Chapter 4

Natural Products as Promising Pharmacological Tools for the Management of Fibromyalgia Symptoms – A Review

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Abstract

Fibromyalgia (FM) is the second most common rheumatologic disorder, affecting 5% of the world population, and has a serious effect on the quality of life of patients, as well as an economic impact through lost workdays. This pain syndrome is a common cause of chronic widespread pain and is characterized by reduced pressure pain thresholds with hyperalgesia and allodynia, nonrestorative sleep, fatigue, cognitive dysfunction, and mood disturbances. The pharmacological treatment strategies for FM include the use of antidepressants, calcium channel modulators, muscle relaxants, and analgesics but have shown limited efficacy and therapeutic adherence. Thus, researchers have been seeking potential substances (new chemical entities or through drug repositioning) that could be used for FM treatment. In this context, natural products (NPs) have been shown to be promising pharmacological tools due to the variety of their pharmacological activity and the number of molecular sites available as possible active targets. Recent clinical and preclinical studies have been conducted to verify the possible applicability

of NPs such as essential oils (EOs), plants extracts, terpenes, sapogenins, and alkaloids in the treatment of FM. The results have shown that natural products have an analgesic effect in different animal models of FM, probably by activation of inhibitory descending pathways, such as the periaqueductal gray and rostroventromedial medulla. Natural products and their secondary metabolites could therefore be a promising source for FM management. However, translational studies that seek to validate the preclinical studies are scarce, incipient, and lacking an approach focused on the traditional pharmaceutical market.

Keywords: natural products, muscle pain, chronic pain, fibromyalgia, pain

1. Introduction

Fibromyalgia (FM) is a painful syndrome caused by changes in the central nervous system. This syndrome is chronic in nature and is present in about 5% of the world population. Generalized musculoskeletal pain and changes in sensitivity, as well as fatigue in the absence of any organic disease, are presented as clinical aspects. Other important symptoms may manifest in patients with FM such as sleep disturbances and cognitive problems, as well as a variety of psychosomatic symptoms. Patients with FM often complain of tingling, numbness, burning, cutaneous hyperalgesia, momentary pain attacks, and depression [1].

Pathophysiological factors are genetic predisposition, autonomic and emotional dysfunctions, physical or environmental stresses, and neurohormonal and inflammatory dysfunctions [2]. Besides that, ischemia and muscular microtraumas, which result in pain during and after exercise, can be considered favorable for the onset of pain in FM. Elvin et al. [3] studied 10 female fibromyalgic patients and 11 female patients in the control group, using Doppler ultrasound in the infraspinatus muscle during low-intensity exercise. Experimental patients presented muscle ischemia when compared to control patients, perhaps because they evoked reflexes in the muscular sympathetic nervous activity, resulting in vasoconstriction. This may be contributed to pain in FM, which could be resulting from possible microtraumas. An abrupt increase in muscle vascularization during and after dynamic exercise was also observed for patients with FM, which did not occur with static exercise when compared to the control patients. Thus, increased muscle sympathetic nerve activity in the FM group may have resulted in imbalance between vasodilation and sympathetic vasoconstriction.

Areas of the descending pathway of pain, such as the periaqueductal gray (PAG) and rostroventromedial area (RVM), which have mainly opioid and serotonergic activation, respectively, may act in endogenous analgesia. These two areas make connections with the dorsal horn of the spinal cord, modulating the transmission of nociceptive messages [3, 4]. Changes in these areas of the central nervous system (CNS) probably occur due to a neurochemical imbalance, with the glutamatergic, 5-HTergic and opioidergic systems being important

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targets to control this neurotransmitter fluidity. This results in the classification of FM as a central pain syndrome, also known as "dysfunctional pain," where there are changes in sensitivity such as allodynia (pain due to a stimulus that normally does not cause pain) and hyperalgesia (increased pain of a stimulus that usually causes pain), without any tissue or nervous injury [5–7].

Due to the complexity of its pathophysiology, the treatment of FM is very difficult. Only 30% of the medicines used to treat FM have some positive effect. Some drugs have high costs (financial or in terms of side effects), being possible triggers of collateral effects such as nausea, edema, tachycardia, and with poor therapeutic efficacy [1, 2, 8–12]. In order to better understand the physiopathology as well as to investigate new treatment options for FM, animal models have been developed that mimic some symptoms of this syndrome. Scientists have used a combination of repetitive stimuli applied to the muscle, coupled with stress added to the nociceptive stimuli applied in the muscle to trigger lasting hyperalgesia, which mimics FM (**Table 1**) [13–16].

In the search for new sources of more effective drugs with fewer side effects, scientists have been focusing on the study of different pharmacological approaches including natural products (NPs) due to their promising effects on the CNS. NPs are considered the main source of new chemical entities in the search for new medicines and may be fundamental to the discovery of new drugs for diseases or syndromes that still do not respond adequately to the current available treatments. In this context, an important approach to discover new painkillers has been developed with NPs such as medicinal plants or their secondary metabolites that could modulate painful conditions, including FM [17].

Medicinal plants (MPs) are natural products that have been used in the control of several diseases by the world's population for thousands of years. Popular knowledge about the use of these plants has directed scientists to conduct new research seeking drugs that act on specific targets or multiple molecular sites such as the pathophysiology of FM usually presents [18, 19]. Many drugs that are commonly used in clinical treatment are derived directly or indirectly from MPs and include analgesics such as aspirin (anti-inflammatory nonsteroidal derived from salicylic acid, which was initially extracted from *Salix alba*) and morphine (opioid analgesic derived from *Papaver somniferum*) [20]. As evidence of the importance of natural products, between 2005 and 2010, the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) approved 19 medicines derived from NPs, including trabectedin (Yondelis™) and cannabidiol (Sativex®), for cancer and pain treatment, respectively [21, 22]. Moreover, the growing number of patents to protect new formulations containing NPs demonstrates the importance of these compounds [23].

In relation to FM, some classes of bioactive compounds extracted from medicinal plants have presented analgesic activity described in the literature, such as essential oils [24–26], extracts [27, 28], monoterpenes [29–31], sesquiterpenes [32], saponins [33], and alkaloids (**Figure 1** and **Table 2**) [34].

Author	Animal model	Induction	Similarities with the clinical condition	Limitations of the model
Sluka, Kalra, Moore [35]	Acid saline-induced pain	Two injections of acid saline (pH 4; im) separated by 2–5 days	Widespread and generalized hyperalgesia including the bilateral hind limbs, muscles, paws, and viscera, and anxiety	It is not clear if there are comorbidities such as depression, anxiety, fatigue, or sleep disturbances, as in FM. Unlike what is observed in FM, the model is sensitive to opioids intrathecally
Dina, Levine, Green [36]; Dina, Green, Levine [37]	Hyperalgesic priming model	An acute inflammatory insult (carrageenan or IL-6) followed by PGE2 injection into the same muscle	Long duration of hyperalgesia may indicate differential processing of muscular or cutaneous pain by peripheral or central pathways	Pharmacological and non-pharmacological treatments for FM or comorbidities, as well as changes in the CNS, have not yet been studied in this model
Yokoyama et al. [38]	Fatigue-enhanced muscle pain	Running wheel for 2 h followed by two injections of acid saline (pH 5)	Muscle fatigue may increase hyperalgesia produced by low-intensity agents	Pharmacological and non-pharmacological treatments for FM or comorbidities have not yet been determined
Nagakura et al. [39]	Biogenic amine depletion model	Repeated administration of reserpine (1 mg/kg/day, for 3 consecutive days; sc)	Animals show signs of comorbidities as depression and anxiety	It is unclear how changes in the serotonergic system contribute to the maintenance of hyperalgesia. All studies so far have been performed only on males. It is not known if there are differences between males and females
Nishiyori et al. [40]	Cold stress model	Maintenance in cold room (−3 to +4°C) overnight for 3 days and transfer between normal room temperature (24°C) and a cold room every 30 min during the day	Pharmacological treatments directed to FM also have an effect in this model, with the exception of opioids, which are not effective in FM and reduce hyperalgesia in the model cited	Comorbidities such as anxiety and depression are not developed
Khasar et al. [41]	Sound stress model	Exposure to pure tones of 5, 11, 15, and 19 kHz, with amplitudes between 20 and 110 dB in random times each minute, lasting from 5 to 10 s, on days 1, 3, and 4	Anxiety is developed as comorbidity	All studies so far have been performed only on males. It is not known if there are differences between males and females

Note: CNS, central nervous system; FM, fibromyalgia.

Table 1. Summary of major animal models of fibromyalgia.

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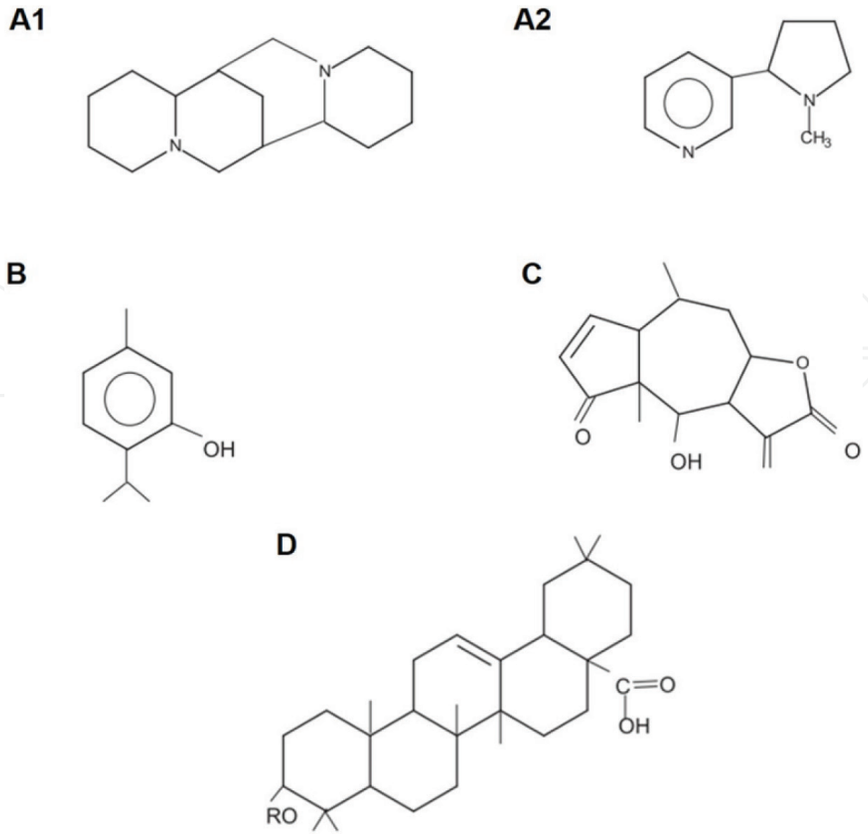

Figure 1. General structures of different categories of bioactive plant compounds studied for the treatment of FM: alkaloids (A1 and A2); monoterpenes (B); sesquiterpenes (C); and triterpenes, saponins, and steroids (D) (adapted from Azmir et al. [42]).

Natural product	Dose/route	Type of study	Sample	Molecular mechanism	References
Essential oils					
Hyptis pectinata	0.3 ml/mouse (5%); sc	Preclinical	Male Swiss mice (n = 8/group)	Opioid, serotoninergic, cholinergic, and reduction of SP, with involvement in the descending pain pathway	Quintans-Júnior et al. [24]
Ocimum basilicum	25, 50, and 100 mg/kg; po	Preclinical	Male Swiss mice (n = 8/group)	Opioid, glutamatergic, TRPV1, and reduction of SP, with involvement in the descending pain pathway	Nascimento et al. [25]
O24™	Not described; to	Clinical	133 subjects of either sex	Stimulation of A-beta sensory fibers and inhibition of bradykinin, histamine, and prostaglandins	Ko et al. [26]

Natural product	Dose/route	Type of study	Sample	Molecular mechanism	References
Plant extracts					
Phyllanthus amarus and *Phyllanthus fraternus*	400 mg/kg; ip	Preclinical	Male Wistar rats (n = 5/group)	Opioid	Chopade and Sayyad [27]
Ginkgo biloba	200 mg/day; po	Clinical	25 subjects of either sex	Antioxidant	Lister et al. [28]
Terpenes					
Linalool	25 mg/kg; po	Preclinical	Male Swiss mice (n = 8/group)	Opioid, glutamatergic, and blocking of neuronal excitability	Nascimento et al. [29]
Citronellal	50 mg/kg; po	Preclinical	Male Swiss mice (n = 7/group)	Opioid, glutamatergic, SP pathway, TRPV1 receptor, involvement in the descending pain pathway, and blocking of sodium channels	Santos et al. [30]
α-Terpineol	25, 50, and 100 mg/kg; po	Preclinical	Male Swiss mice (n = 8/group)	Opioid, serotoninergic, glutamatergic, TRPV1, and reduction of SP, with involvement in the descending pain pathway	Oliveira et al. [31]
β-Caryophyllene	10 and 20 mg/kg; po	Preclinical	Male Swiss mice (n = 8/group)	Opioid and cannabinoid	Quintans-Júnior et al. [32]
Saponin					
Hecogenin acetate	20 mg/kg; po	Preclinical	Male Swiss mice (n = 8/group)	Opioid, SP, ATP-sensitive K (+) channel, with involvement in the descending pain pathway	Quintans et al. [33]
Alkaloid					
Capsaicin	0.075% (3 times/day); to	Clinical	126 women and 4 men	TRPV1 and reduction of SP	Casanueva et al. [34]

*All preclinical studies used the chronic muscle pain model induced by acid saline.

Note: ATP, adenosine triphosphate; ip, intraperitoneal; po, oral administration; sc, subcutaneous; SP, substance P; to, topically; TRPV1, transient receptor potential vanilloid 1.

Table 2. Summary of studies involving bioatctive compounds aimed at the treatment of fibromyalgia and their main mechanisms of action.

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2. Pharmacology of bioactive compounds

Bioactive compounds, produced by plants, are designated secondary metabolites. Metabolites can be divided into primary and secondary. Primary metabolites are those involved in growth and development, such as carbohydrates, amino acids, proteins, and lipids, while secondary metabolites, which often have unusual chemical structures, are not required for primary metabolic processes and are believed to support plant survival with respect to local challenges. Thus, the production of secondary metabolites of a given species will be related to their need for survival. Among the secondary metabolites, some compounds have an effect on biological systems, being considered bioactive, which defines them as secondary metabolites of plants that induce pharmacological or toxic effects in humans or animals [42].

Bioactive compounds can be extracted from various parts of the plant, such as the leaves, seeds, flowers, bark, roots, and fruits [43]. These compounds form the essential oil of the plant, resin, or other plant products, which can be extracted in a concentrated form (containing secondary metabolites) or by means of solvents, such as water, ethanol, methanol, chloroform, dichloromethane, ether, and acetone [42]. The best solvent or extraction procedure will depend on the botanical material to be used as well as of the type of secondary metabolites being obtained. In addition, various substances can be isolated from the essential oil or chemical extracts, such as terpenes, flavonoids, alkaloid, and steroids that already have some known property that can be used in the treatment of FM [43].

2.1. Essential oils

Essential oils (EOs) are derived from the secondary metabolism of aromatic plants and are mainly terpene compounds. They are volatile and usually have a strong and characteristic smell. In nature, they perform plant protection functions against predators and help attract certain animals for pollination. In industry, they are used for numerous purposes including in perfume, as antiseptics, and food preservatives but also have numerous pharmacological properties [44]. They are mixtures and may contain 20–60 compounds (or more) in varying concentrations. Usually, each EO is characterized by its major components, which may be number two or three and usually be between 20 and 70% of the oil [45].

Although the biological effect of EOs are thought to be due to the major components which define their pharmacological profiles, synergism between the molecules present in each oil, even those that are in a smaller quantity, can modulate the effects of the major components [45].

2.2. Plant extracts

Based on non-pharmacological studies and holistic or alternative medicine with the use of medicinal plants (and related products), several researchers have sought to evaluate the effects of materials obtained through NPs in clinical and preclinical studies. This research has been based on the popular and potentially dangerous belief given the chemical diversity of NPs that "what is natural, cannot do you harm." The innovative pharmacological effects that these products are able to produce are promising but due to possible side effects remain challenging at the same time [50–52]. One way to evaluate possible pharmacological effects

and examine their use in folk medicine is to study plant extracts obtained through the use of several solvents [53–55]. The extraction of biological products using solvents is mainly used with fragile or delicate flower materials, which do not tolerate the heat of steam distillation. Examples of solvents which may be used to produce plant extracts are acetone, hexane, ether, methanol, or ethanol [43]. These extracts, in turn, can have a limited use due to their high viscosity, facilitating aggregation and precipitation, or the presence of proteins that induce false results, causing better ways of obtaining and fractionating the crude extracts to be sought [54].

2.3. Terpenes

Terpenes are the largest group of secondary metabolites obtained through natural products, being made from isoprene units (five carbons (C5)). They exhibit a wide variety of structures and are the most common class of chemical compounds found in essential oils [43, 46–48]. Essential oils contain mainly monoterpenes (C10) and sesquiterpenes (C15), which are generally hydrocarbons of the general formula (C5H8)n. At a lower concentration, they are present in essential oils as diterpenes (C20), triterpenes (C30), and tetraterpenes (C40), which are larger molecules. Terpenoids are oxygen compounds that can be derived from terpenes. These compounds may present predominantly as phenols, monoterpene alcohol, sesquiterpene alcohol, aldehydes, ketones, esters, oxides, lactones, and ethers [43].

Although monoterpenes are smaller molecules than sesquiterpenes, the structure and functional properties of these groups are similar [43, 49]. Most monoterpenes are colorless, volatile, and lipophilic, which promote greater penetration through the membrane [49]. Among the activities already described, the antinociceptive properties of these compounds have received a lot of attention [50–52].

2.4. Saponin

Triterpenoid or steroidal aglycones linked to portions of oligosaccharides are called saponins. Saponins are amphipathic because of the combination of the aglycone, having hydrophobic characteristics, and sugar molecules, with a hydrophilic profile. These compounds have been studied for use in the pharmaceutical, cosmetic, agronomic, and food industries [53]. Saponins present some therapeutic activities including powerful membrane-permeabilizing agents with hypocholesterolemic, immunostimulatory, anti-inflammatory, antimicrobial, anticarcinogenic, antiprotozoan, molluscicides, and antioxidant properties [54]. The majority of plant species-producing saponins are dicotyledonous and accumulate mainly triterpenoid saponins. The monocotyledon type mainly synthesizes saponins of the steroidal type [55].

2.5. Alkaloids

Alkaloids are complex compounds that contain nitrogen. These compounds have been used in the production of various drugs, such as metronidazole (derived from azomycin) and bedaquiline (derived from quinolone) [56–60]. Capsaicin is an alkaloid derived from hot chili peppers from the *Capsicum*. This alkaloid interacts with afferent nociceptors by means of the

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vanilloid receptors, resulting in increased sensitivity, which is perceived as pruritus, stinging, or burning. This happens due to selective activation of type C afferent fibers, release of substance P, and cutaneous vasodilation. Capsaicin-based topical creams have been used in the treatment of painful disorders such as musculoskeletal or neuropathic disorders, probably functioning by depletion of substance P in the afferent nerve endings [34, 61–63].

3. Preclinical studies

Recently, Quintans-Júnior et al. [24] evaluated pretreatment with the EO from *Hyptis pectinata* loaded in a nanoemulsion thermoreversible gel in an animal model of noninflammatory chronic muscular pain, an experimental model for FM. This pharmaceutical formulation containing EO and Pluronic F127-based hydrogel produced a long-lasting and consistent anti-hyperalgesic effect for 10 days after a single subcutaneous application, which was reversed by naloxone (opioid antagonist) and methysergide (serotoninergic antagonist). In addition, the formulation produced a significant reduction in substance P (SP) levels in the spinal cord. Moreover, it was also shown to increase neuron activation, by Fos protein expression, in the periaqueductal gray (PAG), the nucleus raphe magnus (NRM), and the locus coeruleus (LC), the CNS areas reported to be involved in the descending pathway of pain, so it appears that the formulation acts by improving the endogenous analgesia mechanism (**Figure 3**). Other studies have demonstrated that *H. pectinata* essential oil exhibits antinociceptive effects, probably mediated by the opioid and cholinergic receptors [64, 65].

Nascimento et al. [25] demonstrated in the same FM animal model that *Ocimum basilicum* essential oil, rich in monoterpenes such as linalool, has an important anti-hyperalgesic profile when complexed or noncomplexed with β-cyclodextrin (β-CD). Moreover, the complexed oil produced a long-lasting anti-hyperalgesic effect when compared to the oil alone, demonstrating that the complexation process allows greater stability and bioavailability of the oil or its main compounds, such as monoterpenes. In this paper, the authors also assessed Fos protein expression in the brains of mice and found that this oil promoted the activation of the PAG, NRM, and LC, which are encephalic regions that participate in the antinociceptive effect by the activation of the pain inhibitory descending pathway.

The results obtained for the *O. basilicum* essential oil may be due to its action on the inhibition of SP or through blocking the neurokinin-1 receptor and the vanilloid receptor (TRPV1). Indeed, this oil also acts by glutamatergic system inhibition or by the inhibition of inflammatory pathways, because it was able to produce a reduction in orofacial nociception when caused by formalin, capsaicin, and glutamate in mice [66]. Furthermore, when assessed using an electrophysiological approach, this oil was able to inhibit an orthodromic response in the dentate hippocampal gyrus, similar to DNQX (a glutamatergic drug), an AMPA and kainate receptor antagonist. In addition, another study carried out by Venâncio et al. [67] demonstrated that the peripheral and central antinociceptive effects of *O. basilicum* essential oil are related to the inhibition of the biosynthesis of pain mediators, such as prostaglandins and prostacyclins, and its ability to interact with opioid receptors.

Some studies using plant extracts for the treatment of FM have been performed. Chopade and Sayyad [27] used aqueous, methanolic, hydromethanolic, and hydroethanolic extracts of the genus *Phyllanthus* in an animal model of FM induced by acid saline. It was observed that the extract was able to reduce hyperalgesia without causing tolerance. Extracts of these plants have shown an antinociceptive effect, including in the hot-plate test [68]. In addition, there are indications these extracts depressed the CNS without apparently causing nervous toxicity or altering motor coordination, which may have corroborated with the anti-hyperalgesic effect obtained in the FM animal model [69].

The variability of the pharmacological mechanisms of terpenes and related compounds is shown in **Figure 2**, especially when incorporated into pharmaceutical formulations which improve their pharmacological properties. Moreover, β-caryophyllene, a major compound of *H. pectinata* leaf essential oil (HpEO), complexed with β-cyclodextrin decreased Fos protein expression in the superficial dorsal horn, which seems to involve the descending inhibitory pain system in an animal model of FM (**Figure 2(C)**). Germacrene D, another major component

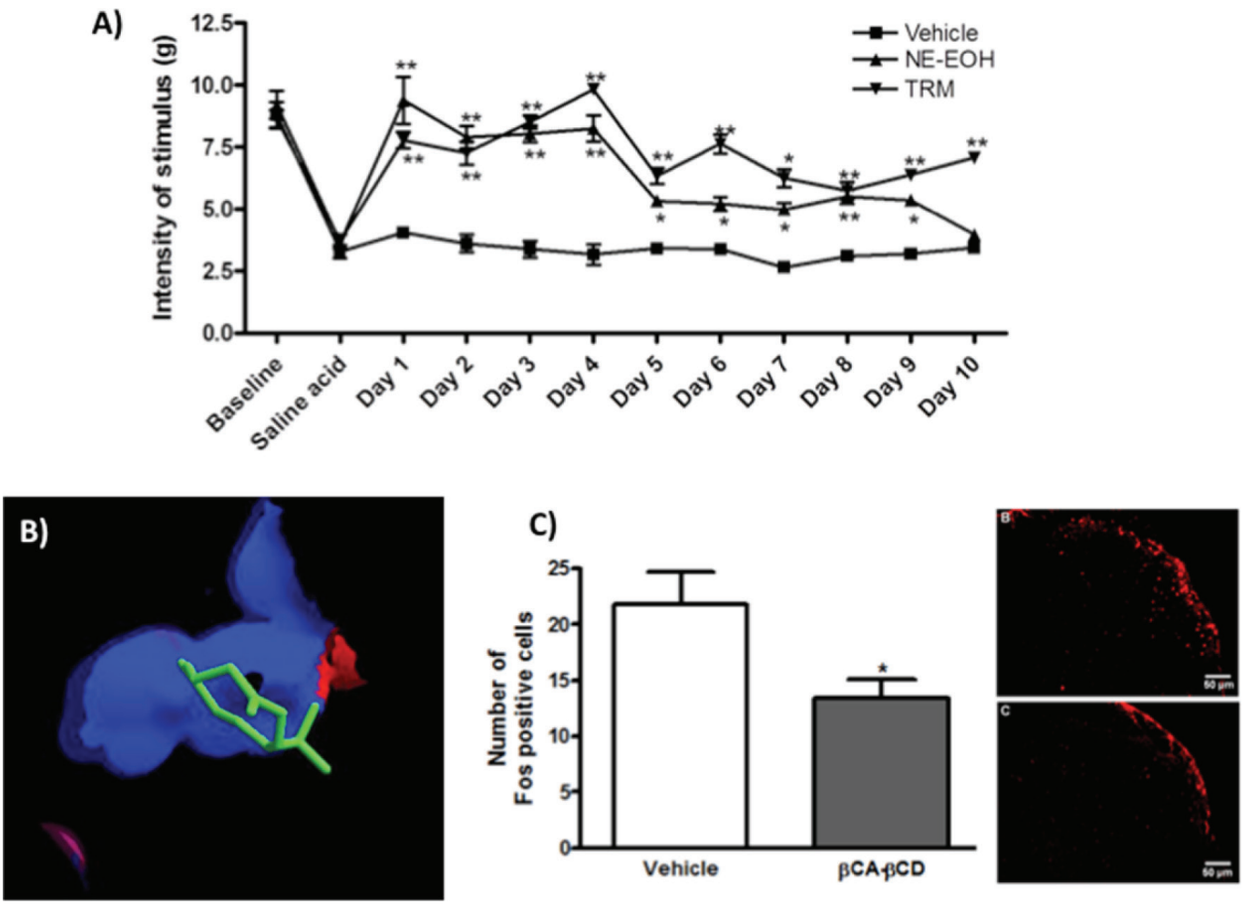

Figure 2. (A) Effect of nanoemulsion pharmaceutical formulation containing *Hyptis pectinata* leaf essential oil (NE-EOH; sc), tramadol (TRM, 10 mg/kg; ip), or vehicle (sc) on mechanical sensitivity induced by acidic saline in mice. Each point represents the mean ± SEM (n = 8, per group) of the ipsilateral paw withdrawal threshold. *p < 0.05 and **p < 0.01 vs. control group (ANOVA followed by Tukey's test). (B) Hydrophobic map of germacrene D (a major compound of *Hyptis pectinata* leaf essential oil) and μ-opioid receptor (μ-OR). Blue, hydrophobic region; red, hydrophilic region. (C) Fos-positive neurons in the lumbar spinal cord lamina I. Vehicle or β-caryophyllene-β-cyclodextrin (20 mg/kg) was administered orally, and, after 90 min, the animals were perfused (adapted from Quintans-Júnior et al. [25, 33]).

of HpEO, has a strong interaction with the μ-opioid receptor (**Figure 2(B)**). A more interesting aspect was that when the HpEO was incorporated in a nanoemulsion thermoreversible pluronic F127-based hydrogel, it produced a long-lasting and consistent anti-hyperalgesic effect (**Figure 2(A)**), suggesting that essential oils and their major components are promising tools for managing FM.

Some studies involving the effects of monoterpenes in FM experimental models have been undertaken due to their possible molecular effects on pain (**Figure 3**) [52]. Nascimento et al. [29] used linalool (**Figure 4**), a monoterpene present in plant species of the family Lamiaceae, complexed and noncomplexed in β-CD, in an animal model of FM and observed that both

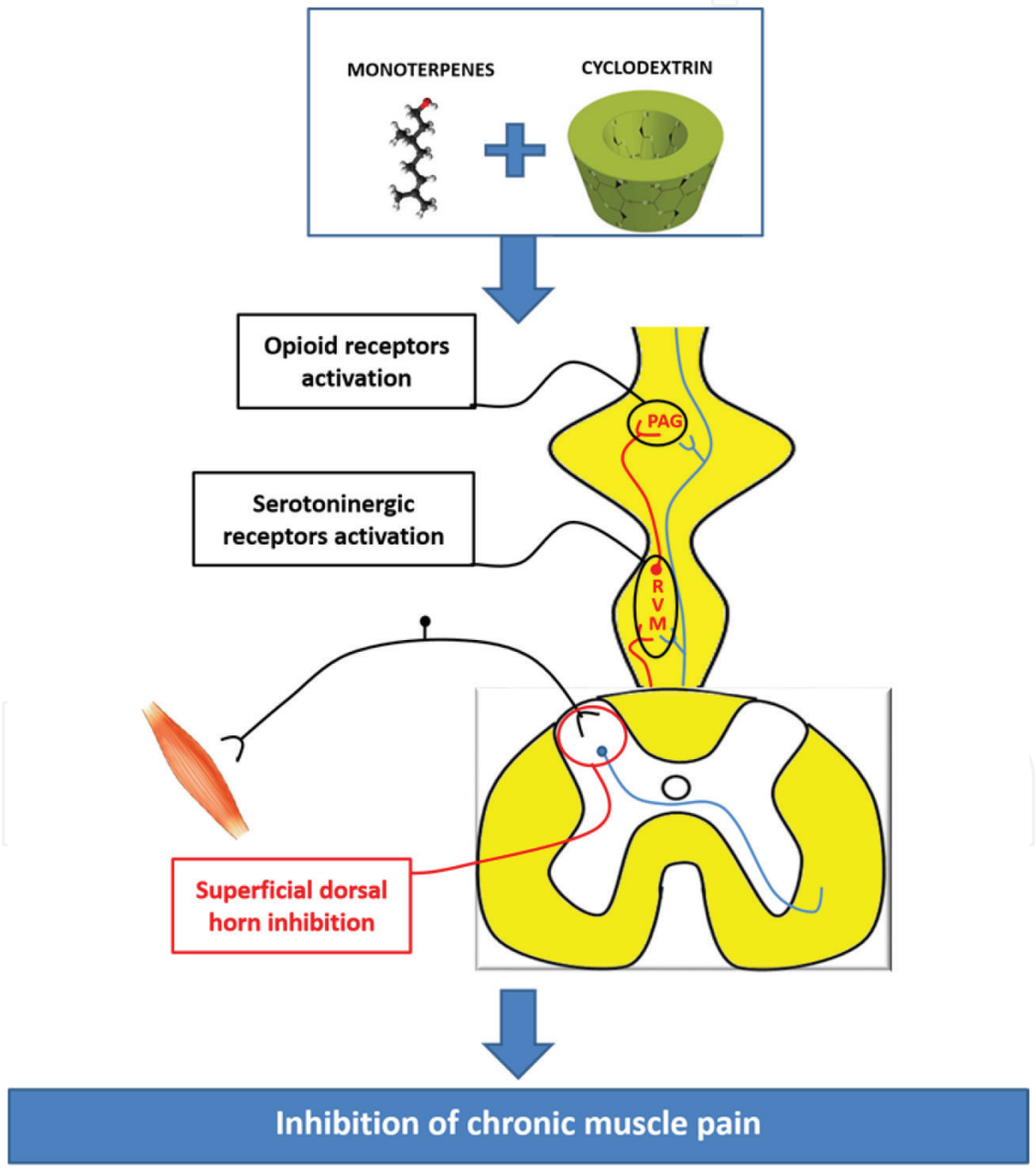

Figure 3. Schematic illustration of descending pain pathway and cyclodextrin complexation with monoterpenes (adapted from Quintans-Júnior et al. [24]).

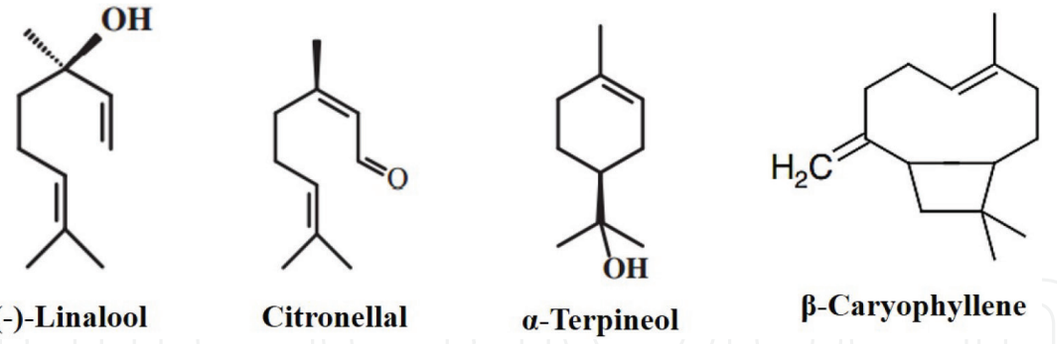

Figure 4. Structure of terpenes studied for the treatment of FM (adapted from Guimarães et al. [23, 52]).

formulations had an anti-hyperalgesic effect, with the complexed form being more effective and producing a longer-lasting effect (for 24 h after administration). Previous studies have shown the analgesic effect of linalool on acute central nociception (hot plate), visceral (acetic acid) [70] and chronic pain models of neuropathic origin [71, 72], and the opioid and glutamatergic systems probably being involved in this action [73]. Moreover, linalool was able to reduce the action potential amplitude assessed using an isolated nerve in the single sucrose-gap technique, showing it blocked neuronal excitability [74].

The possible benefits of the complexation of apolar compounds (such as terpenes) with CDs have been explored by the pharmaceutical industry and by researchers seeking improvements in pharmacological properties such as increased bioavailability, efficacy, and optimization of therapeutic doses (which reduces toxicity and adverse effects) [75, 76]. Clinical and preclinical evidence has shown that the pharmacological effects of analgesic and anti-inflammatory drugs are improved when complexed with CDs [76–78].

Santos et al. [30] evaluated the effect of citronellal (**Figure 4**), a monoterpene present in *Citrus* and *Cymbopogon* plants, complexed in β-CD as a potential agent against FM symptoms. It was observed that complexation in CD improved the anti-hyperalgesic effect when compared to noncomplexed citronellal. This effect probably involves activation of descending pain pathway areas, such as the PAG and rostroventromedial (RVM) areas, with possible interaction with the glutamate receptors, investigated by a docking study. Citronellal has already presented an antinociceptive effect on capsaicin, glutamate, and formalin-induced orofacial pain, showing that this terpene may be acting via SP and TRPV1 receptors or in the glutamatergic pathway [79]. In addition, the analgesic effect of citronellal was reversed by naloxone in hot-plate tests, which strongly suggests its action on the opioid receptors and its ability to reduce neuronal excitability through blocking sodium channels [51, 79].

Another study, also using the chronic noninflammatory widespread pain model in mice (an FM animal model), evaluated the effect of α-terpineol (**Figure 4**), both pure and complexed in β-CD, as CDs are useful tools in improving the pharmacological properties of terpenes [77, 80]. The authors observed an anti-hyperalgesic effect, possibly related to the action of α-terpineol on the opioid and serotonergic receptors; visualized with the use of naloxone and ondansetron antagonists; and confirmed by docking studies [31]. Similarly to citronellal, α-terpineol also showed antinociceptive effect in the capsaicin, glutamate, and formalin-induced orofacial

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nociception tests [81], indicating other possible mechanisms of action of this monoterpene. In summary, it has been shown that monoterpenes complexed in β-cyclodextrin reduce hyperalgesia induced by chronic muscle pain, activating the descending pathway, as described in **Figure 3**.

Sesquiterpenes occur *in nature* as hydrocarbons or in oxygenated forms including lactones, alcohols, acids, aldehydes, and ketones. Biosynthesis of sesquiterpenes can occur by the mevalonic acid and the deoxyxylulose phosphate pathway. These compounds have various pharmacological activities including antileishmanial, antimalarial, antifungal, antibacterial, antiviral, anti-inflammatory, and antinociceptive properties and the ability to inhibit the production of nitric oxide and eliminate hydroxyl radicals [82].

β-Caryophyllene (**Figure 4**) is a bicyclic sesquiterpene compound found in the EO of the *Eugenia caryophyllata* (cloves) and *Piper nigrum* (black pepper) plant species. In an experimental study conducted in an FM model in mice, this compound, complexed in β-CD, reduced primary and secondary hyperalgesia as well as inhibited the superficial dorsal horn of the spinal cord, possibly by activation of descending pain pathway [32]. Antagonism studies, in a capsaicin-induced nociception test, showed that the antinociceptive effect of β-caryophyllene was reversed by naloxone, β-funaltrexamine (a μ-opioid receptor antagonist), and AM630 (a CB2 receptor antagonist) [83]. In addition, in a neuropathic pain model, β-caryophyllene had an effect on thermal hyperalgesia and mechanical allodynia, reducing spinal neuroinflammation. The oral administration of β-caryophyllene was more effective than the subcutaneously injected synthetic CB2 agonist JWH-133 [84].

Quintans et al. [33] evaluated the effect of hecogenin acetate (HA), an acetylated steroidal saponin, complexed with β-CD in a chronic noninflammatory widespread pain model. Hecogenin is already used in the pharmaceutical industry to synthesize some oral contraceptive agents. The effect of noncomplexed or complexed HA caused an increase in the nociceptive threshold and primary and secondary hyperalgesia compared to the vehicle control group. However, the HA/β-CD complex was superior in producing an analgesic profile using lower nominal doses of the active principle (HA). In addition, the interaction of the HA with opioid receptors and a decrease in SP levels in the lumbar spinal cord were verified, which indicate participation of this substance in the descending inhibitory pain pathway [33, 85].

The antinociceptive effect of HA was previously observed in the tail-flick test. This effect was reversed by naloxone, CTOP (μ-opioid receptor antagonist), nor-BNI (κ-opioid receptor antagonist), naltrindole (δ-opioid receptor antagonist), and glibenclamide (ATP-sensitive K (+) channel blocker). Mice pretreated with HA had increased neuronal activation in the PAG area, suggesting the participation of the endogenous analgesia pathway in the hecogenin mechanism of action [85].

Some clinical studies with EOs have been developed in humans with FM. O24™ is a blend of six essential oils: aloe vera, eucalyptus, lemon/orange, camphor, rosemary, and peppermint. This mixture is marketed for the relief of pain. In a double-blinded randomized clinical trial, Ko et al. [26] demonstrated the benefits of using this oil, topically, for FM pain relief. Males and females were recruited for the study through newspapers and internet communications.

FM diagnosis was confirmed before the patients enrolled in the study. The authors reveal that the main mode of action is as a counterirritant to the pain sensation. The mixture of oils promotes stimulation of A-beta sensory fibers, causing inhibition of the A-delta and C fibers. Moreover, the local effects of O24™ include the inhibition of bradykinin, histamine, and prostaglandins, which do not seem to be directly related to the analgesic effect in FM, so it is more reasonable to propose its effect indirectly in the pathways of pain modulation.

Rutledge and Jones [86] also investigated the topical effect of O24 in a double-blind randomized clinical trial associated with exercises multilevel for 12 weeks. Twenty patients with FM and 23 patients of the sham group were submitted to the study. There was no statistical difference between the groups regarding the pain and physical function, but there was improvement of the physical function, without statistical difference, when compared before and after the treatment, keeping the effect of O24 on the FM symptoms unknown. This result for O24 differs from that described by Ko et al. [26], which may result from the small sample and the type of exercise used, since some exercises may contribute to the maintenance of pain in patients with FM [3].

The effect of *Ginkgo biloba* extract and the coenzyme Q10 was evaluated in 23 fibromyalgic patients, before and after the treatment, by oral administration, for 12 weeks, with 64% of patients reporting an improvement in quality of life through the application of questionnaires. The improvement observed by these patients may be related in parts to the antioxidant activities described for both coenzyme Q10 and *Ginkgo biloba* [28].

Due to the properties attributed to capsaicin, Casanueva et al. [34] evaluated the short-term efficacy of topical capsaicin treatment in 130 patients with fibromyalgia who were already using drug therapy. Patients were randomly divided into a control group (same medical treatment that they received before randomization) and topical capsaicin group (medical treatment that they received before randomization + 0.075% capsaicin) by a computer-generated sequence. After 6 weeks, it was observed that the additional topical treatment reduced the myalgia score and improved the quality of life of these patients, showing that capsaicin was also effective in this syndrome.

4. Final considerations

Fibromyalgia is the second most common rheumatologic disorder, being characterized by the manifestation of widespread pain with sensory changes. The treatment strategies for the management of the FM include both pharmacological products (such as duloxetine, pregabalina, and tramadol for pain and amitriptyline, cyclobenzaprine, and pregabalina for sleep disturbance) and non-pharmacological therapies (such as exercise and psychological therapies) [87]. Despite this, fibromyalgia remains difficult to treat and is an important challenge for modern medicine, as the treatments for these conditions are still ineffective with a large number of side effects, making the search for new treatments ever more urgent.

In this context, one important approach to the discovery of new medicines with analgesic activity is research with natural products. For thousands of years, scientists and the pharmaceutical industry have used natural products as a source for new drugs or their

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precursors, aimed at treating diseases or symptomatology that had no effective treatment. Despite of the animal models described for FM, some limitations can be observed, such as the reversion of the pain with opioid treatment and the absence of other signs and symptoms observed in humans. However, these models are the most resembled FM in humans, being tools used in the search for new treatment options. Nowadays, many natural substances have been studied, clinically and preclinically, for their analgesic potential with respect to fibromyalgia. In this context, essential oils, plant extracts, terpenes, and alkaloids are major sources of natural products.

These substances have been shown to have an analgesic effect in animal models of fibromyalgia, acting through different pathways, including activation of the descending inhibitory pain pathway—specifically the opioid, glutamatergic, cannabinoid, and serotoninergic systems; inhibition of SP in the superficial dorsal horn of the spinal cord; blockage of peripheral fibers; and antioxidant activity. In addition, clinical studies have shown the importance of NPs in the pain management of FM, improving their quality of life. The effective use of these products in the clinic, without reports of considerable adverse effects, describes the advances in the use of NPs in the treatment of FM. These finding make natural products a promising source of treatments for the management of chronic pain.

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