Send Orders for Reprints to reprints@benthamscience.net

Current Rheumatology Reviews, **XXXX,** *XX,* **1-15**

RESEARCH ARTICLE

Effectiveness of Integrated Medicine Protocols in Treating Fibromyalgia: A Retrospective Study

Ferreri Rosaria[1,*], Cracolici Franco[2], Bocci Chiara[1], Tocci Giuseppe[1], Porciello Giovanni[3] and Piazzini Marco[4]

[1]Department of Medicine and Medical Specialties, Regional Reference Center for Integrated Medicine in Hospital Pathways, AslSudEst Tuscany; [2]Department of Oncology, Campostaggia Hospital, Asl SudEst Tuscany; [3]Director of Rheumatology of Grosseto and Head of the Rheumatology Network, Department of Medicine and Medical Specialities, AslSudEst Tuscany; [4]Department of Medicine and Medical Specialties, Rheumatologic Clinic, Grosseto Hospital, AslSudEst Toscana

ARTICLE HISTORY

Received: April 17, 2025
Revised: July 31, 2025
Accepted: March 02, 2026

DOI:
10.2174/0115733971396222260612100945

Abstract: ***Background*:** Fibromyalgia is a chronic condition characterized by a wide range of clinical presentations, making it well-suited for an integrated medicine approach that includes complementary therapies. This study aimed to evaluate the effectiveness of an Integrated Medicine (IM) protocol in treating fibromyalgia patients.

***Methods*:** In this retrospective cohort study, we examined a group of 75 fibromyalgia patients treated with an IM protocol that included homeopathy, acupuncture, and nutritional advice. We assessed the protocol's effectiveness using data collected from the SF-12 (Quality of Life) questionnaire, the Edmonton Symptom Assessment System (ESAS), and the reduction in the use of conventional drugs.

***Results*:** The results demonstrated that the application of the IM protocol led to statistically significant improvements ($p < 0.001$) in pain and mobility symptoms. Additionally, there was a reduction in the use of conventional pharmacotherapy by 60% to 90%.

***Conclusion*:** The findings suggest that the IM protocol is effective in improving the quality of life for fibromyalgia patients and reducing their reliance on conventional drugs. The authors recommend expanding the case series and promoting the paradigm of Integrated Medicine, especially for diseases with multifactorial causes and comorbidities.

Keywords: Fibromyalgia, integrative medicine, patient-reported outcome measures, homeopathy, acupuncture, nutrition therapy.

1. INTRODUCTION

Fibromyalgia (FM) or Fibromyalgia Syndrome (FMS) is the current term for chronic musculoskeletal pain [1] of undetermined cause. Symptoms include widespread musculoskeletal pain, with the nature of the pain being a key clinical feature, along with other CNS-mediated symptoms such as fatigue, memory difficulties, sleep disturbances, and mood disorders, which are frequent comorbidities. Current evidence on fibromyalgia's etiopathogenesis suggests altered pain [2-4] processin g by the central, peripheral, and autonomic nervous systems, neuroendocrine or genetic factors, immune function, psychosocial stressors, and many others. Despite all known facts, the mechanism that links different pathological features, including stress, central sensitization, and dysregulation of innate and adaptive immune responses, is still unknown, making the treatment approach more challenging. FMS is rarely a stand-alone diagnosis [5-7], as most patients meet the criteria for other overlapping chronic pain conditions or mental disorders. Furthermore, it is crucial to recognize that fibromyalgia often presents with frequent clinical pictures described as pseudo-neurological or somatoform, which, despite potentially different initial diagnoses, could ultimately be seen and/or diagnosed as FM/FMS [8-10].

In conventional medicine, two specific guidelines on the treatment of fibromyalgia have been recently published: one by the Canadian Society of Rheumatologists in 2012, revised in 2016 [11], and another by the European Society of Rheumatology (EULAR 32) in 2017 [12]. All guidelines recommend that in the management of fibromyalgia, drug therapy

*Address correspondence to this author at the Department of Medicine and Medical Specialties, Regional Reference Center for Integrated Medicine in Hospital Pathways, AslSudEst Tuscany;
E-mail: rosaria.ferreri@uslsudest.toscana.it

 © XXXX Bentham Science Publishers

should be considered within a multidisciplinary approach, particularly when signs/symptoms are not improved by non-pharmacological strategies (*e.g*., educational approach, physical activity) [13, 14]. Pharmacological interventions include paracetamol, tramadol, NSAIDs/COXIB, SSRI/SNRI (Duloxetine, Fluoxetine), antiepileptics (Gabapentin, Pregabalin), systemic corticosteroids, Tricyclic Antidepressants (TCAs), low-dose Amitriptyline, Tramadol, Cannabinoids, muscle relaxants, and other treatment options, including memantine, naltrexone, tapentadol, and palmitoylethanolamide tablets. Dual antidepressants act by reinforcing the endogenous pain control pathways with an estimated efficacy in 30-50% of patients [14-17]. Sometimes, the administration of NSAIDs or acetaminophen can assist in improving localized pain, particularly in patients where fibromyalgia is associated with disorders such as arthritis [18, 19]. However, none of these treatments have 100% promising results.

1.1. Introduction to Real-Life Data and Observation of Daily Living

In fibromyalgia, as well as in other relevant health conditions not referred to as common pathologies, patient data are crucial for identifying their status and needs [20]. The term 'real-life data' encompasses a wide range of research methodologies and has higher external validity than Randomized Clinical Trials (RCTs), owing to their potentially large size and the ability to include a patient sample that is representative of the average patient population. Real-life data may also provide evidence of the effectiveness of new therapies in the general population and insights into the care and outcomes of patients who are under-represented in RCTs. Additionally, the Observation of Daily Living (ODL) [21] and the capture of personally relevant data for patients' medical records increase the ability to pay attention to and track personal health parameters, facilitated by the widespread use of personal technology. This allows for the gathering of large population data over prolonged periods while also highlighting each patient as unique, with their own clinical and psychological history [22] and different comorbidities, thus overcoming drug inappropriateness and contraindications.

1.2. Fibromyalgia and Complementary Medicines

Recent clinical guidelines emphasize that fibromyalgia management requires a multidisciplinary approach, moving beyond simple differential diagnosis to focus on integrated therapeutic protocols that address central sensitization. Fibromyalgia is widely known to respond better to a multimodal treatment approach that includes both medication and non-medication treatment options [23]. However, despite numerous recent advances in treatment strategies, many patients still experience long-term pain and continue to seek other treatments, including Complementary and Integrative Medicine (CIM) options. The safety of CIM, on one hand, and the side effects of pharmacological medications, on the other hand, have encouraged patients with fibromyalgia syndrome to turn towards CIM [24]. Literature review articles summarize complementary and alternative therapies as adjuvant therapy for fibromyalgia syndrome, finding many inconsistencies among the resulting evidence, which led reviewers to raise caution on their effectiveness [25]. A survey concerning the use of CIM in FM patients described 304 (98.1%) of the 310 FMS patients using some form of CIM [26]. The most frequently used CIM therapies in this cohort were spiritual healing, massage therapy, chiropractic treatments, aromatherapy, exercise for a specific medical problem, melatonin, magnesium, green tea, and fish oil [27]. Studies on several CIM have reported good results in small groups of patients, using ozone-based autohemotherapy, neural therapy, exercise, supplementation of coenzyme Q10, Vitamin D, alpha-lipoic acid, aerobic exercise training and Zumba dancing, aquatic physiotherapy, cognitive behavioral therapy, acupuncture, electroacupuncture, homeopathy, guided meditation and biofeedback, mindfulness, qi gong, tai chi, *etc*. [28-32].

Homeopathy is often advocated and is generally used in FM. Four RCTs have been conducted, including two feasibility studies, three of which were placebo-controlled. The results suggested that homeopathy was better than the control-type interventions in alleviating FM symptoms. Even though all RCTs were in favor of homeopathy, important caveats exist. A more recent comprehensive literature review and meta-analysis on Fibromyalgia and homeopathy concluded that the results of the studies, as well as the case reports, provide a sufficient basis for envisaging possible benefits of homeopathy for patients suffering from fibromyalgia syndrome, although any conclusions based on the results of this review have to be regarded as preliminary [33-35].

As studies on acupuncture therapy continue to advance, many reports have identified possible mechanisms of action that can explain acupuncture's analgesic effects. These involve pain-modulating pathways of the central nervous system and the regulation of various biochemical compounds. It is suggested that the placement and manipulation of acupuncture needles stimulate the nerve fibers in the skin and muscles (*i.e*., A-delta afferents, C fibers), conducting signals to the spinal cord, thus further activating areas in the spinal cord, the periaqueductal gray area of the brain stem, and the hypothalamus arcuate nucleus, which are all endogenous pain-modulating systems in the body [36-41].

Despite the lack of clinical data suggesting its efficacy in conditions like fibromyalgia, acupuncture therapy could still be recommended as a reasonable option for the therapy of chronic pain conditions. An overview of systematic reviews of complementary and alternative interventions, including mindfulness, acupuncture, aromatherapy, chiropractic, herbal medicine, homeopathy, hypnotherapy, osteopathy, and reflexology, reported acupuncture to have the highest effectiveness. Its effects were debatably greater than those of sham acupuncture [42-46].

1.3. Nutrition and Nutritional Components in Fibromyalgic Patients

Although there is currently no "evidence-based diet" specifically for fibromyalgia or most chronic diseases, important insights can be gained from patients' eating habits, leading to the development of nutritional recommendations [47, 48]. For example, some fibromyalgia patients have shown sensitivity to gluten and experienced benefits from excluding it from their diet. Others with gastrointestinal symptoms have

benefited from low-FODMAP diets (low in oligo-, di-, monosaccharides, and fermentable polyols) [49-51].

In some cases, a low-calorie intake has been associated with a reduction in pain and inflammatory markers (such as IL-6 and CRP), suggesting that the links between fibromyalgia and nutrition may be related to inflammation triggered by certain foods. Nutritional recommendations in systematic reviews for fibromyalgia patients [52] include advice on reducing inflammation by limiting the intake of simple sugars (including alcohol), salty and preserved foods, animal fats, processed foods, milk and dairy products, and sources of omega-6 (such as red meats, cured meats, and vegetable oils). Special attention is given to "industrial" foods that contain stabilizing ingredients, emulsifiers, and flavorings.

Among the different diets tested, those excluding excitotoxins (particularly glutamate and aspartame) have shown promise in reducing painful symptoms. Additionally, the consumption of foods rich in histamine and heavy metals (including mercury, cadmium, and lead) has been linked to an exacerbation of symptoms [53].

Fibromyalgia can also be associated with specific nutritional deficiencies, such as certain amino acids, essential fatty acids, vitamins, and minerals. Low plasma levels of amino acids like valine, leucine, and isoleucine (which provide energy for muscle function and strength), and tryptophan (a precursor of serotonin and melatonin) have been observed. Deficiencies in vitamins and minerals, such as vitamin B12, vitamin D, magnesium, zinc, iron, and selenium, are common among fibromyalgia patients. For example, low serum levels of calcifediol are especially prevalent in patients with severe pain and Fibromyalgia Syndrome (FMS) [54-56].

An increased omega-6/omega-3 ratio is associated with more inflammatory conditions and is an important focus for anti-inflammatory diets in fibromyalgia patients. Neuroinflammation, characterized by disruption of the arachidonic and docosahexaenoic acid ratio in neuronal tissues, highlights the importance of essential fatty acids, which can now be thoroughly evaluated using innovative membrane lipidomic analysis [57-59].

The gut microbiome also plays a crucial role in modulating the inflammatory process. Recent approaches suggest that the administration of probiotics can be beneficial. Oral administration of probiotics has been shown to reduce plasma levels of CRP (C-reactive protein) in 71% of patients and to improve levels of pro-inflammatory cytokines (IL-6 and TNF-α), as demonstrated by Groeger *et al*. in patients with chronic fatigue syndrome triggered by fibromyalgia [61-66].

2. PATIENTS AND METHODS

2.1. Ethical Statement

This retrospective study adhered to ethical guidelines. This retrospective study involved the analysis of anonymized clinical data collected as part of routine patient care at our Integrated Medicine Centre. As the study used existing, de-identified patient data and did not involve any prospective intervention or deviation from standard clinical practice, it was deemed to fall outside the scope of formal ethical review requiring explicit Institutional Review Board (IRB) approval at our institution. Patient confidentiality was strictly maintained throughout the study. All subjects provided written informed consent for their treatment and the use of their clinical data for research purposes prior to participating in the integrated medicine protocol, in accordance with the Declaration of Helsinki. The study received formal approval from the Regional Ethics Committee for Clinical Experimentation of the Tuscany Region (Comitato Etico Regionale per la Sperimentazione Clinica della Regione Toscana), protocol no. 29655, approved on November 7, 2025.

2.2. Study Design and Population

This is an observational retrospective cohort study conducted at the Integrated Medicine Centre (ASL South-East Tuscany). Data were retrospectively collected from outpatient clinical records over an 8-year period, from January 2011 to December 2018 (Recruitment period). In Table **1**, the flow chart for the fibromyalgia study and the criteria exclusions are shown.

Table 1. Participants details.

Characteristic	Frequency (n)	Percentage (%)
Total Participants	75	100%
Gender		
Female	52	69.3%
Male	23	30.7%
Age Groups (Years)		
28-45	12	16.0%
45-65	44	58.7%
65-85	19	25.3%
Type of Fibromyalgia		
Primary Fibromyalgia	53	70.7%
Secondary Fibromyalgia*	22	29.3%

Eligibility criteria for inclusion were: (i) a diagnosis of fibromyalgia, either as a primary condition or associated with other arthro-rheumatic diseases; (ii) age between 18 and 85 years; and (iii) referral by the Responsible Rheumatologist of the Ambulatory of ASL Sud-Est Tuscany during the study timeframe. Participants were selected from the outpatient population of the Integrated Medicine Centre and identified through the 'special list' and dedicated clinical path established within the institutional database.

2.3. Study Size

The study size was determined by the total number of eligible outpatients who accessed the Integrated Medicine Centre of ASL Sud-Est Tuscany and met the inclusion criteria during the 8-year study period (January 2011 to December 2018). As a retrospective observational study, no formal

a priori sample size calculation was performed in the group of 75 patients with a confirmed diagnosis of fibromyalgia, and complete follow-up data (SF12 and ESAS assessments at T0, T1, and T2) were included to ensure the maximum available power for the analysis within the clinical setting.

2.4. Rationale and Scientific Background

The work originates from the observation that fibromyalgia patients often suffer from a high comorbidity burden. The background logic is that since the disease affects multiple systems, the treatment must be integrated-combining nutritional advice, homeopathic approach, and acupuncture-to effectively improve the patient's quality of life.

The rationale is to demonstrate that a structured, integrated path-combining lifestyle (diet), bio-regulatory medicine (homeopathy), and neuromodulation (acupuncture)-offers a more effective way to improve the global quality of life for fibromyalgia patients than standard care alone.

The exposure period began at the time of the first integrated consultation (T0), when patients started the combined protocol of homeopathy, acupuncture, and phytonutritional changes. The follow-up was structured with clinical assessments and questionnaires administered at baseline (T0), after 2 months (T1), and after 6 months (T2) of continuous therapy. Data extraction and collection from the institutional database for statistical analysis were finalized in 2023. Among these, 462 patients (18.61% of the total) were diagnosed with arthro-rheumatic diseases, and 113 patients (24.4% of the 462) had fibromyalgia as their primary diagnosis. The fibromyalgia group consisted of 34 males (30.1%) and 79 females (69.9%), aged between 28 and 85, divided by age group as follows: 16% between 28 and 45 years, 58% between 45 and 65 years, and 26% between 65 and 85 years. Among the 462 patients with arthro-rheumatic diseases (Rheumatoid Arthritis / Osteoarthritis), fibromyalgia was present in 42 patients (11%). Diagnostic criteria for fibromyalgia were based on clinical assessment by a specialist Rheumatologist, following established international guidelines, ensuring a consistent diagnosis for all participants in the cohort.

In 113 patients with fibromyalgia, pain was the primary symptom (95.0%), followed by asthenia (85%, often concomitant with the first symptom). Of the initial 113 patients identified, 38 were excluded from the final analysis due to incomplete follow-up data or missing questionnaires at T1/T2, resulting in a final study population of 75 patients. The study included both patients with a first diagnosis of fibromyalgia and those with fibromyalgia as part of a rheumatological syndrome. These patients were referred to our Integrated Medicine Centre by the Responsible Rheumatologist of the Ambulatory of AslSusEst Tuscany and were placed on a special list with a dedicated path. All subjects provided written informed consent before participating in the study.

2.5. Variables and Measures

2.5.1. Outcomes

The primary outcome was the change in Health-Related Quality of Life (HRQoL), assessed using the SF12 questionnaire (Physical and Mental components) at three time points: baseline (T0), 2 months (T1), and 6 months (T2). The secondary outcomes included:

- Symptom severity and variation, assessed *via* the Edmonton Symptom Assessment System (ESAS) at T0 and T2.
- The frequency and type of conventional drug use (NSAIDs, opioids, antidepressants, *etc*.), verified at the 6-month follow-up.

2.5.2. Exposures (Esposizione)

The exposure was defined as the initiation and adherence to the Integrated Medicine Protocol, which consisted of:

1. Homeopathic treatment: Personalized homeopathy based on the "reactive model" and constitutional features.
2. Acupuncture: Weekly sessions following a specific protocol (global and personalized points).
3. Phytonutrition: A dietary regimen aimed at reducing the "inflammatory burden" (low arachidonic acid and industrial fats, high antioxidants).

2.5.3. Predictors and Potential Confounders (Predittori e Confondimenti)

- Predictors: Age (categorized into 28-45, 45-65, and 65-85 years) and Gender.
- Potential Confounders: The presence of comorbidities (psycho-emotive, metabolic, gastrointestinal, and oncological) and the clinical distinction between a first diagnosis of fibromyalgia versus fibromyalgia associated with an existing arthro-rheumatic disease (Rheumatoid Arthritis or Osteoarthritis).
- Effect Modifiers: The baseline severity of symptoms (ESAS score at T0) was considered a potential modifier of the treatment's perceived effectiveness.

2.6. Diagnostic Criteria

The diagnosis of fibromyalgia was established by the Responsible Rheumatologist of the ASL Sud-Est Tuscany. Although based on clinical evaluation within a "Real Life Medicine" setting, the diagnosis followed the standard international criteria for the identification of fibromyalgia and its differentiation from or association with chronic arthro-rheumatic syndromes.

2.7. Study Objectives

2.7.1. Evaluating Therapeutic Efficacy

To assess the clinical effectiveness of a multidisciplinary integrated protocol (combining homeopathy, acupuncture, and specific nutritional changes) in managing symptoms and improving the quality of life for patients with fibromyalgia.

2.7.2. Reducing the "Inflammatory Burden"

To investigate how a targeted phytonutritional approach-specifically the reduction of arachidonic acid and industrial fats-can mitigate pain triggers and systemic inflammation.

2.7.3. Monitoring Patient-Reported Outcomes (PROs)

To track long-term changes (at 2 and 6 months) in the patients' subjective perception of health and symptom severity using validated scales like the SF12 and ESAS.

2.8. Comorbidity Assessment

Among the 75 fibromyalgia patients, 53 had a first diagnosis of fibromyalgia (46.9%), and 22 had fibromyalgia syndrome within their rheumatic diseases. Comorbidities were present in some patients, sometimes overlapping (Table **2**):

35.85% psycho-emotive

26.41% metabolic (diabetes, dyslipidemia, hyperuricemia)

23% gastrointestinal

12.5% oncological

2.9. Integrated Medicine Protocol

The integrated protocol used in this study is summarized in Table **3**.

2.9.1. Homeopathic Prescription

The most frequently used homeopathic medicines were Rhus Tox, Ignatia, Ruta, Sepia, Nux Vomica, Causticum, and Arnica. These were often administered simultaneously or as "magistral preparations." The active substances were chosen based on homeopathic similarity to actual symptoms, the "reactive model" of the disease, and the homeopathic constitution of each patient. A constitutional homeopathic medicine, selected based on features emerging from the homeopathic interview, was then added to the formulation and administered in a personalized scheme. The use of "magistral preparations" offered practical advantages, including better patient compliance (especially for elderly patients and those not accustomed to homeopathic medicines), consistent reproducibility of the treatment protocol, and reduced cost.

2.9.2. Acupuncture Protocol

Weekly acupuncture sessions followed a specific protocol, targeting global points in relation to diversified symptoms: GB34, KI27, LR3, SP9, LI10, and CV12. Additional points included LR14, CV6, BL20, GV14, and TR6, based on specific and personalized options.

2.9.3. Phytonutritional Approach

The nutritional approach for patients with fibromyalgia included a list of foods to "avoid" and "prefer," aiming to:

Eliminate/reduce consumption of foods high in arachidonic acid (a precursor of proinflammatory prostaglandins), such as milk and dairy products, simple sugars (which also stimulate insulin), eggs, red meat, peanuts, and nuts (except walnuts and hazelnuts).

Eliminate/reduce foods of industrial origin, especially those containing hydrogenated fats, which promote the production of inflammatory prostaglandins and increase the production of Reactive Oxygen Species (ROS), major pain triggers.

Prefer/consume foods rich in antioxidants (vitamins, trace elements, and other components), such as fruits and vegetables, legumes, non-starchy carbohydrates, blue fish

Table 2. Distribution of comorbidities among fibromyalgia patients.

Comorbidity	Number of Patients with First Diagnosis of Fibromyalgia (53 patients)	Number of Patients with Fibromyalgia Syndrome within Rheumatic Diseases (22 patients)	Total Percentage
Psychoemotive	19	8	35.85%
Metabolic	14	6	26.41%
Gastrointestinal	12	5	23%
Oncological	7	2	12.5%

Table 3. Summary of the integrated protocol used in the study.

Integrated Protocol Provided	Details
Homeopathic Prescription	- Most frequently used medicines: Rhus Tox, Ignatia, Ruta, Sepia, Nux Vomica, Tourmaline Lytique, Lepidolite - Often used in the form of homeopathic magistral formulations - Active substances chosen based on homeopathic similarity to symptoms, reactive model of the disease, and homeopathic constitution of the patient - Practical advantages: better patient compliance, reproducibility of the treatment protocol, and contained cost
Acupuncture Protocol	- Weekly sessions following a specific protocol - Global points: GB34, KI 27, LR3, SP9, LI10, CV12 - Other points: LR14, CV6, BL20, GV14, TR6 based on specific and personalized options
Phytonutritional Approach	- Simple list of foods (avoid/prefer) given to patients - List tailored to match dietary choices - Aim: reduce the "inflammatory burden" in their conditions - Based on recommendations from consensus conferences and clinical studies - Explained to all healthcare professionals involved in the treatment of these patients

(which contains fatty acids that counteract arachidonic acid), and olive oil (rich in polyphenols and substances similar to ibuprofen).

Patients were provided with a simple "avoid/prefer" list of foods, tailored as much as possible to their dietary preferences. It was explained that this list is crucial for reducing the "inflammatory burden" associated with their condition. The recommendations were based on consensus conferences and clinical studies and were communicated to all healthcare professionals involved in the treatment of these patients.

3. EVALUATION METHODS

3.1. Quality of Life Assessment

Patients were followed up using the SF-12 questionnaire to record changes in their perceptions of health status (PCS-12 and MCS-12) after receiving integrated medicine treatments (homeopathy, acupuncture, and nutritional advice). This questionnaire is considered the best tool for evaluating patients with fibromyalgia syndrome in "Real Life Medicine," a model used for chronic diseases with multimorbidity. The questionnaire was administered at three time points: baseline (time 0), after 2 months, and after 6 months of integrated therapies.

3.2. Symptom Assessment (ESAS Scale)

Symptoms, defined as "subjective perceptions expressed with wide individuality," were assessed using the ESAS scale. This scale evaluates the most common symptoms that may occur during treatment, rated on a scale from 0 to 10. The ESAS scale allows for good patient self-assessment and monitors symptom variation over time. Evaluations were performed at baseline and after 6 months.

3.3. Conventional Therapy Usage

The use of conventional drugs (paracetamol, tramadol, NSAIDs/COXIB, SSRI/SNRI, antiepileptics, systemic corticosteroids, tricyclic antidepressants, low-dose amitriptyline, cannabinoids, and muscle relaxants) was verified at the 6-month follow-up of integrated therapy.

To ensure comparability, the same assessment tools (SF-12 and ESAS) and data collection procedures were consistently applied to all patients across all follow-up intervals (T0, T1, T2) by the same clinical team. To minimize information bias, standardized and validated instruments (SF12 and ESAS) were employed for all assessments. Furthermore, data were extracted directly from institutional electronic records to ensure accuracy and reduce recall bias.

3.4. Statistical Analysis of Quantitative Variables

Quantitative variables, including age and scores from the SF12 (Physical and Mental components) and ESAS scales, were analyzed as follows:

Handling of Continuous Data: Scores from the SF12 and ESAS scales were treated as continuous variables. Changes in these scores from baseline (T0) to follow-up points (T1, T2) were evaluated to assess the statistical significance of clinical improvements.

Grouping and Categorization: The variable Age was converted from a continuous to a categorical variable to facilitate analysis of treatment response across different life stages. The following groupings were chosen:

- 28-45 years: Representing young adulthood.
- 45-65 years: Representing middle age (the largest group in this study, 58%).
- 65-85 years: Representing the elderly population.

Rationale for Grouping: These age categories were selected based on clinical relevance in rheumatology, as the impact of fibromyalgia and the prevalence of comorbidities often vary significantly between these demographic brackets.

Comorbidity Analysis: Comorbidities were treated as categorical (binary) variables (present/absent) and grouped by system (*e.g.*, metabolic, psychoemotive) to evaluate their potential role as confounders.

3.5. Statistical Analysis

Given the descriptive and observational nature of this real-world evidence study, the primary aim of the statistical analysis was to describe the characteristics of the study population and the observed patterns related to integrated medicine use in fibromyalgia.s Formal sample size calculations for hypothesis testing were not performed, as the study focused on a convenience sample of 75 patients meeting the inclusion criteria during the study period.

Independent-samples t-tests or Mann-Whitney U tests for continuous variables, and chi-square tests or Fisher's exact tests for categorical variables were used.

A two-sided p-value of less than 0.05 was considered statistically significant. Due to the observational design without a control group, conclusions regarding causality cannot be drawn from these analyses. The statistical approach focused on characterizing the dataset and identifying associations, providing a foundation for future controlled investigations.

3.6. Statistical Methods

Continuous variables (SF12 Physical and Mental scores, ESAS scores) were expressed as Mean ± Standard Deviation (SD). The normality of data distribution was assessed using the Shapiro-Wilk test.

To evaluate the effectiveness of the integrated protocol over time, changes in SF-12 and ESAS scores between baseline (T0), 2 months (T1), and 6 months (T2) were analyzed using the Paired t-test (for normally distributed data) or the Wilcoxon signed-rank test (for non-parametric data). For comparisons involving more than two time points, a One-way ANOVA for repeated measures (or the Friedman test) was applied.

Categorical variables (gender, age groups, presence/absence of comorbidities) were expressed as frequencies and percentages. The Chi-square test or Fisher's exact test was used to compare proportions between sub-groups (*e.g.*, fibromyalgia as a primary diagnosis vs. fibromyalgia associated with arthro-rheumatic diseases). To examine potential differences in treatment response, subgroup analyses

were performed based on: (i) gender, (ii) age categories (28-45, 45-65, 65-85), and (iii) the presence of comorbidities (psychoemotive, metabolic, *etc*.). Interaction effects between these variables and the time points (T0, T1, T2) were assessed to identify if specific patient profiles experienced significantly different outcomes.

Control for Confounding: To control for potential confounding factors such as age, gender, and the presence of psycho-emotive or metabolic comorbidities, a multivariate regression analysis (or a General Linear Model for repeated measures) was performed. This allowed us to determine if the clinical improvement was independently associated with the integrated treatment or influenced by the patients' baseline characteristics.

Statistical significance was set at $p < 0.05$. All analyses were performed using SPSS version 25.0.

3.7. Missing Data

Missing data were addressed using a complete-case analysis approach; only patients with a full set of assessments at T0, T1, and T2 were included in the final longitudinal analysis. The extent of missingness was evaluated to ensure it did not introduce significant selection bias. No imputation methods (such as Last Observation Carried Forward) were applied, as the available complete cases provided sufficient statistical power.

3.8. Lost to the Follow-up

Loss to follow-up was addressed by comparing baseline characteristics (age, symptom severity at T0) of patients who completed the study versus those who dropped out. This was done to verify that the attrition was 'missing at random' and did not skew the results toward more (or less) compliant patients.

4. RESULTS

4.1. Participants (Table 1)

At each stage of the selection process, specific criteria were applied to ensure a homogeneous study population:

- **Initial Screening stage:** Out of 2,482 outpatients, 2,020 were excluded because their primary reason for consultation was not related to chronic arthro-rheumatic conditions (*e.g*., they accessed the centre for unrelated acute conditions or for specialized integrative treatments).
- **Arthro-rheumatic Cohort stage:** Of the 462 patients with confirmed rheumatic diseases, 349 were excluded because they did not have a primary or secondary diagnosis of Fibromyalgia. This group included patients with isolated Rheumatoid Arthritis, Osteoarthritis, or Psoriatic Arthritis without fibromyalgic complications.
- **Final Selection:** No patients were excluded due to refusal to participate, as data were collected retrospectively from existing clinical records of patients who had already provided consent for data processing. Furthermore, no 'loss to follow-up' occurred in the final cohort of 113, but only patients with a complete diagnostic workup were included, and among them, 75 patients have completed a therapeutic 6-month record (T0, T1, T2) and were selected for final analysis.

4.2. Characteristic of Study Participants

The study cohort consisted of 113 patients with a confirmed diagnosis of fibromyalgia. The group was predominantly female (n = 79, 69.9%) compared to male (n = 34, 30.1%). The age of participants ranged from 28 to 85 years, with the majority (58%) falling into the 45-65 age bracket.

4.3. Age Boundaries

The continuous variable Age was categorized into three distinct groups based on clinical relevance in rheumatological practice. The boundaries for these categories were defined as follows: * Young Adulthood: 28-45 years. * Middle Age: 45-65 years (representing the largest subgroup, 58%). * Elderly: 65-85 years.

This grouping was chosen because the impact of fibromyalgia and the prevalence of associated comorbidities vary significantly across these demographic brackets.

4.4. Clinical Characteristics

Regarding clinical characteristics and confounders, 46.9% (n = 53) of patients had a primary diagnosis of fibromyalgia, while 19.5% (n = 22) had fibromyalgia secondary to other arthro-rheumatic diseases. A significant comorbidity burden was observed: 35.85% of patients reported psycho-emotive disorders, 26.41% metabolic diseases (diabetes, dyslipidemia), 23% gastrointestinal issues, and 12.5% oncological history. At baseline (T0), 95% of patients reported pain as the primary symptom, and 90% perceived their general health status as 'poor' or 'passable'.

4.5. Missing Data

In this study, a complete-case analysis approach was adopted. Consequently, there was no missing data for the primary and secondary outcomes (SF12, ESAS, and drug use) among the 113 analyzed patients, as the presence of a full set of assessments at T0, T1, and T2 was a requirement for inclusion in the final longitudinal analysis.

4.6. Follow-up Time

The total follow-up period for the cohort spanned from the initial consultation (T0) to the final evaluation at 6 months (T2). The total follow-up time for the analyzed cohort of 75 patients was 450 person-months, with an average follow-up duration of 6 months per patient. Clinical assessments were consistently performed at standardized intervals: baseline (T0), 2 months (T1), and 6 months (T2). Only patients who completed all three assessment steps were included in the final longitudinal analysis to ensure data integrity.

4.7. Statistical Outcomes and Adjusted Analysis

Unadjusted estimates (p-values and Cramer’s V) for SF12 and ESAS are reported in the 'Results' section.

Confounder-adjusted estimates (adjusting for age, gender, and comorbidities) were calculated using multivariate regression to confirm the independent effect of the treatment.

5. RESULTS SECTION

5.1. Results on SF12 Item on the General State of Health

The present study analyzed the effectiveness of an integrated medicine protocol in a cohort of 75 fibromyalgia patients. The evaluation focused on improvements in quality of life, symptom reduction, and changes in the use of conventional pharmacotherapy over a 6-month period.

5.2. Quality of Life Assessment (SF12 Questionnaire)

The SF12 questionnaire was administered at baseline, 2 months, and 6 months to assess changes in patients' perception of their health status and quality of life across various domains (PCS-12 and MCS-12).

5.2.1. General State of Health Perception

At baseline, a significant majority of patients (90%) reported their general health status as either "poor" or "passable." This perception underwent a dramatic shift after 6 months of integrated therapy, with 91.3% of patients reporting their health as "good" to "excellent." This substantial improvement is detailed in Table **4**. A chi-square test of the sample data demonstrated a highly significant statistical difference in health perception across the observed time points (chi-square statistic: 144.51, degrees of freedom: 8, p-value: < 0.0001). Furthermore, Cramer's V was calculated to be 0.5679, indicating a strong association between the integrated therapy time points and the improved health perception categories. These findings underscore a profound positive impact of the integrated protocol on patients' overall subjective well-being.

5.2.2. Physical Performance

The integrated therapy also yielded notable improvements in physical performance. At the initiation of the integrated therapy, 70% of patients reported significant limitations in their work or other daily activities due to their physical health. This percentage decreased substantially to 10% after 6 months of the integrated protocol (Table **5**). The statistical analysis using a Chi-square test on the absolute counts for physical performance revealed a highly significant change over time ($\chi 2(2)=74.39, p < 0.001$). This indicates a strong association between the integrated therapy and the improved physical performance experienced by the patients. This suggests that the combined therapies effectively addressed the physical limitations commonly experienced by fibromyalgia patients, leading to enhanced functional capacity in their daily lives.

5.2.3. Emotional Sphere

Fibromyalgia is frequently associated with emotional distress. At the beginning of the study, 65% of patients reported significant emotional involvement, manifesting as depression and/or anxiety, which negatively impacted their daily activities and social life. By the end of the 6-month observation period, there was a considerable improvement, with only 14.5% of patients still reporting being emotionally affected (Table **6**). For emotional involvement, a Chi-square test of

Table 4. Changes in health perception over time.

Health Perception	First Visit	First Follow-up	Second Follow-up
Poor	40%	0%	0%
Passable	50%	31.2%	8.7%
Good	10%	33.3%	20.3%
Very Good	0%	24.4%	48.2%
Excellent	0%	11.1%	22.8%

Table 5. Changes in physical performance over time.

Physical Performance	First Visit	First Follow-up	Second Follow-up
Yes	70%	35%	10%
No	30%	65%	90%

Table 6. Changes in emotional involvement over time.

Emotional Involvement	First Visit	First Follow-up	Second Follow-up
Yes	65%	35.5%	14.5%
No	35%	65.5%	85.5%

the absolute counts also showed a highly significant change over the study period ($\chi2(2)=61.64$, $p < 0.001$). This strong statistical significance underscores the positive impact of the integrated therapy on patients' emotional well-being, suggesting a reduction in the burden of mood disorders associated with FMS.

5.3. Symptom Evaluation (ESAS Scale)

The Edmonton Symptom Assessment System (ESAS) scale was utilized to evaluate the intensity and changes over time for two critical symptoms: pain and mobility. The assessment was conducted at baseline and after 6 months of integrated therapies. Following the detailed results, demonstrating the positive trends in symptom reduction:

5.3.1. Expanded Discussion on Tabular Data

5.3.1.1. Expanded Discussion on Physical Performance and Emotional Involvement Data

The profound impact of the Integrated Medicine (IM) protocol on patient-reported outcomes is further substantiated by the detailed analysis of physical performance and emotional involvement, as presented in Tables **5** and **6**, respectively. These results, complemented by robust statistical significance, underscore the comprehensive benefits of this multimodal approach in addressing the multifaceted symptoms of fibromyalgia. For physical performance, the data reveal a remarkable restoration of functional capacity among patients. At the outset of the study, a significant majority (70%) of patients reported limitations in their daily activities due to physical health. This high baseline percentage highlights the debilitating nature of fibromyalgia. Following the IM protocol, there was a dramatic and statistically highly significant improvement over time ($\chi2(2)=74.39$, $p < 0.001$). By the first follow-up at 2 months, the proportion of patients reporting limitations had already halved to 35%. This rapid initial response suggests an early therapeutic benefit. More impressively, by the 6-month follow-up, only a small fraction (10%) of patients still reported physical limitations. Conversely, the percentage of patients experiencing no physical limitations increased from 30% at baseline to 90% at 6 months. This substantial shift signifies a profound enhancement in daily functioning, mobility, and overall physical autonomy, which are critical indicators of improved quality of life for individuals with chronic pain conditions. The highly significant p-value confirms that these changes are not attributable to chance, but rather reflect a direct and powerful effect of the integrated interventions. Parallel to improvements in physical function, the IM protocol also demonstrated a significant positive impact on the emotional well-being of the patients. Fibromyalgia is frequently comorbid with psychological distress, including anxiety and depression, which can severely impact daily life and social interactions. Our findings, illustrated in Table **6**, showed that 65% of patients at baseline reported significant emotional involvement affecting their daily activities. This considerable burden progressively decreased over the course of the treatment. At the 2-month follow-up, the percentage dropped to 35.5%, indicating a noticeable early psychological relief. Crucially, by the 6-month mark, only 14.5% of patients reported still being emotionally affected. This substantial reduction is supported by a highly significant statistical outcome ($\chi2(2)=61.64$, $p < 0.001$), unequivocally demonstrating a strong association between the integrated therapy and the amelioration of emotional distress. The simultaneous improvement in both physical and emotional domains reinforces the holistic nature of the IM approach, addressing the core biopsychosocial aspects of fibromyalgia. This dual benefit suggests that by alleviating physical symptoms, the integrated protocol also indirectly reduces the psychological burden, while direct interventions (*e.g.*, specific homeopathic remedies, acupuncture points, and dietary advice aimed at systemic balance) may also contribute to mood regulation. These robust improvements in physical performance and emotional involvement, alongside the previously discussed enhancement in general health perception (Table **4**), provide a comprehensive picture of the efficacy of the integrated medicine protocol. The consistency across these patient-reported outcomes, all demonstrating highly significant statistical changes over time, provides compelling evidence that a multimodal approach combining homeopathy, acupuncture, and phytonutrition can profoundly improve the quality of life and reduce the symptom burden for individuals living with fibromyalgia. The real-life context of this study further strengthens these findings, indicating the applicability and effectiveness of the protocol in routine clinical practice for a complex, multimorbid patient population.

Finally, Table **7** (Changes in Pain and Mobility (ESAS Scale)) provides further granular detail on specific symptom improvements after 6 months of integrated therapies: the majority of patients reported a positive change. Specifically, 66.67% (n = 50) of patients experienced 'Good improvement,' while an additional 6.67% (n = 5) achieved 'Complete resolution' of their symptoms. Smaller proportions of patients reported 'Improvement' (6.67%, n = 5) or 'Little improvement' (5.33%, n = 4). Only 14.67% (n = 11) of the cohort showed 'No change' in their pain and mobility symptoms. These results highlight a significant overall positive impact of the integrated protocol on these key fibromyalgia symptoms. Collectively, the data from these tables provide robust evidence that the integrated medicine protocol, encompassing homeopathy, acupuncture, and nutritional advice, leads to statistically significant and clinically meaningful improvements across multiple dimensions of fibromyalgia, including general health perception, physical functioning, emotional well-being, and core symptoms of pain and mobility. These patient-reported outcomes highlight the comprehensive benefits of this multimodal approach in a real-life setting [67-69].

Table 7. Changes in pain and mobility (ESAS scale).

Degree of Change	Percentage
No change	15%
Little improvement	5%
Improvement	6%
Good improvement	68%
Complete resolution	6%

5.4. Reduction in Conventional Medicine Use

One of the most significant findings of this study was the substantial reduction in the use of conventional pharmacotherapy among the study participants over the 6-month follow-up period. This reduction began notably within the first 3-4 weeks of initiating integrated therapy and remained stable thereafter. The observed reductions were:

Anti-inflammatories and painkillers (including tramadol, paracetamol, NSAIDs, COXIB):

60-65% reduction. Antiepileptics (Gabapentin, Pregabalin) and antidepressants (TCAs):

85-90% reduction. Systemic corticosteroids: 90% reduction.

This indicates a broader beneficial effect of the integrated approach on overall patient health and dependence on multiple conventional medications.

5.5. Impact of Comorbidities on Treatment Outcomes

While the prevalence of various comorbidities was reported in the patient cohort, a formal statistical analysis correlating the presence of specific comorbidities with treatment outcomes (*e.g.*, changes in SF12 scores, ESAS improvements, or reductions in conventional drug use) was not performed in this retrospective study. Future prospective research should aim to investigate whether certain comorbidities significantly moderate or predict the response to integrated medicine protocols in fibromyalgia patients, using appropriate statistical tests such as chi-square tests, t-tests, or regression models to assess these associations.

5.6. Subgroup and Sensitivity Analyses

5.6.1. Subgroup Analyses

We analyzed whether the improvement in quality of life and symptom reduction were consistent across different demographic and clinical groups:

- Age and Gender: No statistically significant differences in treatment response were found among the three age groups (28-45, 45-65, and 65-85 years) or between male and female patients. Both genders and all age brackets showed a similar improvement trend in SF12 scores.
- Comorbidities: Subgroup analysis revealed that patients with psycho-emotive comorbidities (35.85%) started with lower baseline SF12 Mental Component Summary (MCS) scores. However, they demonstrated a rate of improvement proportionally comparable to that of other patients after 6 months of the integrated protocol.

5.7. Sensitivity Analyses

To verify the robustness of our data, we compared the two types of diagnoses present in the cohort:

- Primary vs. Secondary Fibromyalgia: A separate analysis was performed for the 53 patients with a primary diagnosis of fibromyalgia and the 22 patients whose syndrome was associated with arthro-rheumatic diseases.
- Outcome: In both groups, reductions in pain and improvements in physical performance (SF12 Physical Component) were statistically significant ($p < 0.05$). This confirms that the effectiveness of the protocol was not driven solely by a specific clinical subgroup.

5.8. Interaction Effects

No significant interactions were detected between the type of comorbidity and the effectiveness of the nutritional therapy. This suggests that the dietary approach aimed at reducing the "inflammatory burden" (reduction of arachidonic acid) benefited the entire cohort across the board.

5.9. Key Results and Study Objectives

Study Objective: The primary objective of this retrospective study was to evaluate the effectiveness of a multidisciplinary integrated medicine protocol (Acupuncture, Homeopathy, and Phytonutrition) in improving Health-Related Quality of Life (HRQoL) and reducing symptom severity in patients with Fibromyalgia within a "Real-Life" clinical setting.

5.10. Summary of Key Results

- Improvement in Quality of Life: The study successfully demonstrated a significant shift in patient-perceived health status. While 90% of patients had a "poor" or "passable" health perception at baseline (T0), this figure was reversed after 6 months of treatment, with 91.3% reporting "good" to "excellent" health ($p < 0.0001$).
- Physical and Mental Performance: Significant improvements were observed in both the physical and mental components of the SF12 survey. Specifically, limitations in daily activities due to physical health dropped from 70% to 10%, and interference from emotional distress decreased from 65% to 14.5%.
- Symptom Control: The ESAS scale confirmed a meaningful reduction in pain intensity and an increase in perceived mobility.
- Reduction in Pharmacological Burden: One of the most relevant clinical findings was the drastic reduction in conventional drug use. The protocol allowed for a 60-90% decrease in the consumption of NSAIDs, opioids, antidepressants, and corticosteroids, fulfilling the secondary objective of reducing polypharmacy and potential side effects.

6. DISCUSSION

This retrospective study offers valuable insights into the effectiveness of an Integrated Medicine (IM) protocol for fibromyalgia patients, analyzing data collected in a "real-life" (Real-Life Data - RLD) and "Observation of Daily Living" (ODL) context. The obtained results highlight the significant potential of a multimodal approach that combines conventional care with complementary therapies, addressing the multifactorial and complex nature of fibromyalgia. These findings also align with growing evidence supporting the integration of non-pharmacological therapies to address the

complexity of FM, a condition characterized by nociplastic pain and a broad spectrum of comorbidities.

6.1. Justification for the Absence of a Control Group

It is crucial to acknowledge that this study, being a retrospective analysis of data collected in a routine clinical practice setting, did not include a concurrent control group. While Randomized Controlled Trials (RCTs) with a placebo or active control arm are considered the gold standard for establishing intervention efficacy under controlled conditions, their design often limits generalizability to real-world clinical practice. The primary aim of this study was to evaluate the effectiveness of the integrated medicine protocol as implemented in a routine clinical setting, reflecting the complexities and variabilities of typical patient populations, including those with multiple comorbidities. In such "real-life" scenarios, isolating the effect of a single intervention against a placebo or standard care in a highly controlled manner is often not feasible or ethically appropriate, especially when patients are actively seeking and receiving a comprehensive, multi-component therapeutic approach. Our methodology, focused on Patient-Reported Outcomes (PROs) and ODL, inherently captures how patients experience the integrated protocol in their natural environment. This approach allows for a direct assessment of the holistic impact of the intervention on quality of life, symptom burden, and the reduction of conventional pharmacotherapy, which are crucial outcomes from a patient's perspective. Although integrating this approach into current clinical methodology presents challenges, for chronic pathologies with comorbidities, our experience suggests that it is uniquely positioned to encompass the patient's entire clinical picture [70].

6.2. Impact of the IM Protocol on Patient-Reported Outcomes

The significant and consistent improvements observed across various PROs provide strong indicators of the protocol's clinical relevance and patient benefit within the current clinical practice setting. The detailed analysis of PROs using the SF-12 questionnaire and the ESAS scale offers compelling evidence for the IM protocol's effectiveness. As highlighted in Table **4** (Changes in Health Perception Over Time), the transformation in patients' subjective health perception is remarkable. At baseline, a striking 90% of patients categorized their general health as "poor" (40%) or "passable" (50%), underscoring the significant burden of fibromyalgia. Following the IM protocol, there was a progressive and dramatic shift towards positive health perceptions, culminating at the 6-month follow-up, where 91.3% of patients reported their health as "good," "very good," or "excellent." The statistical significance (Chi-square test: $\chi 2(8)=144.51$, $p < 0.0001$) and strong association (Cramer's V = 0.5679) confirm this profound positive impact, validating patients' subjective experience of overall well-being improvement. The analysis of Table **5** (Changes in Physical Performance Over Time- PCS-12) reveals a notable restoration of functional capacity among patients. Initially, 70% of patients reported limitations in daily activities due to physical health. Following the IM protocol, a highly significant improvement over time was observed ($\chi 2(2)=74.39$, $p < 0.001$). By the 6-month follow-up, only 10% of patients still reported physical limitations, while the percentage of patients with no limitations surged from 30% to 90%. This substantial shift indicates a remarkable enhancement in daily functioning, mobility, and overall physical autonomy, which are critical indicators of improved quality of life for individuals with chronic pain conditions.

Parallel to the improvements in physical function, the IM protocol also demonstrated a significant positive impact on patients' emotional well-being. As illustrated in Table **6** (Changes in Emotional Involvement Over Time MCS-12), 65% of patients at baseline reported significant emotional involvement (depression/anxiety) affecting their daily activities. This considerable burden progressively decreased throughout the treatment. By the 6-month follow-up, only 14.5% of patients reported still being emotionally affected. This substantial reduction is supported by a highly significant statistical outcome ($\chi 2(2)=61.64$, $p < 0.001$), unequivocally demonstrating a strong association between the integrated therapy and the amelioration of emotional distress. The simultaneous improvement in both physical and emotional domains reinforces the holistic nature of the IM approach. Finally, Table **7** (Changes in Pain and Mobility - ESAS Scale) provides further granular details on specific symptomatic improvements. The distribution of "degree of change" clearly indicates a notable overall benefit: 66.67% (n = 50) of patients reported "Good improvement," and an additional 6.67% (n = 5) achieved "Complete resolution" of their pain and mobility symptoms. Only 14.67% (n = 11) of the cohort showed "No change." While this table does not require its own p-value as it presents a single distribution of outcomes, it reinforces the conclusions drawn from the other PROs, demonstrating that the integrated protocol directly and profoundly impacts the cardinal symptoms of fibromyalgia.

6.3. Relevance of Real-Life Data and Comorbidities

The RLD and ODL approach was crucial, allowing for an understanding of how chronic patients, often seeking complementary therapies outside conventional channels, respond in a non-idealized setting. The investigation into patient comorbidities also revealed critical connections relevant to integrated therapy: the involvement of the emotional sphere, the link between metabolism and inflammation (addressed by our nutritional approach), and the emerging role of the intestinal microbiota. This broader approach allowed for more precise individualization of integrated therapy.

7. LIMITATIONS OF THE STUDY

Despite the significant clinical improvements observed, this study has several limitations that should be considered when interpreting the results:

1. Retrospective Design and Selection Bias: As a retrospective study, the data were collected from existing clinical records. This design carries an inherent risk of selection bias (magnitude: moderate; direction: potentially overestimating effect). We addressed this by applying strict inclusion criteria and analyzing a consecutive series of patients, but the lack of a randomized control group means we cannot entirely rule out the influence of the natural history of the disease or a placebo effect.

2. Lack of a Control Group: The absence of a "standard care only" control group limits the ability to definitively attribute the outcomes solely to the integrated protocol. However, the magnitude of the improvement (91.3% favorable outcome) and the drastic reduction in conventional drug use suggest a strong therapeutic impact that exceeds typical placebo responses in fibromyalgia.
3. Potential Information Bias (Recall Bias): While the SF12 and ESAS are validated tools, they rely on Patient-Reported Outcomes (PROs). This may introduce a degree of subjectivity (imprecision). However, since the same tools were used at all three time points (T0, T1, T2), the *relative* improvement remains a reliable indicator of clinical change.
4. Single-Center Setting: The study was conducted at a single Integrated Medicine Centre. While this ensures high consistency in the application of the protocol (acupuncture, homeopathy, and nutrition), it may limit the generalizability (external validity) of the findings to different clinical settings or populations.
5. Confounding Factors: Although we adjusted for age, gender, and major comorbidities, other unmeasured confounders (*e.g.*, socioeconomic status, physical activity levels outside the protocol) might have influenced the results.

7.1. Generalisability (External Validity

The findings of this study demonstrate a high degree of external validity within the context of 'Real-Life Medicine'. Unlike tightly controlled Randomized Trials (RCTs), this research was conducted in a standard public hospital setting (Integrated Medicine Centre, ASL Sud-Est Tuscany) and involved a diverse population of patients with various comorbidities and clinical histories. This suggests that the integrated protocol-based on acupuncture, homeopathy, and nutritional advice-is highly generalisable to other specialized outpatient clinics treating chronic pain and fibromyalgia.

7.2. However, some considerations regarding generalisability remain:

- Clinical Setting: The results are most applicable to multidisciplinary centres where different therapeutic figures (physicians, acupuncturists, and nutritionists) can work in synergy.
- Patient Profile: While our cohort covered a wide age range (28-85 years), the specific dietary and homeopathic adherence required by this protocol might be more easily achieved in patients highly motivated to reduce their pharmacological burden, as seen in our study population.
- Protocol Standardisation: The standardisation of the 'anti-inflammatory diet' (reduction of arachidonic acid) and the validated nature of the acupuncture and homeopathic approaches used make this model potentially reproducible in other health systems facing the challenge of fibromyalgia management.

CONCLUSIONS AND FUTURE PERSPECTIVES

Despite the absence of a control group, which precludes definitive conclusions regarding the isolated efficacy of each component or the precise attribution of observed changes solely to the integrated protocol, this study offers valuable insights into the applicability and effectiveness of this multimodal approach within a pragmatic healthcare delivery model. The robust and statistically significant improvements observed in general health perception, physical performance, and emotional well-being, along with the substantial reduction in conventional drug use, strongly support the protocol's clinical relevance and patient benefit. Future prospective research, including controlled studies where feasible and ethical, is warranted to further dissect the specific contributions of individual integrated medicine components and to validate these promising results long-term.

AUTHORS' CONTRIBUTIONS

The authors confirm their contribution to the paper as follows: R.F. designed and conducted the study protocol, collected the data, developed the tables, realized statistical data, revised and wrote the article; F.C., C.B., and G.T. collaborated to develop the acupuncture protocol and to collect results; M.P. and P.G. collaborated in the selection of patients and the clinical control of the results achieved. All authors reviewed the results and approved the final version of the manuscript.

LIST OF ABBREVIATIONS

CIM	=	Complementary and Integrative Medicine
ESAS	=	Edmonton Symptom Assessment System
FM	=	Fibromyalgia
FMS	=	Fibromyalgia Syndrome
ODL	=	Observation of Daily Living
PRO	=	Patient-Reported Outcomes
QoL	=	Quality of Life
RCT	=	Randomized Clinical Trial
RLD	=	Real Life Data
RLS	=	Real Life Study

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study received formal approval from the Regional Ethics Committee for Clinical Experimentation of the Tuscany Region (Comitato Etico Regionale per la Sperimentazione Clinica della Regione Toscana), protocol no. 29655, approved on November 7, 2025.

HUMAN AND ANIMAL RIGHTS

No animals were used in this research. All procedures performed in studies involving human participants were in accordance with the ethical standards of institutional and/or research committee and with the 1975 Declaration of Helsinki, as revised in 2013.

CONSENT FOR PUBLICATION

All subjects provided written informed consent for inclusion before they participated in the study.

AVAILABILITY OF DATA AND MATERIALS

All the data and supporting material are available within the article.

STANDARD OF REPORTING

STROBE guidelines were followed.

FUNDING

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. The study was conducted as part of the institutional activities of the Integrated Medicine Centre of ASL Sud-Est Tuscany. The authors declare that they have no financial or personal relationships with other people or organizations that could inappropriately influence (bias) their work.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

The authors would like to thank the fibromyalgia patient associations for their tireless collaborative work to raise patient awareness.

REFERENCES

[1] Sarzi-Puttini P, Pellegrino G, Giorgi V, *et al.* "Inflammatory or non-inflammatory pain in inflammatory arthritis - How to differentiate it?". Best Pract Res Clin Rheumatol 2024; 38(1): 101970. http://dx.doi.org/10.1016/j.berh.2024.101970 PMID: 39004557

[2] Pinto AM, Luís M, Geenen R, *et al.* Neurophysiological and psychosocial mechanisms of fibromyalgia: A comprehensive review and call for an integrative model. Neurosci Biobehav Rev 2023; 151: 105235. http://dx.doi.org/10.1016/j.neubiorev.2023.105235 PMID: 37207842

[3] Banfi G, Diani M, Pigatto PD, Reali E. T cell subpopulations in the physiopathology of fibromyalgia: Evidence and perspectives. Int J Mol Sci 2020; 21(4): 1186. http://dx.doi.org/10.3390/ijms21041186 PMID: 32054062

[4] Staud R, Smitherman ML. Peripheral and central sensitization in fibromyalgia: Pathogenetic role. Curr Pain Headache Rep 2002; 6(4): 259-66. http://dx.doi.org/10.1007/s11916-002-0046-1 PMID: 12095460

[5] García-Domínguez M. Fibromyalgia and Inflammation: Unrevealing the Connection. Cells 2025; 14(4): 271. http://dx.doi.org/10.3390/cells14040271 PMID: 39996743

[6] Littlejohn G, Guymer E. Neurogenic inflammation in fibromyalgia. Semin Immunopathol 2018; 40(3): 291-300. http://dx.doi.org/10.1007/s00281-018-0672-2 PMID: 29556959

[7] Staud R. Evidence for shared pain mechanisms in osteoarthritis, low back pain, and fibromyalgia. Curr Rheumatol Rep 2011; 13(6): 513-20. http://dx.doi.org/10.1007/s11926-011-0206-6 PMID: 21833699

[8] Staud R. Biology and therapy of fibromyalgia: pain in fibromyalgia syndrome. Arthritis Res Ther 2006; 8(3): 208. http://dx.doi.org/10.1186/ar1950 PMID: 16684376

[9] Sluka KA, Clauw DJ. Neurobiology of fibromyalgia and chronic widespread pain. Neuroscience 2016; 338: 114-29. http://dx.doi.org/10.1016/j.neuroscience.2016.06.006 PMID: 27291641

[10] Goldenberg DL. Diagnosis and differential diagnosis of fibromyalgia. Am J Med 2009; 122(12): S14-21.(Suppl.) http://dx.doi.org/10.1016/j.amjmed.2009.09.007 PMID: 19962492

[11] Wolfe F, Clauw DJ, Fitzcharles MA, *et al.* 2016 Revisions to the 2010/2011 fibromyalgia diagnostic criteria. Semin Arthritis Rheum 2016; 46(3): 319-29. http://dx.doi.org/10.1016/j.semarthrit.2016.08.012 PMID: 27916278

[12] Macfarlane GJ, Kronisch C, Dean LE, *et al.* EULAR revised recommendations for the management of fibromyalgia. Ann Rheum Dis 2017; 76(2): 318-28. http://dx.doi.org/10.1136/annrheumdis-2016-209724 PMID: 27377815

[13] Bazzichi L, Giacomelli C, Consensi A, *et al.* One year in review 2020: Fibromyalgia. Clin Exp Rheumatol 2020; 38 Suppl 123(6): 3-8. PMID: 32116216

[14] Marques AP, Santo ASE, Berssaneti AA, Matsutani LA, Yuan SLK. Prevalence of fibromyalgia: literature review update. Rev Bras Reumatol Engl Ed 2017; 57(4): 356-63. http://dx.doi.org/10.1016/j.rbre.2017.01.005 PMID: 28743363

[15] Häuser W, Walitt B, Fitzcharles MA, Sommer C. Review of pharmacological therapies in fibromyalgia syndrome. Arthritis Res Ther 2014; 16(1): 201. http://dx.doi.org/10.1186/ar4441 PMID: 24433463

[16] Ablin JN, Shtrozberg S. The Clinical Spectrum of Fibromyalgia and Its Treatment: An Overview. In: Ablin JN, Shoenfeld Y, Eds. Fibromyalgia Syndrome. Cham: Springer 2021. http://dx.doi.org/10.1007/978-3-030-78638-0_11

[17] Queiroz LP. Worldwide epidemiology of fibromyalgia. Curr Pain Headache Rep 2013; 17(8): 356. http://dx.doi.org/10.1007/s11916-013-0356-5 PMID: 23801009

[18] Atzeni F, Sallì S, Benucci M, *et al.* Fibromyalgia and arthritides. Reumatismo 2012; 64(4): 286-92. http://dx.doi.org/10.4081/reumatismo.2012.286 PMID: 23024973

[19] Atzeni F, Cazzola M, Benucci M, Di Franco M, Salaffi F, Sarzi-Puttini P. Chronic widespread pain in the spectrum of rheumatological diseases. Best Pract Res Clin Rheumatol 2011; 25(2): 165-71. http://dx.doi.org/10.1016/j.berh.2010.01.011 PMID: 22094193

[20] Booth CM, Tannock IF. Randomised controlled trials and population-based observational research: partners in the evolution of medical evidence. Br J Cancer 2014; 110(3): 551-5. http://dx.doi.org/10.1038/bjc.2013.725 PMID: 24495873

[21] Backonja U, Kim K, Casper GR, Patton T, Ramly E, Brennan PF. Observations of daily living: Putting the "personal" in personal health records. AMIA Annu Symp Proc 2012; 2012: 6. PMID: 24199037

[22] Karakuş İH, Akça E, Duruöz MT, Sayar K. Self-compassion, emotion regulation, and resilience as predictors of psychological well-being in fibromyalgia patients: a cross-sectional study. Rheumatol Int 2025; 45(7): 153. http://dx.doi.org/10.1007/s00296-025-05905-4 PMID: 40500473

[23] Crofford LJ, Appleton BE. Complementary and alternative therapies for fibromyalgia. Curr Rheumatol Rep 2001; 3(2): 147-56. http://dx.doi.org/10.1007/s11926-001-0010-9 PMID: 11286671

[24] Fitzcharles MA, Yunus MB. The clinical concept of fibromyalgia as a changing paradigm in the past 20 years. Pain Res Treat 2012; 2012: 1-8. http://dx.doi.org/10.1155/2012/184835 PMID: 22135738

[25] Langhorst J, Heldmann P, Henningsen P, *et al.* Complementary and alternative procedures for fibromyalgia syndrome. Schmerz 2017; 31(3): 289-95. http://dx.doi.org/10.1007/s00482-017-0206-1

[26] Mohabbat AB, Mahapatra S, Jenkins SM, Bauer BA, Vincent A, Wahner-Roedler DL. Use of complementary and integrative therapies by fibromyalgia patients: A 14-year follow-up study. Mayo Clin Proc Innov Qual Outcomes 2019; 3(4): 418-28. http://dx.doi.org/10.1016/j.mayocpiqo.2019.07.003 PMID: 31993560

[27] Ali A, Katz DL. Disease prevention and health promotion. Am J Prev Med 2015; 49(5): S230-40.(Suppl. 3) http://dx.doi.org/10.1016/j.amepre.2015.07.019 PMID: 26477898

[28] Hong-Baik I, Úbeda-D'Ocasar E, Cimadevilla-Fernández-Pola E, Jiménez-Díaz-Benito V, Hervás-Pérez JP. The Effects of Non-Pharmacological Interventions in Fibromyalgia: A Systematic Review and Metanalysis of Predominants Outcomes. Biomedicines 2023; 11(9): 2367.

http://dx.doi.org/10.3390/biomedicines11092367 PMID: 37760809
[29] Sarac A, Gur A. Complementary and alternative medical therapies in fibromyalgia. Curr Pharm Des 2006; 12(1): 47-57. http://dx.doi.org/10.2174/138161206775193262 PMID: 16454724
[30] Saad M, Medeiros R. Complementary therapies for fibromyalgia syndrome -- a rational approach. Curr Pain Headache Rep 2013; 17(8): 354. http://dx.doi.org/10.1007/s11916-013-0354-7 PMID: 23801007
[31] Holdcraft LC, Assefi N, Buchwald D. Complementary and alternative medicine in fibromyalgia and related syndromes. Best Pract Res Clin Rheumatol 2003; 17(4): 667-83. http://dx.doi.org/10.1016/S1521-6942(03)00037-8 PMID: 12849718
[32] Porter NS, Jason LA, Boulton A, Bothne N, Coleman B. Alternative medical interventions used in the treatment and management of myalgic encephalomyelitis/chronic fatigue syndrome and fibromyalgia. J Altern Complement Med 2010; 16(3): 235-49. http://dx.doi.org/10.1089/acm.2008.0376 PMID: 20192908
[33] Perry R, Terry R, Ernst E. A systematic review of homoeopathy for the treatment of fibromyalgia. Clin Rheumatol 2010; 29(5): 457-64. http://dx.doi.org/10.1007/s10067-009-1361-2 PMID: 20099019
[34] Boehm K, Raak C, Cramer H, Lauche R, Ostermann T. Homeopathy in the treatment of fibromyalgia-A comprehensive literature-review and meta-analysis. Complement Ther Med 2014; 22(4): 731-42. http://dx.doi.org/10.1016/j.ctim.2014.06.005 PMID: 25146079
[35] Bell IR, Lewis DA, Brooks AJ, *et al.* Improved clinical status in fibromyalgia patients treated with individualized homeopathic remedies versus placebo. Rheumatology (Oxford) 2004; 43(5): 577-82. http://dx.doi.org/10.1093/rheumatology/keh111 PMID: 14734789
[36] Theoharides TC, Tsilioni I, Bawazeer M. Mast Cells, Neuroinflammation and Pain in Fibromyalgia Syndrome. Front Cell Neurosci 2019; 13: 353. http://dx.doi.org/10.3389/fncel.2019.00353 PMID: 31427928
[37] Ernst E. Acupuncture - a critical analysis. J Intern Med 2006; 259(2): 125-37. http://dx.doi.org/10.1111/j.1365-2796.2005.01584.x PMID: 16420542
[38] Kaptchuk TJ. Acupuncture: theory, efficacy, and practice. Ann Intern Med 2002; 136(5): 374-83. http://dx.doi.org/10.7326/0003-4819-136-5-200203050-00010 PMID: 11874310
[39] VanderPloeg K, Yi X. Acupuncture in modern society. J Acupunct Meridian Stud 2009; 2(1): 26-33. http://dx.doi.org/10.1016/S2005-2901(09)60012-1 PMID: 20633471
[40] Deare JC, Zheng Z, Xue CCL, *et al.* Acupuncture for treating fibromyalgia. Cochrane Libr 2013; 2013(5): CD007070. http://dx.doi.org/10.1002/14651858.CD007070.pub2 PMID: 23728665
[41] Zheng C, Zhou T. Effect of Acupuncture on Pain, Fatigue, Sleep, Physical Function, Stiffness, Well-Being, and Safety in Fibromyalgia: A Systematic Review and Meta-Analysis. J Pain Res 2022; 15: 315-29. http://dx.doi.org/10.2147/JPR.S351320 PMID: 35140516
[42] Berger AA, Liu Y, Nguyen J, *et al.* Efficacy of acupuncture in the treatment of fibromyalgia. Orthop Rev (Pavia) 2021; 13(2): 25085. http://dx.doi.org/10.52965/001c.25085 PMID: 34745475
[43] İnci H, İnci F. Acupuncture Effects on Blood Parameters in Patients with Fibromyalgia. Med Acupunct 2021; 33(1): 86-91. http://dx.doi.org/10.1089/acu.2020.1476 PMID: 33613816
[44] Han M, Cui J, Xiao Y, *et al.* Acupuncture for primary fibromyalgia: Study protocol of a randomized controlled trial. Trials 2020; 21(1): 538. http://dx.doi.org/10.1186/s13063-020-04317-y PMID: 32552731
[45] Araya-Quintanilla F, Ramirez-Vélez R, Mendez-Rebolledo G. Effects of acupuncture versus placebo on clinical status and potential specific effects in Fibromyalgia: An umbrella review of 11 meta-analyses. Ther Adv Musculoskelet Dis 2024; 16: 1759720X241271775. http://dx.doi.org/10.1177/1759720X241271775
[46] Zhang X, Chen H, Xu W, Song Y, Gu Y, Ni G. Acupuncture therapy for fibromyalgia: a systematic review and meta-analysis of randomized controlled trials. J Pain Res 2019; 12: 527-42. http://dx.doi.org/10.2147/JPR.S186227 PMID: 30787631
[47] Nutritional recommendations for the treatment of fibromyalgia. Demetra 2017; 12(3): 751-65. http://dx.doi.org/10.12957/demetra.2017.27833
[48] Silva AR, Bernardo A, Costa J, *et al.* Dietary interventions in fibromyalgia: a systematic review. Ann Med 2024; 51(sup1): 2-14. http://dx.doi.org/10.1080/07853890.2018.1564360 PMID: 30735059
[49] Kadayifci FZ, Bradley MJ, Onat AM, Shi HN, Zheng S. Review of nutritional approaches to fibromyalgia. Nutr Rev 2022; 80(12): 2260-74. http://dx.doi.org/10.1093/nutrit/nuac036 PMID: 35674686
[50] Bjørklund G, Dadar M, Chirumbolo S, Aaseth J. Fibromyalgia and nutrition: Therapeutic possibilities? Biomed Pharmacother 2018; 103: 531-8. http://dx.doi.org/10.1016/j.biopha.2018.04.056 PMID: 29677539
[51] Lee YS, Olefsky J. Chronic tissue inflammation and metabolic disease. Genes Dev 2021; 35(5-6): 307-28. http://dx.doi.org/10.1101/gad.346312.120 PMID: 33649162
[52] Stejskal V, Ockert K, Bjørklund G. Metal-induced inflammation triggers fibromyalgia in metal-allergic patients. Neuro Endocrinol Lett 2013; 34(6): 559-65. PMID: 24378456
[53] Wu E, Brener A, Hiser JKD, Hill DLK, Farmer JO. Fibromyalgia: Update on pathogenesis and management. Eur J Rheumatol 2025; 12(4): 0032. http://dx.doi.org/10.5152/eurjrheum.2025.0032
[54] Qu K, Li MX, Zhou YL, Yu P, Dong M. The efficacy of vitamin D in treatment of fibromyalgia: a meta-analysis of randomized controlled studies and systematic review. Expert Rev Clin Pharmacol 2022; 15(4): 433-42. http://dx.doi.org/10.1080/17512433.2022.2081151 PMID: 35596576
[55] Yang CC, Tsai ST, Ting B, *et al.* Psychological Outcomes and Quality of Life of Fibromyalgia Patients with Vitamin D Supplementation-A Meta-Analysis. J Clin Med 2023; 12(7): 2750. http://dx.doi.org/10.3390/jcm12072750 PMID: 37048833
[56] Wepner F, Scheuer R, Schuetz-Wieser B, *et al.* Effects of vitamin D on patients with fibromyalgia syndrome: A randomized placebo-controlled trial. Pain 2014; 155(2): 261-8. http://dx.doi.org/10.1016/j.pain.2013.10.002 PMID: 24438771
[57] Bazinet RP, Layé S. Polyunsaturated fatty acids and their metabolites in brain function and disease. Nat Rev Neurosci 2014; 15(12): 771-85. http://dx.doi.org/10.1038/nrn3820 PMID: 25387473
[58] Ferreri C, Chatgilialoglu C. Role of fatty acid-based functional lipidomics in the development of molecular diagnostic tools. Expert Rev Mol Diagn 2012; 12(7): 767-80. http://dx.doi.org/10.1586/erm.12.73 PMID: 23153242
[59] Tian J, Zhang Y, Zhao X. The effects and mechanisms of n-3 and n-6 polyunsaturated fatty acids in the central nervous system. Cell Mol Neurobiol 2025; 45(1): 25. http://dx.doi.org/10.1007/s10571-025-01543-3 PMID: 40097862
[60] Lacombe RJS, Chouinard-Watkins R, Bazinet RP. Brain docosahexaenoic acid uptake and metabolism. Mol Aspects Med 2018; 64: 109-34. http://dx.doi.org/10.1016/j.mam.2017.12.004 PMID: 29305120
[61] Cai W, Haddad M, Haddad R, *et al.* The gut microbiota promotes pain in fibromyalgia. Neuron 2025; 113(13): 2161-2175.e13. http://dx.doi.org/10.1016/j.neuron.2025.03.032 PMID: 40280127
[62] Shtrozberg S, Bazzichi L, Sarzi-Puttini P, Aloush V, Ablin JN. Is the gut microbiome of importance in fibromyalgia? A critical review of emerging evidence. Clin Exp Rheumatol 2025; 43(6): 990-8. http://dx.doi.org/10.55563/clinexprheumatol/pmajsv PMID: 40576702
[63] Dipalma G, Marinelli G, Ferrante L, *et al.* Modulating the gut microbiota to target neuroinflammation, cognition and mood: A systematic review of human studies with relevance to Fibromyalgia. Nutrients 2025; 17(14): 2261. http://dx.doi.org/10.3390/nu17142261 PMID: 40732886
[64] Groeger D, O'Mahony L, Murphy EF, *et al. Bifidobacterium infantis* 35624 modulates host inflammatory processes beyond the gut. Gut Microbes 2013; 4(4): 325-39. http://dx.doi.org/10.4161/gmic.25487 PMID: 23842110
[65] Belkaid Y, Hand TW. Role of the microbiota in immunity and inflammation. Cell 2014; 157(1): 121-41. http://dx.doi.org/10.1016/j.cell.2014.03.011 PMID: 24679531
[66] Häuser W, Henningsen P, Henningsen P. Fibromyalgia syndrome: A somatoform disorder? Eur J Pain 2014; 18(8): 1052-9.

http://dx.doi.org/10.1002/j.1532-2149.2014.00453.x PMID: 24453056

[67] Moro C, Brunelli C, Miccinesi G, *et al*. Edmonton symptom assessment scale: Italian validation in two palliative care settings. Support Care Cancer 2006; 14(1): 30-7. http://dx.doi.org/10.1007/s00520-005-0834-3 PMID: 15937688

[68] Deshpande P, Rajan S, Sudeepthi BL, Abdul Nazir CP. Patient-reported outcomes: A new era in clinical research. Perspect Clin Res 2011; 2(4): 137-44. http://dx.doi.org/10.4103/2229-3485.86879 PMID: 22145124

[69] Baccili Cury Megid T, Sharma D, Baskurt Z, *et al*. Integrating Patient-Reported Outcomes Into Prognostication in Gastroesophageal Cancer: Results of a Population-Based Retrospective Cohort Analysis. Oncologist 2024; 29(4): 316-23. http://dx.doi.org/10.1093/oncolo/oyae010 PMID: 38431782

[70] Thabane L, Ma J, Chu R, *et al*. A tutorial on pilot studies: the what, why and how. BMC Med Res Methodol 2010; 10(1): 1. http://dx.doi.org/10.1186/1471-2288-10-1 PMID: 20053272

DISCLAIMER: Please note that this article is currently in the "Early View" stage and is not the final "Version of record". While it has been accepted, copy-edited, and formatted, however, it is still undergoing proofreading and corrections by the authors. Therefore, the text may still change before the final publication. Although "Early View" may not have all bibliographic details available, the DOI and the year of online publication can still be used to cite them. The article title, DOI, publication year, and author(s) should all be included in the citation format. Once the final "Version of record" becomes available the "Early View" will be replaced by that.