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REVIEW

The anti-inflammatory and analgesic effects of formulated full-spectrum cannabis extract in the treatment of neuropathic pain associated with multiple sclerosis

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Abstract

Purpose Cannabis has been used for thousands of years in many cultures for the treatment of several ailments including pain. The benefits of cannabis are mediated largely by cannabinoids, the most prominent of which are tetrahydrocannabinol (THC) and cannabidiol (CBD). As such, THC and/or CBD have been investigated in clinical studies for the treatment of many conditions including neuropathic pain and acute or chronic inflammation. While a plethora of studies have examined the biochemical effects of purified THC and/or CBD, only a few have focused on the effects of full-spectrum cannabis plant extract. Accordingly, studies using purified THC or CBD may not accurately reflect the potential health benefits of full-spectrum cannabis extracts. Indeed, the cannabis plant produces a wide range of cannabinoids, terpenes, flavonoids, and other bioactive molecules which are likely to contribute to the different biological effects. The presence of all these bioactive molecules in cannabis extracts has garnered much attention of late especially with regard to their potential role in the treatment of neuropathic pain associated with multiple sclerosis.

Methods Literature review was performed to further understand the effect of clinically used full-spectrum cannabis extract in patients with multiple sclerosis.

Results Herein, the current knowledge about the potential beneficial effects of existing products of full-spectrum cannabis extract in clinical studies involving patients with multiple sclerosis is extensively reviewed. In addition, the possible adverse effects associated with cannabis use is discussed along with how the method of extraction and the delivery mechanisms of different cannabis extracts contribute to the pharmacokinetic and biological effects of full-spectrum cannabis extracts.Herein, the current knowledge about the potential beneficial effects of existing products of full-spectrum cannabis extract in clinical studies involving patients with multiple sclerosis is extensively reviewed. In addition, the possible adverse effects associated with cannabis use is discussed along with how the method of extraction and the delivery mechanisms of different cannabis extracts contribute to the pharmacokinetic and biological effects of full-spectrum cannabis extracts.

Keywords Full-spectrum cannabis extract · Neuropathic pain · THC · CBD · Terpenes

Introduction

Neuropathic pain results from damage to the nervous system and is a common and often infuriating condition for affected patients. Damage to the nervous system is frequently due to either peripheral nerve injury or disease states such as multiple sclerosis (MS) [1, 2]. MS is one of the main, non-injurious neuronal disorder in adults affecting around 2.5 million individuals in the world [1, 2]. Despite the considerable progress made towards identifying new therapeutic approaches for the treatment of symptoms associated with MS such as neuropathic pain [3, 4], the current therapeutic modalities are limited. Thus, there remains a crucial need to identify new

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therapies to combat the pain associated with MS and improve the quality of life of these patients.

Cannabis has been used for centuries to treat ailments in many cultures [5] with the earliest peer-reviewed clinical study reported in 1843 [6]. Although *Cannabis sativa* produces a large number of cannabinoids, the pharmacological effects of cannabis are usually attributed to two main cannabinoids, Δ^9-tetrahydrocannabinol (refered to herein as simply THC) and cannabidiol (CBD). As such, THC and CBD have been extensively investigated in pre-clinical and clinical studies for the treatment of many disorders [7, 8]. Though a plethora of studies have examined the biochemical effects of purified THC and/or CBD [7, 8], only fewer have focused on the effects of full-spectrum cannabis extract [9–11]. This limitation is becoming increasingly important as *Cannabis sativa* naturally produces more than 100 different cannabinoids as well as approximately 460 other known biologically relevant products including terpenes and others [12]. Thus data from human trials using the entire plant cannot be attributed solely to THC or CBD. Of relevance, the presence of cannabinoids, along with terpenes and other compounds in cannabis extracts has garnered much attention of late [13–16], especially with regard to their potential role in the treatment of neuropathic pain associated with MS [14, 16, 17].

The objective of this review is to discuss the current knowledge about the potential beneficial effects of existing products of full-spectrum cannabis extract in clinical studies involving patients with neuropathic pain and inflammation associated with MS.

The role of purified cannabinoids in the treatment of MS

Purified cannabinoids such as Dronabinol consist of purified THC suspended in sesame oil (Syndros®) and available in capsules (Marinol®) [18]. Dronabinol is used for the treatment of nausea and vomiting induced by chemotherapy and for appetite stimulation in patients with HIV/AIDS [18]. In addition to Dronabinol, Namisol is a novel dosage form of purified THC that has been recently tailored to enhance the oral bioavailability of Dronabinol using an emulsifying drug delivery approach which help increase the uptake of hydrophobic compounds [19, 20]. Of importance, both formulations of purified THC (i.e. Dronabinol and Namisol) have been studied for their effectiveness in the treatment of symptoms associated with MS.

The cannabinoid use in progressive inflammatory brain disease (CUPID) trial

The CUPID trial is aimed to investigate the efficacy of purified oral THC (Dronabinol) in the treatment of MS [21]. Using expanded disability status scale (EDSS) score, treatment with purified oral THC did not show any overall beneficial effect on the progression of MS suggesting that purified oral THC is not effective in the treatment of MS [21].

While the progression of MS was not improved by purified oral THC in the CUPID trial [21], the possibility that purified oral THC may reduce neuropathic pain in patients with MS could not be excluded. Thus, the efficacy of Dronabinol in the treatment of neuropathic pain was investigated in a randomized, double-blind, placebo-controlled parallel group trial [22]. Using the numerical rating scale (NRS) as a primary end point for pain severity, patients who received purified oral THC did not demonstrate a significant improvement in pain intensity over the baseline or the placebo group suggesting a lack of efficacy of purified oral THC in the treatment of neuropathic pain associated with MS [22].

The lack of efficacy of Dronabinol in the treatment of MS has been attributed to the variability of the oral bioavailability of THC due to a significant first pass metabolism [19]. Thus, a new formulation of purified oral THC, Namisol, was formulated to enhance the bioavailability of THC [19]. Because Namisol showed better pharmacokinetic and oral bioavailability than Dronabinol [19], a randomized, placebo-controlled, double-blind parallel group trial was designed to evaluate the efficacy of Namisol in the treatment of patients with MS [20]. While the pain intensity was significantly lessened when measured immediately after administration of Namisol in the clinic, no significant differences were reported after 2 and 4 weeks of Namisol treatment compared to the placebo group. Though Namisol showed a stable pharmacokinetic profile [19], it was not effective in the treatment of MS [20] suggesting that the variability of the oral bioavailability of purified oral THC might not be the main contributor for the lack of efficacy of purified oral THC. Nevertheless, the lack of effectiveness of purified THC in the treatment of MS does not exclude the possibility that THC may be effective when it is a part of full-spectrum cannabis extract. Indeed, full-spectrum cannabis extract contains a large number of cannabinoids along with numerous other biologically relevant products including terpenes and others [12] which might help improve the efficacy of THC in the treatment of MS.

Potential health benefits of full-spectrum cannabis extracts in the treatment of MS

Existing products such as Sativex, Cannador, and Epidiolex have been used most extensively in clinical trials for the treatment of various diseases [9, 15, 23]. For instance, Sativex, an oromucosal spray, and Cannador, an oral capsule, have been approved in many countries including Canada, UK, Spain, and Germany for the treatment of symptoms

associated with MS [9, 23]. Recently, Epidiolex, an oil formulation of purified plant-derived CBD, has been approved by FDA for the management of treatment-resistant epilepsy [15]. All the products have been used for the treatment of symptoms associated with MS, with varying degrees of success.

The role of Sativex in the treatment of MS

Sativex is an oromucosal spray containing a full-spectrum cannabis extract with 2.7 mg of THC and 2.5 mg of CBD/100μL in addition to other cannabinoids and terpenes in an aromatized water–ethanol solution [24]. Sativex has been approved in many countries such as Canada, UK, Spain, and Germany for the treatment of neuropathic pain, spasticity, and other symptoms associated with MS [23]. The apparent advantage of Sativex is quick access to the circulation through the buccal cavity with a rapid maximum plasma concentration, avoiding the problems of the oral route [25] (Table 1).

Multiple clinical trials using Sativex have been performed (Table 2) on patients with MS. Notably, patients receiving Sativex showed an improvement in sleep quality [10, 26, 27], a reduction in pain [10, 16, 26–36], bladder disorder [27, 32, 33, 36], muscle stiffness, and spasticity [16, 27, 29, 31–33, 35–38] (Table 2). Results from recent trials indicate that Sativex provided a significant improvement of resistant MS-related symptoms when administered as an add-on therapy implicating Sativex as an adjuvant therapy for the treatment of symptoms associated with MS (Table 2) [16, 35, 36]. While cognitive function was not altered in patients on Sativex [10, 16, 27], somnolence, dizziness, confusion, fatigue, dry mouth, white and red buccal mucosal patches, and nausea have been reported [10, 28, 31]. Collectively, these studies support the notion that Sativex was safe and effective for the treatment of symptoms associated with MS.

The mechanism by which Sativex controls pain and spasticity has been investigated in MS patients using electrophysiological parameters such as spinal excitability, intracortical excitability, and sensory–motor integration [39, 40]. Of interest, the beneficial effect of Sativex was associated with the activation of gamma aminobutyric acid-A (GABA-A) receptor as indexed by the increase in the short intracortical inhibition (SICI), fronto-central γ-band oscillation, and pain–motor integration strength [39, 41]. On the other hand, Sativex significantly reduced the glutamatergic pathway as evidenced by the inhibition of intracortical facilitation (ICF), long intracortical inhibition (LICI) and the spinal H/M ratio, and recovery curve of the H-reflex (HRC) [39, 40]. Together, these data suggest that Sativex reduces the intracortical and spinal excitability through regulating the yin-–yang between excitatory and inhibitory neurotransmitters, resulting in analgesia and muscle relaxation (Fig. 1).

The beneficial effects of Sativex might also be explained by its significant peripheral effect on the immune and inflammatory cells [42]. This concept was supported by a recent finding that a full-genome expression profile and showed that Sativex treatment significantly suppresses several immune- and inflammatory-associated pathways such as nuclear factor-kB (NF-kB) in MS patients [42]. The anti-inflammatory effect of Sativex was confirmed by a significant inhibition of lipopolysaccharide (LPS)-induced tumor necrosis factor (TNF-α) in peripheral blood mononuclear cells collected from patients with MS [42]. Overall, the study suggests that Sativex improves MS-related symptoms through immunosuppressant and anti-inflammatory effects (Fig. 1).

The peripheral anti-nociceptive mechanism of Sativex has also been assessed in MS patients by subjecting them to cold and hot painful stimuli on their hands and feet [43]. While patients on Sativex demonstrated an upregulation in cold pain threshold in their hands and a significant downregulation in abnormal cold perception thresholds using quantitative sensory testing (QST) and laser-evoked potentials (LEPs), no significant changes have been observed in their heat pain thresholds [43]. Given that the thermal sensation is known to be mediated by the transient receptor potential (TRP) ion channels, the authors suggested that Sativex may produce pain relief in MS patients through the modulation of peripheral cold-sensitive TRP channels (Fig. 1).

Mechanistically, Sativex likely activates cannabinoid 1 (CB1) and 2 (CB2) receptors, 7-domain Gi/o-protein coupled receptors, to lesson neuropathic pain and suppress inflammation [44]. Once these receptors are activated, the intracellular level of cyclic-AMP is decreased as a result of the downregulation of adenylate cyclase [44]. Of interest, the expression of CB1 receptor in the central nervous system (CNS) enables the THC contained within Sativex

Table 1 Cannabis extract dosage forms and uses

Name	Origin	Dosage form	Uses	References
Epidiolex	CBD extract	Sesame oil suspension	Childhood-onset epilepsy such as Lennox–Gastaut Syndrome and Dravet Syndrome	[15]
Nabiximols	THC-CBD extract	Oromucosal spray (Sativex®)	Symptoms associated with MS	[24]
Cannador	THC-CBD extract	Capsule	Symptoms associated with MS	[9]

Table 2 The effect of Sativex on MS-related symptoms in clinical studies

Study population	Study design	Sativex dose/duration	Effect	References
Patients with MS ($n=160$)	Randomized, placebo-controlled, double-blind parallel group	9 sprays/day for 10 weeks	Reduction of VAS for pain, spasticity, and bladder dysfunction, and an improvement in the quality of sleep	[27]
Patients with MS ($n=137$)	Randomized, placebo-controlled, double-blind parallel group	9 sprays/day for 82 weeks	Reduction of VAS for pain, spasticity, and bladder dysfunction	[33]
Patients with MS ($n=66$)	Randomized, double-blind, placebo-controlled parallel group	9 sprays/day for 4 weeks	An improvement in NRS for pain	[34]
Patients with neurological defects ($n=70$)	Multi-center, randomized, double-blind, placebo-controlled parallel group	9 sprays/day for 3 weeks	An improvement in NRS for pain	[34]
Patients with MS associated chronic refractory pain ($n=64$)	Single-center, randomized, double-blind, placebo-controlled, parallel-group	9.6 sprays per day for 5 weeks	An improvement in NRS for pain and sleep quality	[10]
Patients with MS ($n=189$)	Phase-3, randomized, double-blind, placebo-controlled, multi-centers	9.4 sprays per day for 6 weeks	Reduction in NRS of spasticity	[38]
Patients with MS ($n=337$)	Multicenter, double-blind, randomized, placebo-controlled, parallel-group	24 sprays per day for 15 weeks	Reduction in spasticity	[37]
Patients with MS associated central neuropathic pain ($n=66$)	An uncontrolled, open-label, extension-trial	8 sprays per day for 2 years	Reduction in pain score using NRS	[28]
Patients with MS associated central neuropathic pain ($n=339$)	Randomized, double-blind placebo-controlled, parallel group	12 sprays per day for 14 weeks (Phase A), 12 sprays per day for 18 weeks (Phase B)	An improvement in neuropathic pain and sleep quality	[26]
Patients with MS who did not fully respond to baclofen ($n=572$)	A single-blind study (Phase A), a double-blind randomized placebo control (Phase B)	12 sprays per day for 4 weeks (Phase A), 12 sprays per day for 12 weeks (Phase B)	An improvement in spasticity and pain	[29]
Patients with MS ($n=34$)	Randomized, placebo-controlled, parallel group	24 sprays per day for 10 weeks (Phase A), 24 sprays per day for 5 weeks (Phase B)	An improvement in MS associated symptoms using global impression of change scales	[30]
Patients with MS ($n=144$)	A real-world monocentric Italian cohort	7.2 sprays per day for 48 weeks	Reduced spasticity and neuropathic pain	[31]
Patients with MS ($n=276$)	An observational, non-interventional, multicenter, prospective	7 sprays per day for 3 months	Reduced pain, restricted mobility, muscle stiffness, and bladder disorders using NRS and questionnaires	[32]
Patients with MS ($n=322$)	Large observational, prospective, non-interventional mobility improvement (MOVE 2) study	6 sprays per day for 3 months a add on therapy to	An improvement in pain, fatigue, and spasticity symptoms using questionnaires and NRS	[35]
Patients with MS-related drug-resistant ($n=281$)	An observational, prospective, multicenter, non-interventional study (MOVE-2 EU)	6 sprays per day for 3 months as add-on therapy to baclofen/tizanidine	Reduced pain, spasm, sleep quality, fatigue, and bladder dysfunction	[36]
Patients with MS-related drug-resistant ($n=191$)	A prospective, randomized, parallel group, double-blind, placebo-controlled two-phase trial (SAVANT)	7 sprays per day for 3 months as add-on therapy to baclofen/tizanidine	An improvement in pain and spasticity using NRS and mean modified Ashworth's scale	[16]

VAS visual analog scale daily ratings, *NRS* numerical rating scale

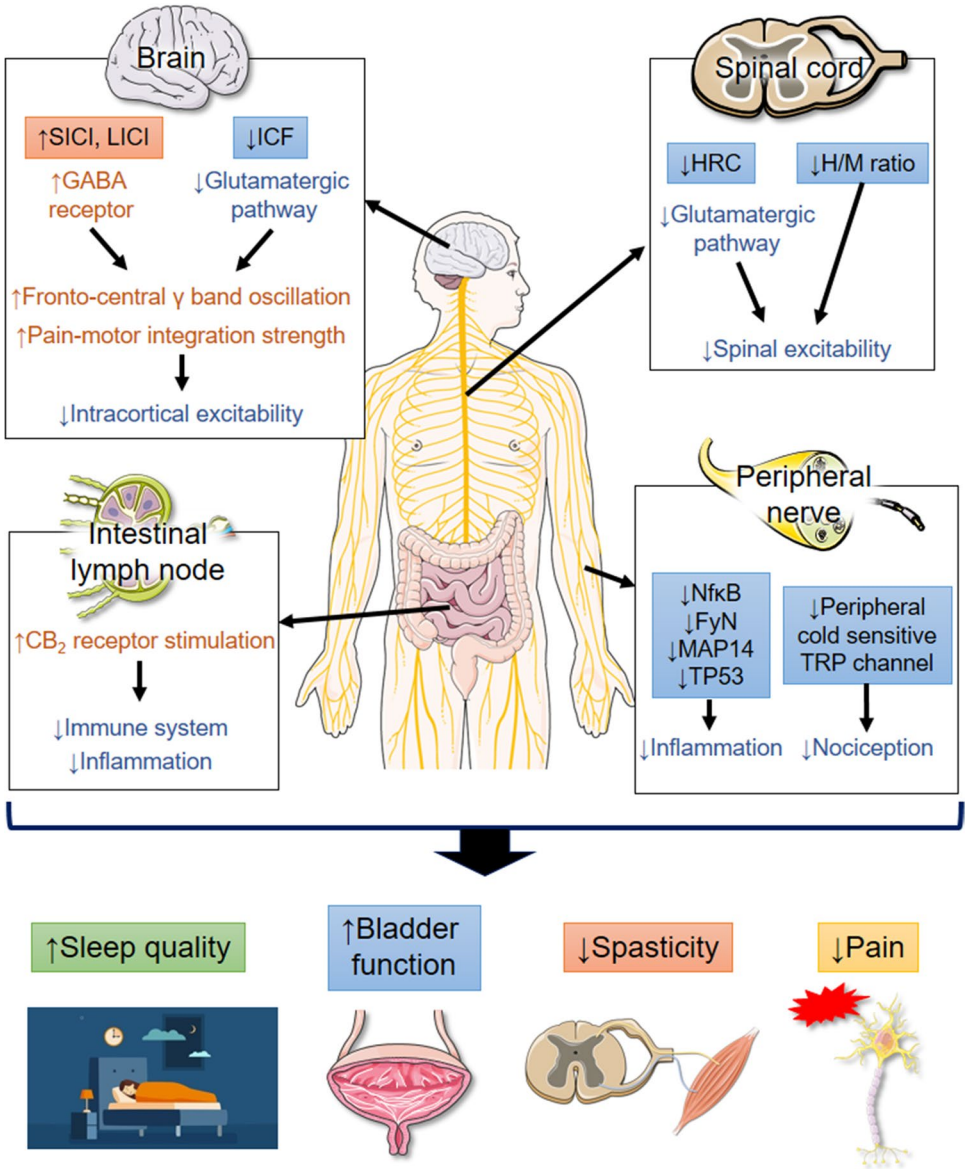

Fig. 1 Proposed mechanism of action of Cannabinoids. *SICI* short intracortical inhibition, *LICI* long intracortical inhibition, *ICF* intracortical facilitation, *HRC* H/M ratio and recovery curve of the H-reflex, *TRP channel* transient receptor potential channels, *NF-κB* nuclear factor kappa-light-chain enhancer of activated B cells, *Fyn* proto-oncogene tyrosine-protein kinase, *MAP14* mitogen-activated protein kinase14, *TP53* tumor protein p53, *QOL* quality of life

to reduce intracortical and spinal excitability by regulating the balance between excitatory neurotransmitters like glutamate and inhibitory neurotransmitters such as GABA, resulting in analgesia and muscle relaxation [45, 46] (Fig. 1). While CB2 receptors are also expressed in CNS [47], the activation of peripheral CB2 receptors by Sativex likely reduces the sensitivity of nociceptive nerve terminals and produces a robust immunomodulatory and anti-inflammatory effect on the intestinal lymphatic system [47, 48] (Fig. 1). Unlike the THC contained in Sativex, the pharmacological effects of CBD within Sativex are entirely mediated through CB1 and CB2 receptor-independent mechanism [17]. For instance, CBD reduces nociception by suppressing transient receptor potential cation channel subfamily V member 1 (TRPV1) and T-type Ca^{2+} channels as well as through the activation of glycine and GABA receptors [17, 49–51]. In addition to THC and CBD, Sativex contains other cannabinoid and non-cannabinoid components such as terpenoids and flavonoids, which may also synergize the overall beneficial effects of THC and CBD [52].

The efficacy and long-term safety of Cannador® in the treatment of MS

Cannador® is a soft gelatin oral capsule standardized on CBD (0.8–1.8 mg) and THC (2.5–25 mg) and it is used in the treatment of symptoms associated with MS (Table 1) [9].

Cannabinoids in multiple sclerosis (CAMS) trial

The first trial designed to test the effectiveness of Cannador was reported in 2003 [53]. This trial was performed to investigate the beneficial effect of Cannador on spasticity and pain in a patient with MS [cannabinoids in multiple sclerosis (CAMS)] [53]. Using the Ashworth scale, treatment with Cannador or THC did not show a favorable effect on spasticity on the primary outcome [53]. However, patients receiving either Cannador or THC reported an improvement in pain, spasticity, spasms, and sleep quality using category rating scales [53]. Overall, while this study suggests that the administration of dried oral full-spectrum cannabis extract might be clinically useful, the beneficial effect was not different from the administration of THC alone.

The long-term safety and effectiveness of Cannador in MS patients was investigated in a double-blind, placebo-controlled study [54]. This study was a 1-year follow-up of patients in the CAMS study [53] who reported improved symptoms of spasticity, spasms, pain, and tiredness [54]. Of interest, while no major safety concerns were reported, 45% of the patients on either THC or Cannador terminated the study as they do not experience improvement resulting from these treatments [54].

The multiple sclerosis and extract of cannabis (MUSEC) trial

The multiple sclerosis and extract of cannabis (MUSEC) trial is a substantiated evidence-based approach of the CAMS study [55]. The major distinction of the MUSEC over the CAMS trial was the use of fast dose titration in the MUSEC trial up to the maximum tolerated dose to ensure that none of the potential efficacy of the Cannador was missed (Table 3). A standard category rating scale was used to assess patient-reported changes in the muscle stiffness, pain, and sleep from baseline [55]. Using this scale, 29.4% of the patients who received full-spectrum cannabis extract demonstrated a significant improvement in muscle stiffness, muscle spasms, and sleep quality [55]. While some patients demonstrated adverse CNS effects such as disorientation and confusion, these effects were mild and no major side effects were observed [55]. Consistent with the previous clinical trial [53], these data point toward the potential of full-spectrum cannabis extract as a treatment of MS-associated spasticity and pain (Table 3).

The potential use of Epidiolex® in the treatment of symptoms associated with MS

Epidiolex is an oil formulation of purified, plant-derived CBD [15]. Epidiolex has been approved by the FDA for the management of treatment-resistant epilepsy and it has been used in clinical trials for the treatment of neuropathic pain [56]. However, Epidiolex has not been extensively investigated in humans for the treatment of neuropathic pain and inflammation associated with MS [15]. Nevertheless, preclinical evidence suggests that plant-derived CBD may provide therapeutic relief of neuropathic pain and reduce inflammation [17, 47]. The apparent advantage of purified CBD is that it does not show a signal for abuse liability in humans [57]. However, it may have some minor side

Table 3 The effect of Cannador on MS-related symptoms in clinical studies

Study population	Study design	Dose/duration Cannador	Effect	References
Patients with MS ($n=667$)	A multi-center randomized placebo-controlled trial (CAMS)	10 capsules of Cannador or delta 9-THC per day for 15 weeks	An improvement in pain, spasticity, spasms, and sleep quality using category rating scales	[53]
Patients with MS ($n=630$)	A double-blind, placebo-controlled study (follow up of CAMS)	10 capsules of Cannador or delta 9-THC per day for 1 year	An improvement in spasticity, spasms, pain, and tiredness	[54]
Patients with MS associated urge incontinence episodes ($n=630$)	A double-blind, placebo-controlled study (CAMS-LUTS)	10 capsules of Cannador or delta 9-THC per day for 15 weeks	Decreased urge incontinence episodes	[65]
Patients with MS ($n=57$)	Randomized, double-blind, placebo-controlled, crossover study	12 capsules of Cannador per day for 2 weeks	An improvement in mobility and spasm frequency	[66]
Patients with MS ($n=279$)	Double-blind, placebo-controlled, phase III study	2-week dose titration phase from 2 capsules to a maximum of 10 capsules of Cannador daily and a 10 week maintenance phase (10 capsules of Cannador per day)	Reduced muscle stiffness, muscle spasms, and improved sleep quality	[55]

effects such as diarrhea, decreased appetite, fatigue, and somnolence. Adverse effects such as an increase in aspartate transaminase (AST) and alanine transaminase (ALT), which may indicate a risk of hepatotoxicity, in addition to suicidal thoughts have also been reported with a high dose of extracted CBD [58].

Discussion

Herein, we have reviewed how the full-spectrum cannabis extract has been shown to improve some symptoms associated with MS such as neuropathic pain. In general, clinical studies involving different dosage forms of cannabis yielded exciting results for the prevention and/or treatment of neuropathic pain [10, 16, 25–34, 36, 38–43, 53–55, 59–66]. While several positive clinical studies have been published, other clinical studies have refuted the beneficial effects of purified THC and/or CBD for the treatment of certain forms of neuropathic pain [20–22, 67, 68]. This is in contrast to the clinical studies that supported a crucial role of the full-spectrum cannabis extract in the treatment of neuropathic pain [10, 16, 25–34, 36, 38–43, 53–55, 59–66]. Together, this suggests that studies using a purified THC or CBD may not accurately reflect the potential health benefits of the complete cannabis extract.

The variety of different effects and indications for cannabis likely extend from numerous different terpenes and cannabinoids that are present in the different cultivars of the plant [12] and contribute to the "entourage effect" [69, 70]. Indeed, this "entourage effect" (which is essentially a cooperative effect of cannabis compounds) has been experimentally validated in which various terpenes and cannabinoids have been shown to modulate the binding of both endogenous endocannabinoids and exogenous THC and CBD [71]. Together, these findings demonstrate the importance of understanding how all of these molecules interact to produce specific biological effects in the human body.

Cannador is an example of a full-spectrum cannabis extract used in some of the studies that we have presented in the current review. Cannador was prepared from *Cannabis sativa* using extraction medium ethanol 96%. Then the extract was dried and collected in soft gelatin capsules and standardized based on CBD (0.8–1.8 mg) and THC (2.5–25 mg) [55]. While Cannador has shown a promising effect in the treatment of MS-associated symptoms, it has low oral bioavailability which is perhaps one of the largest challenges [55]. Notably, oral administration of full-spectrum cannabis extract in the dried form, such as Cannador, limits the absorption of THC and CBD [72, 73]. Although Cannador capsules are standardized for CBD and THC concentrations, the drying process may affect the quality and concentration of the non-cannabinoid components, in particular terpenes, resulting in the loss of additional therapeutic potential [74].

The low bioavailability of Cannador might be overcome by the administration of full-spectrum cannabis extract through the buccal route. Indeed, Sativex is a full-spectrum cannabis extract that has been approved as a mouth spray to mitigate neuropathic pain and other symptoms of MS [25]. Apparently, the buccal spray of Sativex helps THC and CBD to reach the circulation with a maximum of 15 min [52, 75]. While the oromucosal administration of Sativex seems to be more desirable than the oral administration of dried extract [52], Sativex administered this way will not have an impact on the gastrointestinal tract and thus this route of administration may bypass crucial targets that might contribute to the anti-nociceptive and anti-inflammatory action of cannabis induced via the microbiota [72]. For instance, the accumulation of *Akkermansia muciniphila* as a result of oral cannabis administration was shown to contribute to the anti-inflammatory and analgesic effect [76, 77]. However, oromucosal administration of Sativex would not elicit these effects.

Another important pharmacological target that has an essential impact on the treatment of symptoms associated with MS is the intestinal lymphatic system [78]. Targeting the intestinal lymph system can only be achieved with an oral administration of cannabis [72]. Recently, it has been shown that the formulation of THC and CBD with lipids such as sesame oil results in the accumulation of these cannabinoids in the intestinal lymphatic system with a substantial immunomodulatory effect [72]. Given that the immunosuppressant effect of THC and CBD is more prominent on immune cells obtained from patients with MS than the cells derived from healthy controls [79], it is reasonable to suggest that targeting the lymphatic system would be crucial for MS patients [72]. Furthermore, the formulation of THC and CBD with lipids like sesame oil improves the absorption and enriches the oral bioavailability of these cannabinoids in comparison to non-lipid dosage forms [80], suggesting that the administration of THC and CBD using oil-based formulations might be the best oral dosage form to deliver THC and CBD to MS patients.

In summary, small scale clinical studies suggest that full-spectrum cannabis extract is effective in the treatment of MS-associated symptoms such as neuropathic pain [16, 36, 81, 82]. Nevertheless, there remains a crucial need to test whether the other dosage formulations of cannabis extracts such as oil formulation and vaporizers can help patients with inflammation and neuropathic pain associated with MS.

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