

REVIEW



Implication of intestinal microbiota in the etiopathogenesis of fibromyalgia: A systematic review

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Abstract

Fibromyalgia (FM) is a highly prevalent chronic disease. About 4.7% of the world's population suffers from generalized pain and hypersensitivity, in addition to a wide range of physical and psychological symptoms. The etiopathogenesis of this disease is multifactorial, which makes its diagnosis and treatment challenging. Recently, the increase in the number of studies on microbiota has provided new data that can help to understand the onset and development of FM. An updated systematic review of the causes of FM has been carried out in this work. Particularly in the last decade, research has focused on the gut-brain axis, which has emerged as a crucial mechanism for microbiota-host crosstalk. In FM patients, quantitative imbalances of the intestinal microbiota (dysbiosis) and bacterial metabolites with differential relative abundance have been found, especially short-chain fatty acids and lipopolysaccharides. Furthermore, the microbiota has been found to indirectly influence host neurotransmitter mechanisms, mainly through the serotonin precursor, glutamate, and gamma-aminobutyric acid. Thus, all these mechanisms and their influence on the etiopathogenesis of FM are discussed in this review.

KEYWORDS

etiopathogenesis, fibromyalgia, gut microbiota, gut-brain axis, metabolome

1 | INTRODUCTION

Fibromyalgia (FM) is a chronic disease characterized by continuous hyperalgesia and allodynia at the musculoskeletal level for at least 3 months.¹ Global prevalence values for FM are high, ranging between 0.2% and 4.7%.² Classically considered a painful syndrome that occurs with musculoskeletal dysfunctions such as muscle cramps or joint stiffness, FM is also associated with neuropsychological symptoms. Currently, the myriad of symptoms and the absence

of therapeutic targets hamper the search for specific and precise diagnosis and treatment.¹ This obstacle greatly affects patients, who suffer from extreme physical limitations and a marked deterioration of their quality of life.³

The etiopathogenesis of FM is multifactorial and poorly understood. At present, a plethora of pathogenic and etiological processes have been described as potential triggers for the development of the disease. These processes equally affect the peripheral (PNS) and central (CNS) nervous systems (Figure 1) and could be briefly

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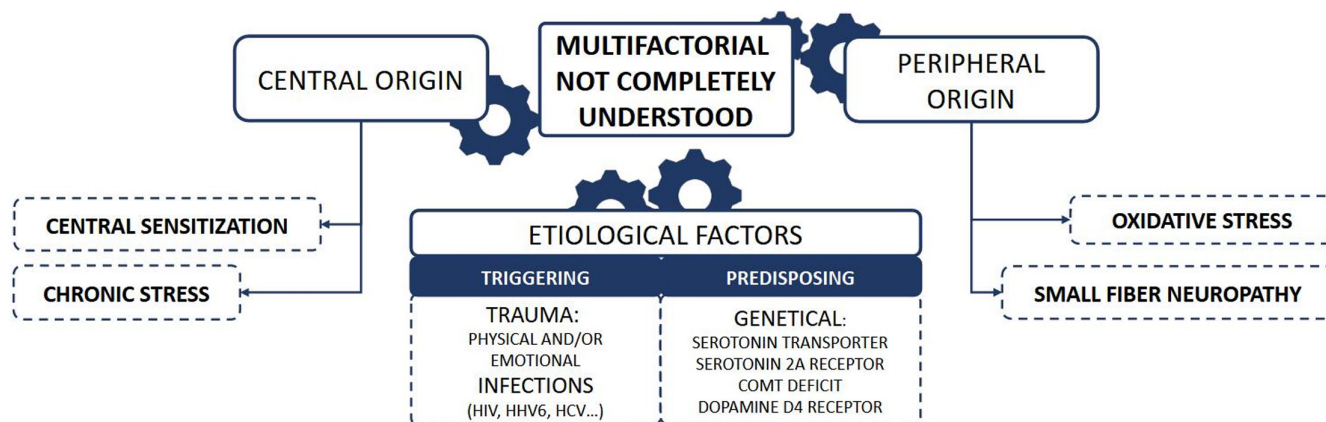


FIGURE 1 The etiopathogenesis of fibromyalgia and mechanisms discovered.

classified as triggering and predisposing factors.^{1,3,4} Among those factors, physical trauma (such as traffic accidents or accidental falls) and psychological trauma (such as physical or psychological abuse or the traumatic loss of a family member) stand out.³ Likewise, it is common for the development of FM to be associated with viral infections such as human immunodeficiency virus, human herpesvirus 6, or hepatitis C virus.⁴

In addition to traumas and infections, genetic polymorphisms such as serotonin transporter and 2A receptor, catechol-O-methyltransferase enzyme, and the dopaminergic pathway (D4 receptor gene) have been shown to play a predisposing role in FM.⁵ Whether or not they are a consequence of these mutations, the neurological pathways responsible for the management of painful stimuli are undoubtedly compromised in FM patients whose perception of pain is compounded and intensified by an imbalance that facilitates the entry of nociceptive signals and a deficit in the response of the pain inhibitor system.⁶ For the most part, this situation seems to be related to a small fiber neuropathy that has already been confirmed in some skin biopsies of patients with FM.^{7,8} Regarding the CNS, phenomena of spatio-temporal summation and neuronal adaptation to repeated stimulation have been found in the posterior horn of the spinal cord (a process known as central sensitization). Furthermore, depletion of the neurohormonal pathways responsible for responding to chronic stress has been demonstrated in these patients.^{1,9–11} At the cellular level, other biological processes that could be related to the pathology have been investigated.^{7,12,13} For example, a dysfunction has been found in the mitochondria of patients with FM, which show an important deficit to reduce free radicals and cause a situation of oxidative stress that, ultimately, is associated with nociceptive hypersensitization.^{12,14}

However, in recent years, the involvement of the nervous system and its associated molecular processes in FM have become a commonly discussed hypothesis in scientific literature, especially those linked to the gut-brain axis. This association is largely explained on the basis of the close relationship between gut microbiota, neurotransmitter metabolism, and immune system response. In

fact, numerous studies published in the last decade have highlighted the potential of the intestinal microbiota as a therapeutic target for the management of FM.¹⁵ Previous reviews¹⁵ include studies that consider and widely discuss the hypothesis of the role of intestinal microbiota in the etiopathogenesis of FM. In order to clarify this hypothesis, this review focuses on describing the associations between alterations in the intestinal microbiota and the different neuroimmunological processes that have been classically associated with the etiopathogenesis of FM.

2 | METHODS

The bibliographic searches conducted focused on the last decade (from January 2010 to August 2023), using the databases of Pubmed (<https://pubmed.ncbi.nlm.nih.gov/>), SCOPUS (<https://www.scopus.com/home.uri>), COCHRANE (<https://www.cochranelibrary.com/es/>), MEDES (<http://www.medes.fr/en/index.html>), Web of Science (www.webofknowledge.com), DIALNET (<https://dialnet.unirioja.es/>), and ProQuest (<https://www.proquest.com/>). The search strategies were based on the use of a set of keywords in accordance with the objective of the review. Specifically, the terms “fibromyalgia,” “etiopathogenesis,” “microbiome,” or “microbiota” have been used, combined with Boolean operators (AND, OR, parentheses, wildcards, and truncations) to explore the different combinations (Table 1).

A bibliography meeting the following inclusion criteria was accepted for the review:

1. Reviews, observational studies, and randomized clinical trials published in scientific journals (regardless of sample size).
2. Published between January 2010 and the current date of the search.
3. Documents whose title and/or abstract contain information on FM or associated chronic pain and, in turn, on the intestinal microbiota and/or etiopathogenesis of FM.



TABLE 1 Record of results obtained and articles collected after searching the main databases.

Search strategies						
Databases	Search profile	Filters ^a	Results	Documents	Search date	
PUBMED	<i>fibromyalgia AND etiology AND (gut OR microbio* OR "gut-brain axis")</i>	January 2010–present Free full text	18	6	31/01/2021	
WOS	<i>fibromyalgia AND etiology AND (gut OR microbio* OR brain axis)</i>	January 2010–present All open access	3	1	31/01/2021	
PUBMED	<i>fibromyalgia AND microbio* AND ("gut-brain" OR "gut brain" OR "brain gut" OR gut)</i>	2010–present, Free full text.	13	3	01/02/2021	
SCOPUS	<i>fibromyalgia AND microbio* AND ("gut-brain" OR "gut brain" OR "brain gut" OR gut)</i>	January 2010–present All open access Discipline: medicine	16	2	01/02/2021	
WOS	<i>fibromyalgia AND microbio* AND ("gut-brain" OR "gut brain" OR "brain gut" OR gut)</i>	January 2010–present All open access	15	1	01/02/2021	
DIALNET	<i>fibromialgia AND microbio*</i>	–	4	1	01/02/2021	
PROQUEST	<i>fibromyalgia AND etiology AND microbiota AND (gut brain)</i>	Full text January 2010–present Scientific journals English and Spanish	123	3	02/02/2021	
WOS	<i>microbio* AND "gut-brain axis" AND "chronic pain"</i>	January 2010–present	12	1	13/02/2021	
PUBMED	<i>("short-chain fatty acids" OR SCFAs) AND chronic-pain</i>	January 2010–present Free full text	8	1	22/02/2021	

Note: Inclusion and exclusion criteria allowed by each database were added; those not allowed were applied manually.

^a"Present" refers to the day on which the search was conducted (last column).

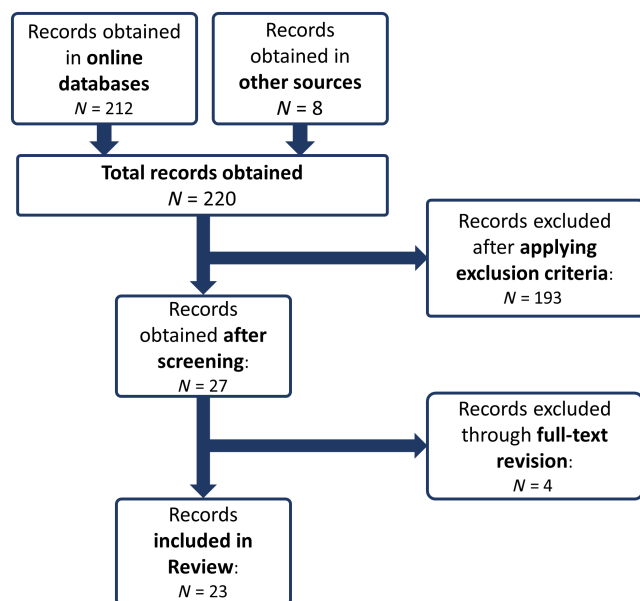


FIGURE 2 Flow chart on bibliography processing.

Additionally, some exclusion criteria were applied to disassociate those articles:

1. Without free access.
2. Not written in English or Spanish.
3. Without summary.
4. Already collected in previous searches (duplicates).
5. Unrelated to medicine (in multidisciplinary databases).

6. Not linked to the objective of this review or without relevant information.

At the end of the filtering process, 16 articles remained eligible for the proposed systematic review (Figure 2).

3 | RESULTS

The hypothesis regarding the role of gut microbiota in FM is divided into the following bullet points:

1. Mechanisms that allow communication between gut microbiota and the CNS: the gut-brain axis.
2. Variations in the composition of the gut microbiota in patients with FM and the main consequences at the etiopathogenic level.
3. Effects of microbial metabolome on the host.
4. Relationships and influence of the microbiota on host neurotransmission.

The most relevant findings of this review have been summarized graphically in Figure 3.

3.1 | Gut-brain axis

The gut-brain axis is composed of a complex communication system between the gut microbiota and the CNS in which the two entities

Quantitative in microbiota populations and qualitative alterations in metabolome through Gut–Brain Axis are shown as etiopathogenic factors in FM

Fibromyalgia, etiopathogenesis, gut microbiota, gut–brain axis, metabolome

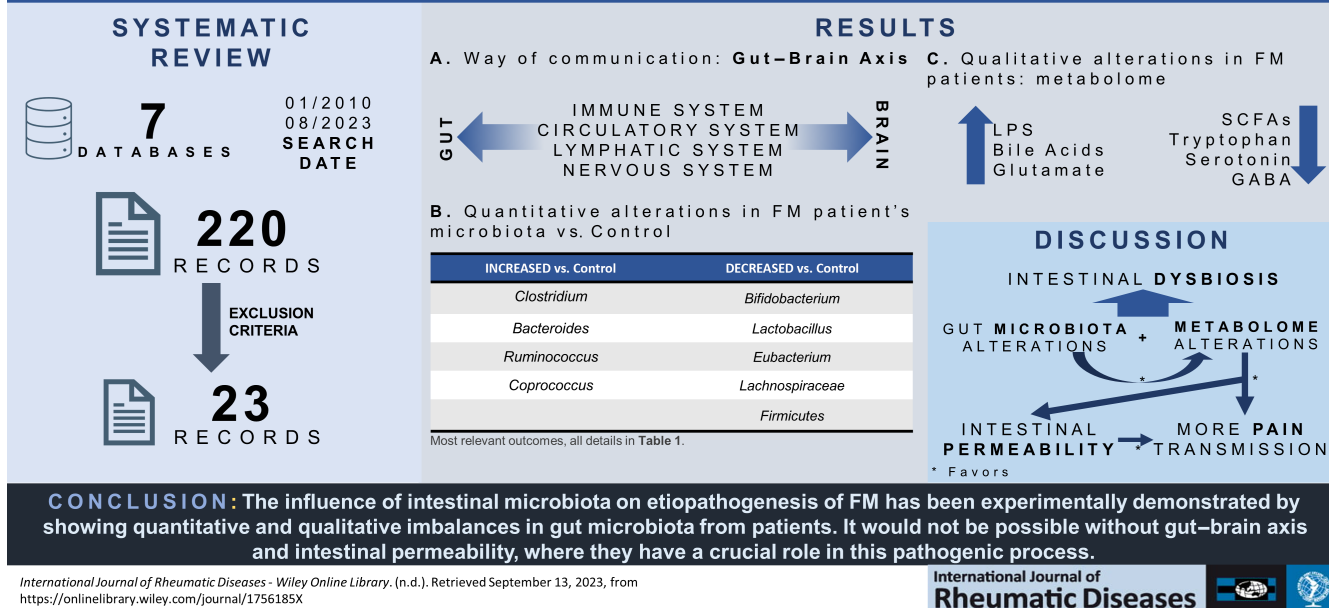


FIGURE 3 Graphical abstract with the most relevant findings in the field of gut microbiota in fibromyalgia FM patients.

interact and feed back in both directions.^{16–19} Microbiota influences the brain in two ways: by directly stimulating the receptors of the intestinal epithelium or the nerve endings that innervate the intestine^{17,20} or by secreting bacterial metabolites (such as neurotransmitters, cytokines, and neuropeptides).^{16,17} In contrast, the central CNS influences the microbiota by modifying the patterns of peristalsis and neuroendocrine secretion, which control the biodiversity and proliferation of the different bacterial populations.¹⁷ According to Rea et al.,¹⁶ this two-way communication takes place in four ways:

1. Circulatory and lymphatic systems: the biomolecules secreted by microbiota act through these two pathways, taking advantage of physiological transport functions to reach the brain after passing through the blood–brain barrier.¹⁶
2. Immune system: as a result of interaction between antigens, bacterial metabolites, and immune cells^{16,21,22} (such as macrophages, mast cells, dendritic cells, or lymphocytes), an immune response is generated, stimulating pain signals at the gastrointestinal level.^{16,23} In this case, the intestinal epithelial barrier loses its integrity, an alteration known as “leaky gut” or “intestinal transcytosis” that acts as an etiopathogenic factor in FM.^{17,18}
3. Nervous system: This could be defined as the most relevant pathway in the link between the gut–brain axis and FM, due to the involvement of neural circuits related to the etiopathogenesis of the disease. It must be considered that lateral spinothalamic pathway fibers whose first neuron synapses in the medullary posterior horn are related to the abovementioned central sensitization phenomena and also that neurons of the autonomic nervous system,

through stimulation of the myenteric plexuses of Auerbach and submucosal of Meissner, maintain intestinal homeostasis by regulating their motility. Finally, the vagus nerve has also been linked to pain-related disorders, as its afferents conduct signals from the gut environment directly to the brainstem.¹⁶

In fact, the gut–brain axis has been associated with numerous health problems and various diseases, including FM (Figure 4).^{17,19}

3.2 | Composition of microbiota and intestinal dysbiosis

The gut microbiota is comprised of a set of microorganisms (essentially from the bacterial kingdom) that naturally reside in the lumen of the intestine. Its composition is unique to each individual, being influenced by the host's intestinal environment and by external factors.^{19,24} Its variation, both quantitatively and qualitatively, is known as intestinal dysbiosis^{17,18,20,25–28} and can lead to several pathogenic situations that favor the development of various systemic diseases. Intestinal dysbiosis starts during childhood and is strongly affected by long-lasting and frequent antibiotic treatments, as pointed out by Berstad et al.²⁴ The significant dynamism of the microbiota has been identified as a characteristic of FM, as similar imbalances have been detected among patients^{17,24} accompanied by intestinal permeability, as reported by Clos-García et al.,²⁵ a circumstance that heightens the immune response at the local level. This phenomenon has been studied as a pathogenic agent in irritable bowel syndrome^{18,27} and was recently

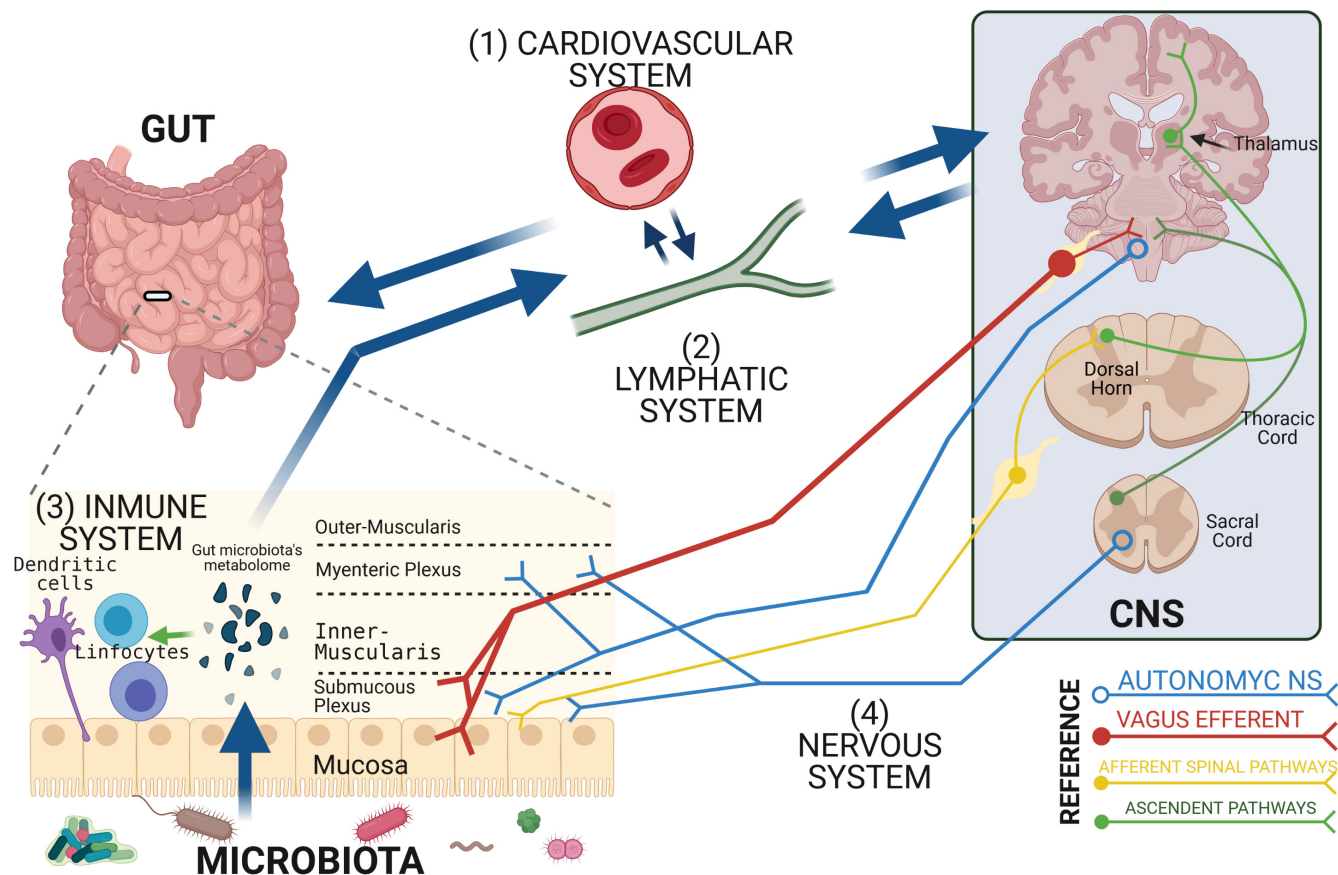


FIGURE 4 The gut-brain axis and its main communication pathways.

related to other conditions such as FM and some of its comorbidities, especially chronic fatigue syndrome and myalgic encephalopathy.²⁷ In fact, intestinal dysbiosis in FM patients has been reported in numerous studies, most of which were based on sequencing techniques and microbiome analysis.^{17,19,25,29,30} In contrast, Minerbi et al.¹⁹ did not find any variation in composition between individuals with FM and healthy controls. However, with higher-resolution molecular techniques, significant and similar variations have been observed in these patients.²⁹ Specifically, Clos-García et al.²⁵ found lower biodiversity in the intestinal microbiota of patients with FM. Freidin et al.³¹ make a similar statement in relation to patients suffering widespread chronic pain. Some genera, such as *Clostridium*, *Bacteroides*, *Coprococcus*, or *Ruminococcus*, showed higher levels in patients with the disease.^{18,19,22,28} Conversely, *Bifidobacterium*, *Lactobacillus*, *Eubacterium*, *Lachnospiraceae*, *Blautia faecis*, *Prevotella copri*, or *Faecalibacterium prausnitzii* showed decreased levels.^{18,25,28,29} These quantitative variations consequently generate qualitative dysfunctions that are primarily linked to some pathogenic effects and differential levels of various bacterial metabolites in FM patients.¹⁷ *Clostridium* and *Bacteroides* levels are related to the metabolism of bile acids.^{18,19,29} The presence of *Ruminococcus* has been linked to low levels of serotonin,¹⁸ and *Coprococcus* indirectly causes higher levels of lipopolysaccharides (LPS),¹⁸ whereas *Eubacterium* and *Firmicutes Lachnospiraceae* are related to a deficit in the synthesis of short-chain fatty acids (SCFA).^{19,20,25,29} Lastly, *Bifidobacterium* or

Lactobacillus are responsible for the lower conversion of glutamate to gamma-aminobutyric acid (GABA)²⁵ (Table 2).

The diagnosis of bacterial overgrowth in the small intestine (SIBO) is very common in FM patients and is usually accompanied by abdominal pain and distention, fatigue, anxiety, depression, and weakness.^{17–19} Slim et al.¹⁷ point out a study of 123 patients with FM in which it is shown that 78% of the patients suffered from SIBO, diagnosed by the lactulose-H₂ breath test. Tomasello et al.¹⁸ describe a study in which 100% of the FM patients who were evaluated were diagnosed with SIBO. This coincidence of SIBO and FM is also mentioned in the study conducted by Minerbi et al.¹⁹ In addition, the presence of SIBO may lead to other diseases and can cause greater permeability of the intestinal epithelial barrier as a result of the greater growth of LPS-generating species.²¹ Galland et al.²¹ also consider SIBO to be a direct and independent cause of intestinal permeability. Based on these results, it can be hypothesized that SIBO plays a role in FM,^{17,18} especially in patients with gastrointestinal symptoms.

3.3 | New findings on bacterial metabolites

Variations in the composition of the intestinal microbiota are undeniably associated with variations in the metabolites they produce. Thus, the scientific literature points to LPS, SCFA, D-lactic



TABLE 2 Quantitative alterations in composition of intestinal microbiota of FM patients compared with control group.

FM versus Healthy controls abundance	Species and genera	Impact on FM	References
Increased	<i>Clostridium</i>	1, 2	B
	<i>Bacteroides</i>	1, 2	A, B
	<i>Faecalibacterium</i>	2	A
	<i>Roseburia</i>		A, D
	<i>Dorea</i>		A, D
	<i>Coprococcus</i>	5	A
	<i>Clostridium scindens</i>	2, 3	B, C, F
	<i>Ruminococcus</i>	4	A
	<i>Coproacillus</i>		A, E
	<i>Papillibacter</i>		D
	<i>Subdoligranulum</i>		D
	<i>Intestimonas butyriciproducens</i>	6	B, F
	<i>Flavonifractor plautii</i>	6	B, F
	<i>Butyrucoccus desmolans</i>	3, 6	B, F
	<i>Eisenbergiella tayi</i>	6	B, E, F
	<i>Eisenbergiella massiliensis</i>	6	B, E, F
	<i>Parabacteroides merdae</i>	7	F, G
	<i>Rikenellaceae</i>		C
Decreased	<i>Firmicutes</i>	8, 10	A, C, D
	<i>Bifidobacterium</i>	9	C, D
	<i>Lactobacillus</i>	10	D
	<i>Eubacterium</i>	10	D, E
	<i>Lachnospiraceae</i>	10	D
	<i>Blautia faecis</i>	10	B, E
	<i>Prevotella copri</i>	10, 12	B, E, F
	<i>Faecalibacterium prausnitzii</i>	10, 11	B, C, F
	<i>Bacteroides uniformis</i>	12	B
	<i>Haemophilus parainfluenza</i>	12	B

Note: 1: Diagnostic marker in other diseases; 2: bile acids metabolism; 3: androgen cortisone conversion; 4: decreased cortisone and serotonin; 5: decreased vitamin D and increased LPS; 6: increased butyrate (SCFA); 7: increased GABA/glutamate ratio in mice; 8: irritable bowel syndrome pathogenesis; 9: decreased conversion of glutamate to GABA; 10: decreased butyrate and butyric acid (SCFA) synthesis; 11: anti-nociceptive and anti-inflammatory activity; 12: pro-inflammatory and linked to inflammatory arthritis. A: Tomasello et al.¹⁸ B: Minerbi et al.¹⁹ C: Garofalo et al.²⁰ D: Clos-García et al.²⁵ E: Kim et al.²⁸ F: Minerbi et al.²⁹ G: Erdrich et al.³⁰

acid, and secondary bile acids as potential causative agents of some symptoms of FM.

3.3.1 | LPS

Although this group of molecules is widely known to cause infectious diseases, a feasible relationship with FM has recently been investigated. LPS is one of the most important proteins involved in the immune pathway of the gut-brain axis. Higher plasma LPS levels have been observed in FM compared with healthy individuals. The higher levels have been inversely associated with low levels of vitamin D due to the excessive proliferation of *Coprococcus* in patients with FM. In turn, elevated levels of LPS are significantly associated

with greater severity of FM symptoms such as muscle tension, fatigue, or difficulties in concentration and memory.¹⁸ Galland et al.²¹ pointed out two possible links between this molecule and intestinal homeostasis alteration: the capacity of some LPS-generating species to act as an indirect cause of intestinal permeability and their ability to induce cytokine secretion such as interleukin 1B (IL-1B) or tumor necrosis factor alpha (TNF α) by way of macrophages and T lymphocytes that reside in the gut submucosa. Moreover, the author linked these molecules (LPS, IL-1B, and TNF α) to the induction of REM sleep, since the circadian rhythm of TNF α and IL-1B secretion is regulated by an inverse pattern to cortisol, the hormone that controls the sleep cycle.²¹ These direct and indirect functions of LPS could explain some of the most common symptoms of FM, such as intestinal pain or the absence of restful sleep.



3.3.2 | SCFA

SCFA are fatty acids with six or fewer carbon molecules (e.g., acetate, butyrate, and propionate) that are synthesized by the gut microbiota. They come from carbohydrate fermentation and fiber degradation^{32,33} by genera such as *Eubacterium*, *Firmicutes*, and *Lachnospiraceae*, all of which are decreased in FM patients.^{20,25} In line with these results, further studies have revealed SCFA imbalances in serum from FM patients. Minerbi et al.²⁹ found lower levels of isobutyric acid and propionate in these patients compared to the control group. However, results on butyrate are contradictory.^{25,29} While Minerbi et al.²⁹ found higher levels of butyrate in FM patients (possibly linked to the increase in butyrate-producing species such as *Intestinomonas butyriciproducens*, *Flavonifractor plautii*, *Butyricoccus desmolans*, *Eisenbergiella tayi*, or *Eisenbergiella massiliensis*), Clos-García et al.²⁵ could not replicate these results. Conversely, they found lower concentrations of this SCFA in patients compared with healthy controls. The imbalance in SCFA levels in FM is especially relevant, since these metabolites have been widely studied in the pathogenesis of chronic pain and depression.³² Moreover, these metabolites provide beneficial anti-inflammatory and immunomodulatory effects through the following mechanisms:

1. They prevent intestinal permeability^{19,20,32,34} by increasing the secretion of interleukin-8 (IL-8) and interleukin-10 (IL-10) through the intermediate action of the NLRP3 inflammasome and the G protein-coupled receptor GPR43 located in the intestinal epithelial cells, respectively.^{20,32}
2. Butyrate and propionate act as immunomodulators, blocking dendritic cell differentiation and enhancing the development of regulatory T lymphocytes with inflammatory action.^{19,32} Furthermore, SCFAs reduce the response of neutrophils to the presence of LPS.³²
3. They collaborate in the homeostasis of the CNS by maintaining the blood-brain barrier in the regulation of neuroinflammation and in neuronal energetic metabolism.^{25,32}

However, the bibliography suggests that the data are contradictory insofar as how SCFAs influence pain perception.^{19,32} Minerbi et al.¹⁹ hypothesize that SCFA receptors (FFARs) are associated with pain sensitization, especially with butyrate linking, which has been shown to increase visceral sensitivity in mice. However, Li et al.³² proposed that SCFAs might play a beneficial role in pain transduction. These conflicting findings reveal the need for more detailed studies to help clarify the role of these molecules in the management of painful stimuli.

3.3.3 | D-Lactic acid

D-Lactic acid is a product generated by the intestinal microbiota, deriving from the fermentation of carbohydrates, while its

isomer L-Lactic acid is endogenously generated by muscle tissue.³⁰ Situations in which carbohydrates reach the colon in high quantities facilitate the synthesis of D-lactic acid. Lactic acidosis is associated with neurotoxic effects such as encephalopathy^{21,30} and has been classically investigated in chronic fatigue syndrome,²¹ although in FM scant progress has been made and the results are contradictory. Erdrich et al.³⁰ suggested that there is no evidence to link FM to the cognitive symptoms associated with D-lactate. Regarding the quantitative measurement of serum metabolites carried out by Minerbi et al.³⁴ in patients with FM, these values did not show significant differences in D-lactic acid concentrations. However, Malatji et al.³⁵ found elevated lactic acid concentrations in FM patients, although the measurements were taken in urine. These results reveal the importance of the sample used in certain potentially interesting metabolite measurements in FM and highlight the need for studies in larger and more homogeneous groups of patients.

3.3.4 | Secondary bile acids

Secondary bile acids are a group of metabolites generated by catabolic deconjugation reactions or 7-alpha-dehydroxylation of bile acids from bile, such as lithocholic, deoxycholic, or ursodeoxycholic acid.³² Secondary bile acids mediate metabolic, inflammatory, and oncological processes through bile acid receptors,^{19,32} which may be located in the membrane or the nucleus.³² Li et al.³² supported the relevance of membrane receptors, mentioning the G protein-coupled bile acid receptor (TGR5), which has already been studied in mouse models as a cause of hypersensitivity after infusion of TGR5 agonists. Regarding nuclear receptors, the farnesoid X receptor (FXR) is associated with visceral hypersensitivity in irritable bowel syndrome and with the pathogenesis of depression^{19,32} conditions that are comorbid to FM. Strikingly, the molecular route associated with this receptor has been identified as an altered route in FM patients,³⁶ pointing to the central role that FXR and its associated molecules could have in this condition.

3.4 | Gut microbiota and neurotransmission

The gut microbiota has an indirect link to the availability of neurotransmitters such as glutamate and GABA and to the metabolism of some of their precursors, as it does in the case of serotonin and tryptophan.

3.4.1 | Glutamate and GABA

Glutamate is a key neurotransmitter in pain processing in spinothalamic pathways.^{25,30} In addition, GABA exerts an inhibitory function on the CNS, including pain control. These neurotransmitters have been found to be altered in FM patients, with higher levels of



glutamate and lower levels of GABA compared with healthy controls.²⁵ In this sense, it has been observed that the absorption of glutamate is facilitated when there is increased intestinal permeability. Furthermore, a lower conversion of glutamate to GABA has been related to the deficit of bacterial genera such as *Bifidobacterium* and *Lactobacillus*, both reduced in FM patients, which would also explain the lower availability of GABA. In this sense, maintaining *Bifidobacterium* and *Lactobacillus* levels in FM patients could contribute to better management of pain stimuli due to their link to the metabolism of the main neurotransmitters responsible for this function.¹⁸

3.4.2 | Serotonin and tryptophan

Serotonin performs multiple regulatory functions in the CNS, including pain control.³⁷ This neurotransmitter requires a precursor for its synthesis, tryptophan, which is an essential amino acid that can only be obtained through diet.^{18,25,32,37} These two molecules have drawn interest in FM research, since both have been found at lower levels in patients with this disease.^{18,37} Furthermore, Tomasello et al.¹⁸ correlated a low concentration of serotonin with a higher perception of pain. These low levels of serotonin can be explained by a lower uptake of tryptophan, since this precursor is able to cross the blood-brain barrier whereas serotonin is not.^{25,32,37} Several reasons have been suggested to explain this low uptake. For example, intestinal dysbiosis can increase the catabolization of tryptophan, consequently preventing its absorption by the host. Another feasible cause is the presence of other non-absorbable molecules in the intestine, such as fructose, which can block the uptake of tryptophan. In addition, the malabsorption of this monosaccharide generates deterioration of the intestinal microbiota and, consequently, the situation of dysbiosis, generating a vicious circle. Tryptophan also participates as a substrate for other metabolic pathways, some of which are carried out by the gut microbiota.³³ The most relevant are those that generate indole and skatole derivatives, molecules that, according to Li et al.,³² are ligands for aryl-hydrocarbon receptors (AhR). Activation of these receptors is associated with the maintenance of intestinal homeostasis, which improves the integrity of the intestinal barrier.³² However, Tomasello et al.¹⁸ revealed that high levels of indole and skatole compromise the bioavailability of tryptophan, which may occur in situations of intestinal dysbiosis, as mentioned above. In the particular case of tryptophan and serotonin, their ubiquity makes it difficult to find the link between their altered levels and the etiopathogenesis of FM, although their relationship with pain management in the CNS indicates that they are molecules of interest in the study of the disease.

4 | DISCUSSION

Although there is not enough evidence to solidly support the intestinal microbiota as an etiological agent of FM, we can nonetheless

enumerate a series of principles that would define the etiopathogenesis of this disease:

1. The gut-brain axis, through its communication pathways, allows the interrelation between microbiota and the CNS, and the different metabolites that microbiota generates affect the host. This communication system is essential to the identification of microbiota as an etiopathogenic factor in FM.
2. The composition of the intestinal microbiota in FM patients shows quantitative imbalances and qualitative dysfunctions due to various metabolites of bacterial origin, in addition to pathogenic and morbid situations. The existence of intestinal dysbiosis has been experimentally demonstrated in these patients. Nonetheless, comparison of the different results must be undertaken carefully, as they involve different control groups (healthy controls or controls with symptoms suggestive of FM without a specific diagnosis).
3. The etiopathogenic process of gut microbiota in FM is mainly based on the generation of qualitative dysfunctions in the host due to imbalances in the composition of various bacterial genera and species, either in excess or in deficiency.

Based on these principles, the main effects that these imbalances in microbiota could cause in FM are (i) the establishment of intestinal permeability and (ii) greater transmission of pain.

4.1 | Intestinal permeability

Although the permeability of the intestinal epithelium is quite selective in physiological conditions, this barrier loses its integrity in certain conditions, allowing metabolites or even bacteria to enter the submucosa. This circumstance stimulates the immune pathway of the gut-brain axis. SIBO has been implicated as a cause of intestinal permeability. This condition has been diagnosed in over 78% of FM patients with gastrointestinal symptoms. In addition, some metabolites favor the loss of epithelial integrity due to their role in either maintaining the barrier (SCFA) or generating inflammation (LPS). At the same time, intestinal permeability negatively influences the absorption of nutrients, making it difficult to incorporate molecules with a beneficial effect on the organism, such as GABA and tryptophan. Difficulties in the processing of the latter may compromise the synthesis of serotonin. In this situation, the promotion of the absorption of molecules such as glutamate has pronociceptive effects and, therefore, presents a clear pathogenic factor. The response to all the exposed serum imbalances of these molecules in FM patients may lie in increased intestinal permeability. Although it is true that variations in the composition of the intestinal microbiota are the first step in the etiopathogenesis of FM, these imbalances per se do not generate morbidity in the host. On the contrary, intestinal permeability does generate inflammation and malabsorption, which in turn can be considered a triggering factor in the etiopathogenesis of FM.



4.2 | Transmission of pain

Hyperalgesia is also associated with impaired intestinal permeability, because overstimulation of the immune system triggers an inflammatory response and the consequent generation of nociceptive signals. The gut-brain axis favors pain signaling, as the lateral spinothalamic pathway innervates the digestive tract. This situation, together with repeated stimulation from the gut microbiota, could participate in the phenomenon of central sensitization, a pathogenic process widely known and classically linked to the etiopathogenesis of FM. Another aspect that favors the transmission of pain are quantitative imbalances of glutamate, GABA, and serotonin, which are influenced by the indirect action of intestinal microbiota. These imbalances may be caused by situations of the intestinal permeability or lower conversion linked to the lack of several bacterial genera. Additionally, some metabolites of bacterial origin, such as secondary bile acids or LPS, have also been associated with pain sensitization. In these circumstances, numerous causes that generate sensitization to pain in FM coincide, facilitating pain signaling in these patients. The gut microbiota actively participates in this sensitization, especially by altering the bioavailability of various neurotransmitters.

4.3 | Child and juvenile population

Although research articles about gut microbiota in FM are numerous, there is an evident lack of information at this end for patients under 18. The close link between the gut microbiota and other prevalent chronic diseases among this population, such as rheumatoid arthritis, amyotrophic lateral sclerosis, multiple sclerosis, and autism spectrum disorders, suggest that further investigation is mandatory. Interestingly, a recent study in the field of neuroimaging describes promising findings on juvenile FM.³⁸ Suñol et al. found differences in neuronal metabolism in the sensorimotor and mid-cingulate cortex that are related to central sensorial processing. Besides, these patients showed an increased excitability and sensory responsiveness in the thalamus. Whether this altered pain signaling in young FM patients might be the cause or consequence of an imbalanced gut microbiota needs to be addressed.

5 | CONCLUSIONS

According to the existing bibliography, it may be concluded that:

1. The influence of intestinal microbiota on the etiopathogenesis of FM has been experimentally demonstrated by showing quantitative (e.g., *Coprococcus*, *Lactobacillus*, and *Bifidobacterium*) and qualitative (SIBO) imbalances in the microbiota from patients. Furthermore, bacterial metabolites such as LPS or SCFA have shown a negative influence on FM symptoms such as pain and restless sleep.

2. The most feasible link between the intestinal microbiota and the etiopathogenesis of FM is the gut-brain axis, which highlights the role of the vagus nerve. Intestinal permeability has shown a crucial role in this link, in view of the increase in absorption of nociceptive neurotransmitters (e.g., glutamate) and the prevention of the absorption of beneficial precursors (e.g., tryptophan).

AUTHOR CONTRIBUTIONS

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CONFLICT OF INTEREST STATEMENT

No potential conflict of interest relevant to this article was reported.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in PUBMED at <http://doi.org/10.3390/BIOMEDICINES11061701>, reference number [16]. The data that support the findings of this study are openly available in PROQUEST at <http://doi.org/10.1007/s00296-014-3109-9>, reference number [17]. The data that support the findings of this study are openly available in Web of Science at <http://doi.org/10.5507/bp.2018.051>, reference number [18]. The data that support the findings of this study are openly available in PUBMED at <https://pubmed.ncbi.nlm.nih.gov/32116215/>, reference number [19]. The data that support the findings of this study are openly available in PUBMED at <http://doi.org/10.3390/BIOMEDICINES11061701>, reference number [20]. The data that support the findings of this study are openly available in PUBMED at <http://doi.org/10.1089/jmf.2014.7000>, reference number [21]. The data that support the findings of this study are openly available in PUBMED at <http://doi.org/10.55563/CLINEXP RHEUMATOL/257E99>, reference number [22]. The data that support the findings of this study are openly available in PUBMED at <http://doi.org/10.7759/CUREUS.29923>, reference number [23]. The data that support the findings of this study are openly available in PUBMED at <http://doi.org/10.3390/IJERPH19063254>, reference number [24]. The data that support the findings of this study are openly available in PUBMED at <http://doi.org/10.1016/j.ebiom.2019.07.031>, reference number [25]. The data that support the findings of this study are openly available in PUBMED at <http://doi.org/10.3390/pathogens2040606>, reference number [26]. The data that support the findings of this study are openly available in PUBMED at <http://doi.org/10.1016/j.mehy.2020.109648>, reference number [27]. The data that support the findings of this study



are openly available in PUBMED at <http://doi.org/10.3390/IJERP H20043183>, reference number [28]. The data that support the findings of this study are openly available in SCOPUS at <http://doi.org/10.1097/j.pain.0000000000001640>, reference number [29]. The data that support the findings of this study are openly available in PUBMED at <http://doi.org/10.1186/s12891-020-03201-9>, reference number [30]. The data that support the findings of this study are openly available in PUBMED at <http://doi.org/10.1093/RHEUMATOLOGY/KEAA847>, reference number [31]. The data that support the findings of this study are openly available in PUBMED at <http://doi.org/10.1093/ijnpyz061>, reference number [32]. The data that support the findings of this study are openly available in DIALNET at <https://dialnet.unirioja.es/servlet/articulo?codigo=7016306&info=resumen&idioma=ENG>, reference number [33]. The data that support the findings of this study are openly available in PUBMED at <http://doi.org/10.3390/cells9020288>, reference number [34]. The data that support the findings of this study are openly available in PUBMED at <http://doi.org/10.1186/s12883-017-0863-9>, reference number [35]. The data that support the findings of this study are openly available in PUBMED at <http://doi.org/10.1016/J.JPROT.2018.07.009>, reference number [36]. The data that support the findings of this study are openly available in PUBMED at <http://doi.org/10.3389/fmed.2017.00198>, reference number [37]. The data that support the findings of this study are openly available in PUBMED at <http://doi.org/10.1002/art.42691>, reference number [38].

ETHICAL APPROVAL

This review does not need an Ethics Committee's approval since it does not manage patients' clinical information directly.

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