

Review

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Review

Effectiveness of Fecal Microbiota Transplantation in Nociceptive Pain Management: A Systematic Review

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Abstract: Nociceptive pain, commonly observed in conditions like fibromyalgia, chronic fatigue syndrome, and irritable bowel syndrome, stems from altered central pain processing and is often inadequately managed by conventional therapies due to its complex pathophysiology involving gut-brain axis interactions and immune dysregulation. Fecal microbiota transplantation offers a potential means of symptom relief through the restoration of gut microbial balance. This systematic review, adhering to PRISMA guidelines and pre-registered with PROSPERO CRD42024611939, evaluated the efficacy and safety of Fecal microbiota transplantation in nociceptive pain management. Searches across databases, including MEDLINE (*PubMed*), ELSEVIER (*Scopus*), EBSCOhost, Cochrane Library, and Web of Science, identified eligible studies comprising clinical trials, case reports, and retrospective analyses on adult populations receiving microbiota transplantation for nociceptive pain. Quality assessment utilized tools such as Cochrane RoB 2, ROBINS-I, NOS, and CARE. The review included 13 studies with $n = 409$ subjects, demonstrating reductions in pain intensity, fatigue, and quality-of-life improvements, particularly in Fibromyalgia and IBS patients. However, outcomes for CFS and psoriatic arthritis were mixed, potentially influenced by differences in Fecal transplantation protocols, donor selection, and patient characteristics. Reported adverse events were minimal. Although FMT shows promise for treating nociceptive pain, further high-quality, standardized studies are necessary to confirm its long-term efficacy and optimize clinical protocols.

Keywords: Faecal microbiota transplantation; chronic inflammation; immune modulation; gut microbiota; systemic inflammation; therapeutic intervention

1. Introduction

Nociceptive pain is a complex chronic pain condition characterized by altered central pain processing and increased sensitivity, often in the absence of detectable tissue damage or ongoing inflammation [1-3]. This type of pain is prevalent in conditions such as fibromyalgia [4,5], chronic fatigue syndrome (CFS) [6,7], neuropathy [8] and irritable bowel syndrome (IBS) [9,10], profoundly impacting patients' quality of life and posing a substantial burden on healthcare systems due to its persistent and treatment-resistant nature. Conventional therapies, often aimed at symptomatic relief, have demonstrated limited success, as they fail to adequately address the underlying pathophysiological drivers of nociceptive pain, including central sensitization, immune dysregulation, and gut-brain axis interactions [11,12].

The gut microbiota, a key modulator of systemic inflammation and neuroimmune pathways, has gained recognition for its role in influencing nociceptive pain [13,14]. *Dysbiosis*—an imbalance in

the gut microbial ecosystem—may worsen nociplastic pain by triggering inflammatory responses and disrupting immune regulation, contributing to both central and peripheral sensitization [15-17]. This highlights the gut-brain axis as a promising therapeutic target, with the potential to mitigate chronic inflammation and alter pain perception through the restoration of microbial balance [18,19]. In this context, therapies aimed at modifying the gut microbiota, such as fecal microbiota transplantation (FMT), have garnered growing interest [20,21].

FMT involves transferring processed stool from a healthy donor to a recipient with dysbiosis to restore microbial balance and diversity (*eubiosis*) [22]. This intervention requires meticulous donor screening, careful preparation and preservation of beneficial microorganisms [23], and precise administration via colonoscopy [24], nasogastric tube [25], or encapsulated formulations [26]. While FMT has shown significant efficacy in treating recurrent *Clostridium difficile* infections by re-establishing microbial equilibrium, its potential application to manage nociplastic pain remains a novel and emerging area of exploration [27].

Preliminary evidence suggests that FMT may offer a novel therapeutic approach for reducing nociplastic pain by directly targeting and correcting gut dysbiosis. Restoration of a balanced microbiota through FMT is believed to modulate immune responses and reduce systemic inflammation [28,29], both critical contributors to the persistence and sensitization of nociplastic pain. By attenuating systemic and localized inflammation, FMT may suppress hyperactivity within nociceptive pathways [30]. Moreover, changes in neurotransmitter synthesis and enhancements in gut-brain signaling pathways play a pivotal role in modulating pain perception and processing [31]. This biochemical modulation, mediated by shifts within the gut-brain axis, suggests that FMT can address the root causes of nociplastic pain rather than merely alleviating symptoms [32].

Despite preliminary promising findings, there remains a notable gap in understanding FMT's full therapeutic potential in managing nociplastic pain, with limited existing evidence necessitating further research into its mechanisms, safety, efficacy, and long-term outcomes. This systematic review aims to synthesize current knowledge on the impact of FMT in modulating nociplastic pain, focusing on its influence on immune and inflammatory responses, pain modulation, microbiota composition, and patient-centered outcomes such as pain reduction and quality of life.

2. Materials and Method

2.1. Data Sources and Search Strategy

A systematic review of the literature was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [33]. The protocol for this systematic review was pre-registered with PROSPERO database CRD42024611939. The search was performed from November 10, 2024, to December 10, 2024, to identify all available studies examining the efficacy of FMT in addressing nociplastic pain syndrome in various conditions across the following databases: MEDLINE (*PubMed*), ELSEVIER (*Scopus*), EBSCOhost, Cochrane Library, and Web of Science (WOS). The strategy used in MEDLINE (*PubMed*) was as follows: ("*faecal microbiota transplant*") [Title/Abstract] OR "*fecal microbiota transplantation*" [Title/Abstract] OR "*fecal transplantation*" [Title/Abstract] OR "*faecal transplant*" [Title/Abstract] OR "*gut microbiota*" [Title/Abstract]) AND ("*nociplastic pain*" OR "*chronic pain*" OR "*pain sensitization*" OR "*central sensitization*" OR "*gut-brain axis*" OR "*pain modulation*")

Two independent researchers (NHG and HAA) conducted the search, and a blinded investigator (URC) evaluated all retrieved articles by title and abstract, followed by a full-text assessment to determine eligibility. In the event of discrepancies, a fourth author (SMP) acted as an arbitrator.

Table 1. outlines the detailed search strategy.

Search date	Database	Search terms	Search string
30/11/2024	EBSCOhost	"faecal microbiota transplantation", "nociplastic pain", "FMT", "gut microbiota", "immune response"	((faecal microbiota transplantation OR FMT) AND (nociplastic pain OR FMT)) AND (gut microbiota OR immune response modulation OR FMT)

		<i>modulation", "FMT intervention strategies", "chronic pain management", "central sensitization"</i>	intervention strategies OR chronic pain management OR central sensitization)
14/11/2024	EBSCOhost	<i>"nociplastic pain treatments", "FMT approaches in pain", "gut microbiome modulation", "FMT for nociplastic pathways", "immune modulation in pain disorders", "chronic inflammatory response modulation"</i>	((nociplastic pain treatments OR FMT approaches in pain OR gut microbiome modulation) AND (FMT for nociplastic pathways OR immune modulation in pain disorders OR chronic inflammatory response modulation))
30/10/2024	Scopus	<i>"nociplastic pain", "gut-brain axis", "FMT efficacy for pain", "chronic pain disorders", "gut microbiome modulation", "FMT and nociplastic pain", "inflammatory response in chronic pain"</i>	(TITLE-ABS-KEY("nociplastic pain") OR TITLE-ABS-KEY("gut-brain axis") OR TITLE-ABS-KEY("FMT efficacy for pain")) AND (TITLE-ABS-KEY("chronic pain disorders") OR TITLE-ABS-KEY("gut microbiome modulation") OR TITLE-ABS-KEY("FMT and nociplastic pain") OR TITLE-ABS-KEY("inflammatory response in chronic pain"))
10/10/2024	MEDLINE (PubMed)	<i>"faecal microbiota transplant", "fecal microbiota transplantation", "nociplastic pain", "chronic pain", "pain sensitization", "central sensitization", "gut-brain axis", "pain modulation"</i>	("faecal microbiota transplant"[Title/Abstract] OR "fecal microbiota transplantation"[Title/Abstract] OR "faecal transplant"[Title/Abstract] OR "gut microbiota"[Title/Abstract]) AND ("nociplastic pain" OR "chronic pain" OR "pain sensitization" OR "central sensitization" OR "gut-brain axis" OR "pain modulation")
05/10/2024	EBSCOhost	<i>"FMT for pain disorders", "immune modulation in chronic pain", "gut microbiota interventions", "pain sensitization modulation", "nociplastic pain strategies", "chronic pain inflammatory response", "gut-brain modulation"</i>	((FMT for pain disorders OR gut microbiota interventions) AND (immune modulation in chronic pain OR pain sensitization modulation OR nociplastic pain strategies OR chronic pain inflammatory response OR gut-brain modulation))
01/10/2024	Web of Science (WOS)	<i>"gut microbiota interventions", "FMT treatment strategies", "nociplastic pain pathways", "chronic pain"</i>	TS=("gut microbiota interventions" OR "FMT treatment strategies" OR "nociplastic pain pathways") AND TS=("chronic pain treatment" OR "immune modulation therapies" OR

		<i>treatment", "immune modulation therapies", "gut-brain immune connection", "FMT in pain modulation"</i>	"gut-brain immune connection" OR "FMT in pain modulation")
20/09/2024	MEDLINE (PubMed)	<i>"FMT for chronic pain", "faecal microbiota transplantation", "immune modulation in pain", "microbiota interventions", "pain disorders", "gut-brain immune axis", "chronic nociceptive pain", "gut microbiome"</i>	("FMT for chronic pain"[Title/Abstract] OR "faecal microbiota transplantation"[Title/Abstract] OR "microbiota interventions"[Title/Abstract]) AND ("immune modulation in pain" OR "pain disorders" OR "gut-brain immune axis" OR "chronic nociceptive pain" OR "gut microbiome")
15/09/2024	Scopus	<i>"chronic pain treatment", "FMT intervention", "gut microbiota therapy", "pain modulation therapies", "central sensitization disorders", "nociplastic pain interventions"</i>	(TITLE-ABS-KEY("FMT intervention") OR TITLE-ABS-KEY("gut microbiota therapy") OR TITLE-ABS-KEY("chronic pain treatment")) AND (TITLE-ABS-KEY("pain modulation therapies") OR TITLE-ABS-KEY("central sensitization disorders") OR TITLE-ABS-KEY("nociplastic pain interventions"))
14/09/2024	Web of Science (WOS)	<i>"FMT for chronic inflammatory pain", "nociplastic pain interventions", "gut-brain axis modulation", "immune modulation and pain", "FMT for nociplastic mechanisms", "chronic inflammation modulation"</i>	TS=("FMT for chronic inflammatory pain" OR "nociplastic pain interventions") AND TS=("gut-brain axis modulation" OR "immune modulation and pain" OR "FMT for nociplastic mechanisms" OR "chronic inflammation modulation")
12/09/2024	Scopus	<i>"faecal microbiota transplant", "fecal microbiota transplantation", "gut microbiota modulation", "nociplastic pain mechanisms", "FMT for chronic pain", "chronic inflammatory pain", "pain modulation strategies"</i>	(TITLE-ABS-KEY("faecal microbiota transplant") OR TITLE-ABS-KEY("fecal microbiota transplantation") OR TITLE-ABS-KEY("gut microbiota modulation") OR TITLE-ABS-KEY("FMT for chronic pain")) AND (TITLE-ABS-KEY("nociplastic pain mechanisms") OR TITLE-ABS-KEY("chronic inflammatory pain") OR TITLE-ABS-KEY("pain modulation strategies"))
07/09/2024	Cochrane Library	<i>"faecal microbiota transplant", "fecal microbiota transplantation", "gut microbiota modulation", "nociplastic pain"</i>	("faecal microbiota transplant" OR "fecal microbiota transplantation" OR "gut microbiota modulation" OR "FMT for chronic pain") AND ("nociplastic pain mechanisms" OR "chronic inflammatory pain" OR "pain modulation strategies")

		<i>mechanisms", "FMT for chronic pain", "chronic inflammatory pain", "pain modulation strategies"</i>	
04/09/2024	MEDLINE (PubMed)	<i>"gut microbiota modulation", "FMT efficacy", "pain modulation", "nociplastic mechanisms", "microbiota-gut-brain axis", "inflammatory modulation", "central pain sensitization", "gut dysbiosis"</i>	("gut microbiota modulation"[Title/Abstract] OR "FMT efficacy"[Title/Abstract] OR "faecal microbiota transplant"[Title/Abstract]) AND ("nociplastic mechanisms" OR "microbiota-gut-brain axis" OR "pain modulation" OR "inflammatory modulation" OR "central pain sensitization" OR "gut dysbiosis")
04/09/2024	Web of Science (WOS)	<i>"faecal microbiota transplantation", "nociplastic pain", "chronic inflammatory disorders", "gut microbiota", "central sensitization", "pain disorders", "immune modulation", "pain treatment", "FMT therapy"</i>	TS=("faecal microbiota transplantation" OR "FMT" OR "faecal transplant") AND TS=("nociplastic pain" OR "chronic inflammatory disorders" OR "central sensitization" OR "pain disorders" OR "gut microbiota" OR "immune modulation" OR "pain treatment")
02/09/2024	Cochrane Library	<i>"gut microbiota modulation", "FMT efficacy", "pain modulation", "nociplastic mechanisms", "microbiota-gut-brain axis", "inflammatory modulation", "central pain sensitization", "gut dysbiosis"</i>	("gut microbiota modulation"[Title/Abstract] OR "FMT efficacy"[Title/Abstract] OR "faecal microbiota transplant"[Title/Abstract]) AND ("nociplastic mechanisms" OR "microbiota-gut-brain axis" OR "pain modulation" OR "inflammatory modulation" OR "central pain sensitization" OR "gut dysbiosis")

Table 1. Search strategy. The table provides a summary of the systematic review search strategy. It outlines the search dates, databases used, search terms, and search strings employed to identify relevant studies for the review. Each row details a specific search instance conducted within a particular database using a combination of terms related to fecal microbiota transplantation and nociplastic pain conditions. The search strings consist of specific terms and Boolean operators designed to capture studies focusing on FMT's effects on nociplastic pain, pain modulation, gut microbiota interventions, immune modulation, and related mechanisms. This comprehensive approach ensured a broad and thorough identification of potential studies across multiple databases and time frames.

2.2. Inclusion and Exclusion Criteria

This review considered studies that met the following criteria: clinical trials (*randomized* and *non-randomized*) and observational studies as case series and case-control studies. Eligible publications were required to be (1) published between January 1, 2014, and November 30, 2024, and (2) available

in full-text format in (3) English, Spanish, French, Portuguese, or Arabic. The focus was on (4) adult populations undergoing FMT with an emphasis on its (5) therapeutic impact on nociplastic pain and conditions characterized by central sensitization. These included chronic inflammatory states such as Fibromyalgia, IBS, CFS, neuropathic pain syndromes, and other disorders where nociplastic pain is a critical component. Eligible studies assessed outcomes related to (6) pain modulation, physical and psychological symptoms, immune and inflammatory markers, safety profiles, or quality of life improvements following FMT.

Studies were excluded if they did not match the specified (1) study types or (2) were published outside the defined timeframe. Publications (3) without full-text access or (4) those not available in English, Spanish, French, Portuguese, or Arabic were also excluded. Further exclusions (5) applied to studies involving non-adult populations, such as pediatric cases, or studies that did not directly evaluate the therapeutic impact of FMT on conditions involving central sensitization. (6) Abstract-only publications, commentaries, opinion pieces, and conference proceedings were not considered for inclusion.

2.3. Data Extraction

Data extraction was conducted independently by two authors (NHG and HAA), with a third author (UGR) available to resolve any discrepancies. A standardized data extraction template, structured according to the PICO (*Population, Intervention, Comparison, Outcomes*) framework, was utilized to collect comprehensive details. This included authorship, year and country of publication, study design, study objectives, results, participant characteristics (e.g., *disease characteristics, intervention specifics, sample size, gender distribution*), details of the intervention and control groups, measured outcomes, and study conclusions. The data extraction process adhered to the guidelines outlined in the Cochrane Handbook for Systematic Reviews of Interventions v.5.1.0 [33]. The reliability of the data table was evaluated using a representative sample of studies to ensure consistency and accuracy.

2.4. Methodological Quality Assessment

2.4.1. Randomized Controlled Trials

The Cochrane RoB 2 tool was utilized for randomized controlled trials (RCTs), including double-blind and placebo-controlled designs [34]. This instrument assesses potential biases across several key domains: the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported results. Each domain is rated as “*low risk*,” “*some concerns*,” or “*high risk*” of bias, culminating in an overall risk-of-bias judgment for each study. This tool is widely recognized for its rigor and utility in evaluating the internal validity of RCTs, ensuring the methodological integrity and transparency of study findings.

2.4.2. Non-randomized Clinical Trials

This tool was employed for assessing non-randomized, open-label trials. The ROBINS-I (Risk Of Bias In Non-randomized Studies-of Interventions) tool [35] evaluates bias across seven distinct domains, including confounding, participant selection, classification of interventions, deviations from intended interventions, missing data, outcome measurement, and selection of the reported result. Studies are categorized as presenting “*low*,” “*moderate*,” “*serious*,” or “*critical*” risk of bias. The tool is specifically designed to address biases that arise from non-randomized intervention designs, highlighting areas where study design may impact the reliability of outcomes.

2.4.3. Case Reports

The Consensus-based Clinical Case Reporting Guideline Development (CARE) guidelines [36] were applied for the assessment of case reports. This instrument ensures comprehensive and structured reporting by evaluating key elements such as patient information, clinical findings, diagnostic assessment, therapeutic intervention, timeline, follow-up, and outcomes. The adherence to these guidelines allows for a detailed and transparent presentation of individual patient cases.

While case reports inherently lack generalizability and control groups, adherence to CARE guidelines ensures that they provide valuable, high-quality insights into specific clinical scenarios.

2.4.4. Observational Study

The Newcastle-Ottawa Scale (NOS) [37] was used to evaluate the quality of non-randomized studies, particularly retrospective outcome studies. This tool assesses studies across three broad categories: selection of study participants, comparability of cohorts, and ascertainment of exposure or outcomes. Studies are rated based on their adherence to methodological rigor, with a “star” system that identifies strengths and potential sources of bias. The NOS is widely used for assessing the methodological robustness of cohort and case-control studies, providing a reliable framework for evaluating study quality and minimizing the impact of potential biases.

3. Results

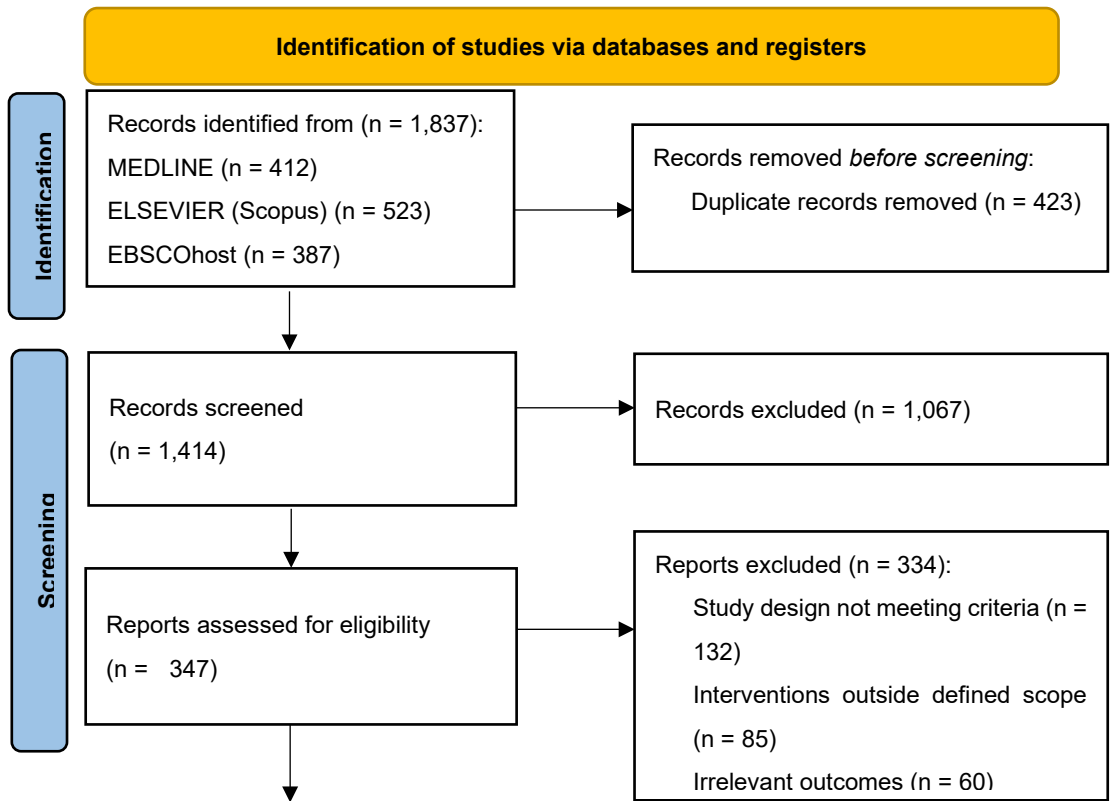
3.1. Study Selection

The selection process for publications commenced with an extensive search across multiple academic databases, resulting in the identification of a total of 1,837 studies. The contributions from individual databases were as follows: MEDLINE (*PubMed*) (n = 412 studies), ELSEVIER (*Scopus*) (n = 523 studies), EBSCOhost (n = 387 studies), Cochrane Library (n = 200 studies), and Web of Science (WOS) (n = 315 studies).

Following the removal of 423 duplicate entries, a total of 1,414 unique articles were retained for the screening phase. During this phase, the titles and abstracts of these articles were evaluated for their relevance to the research question, resulting in the exclusion of 1,067 articles for reasons such as a lack of relevance to the study’s scope, focus on non-target populations, or the absence of primary data. Consequently, 347 articles were selected for a detailed full-text eligibility review.

Among the 347 articles assessed at the full-text stage, 335 were excluded for various reasons, including differing study designs that did not fit the inclusion criteria (e.g., systematic or narrative reviews) (n = 131), interventions outside the defined scope of interest (n = 85), the absence of relevant outcome measures (n = 60), publications in non-target languages (n = 33), and articles with access restrictions or limited data (n = 26).

The final selection comprised 13 studies for qualitative synthesis, including clinical trials [38-45,50], case reports [46-48], and retrospective outcome studies [49]. This systematic approach ensures a comprehensive and focused evaluation of the available evidence relevant to the research objectives. Figure 1 illustrates the PRISMA 2020 flowchart for the study selection process.



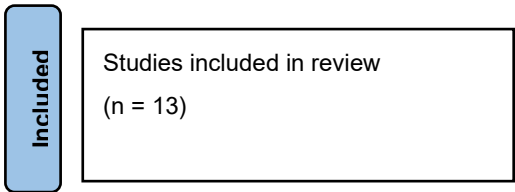


Figure 1. The PRISMA 2020 flowchart shows the systematic review process. Out of n = 1,837 identified records, n = 423 duplicates were removed, leaving n = 1,414 articles screened by title and abstract, excluding n = 1,067. From n = 347 full-text assessments, n = 334 were excluded due to reasons such as differing study designs, irrelevant interventions, or access issues. 13 studies were included in the final qualitative synthesis, comprising clinical trials, case reports, and retrospective studies. Source: Own work.

3.2. Characteristics of Included Studies

The 12 included studies focused on clinical trials involving Fecal Microbiota Transplantation (FMT). Of these, 6 were randomized, double-blind, placebo-controlled trials [39,42,44,45,47,48], 2 were open-label, randomized trials [38,40], 2 were randomized, placebo-controlled pilot studies [39,40], 2 were case reports [43,49], and 1 was a retrospective outcome study [46]. The included studies examined populations with different nociceptive pain conditions such as IBS [40,41,45-48,50], Fibromyalgia [38,50], CFS [39,46,50], psoriatic arthritis [42], Rheumatoid Arthritis [43], Systemic Sclerosis [44], and diabetic neuropathy [49], totaling a diverse sample.

Patient groups varied widely, including 60 Fibromyalgia patients in a Chinese open-label trial [38], 11 CFS patients in a Finnish pilot study [39], and smaller cohorts, such as individual case reports for RA and diabetic neuropathy [43,49]. Interventions typically involved FMT delivered via colonoscopy [38,40,43,45,47-49], gastroscopy [42,43,48], or rectal catheterization [46], with follow-up periods ranging from 4 months [43] to over a year [41]. Comparators included placebo groups using autologous stool or continued standard treatment. Outcomes varied, encompassing symptom reduction (e.g., pain and fatigue) engraftment rates [40], gut microbiota composition changes [44], quality of life improvements [47,48], and adverse events [42,44].

Notable findings included significant symptom relief in some cases [38,43], while other studies reported limited or no efficacy compared to placebo [39,42], emphasizing the need for further research. Geographically, the studies were conducted in countries such as China [38,43,49], Finland [39,45], Denmark [32], Norway [44,47,48], India [40], Belgium [41], the United Kingdom [46], and Germany [50]. More details in **Table 2**. Characteristics of the included studies.

3.3. Methodological Quality Assessment

3.3.1. Randomized Controlled Trials

For the randomized controlled trials, including those with double-blinding and placebo controls [39,42,44,45,47,48] the Cochrane Risk of Bias (RoB) 2 tool was used. These studies generally exhibited strong methodological rigor, demonstrating robust random sequence generation and allocation concealment. However, concerns were noted in some studies regarding the blinding of outcome assessment and selective reporting, which may have affected the reliability of specific outcomes.

3.3.2. Open-Label Trials

The open-label trials [38,40] were evaluated using the ROBINS-I tool (Risk Of Bias In Non-randomized Studies-of Interventions). This assessment revealed a moderate risk of bias predominantly arising from the open-label nature of the studies, which may introduce potential performance and detection biases that could affect the interpretation of the results.

3.3.4. Case Reports

Case reports [43,49,50] were evaluated according to the CARE (Case Report) guidelines. All reports adhered well to structured presentation standards and offered detailed patient data. However, they were inherently limited due to the absence of control groups, small sample sizes, and restricted generalizability. Notably, Thurm et al. (2017) [50] presented a unique combination of case report and literature review, providing insights into complex functional disorders treated with self-administered FMT, though the findings underscore the necessity for randomized trials.

3.3.5. Retrospective Outcome Study

The retrospective outcome study [46] was assessed using the Newcastle-Ottawa Scale (NOS) for non-randomized studies. This evaluation indicated moderate quality, with primary concerns related to cohort selection and comparability, which could influence outcome interpretations. In summary, while many studies demonstrated a sound methodological basis, further rigorous trials with larger, more diverse samples are warranted to validate findings and bolster evidence for the efficacy of FMT across various conditions. For further details, refer to **Table 3. Methodological Quality Assessment.**

Table 2. Characteristics of the included studies **Abbreviation:** FMT (Fecal Microbiota Transplantation), GI (Gastrointestinal), IBS (Irritable Bowel Syndrome), IBS-D (Diarrhea-Predominant Irritable Bowel Syndrome), HRQOL (Health-Related Quality of Life), VAS (Visual Analog Scale), MFIS (Modified Fatigue Impact Scale), 15D (15-Dimensional Measure of HRQOL), EQ-5D-3L (EuroQol-5 Dimension-3 Level), HAQ-DI (Health Assessment Questionnaire Disability Index), CFS (Chronic Fatigue Syndrome), RR (Risk Ratio), ACR20 (American College of Rheumatology 20% Improvement Criteria), and DAS28 (Disease Activity Score for 28 Joints). .

Year, Author	Study design	Participants	Intervention	Comparison	Outcomes	Conclusion
					Fibromyalgia Symptom Reduction: Significant reduction in pain intensity, fatigue, and other symptoms compared to control; no specific numerical values provided for exact reductions.	
Fang et al. (2024) [38] China	Open-label, randomized, non-placebo-controlled study	N = 60 (<i>Fibromyalgia Syndrome</i>)	FMT vs. continued standard treatment	Standard treatment	Quality of Life Improvement and Gut Microbiota Changes: Observed improvements without detailed	FMT may relieve Fibromyalgia symptoms by modulating gut microbiota. Further research is needed for confirmation.

					quantification.
Salonen et al. (2023) [39]	Randomized, double-blinded, placebo-controlled pilot study	N = 11 (Chronic Fatigue Syndrome patients, 10 female, 1 male, mean age 42.2 years)	Dose: Universal donor stool. Route: Colonoscopy. Follow-up: 1 and 6 months.	Placebo (autologous FMT)	Fatigue & QoL: No statistically significant improvements. Adverse Events: None reported. FMT was safe but did not improve QoL for CFS patients
Singh et al. (2022) [40]	Randomized, placebo-controlled, single-center study	N = 44 (Irritable Bowel Syndrome-D patients)	Dose: FMT alone or with antibiotic pretreatment. Route: Colonoscopy. Follow-up: 10 weeks.	Placebo	Engraftment: Higher (15.5%) in FMT alone vs. 5% (rifaximin pre-FMT) and 2.4% (CM-FMT). Symptom Scores: No significant difference in IBS severity. FMT alone may provide better microbiota engraftment for IBS-D
Holvoet et al. (2021) [41]	Randomized, placebo-controlled trial	N = 62 (Irritable Bowel Syndrome patients with bloating)	Dose: 50 g donor stool. Route: Nasojejunal tube. Follow-up: 12 weeks (up to 1 year).	Autologous stool (placebo)	Symptom Improvement: 56% FMT vs. 26% placebo (p=0.03). Quality of Life: Significant improvement initially, effects diminished over a year. FMT effective for IBS, but long-term effects vary
Kragsnaes et al. (2021) [42]	Randomized, double-blind, placebo-controlled trial	N = 31 (Psoriatic arthritis)	Dose: Single FMT. Route: Gastroscopy (Duodenum). Follow-up: 26 weeks.	Sham (Placebo)	Treatment Failure: Higher in FMT (60%) vs. sham (19%). HAQ-DI Score: Lesser improvement (-0.07 vs. -0.30, p=0.031). FMT appears less effective than placebo for PsA symptoms

					ACR20 Response: No significant difference
					Rapid and significant improvement in symptoms: HAQ-DI dropped from 1.4 to 0.05.
Zeng et al. (2021) [43] China	Case report	N = 1 (20- year-old female with rheumatoid arthritis)	Dose: Single FMT. Route: Colonoscopy. Follow-up: 4 months.	No comparison	Reduction in DAS28 from 6.6 to 1.4. Titer of rheumatoid factor decreased significantly. Symptoms maintained for 4 months with reduced need for medication.
					FMT shows potential for RA but requires further research
					Reduction in GI Symptoms: 80% (4/5) of patients receiving FMT improved compared to 50% (2/4) in the placebo group.
Fretheim et al. (2020) [44] Norway	Double- blind, placebo- controlled randomized pilot trial	N = 10 (patients with systemic sclerosis)	Dose: Commercial anaerobic human intestinal microbiota (ACHIM). Route: Gastroduodenoscopy. Follow-up: 16 weeks with two FMT sessions at weeks 0 and 2.	Placebo	Changes in Gut Microbiota Composition: Quantitative changes in IgA-, IgM- coated bacteria
					FMT reduced GI symptoms but had procedural risks

					observed (no exact values provided). Procedure-Related Adverse Events: 2 serious events in the placebo group (1 case of laryngospasms, 1 case of duodenal perforation).
Lahtinen et al.(2020) [45] Finland	Randomized clinical trial	N = 49 (<i>Irritable Bowel Syndrome</i>)	Dose: 30 g donor stool. Route: Colonoscopy. Follow-up: 12 weeks.	Autologous FMT (placebo)	IBS Symptoms: Improvement at 12 weeks (p=0.01), but no sustained effects. Microbiota Composition: Resembles donor. FMT provided transient symptom relief, but not a sustained improvement over placebo, limiting its clinical use.
Kenyon et al. (2019) [46] United Kingdom	Retrospective outcome study	N = 42 (<i>Chronic Fatigue Syndrome, 30 with Irritable Bowel Syndrome</i>)	Dose: 10 rectal FMTs from different donors. Route: Rectal catheter. Follow-up: Not specified.	Standard oral approaches	Improvement: Greater for sham (median change in HAQ-DI score -0.30 vs. -0.07 FMT). Treatment Failure: Higher for FMT (60%). FMT appears less effective for some CFS patients; further trials recommended
Johnsen et al. (2019) [47] Norway	Double-blind, randomized, placebo-controlled trial	N = 90 (non-constipated <i>Irritable Bowel Syndrome</i> patients)	Dose: 50-80 g donor stool. Route: Colonoscopy. Follow-up: 6 months.	Placebo (own stool)	QoL Improvement: OR = 3.801 (p=0.011). Fatigue Reduction: OR = 4.398 (p=0.020). QoL and fatigue improved in select IBS patients

El-Salhy et al. (2019) [48]	Randomized, double-blind, placebo-controlled study	N = 165 (<i>Irritable Bowel Syndrome</i>)	Dose: 30 g or 60 g donor stool. Route: Gastroscope. Follow-up: 12 weeks.	Placebo (own stool)	Response Rate: 30 g = 76.9%, 60 g = 89.1%, placebo = 23.6% (p < 0.0001). Fatigue & QoL: Improved. Adverse Events: Mild.	FMT is effective for IBS, showing a dose-dependent response with emphasis on donor selection.
Cai et al. (2018) [49]	Clinical case report	N = 1 (female, <i>diabetic neuropathy</i>)	Dose: Two FMTs over 3 months. Route: Colonoscopy. Follow-up: 3 months.	No explicit comparison group	Pain Relief: Significant improvement. Glycemic Control: Noted improvement. Adverse Events: None observed.	FMT may offer therapeutic benefit for diabetic complications
Thurm et al. (2017) [50]	Case report and literature review	N = 1 (58-year-old male with <i>Fibromyalgia, Irritable Bowel Syndrome</i> with <i>Chronic Fatigue Syndrome</i>)	Dose: 6 self-administered FMTs. Route: Enema. Follow-up: 9 months.	No formal comparison	FMT group showed significantly greater improvement compared to the oral treatment group (Mann-Whitney U = 111.5, p = 0.003). Median improvement in the FMT group was markedly higher than oral treatment. No significant adverse effects except minor	FMT may help complex functional disorders, though randomized trials are needed

	intolerance in 2 patients (1 with diarrhea; 1 tolerated half the implants).
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Table 3. Methodological Quality Analysis. This table presents the methodological quality analysis of the included studies. The table evaluates key domains such as risk of bias, study design, intervention classifications, and outcome measurements to ensure a comprehensive assessment of methodological rigor and potential limitations across all included studies. This analysis underscores the strengths and limitations of each study, providing critical insight into the reliability and validity of the findings.

Study	Design	Methodo logical Quality Tool	Final Score	Observed Biases
Fang et al. (2024) [38]	Open-label, randomized	ROBINS- I	Moderat e	Open-label design leading to potential performance and detection biases.
Salonen et al. (2023) [39]	Randomized, double-blind, placebo- controlled	Cochrane RoB 2	Moderat e	Concerns with blinding of outcome assessment and selective reporting.
Singh et al. (2022) [40]	Open-label, randomized	ROBINS- I	Moderat e	Open-label nature affecting blinding and performance outcomes.
Holvoet et al. (2021) [41]	Randomized, double-blind, placebo- controlled	Cochrane RoB 2	Low	Appropriate randomization and effective blinding; potential unclear risk from missing data handling and selective reporting.
Kragsnaes et al. (2021) [42]	Randomized, double-blind, placebo- controlled	Cochrane RoB 2	Moderat e	Issues with selective reporting noted.
Zeng et al. (2021) [43]	Case report	CARE	Good	Limited by lack of comparative data and generalizability.
Fretheim et al. (2020) [44]	Randomized, double-blind, placebo- controlled	Cochrane RoB 2	Moderat e	Limited by small sample size and short follow-up.
Lahtinen et al. (2020) [45]	Randomized, double-blind, placebo- controlled	Cochrane RoB 2	Moderat e	Potential blinding bias.
Kenyon et al. (2019) [46]	Retrospective outcome study	NOS	Moderat e	Issues with selection bias and comparability between cohorts.
Johnsen et al. (2019) [47]	Randomized, double-blind, placebo- controlled	Cochrane RoB 2	High	Minor concerns regarding selective reporting.

El-Salhy et al. (2019) [48]	Randomized, double-blind, placebo-controlled	Cochrane RoB 2	High	Minimal concerns noted.
Cai et al. (2018) [49]	Case report	CARE	Good	Inherent limitations due to case report nature
Thurm et al. (2017) [50]	Case report and literature review	CARE	Good	Detailed patient outcomes but limited generalizability and need for controlled trials.

3.4. Main Results

3.4.1. Severity of Nociplastic Pain Following FMT

Fibromyalgia and CFS are conditions characterized by chronic nociplastic pain, often stemming from central sensitization. Fang et al. (2024) [38] conducted an open-label randomized trial on 60 Fibromyalgia patients, demonstrating significant reductions in pain intensity and fatigue following FMT compared to standard treatment, suggesting that FMT may impact nociplastic pain through gut microbiota modulation.

Conversely, Salonen et al. (2023) [39] evaluated 11 CFS patients in a double-blind, placebo-controlled pilot study, finding no significant improvements in fatigue or quality of life. Similarly, Kenyon et al. (2019) [46], in a retrospective study of 42 patients with CFS and IBS, found limited efficacy of FMT compared to standard treatments, highlighting the complexity of nociplastic pain in CFS. Notably, Thurm et al. (2017)[50] reported significant improvement in a patient with Fibromyalgia, IBS, and CFS following self-administered FMTs, pointing to potential benefits of gut microbiota modulation in complex nociplastic pain syndromes, though further randomized trials are needed.

Irritable bowel syndrome is a functional gastrointestinal disorder often associated with nociplastic pain due to disrupted gut-brain communication. In this sense, Singh et al. (2022)[40] conducted a randomized, placebo-controlled study on IBS patients, noting improved microbiota engraftment with FMT, but no significant impact on symptom severity. This suggests that while FMT may modify gut microbiota, its influence on nociplastic pain symptoms in IBS can be limited. Holvoet et al. (2021) [41] and Lahtinen et al. (2020) [45] observed initial symptom relief in IBS patients receiving FMT, but effects diminished over time, indicating challenges in achieving sustained modulation of nociplastic pain pathways. However, Johnsen et al. (2019) [47] and El-Salhy et al. (2019) [48] highlighted improvements in fatigue and quality of life among IBS patients, showing FMT's potential to impact nociplastic pain-related symptoms, particularly where gut dysbiosis is implicated.

Psoriatic arthritis and rheumatoid arthritis present a combination of inflammatory and nociplastic pain. Kragstnaes et al. (2021) [42] found FMT less effective than placebo for psoriatic arthritis symptoms in a double-blind, placebo-controlled trial, underscoring the difficulty of modulating nociplastic pain through gut interventions in autoimmune conditions. Conversely, Zeng et al. (2021) [43] reported significant improvements in a young RA patient following FMT, including reduced pain and inflammatory markers, suggesting that gut microbiota may influence nociplastic pain pathways in RA, though more robust evidence is needed.

In systemic sclerosis and diabetic neuropathy, nociplastic pain often coexists with other symptoms. Fretheim et al. (2020) [44] found FMT effective in reducing gastrointestinal symptoms in systemic sclerosis patients, though procedural risks were noted. This underscores the potential role of gut interventions in modulating nociplastic pain within complex chronic conditions. Similarly, Cai et al. (2018) [49] reported pain relief and improved glycemic control in a diabetic neuropathy patient following FMT, indicating potential therapeutic benefits for conditions with nociplastic pain features.

3.4.2. Functionality and Quality of Life of Nociplastic Pain Following FMT

Several studies evaluated the impact of FMT on physical functionality, particularly in conditions with chronic pain or inflammatory components. Fang et al. (2024) [38] examined Fibromyalgia

Syndrome patients and observed significant reductions in pain intensity, fatigue, and other physical symptoms, suggesting potential improvements in physical functioning through gut microbiota modulation.

Similarly, Zeng *et al.* (2021) [43] reported a notable reduction in physical symptoms for a rheumatoid arthritis patient, with the Health Assessment Questionnaire-Disability Index (HAQ-DI) score dropping from 1.4 to 0.05 and a reduction in disease activity score (DAS28) from 6.6 to 1.4, indicating enhanced physical functionality and decreased disability.

Kragsnaes *et al.* (2021) [42] explored FMT's effects on psoriatic arthritis, finding a lesser improvement in the HAQ-DI score among the FMT group compared to placebo, reflecting limited benefits for physical functionality. In systemic sclerosis patients, Fretheim *et al.* (2020) [44] found that 80% of those receiving FMT experienced reductions in gastrointestinal symptoms, potentially contributing to overall physical functionality improvements, albeit with risks associated with the procedure.

For IBS patients, physical functionality improvements were reported inconsistently. Holvoet *et al.* (2021) [41] found symptom improvement, including bloating relief, which could enhance daily functioning. However, effects diminished over time, reflecting variability in long-term outcomes.

Psychological functionality and QoL were also evaluated across several studies. Salonen *et al.* (2023) [39] examined CFS patients but found no statistically significant improvements in fatigue or QoL after FMT, suggesting limited psychological benefits in this cohort. Conversely, Johnsen *et al.* (2019) [47] and El-Salhy *et al.* (2019) [48] observed improvements in QoL and reductions in fatigue in IBS patients, indicating a positive psychological impact from FMT. Moreover, they highlighted a dose-dependent response in QoL improvement, emphasizing the role of donor stool quantity.

Moreover, Kenyon *et al.* (2019) [46] assessed CFS patients, noting that FMT was less effective compared to standard oral approaches for symptom management and failed to improve psychological outcomes for most patients. In a case study, Thurm *et al.* (2017) [50] reported significant improvement in psychological functionality, with reduced fatigue and enhanced overall well-being following self-administered FMT for a patient with Fibromyalgia, IBS, and CFS.

Besides, Fang *et al.* (2024) [38] and Zeng *et al.* (2021) [43] showed potential combined benefits of FMT on both physical and psychological functionality in Fibromyalgia and rheumatoid arthritis patients, respectively, through reduced symptom severity and improved daily functioning. Furthermore, Fretheim *et al.* (2020) [44] also suggested potential combined improvements in systemic sclerosis, albeit with procedural risks. Lahtinen *et al.* (2020) [45] and Singh *et al.* (2022) [40], however, noted that while there might be initial symptom relief or microbiota changes, the sustained impact on physical and psychological functionality was limited, emphasizing the need for further, larger-scale trials.

3.4.2. Other Effects in Nociceptive Pain Following FMT

In addition to physical and psychological functionality, several studies highlighted other variables influenced by FMT interventions. Microbiota composition changes were a common outcome across studies, with Fretheim *et al.* (2020) [44] observing quantitative changes in IgA- and IgM-coated bacteria among systemic sclerosis patients, while Singh *et al.* (2022) [40] reported varying rates of engraftment in IBS-D patients. These findings underscore the role of microbiome alterations in therapeutic outcomes.

Adverse events were also documented, ranging from none in some studies [39,49] to serious events like laryngospasms and duodenal perforation in Fretheim *et al.* (2020) [44]. Engraftment rates and donor stool characteristics emerged as variables of interest, influencing the degree of symptom relief, as evidenced by El-Salhy *et al.* (2019) [48], who noted a dose-dependent response in IBS patients.

4. Discussion

4.1. Severity of Nociceptive Pain Following FMT

Nociplastic pain, central to conditions such as Fibromyalgia and CFS, arises from altered pain processing and heightened central sensitization [1-3,51]. The gut-brain axis, a bidirectional communication network connecting the gut microbiota and the CNS, plays a crucial role in modulating nociceptive processing [52]. FMT may influence nociplastic pain through neurophysiological and biochemical pathways by restoring gut microbiota balance, thereby impacting systemic inflammation [53], neuroinflammation [54], and neurotransmitter signaling [55].

One key pathway involves the modulation of pro-inflammatory cytokines and immune signaling. Chronic nociplastic pain is often associated with elevated levels of pro-inflammatory cytokines such as interleukin-6, tumor necrosis factor-alpha, and C-reactive protein [56,57]. FMT has the potential to reduce systemic inflammation by promoting the growth of anti-inflammatory commensal bacteria, thereby downregulating inflammatory mediators [58,59]. Fang *et al.* (2024) [38] observed reductions in pain intensity among Fibromyalgia patients, which may be explained by decreased neuroinflammatory signaling that otherwise perpetuates central sensitization and pain hypersensitivity.

The gut microbiota is also integral to the production and metabolism of neurotransmitters that regulate pain perception, including serotonin, dopamine, GABA, and tryptophan metabolites [60,61]. Serotonin, predominantly produced in the gut, plays a vital role in pain modulation and mood regulation. Dysbiosis can disrupt serotonin synthesis, leading to altered pain sensitivity and depressive symptoms commonly seen in nociplastic pain syndromes [62]. FMT, by restoring a balanced gut microbiome, may enhance serotonin availability and modulate serotonergic pathways in the CNS, contributing to pain relief [63]. However, Salonen *et al.* (2023) [39] reported no significant changes in fatigue and quality of life in CFS patients post-FMT, suggesting as Hartikainen *et al.* (2024), that FMT's efficacy on symptoms may depend on specific microbiota profiles or host factors that influence neurotransmitter biosynthesis and signaling [64].

The modulation of microglial cells, the resident immune cells of the CNS, is another critical mechanism by which FMT may impact nociplastic pain. Microglial activation, driven by systemic inflammation and gut-derived metabolites, contributes to neuroinflammation and pain hypersensitivity [65]. By altering the gut microbiota, FMT may suppress pro-inflammatory microglial activation, thereby reducing central sensitization [66]. This mechanism is supported by evidence of symptom improvement in Fibromyalgia patients [50,67,68], though further studies are necessary to confirm FMT's impact on neuroimmune crosstalk.

4.2. Functionality and Quality of Life in Nociplastic Pain Following FMT

Physical and psychological functionality improvements following FMT may be attributed to its impact on neuroendocrine signaling pathways and systemic immune modulation. Zeng *et al.* (2021) [43] reported significant reductions in disease activity and improvements in physical functionality in a Rheumatoid Arthritis patient post-FMT. These outcomes likely result from a decrease in systemic inflammation mediated by changes in gut microbiota composition, reducing peripheral nociceptive signaling and central sensitization.

Moreover, FMT's influence on the hypothalamic-pituitary-adrenal (HPA) axis is also relevant, as dysregulation of the HPA axis is common in nociplastic pain syndromes, leading to altered stress responses, increased cortisol levels, and exacerbated pain perception [69]. By restoring gut microbiome balance, FMT may recalibrate HPA axis activity, mitigating stress-related amplification of pain signals [70]. This mechanism may partly explain improvements in fatigue and quality of life observed in IBS patients [47,48].

On the other hand, psychological improvements following FMT, including enhanced mood and reduced anxiety, can be linked to gut microbiota's ability to synthesize and modulate neurotransmitters such as GABA, which exerts inhibitory effects on neural excitability and stress responses [71]. Enhanced GABAergic signaling, along with increased production of Short-chain fatty acids (SCFAs) like butyrate [72,73], may stabilize the blood-brain barrier (BBB), reduce neuroinflammation, and promote resilience to nociplastic pain triggers [74]. However, inconsistent

outcomes, as noted by Kenyon *et al.* (2019) [46], suggest variability in individual responses based on baseline gut microbiota composition and other host factors.

4.3. Other Physiological and Biochemical Effects of FMT on Nociceptive Pain

Beyond its impact on nociceptive signaling and neurotransmitter modulation, FMT can alter the gut microbiome's production of key metabolites, such as SCFAs (e.g., butyrate, propionate, and acetate) [75]. SCFAs exert anti-inflammatory and neuroprotective effects by modulating immune cell activity, reducing oxidative stress, and promoting gut barrier integrity [76]. By mitigating systemic inflammation and enhancing intestinal permeability, FMT may decrease the translocation of bacterial endotoxins (e.g., *lipopolysaccharides*) [77] that trigger neuroinflammation and worsen nociceptive pain.

Microbial metabolites such as tryptophan-derived kynurenine also play a role in pain modulation and neuroinflammation [78]. Dysregulation of the kynurenine pathway can lead to neurotoxic metabolite accumulation, contributing to heightened pain sensitivity and depression in nociceptive pain syndromes [79]. FMT may restore a balanced microbial metabolite profile, reducing neurotoxicity and improving pain outcomes. Fretheim *et al.* (2020) observed changes in IgA- and IgM-coated bacteria, indicating shifts in mucosal immunity that may further modulate systemic and neuroinflammatory responses [80,81].

While adverse events such as those reported by Fretheim *et al.* (2020) [44] highlight potential risks associated with FMT, optimizing donor selection, engraftment protocols, and microbiota composition can enhance therapeutic outcomes while minimizing complications. Collectively, these neurophysiological and biochemical pathways underscore FMT's complex and multifaceted role in modulating nociceptive pain, necessitating a precision-medicine approach to maximize its therapeutic potential.

4.4. Implications for Practice

FMT presents considerable promise in the management of nociceptive pain—a chronic pain state marked by altered pain processing and central sensitization, prevalent in disorders such as Fibromyalgia, IBS, and CFS. Current evidence indicates that FMT can alter gut microbiota composition, thereby modulating systemic inflammation, gut-brain communication, and immune responses implicated in nociceptive pain. This modulation may reduce pain intensity, alleviate fatigue, and improve gastrointestinal symptoms, serving as a potential complementary or alternative intervention to conventional pharmacological therapies, which often show limited effectiveness and significant side effects.

In clinical settings, incorporating FMT into nociceptive pain management strategies could transform treatment paradigms by offering a natural and potentially sustainable means of symptom alleviation through microbiome restoration. By attenuating systemic inflammation and enhancing gut barrier integrity, FMT may reduce reliance on conventional pain medications, thereby mitigating risks such as opioid dependence and associated adverse effects. Furthermore, its capacity to modulate neuroinflammatory pathways offers the potential for significant improvements in both physical and psychological patient well-being.

The establishment of standardized protocols for donor selection, preparation, and FMT administration will be essential to ensure safety and efficacy, promoting consistent therapeutic outcomes. Ultimately, FMT may not only provide symptomatic relief but also target the underlying mechanisms of pain sensitization, presenting a transformative opportunity in the care of patients with nociceptive pain.

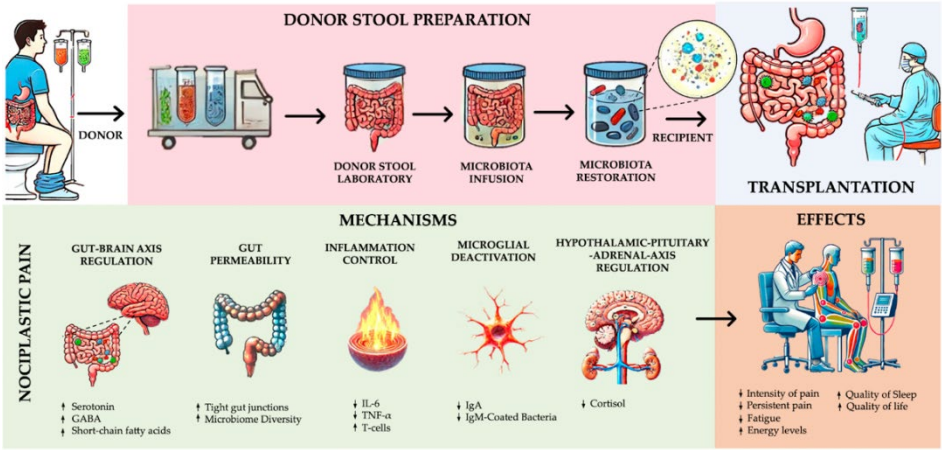


Figure 2. Mechanisms and analgesic effects of Fecal Microbiota Transplantation in Nociceptive Pain Management. Source: Own work.

4.5. Implications for Research

Future investigations into the role of FMT in managing nociceptive pain present several critical research opportunities. First, it is imperative to refine and standardize FMT protocols, encompassing optimal donor selection criteria, preparation techniques, and delivery routes tailored specifically to nociceptive pain conditions. Unraveling the mechanisms through which FMT modulates the gut-brain axis, immune system responses, and pathways involved in central sensitization can offer more deeper insights into its therapeutic potential and inherent limitations within chronic pain syndromes.

Longitudinal studies are essential to evaluate the long-term safety and efficacy of FMT across diverse patient populations affected by nociceptive pain. Investigating inter-individual differences in treatment response, which may be influenced by factors such as microbiota composition, genetic predisposition, and other patient-specific variables, will be crucial in optimizing personalized care strategies. Expanding research beyond conventional gastrointestinal disorders to encompass the neurobiological and immune-mediated dimensions of nociceptive pain can further elucidate FMT's broader applicability and therapeutic value.

Moreover, assessing FMT's potential as an adjunctive therapy for conditions such as Fibromyalgia, IBS, and related disorders offers an opportunity to develop comprehensive, multi-targeted treatment strategies. By addressing the root causes of nociceptive pain through modulation of the microbiota, FMT holds promise for substantially improving clinical outcomes and providing renewed hope for individuals experiencing chronic, refractory pain conditions.

5. Conclusions

This systematic review underscores the potential of FMT in managing nociceptive pain, characterized by altered pain processing and central sensitization. Evidence indicates that FMT may influence systemic inflammation, gut-brain signaling, and neuroimmune pathways, showing promise in conditions such as Fibromyalgia, CFS, IBS, and autoimmune disorders. However, results vary widely, reflecting the complexity of nociceptive pain and the multifactorial factors affecting outcomes. Further research is necessary to standardize protocols, improve study designs, and better define FMT's role in chronic pain management.

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