.96	28.9	0.174	8 weeks - 4 weeks	77.32	29.35	0.155	8 weeks - 4 weeks
	8 weeks	72.89	25.97		8 weeks - baseline	75	26.29		8 weeks - baseline
LDH (U/L)	Baseline	175.12	31.32			4 weeks - baseline	173.35		31.84
	4 weeks	170.88	23.53	0.391	8 weeks - 4 weeks	169.13	23.83	0.368	8 weeks - 4 weeks
	8 weeks	170.31	22.11		8 weeks - baseline	168.48	22.17		8 weeks - baseline
Blood Urea Nitrogen (BUN) (mg/dL)	Baseline	15.76	4.17			4 weeks - baseline	15.86		3.96
	4 weeks	14.96	4.29	0.725	8 weeks - 4 weeks	15.14	4.11	0.708	8 weeks - 4 weeks
	8 weeks	14.92	4.46		8 weeks - baseline	15.09	4.32		8 weeks - baseline
Serum creatinine (mL/min)	Baseline	0.74	0.12			4 weeks - baseline	0.74		0.13
	4 weeks	0.72	0.12	0.341	8 weeks - 4 weeks	0.72	0.12	0.46	8 weeks - 4 weeks
	8 weeks	0.73	0.12		8 weeks - baseline	0.73	0.12		8 weeks - baseline
CPK (µmol/L)	Baseline	93.87	48.12			4 weeks - baseline	96.52		49.88
	4 weeks	101.23	71.26	0.494	8 weeks - 4 weeks	104.41	74.09	0.475	8 weeks - 4 weeks
	8 weeks	103.4	56.13		8 weeks - baseline	106.81	57.65		8 weeks - baseline

ITT, intention to treat; PP, per protocol; SD, standard deviation; AST, aspartate aminotransferase test; ALT, alanine aminotransferase test; LDH, lactate dehydrogenase; CPK, creatine phosphokinase

## Discussion

It has been suggested that, for ethical purposes, researchers should conduct and report pilot studies to inform best practices, identify potential outcomes, and guide improvements of study design.<sup>29</sup> Therefore, although our sample size is limited to provide conclusive results, the findings of our present pilot study provide valuable information for further assessment of Fibrofix Plus in larger trials.

All potential participants approved of the investigation of a new nutritional supplement for FM, indicating that it will not be difficult to enroll participants in a large-scale trial. Three patients (10%) withdrew from our pilot study, but two left for reasons unrelated to the supplement (constipation, and dental intervention). Only one participant (3%) left because the supplement was not compatible with a vegetarian diet. These attrition rates suggest that future trials should include detailed explanations of the supplement components in informed consent, and sample size calculations should anticipate a minimum 10% dropout rate.

Therapeutic compliance was high, with only two mild adverse effects observed, both allowing the patients to complete the treatment. Informed consents should note the possibility of mild gastrointestinal discomfort and nocturnal polyuria with Fibrofix Plus intake.

After 8 weeks of ingesting the supplement, preliminary significant improvements were observed. Thus, a larger scale trial may not require a longer time of administration to uncover similar effects.

After 4 weeks of ingesting Fibrofix Plus, patients exhibited improved functionality, when measured with the sFIQ, and this potential improvement was sustained at 8 weeks. FHAQ improvements were only evident at 8 weeks. The effect size was larger for sFIQ compared to FHAQ, with one-third of participants reporting an improvement above the MCID on both questionnaires. While FHAQ exhibits appropriate construct validity, its sensitivity to change is questionable.<sup>20</sup> Thus, sFIQ appears to be more suitable for assessing functionality in future trials.

Potential improvements were observed in terms of pain intensity, SF-36 Bodily Pain subscale, widespread body pain and centralized pain symptoms. Few participants reached the MCID on the VAS pain; however, over 50% reached the MCID on the Bodily Pain scale, and 60% no longer met the FM diagnostic criteria. Therefore, the benefits of Fibrofix Plus might be better detected on the degree of widespread pain and severity of centralized pain, compared to on raw VAS pain. Indeed, VAS pain behavior may be nonlinear—with standardized response means overestimating responsiveness, and reverse patterns of change over time at the lower and higher ends of the scale compared

to the middle of the scale<sup>30</sup>—such that MCIDs based on VAS pain might be unreliable. Future trials should focus on the assessment of widespread pain and centralized pain, and should avoid using VAS as the only outcome.

A small percentage of patients showed improvement of fatigue, and SF-36 Vitality did not improve. This might suggest that fatigue assessment might be omitted from future trials. However, nutraceuticals have shown benefits in meta-analyses of conditions like cancer-related fatigue,<sup>31</sup> justifying further assessment in FM patients. In our study, fatigue was measured solely with a VAS. Despite its content validity,<sup>28</sup> other measures might be more appropriate for future assessments of fatigue—for example, the 6-minute walk distance, which has a defined MCID and is perceived by patients as clinically meaningful.

Patients reported slightly improved perception of their general health, suggesting lingering concerns about future health worsening. One limitation of our study is the omission of variables like catastrophizing or neuroticism related to the salience of somatic symptoms. The inclusion of these variables in future trials might allow controlling for potential interaction and confusion sources due to an overvalued relevance of somatic symptoms.

We did not observe any significant improvements in role limitations due to physical problems (SF-36 Role Physical), subjective mental health, role limitations due to emotional problems, or anxiety or depressive symptoms. Future trials might not include assessment of these variables.

After 8 weeks of Fibrofix Plus intake, patients' hemogram and biochemical values remained unchanged. Patients with elevated CRP levels (possibly linked to factors like obesity and depression) exhibited minor reductions of these levels after 8 weeks. Future large-scale trials might omit blood tests, except for monitoring CRP levels. Notably, if CRP is monitored, the analysis should control for confounding factors, such as obesity, depression, and sedentary lifestyle.

Pain and infections warranted our patients' occasional use of paracetamol, tramadol, or both. Thus, beyond a potential placebo effect, our preliminary results may not solely reflect the effects of the nutritional supplement. Larger-scale trials could control for this by comparing the efficacy of Fibrofix Plus in subgroups based on concurrent pharmacologic treatments.

## Conclusions

Our study aimed to evaluate the viability and relevance of broader research of a new nutritional supplement, which combines unique and potentially beneficial ingredients to address the multifaceted nature of the symptoms of fibromyalgia, based on previous and meta systematic reviews—analysis. The results of our pilot study support the safety and tolerability of Fibrofix Plus, and suggest the feasibility of conducting a larger trial lasting no longer than 8 weeks. Informed consents should provide details about the supplement's origin and potential mild side effects. Primary outcomes should include functionality (sFIQ), widespread pain, and centralized pain features. Fatigue improvement should be assessed using alternative tests to the VAS. Analyses should include variables like neuroticism, catastrophizing, and social support. The evaluation of sleep and emotional problems may be negligible. Blood tests may be omitted, except for monitoring of CRP levels controlled for obesity, depression, and lifestyle. Based on functionality improvement (sFIQ), a sample size of at least 43 participants per group in a subsequent trial (considering a dropout rate of 10%) will be

necessary to detect the statistical significance of a difference greater than or equal to 9.22 units. Besides a control (placebo) group, larger sample sizes may enable subgroup comparisons based on concurrent pharmacologic treatments.

## Data availability statement

The data that support the findings of this study are available on reasonable request from Author 1 or the corresponding author.

## Author contributions

**Author 1:** Conceptualization (lead), funding acquisition (lead), investigation (equal), methodology (equal), review and editing (equal).

**Author 2:** Data curation (lead), investigation (equal), methodology (equal), supervision (lead), review and editing (equal).

**Author 3:** Investigation (equal), formal analysis (lead), methodology (equal), writing original draft (lead), review and editing (equal).

**Author 4:** Methodology (equal), review and editing (equal).

**Author 5:** Methodology (equal), review and editing (equal).

**Author 6:** Investigation (equal), methodology (equal), review and editing (equal).

**Author 7:** Investigation (equal), methodology (equal), validation (lead), review and editing (equal).

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## Conflict of interest statement

Authors 1 and 7 have a conflict of interest to declare: Arafarma Group, the industry financed their attendance at the 3rd National Congress of the Sociedad Española Multidisciplinar del Dolor (SEMDOR). The rest of the authors have no conflicts of interest to declare.

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