Chapter

Pathogenic Role of iNOs+ M1 Effector Macrophages in Fibromyalgia

Vishwas Tripathi, Amaresh Mishra, Yamini Pathak, Aklank Jain and Hridayesh Prakash

Abstract

Fibromyalgia (FM) or Fibromyalgia Syndrome (FMS) is a neurodegenerative disorder causing musculoskeletal pain, tenderness, stiffness, fatigue, and sleep disorder in the body. It is one of the most common chronic pain conditions, affecting about 6% of the world population. Being refractory, till date, no specific treatment of this disease is available. Accumulating evidences over the last few decades indicate that proinflammatory macrophages, cytokines, & chemokines as the key players in this disease. Recent findings suggest activation of Microglial cells and associated pro-inflammatory signals as one of the major causes of chronic pain in patients suffering from fibromyalgia. Increased density of iNOs/CD68+ M1 effector macrophages has been associated with neuropathic pain models. In light of this, depletion of these pro-inflammatory macrophages has been shown to reduce sensitivity to neuropathic pain. On the other hand, modulating pattern of AGEs (Advanced Glycation End-Products) can also contribute to inactivation of macrophages. These findings strongly suggest that macrophages are critical in both inflammatory and neuropathic pain. Therefore, this chapter highlights the impact of macrophage plasticity in various immunopathological aspects of fibromyalgia.

Keywords: fibromyalgia, Th1/Th2 immune response, M1/M2 macrophages, neurodegeneration

1. Introduction

Fibromyalgia has been considered a rheumatologic disease, also known as fibrositis and myofascial pain syndrome. Fibromyalgia affects the muscles, ligaments & tendons, and bones with no signs of inflammation of the tissue [1]. The origin of fibromyalgia is still not clear, although several hypotheses stated fibromyalgia condition associated with depression and brain-based neuronal dysfunctions i.e. coaxially linked with non-uniform signal transduction mechanism. Preclinical studies addressing the symptoms of fibromyalgia are increased levels of substance P (SP) in the cerebrospinal fluid (CSF) of the individuals. SP is a peptide which is composed of 11 amino acids and acts as a neurotransmitter. It plays a significant role in pain stimulations from the peripheral nervous system to the central nervous system [2]. Fibromyalgia patients showed a 3-fold increase in the levels of substance P in CSF which possibly activates neurokinin (NK) receptors that induce chronic pain [3, 4].

Moreover, besides NK receptors, the excitation of amino acid receptors such as N-methyl D-aspartate (NMDA) receptors also leads to hyperalgesia in fibromyalgia [5]. This is associated with the deficiency of Dopamine during chronic pain in fibromyalgia [6]. It is a neurotransmitter of the Central nervous system (CNS) and regulates the pain processing of CNS. On the other hand, several studies indicating that macrophages, cytokines/chemokines, and oxidative stress are the key mediator of immune activation and inflammation in fibromyalgia condition [7].

Nitric oxide (NO), is a principal determinant of normal endothelial and vascular function. During inflammatory reactions, NO production increases considerably and, contributes to oxidative stress together with other reactive oxygen species (ROS) [8]. Macrophages that have a pro-inflammatory role are called classically-activated (M1) macrophages. Classically-activated (M1) macrophages are activated by Lipopolysaccharide (LPS) and Interferon-gamma (IFN-γ). The role of activated M1 macrophages is to secrete pro-inflammatory cytokines and chemokines and present antigens [9, 10]. Cytokines produced by T helper type 1 (Th1) cells, induce the differentiation of classically activated (M1) macrophages [11, 12]. Some of the pro-inflammatory cytokines including TNF-α, IL-1, IL-6, and IL-8 have been reportedly linked with the immunopathology of fibromyalgia. Prolonged activation of M1 macrophages has been reported to encourage neuro-inflammation which may responsible for the pathogenesis of neuropathic pain among the fibromyalgia patients [13–15]. There is no successful medication yet that has been proven to treat fibromyalgia completely.

1.1 Epidemiology

Fibromyalgia prevalence is more common among women as compared to men and risk increases significantly after growing age [16]. Apparently, in population studies indicate that there is a need for a standardized gender-based diagnostic approach that can allow for more reliable diagnosis and some of the gender biases that relate to women suffering the most. It is estimated globally that there is about 6% of the patient that suffers from this chronic disease out of which 68 percent are females [17]. Patients who need tertiary care pain clinic help, more than 40% outcome measure is a resolution of symptoms of fibromyalgia [18]. Patients with existent chronic rheumatic diseases are having high risk of fibromyalgia (**Figure 1**).

1.2 Etiology and pathophysiology

Fibromyalgia is a chronic pain disorder but the etiology of the disease still not clear [19, 20]. Fibromyalgia is triggered by multiple physical and/or emotional stress factors. There is increasing evidence that revealed the role of macrophages including activated M1 macrophages, and inducible nitric oxide synthase (iNOS) in pain conditions in fibromyalgia [21]. Significantly, macrophages can mediate microglial activation through the production of pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α [22]. In addition, levels of pro-inflammatory cytokines and chemokines are enhanced in serum and could contribute to inflammation at the systemic level. On the other hand, alteration of central nervous system (CNS) cells occurs in fibromyalgia cause discomfort and sensory perception [5]. The functional neuroimaging technique rests crucially on the identification of pain-sensitive areas in regions of the Brain. Furthermore, differences in activation of pain-sensitive areas of the brain by functional neuroimaging techniques have been revealed in fibromyalgia condition. Several pharmacological studies have shown a genetic predisposition for fibromyalgia though there is no documentation of a definitive candidate gene [23]. About one-third of fibromyalgia patients have a close relative with rheumatic disease/fibromyalgia history (**Figure 2**) [24].

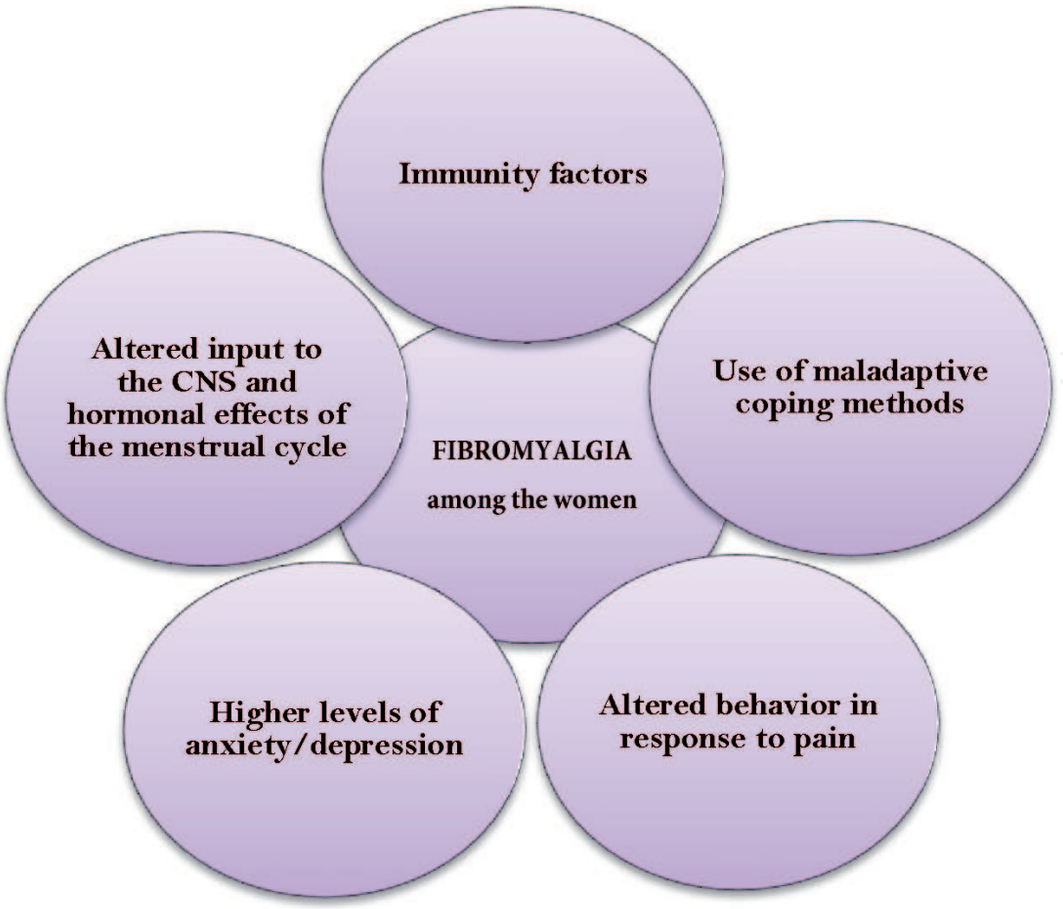

Figure 1.
Reason of high prevalence rate of fibromyalgia among women.

1.2.1 Psychological stress and trauma

Research has also shown that stress is linked with the increasing risk of developing fibromyalgia [25]. Psychologic factors including stress, trauma, anxiety, and depression have been shown their role in pain severity in fibromyalgia patients [26, 27]. Corticotrophin-releasing hormone (CRH), is a well-known hormone for stress response mediators, was found high in the cerebrospinal fluid (CSF) among fibromyalgia patients and was linked with pain [28]. Fibromyalgiais quite common in individuals with mastocytosis [29] where mast cells influence the infiltration, in situ differentiation and inflammatory response of macrophages and neutrophils; in various organs. This type of rapid proliferation of mast cells causes itchy bumps on the skin, diarrhea, and bone pain. Emotional stress is the primary symptom among the individuals suffering from mastocytosis and reportedly found high serum levels of CRH in mastocytosis patients [30]. CRH, nerve growth factor, neurotensin and substance P are known as stress peptides which released in peripheral tissues like blood vessels, muscles, and skin during allergic, immune, and stress reaction in the body. In another study, upregulation of nerve growth factor in the CSF among the patients suffering from fibromyalgia [31] and has been considered as a target for analgesic therapy [32].

1.2.2 Neuro-inflammation

A correlation between macrophages and mast cells (MCs) has been revealed in fibromyalgia [33, 34]. Numerous studies suggested macrophages and MCs play a key role during the pain and inflammation [35–38]. Macrophages and MCs also

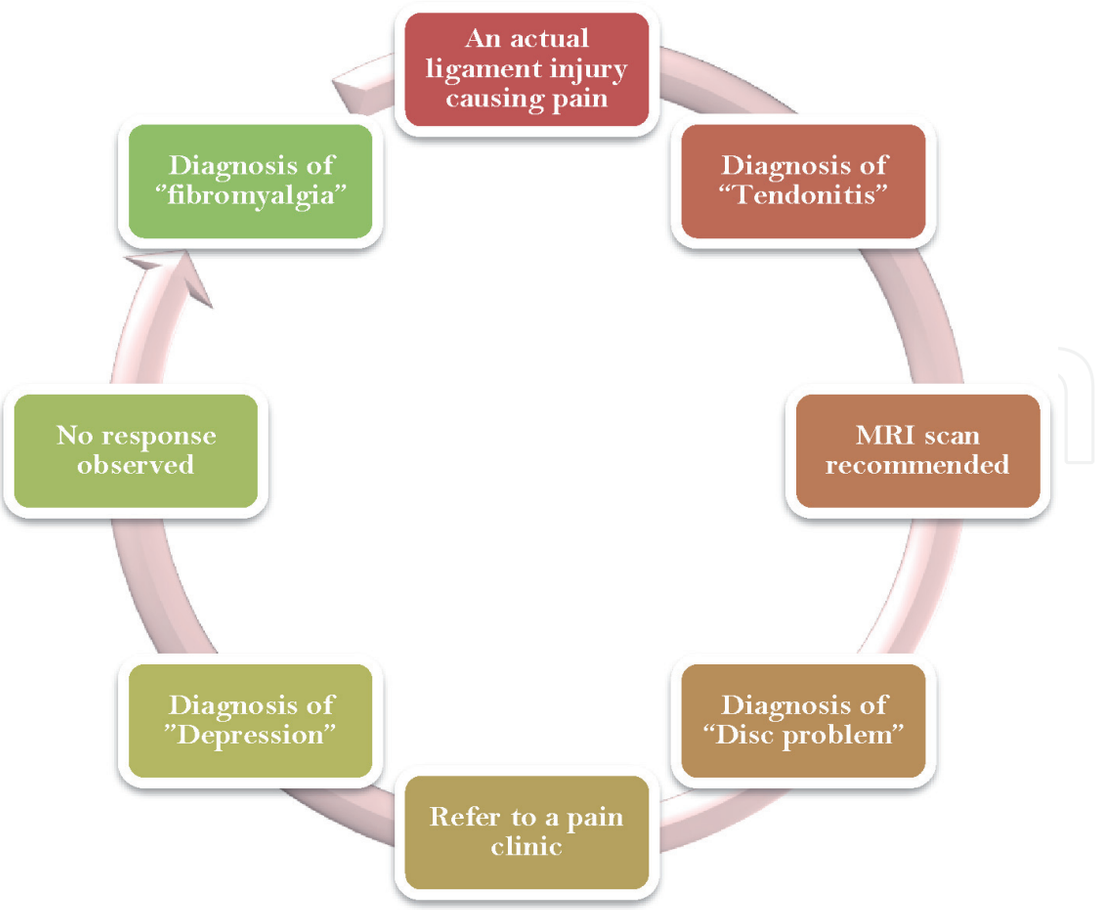

Figure 2.
Progression and diagnosis process of fibromyalgia.

release pro-inflammatory and neuro-sensitizing molecules such as cytokines and chemokines which act as modulators of nociception, and elevated pain sensitivity through their receptors [39–41]. In addition, a growing body of evidence indicated the increased levels of the pro-inflammatory chemokines in both serum and CSF of fibromyalgia patients [42–44]. CSF and IL-17 are also associated with pain, depression, and anxiety which are the key symptoms among the individuals suffering from fibromyalgia [45, 46].

1.2.3 Central sensitization

By far the most important thing to understand about the pain and fatigue induced by fibromyalgia is central pain sensitization. Many nociceptive dorsal root ganglion (DRG) neurons express pro-inflammatory cytokine and chemokine receptors that are upregulated after nerve injury [47]. Long-lasting neuro-inflammation through the upregulation of inflammatory molecules can contribute to the ectopic discharge of sensory neurons, resulting in peripheral sensitization. Prolonged abnormal transmission of pain signaling due to peripheral sensitization triggers central sensitization [48–50], mediated by pain-processing neurons and activation of glial cells (**Figure 3**) [51–54]. Glial cells are activated by various neurotransmitters, such as cytokines, chemokines, and nucleotides and these activated glial cells directly or indirectly involved in central sensitization [10, 55–58]. Moreover, these cells can contribute to brain inflammation and pathogenesis of different brain disorders [59–65].

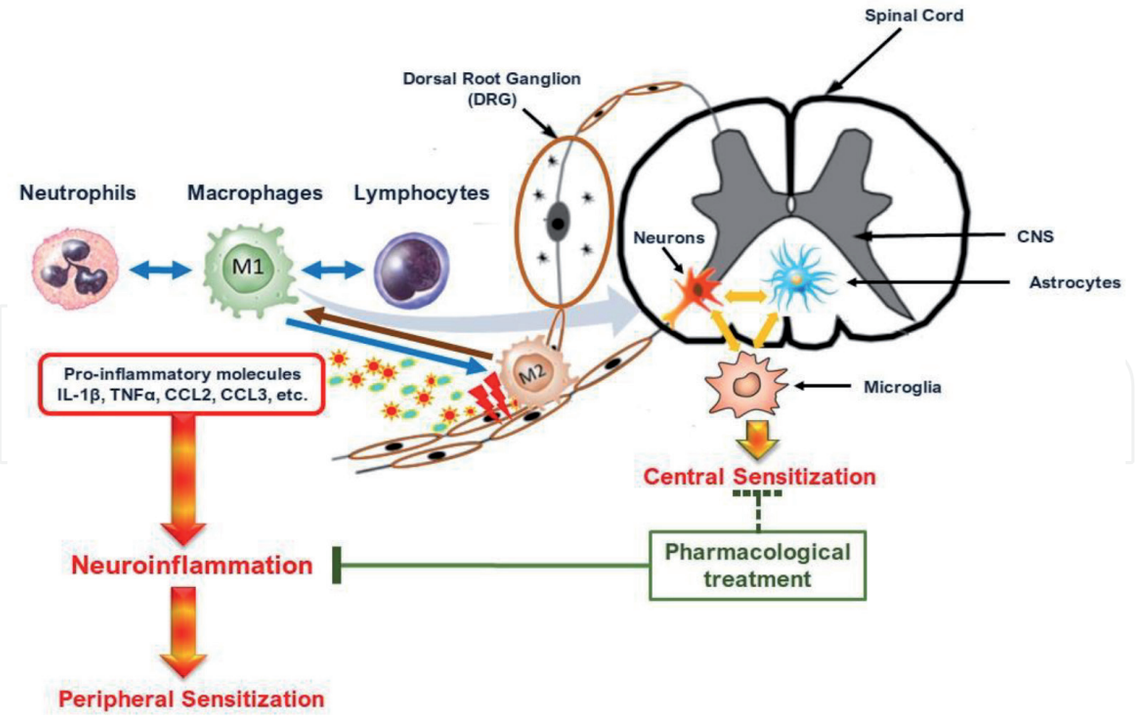

Figure 3.
Contribution of macrophage derived inflammatory response in neuropathic pain in peripheral nervous system.

1.2.4 Fascia

It has been hypothesized that inflammation of fascia is a secondary source of the increased pain transmitting to the spinal cord. Fascia is the thick connective tissue surrounding the cells of the muscles etc. The fascial system covers every part of a muscle and is a thick gel of ground material that suspends muscle cells and fibers [66]. Additionally, muscle innervation is found primarily in the fascia, hence the fascia is highly susceptible. Muscle biopsy, cell studies of FM patients result in higher levels of collagen and symptoms of oxidative stress and tissue damage, indicating fascial inflammation. Although findings were not consistent in considering the hypothesis of fascial inflammation as the fibromyalgia etiology [67]. Conversely, these inflammations may be due to low growth hormone production and HPA axis dysfunction, resulting in increased nociception, central sensitization, and chronic pain [68].

1.2.5 Altered biochemistry

Substance P (SP) is an 11-amino acid peptide IS primarily responsible in the neurotransmission of pain to the central nervous system (CNS). Substance P (SP) is associated with chronic pain found to be elevated with fibromyalgia in the cerebral spinal fluid (CSF) compared to controls [4, 5]. However, the diagnostic study also revealed low neurotransmitter levels involved in regulating sensory perception and also inhibit pain transmission, such as serotonin, norepinephrine, and dopamine, etc.

1.2.6 Nitric oxide synthase (NOS)

Fibromyalgia patients have higher oxidative stress index and lower total nitrite levels than healthy controls [69, 70]. NO plays a crucial role in chronic pain states with

cyclooxygenase-2 (COX-2) as termed in central sensitization [71]. Numerous studies considered NO as an important neurotransmitter involved in the pain and sensitization pathways related to NOS activation. Therefore, the NO can actively participate in the hyper sensitization in patients with fibromyalgia. The NO is synthesized by the nitric oxide synthase (NOS) enzyme which has four isoforms i.e. neuronal nitric oxide synthase (nNOS), endothelial nitric oxide synthase (eNOS), mitochondrial nitric oxide synthase (mtNOS), and inducible nitric oxide synthase (iNOS) [72, 73]. The nNOS, eNOS, and mtNOS are expressed in the majority of the cells. The nNOS and eNOS are regulated by Ca2+ fluxes, whereas iNOS is regulated by cytokines. iNOS is expressed only in response to some pathological stimuli typically bypro-inflammatory cytokines and/or bacterial lipopolysaccharide (LPS) [74, 75]. Inducible nitric oxide synthase (iNOS) together with oxidative stress plays an important role in the development of vascular dysfunction in sepsis. In fibromyalgia, a key mediator of immune activation and inflammation is inducible nitric oxide synthase (iNOS), which produces nitric oxide (NO) [8]. Various studies have revealed the iNOS role in the development of inflammatory and neuropathic pain including fibromyalgia. Nitric oxide (NO) has various physiological functions such as vasodilation, muscle relaxation, learning, memory, neurotransmission, several degenerative processes and inflammation [8]. Copious amount of NO production is critical for the inflammatory response and the innate immune system. Overexpression or dysregulation of iNOS is linked with local inflammatory reactions and contributed to various human diseases [75, 76]. Considering this, iNOS inhibitory therapeutics could be promising for the treatment of neurodegenerative pain including fibromyalgia.

2. Role of activated macrophages/myeloid cells in the neuromyalgia

In turn, mast cells interplay with microglia, which are the resident macrophages of the central nervous system that may contribute to increased inflammation through the secretion of cytokines [59, 77]. The cytoplasmic receptor Nod-like receptor-2 (NOD2), and its adaptor-signaling molecule RIPK2, have been shown to be involved in the development of neuropathic pain after peripheral nerve injury. The activation of NOD2 signaling in peripheral macrophage mediates the

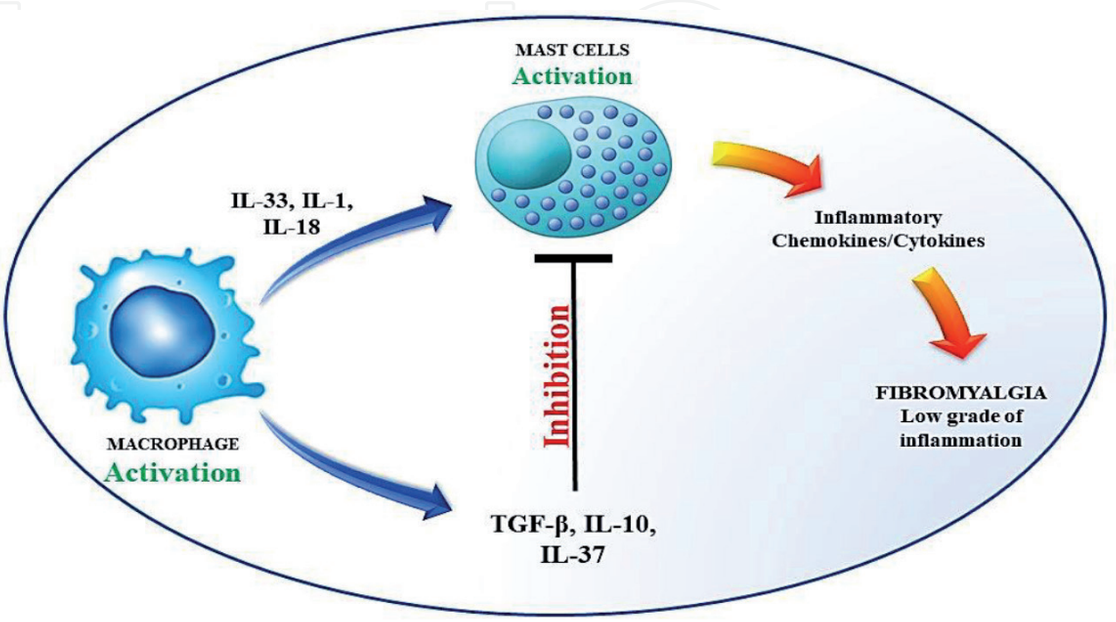

Figure 4.
Pathogenic role of Th1 primed (iNOS+) macrophages and mast cells during progression of fibromyalgia.

development of neuropathic pain through the production of a wide of pro-nociceptive cytokines. The studies strongly suggest the undetermined significance of NOD2 signaling in the development of neuropathic pain and to highlight potential new means of the target for preventing neuropathic pain [78]. Macrophages are important participants in regulating neuro- inflammation (**Figure 4**); consequently, they are considered to be a common peripheral regulator of neuropathic pain [79–81].

3. Current therapies

There is no effective therapeutic approach available for fibromyalgia, but many drugs have been available to reduce its symptoms and pain. Patients suffering from fibromyalgia should integrate pharmacologic therapy with non-pharmacologic therapies [82]. In a study, it has been revealed that multi-component treatment could be effective in the short term for improving key symptoms of fibromyalgia including pain, fatigue, depression, and quality of life [83]. Modern medicine has most certainly come a long way in providing relief from the conditions and diseases of the day, sometimes other options can be just as helpful, if not more beneficial, in providing relief of fibromyalgia symptoms. Moreover, the prescription medications that are commonly used for the treatment of fibromyalgia symptoms can cause negative side effects that the individual must then deal with in addition to the problems along with symptoms of fibromyalgia. In order to regulate inflammation, role of macrophages is very crucial. As we described previously also, macrophages are important to sense damage to the tissue and initiate the recruitment of circulating leukocytes through triggering the chemokines secretion. The direct physical interaction stimulates production of reactive oxygen species (ROS) at the site of the injury. At the late stages of muscle regeneration, macrophages refrain the expression of both pro-inflammatory and anti-inflammatory cytokines and turned to a silenced mode. Conversely, interleukin 4 (IL-4) actions are considered to be regulated by the inhibition of pro inflammatory mediators. In a study, IL-4 blood levels were found reduced among the patients suffering with chronic widespread pain including fibromyalgia when compared with controls [84, 85]. Several study indicating that the endogenous opioid system is essential to the actions of IL-4 and M2 macrophages in pain control [21]. Concluding this, macrophages play a central role in the regulation of inflammation from the beginning to the end. This is a timely area of research to explore the role of macrophages particularly M2 macrophages which sounds more promising for tackling pathological pain.

However, there are some alternative therapeutic approaches to fibromyalgia that have been proven by research to aid in providing relief from its symptoms (**Figure 5**).

3.1 Non-pharmacologic therapy

Patients diagnosed with fibromyalgia must know their illness before starting their medications [86–88]. It was found that educational intervention had significantly better improvement among fibromyalgia patients [82]. In another study, fibromyalgia patients reduce the fear of pain and fear of disease complications using cognitive behavioral therapy [83]. Cardio exercise is suggested for fibromyalgia patients as it helps to improve the sleep and reduce the pain as well [89, 90]. In a study, they uses Chinese stress reduction exercise programs and improvement reported among the fibromyalgia patients to reduce the key symptoms of fibromyalgia [91, 92]. Nutritional supplementation is often used in fibromyalgia, but the objective findings are limited [93, 94]. Coenzyme Q_{10}supplementation in fibromyalgia patients improved the disease symptoms as it reduces the oxidative damage that

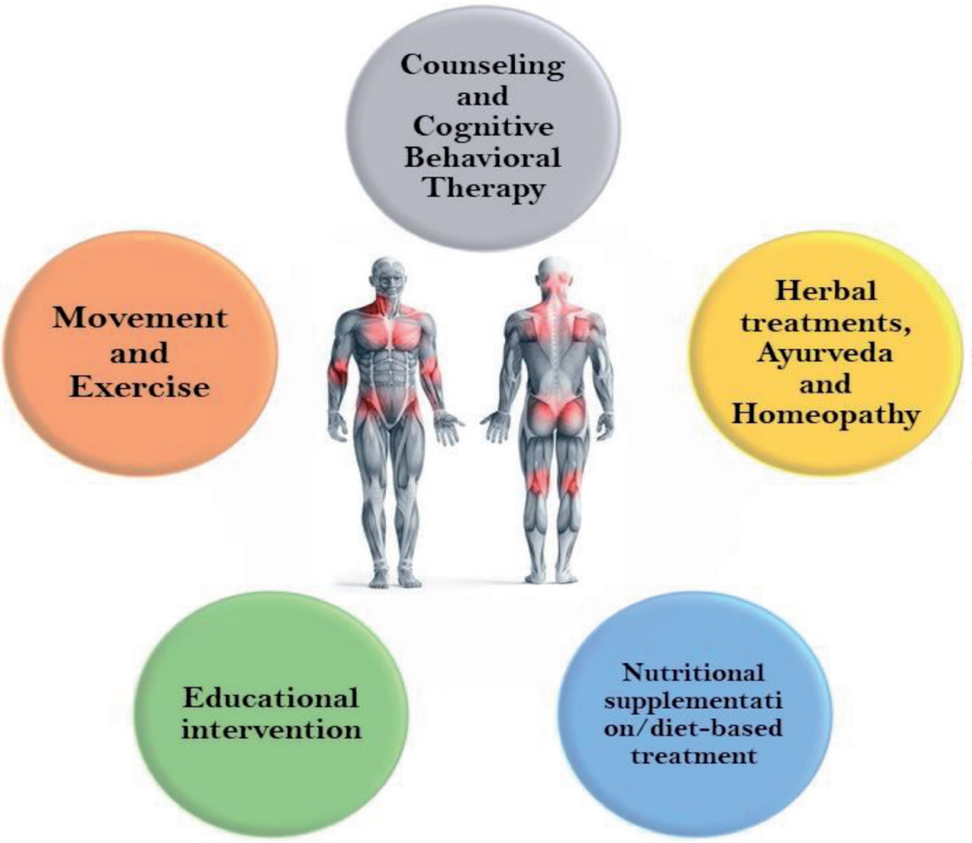

Figure 5.
Effective alternative therapeutic approaches suggested for fibromyalgia patients.

leads to muscle fatigue [95, 96]. Another study revealed that500mg L-carnitine for 20 days has significant benefits to fibromyalgia patients which lasts up to 10 weeks [97]. Natural flavonoids like quercetin and luteolin giving promising results to reduce the key symptoms of fibromyalgia due to its anti-inflammatory, antioxidant, and anti-allergic property [98–101]. Moreover, flavonoids have been discussed as a possible treatment of central nervous system disorders [102, 103].

3.2 Pharmacologic therapy

There's no complete cure available for fibromyalgia, but there are many medicines available to treat fibromyalgia symptoms. Some drugs ease aches, fatigue, and pains, while others may boost your energy or improve your sleep. Fibromyalgia drugs mainly target pain modulatory mechanisms. There is an urgent need to develop new drugs targeting the fibromyalgia mechanism and treat its symptoms (**Table 1**).

4. Immune mediated therapeutic interventions

It is a well-established concept that the immune system plays a crucial role in various chronic pain conditions including fibromyalgia. The immune system involves the release of autoantibodies, pro-inflammatory cytokines, chemokines, substance P, histamine, tumor necrosis factor, interleukins, and prostaglandins [9]. In a study, IL-8 level elevated in the serum of patients suffering from fibromyalgia confirming the relation between fibromyalgia and higher levels of pro-inflammatory cytokines [136]. In another study, the role of the NLRP3 inflammasome in

S.N.	Drug type	Drugs name	Effects on fibromyalgia	Side-effects	References
1.	Antidepressants	Amitriptyline Citalopram,Escitalopram, Fluvoxamine, Fluoxetine, Paroxetine, Sertraline	Improvement in pain, fatigue, and sleep	Drowsiness, Weight gain, Nausea fatigue, Dry mouth, Blurred vision, Constipation, Dizziness, and Change in appetite	[104–107]
2.	Anti-Seizure Medicines	Pregabalin, Gabapentin	Improvement in pain, fatigue, and sleep	Blurry vision, dizziness, Drowsiness, Weight gain, and Swelling of hands/feet	[18, 28, 83, 87, 104, 108–111]
3.	Pain Relievers	acetaminophen and Non-steroidal anti-inflammatory drugs (NSAIDs) like aspirin, ibuprofen, naproxen, and tramadol	Improvement in aches and pains	Heart attack, Stroke ulcers & bleeding in the stomach, Intestines liver damage, Stomach pain, Constipation, Nausea, and Trouble concentrating	[112]
4.	Muscle Relaxants	Cyclobenzaprine (Flexeril) Tizanidine (Zanaflex)	Improvement in pain, fatigue, and sleep	Dry mouth, Dizziness, Blurry vision, Headaches, Chest pain, Nausea, and Fever	[113]
5.	Serotonin inhibitors	Duloxetine, Milnacipran, Reboxetine, Esreboxetine, Citalopram, escitalopram, fluoxetine, paroxetine	Improvement in pain, and depression	Difficulty in sleeping, Headaches, Dizziness, Blurry vision,Constipation/diarrhea, Nausea/vomiting, Dry mouth, and sweating	[104, 105, 114–121]
6.	Gabapentinoid	Pregabalin, gabapentin, Lacosamide	Improvement in pain, fatigue, and sleep	Abnormal eye movements (continuous, & uncontrolled, rolling), Clumsiness, Constipation/ diarrhea, Difficulty speaking, Tiredness, Dry mouth, and Nausea.	[93, 104, 105, 109, 121–124]
7.	Cannabinoid	Nabilone, Dronabinol	Improvement in pain, fatigue, anxiety, and sleep.	Dizziness, Drowsiness, Dry mouth, Feeling "high," Lightheadedness, Headache, and Insomnia	[125–128]
8.	NMDA antagonist	Ketamine	Improvement in pain	High/Low blood pressure, Increased cardiac output, Visual hallucinations, Vivid dreams, and Double vision	[129–132]
9.	Nitrogen-containing bases inhibitors	Methotrexate, Azathioprine, Leflunomide	Improvement in pain	Dizziness, Headache, Tender gums, Decreased appetite, Reddened Eyes, and Hair Loss	[133]
10.	Tumor Necrosis Factor (TNF) inhibitors	Hydroxychloroquine, Adalimumab, Golimumab, Certolizumab, Infliximab, Sulfasalzine and Etanercept	Improvement in pain, and fatigue	Swelling, Redness or itchy skin where your injection was given, A mild nose, throat or sinus infection,Headache, Stomach pain, and Dizziness	[134, 135]

Table 1.
Available pharmacological interventions for fibromyalgia.

fibromyalgia patients along with animal models was investigated. In the outcome of the same study, it has been revealed that increased levels of IL-1b were positively linked with pain in both mice and fibromyalgia patients [137]. This was the first of its kind study to show the relation between inflammasome and increased pro-inflammatory cytokines among the fibromyalgia patients which confirm the direct link between inflammation and pain. Naltrexone and naloxoneisan antagonist of mu-opioid receptors and both were effective to inhibit cytokine expression [138, 139]. Using neuron–glia co-cultures pre-treated with naloxone and subsequently treated with LPS, it was demonstrated that naloxone protects against lipopolysaccharide (LPS)-induced neurotoxicity through the inhibition of the proinflammatory factors and free radicals [139]. Similarly, naltrexone also blocked LPS-induced inflammation and microglial activity and inhibited TNF-α production [139, 140]. Due to the promising preclinical data, clinical trial was conducted for the naltrexone and it has been found that it effectively reduced the key disease symptoms among the fibromyalgia patients [141]. Observational studies provide evidence that vagus nerve activation can down-regulated inflammation through nAChR-mediated inhibition of macrophage function [142–145]. Treatment with nicotine can inhibit the development of inflammatory cytokines release by LPS-stimulated macrophages through the activation of α7 nAChR signaling [143, 144, 146–148]. Following this, anti-inflammatory treatments could be promising in the therapeutics in fibromyalgia condition.

5. Conclusion

Fibromyalgia condition is defined by widespread musculoskeletal pain followed by fatigue, sleep, depression, and anxiety. The available allopathic medicines have their limitations and side effects and to date no permanent treatment of fibromyalgia is available. However, research is going on to find out more alternative options that can be used for treating various chronic conditions. Hence the need of the hour is to explore various alternative therapies for this condition. Despite various research and findings on fibromyalgia, it is found by most of the scientist that this disease is characterized by the abnormal nerve to signal transduction thus "the hypothesis of pain in the brain" is proven here and therefore effective neuronal diagnosis should be conducted before designing the treatment protocols. Thus, the emphasis of treatment must be in-combat with the brain to muscle co-ordinations. It has been well established that the immune system is an important part and plays a key role in the complex pathogenesis of fibromyalgia. Macrophages, inflammatory cytokines, and reactive oxygen species play distinct roles in the inflammatory response. Inducible nitric oxide synthase (iNOS) dysregulation is implicated in a variety of chronic and acute diseases and inhibitors of iNOS show noteworthy results in animal models for septic shock, pain, and other conditions, but failed in clinical trials. Conversely, macrophages play a crucial role to regulate peripheral sensitization, cytokines, and chemokines derived from these cells and are potential novel therapeutic targets. Few studies were conducted in order to explore macrophage therapeutics in the animal model and have been shown to prevent/relieve neuropathic pain, but their efficacy has not yet been evaluated in clinical trials. To move evidence-based interventions into practice, pharmacotherapies that target macrophage-driven neuro-inflammation will undoubtedly open up new avenues for beneficial treatment of intractable neuropathic pain.

Concluding this, further research is required to clarify the role of inflammation and the mechanisms that regulate neuropathic pain in fibromyalgia as well as to shed light on potential therapeutic options.

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Author details

Vishwas Tripathi[1], Amaresh Mishra[1], Yamini Pathak[1], Aklank Jain[2] and Hridayesh Prakash[3]*

1 School of Biotechnology, Gautam Buddha University, Greater Noida, India

2 Centre for Animal Sciences, School of Basic and Applied Sciences, Central University of Punjab, Bathinda, India

3 Amity Institute of Virology and Immunology, Amity University Uttar Pradesh, Noida, Uttar Pradesh, India

*Address all correspondence to: hprakash@amity.edu

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