Review

DOI: 10.14235/bas.galenos.2024.52297
Bezmialem Science 2024;12(2):266-78

Approach to Fibromyalgia and the Role of Phytotherapy in Treatment

Fibromiyaljiye Yaklaşım ve Tedavide Fitoterapinin Rolü

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ABSTRACT

Fibromyalgia (FM) is characterized by chronic widespread pain accompanied by fatigue, poor sleep quality, and numerous accompanying conditions. Its prevalence worldwide is around 2.7%, and it is more common in women. Although its epidemiology and pathophysiology cannot be precisely explained, it is known that various factors coexist. Over the years, guidelines containing various criteria have been established for the diagnosis of the disease. The goal of treatment in FM is to improve the patient's quality of life and minimize symptoms as much as possible. The success of treatment in FM is limited. Many patients seek alternative treatment methods, including diet and lifestyle changes. Recently, medical nutritional therapies and phytotherapy products have been at the forefront of research in this area. Phytotherapy products can be added alone or in combination with other treatment methods and can enhance the success of treatment. In this article, the epidemiology, pathophysiology, diagnostic methods, pharmacological and non-pharmacological methods used in the treatment of FM syndrome will be discussed, and the most widely used phytotherapeutic products will be addressed.

Keywords: Fibromyalgia, phytotherapy, pharmacological treatments, non-pharmacological treatments, etiopathogenesis

ÖZ

Fibromiyalji (FM), kronik yaygın ağrının yanı sıra yorgunluk, kötü uyku kalitesi ve çok sayıda eşlik eden hastalıkla karakterizedir. Dünya çapında yaygınlığı %2,7 civarındadır ve kadınlarda daha sık görülür. Epidemiyoloji ve patofizyolojisi kesin olarak açıklanamamakla birlikte çeşitli etmenlerin birliktelik gösterdiği bilinmektedir. Hastalığın tanısı için yıllar boyunca çeşitli kriterleri içeren kılavuzlar oluşturulmuştur. FM tedavisinde amaçlanan hastanın yaşam kalitesini artırmak, semptomları mümkün olduğunca azaltmaktır. FM'de tedavinin başarısı sınırlıdır. Birçok hasta diyet ve yaşam tarzı değişiklikleri de dahil olmak üzere alternatif tedavi yöntemleri aramaktadır. Bu noktada son zamanlarda araştırmaların odağında tıbbi beslenme tedavileri ve fitoterapi ürünleri yer almaktadır. Fitoterapi ürünleri tek başına ya da kombine şekilde diğer tedavi yöntemlerine eklenebilmekte ve tedavinin başarısını artırabilmektedir. Bu yazıda FM sendromunun epidemiyolojisi, patofizyolojisi, tanı yöntemleri, tedavide kullanılan farmakolojik ve non-farmakolojik yöntemlere değinilecek ve en çok kullanım alanı bulan fitoterapötik ürünler ele alınacaktır.

Anahtar Sözcükler: Fibromiyalji, fitoterapi, farmakolojik tedaviler, non-farmakolojik tedaviler, etiyopatogenez

1. Definition of Fibromyalgia

Fibromyalgia (FM) is a syndrome characterized by chronic musculoskeletal pain. The main symptoms of this disease are muscle and joint stiffness, insomnia, fatigue, mood disorders, cognitive dysfunction, anxiety, depression, general sensitivity, and inability to adequately perform normal daily activities. FM is also associated with specific diseases such as infections, diabetes, rheumatic, psychiatric or neurological disorders. There are similarities with neuropathic pain in terms of clinical findings, pathophysiology and neuropharmacology. Although FM is not a musculoskeletal system disease, most of the symptoms occur in this system (1,2). It is known that hypersensitivity is observed in some anatomical areas called tender points in FM syndrome

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Received: 22.04.2024
Accepted: 22.04.2024

Cite this article as: Akçakaya A. Approach to Fibromyalgia and the Role of Phytotherapy in Treatment. Bezmialem Science 2024;12(2):266-78

(3,4). FM, which was initially perceived primarily as a rheumatic disorder, is now recognized as a pain processing disorder and central nervous system sensitization (5,6).

2. Epidemiology and Etiology

It has been stated that the prevalence of FM is between 0.2% and 6.6%, 2.4% to 6.8% in women, 0.7% to 11.4% in urban areas, and 0.1% to 5.2% in rural areas (7). Although the incidence varies depending on the diagnostic criteria used in a prevalence study; it was found to be 3.6-5.6% in Türkiye, 2.64% in Europe and 2.7% worldwide (8,9). Studies on FM report that it is 9-10 times more common in women than in men (2,10).

Although the etiopathogenesis of FM syndrome is not clear, its causes include genetic, neurological, psychological, sleep-related factors and immunological factors (2,11).

Various hypotheses have been put forward about the emergence of the disease. There are studies revealing the relationship between immune system disorders, sleep disorders, neuroendocrine disorders, peripheral and central nervous system abnormalities and FM symptoms; however, the findings of these studies are not sufficient to determine the mechanism of formation of the disease (2,4,12,13).

2.1. Genetic Factors

The heritability of FM is estimated to be approximately 50%, indicating that genetics has an important role in etiopathogenesis (14). The probability of having FM in first-degree relatives of patients with FM is 8 times higher than in the healthy population (15). However, it has been observed that the risk of any sensitivity and chronic pain in family members of patients with FM is higher than healthy controls (16). Recent genetic studies focus on specific gene polymorphisms, especially in the serotonergic, dopaminergic and catecholaminergic systems. In patients with FM, it has been shown that the disease is worse in those carrying serotonin transporter, dopamine 4 receptor, serotonin 5-HT2A receptor (T/T phenotype) and catecholamine o-methyl transferase polymorphisms and gene alleles with increased monoamine oxidase activation (4,17). The *TRPV2* gene was found to be responsible for the decrease in pain threshold in FM (18). A study by D'Agnelli et al. (19) shows that potential candidate genes associated with FM are SLC64A4, TRPV2, MYT1L, and NRXN3, and a gene-environment interaction involving epigenetic changes is suggested as a triggering mechanism. Additionally, it has been shown that FM exhibits a hypomethylated DNA pattern in genes related to stress response, DNA repair, autonomic system response, and subcortical neuronal abnormalities (19).

In a study investigating the risk of FM in siblings, the risk of recurrence in siblings was found to be 27%, and in this study, a genome scan was performed and a suggestive link to FM was shown in a region on chromosome 17p11.2-q11.2. The best signal was found to be at the D17S2196 mark on chromosome 17p11.2-q11.2 (20).

2.2. Endocrine Factors

FM is more common among women than men (2). Although the reasons behind this gender dominance are not fully understood, they may include hormonal, genetic, and psychosocial factors (21). Hormonal fluctuations, especially during reproductive periods such as menopause, are thought to affect the severity and prevalence of symptoms in women. In one study, pain was found to be most severe on days when progesterone level was low and cortisol level was high. Additionally, an inverse relationship has been detected with testosterone level (2).

Recently, emphasis has been placed on the relationship between FM and sex hormones. Studies have shown that there is a relationship between estrogen and substance P, and serotonin, and that these two neurotransmitters are modulated by estrogen in the brain (22,23). It is thought that neuroendocrine disorders caused by dysregulation of the hypothalamo-pituitary-adrenal (HPA) axis may be related to the etiopathogenesis of FM (2,12). In another study, it was found that the low cortisol level in patients with FM was more pronounced in patients with high depression scores (9,24).

Circulating somatomedin C levels were found to be lower in patients with FM compared to the control group. Low somatomedin C levels cause persistent impairment of growth hormone (GH) secretion and, as a result, cause dysregulation in the HPA axis response and a decrease in GH secretion (9,25).

2.3. Neurotransmitter Dysregulation

Neurotransmitter dysregulation is important in the pathophysiology of FM and affects the processing of pain signals in the central nervous system. Several neurotransmitters, such as serotonin, norepinephrine, and dopamine, play a role in the altered pain perception observed in patients with FM (26). Low serotonin levels have been observed in patients with FM, and a positive and significant relationship has been found between serotonin levels and tender points (2). Dopamine has been associated with mental disorders frequently observed in FM.

It has been determined that dopamine, norepinephrine and serotonin levels decrease in the cerebrospinal fluid in patients with FM, while glutamate and substance P levels increase. It has been shown that abnormal pain perception related to FM is associated with increased substance P levels and low serotonin levels (27). Although low serotonin causes a decrease in pain threshold, it may also shed light on the relationship between FM and sleep and cognitive disorders (9,28).

2.4. Immunological Factors

Emerging evidence suggests that abnormalities in immune function, including immune system dysregulation and increased levels of inflammatory cytokines, may contribute to the pathophysiology of FM (29).

In addition, the fact that FM frequently accompanies autoimmune diseases suggests that there may be an immunological factor in its etiology (30). FM is common in autoimmune diseases such as

rheumatoid arthritis, systemic lupus erythematosus, and Sjögren's syndrome. It has been observed that tumor necrosis factor-α, interleukin (IL)-8, and IL-10 levels are high in patients diagnosed as having FM, and a correlation has been found between these cytokine levels and other FM symptoms, especially pain (5,9,17). The fact that FM may develop after human immunodeficiency virus, coxsackie virus, and parvovirus infection suggests that there may be an immunological mechanism in the etiology (31).

2.5. Psychiatric Disorders and Sleep Disorders

There are studies arguing that psychiatric disorders exist in patients with FM before diagnosis and accompany them throughout life (9,32). Psychiatric disorders are more common in FM compared to other rheumatic diseases. The most common psychiatric diseases were found to be depressive disorder (20-80%) and anxiety disorder (13-65.8%) (2,33). It has been found that pain sensitivity increases even more in patients with FM with depressive symptoms (34). It has been determined that abnormalities in alpha and delta wave patterns in deep sleep are common in sleep disorders in patients with FM (35). It has been observed that poor sleep quality is associated with increased both pain intensity and fatigue (5,12). The most common sleep-related complaints in patients with FM are daytime sleepiness, frequent awakenings, nocturnal restlessness, and involuntary leg movements (36). It has been observed that sleep disturbance affects the pain threshold, but there is a mutual interaction between pain and the sleep process (9,12,37).

2.6. Central Sensitization

Central sensitization has an important place in understanding the amplification of pain signals in FM. This involves an abnormal response of the central nervous system to stimuli, leading to an exaggerated and prolonged experience of pain. Changes in the function of N-methyl-D-aspartate (NMDA) receptors are associated with imbalances in excitatory and inhibitory neurotransmitter systems (38).

2.7. Concomitant Conditions

FM often occurs with other medical and psychiatric conditions, reflecting the complex and interconnected nature of the syndrome (2). Rheumatic diseases, psychiatric disorders, chronic fatigue syndrome and sleep disorders may occur together with FM (39). Additionally, a link has been found between obesity and increased risk, development and severity of symptoms.

3. Pathophysiology of Fibromyalgia

Although the pathophysiological factors of FM are not well known, it is thought to be related to a pain processing problem in the brain. In many cases, patients become hypersensitive to pain. Constant hypervigilance to pain is also associated with psychological problems (40). The main changes observed in FM are dysfunction in mono-aminergic neurotransmission. It leads to an increase in the levels of excitatory neurotransmitters such as glutamate and substance P and a decrease in the levels of serotonin and norepinephrine at the level of descending anti-nociceptive pathways in the spinal cord. Other abnormalities observed are dopamine dysregulation and altered activity of endogenous cerebral opioids. Taken together, these components appear to explain the central pathophysiology of FM (41).

Peripheral abnormalities may contribute to increased nociceptive tonic support in the spinal cord, resulting in central sensitization. Other factors that appear to play a role in the pathophysiology of FM are neuroendocrine factors, genetic predisposition, oxidative stress, and environmental and psychosocial changes.

Chronic pain is defined as pain that lasts longer than three months or is recurring. In chronic pain syndromes, pain is usually the only complaint. In syndromes such as FM or non-specific low back pain conditions, chronic pain may be perceived as a disease in itself and described as "chronic primary pain". Although the exact pathogenesis is still unclear, this type of pain persists despite receiving adequate treatment and in the absence of any signs of inflammation, prompting the search for evidence of central sensitization. It is now clear that FM is related to neural hypersensitization and reduced conditioned pain modulation (42). Patients with FM have a lower pain threshold, resulting in a generalized state of hyperalgesia and/or allodynia. This indicates that there may be an increase in pain or a problem with sensory processing in the central nervous system.

Various studies have revealed findings indicating neurological damage (43). Clinical studies based on functional magnetic resonance imaging (fMRI) have confirmed a central neuronal change in nociceptive processes. In particular, following the same amount of pressure stimulation, patients with FM have greater neuronal activation in pain processing areas of the brain than control subjects (44). Subtle differences in fMRI results in studies of FM or other chronic pain conditions are due to the fact that the pain-triggering stimulus is not normalized and therefore the intensity may differ with each scan. fMRI studies have also been useful in determining the role of psychological factors in pain processing in FM and in examining the degree of connectivity between various brain regions (45). The degree of connection between these regions depends on the intensity of spontaneous and continuous pain (46). For example, in patients with FM, a decrease in the connection between anti-nociceptive areas in the brainstem is observed following a painful stimulus. Additionally, increased glutamate levels have been observed in the brains of FM patients in clinical studies. When proton magnetic resonance spectroscopy was used, it was stated that these levels increased in the main areas of pain processing such as the insula (47,48).

Increasing evidence shows that neurogenic inflammatory processes occurring in peripheral tissues, spinal cord and brain are also responsible for the pathophysiology of FM (49). In fact, the release of biologically active agents such as chemokines and cytokines leads to the activation of the innate and adaptive immune system. All of these correspond to many of the peripheral clinical features reported by patients with FM, such as swelling and dysesthesia, and these may also affect central symptoms such as cognitive changes and fatigue. Additionally, physiological mechanisms related to stress and emotions are thought to be upstream drivers of neurogenic inflammation in FM (50).

The role of stress in exacerbating FM symptoms has been widely described epidemiologically, both through self-reports and clinical surveys. Despite the inconsistency between different studies regarding possible changes in plasma cortisol levels in patients with FM, dysregulation of circadian variation is frequently observed. In particular, a flattening of the plasma cortisol concentration curve is observed during the day. In addition, decreased cortisol secretion in response to adrenocorticotropic hormone tests has also been described. The HPA axis involves neurotransmitter and neuroendocrine response systems to stress and may be activated in FM. This system may explain some of the symptoms seen in FM (51,52).

4. Diagnostic Biomarkers

The diagnosis of FM is currently based solely on a complete clinical evaluation.

Among the 1990 American College of Rheumatology (ACR) FM Syndrome Diagnostic Criteria; The criteria for widespread chronic body pain (ongoing for at least 3 months) and tender points (pain in at least 11 of the 18 defined tender points) were changed in 2010. In the 2010 ACR diagnostic criteria, tender point examination was abandoned and instead of a symptom-based evaluation, a common pain index and symptom severity scale (SSS) that patients filled out themselves were developed. The first diagnostic criteria were as follows;

1. Widespread pain index (WPI) ≥7, SSS ≥5 or WPI: 3-6 and SSS ≥9,

2. Chronic symptoms (>3 months),

3. There is no other disease that can explain the pain.

Later, in 2016, the 2010 ACR diagnostic criteria were renewed, and the areas of pain evaluated in the WPI were divided into regions, and pain in at least 4 of these 5 regions was added to the diagnostic criteria. These 5 regions are as follows: upper right region, lower right region, upper left region, lower left region, axial region. The presence of other painful disorders does not exclude this diagnosis (2,5,53-55).

Individual phenotypic variability and the coexistence of other pathologies make clinical examinations inadequate for definitive diagnosis, making it impossible to decide on universal criteria for this disease. Moreover, specific biomarkers are not yet available, and therefore research has been directed towards the search for new indicators for the objective diagnosis of affected individuals through the identification of genetic, environmental and epigenetic factors underlying the pathophysiology of FM.

There is great interest in using a simple blood test to diagnose FM. Therefore, various attempts have been made to identify unique serological markers. These findings, as well as genetic testing, are often contradictory, and no clinical tests have been confirmed to date (34). Among the parameters to be checked for diagnosis: autoantibodies (antipolymer antibody, antiserotonin, antiganglioside and antiphospholipid), neuropeptides (plasma neuropeptide Y and substance P), inflammatory cytokines (IL-8), glutamate.

Various functional neuroimaging techniques and studies show measurable changes in patients with FM. One of the first functional neuroimaging techniques to be used to study FM was single photon emission computed tomography (SPECT). This method provides measurement of regional cerebral blood flow (rCBF), which reflects neural activity in the brain following the injection of a radioactive tracer. Similar to SPECT, positron emission tomography (PET) uses radioactive tracers but has higher temporal and spatial resolution. fMRI, which has higher temporal and spatial resolution than SPECT or PET, provides more accurate results in both of these areas (56).

5. Clinical Findings

The most common symptom at presentation is chronic musculoskeletal pain. Pain is usually present on both sides of the body, above and below the waist, and along the spine (57,58). It may be in the form of widespread body pain or it may be regional. Patients may describe the pain as burning, aching, or stinging. Stressors, comorbidities, chronic fatigue, and temperature changes are among the factors that worsen pain (59).

Another common symptom is fatigue. There is a state of deep fatigue, especially in the morning, that often continues throughout the day, regardless of the amount or quality of sleep (2,60). Sleep disorders are common. Difficulty falling asleep, frequent awakenings, deterioration in sleep quality, and feeling unrested are often observed (59). Most of them have paresthesia complaints such as numbness and tingling in any part of the body, often in the extremities (61). It is thought that the cognitive disorders seen in FM are often associated with chronic pain (62). Cognitive complaints such as forgetfulness, inability to concentrate, and difficulty finding words are common, and this condition is called "fibro fog" (2,63). Patients may also experience a variety of other symptoms, such as headache, irritable bowel syndrome, temporomandibular joint disorders, anxiety, and depression (64-66).

6. Differential Diagnosis

The first things that come to our mind in differential diagnosis are; rheumatic diseases such as myofascial pain syndrome, chronic fatigue syndrome, rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis, polymyalgia rheumatica, Sjögren's syndrome, myositis, chronic viral infections, osteoarthritis, pain of psychogenic origin, hypothyroidism, depression and neuropathies (67,68).

7. Treatment

The aim of FM treatment should be to improve the patient's quality of life, reduce symptoms as much as possible, and enable the patient to perform daily activities. There is no treatment method that completely eliminates the symptoms or provides complete recovery. Although there is no single effective treatment method for this disease, of which etiology is multifactorial,

a multidisciplinary treatment approach is applied in clinical practice by using both drug and non-drug treatment methods (69).

7.1. Non-pharmacological Treatment Methods

Exercise, cognitive behavioral therapy, occupational therapy, hyperbaric oxygen, acupuncture, massage, yoga, tai chi, and aerobics have been found effective in relieving symptoms.

Lifestyle changes such as regular, low-impact exercise, walking, swimming or cycling, creating a comfortable sleeping environment and maintaining good sleep hygiene, stress management, deep breathing exercises, a balanced diet, reducing caffeine or avoiding certain trigger foods are recommended for patients.

7.2. Pharmacological Treatment Methods

Pharmacological treatment options with proven effectiveness in the treatment of FM;

- Painkillers; Paracetamol is the most used. Non-steroidal anti-inflammatory drugs (NSAIDs) reduce inflammation and pain but have limited effectiveness.

- Seratonin reuptake inhibitors (SSRI); medications such as fluoxetine (Prozac), sertraline (Zoloft), paroxetine (Paxil), fluvoxamine (Luvox), and escitalopram (Lexapro).

- Seratonin noradrenaline reuptake inhibitors (SNRI); Effective dose of duloxetine is 60 mg. Milnacipran relieves pain and improves mood.

- Tricyclic antidepressants (TCA); Amitriptyline and nortriptyline are used to improve sleep patterns and reduce pain.

- Tramadol is an opioid pain medication used to treat moderate to moderately severe pain.

- Antiepileptics (pregabalin and gabapentin); Pregabalin shows its anxiolytic, analgesic and antiepileptic effects by binding to calcium channel receptors of presynaptic neurons in the brain and reducing the release of neurotransmitters such as substance P and glutamate. It reduces neuropathic pain and improves sleep patterns.

- Muscle relaxants; Cyclobenzaprine relieves muscle spasm and improves sleep quality

- 5-HT3 receptor antagonists; Treatments such as Dolasetron, Granisetron, Ondansetron, Tropisetron and Palonosetron are also used.

However, the 3 drugs that received FDA approval are Pregabalin, Duloxetine, and Milnacipran (70).

7.3. Phytotherapy and Supportive Treatments in Fibromyalgia

7.3.1. Herbal Ingredients

7.3.1.1. Capsaicin

Latin name: *Capsicum annuum L.*

Active ingredient: Capsaicinoids

Mechanism of action: Capsaicin is an alkaloid substance that gives red hot pepper its hotness. It is thought that capsaicin blocks the transmission of pain signals by affecting nerve endings. Capsaicin is a vanilloid derivative of vanillic acid and interacts with receptors located in peripheral nerves. Vanilloid receptor-1, to which capsaicin binds, shapes the flow of sodium, potassium and calcium into the cell, causing depolarization in the neuron and the secretion of neurotransmitters. Studies have been conducted to clarify that capsaicin has a direct relationship with the sensation of pain. Capsaicin is included in the group of painkillers that act through primary sensory neurons. It has been reported that by eliminating the sensitivity of these neurons, they can be used in posthepatic neuropathy, diabetic and other neuropathic pain.

Scientific studies:

In a randomized controlled study, the effectiveness of local application of 0.025% capsaicin in the treatment of FM was tested compared to placebo cream. Forty-five patients were randomly selected into groups so that capsaicin, control and placebo groups could be examined comparatively. After 4 weeks of this double-blind treatment, patients were evaluated for pain, tenderness, and sleep quality. Pain and sleep quality were assessed using a visual analogue scale (VAS), while tenderness was measured using a dolorimeter. A significant improvement in sensitivity has been associated with capsaicin. However, no improvement in pain or sleep quality was seen (71,72).

7.3.1.2. Chlorella

Latin name: *Chlorella pyrenoidosa*

Active ingredient: In addition to high levels of provitamin A, protein, vitamins, minerals, monosaccharides, polysaccharides, agar and antioxidants.

Mechanism of action: It is a single-celled green algae that grows in freshwater sources. It has the highest chlorophyll content among known plants and also contains high concentrations of many vitamins and minerals, as well as fiber, nucleic acids, amino acids, enzymes and other substances. Chlorella is generally known to have antioxidant properties. Antioxidants help protect cells against damage from oxidative stress. Conditions such as FM have been linked to increased oxidative stress. For this reason, Chlorella is used as a treatment support with its antioxidant properties.

Scientific Studies

Nutritional supplementation with *Chlorella pyrenoidosa* was associated with improvement in FM symptoms in two studies by the same research group. In the first study, an uncontrolled open-label study, participants with FM supplemented their diet with 10 g of Chlorella and 100 mL of Chlorella extract daily for 2 months. The average number of tender points decreased significantly.

In a larger, well-designed, randomized placebo-controlled, double-blind crossover clinical trial in 37 patients with FM, a

significant reduction in the number of tender points was observed in the treatment group. When this decrease was compared to the slight increase in the placebo group, a significant increase in function was also observed (73,74).

7.3.1.3. Ganoderma (Reishi Mushroom)

Latin name: *Ganoderma lucidum*

Active ingredient: Triterpenoids, polysaccharides and proteoglycans

Mechanism of effect: Ganoderma lucidum is a type of mushroom commonly known as the "mushroom of immortality" and has medicinal properties such as strengthening effects, increasing life energy and strengthening heart function. Ganoderma has been used in traditional Chinese medicine for thousands of years to promote health, lasting youth, vitality and longevity. Modern medical studies have shown that this mushroom has a wide range of bioactivities, including anti-inflammatory, anti-oxidant, anti-glycemic, anti-ulcer, anti-cancer and immunostimulatory effects. Ganoderma has also been used in the treatment of various chronic diseases such as hepatopathy, nephritis, hypertension, arthritis, migraine, insomnia, bronchitis, asthma, diabetes and cancer (75).

Scientific studies: One randomized, double-blind clinical study evaluated the effect of Ganoderma Lucidum supplementation on physical performances in patients with FM. Sixty four women with FM were divided into two groups to receive 3 grams of G. Lucidum twice daily (n=32) or 6 grams of C. siliqua daily (n=32). At the end of the study period, an improvement in aerobic endurance, walking speed, and body flexibility (chair sit-and-reach test, 6-minute and 20-minute walk test) was observed in patients with FM over 6 weeks (76).

7.3.1.4. Turmeric

Latin name: *Curcuma longa L.*

Active ingredient: Curcuminoids

Mechanism of action: Anti-inflammatory, antioxidative, antinociceptive.

It has been found in *in vivo* and *in vitro* studies that the anti-inflammatory effect is due to the curcumin substance found in plant rhizomes. It limits the expression of 5-lipoxygenase and COX-2, an enzyme that plays a role in most inflammations, and inhibits thromboxane B2, suppresses the activation of the transcription factor NF-kB, TNF, IL-1, IL-6, IL-8. It has been noted that it limits the expression of inflammatory cytokines such as and chemokines and many cell surface adhesion molecules associated with inflammation, and therefore shows anti-inflammatory activity. Curcuma longa is considered to be the most effective compounds in reducing pain in osteoarthritis in the short term.

Scientific studies: Turmeric is one of the most common herbs proven to provide relief from the chronic pain of FM. Its mechanism-based effectiveness in neuropathic pain has been demonstrated in many experimental models (77).

7.3.1.5. Ginkgo Biloba

Latin name: *Ginkgo biloba L.*

Active ingredient: Flavonoids and terpenic lactones.

Mechanism of action: It has been suggested that some of the symptoms of FM may be due to the excessive presence of oxygen-derived free radicals. These are known to trigger pain and inflammation and impair muscle function. Ginkgo biloba extract has antioxidant properties, which may explain some of its benefits (78).

How to use: For 1 cup of tea, add 1 teaspoon of leaves to water and brew for 5-10 minutes. It becomes drinkable after brewing. If it is to be used as ready-made herbal tea, a glass of hot water should be added to the herbal tea and it should be consumed after brewing for 5 minutes.

When it is brought into capsule or tablet form as an extract, 1-2 capsules are consumed per day in determined doses. When consumed as tea, it is recommended to drink 1-2 cups a day.

7.3.1.6. Saffron

Latin name: *Crocus Sativus L.*

Active ingredient: Crocin, picrocrocin, safranal.

Mechanism of action: Saffron shows similar efficacy to SSRIs and TCAs in treating depression, with a good safety profile as reported in previous studies.

Scientific studies: In a double-blinded study, Shakiba et al. (79) compared the effectiveness of Crocus Sativus (saffron) with duloxetine in patients with FM, in which groups received 15 mg *Crocus Sativus* or 30 mg duloxetine for a total of 8 weeks, starting with one capsule per day in the first week and two capsules per day after the second week. As a result of a randomized control study, *Crocus sativus* showed comparable effectiveness in the treatment of FM (79).

In the study conducted by Barmaki et al. (80) to evaluate the effectiveness and safety of a herbal treatment compared to the current therapeutic regimen in patients with FM, all conventional treatment was continued for a 6-month follow-up. As a result, a therapeutic effect was detected on fatigue, emotion and social life, and disease-related depression in patients with FM receiving conventional treatment, according to the Fib-19-01 evaluation (80).

7.3.1.7. Devil's Claw

Latin name: *Harpagophytum procumbens*

Active ingredient: Harpagofitum iridoid glycosides, phytosterols, aromatic acids and flavonoids

Mechanism of action: This herb is a well-known traditional treatment for joint pain and has recently gained attention for its role in relieving muscle pain.

Scientific study: Scientific research has also found that Devil's claw has favorable benefits compared to NSAIDs, in fact, it is a better alternative treatment (81). In a trial designed to test this herb's ability to relieve muscle pain, low doses of devil's claw showed improvement in pain over a four-week period.

Devil's claw has no significant side effects, but it may interact with warfarin. High doses of devil's claw may cause gastric disorders. It is not recommended for pregnant or breastfeeding women (82).

7.3.1.8. Grape Seed Extract

Latin Name: *Vitis vinifera*

Active ingredient: Proanthocyanidin and resveratrol.

Grape seed extract (GSE), rich in polyphenol groups, is a natural plant derivative that is often produced as a waste byproduct in the winemaking process. The oil of wine grape seeds contains natural anti-inflammatory compounds such as powerful antioxidants, procyanidins, anthocyanins, and gallic acid. Neuroprotective, antioxidant and anti-inflammatory effects have been reported in in vitro and animal studies (83).

Mechanism of action: Anti-inflammatory.

GSE can be consumed in liquid form, as an addition to the nutrition program, through tablets or capsules.

Scientific studies: Fujishita et al. (84) showed that Koshu grapes (rich in higher polyphenol and procyanidin oligomer) reduced H_2O_2-induced neuronal cell death by upregulating IL-6, COX-2, and IL-1a in astrocytes with oxidative stress states, suggesting the neuroprotective effect of GSE.

Regarding FM-like symptoms in animals, Mun et al. (85) reported that oligomeric proanthocyanidin complex (OPC) administration had anti-hyperalgesic effects in an acidic saline animal model mimicking FM due to the antioxidant and anti-inflammatory properties of OPC. In the same animal study, they found that the expression of ASIC3, an ion-sensing channel located in the central and peripheral nervous systems, was reduced in the M1 and M2 brains of hyperalgesic animals (85).

In a double-blind, randomized, crossover study comparing three doses of anthocyanidins and placebo, anthocyanins were found to have small but significant results at a dose of 80 mg/day in patients diagnosed as having moderate to severe FM for three months. Patients showed significant decreases in their sleep disturbances and fatigue levels from the first month to the last month of treatment. The recommended daily anthocyanin dose has been increased from 40 mg/day to 80 mg/day due to the optimal benefits seen at this dosage level. Although the results are encouraging, further research is needed due to the small number of experiments (n=12) (86).

7.3.1.9. White Willow Bark

Latin name: *Salix alba*

Active ingredient: Salicin

Mechanism of action: Anti-inflammatory

Willow bark extract is one of the first examples of modern drug development from herbal medicine. It is derived from the willow tree, also known as salix, and is often standardized with salicin; but may also contain other salicylates as well as flavonoids and polyphenols. It has been used for thousands of years for its antipyretic, analgesic and anti-inflammatory effects. The active substances of willow bark extract inhibit COX-2-mediated prostaglandin E2 release and the release of IL-1β and tumor necrosis factor-α (87). This herb acts by reducing inflammation in the body. Salicin, the active ingredient in this herb, lowers fever and reduces inflammation, which in turn relieves pain. It reduces the level of prostaglandins.

Scientific studies: In the open, multicenter observational study of Beer and Wegener (88) with reference treatment; 90 patients received standardized willow bark extract preparation, 41 received standard treatment, and 8 patients received a combination of the two. The tablet containing 60 mg salicin was given twice a day. At the end of the 6-week treatment and follow-up period, it was stated that willow bark extract was at a level comparable to standard treatments without side effects (88).

How to use: It is recommended to add 3 cups of water to a tablespoon of dried white willow bark, boil it well, then squeeze 5 drops of lemon and consume it as a cup of tea during the day.

Expected side effects and conditions when it should not be used: Willow bark is not recommended for people using anticoagulant therapy and may cause gastric disorders in high doses. White willow bark should not be used by people who are allergic to Aspirin.

7.3.1.10. Corydalis

Latin name: *Corydalis alpestris*

Active ingredient: Corydalis, dehydrocorybulbine (DHCB)

Mechanism of action: Corydalis family is a medicinal plant widely used in Chinese herbal medicine. It is mostly used to treat pain and often in combination with other herbs.

Recently, corydalis has attracted attention as a possible treatment for FM due to DHCB compound found in the root of the plant. DHCB is an alkaloid believed to have non-opioid analgesic properties. Synthetic DHCB is used to demonstrate that it is effective in relieving thermally and chemically induced acute pain and persistent tonic pain of inflammatory origin. It is effective at doses that do not induce sedation and produces an antinociceptive response similar to that obtained with high doses of morphine. Additionally, DHCB is effective in relieving neuropathic pain caused by injury. Since the antinociceptive effects of DHCB have been demonstrated in both the acute and inflammatory phases of the formalin assay, its activity may result from direct effects on the central nervous system (89-91).

How to use: Corydalis is commercially available as a whole plant or in granule, tincture and capsule form.

7.3.1.11. Ginseng

Latin name: *Panax ginseng Meyer*

Active ingredient: Ginsenoside

Mechanism of action: Panax ginseng is a plant that has been used in Eastern medicine for years. The molecular and cellular mechanisms of functioning of ginsenosides, the active component of ginseng, include modulation of neurotransmitter function in both peripheral and central systems, inhibition of inflammatory cytokine expression, modulation of ion channel activity in spinal cord neurons, regulation of the TLR4/NF-κB signal transduction axis, and anti-inflammatory effects.

Scientific studies: To evaluate the effectiveness of Panax ginseng extract (100 mg/day) against amitriptyline (25 mg/day) and placebo, patients were evaluated for 12 weeks in a randomized/double-blind study conducted on 38 patients diagnosed as having FM.

Compared with baseline, decrease in pain in terms of VAS score ($p<0.0001$), improvement in fatigue ($p<0.0001$) and improvement in sleep quality ($p<0.001$) were found in the Ginseng group. Ginseng reduced the number of tender points and improved patients' quality of life (using the FM Impact Questionnaire - FIQ) (92).

7.3.1.12. Cannabis

Latin name: *Cannabis indica, Cannabis sativa and Cannabis ruderalis*

Active ingredient: Tetrahydrocannabinol

Mechanism of action: It is an ancient substance that has been used since ancient times to treat various painful conditions. Recent evidence suggests that cannabis may be an effective treatment for FM. Cannabis interacts with the central nervous system through endocannabinoid receptors and signaling molecules and produces analgesic and psychoactive effects.

Scientific studies: In recent years, cannabis and its derivatives have become the focus of attention in the treatment of FM and other rheumatic diseases. Evidence for the use of cannabis in FM is limited; Preliminary clinical data support the molecular basis for the analgesic effects of cannabinoids. However, as cannabis and cannabinoid products become increasingly legal and accessible, more data is being collected regarding its use in patients (93).

7.3.2. Vitamins

Studies have determined that patients with FM are often prescribed nutritional supplements and dietary changes after the disease is diagnosed. Multivitamins and mineral supplements are commonly used.

7.3.2.1. Vitamin C (Ascorbic Acid)

Vitamin C, which has antioxidant properties, can help prevent cell damage by reducing oxidative stress. This may contribute to the relief of FM symptoms.

7.3.2.2. Vitamin B12

Some patients with FM may be deficient in vitamin B, especially B12 level. Positive effects of B12/folic acid supplementation have been reported for patients with FM. In the study of patients with FM who reported themselves as "very advanced", higher and more frequent doses were given over a long period of time and it was determined that the patients' complaints improved.

7.3.2.3. Vitamin D

Low levels of vitamin D have been detected in patients with FM, which also inhibits Mg absorption. Studies on the muscles of patients with vitamin D deficiency have shown a decrease in adenosine triphosphate levels, similar to patients with FM, causing acute pain.

One study showed that vitamin D deficiency was also associated with depression and anxiety in FM. It was reported that vitamin D supplementation could improve the quality of life in patients with FM.

7.3.2.4. Vitamin E (Tocopherol)

It can reduce oxidative stress by protecting cell membranes and providing antioxidant activity. This may help reduce pain and inflammation in patients with FM (94-96).

7.3.3. Antioxidants

In addition to vitamins such as vitamin c (ascorbic acid), vitamin E (tocopherol), herbal products containing resveratrol and elliagic acid have known antioxidant properties. Antioxidants are potential treatments that help relieve symptoms of FM by reducing oxidative stress and inflammation. Glutathione is the most powerful antioxidant the body can produce on its own. Glutathione helps reduce oxidative stress and support the immune system. Selenium is necessary for the production of antioxidant enzymes and supports the function of the immune system. It relieves FM symptoms by reducing oxidative stress. Alpha-Lipoic Acid reduces oxidative stress by reducing intercellular oxidative damage and increasing antioxidant capacity. Additionally, it reduces insulin resistance and relieves neuropathic pain.

7.3.3.1. Coenzyme Q10 (Ubiquinone)

One of the commonly used supplements for FM is coenzyme Q10 (CoQ10). This coenzyme, which has antioxidant properties, increases energy production and reduces oxidative stress. It increases energy levels in patients with FM.

The use of coenzyme Q10 supplements has become widespread after many studies observed CoQ10 deficiency in patients with FM.

One study evaluated four studies on the use of CoQ10 supplements (300 mg/day). Three of these four studies were controlled and one was a clinical study. Findings from controlled studies reported that after CoQ10 treatment alone, patients with FM showed significant improvement in clinical symptoms demonstrated through the FIQ and VAS ($p<0.01$) (97,98).

7.3.4. Combined Products

7.3.4.1. Turmeric and Boswellia serrata

Turmeric and boswellia are well-studied anti-inflammatory compounds that are gaining popularity and are used as adjuncts and also alternatives to traditional treatments for musculoskeletal pain. Curcumin and boswellic acids, the active components of turmeric rhizomes and Boswellia serrata gum resin, are known to inhibit the nuclear factor κB signaling pathway, which is directly involved in inflammatory processes.

Dietary supplements containing Curcuma longa and Boswellia serrata are considered effective compounds in reducing pain in osteoarthritis in the short term.

It was shown that a single-center, active-controlled, open-label pilot study involving 232 participants used turmeric-boswellia formulation (1000 mg daily for 7 days) for acute musculoskeletal pain in the resting position, with results showing pain relief similar to paracetamol (inactivation of neurons/anti-inflammatory effect).

Turmeric and boswellia both have anti-inflammatory properties, but their mechanisms of action are different. Turmeric works by blocking the production of pro-inflammatory cytokines and enzymes; Boswellia shows its anti-inflammatory effect by modulating the immune system and reducing the sensitivity of pain receptors (99-101).

7.3.4.2. Ginkgo Biloba and Q10

It has been suggested that some of the symptoms of FM may be due to the excessive presence of oxygen-derived free radicals. These are known to trigger pain and inflammation and impair muscle function. Both coenzyme Q10 and Ginkgo biloba extract have antioxidant properties, which may explain some of the benefits. Coenzyme Q10 may also improve muscle function and Ginkgo biloba extract may improve vascular function.

The subjective effects of coenzyme Q10 and Ginkgo biloba extract were measured in an open, uncontrolled study in volunteer subjects diagnosed as having FM. The subjects were given oral doses of 200 mg coenzyme Q10 and 200 mg Ginkgo biloba extract per day for 84 days, and their quality of life was monitored at 0, 4, 8 and 12 week intervals.

A gradual improvement in quality of life scores was observed over the study period, with scores at the end showing a significant difference from baseline scores (64% felt better, only 9% felt worse) (78).

7.3.4.3. Turmeric and Pomegranate Peel extract (CurcuNar®)

The anti-inflammatory activity of turmeric has been proven in many studies. Polyphenolic compounds, curcumin, demethoxy curcumin and bisdemethoxy curcumin, collectively known as curcuminoids, are the main components responsible for the biological effects of turmeric. Curcumin is considered the key chemical component contributing to the observed anti-inflammatory activity. In addition to being the best known antioxidants, ellagic acid and pumigalacin found in pomegranate peel also have a synergistic effect with Curcumin in FM due to their anti-inflammatory and neuroprotective properties. Additionally, the ethanolic extract of pomegranate peel and leaves has been shown to inhibit acetylcholine esterase in many neuronal tissues (102-104).

7.3.5. Probiotics

In recent years, altered gut microbiota has been associated with FM, suggesting that altering the gut microbiota (e.g., through probiotics) may be an effective therapeutic treatment. Probiotics are naturally found in fermented foods. These foods include homemade natural yoghurts without additives, pickles, kefir, pickled olives, apple cider vinegar, kombucha tea, and cheese. In addition, various fiber-rich vegetables, nuts, seeds, beans and whole grains also contribute to the protection of intestinal flora.

7.4. New Treatments and Research

Advances in neurobiological research aim to uncover the complex mechanisms in FM. Imaging studies such as fMRI and PET have provided insight into the central nervous system abnormalities associated with FM.

Borsook et al. (105) have changed our perception of chronic pain. From a somatosensory system-focused approach, it has been established that emotional, cognitive, and regulatory brain areas as well as degenerative processes are involved and contribute to the development and persistence of pain symptoms. However, it has revealed associated features such as anxiety, depression and cognitive changes (105).

Genetic research continues to identify potential genetic markers that may be associated with susceptibility to FM. This can facilitate diagnosis, assess disease severity, and guide treatment decisions. There are currently no definitive biomarkers for FM, but research is advancing to define objective measures that may increase diagnostic accuracy (106).

Glutamate, a neurotransmitter, plays a role in pain signaling. Investigational treatments targeting glutamate receptors, such as NMDA receptors, are being investigated to modulate pain perception in FM. These include promising drugs such as ketamine (107).

Increasing evidence links the gut microbiome to a variety of health conditions, including FM (108). Research suggests that results can be obtained through fecal microbiota transplantation (109). Integration of digital health tools, wearable devices, and telemedicine may improve the monitoring and management of FM. These technologies can provide remote symptom monitoring, real-time feedback, and improve access to healthcare resources (110).

8. Conclusion

In conclusion, FM, characterized by widespread musculoskeletal pain and associated symptoms, has a complex and variable clinical picture. FM, which was defined as

a rheumatic disorder in the past and is now understood to have completely different characteristics, appears to require a lot of research in both diagnosis and treatment modalities. Advances in research have elucidated the complex nature of FM, which includes genetic, neurological, immunological, and psychosocial factors. FM severely impairs the quality of life. It affects daily activities, sleep patterns, cognitive function and social interactions.

Diagnosis has now evolved into a more comprehensive assessment that emphasizes the extent of pain and associated symptoms rather than relying solely on tender points. Risk factors such as gender predominance, genetic predisposition, and comorbid conditions still pose questions that need to be investigated. Treatment requires approaches that are specific to the individual and prioritize the symptom. Methods such as pharmacological treatments, non-pharmacological methods, lifestyle changes, alternative and complementary treatments, diet regulation, phytotherapy, use of vitamins and supplements can be used alone or in combination. The inadequacy of pharmacological treatments has made it necessary to turn to other methods. In this field, phytotherapy seems to be a good alternative to be combined with pharmacological treatments. In phytotherapy, combined herbal products or combinations of herbal products and vitamins appear to be more effective. FM is a syndrome that has been forgotten recently and requires a holistic approach to the patient. However, holistic treatment methods that address physical, emotional and social dimensions can be successful and increase the individual's quality of life.

Ethics

Financial Disclosure: The author declared that this study received no financial support.

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