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Therapeutic Prospects of Cannabinoids in the Immunomodulation of Prevalent Autoimmune Diseases

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Abstract

Introduction: Cannabinoids such as Δ-9-THC and CBD can downregulate the immune response by modulating the endocannabinoid system. This modulation is relevant for the treatment of prevalent autoimmune diseases (ADs), such as multiple sclerosis (MS), systemic lupus erythematosus (SLE), diabetes mellitus type 1 (DMT1), and rheumatoid arthritis (RA). These conditions require new therapeutic options with fewer side effects for the control of the autoimmune response. Objective: to conduct a literature review of preclinical scientific evidence that supports further clinical investigations for the use of cannabinoids (natural or synthetic) as potential immunomodulators of the immune response in ADs.

Methodology: A systematic search was carried out in different databases using different MeSH terms, such as *Cannabis sativa* L., cannabinoids, immunomodulation, and ADs. Initially, 677 journal articles were found. After filtering by publication date (from 2000 to 2020 for SLE, DMT1, and RA; and 2010 to 2020 for MS) and removing the duplicate items, 200 articles were selected and analyzed by title and summary associated with the use of cannabinoids as immunomodulatory treatment for those diseases.

Results: Evidence of the immunomodulatory effect of cannabinoids in the diseases previously mentioned, but SLE that did not meet the search criteria, was summarized from 24 journal articles. CBD was found to be one of the main modulators of the immune response. This molecule decreased the number of Th1 and Th17 proinflammatory cells and the production of the proinflammatory cytokines, interleukin (IL)-1, IL-12, IL-17, interferon (IFN)-γ, and tumor necrosis factor alpha, in mouse models of MS and DMT1. Additionally, new synthetic cannabinoid-like molecules, with agonist or antagonist activity on CB1, CB2, TRPV1, PPAR-α, and PPAR-γ receptors, have shown anti-inflammatory properties in MS, DMT1, and RA.

Conclusion: Data from experimental animal models of AD showed that natural and synthetic cannabinoids downregulate inflammatory responses mediated by immune cells responsible for AD chronicity and progression. Although synthetic cannabinoid-like molecules were evaluated in just two clinical trials, they corroborated the potential use of cannabinoids to treat some ADs. Notwithstanding, new cannabinoid-based approaches are required to provide alternative treatments to patients affected by the large group of ADs.

Keywords: autoimmune disease; cannabidiol; cannabinoids; *Cannabis sativa* L; delta-9-tetrahydrocannabinol; literature review

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Introduction

Autoimmune diseases (ADs) include more than 80 chronic illnesses with an overall estimated prevalence of 4.5% (males, 2.7%; females, 6.4%), and it has become the fourth cause of work-related disability.[1,2] Worldwide, the most prevalent ADs are systemic lupus erythematosus (SLE) with about 241 cases per 100,000 population in North America,[3] multiple sclerosis (MS) (30.1 cases per 100,000 global population),[4] diabetes mellitus type 1 (DMT1) (0.8 to 4.6 cases per 100,000 global population),[5] and rheumatoid arthritis (RA) (0.24 cases per 100,000 global population).[6]

The etiology of ADs is still unknown. However, their development is associated with different factors, such as genetic susceptibility and environmental conditions that generate the loss of immunological self-tolerance.[7] The dysregulated activation of the immune system (IS) against self-antigens, mediated by T and B cells triggers an abnormal attack against self-tissues leading to systemic or specific-organ diseases.[8]

Currently, pharmacotherapy for ADs is based on nonsteroidal anti-inflammatory drugs (NSAIDs) and disease-modifying antirheumatic drugs that alleviate symptoms of many patients, but at the cost of multiple side effects.[9] Research in plant pharmacology has been under development since 1955 when it initiated the investigation of active plant components to be used as a source of new drugs aimed at cancer treatments,[10] and more recently for modulating the immune response.[11]

One plant that has captured the attention of researchers and physicians for its immunomodulatory potential is *Cannabis sativa* L. This plant has been recognized since ancient times for its medicinal properties, which are currently known to be mediated through its content of 565 secondary metabolites. These components include 120 cannabinoids, such as △-9-THC, CBD, cannabinol (CBN), and cannabigerol (CBG), among others, as well as terpenes, flavonoids, and nitrogenous compounds; all of them can exert combined (entourage)[12,13] as well as individual effects that determine its therapeutic use.[14]

Experiments carried out since 1976 by Dr. Mechoulam have revealed that cannabinoids, such as △-9-THC, can interact with cannabinoid receptors (CB1 and CB2) present in human cells.[15–17] These receptors belong to the endocannabinoid system (ECS), located in the central nervous system (CNS) and different peripheral tissues.[18] CB1 receptors are mainly found in the CNS, in areas of the brain that regulate crucial functions such as pleasure, memory, concentration, sensory and time perception, as well as coordinated movement. On the other hand, CB2 receptors are widely distributed in cells of the IS, which includes the thymus, tonsils, bone marrow, and spleen.[18,19]

In mammals, the natural ligands for the ECS receptors are 2-arachidonoylglycerol (2-AG) and N-arachidonoylethanolamine or anandamide (AEA); they derive from the breakdown of arachidonic acid present in the membrane of all the cells[20]; and are continuously synthesized and released by neurons and immune cells to regulate this system.[21]

CB2 receptors seem to be the principal ECS receptors involved in the regulation of the immune responses because of their differential expression in cells of the IS (CB2 receptor mRNA levels: B lymphocytes (LB) > Natural killer (NK) cells > monocytes > polymorphonuclear neutrophils > $CD8^+$ T cells > $CD4^+$ T cells).[21,22]

Recently, non-CB1 and non-CB2 receptors that also belong to the ECS have been involved in the modulation of the IS. Ionotropic receptors include the transient receptor potential (TRP) channels TRPV1-TRPV4, transient receptor potential ankyrin 1 (TRPA1), and transient receptor potential melastatin 8 (TRPM8).[23] Additionally, the nuclear receptors include the peroxisome proliferator-activated receptors (PPARs) and the other receptors that comprises G protein-coupled receptor 55 (GPR55), nicotine receptor (5HT3), and adenosine A2A receptors (ADORA2A) are also involved in the cannabinoid-induced signal transduction pathways.[24,25]

The TRP ion channels were primarily considered sensors of many physiological (temperature sensation) and pathological processes (pain, itchiness).[26,27] However, recent investigations have shown the expression of TRPs in cells of the IS: dendritic cells (DCs), macrophages, and T cells. TRPV1 regulates calcium-mediated signaling pathways and is crucial for many cellular processes; for example, proliferation, apoptosis, cytokine secretion, and T cell activation.[28] The TRPV1 overexpression has been associated with neurogenic inflammation, neuropathic pain (NeP), autoimmune disorders, cancer, and functioning of cells of the IS.[25]

TRPV1 is a natural receptor of AEA. The TRPV1-AEA interaction leads to the release of the substance P and calcitonin gene-related peptide (CGRP), which exert local vasodilatory and proinflammatory effects.[29,30] These observations could explain the association between the TRPV1 overexpression and the development of different diseases of the IS.

On the other hand, PPARs have three isoforms (α, γ, and β/δ) that regulate the expression of distinct genes

involved in metabolism, energy homeostasis, cell differentiation, and inflammation.[31–33] PPARs are expressed in the nucleus of macrophages, DCs, T, and B cells, and regulate cytokine secretion and lymphocyte proliferation.[34] Further research has shown that endocannabinoids and phytocannabinoids act selectively through PPAR-α (AEA, △-9-THC) and PPAR-γ (AEA, 2-AG, △-9-THC, CBD, CBC, CBG) to modulate the response of cells mentioned above.[35]

△-9-THC and CBD are involved in the regulatory activity between the ECS and the immune response. The research in this area indicates that △-9-THC (a partial agonist of the CB1 receptor) has anti-inflammatory activity resulting from the inhibition of prostaglandin E2 (PGE2) synthesis,[36] the reduction of platelet aggregation,[37] and the stimulation of lipoxygenase.[38] The signal generated by △-9-THC has 20 times the anti-inflammatory potency of aspirin and twice that of hydrocortisone,[39] but in contrast to all NSAIDs, it does not inhibit cyclooxygenase (COX) at physiological concentrations.[40]

Moreover, CBD, a nonpsychoactive metabolite of *C. sativa* L., is known to have the highest anti-inflammatory effect. CBD modulates the responses of human immune cells in culture and the immune response of animal models of ADs because it is an exogenous ligand of multiple receptors (CB1, CB2, 5-HT1A, and PPAR-γ; ADORA2A and GPR55)[41] that are expressed by different cells of the IS.[22,42] Signals derived from these multiple cannabinoid/receptor interactions decrease the secretion of proinflammatory cytokines (interleukin [IL]-1β, IL-8, IL-10, IL-12, tumor necrosis factor alpha [TNF-α], and INF-γ) and balance the immune response.[43–45]

Recently, the Food and Drug Administration (FDA) approved the use of CBD in the United States of America to treat refractory epileptic conditions associated with the Lennox/Gastaut and Dravet syndromes.[46] However, despite the evident immunomodulatory activity of CBD, no clinical trials have been carried out to investigate the mechanisms by which this molecule regulates the immune responses.

CBN is another cannabinoid compound with immunomodulatory properties. CBN is derived from △-9-THC but is less psychoactive. It binds to CB2 receptors present in splenocytes and thymocytes and has high immunomodulatory activity due to its ability to decrease IL-2 production.[40,47]

Considering that many of the ligands and endogenous receptors of the ECS are present in cells of the innate and adaptive IS, it is currently postulated that the ECS could be involved in the immune response's homeostasis.[48] This hypothesis offers new expectations for the management and treatment of ADs through cannabinoids.

The purpose of the present study is to conduct a literature review of preclinical scientific evidence that could support more clinical investigations into the use of natural and synthetic cannabinoids as potential modulators of the immune response in prevalent ADs.

Methodology

Two independent investigators reviewed the EBSCO-Host, PubMed-National Library Medicine (NLM), and Virtual Health Library (VHL) databases, in search of the following MeSH terms: "*Cannabis sativa*" OR "Cannabinoids" OR "Phytocannabinoid" AND "Autoimmune disease" AND "Immunomodulation"/"Immunomodulator"/"Biomodulator"/"Biological response modifier"/"Inflammation"/"Immunologic factor"/"Anti-inflammatory agents". Both investigators found the same 677 articles. After filtering by publication date from 2010 to 2020, 454 articles remained. Duplicate data were removed using the Zotero software with a final yield of 200 single articles.

These articles were evaluated by title and abstract to select those associated with any of the following terms: "Multiple sclerosis", "Systemic Lupus Erythematosus", "Diabetes mellitus type 1", and "Rheumatoid arthritis", and reporting the use of natural or synthetic cannabinoids as immunomodulatory therapy. However, considering the scant information reported for SLE, DMT1, and RA between 2010 and 2020, the publication date range was extended to 20 years: from 2000 to 2020. Notwithstanding, there were no articles for SLE that met the search criteria. Finally, 24 articles on preclinical data providing scientific evidence of the cannabinoid-mediated immunomodulation in the ADs mentioned above were analyzed for the present review.

Results

This review summarizes data derived from cellular and animal models, about the immunomodulatory role of natural and synthetic cannabinoids, and terpenes in autoimmunity.

Natural and synthetic cannabinoids, and β-caryophyllene decrease the inflammatory response in MS

MS is an autoimmune disorder mediated through myelin-specific self-reactive T cells, and macrophages/microglial cells, and astrocytes.[49] Although the etiology

and pathophysiology of MS are not clearly understood, different researchers suggest that the disease could be associated to various genetic, environmental, and infectious factors[50–52] that result in chronic inflammation of the CNS. Tissue damage is mediated by infiltrating Th1/Th17 cells in association with activated macrophages and the synthesis of proinflammatory cytokines that cause oligodendrocyte death, demyelination, and axonal damage.[53,54] The abnormal response results in many signs and symptoms of the disease, such as muscle spasms, tremors, ataxia, weakness or paralysis, constipation, and loss of bladder control.[55,56]

Recently, Sativex (Nabiximols), a drug obtained from *C. sativa* L. has been approved to treat some clinical manifestations of MS, such as muscle stiffness and chronic NeP. Sativex is a natural extract with a 1:1 △-9-THC:CBD ratio that interacts with cannabinoid CB1, CB2, PPARs, and GPR55 receptors. Sativex inhibits ascending nociceptive transmission at the supraspinal level, mainly at the thalamus, modifies the emotional component of pain by acting at the limbic system and cortical areas, and activates the descending inhibitory pathway through the inhibition of GABA release in the periaqueductal gray and rostral ventral medulla.[57,58]

Despite much evidence about the positive effects of Sativex on pain and spasticity observed in MS, its immunomodulatory potential in ADs is still unknown; however, different natural and synthetic cannabinoids with anti-inflammatory activity are currently under investigation (Table 1).

CBD is considered a promising modulator of the immune response due to its interaction with many cannabinoid receptors expressed by the IS cells.

In experimental autoimmune encephalitis (EAE), the murine model for MS, the CBD decreases the T cell infiltration into the CNS and the secretion of IL-17 and interferon (IFN)-γ through a mechanism associated with increased numbers of myeloid-derived suppressor cells (MDSC), which have anti-inflammatory activity.[59] Additionally, CBD prevents the activation of the Fas and the phospho-ERK p42/44 pathways, and the cleaved caspase-3, blocking this way the apoptosis of oligodendrocytes in the spinal cord.[60] Furthermore, CBD increases phosphorylation of phosphatidylinositol 3-kinase (PI3K), PKB and mammalian target of rapamycin, leading to reduced activity of Th17 cells. In summary, the therapeutic effect of CBD in MS is mainly mediated through decreased levels of proinflammatory cytokines (IFN-γ and IL-17) together with upregulation of PPAR-γ receptors.[61]

Additionally, Al-Ghezi et al. demonstrated that the combination of △-9-THC and CBD for treatment of mice with EAE decreased the numbers of Th1 and Th17 cells in CNS, resulting in lower levels of proinflammatory (IL-1, IL-6 IL-17, INF-γ, TNF-α) cytokines. This treatment also induced an anti-inflammatory phenotype characterized by higher expression of forkhead box P3 (FoxP3), STAT5b, IL-4, IL-10, and transforming growth factor-beta (TGF-β) by regulatory T cells (Treg cells) in the CNS.[62]

CBG is another phytocannabinoid with immunomodulatory properties. It is a nonpsychoactive molecule with agonist activity on CB2 and PPAR-γ receptors.[63] VCE-003, a synthetic CBG derivative, inhibits the Th1/Th17 response associated with IL-17 secretion; through this way, VCE-003 participates in the M1 (proinflammatory) toward M2 (anti-inflammatory) macrophage polarization. Consequently, VCE-003 reduces the $CD4^+$ T cell infiltration in the spinal cord and decreases microglial cells' activation.[64]

Given the advances in the chemical characterization of new metabolites of *C. sativa* L., the therapeutic effects of terpenes have started to be studied in MS. For instance, the terpene β-caryophyllene (BCP), a selective CB2 agonist, was evaluated in the mouse model of EAE, where it inhibited the activation of $CD4^+$/$CD8^+$ T cells and M1 macrophages. Besides, BCP also reduced the expression of proinflammatory cytokines (IL-1, IL-6, and TNF-α) and decreased the number of Th1 cells in the CNS.[65] Furthermore, Askari et al. found that the combination of BCP and the SMase imipramine exerts a modulatory effect on Th1 and Th17 cells and M1 macrophages and reduced the proinflammatory cytokines. These results indicate that BCP is another molecule from *Cannabis* that could regulate the inflammatory responses observed in MS.[66]

The search for new CB1 and CB2 receptor agonists involves some synthetic components, such as WIN 55 (an aminoalkylindole derivative, CB1 agonist) and COR167 (based on a quinolone-3-carboxylic acid core structure, CB2 agonist). In the mouse model of EAE, WIN 55 reduced the response of Th1 cells and M1 macrophages, and thereby the levels of proinflammatory cytokines (IL-2, IL-6, RANTES, TNF-α, and TGF-β).[67] Additionally, WIN 55 reduced the T cell infiltration and lowered the activation of M1 macrophage in the CNS, leading to a lower expression of proinflammatory cytokines.[68] It is important to note that in the EAE model, WIN 55 also bound to PPAR-α receptor, increasing the anti-inflammatory response through a higher expression of IFN-β.[69]

Table 1. Immunomodulatory Activity of Natural and Synthetic Cannabinoids and Terpenes in Multiple Sclerosis

Immunomodulatory activity	Model	Phytocannabinoid	Synthetic cannabinoid	Outcome	Year	References
Anti-inflammatory	Mouse EAE Dark Agouti	—	WIN 55	↓ Calpain-1 and proinflammatory cytokines (IL-2, IL-6, IL-10, RANTES, TGF-β). ↓ T cells and macrophages/microglia in CNS.	2011	[68]
	TMEV	—	WIN 55	↑Treg cells $CD4^+$ $CD25^+$ $Foxp3^+$ in CNS.	2012	[70]
	Mouse EAE C57BL/6	—	WIN 55	↓ Proinflammatory markers (COX-2, iNOS, and TNF-α) in the spinal cord.	2012	[67]
	Mouse EAE SJL/J	—	WIN 55	↑TLR3-induced IFN-β expression through PPARα.	2012	[69]
	Mouse EAE C57BL/6	—	VCE-003	↓ Th1/Th17 cytokines. ↓ Transcription of IL-2, IL-17, and TNF-α promoters induced by CD3/CD28.	2014	[64]
Anti-inflammatory and antiapoptotic	Mouse EAE C57BL/6	CBD	—	↓ TNF-α and IL-1. Prevents activation of the Fas pathway, fosfo-ERK p42/44, and the activation of cleaved caspase-3 in the spinal cord tissues.	2015	[60]
Anti-inflammatory and antiproliferative	Human PBMCs of patients with MS	—	COR 167	Exerts a dose-dependent inhibitory effect on T cell proliferation. ↓ Proinflammatory cytokines (IL-6, IL-17) and Th17 cells.	2017	[71]
Anti-inflammatory	Mouse EAE C57BL/6	BCP	—	↓ Proinflammatory cytokines TNF-α, IL-6, and IL-1β and NF-κB ↑ Treg cells.	2017	[65]
	Mouse EAE C57BL/6	CBD	—	↑ PI3K, Akt, and mTOR. ↓ Th17 responses.	2017	[61]
	Mouse EAE C57BL/6	CBD	—	↓ T cells, IL-17, and IFN-γ. ↑ MDSC.	2018	[59]
	Mouse EAE C57BL/6	BCP + IMP	—	↓ Th1 cells. ↑ Treg and Th2 cells and M2 Macrophages.	2019	[66]
	Mouse EAE C57BL/6	△-9-THC CBD	—	↓ Th1, Th17 cells. ↓ Proinflammatory cytokines (IL-17, INF-γ, TNF-α, IL-1, IL-6, and TBX21). ↑ Anti-inflammatory molecules (Foxp3, STAT5b, IL-4, IL-10, and TGF-β).	2019	[62]

Experimental controls were done in all studies.

AEA, anandamide; Akt, Ak strain transforming, serine/threonine protein kinase; BCP, β-caryophyllene; CBG, cannabigerol; CD, cluster of differentiation; CNS, central nervous system; COR167, based on a quinolone-3-carboxylic acid core structure (CB2 agonist); COX-2, cyclooxygenase-2; EAE, experimental autoimmune encephalomyelitis; ERK, extracellular signal-related kinase; Foxp3, forkhead box P3; IFN, interferon; IL, interleukin; IMP, imipramine (sphingomyelinase inhibitor); iNOS, inducible nitric oxide synthase; MDSC, myeloid-derived suppressor cells; MS, multiple sclerosis; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor-κB; PBMC, peripheral blood mononuclear cells; PI3K, phosphatidylinositol 3-kinase; PPAR-α, peroxisome proliferator-activated receptor α; RANTES (CCL5), regulated on activation, normal T cell expressed and secreted (C-C Chemokine ligand 5); STAT5b, signal transducer and activator of transcription 5B; TBX21, T-box transcription factor; TGF-β, transforming growth factor beta; Th, T helper; TLR, Toll-like receptor; TMEV, Theiler's murine encephalomyelitis virus; TNF-α, tumor necrosis factor alpha; Treg cells, regulatory T cells; VCE-003, synthetic CBG derivative, PPAR-γ and CB2 agonist; WIN 55, WIN 55212-2 (CB1 receptor agonist).

WIN 55 showed similar results in the Theiler's murine encephalomyelitis virus (TMEV) model for MS, decreasing the activation of $CD4^+$ $CD25^+$ T cells and increasing the number of Treg cells ($CD4^+$ $CD25^+$ $Foxp3^+$) in the CNS of mice. These events were accompanied by lower synthesis of proinflammatory cytokines by T cells and higher levels of anti-inflammatory cytokines by Treg cells.[70] On the other hand, COR167 exhibited an anti-inflammatory activity, evidenced by the decreased number of circulating Th17 cells that resulted in lower levels of IL-6 and IL-17.[71]

Evidence shows that the immunomodulatory activity of the different cannabinoids indicates a decrease in proinflammatory cytokines and apoptotic pathways in CNS cells[60] as well as an increase in Treg cells and anti-inflammatory cytokines.[65,66,70] The studies reported in this review showed promising results for future MS treatment; however, more clinical studies are needed to evaluate if the immunomodulation generated by these molecules causes significant changes associated with the reduction and maintenance of an anti-inflammatory environment in this chronic illness.

Modulation of the inflammatory response by cannabinoids delays the progression and complications of DMT1

DMT1, also known as insulin-dependent diabetes, is a chronic AD characterized by the destruction of pancreatic β cells and autoantibodies against some proteins synthesized by them, such as insulin, glutamate decarboxylase, islet antigen 2, zinc transporter 8, and tetraspanin-7. DMT1 results from a complex interaction of environmental factors, the microbiome, genome, metabolism, and inadequate maintenance of immune self-tolerance.[72,73]

DiMeglio et al. described that DMT1 initiates when APCs of the pancreatic lymph nodes present β cell-derived peptides to autoreactive $CD4^+$ T cells, which in turn activate $CD8^+$ T cells. β cells are then destroyed by a high amount of proinflammatory cytokines released by effector $CD8^+$ T cells and reactive oxygen species (ROS) from innate immune cells (macrophages, NK cells, and neutrophils). Additionally, Treg cells are unable to suppress the inflammation and favor the production of autoantibodies by B cells.[73] Thus, the so-called "insulitis" develops, resulting in low insulin production and consequent hyperglycemia that causes neurological and vascular complications in patients with DMT1.[74]

Different investigations show that natural and synthetic cannabinoids could modify the inflammatory process (Table 2) and delay the appearance of hyperglycemia-related complications observed in patients with DMT1. In the nonobese diabetic (NOD) mouse model, Weiss et al. observed that CBD treatment reduced significantly the plasma levels of proinflammatory cytokines (TNF-α, IFN-γ), produced by activated Th1 cells and peritoneal macrophages, and increased the synthesis of the Th2-associated cytokines, IL-4 and IL-10.[75,76] Moreover, Lehmann et al. used CBD as a prophylactic anti-inflammatory in NOD mice and observed a reduced activation of immune cells within the pancreatic microcirculation in the early stages of the disease that delayed the development of insulitis.[77]

On the other hand, different studies have shown that Δ-9-THC also has an antioxidant effect. In fact, in the streptozotocin-induced diabetic mouse model, Δ-9-THC reduced not only the expression of proinflammatory cytokines (IL-1 and IL-6) but also diminished the levels of malondialdehyde (the final product of polyunsaturated fatty acids peroxidation) and increased the levels of nitric oxide (NO). The authors highlighted that the combined anti-inflammatory and antioxidant effects of Δ-9-THC delayed the progression of this disease.[78,79]

Additionally, it is essential to note that diabetic peripheral neuropathy (DPN) and NeP are related to proinflammatory cytokines (IL-1β, IL-6, and TNF-α) primarily produced by glial cells in the spinal cord.[80,81]

Bearing in mind that cannabinoid receptors (CB1 and CB2) are expressed in activated microglia cells, alternative cannabinoid therapy has become more relevant in recent years in the treatment of complications of DMT1.[74] Accordingly, Toth et al. determined the impact of different natural phytocannabinoids as CBD (CB2 and GPR55 antagonist,) and synthetic cannabinoids: SR144528 (CB2 receptor antagonist), WIN 55 (CB1 receptor agonist), SR141716A (selective CB1 antagonist), and nabilone (nonselective CB1 and CB2 agonist) on NeP. They found that just CBD limited pain development at the onset of diabetes by a restriction in elevation of microglial density and the expression of Phospho-P38 (p-p38) mitogen-activated protein kinase in the dorsal spinal cord of CD1 mice.

Therefore, cannabinoids can block ectopic signals released by a damaged nervous system by inhibiting the activity of inflammatory cells. However, more studies are needed to delve into the underlying mechanisms

Table 2. Immunomodulatory Activity of Natural and Synthetic Cannabinoids in Diabetes Mellitus Type 1

Immunomodulatory Activity	Model	Phytocannabinoid	Synthetic cannabinoid	Outcome	Year	References
Anti-inflammatory	CD-1 mouse B6C3F1	[a]	[a]	↓ mRNA expression of proinflammatory cytokines (IFN-γ, TNF-α, and IL-12).	2001	79
	NOD mouse	CBD	—	↓ Plasma levels of IFN-γ, TNF-α.	2006	75
				↑ Th2 regulatory cytokines (IL-4 and IL-10).		
	NOD mouse	CBD	—	↓ Proinflammatory IL-12 in splenocytes.	2008	76
				↑ Anti-inflammatory IL-10.		
	CD-1 mouse	CBD		Lower densities of microglia in the dorsal spinal cord, expression of p-p38 MAPK was diminished and also alleviation of development of thermal hypersensitivity and tactile allodynia.	2010	74
			WIN 55			
			Nabilone			
			SR144528	Alleviation of development of thermal hypersensitivity and tactile allodynia.		
			SR141716A	Was no observed effect with any intervention.		
	NOD mouse	CBD	—	↓ Inflammation markers and infiltrating leukocytes in pancreatic microcirculation (studied by intravital microscopy).	2017	77
Antioxidant	Wistar-Kyoto rats	↑[b]	↑[b]	↓ Oxidative stress, lipid peroxidation, and blood glucose.	2017	78

[a]CB1 agonist, unspecified source.
[b]Agonist (receptor not specified) ↑ unspecified source. Experimental controls were done in all studies.
CD-1, wild mouse; MAPK, mitogen-activated protein kinase; Nabilone, CB1 and CB2 agonist; NOD, nonobese diabetic; SR144528, CB2 antagonist; SR141716A, CB1 antagonist; WIN 55, WIN 55212-2 (CB1 receptor agonist).

of the antinociceptive effects of CB1 and CB2 agonists in addition to studies where treatment can be administered at the time of injury or neuronal disease.[74]

Decreased proinflammatory cytokine production induced by cannabinoids is critical for delaying the articular cartilage degeneration in RA

RA is an inflammatory and degenerative joint disease mainly characterized by the loss of articular cartilage. The joint damage is mediated through matrix metalloproteinases (MMPs), particularly MMP-2, MMP-3, and MMP-13. These enzymes increase in response to the high production of proinflammatory cytokines (IL-1 and TNF-α) by articular chondrocytes.[82]

Natural and synthetic cannabinoids have anti-inflammatory activity and reduce the joint damage in animal models of arthritis, as summarized in Table 3. According to *in vitro* studies, synthetic cannabinoids, such as WIN 55, HU-210, and CP55.940 decrease the number of Th1 cells; additionally, WIN 55 reduces PGE2 production, inducible NO synthase, COX-2, and nuclear factor-κB (NF-κB) activation. Consequently, they induce less degradation of collagen and proteoglycans and production of MMP by fibroblasts. Altogether, these effects contribute to reducing the extracellular matrix degradation in the articular cartilage.[83–85]

It is also essential to highlight the immunomodulatory activity of Ajulemic acid, a nonpsychoactive synthetic cannabinoid derived from 11-Nor-9-carboxy-THC.[86] This acid is a CB2 receptor agonist that increases the synthesis of lipoxin A4 (LXA4), an endogenous eicosanoid with anti-inflammatory properties that reduces the synthesis of proinflammatory cytokines (IL-1, IL-6, and TNF-α).[83]

The synthetic cannabinoid WIN 55 also modulates the inflammatory response by decreasing the synthesis of proinflammatory cytokines and IFN-β.[87] Likewise, HU-320 (synthetic cannabinoid) reduces MMP-3 and MMP-13 expression in the presence of IL-1 and significantly downregulates the expression of genes coding for the tissue inhibitors of metalloproteinases, *TIMP-1* and *TIMP-2*.[88]

Similarly, the TRPV2 agonists, O1821 and especially LER13, reduced the expression of MMP-2 and MMP-3 (critical metalloproteinases involved in joint damage) in fibroblast-like synoviocytes from patients with RA and animal models of arthritis; besides, those TRPV2 agonists controlled the severity of inflammation.[89] Other synthetic CB2 agonists exhibit anti-inflammatory properties; for instance, HU-308 can

Table 3. Immunomodulatory Activity of Natural and Synthetic Cannabinoids in Rheumatoid Arthritis

Immunomodulatory activity	Model	Phytocannabinoid	Synthetic cannabinoid	Outcome	Year	References
Anti-inflammatory	Human PBMCs FLS	—	Ajulemic acid	↓ IL-1, IL-6, MMPs.	2003	[83]
	Mouse C57B/6	—	HU-320	↓ Production of TNF-α and ROS from macrophages.	2004	[88]
	Bovine articular chondrocytes	—	HU-210 WIN 55	↓ IL-1 stimulated proteoglycan and collagen degradation ↓ PGE2 production, iNOS, COX-2, and NF-kB	2006	[85]
	FLS	—	CP55,940 WIN-55	↓ Proinflammatory cytokines (IL-1, IL-6, IL-8.).	2008	[84]
	C57BL/6 mouse FLS	—	O1821 LER13	↓ IL-1β-induced expression of MMP-2 and MMP-3.	2015	[89]
	CIA mouse model	—	HU-308	↓ Proinflammatory cytokines (IL-6 and TNF-α) in murine peritoneal macrophages.	2015	[90]

Experimental controls were done in all studies.
FLS, fibroblast-like synovial cells; HU-210, CB1/CB2 agonist; HU-320, CB1/CB2 agonist; HU-308, CB2 agonist; LER13, TRPV2 receptor agonist; MMP, matrix metalloproteinase; O1821, cannabidiol analog; PGE2, prostaglandin E2; ROS, reactive oxygen species; WIN 55212-2 (CB1 agonist).

reduce the production of proinflammatory cytokines (IL-6 and TNF-α).[90]

Our research group has evaluated the immunomodulatory activity of *Cannabis* extracts enriched in different proportions of the cannabinoids CBD, △-9-THC, CBG, and terpenes, on peripheral blood mononuclear cells (PBMCs) and macrophages (M1/M2) in patients with RA. Preliminary results showed that extracts with a CBD:THC (2:1) ratio and a higher content of terpenes have a better antiproliferative effect on stimulated PBMCs in these patients (article in preparation).

All these data show that the immune response's modulation by cannabinoids is linked to the CB1/CB2 and TRPV2 receptors and that cannabinoids could become a new therapeutic strategy in the treatment of RA These results warrant future research into the pathways responsible for the benefits that an alternative cannabinoid-based treatment could offer to patients with RA.

Discussion

Autoimmune responses are generated mainly by T and B cells that, during the triggering of an imbalanced immune response, differentiate into $CD8^+$(cytotoxic), $CD4^+$ helper (Th1, Th2, Th17), and regulatory Treg cells, and antibody secretory cells.[91] These effector cells promote the chronic inflammation associated with the degenerative tissue damage typical of these diseases.[91–94] Despite the availability of pharmacological treatments for patients with AD, medication adherence is increasingly lower due to treatment failure and adverse effects.[95–97] Therefore, this review summarizes preclinical evidence about the immunomodulatory potential of natural and synthetic cannabinoids in animal models of human ADs, which supports the development of alternative approaches to treat patients affected by these pathologies.

In this review, we found that many of the studies that have been carried out in models of MS and DMT1 explore the anti-inflammatory properties of natural CBD, presumably because these do not have any psychoactive properties and regulate the immune responses through agonist interaction with different receptors (CB2, TRPV1, PPARs, and GRP55) that are expressed by cells of the IS.[22,42] In these models, CBD decreased the numbers of Th1 and Th17, the production of the proinflammatory cytokines as IFN-γ, TNF-α, IL-1, IL-12, and IL-17,[59,74–76] and increased the numbers of MDSC, Treg cells, and the production of IL-10, which play a dominant role in the suppression of the autoimmune pathology.[98,99]

One of the etiopathogenetic factors widely investigated in the development of MS is the aberrant autoimmune response generated in the CNS by the infiltration and activation of T and B cells and the destruction of the neuron myelin sheath.[53,54,100] CBD is used to manage muscle stiffness and chronic NeP in patients with MS[57,58]; however, it also decreases the infiltration of $CD4^+$ T cells and the release of IL-4 associated with the demyelination process of neurons.[101] Besides, CBD protects cells of the spinal cord from caspase-mediated apoptosis (cleaved caspase 3).[60] These data evidence that CBD treatment could be extended to various diseases associated with neuroinflammation and

neuronal protection as Alzheimer's and Parkinson's diseases.[102,103]

Moreover, the use of intranasal and intraperitoneal CBD in animal models of DMT1 was associated with reduced microglia cell density in the dorsal spinal cord and lesser NeP in the DPN.[74] There is a large body of evidence that cannabinoids are effective painkillers in cases of acute, inflammatory, and NePs.[104–106] Nevertheless, the mechanism by which CBD modulates NeP is uncertain, but it is likely to be related to the inhibition of cells with inflammatory activity.[74]

On the other hand, △-9-THC acts through CB1 receptors expressed in the CNS and CB2 receptors expressed by cells of the IS,[107] increasing the synthesis of anti-inflammatory cytokines and decreasing the production of proinflammatory ones.[59,108,109] Furthermore, △-9-THC modulates the immune response by inducing the apoptosis of Th1 cells responsible for inflammation[110] and by increasing the number of FoxP3$^+$ Treg cells through miRNA induction and epigenetic modifications.[108,111] These findings were also reported and confirmed in the context of autoimmunity, further supporting the modulatory role of △-9-THC on the ECS and its therapeutic potential as regulator of the immune response.

Interestingly, in mice with EAE, the combination of CBD and △-9-THC, but not the individual molecules, could inhibit the neuroinflammation by reducing Th1 and Th17 cells.[62] This evidence supports the idea that combined cannabinoids can generate a broader response by activating different receptors that give rise to a better regulation of the immune responses.[12,13]

Besides its anti-inflammatory properties in DMT1, the △-9-THC has antihyperglycemic and antioxidant activities, which protects the cardiac tissue and the vasculature.[78] Similar findings have been reported in CBD-treated diabetic C57BL/6J mice.[112] These results indicate that cannabinoid receptor agonists or antagonists can regulate metabolic aspects that in turn benefit patients with this disease.[113]

Interestingly, different studies are currently carried out with terpenes, such as BCP from *Cannabis*, which decrease the inflammatory response in MS.[65,66] BCP obtained from other plants, such as *Copaifera reticulata*, also reduces the systemic inflammation and oxidative state of arthritic rats without hepatotoxic effects.[114] These results evidence the potential anti-inflammatory properties of terpenes; they could be used in combination with △-9-THC or CBD to improve the IS regulation.[12,13]

On the other hand, there are many published articles about the immunomodulatory role of synthetic cannabinoids (WIN 55, VCE-003, COR167, Ajulemic acid, HU-230, HU-210, CP55.940, O1821, LER13, and HU-308) in the autoimmune response in MS, DMT1, and RA.

The synthetic cannabinoid WIN 55 is one of the most studied molecules. It is a potent CB1 receptor agonist and its effects have been studied in all ADs reviewed in this article. WIN55 is less psychoactive than △-9-THC and is active at low doses.[67–70] WIN55 acts through the PPAR-α receptor favoring the production of IFN-β,[69] which is widely used in the treatment of MS. IFN-β suppresses the inflammatory responses by controlling the secretion of pro- and anti-inflammatory cytokine, inhibiting T cell activation, inducing the differentiation of neural stem cells to oligodendrocytes that results in repair of damaged neurons, preventing the migration of activated immune cells through the blood–brain barrier, and other mechanisms.[115,116]

It is essential to highlight that in DMT1, the use of WIN55 (a synthetic CB1 receptor agonist) or SR141716A and SR144528 (CB1 and CB2 receptors antagonists) generates differential effects in the induction of analgesia in this disease: WIN55 acts as an analgesic and antihyperalgesic mediator. In contrast, the signal triggered by the CB2 receptor does not have this activity.[74] Other studies of the CB2 receptor agonists have shown the development of antinociception and the modulation of tactile allodynia in rats and mice with nerve damage.[105,106] These findings confirm that the analgesic effect of these molecules is mediated through their agonist activity.[74,117]

Likewise, in animal RA models, WIN 55 reduces the production of the proinflammatory cytokines, IL-1, IL-6, and IL-8, which are involved in the disease's pathogenesis and maintenance.[84] Therefore, the regulation of these cytokines, as well as the inhibition of NO, PGE2, and COX-2 production by synthetic cannabinoids, is a promising alternative to managing the disease given their ability to avoid cartilage destruction and joint damage.[85,118,119] Similarly, CP55, 940, HU-210, and ajulemic acid regulated the production of IL-1[83–85] and the synthesis of proteases, NO, and PGE2 by chondrocytes; this latest mechanism helped to delay the appearance of tissue injury that causes the typical cartilage destruction observed in this disease.[120–122]

In MS, the cannabinoid VCE-003 (CB2 and PPAR-γ agonist) has been evaluated given its low psychoactive

properties. VCE-003 reduced the spinal cord infiltration by $CD4^+$ T cells evidencing a potential role to reduce the chronicity of MS.[64]

It is important to note that many of the MS studies were performed in mouse models, and that just one study used PBMCs from patients. In this study, the COR167 (CB2 agonist) effect was directly evaluated and showed a powerful dose-dependent inhibitory effect on both nonantigen and antigen-driven T cell proliferation and the release of proinflammatory cytokines.[71]

HU-308 is another synthetic CB2 agonist cannabinoid that was tested in RA. HU-308 reduced the production of IL-6 and TNF-α, which are key pathophysiological mediators of RA.[90] In previous studies, HU-308 also inhibited the IL-1 induced production of MMP-3, MMP-13 and IL-6,[123] indicating that this synthetic cannabinoid could also decrease the clinical symptoms and joint damage characteristics of this disease.[90]

Other synthetic cannabinoids, O1821 and LER13 (TRPV2 agonist), reduced the IL-1β-induced expression of MMP-2 and MMP-3; these molecules are mediators of cellular joint invasion and damage.[89] However, the authors highlighted that LER13 was more potent than O1821 because it had greater efficacy at lower doses,[89] and suggested the use of TRPV2 agonists as a novel therapeutic strategy in RA. HU-320 (CB2 agonist) was also studied in RA and showed to reduce cartilage damage and bone resorption; the effect was attributed to reduced production of TNF-α and ROS, which in turn reduced the production of IL-1.[124–126]

In contrast to the scarce studies of the synthetic cannabinoids previously described, there are many articles related to ajulemic acid (AJA, CT-3, IP-751, JBT-101, anabasum) in RA.[127] AJA helped to prevent bone damage and articular cartilage destruction in an experimental rat model of arthritis.[128] Additionally, Berstein's review[127] summarized preclinical evidence and clinical data of AJA effects and concluded that it could be a safe and effective treatment for diseases characterized by chronic inflammation. Table 4 summarizes the main findings of the preclinical studies reported in this review.

It is important to note that we only found literature from preclinical studies about the use of some cannabinoids in MS, DMT1, and RA for the present review. However, we also found out that JBT-101 is being evaluated to treat SLE and dermatomyositis in two phase-II clinical trials and of diffuse cutaneous systemic sclerosis in one phase-III clinical trial.[129]

As mentioned above, no experimental articles associated with SLE were found for the present review. Therefore, we considered that SLE is characterized by inadequate clearance of immune complexes and apoptotic cells that triggers plasmacytoid dendritic cells (pDCs) to initiate and enhance the synthesis of proinflammatory cytokines associated with the disease's progression.[130,131] In this context, Henriquez et al. showed that $\triangle$-9-THC and CB2 agonists (JWH-133 and JWH-015) inhibited the phosphorylation of some proteins involved in the downstream signaling pathway of INF-α and TNF-α, such as TANK-binding kinase 1 (TBK1), interferon regulatory factor 7 (IRF7), NF-κB, and IKK-γ that modulate the pDC-mediated proinflammatory responses.[131]

These findings indicated once again that the modulation of the CB1/CB2 receptor-associated signaling could be an effective therapeutic strategy in SLE models and, therefore, promising for the development of an alternative cannabinoid-based treatment of patients with this disease.

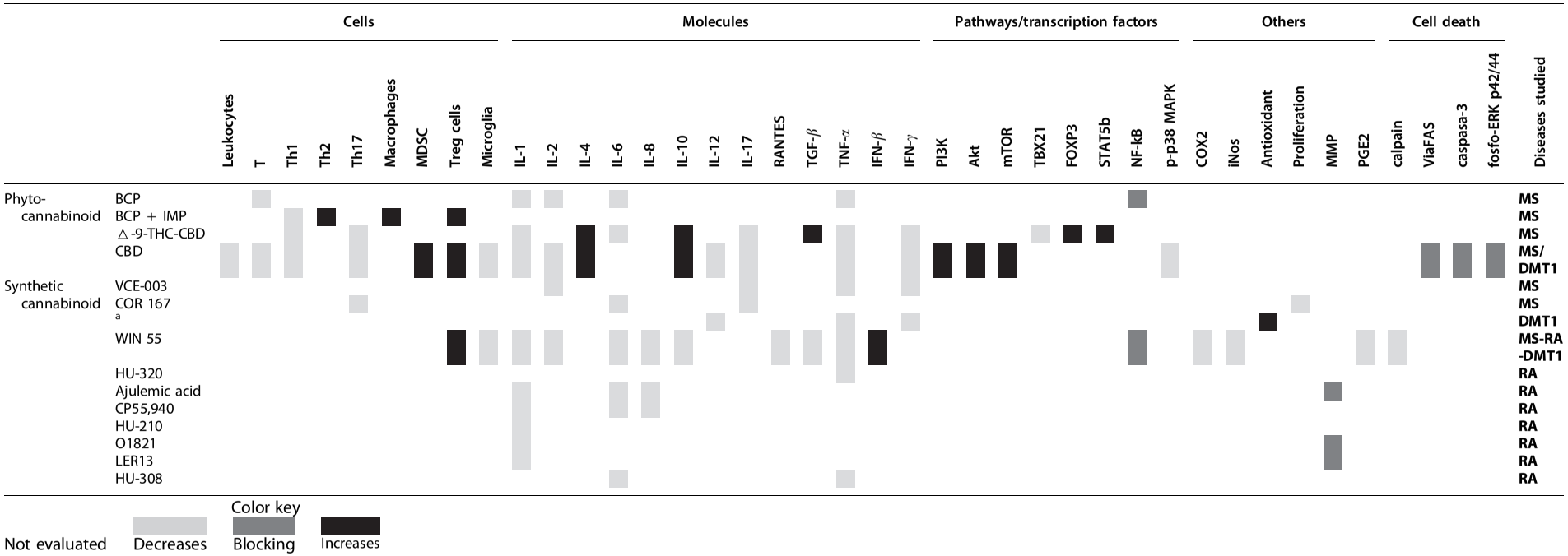
Conclusions

Cannabinoids and terpenes derived from *C. sativa L.* and synthetic cannabinoids interact with the ECS and produce an anti-inflammatory effect by attenuating the immune response in various animal models of human ADs (MS, DMT1, and RA). Specifically, cannabinoids act through agonist or antagonist signals on different receptors (CB1, CB2, TRPV1–2, PPAR-α/γ, and GRP55) regulating downstream inflammatory responses.

All the evidence found in the literature review suggests that different chemical components obtained from or chemically similar to *C. sativa* used alone or in combination could downregulate the immune response in ADs. The evidence also supports the concept that the anti-inflammatory *Cannabis* properties come from the entourage activity of different components that could be better to treat different biological issues involved in these diseases.

These findings should be better exploited to design further preclinical and clinical studies to gather evidence about the therapeutic potential of cannabinoids as alternative approaches for alleviating or inhibiting the symptoms and tissue damage of patients affected by ADs.

Table 4. Summary of the Immunomodulatory Mechanisms of Phytocannabinoids and Synthetic Cannabinoids in Autoimmune Disease Models



[a]CB1 agonist, unspecified source.

Akt, Ak strain transforming, serine/threonine protein kinase; COR167, based on a quinolone-3-carboxylic acid core structure (CB2 agonist); DMT1, diabetes mellitus type 1; HU-210, CB1/CB2 agonist; HU-320, CB1/CB2 agonist; HU-308, CB2 agonist; IMP, imipramine (sphingomyelinase inhibitor); LER13, TRPV2 receptor agonist; O1821, cannabidiol analog; RA, rheumatoid arthritis; STAT5b, signal transducer and activator of transcription 5B; TBX21, T-box transcription factor; VCE-003, Synthetic CBG derivative, PPAR-γ and CB2 agonist; WIN 55, WIN 55212-2 (CB1 receptor agonist).

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Abbreviations Used

2-AG = 2-arachidonoylglycerol
5HT3 = nicotine receptor
ADORA2A = adenosine A2A receptors
ADs = autoimmune diseases
AEA = N-arachidonoylethanolamine or anandamide
AJA = ajulemic acid
Akt = serine/threonine protein kinase
BCP = β-caryophyllene
CBD = cannabidiol
CBG = cannabigerol
CBN = cannabinol
CD = cluster of differentiation
CD-1 = wild mouse
CGRP = calcitonin gene-related peptide
CNS = central nervous system
COR167 = based on a quinolone-3-carboxylic acid core structure-CB2 agonist
COX = cyclooxygenase
DCs = dendritic cells
$\triangle$-9-THC = delta-9-tetrahydrocannabinol
DMT1 = diabetes mellitus type 1
DPN = diabetic peripheral neuropathy
EAE = experimental autoimmune encephalomyelitis
ECS = endocannabinoid system
ERK = extracellular signal-related kinase
FLS = fibroblast-like synovial cells
Foxp3 = forkhead box P3
GPR55 = G protein-coupled receptor 55
HU-210 = CB1/CB2 agonist
HU-320 = CB1/CB2 agonist
HU-308 = CB2 agonist

Abbreviations Used (Continued)

IFN = interferon
IKK-γ = the inhibitor of nuclear factor κB kinase subunit gamma
IL = interleukin
IMP = imipramine (sphingomyelinase inhibitor)
iNOS = inducible nitric oxide synthase
IRF7 = interferon regulatory factor 7
IS = immune system
LER13 = TRPV2 receptor agonist
LXA4 = lipoxin A4
MAPK = mitogen-activated protein kinase
MDSC = myeloid-derived suppressor cells
MMPs = matrix metalloproteinases
MS = multiple sclerosis
mTOR = mammalian target of rapamycin
NeP = neuropathic pain
NF-κB = nuclear factor-κB
NK = Natural killer cells
NSAIDs = nonsteroidal anti-inflammatory drugs
NO = nitric oxide
NOD = nonobese diabetic
O1821 = cannabidiol analog
PBMC = peripheral blood mononuclear cells
pDCs = plasmacytoid dendritic cells
PGE2 = prostaglandin E2
PI3K = phosphatidylinositol 3-kinase
PPARs = peroxisome proliferator-activated receptor
RA = rheumatoid arthritis
RANTES (CCL5) = regulated on activation, normal T cell expressed and secreted (C-C Chemokine ligand 5)
ROS = reactive oxygen species
SLE = systemic lupus erythematosus
SMase = sphingomyelinase inhibitor
SR141716A = CB1 antagonist
SR144528 = CB2 antagonist
STAT5b = signal transducer and activator of transcription 5B
TBK1 = TANK-binding kinase 1
TBX21 = T-box transcription factor
TGF-β = transforming growth factor-beta
Th = T helper
TLR = Toll-like receptor
TMEV = Theiler's murine encephalomyelitis virus
TNF-α = tumor necrosis factor alpha
Treg cells = regulatory T cells
TRP = transient receptor potential
TRPA1 = transient receptor potential ankyrin 1
TRPV = TRP vanilloids
TRPM8 = transient receptor potential melastatin 8
VCE-003 = synthetic CBG derivative, PPAR-γ, and CB2 agonist
WIN 55 = WIN 55212-2 (CB1 receptor agonist)