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Cannabis and Autoimmunity: Possible Mechanisms of Action

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Abstract: Medical cannabis (MC) describes the usually inhaled or ingested use of a cannabis plant or cannabis extract for medicinal purposes. The action of whole cannabis plants is extremely complex because their large number of active compounds not only bind to a plethora of different receptors but also interact with each other both synergistically and otherwise. Renewed interest in the medicinal properties of cannabis has led to increasing research into the practical uses of cannabis derivatives, and it has been found that the endocannabinoid system (particularly CB2 receptor activation) is a possible target for the treatment of inflammatory and the autoimmune diseases related to immune cell activation. However, in vivo findings still lack, creating difficulties in applying translational cannabinoid research to human immune functions. In this review, we summarized the main mechanisms of action of medical cannabis plant especially regarding the immune system and the endocannabinoid system, looking at preliminary clinical data in three most important autoimmune diseases of three different specialties: rheumatoid arthritis, multiple sclerosis and inflammatory bowel disease.

Keywords: cannabis, cannabis derivatives, cannabidiol, tetrahydrocannabinol, terpenes, autoimmunity, auto-antibodies

Introduction

Cannabis is one of the oldest of cultivated plants, and has been used as a raw material, food and medicinal drug for thousands of years.¹⁻⁴ It contains 538 chemical compounds, of which just 100 are natural phytocannabinoids (PCs),⁵ which are usually divided into the 10 subclasses of delta 9-tetrahydrocannabinol (THC), D8THC, cannabigerol (CBG), cannabichromene (CBC), cannabidiol (CBD), cannabinodiol, cannabielsoin, cannabicyclol, cannabinol (CBN), cannabistriol, and miscellaneous. The CBD and D9THC subclasses have so far received the most scientific attention: Gaoni and Mechoulam were the first to isolate THC and CBD in order to determine their structure and stereochemistry, and they subsequently synthesised them in the 1960s.⁶ PCs are mainly secreted by the trichomes of female plants (the glandular protuberances found on the leaves and stems) in the form of a resin whose wealth of PCs (mainly THC) and terpenoids (eg, pinene, limonene, caryophyllene) give the plants their characteristic smell.

In this paper, we provided a brief description of cannabis as a medicinal remedy, synthesized the main sites of action of the cannabis plant with a special regard to the immune system, and tried to explain whether medical cannabis action on the endocannabinoid system may be of help for patients with autoimmune diseases. In conclusion, we summarized preliminary clinical data about medical cannabis in the

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three most important autoimmune diseases of three different specialties: rheumatoid arthritis, multiple sclerosis and inflammatory bowel disease.

Medical Cannabis

Medical cannabis (MC) refers to the plant or an extract (usually with a specific relative amount of THC and CBD) used for medical purposes. The preparations may be administered by means of vaporisation and inhalation, ingestion, or topical applications; the use of vaginal, rectal or sublingual administrations is less frequent.⁷ Oral cannabis formulations take effect 30–90 minutes after ingestion, and their effect peaks after 2–4 hours; and the approximate half-life of THC is eight days in fat,^{8,9} since PCs are highly lipophilic.¹⁰ Furthermore, it seems that the bio-distribution of orally ingested CBD and THC is greater in the lymphoid tissues of the intestinal lymphatic system than in the larger lymphatic tissue of the central compartment,¹¹ which may be particularly useful when treating chronic intestinal conditions. Conversely, its delivery to the lungs aids rapid absorption and leads to an early onset of action (after only one minute) that peaks after 30 minutes at most. This suggests that this route of administration is best in the case of more acute conditions, such as multiple sclerosis-associated spasticity. The drawback is that the faster THC reaches the brain, the more likely the occurrence of side effects.¹² Mild, dose-dependent, acute adverse events are well documented: the most frequent are drowsiness, dry mouth, dizziness, vertigo, and nausea, but others include blurred vision, tachycardia, gastrointestinal disturbances (diarrhea/stipsis, lost/increased appetite, dyspepsia), and muscle spasms.^{13–16} THC-related side effects (fatigue, tachycardia and dizziness) can be avoided by very slow dose titration, which also promotes tolerance to its psychoactive side effects.¹⁶

Pharmacodynamics and the Endocannabinoid System

THC binds to PPAR γ receptors, GPR55, GPR18, TRPA1 (or capsaicin receptors, which are predominantly expressed in the nociceptive neurons of the peripheral nervous system but are also found in the central nervous system), TRPV2, TRPV3, TRPV4, several glutamate receptors, glycine receptors, and adenosine receptors, and acts as an antagonist of 5-hydroxytryptamine (HT)3 receptors and TRPM8. It has recently been discovered that GPR55, which is coupled to a G- α protein and was

once considered an orphan receptor, is activated not only by THC but also by CBD, certain synthetic cannabinoids, AEA and 2-AG, and its activation increases intracellular calcium levels.¹⁷

CBD acts as an agonist of TRPA1, TRPV1, TRPV2, TRPV3, PPAR γ , 5-HT1A, A2 and A1 adenosine, an antagonist of GPR55, GPR18, and 5-HT3A, and an inverse agonist of GPR3, GPR6, and GPR12,¹⁸ and can also down-regulate the enzymes FAAH and 5-LOX.^{19–21}

In the last decade, most of the attention has been drawn on the endocannabinoid system. The endocannabinoid system is a human biological system that consists of cannabinoid (CB) receptors and their endogenous ligands (endocannabinoids) and modulating enzymes. An increasing number of endocannabinoids have recently been discovered, including arachidonoyl ethanolamide, also called anandamide (AEA), 2-arachidonoyl glycerol (2-AG),^{22,23} 2-arachidonoyl glyceryl ether (noladin ether, 2-AGE), O-arachidonoyl ethanolamine (virodhamine), N-arachidonoyldopamine (NADA), and oleic acid amide (oleamide, OA).²⁴ Endocannabinoid-degrading enzymes include fatty acid amide hydrolases (FAAH) and monoacylglycerol lipase (MAGL). Anandamide is mainly degraded by FAAH, but also by cyclooxygenase-2 (COX-2) and lipoxygenases (LOXs); 2-AG is degraded by MAGL, and sometimes by COX-2, LOXs and minor enzymes such as α/β hydrolase-6 and α/β hydrolase-12.²⁵ Endocannabinoids are lipophilic and it is believed that, like eicosanoids, they are produced and released on demand. In addition to their interactions with CB receptors, their interactions with other molecular targets make them highly flexible, which accounts for the complexity of the system as a whole and the biological action of the individual cannabinoids.²⁶

CB1 receptors are mainly present in the central nervous system (CNS), but also found peripherally in hepatic, intestinal and adipose tissue,²⁷ the eye, cardiovascular system, pancreas, immune system, bone, skin, and skeletal muscle, thus suggesting a potentially enormous periphery/brain network of connections.²⁸ CB2 receptors are often called peripheral not only because they are mainly found in the immune system,²⁹ but also because their activation is largely devoid of psychotropic effects.³⁰ They are also present in microglial cells,³¹ and on chondrocytes, osteocytes, and fibroblasts – all cells that take part in the inflammation of the autoimmune diseases discussed in this article. Within the immune system, CB2 expression is higher in lymph nodes and spleen than in peripheral

blood cells, and varies in different cell sub-populations (B cells > NK cells > monocytes > neutrophils > CD8+ T cells > CD4+ T cells).^{32,33}

Much of CBD biological activity is independent of CB receptors, as has been demonstrated by its suppression of cytokine production in CB1 and CB2 receptor knock-out mice.³⁴ Some data suggest that CBD can indirectly activate CB1 and CB2 by increasing AEA and 2-AG levels.³⁵ Indirect targeting of the CB system is actually a well-known pharmacological technique: the most widely used analgesic drug is the decades-old paracetamol, which acts by producing AM404 and thus interfering with the reuptake of anandamide.³⁶

THC has quite a high affinity for both CB receptors, but its efficacy depends on receptor density and coupling efficiency.³⁷ ie, it mainly acts as an antagonist of endocannabinoids in tissues characterised by lower CB receptor density. CBD has less affinity for CB receptors and, more particularly, is a negative allosteric modulator of CB1, thus probably making it an antagonist of some of the effects of THC when they are concomitantly administered.^{38–40} However, a recent *in vivo* study did not confirm this hypothesis.⁴¹

Medical Cannabis and the Immune System

The activities of the large number of compounds contained in whole cannabis plants is extremely complex because the compounds themselves not only bind to a plethora of different receptors but also interact with each other both synergistically and otherwise.⁴² for example, pinene is an acetylcholinesterase inhibitor that may decrease the short-term memory impairment induced by THC.¹⁶ What follows is a brief summary of the activity of other PCs and terpenes (which have been more extensively reviewed elsewhere).⁴³

CBG is an AEA reuptake inhibitor which, when combined with CBD, has anti-inflammatory activity as it reduces the expression of tumour necrosis factor (TNF) and up-regulates interleukin (IL)-10 and IL-37 levels.⁴⁴ CBC is also an agonist of CB receptor 2,⁴⁵ and CBN inhibits COX, LOX, and P450 cytochrome enzymes.

Terpenes are very promising compounds as they have a variety of positive (analgesic, anti-depressant, anti-oxidant, and anti-bacterial) functions,⁴² but the possible contribution of adding terpenoids to cannabinoids is uncertain.⁴³ It has been reported that caryophyllenes are anti-microbial, anti-proliferative, anti-fungal, anti-oxidant and anti-inflammatory acetylcholinesterase inhibitors;⁴⁶ D-limonene may be anti-inflammatory as it mediates the inhibition of pro-

inflammatory mediators, leukocyte migration, and vascular permeability.⁴⁷ Gamma-terpinene has an effect on the pro- and anti-inflammatory macrophage production of cytokines, particularly through the IL-10 axis.⁴⁸

CB receptors are G protein-coupled receptors whose activation inhibits adenylate cyclase. By reducing cAMP levels, they decrease protein kinase A inhibition of K⁺ channels, thus decreasing cell K⁺ levels. Other signalling routes are the activation of mitogen-activated protein kinase and phosphoinositide-3-kinase.⁴⁹ CB receptor activation also activates K_{ir} channels and inhibits N- or P/Q-type Ca²⁺ channels. A post-synaptic increase in neuronal calcium can trigger the biosynthesis and release of endocannabinoids, which then bind pre-synaptically to CB1 and inhibit neurotransmitter release in the synaptic cleft in a process known as retrograde signalling.⁵⁰

The final effect clearly depends on the location of the CB1 receptors. It has been demonstrated that *in vivo* THC administration increases the release of acetylcholine, dopamine and glutamate in certain rat brain areas, probably as a result of a CB1-mediated decrease in inhibitory neurotransmitters.^{51,52} It has also been demonstrated that CB1 receptor activation may play a neuroprotective role in some of the modulatory systems involved in neurodegeneration^{53,54} and neuroinflammation.^{55,56} The mechanism of action of CB2 receptors is similar.

CB receptor binding has many effects on immune cells, but it mainly decreases immune system activation and immune cell migration by inhibiting immune cell mobilisation, inducing apoptosis, and suppressing transcription factors and cytokine release. Table 1 summarises these functions by type of immune cell.

B cells are the immune cells with the highest levels of CB1 and CB2 receptors. Cannabinoids can decrease the production of antibodies in animals and humans,^{76–78} but their effect on B cell proliferation is still unclear. In T cells, cannabinoids clearly regulate T cell proliferation as T cell apoptosis is increased by AEA and CBD and decreased in CB2-deficient mice, and both AEA and THC decrease T cell proliferation^{79–81} (although some studies suggest that CBD has a more potent anti-proliferative effect than THC).¹¹

Macrophages also express CB receptors.^{82,83} the activation of CB2 receptors blocks monocyte migration,^{84,85} but induces phagocytosis and chemokine release.⁸⁶ THC increases macrophage apoptosis and inhibits the differentiation of human monocytes into antigen-presenting dendritic cells.^{80,87}

Immunomodulation is apparently mainly regulated by inhibiting immune cell mobilisation and increasing apoptosis: endocannabinoids decrease neutrophil and

Table I Cannabinoid Mechanisms of Immune Suppression

Targets	Mechanism of Action	In vivo	In vitro	References
PBMCs	Decreasing levels of cytokines TNF- α , IFN- γ , and IL-1 α . Increasing apoptosis		✓	Watzl B et al. ⁵⁷ Watzl B et al. ⁵⁸ Nichols JM et al. ⁵⁹ Wu HY et al. ⁶⁰ Jenny M et al. ⁶¹
T lymphocytes	Influencing the balance of inflammatory Th17 and regulatory T-cells by inducing a regulatory phenotype. Decreasing T cell infiltration and proliferation by down-regulating IL-2, IL-6, IL-8, TNF α , IFN- γ , and IL-17 production, and IL-17A mRNA transcripts	✓	✓	Almogi-Hazan O et al. ¹⁸ Kozela E et al. ⁶² Jan TR et al. ⁶³ Chen W et al. ⁶⁴ Devinsky O et al. ⁶⁵ Elliott DM et al. ⁶⁶ Selvi E et al. ⁶⁷ Kinsey SG et al. ⁶⁸ Gentili M et al. ⁶⁹ Malfait AM et al. ⁷⁰
B lymphocytes	Increasing antibody responses	✓		Shapiro CM et al. ⁷¹
Neutrophils	Reducing the stimulation of neutrophil degranulation, chemotaxis, and mast cell/basophil activation.		✓	McHugh D et al. ⁷² Walter L et al. ⁷³ Giudice ED et al. ⁷⁴ Cassol OJ Jr et al. ⁷⁵

Note: ✓ Indicates the presence of either in vitro or in vivo studies, or both.

Abbreviations: PBMCs, peripheral blood mononuclear cells; TNF- α , tumour necrosis factor- α ; IFN- γ , interferon- γ .

macrophage mobilisation to sites of inflammation,^{85,88} and dendritic cell migration.⁸⁹ CB1 receptor agonists down-regulate mast cell activation and relieve the inflammatory symptoms mediated by hypersensitivity reactions.⁹⁰ On the other hand, CBD can decrease the number of neutrophils and compromise myeloperoxidase activity.⁵⁹

Another mechanism by means of which cannabinoids control immune function is the induction of regulatory cells. CBD can induce myeloid-derived suppressor cells in a mouse model of hepatitis,⁹¹ and CBD, THC and CB2-selective cannabinoids can induce a regulatory phenotype by shifting the balance between inflammatory Th17 and regulatory T cells,^{59,67,80,92,93} which is mirrored by the induction of anti-inflammatory cytokines and reduction in pro-inflammatory cytokines. CBD can suppress many transcription factors, including NFAT, AP-1 and NF- κ B, and this probably accounts for its widespread suppression of many cytokines.⁵⁹ It also prevents NLRP3/inflammasome pathway activation and suppresses the gene expression of downstream proteins, thus decreasing the production of IL-1 β .⁹⁴

The selective activation of CB2 receptors induces IL-10 by increasing its production by macrophages,⁹⁵ down-regulates NF- κ B⁹² (it is known that IL-10 production is increased in cannabis users),⁹⁶ and reduces the LPS-

induced up-regulation of the genes associated with inflammation in macrophages.⁸⁵

THC inhibits interferon (IFN)- γ secretion, which is also inhibited by CBD^{11,59} both directly (by means of a transcriptional mechanism) and indirectly by suppressing the expression of IFN- γ receptors and increasing the IFN- γ -induced genes that subsequently attenuate other immune targets. Consistently, CBD decreases IL-2 production in T cells,⁹⁷ and the engagement of both CB receptors reduces IL-2 synthesis.⁹⁸ CBD and THC also attenuate the expression of TNF- α .¹¹

Finally, various studies have shown that both THC and CBD decrease the production and release of IL-6,⁹⁹ and the action of CBD has been replicated in animal models of inflammation.⁵⁹

These findings are particularly important in the context of autoimmune diseases, but it is always necessary to remember the difficulties of applying translational cannabinoid research to human immune functions. Some in vitro and animal data suggest that the immunomodulatory activity of THC and CB2 agonists can decrease resistance to infectious agents, which is comparable with the immunosuppressive effect of the drugs used to treat autoimmune diseases,⁹ whereas other data suggest that chronic THC exposure may actually help in the case

of some viral diseases.¹⁰⁰ Another example is the higher expression of a translocator protein in long-term cannabis users, which is a marker of microglial activation and inflammation.¹⁰¹ Furthermore, although CB receptor binding is important in the immunomodulatory action of the cannabis plant, it has to be reminded that some compounds, mainly CBD, have many CB receptor independent activities.

Medical Cannabis and Autoimmune Diseases

Cannabinoids immunomodulating traits span on a variety of cell, from lymphocytes and macrophages to chondrocytes. These cells, all take place in the pathogenesis of various autoimmune disease. As each autoimmune disease differ in symptoms, it also differs in the “culpable” immune cells and cytokines inciting the disease. Hence, declaring that cannabis treatment is beneficial for autoimmune diseases does not suffice, and treatment options should be tailored for each disease. For instance, RA is characterized by elevated levels of TNF- α , IL-1 and IL-6 while IL-10 has an attenuating effect on the inflammation. Focusing on specific cannabinoids reveals that CBD, THC and CBG all reduce the levels of TNF- α , a known therapeutic target in the case of RA. Moreover, CBD also reduces IL-6 levels as mentioned above, pinpointing him as possibly the most suitable

treatment for RA. While TNF- α is also a valid target in the treatment of MS, and naturally there is an overlap in cytokine profile of various autoimmune disease, MS is also driven by the presence of IFN- γ , thus highlighting THC as a likely candidate for therapeutic options. The vast diversity of cannabinoids and their wide range of action on immune cells advocates a tailored approach. Moreover, some autoimmune diseases such as juvenile idiopathic arthritis have been shown to associate with a variation in CB2 receptor, suggesting that cannabis or cannabinoid treatment should possibly be tailored not only per disease but also per person.

The endocannabinoid system, particularly CB2 receptor activation, is a possible target for the treatment of diseases characterised by immune cell activation, such as inflammatory and autoimmune diseases,^{18,102–104} on the basis of the mechanisms described above and shown in Figure 1. The data concerning the efficacy and side effects of the different MC preparations are still limited, and many physicians prefer to avoid suggesting their use,^{18,105} however, there has been abundant pre-clinical research in this area, as can be seen from the following examples.

Rheumatoid Arthritis (RA)

Cannabinoids interrelation with RA is implied by CB receptors expression in synovia of RA patients along

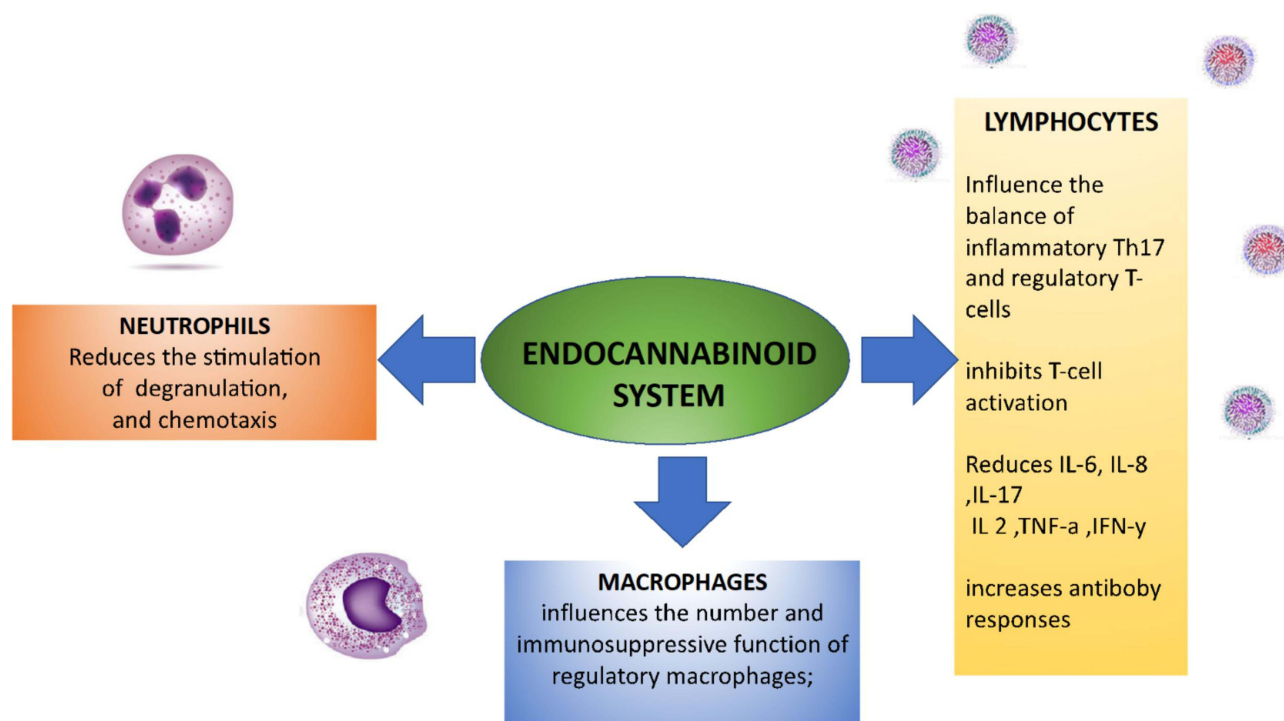


Figure 1 The endocannabinoid system is a key regulator of the immune system and therefore may be used as a target for the treatment of autoimmune diseases.

with relatively high levels of endocannabinoids.¹⁰⁶ The expression of CB receptors in the inflamed joint advocates the application of cannabinoids as therapeutic agents in RA due to their immunomodulating properties as mentioned in the previous sections.

It has been shown *in vitro* that non-selective synthetic cannabinoids reduce the production of IL-6 and IL-8 by RA fibroblast-like synovial cells,⁶⁷ and that CBD increases intracellular calcium levels and reduces the viability and IL-6/IL-8/MMP-3 production of RA synovial fibroblasts.¹⁰⁷ This is particularly interesting as IL-6 is considered a key player not only in RA inflammation but also in the pain, fatigue and mood disorders of RA patients.^{108,109} In mouse models, CBD (and particularly CB2 receptor activation) decreases synovitis and attenuates the progression of arthritis by reducing inflammatory cell infiltration, bone destruction, the production of anti-collagen type II, IgG1 and IFN-gamma, and the release of TNF.^{70,110} The anti-inflammatory effects of endocannabinoids on synovial fibroblasts may also be achieved indirectly using FAAH inhibitors.⁶⁸ Interestingly, *in vitro* culture in the presence of CBD significantly increased Th17 cell differentiation in CD4⁺ T cells from the peripheral blood of patients with RA.¹¹¹

There are currently no randomised clinical trials investigating the use of cannabis in the treatment of RA, partly because of the availability of effective biological anti-inflammatory agents in the therapeutic armamentarium.¹¹² However, one preliminary randomised, placebo-controlled study has assessed the efficacy, tolerability and safety of five weeks' treatment with a synthetic THC analogue in 58 RA patients, and found that pain was significantly reduced and disease activity significantly suppressed.¹¹³

Multiple Sclerosis (MS)

In mouse models of MS, which are created using mice with experimental autoimmune encephalomyelitis (EAE), the crucial role of the endocannabinoid system in attenuating disease activity is highlighted by the fact that clinical remission is observed in mice with lower FAAH levels¹¹⁴ and that CB2 receptor knock-out mice have worse clinical EAE scores than wild-type mice. CB2-negative T cells are characterised by reduced levels of apoptosis, higher proliferation rates, and increased inflammatory cytokine production⁷⁹ and, in line with this, CB2 receptor engagement in EAE models reduces many markers of inflammation (including iNOS, COX-2, TNF, and IL-1b).¹¹⁵ CB1 receptors may also be involved given their abundance in the central nervous system.¹¹⁶ MC

and cannabinoid-based medicines are currently being investigated and used to treat MS-associated spasticity,^{117–119} but whether they can modify the neuroinflammation that causes progressive disability is still an open question: however, even if they cannot induce robust immunosuppression, they could still help by inhibiting the glial responses that facilitate neurodegeneration.¹²⁰

Inflammatory Bowel Disease (IBD)

The use of MC to treat inflammatory bowel disease is supported by the findings of preclinical studies showing that the endocannabinoid system plays a role in regulating intestinal inflammation.¹²¹ In many animal models of colitis, the administration of CB1 or CB2 receptor agonists^{122–124} and the inhibition of FAAH has prevented or reduced colonic inflammation,^{125,126} and it has been found that CB1 and CB2 knockout mice are more susceptible to chemically induced colitis.^{123,127}

Furthermore, immunohistochemical studies of humans have shown that the expression of CB2 receptors is amplified during inflammatory flares, thus suggesting that they are a potential therapeutic target.^{128,129} It is possible that the use of oral formulations may be more successful as it has been discovered that the THC and CBD they contain can efficiently reach the intestinal lymphatic system.¹¹ MC can also have beneficial effects on the permeability of the gastrointestinal tract.¹³⁰

Surveys and cross-sectional studies of IBD patients have shown that many of them smoke usually illegally obtained cannabis in order to alleviate their symptoms. The symptoms that are reported to improve the most are abdominal pain and cramps, appetite,^{131,132} and nausea.¹³³ One 2014 study¹³² found that the use of cannabis correlated with a need for surgery, but a more recent study¹³⁴ showed that the prevalence of partial or total colectomy was lower in cannabis users than non-users, and that there was also a trend towards a lower prevalence of bowel obstruction. A recent Australian survey found that clinical severity ratings were not different between cannabis users and non-users, but the former reported more hospitalisations, less engagement with specialist services, and less adherence to prescribed medications; the IBD that were positively affected by cannabis included abdominal pain, stress, sleep, cramping, and anxiety.¹³⁵

The first retrospective study of the clinical use of MC dates back to 2011¹³⁶ and, since then, researchers have concentrated more on the different compositions of the MC preparations used to treat IBD. The findings of one

study suggest that CBD-only MC preparations are not effective for Crohn's disease,¹³⁷ and a study of a very small patient cohort by the same group found that a more THC-rich preparation induced significant, steroid-free clinical benefits.¹³⁸ Furthermore, the use of MC capsules with a high CBD/THC ratio has led to improvements in the partial Mayo score, the patients' subjective global impression of disease activity, and physicians global assessments of disease severity,¹³⁹ although there were many dropouts due to THC-related adverse events. Finally, a recent small study found that inhaled THC did not improve disease markers or remission rates in a cohort of 127 ulcerative colitis patients, but did improve disease activity scores.¹⁴⁰

Conclusions

The complexity of PCs and their wide range of interactions with multiple potential therapeutic targets support the legalisation of the medicinal use of the world's oldest and best-known illicit drug, especially on the basis of observational studies,¹⁴¹ and emerging knowledge of autoimmunity and the high density of CB2 receptors on immune cells makes the endocannabinoid system a natural target for the treatment of inflammatory and autoimmune diseases.¹⁴² In vitro and animal studies of multiple sclerosis have provided convincing evidence of the immunomodulatory properties of cannabis, although there is still a lack of clinical evidence from randomised and controlled clinical trials. However, given our limited knowledge of the long-term safety and efficacy of cannabis and its possible drug–drug interactions, it is still too early to make any definite recommendations concerning the cannabinoid treatment of autoimmune diseases, and this should only prompt further research in order to fill these gaps.

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Disclosure

All of the authors declare that they have no conflict of interest in relation to this paper.

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