Review

NeuroImmunoModulation

Neuroimmunomodulation 2017;24:183–199
DOI: 10.1159/000481824

Received: February 8, 2017
Accepted after revision: September 28, 2017
Published online: November 18, 2017

Immunoregulatory Role of Cannabinoids during Infectious Disease

Rosalía Hernández-Cervantes[a] Mónica Méndez-Díaz[b] Óscar Prospéro-García[b]
Jorge Morales-Montor[a]

[a]Departamento de Inmunología, Instituto de Investigaciones Biomédicas and [b]Grupo de Neurociencias, Laboratorio de Cannabinoides, Departamento de Fisiología, Facultad de Medicina, Universidad Nacional Autónoma de México, Mexico City, Mexico

Keywords
Endocannabinoids · Infections · Virus · Bacteria · Parasites

Abstract
Although the endocannabinoid system (ECS) is involved in the regulation of several physiological processes, including sleep and the immune response, its role during infections has not been fully studied. It is well known that the use of this drug increases susceptibility to infections because of the impact on the modulation of the immune system. Concerning the medicinal or recreational use of marijuana, its influence on the course of an infection, whether this has been caused by bacteria, viruses, parasites, and to a lesser degree, fungi, has been reported. Furthermore, there is evidence suggesting the involvement of the ECS in the control and elimination of infectious agents such as bacteria, viruses, and some protozoa; in the case of fungi, few studies are available so far. The purpose of this review is to present the existing studies related to infections and the ECS, the microbicidal effects of compounds isolated from *Cannabis sativa*, and the association between marijuana use and the development of rare pathologies in specific diseases.

Immune System

The immune system has the important function of defending the host from foreign agents or pathogens, and, depending on the nature of these, it makes use of innate and/or adaptive immunity mechanisms to eliminate them. In both cases, proteins and specialized cells are involved in eliminating pathogens. Briefly, innate immunity involves natural barriers as well as the complement system, e.g., the skin and mucous membranes contain phagocytic cells able to recognize pathogen-associated molecular patterns (PAMPs) through pattern recognition receptors (PRRs). These mechanisms isolate the infectious agent by an inflammation process, thereby preventing replication, spreading, and damage. If the infectious agent evades the innate immunity response, the components of adaptive immunity are initiated. This response is pathogen-specific and involves T and B lymphocytes. T lymphocytes recognize antigens via T cell receptors and resulting in the activation of different pathways, depending on the nature of the lymphocyte. CD4+ T helper cells recognize the antigen through the major histocompatibility complex class II (MHC II) whereas CD8+ T cytotoxic cells achieve this through the MHC I.

E-Mail karger@karger.com
www.karger.com/nim

Jorge Morales-Montor
Departamento de Inmunología, Instituto de Investigaciones Biomédicas
Universidad Nacional Autónoma de México, AP 70228
Mexico City, DF 04510 (Mexico)
E-Mail jmontor66@biomedicas.unam.mx

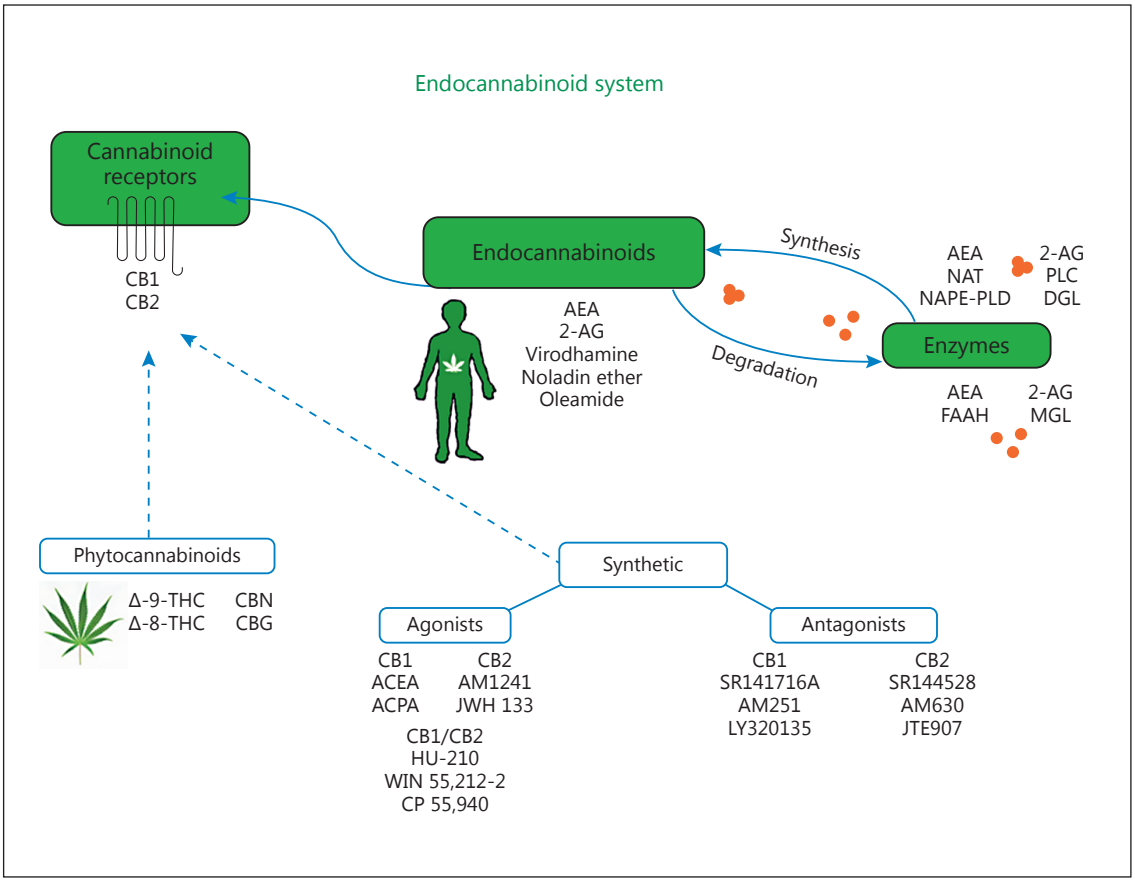

Fig. 1. The endocannabinoid system is composed of 2 cannabinoid receptors, CB1 and CB2; endocannabinoid compounds, such as AEA and 2-AG; and enzymes for the synthesis and degradation of eCBs. Cannabinoid receptors can be activated by phytocannabinoids present in the *C. sativa* plant, and also by synthetic cannabinoids used for experimental purposes. Both can be either agonists or antagonists.

B lymphocytes can also recognize antigens, and are known to participate in antibody-mediated immunity. An effective immune response also involves other cells such as monocytes, neutrophils, eosinophils, macrophages, dendritic cells, natural killer (NK) cells, and Tγδ cells, among others. The participation of these cells depends on the site of the infection, the infectious agent, and other factors to be able to identify, isolate, and eliminate pathogens. Thus, the immune system puts in place a complex mechanism to fulfill its function, including responding to hormones, neurotransmitters, and proteins, and specific lipids, such as endocannabinoids (eCBs). As some of these cells bear cannabinoid membrane receptors, i.e., cannabinoid receptor 1 (CB1) and CB2 [1], it may be that the activation of the endocannabinoid system (ECS) plays a decisive role in preventing the development of a disease.

The Endocannabinoid System

The ECS is composed of eCBs and enzymes (for the synthesis and breakdown of eCBs), as well as the cannabinoid receptors, CB1 and CB2, which are widely distributed throughout the body. Cannabinoid receptors are activated by different ligands that are either endogenous, such as eCBs, or exogenous, such as marijuana derivatives and synthetic compounds.

The term cannabinoid includes compounds of different origin: endogenous cannabinoids (i.e., the eCBs), cannabinoids from vegetable origin or phytocannannabinoids, and cannabinoids from synthetic origin, either agonists or antagonists to the cannabinoid receptors (Fig. 1).

Based on their chemical structure, cannabinoids are divided into 4 groups: classical, nonclassical, aminoalkylindoles, and eicosanoids. Classical cannabinoids are

dibenzopyran derivatives, such as 9-tetrahydrocannabinol (9-THC) and HU-210; nonclassical cannabinoids contains bicyclic and tricyclic analogs of 9-THC that lack a pyran ring like CP 55,940; aminoalkylindoles have structures that differ markedly from those of both classical and nonclassical cannabinoids and are well represented by WIN 55,212–2, a derivative of pravadoline; and eicosanoids have structures quite unlike those previously mentioned, with N-arachidonoylethanolamine (anandamide [AEA]) and 2-arachidonoylglycerol (2-AG) being the main ones [2].

Approximately 60 phytocannabinoids are synthesized by *Cannabis sativa* [3, 4]; of these, Δ-9-THC (THC) is the main psychoactive compound [5]. Other cannabinoids found in cannabis are Δ-8-THC, cannabidiol (CBD), cannabinol (CBN), cannabigerol (CBG), and cannabichromene (CBC) [6], among others. Furthermore, other organisms also produce their own cannabinoids, i.e., eCBs, derived from arachidonic acid, such as AEA and 2-AG, O-arachidonyl ethanolamine (virodhamine), 2-arachidonylglycerylether (noladin ether), N-arachidonoyl dopamine (NADA), and oleamide. There are cannabinoid-related molecules called N-acylethanolamides, such as palmitoylethanolamide (PEA) and oleoylethanolamide (OEA), that do not activate the CB1 receptor but instead interact with the peroxisome proliferator-activated receptor (PPAR)α, mediating anti-inflammatory processes [7, 8].

There are a large number of cannabinoids of synthetic origin, differing in their affinity to one or both cannabinoid receptors; in addition, there are also agonists or antagonists which have been useful in the experimental study of the ECS.

eCBs can be defined as endogenous lipids, derivatives of amides, esters, and ethers, and comprise long-chain polyunsaturated fatty acids, mainly arachidonic acid. eCBs are located in lipid membranes, synthesized on demand in a Ca^{+2}-dependent fashion in response to either physiological or pathological stimuli [9] and, in the case of AEA, accumulation and breakdown in liposomes [10]. AEA and 2-AG are the most studied eCBs and, despite being arachidonic acid derivatives, they can be synthesized by several pathways; however, the enzymes required are not the same in all instances. The enzymes required for AEA synthesis are N-acyltransferase (NAT) and N-acyl phosphatidylethanolamine phospholipase D (NAPE-PLD). For 2-AG synthesis, the enzymes phospholipase C (PLC) and diacylglycerol lipase (DGL) are required, among others. Breakdown enzymes also differ between AEA and 2-AG; fatty acid amide hydrolase (FAAH) is responsible for AEA hydrolysis whereas monoacylglycerol lipase (MGL) is required in the case of 2-AG [9] (Fig. 1; [11]).

In addition to CB1 and CB2, the existence of a third cannabinoid receptor (CB3) has been suggested [12], and there are also 2 orphan G protein-coupled receptors (GPCRs) which overlap with CB1 and CB2, namely, GPR18 and GPR55 [13]. CB1 and CB2 are associated with the G proteins of the Gi/o family (Gi1–3 and Go1 and 2) via the intracellular loops of the protein. Both cannabinoid receptors inhibit adenylyl cyclase via Gi and stimulate MAPK activity. By inhibiting adenylate cyclase, the reduction of the second messenger cAMP leads to the opening of rectifying potassium channels. CB1 also mediates the inhibition of N-type and P/Q-type calcium currents [14, 15].

The cannabinoid receptors are widely distributed; CB1 is expressed mainly in the central nervous system (CNS), particularly in the cerebral cortex, olfactory bulb, cerebellum, and spinal cord [16]. It can also be located in peripheral tissues such as the adrenal glands, thymus, tonsils, lungs, heart, bone marrow, prostate, uterus, ovaries, and testes [17]. Although CB1 mRNA levels represent only 1–10% of the CB2 content in immune tissues, they are expressed (from the highest to the lowest expression level) in B lymphocytes, NK cells, polymorphonuclear neutrophils, CD8 T cells, and CD4 T cells [1]. CB2, on the other hand, is also expressed in the CNS but is most highly expressed in immune tissues such as the spleen and thymus [1, 18] as well as in blood cell subpopulations such as CD4 and CD8 lymphocytes, neutrophils, monocytes, NK cells, and B lymphocytes [1].

CB1 and CB2 and Physiological Regulation

The activation of cannabinoid receptors is involved in biological processes such as appetite, or in antiemetic and analgesic effects. Moreover, the therapeutic use of cannabinoids has proved effective in the treatment of neuropathic pain [19–21], epilepsy, multiple sclerosis (MS), feeding disorders, and glaucoma [15, 22, 23]. However, since cannabinoid receptors are present on immune cells, they can modulate the function of the immune system, potentially inducing immunosuppression [24, 25]. As an example, the eCBs AEA and 2-AG can modulate inflammation, although not always in association with cannabinoid receptor binding, due to an arachidonic acid molecule within the structure, which is a precursor of bioactive or anti-inflammatory lipids; moreover, they can be metabolized by biosynthetic eicosanoid molecules producing additional lipids [11].

Synthetic cannabinoids are widely used in biomedical research, in the form of compounds with preferential activity over CB1, e.g., arachidonyl-2-chloroethanolamide (ACEA) and arachidonyl-cyclopropylamide (ACPA). CB2 is activated by compounds such AM1241, JWH-133, HU-910, and HU-308 [26]; in addition, there are compounds without special selectivity for either cannabinoid receptor, such as HU-210, CP 55,940, and R–(+)–WIN 55,212–2. On the other hand, there are CB1 antagonists such as SR141716A and AM251; and CB2 antagonists such as SR144528 and AM630 [14, 26] (Fig. 1). Their use in research has been crucial in unraveling the role of ECS activation in some diseases caused by infectious agents.

The Role of the ECS in Bacterial Infections

Phylogenetic analyses have reported the presence of cannabinoid receptors in phylum Chordata organisms, such as *Ciona intestinalis* [27] or *Branchiostoma floridae* [28]. Although there are no available reports regarding the presence of cannabinoid receptors in organisms belonging to other phyla like Proteobacteria, Vira, Nematoda, or Deuteromycota, this is very likely because the exogenous activation of the ECS plays an important role in the development of bacterial infections, both in vitro and in vivo (Table 1).

In the 1970s, the combination of THC and lipopolysaccharide (LPS) was shown to be highly toxic in mice, as tested by the combination of a raw THC preparation (distilled marijuana), LPS obtained from different bacteria (*Escherichia coli* and 3 species of the genus *Salmonella, S. minnesota*, *S. typhi*, and *S. abortus*), and a commercial *Pseudomonas* vaccine [29]. Moreover, it was found that the lethal capability of heat-killed bacteria was enhanced when THC was also administered. Therefore, it was clear that the combination of bacterial endotoxins and THC was more toxic than expected when compared to their individual effects. The authors suggested that this enhanced toxicity could also occur in humans because common enteric bacteria, opportunistic bacteria, and foodborne gram-negative bacteria can serve as LPS sources, potentially exacerbating enteric diseases when combined with marijuana use.

In contrast, *C. sativa* extracts exert microbicidal activity on gram-positive bacteria such as *Baccilus subtilus*, *Baccilus pumilus*, *Staphylococcus aureus*, *Micrococcus flavus* [30], *Clostridium sporogens*, *Enterococcus faecium*, and *Streptococcus salivarius* [28]; and on gram-negative bacteria like *Proteus vulgaris*, *Bordetella bronchioseptica* [30], *Pectobacterium carotovorum*, and *Pseudomonas savastanoi* [31]; as well as in some fungi, such as *Aspergillus niger* [30]. However, it should be highlighted that the microbicidal effect of cannabinoids has only been seen in experiments in vitro.

The following paragraphs will discuss specific studies on specific bacteria species. We acknowledge our lack of information regarding the presence of a cannabinoid receptor; we suggest that one possibly does exist, or that cannabinoids might modulate parasites through other means such as enzyme/transporter inhibition. The impact of cannabinoids on bacterial infections and on the growth of bacteria in vitro is shown in Table 1.

Sepsis

Sepsis is defined as a systemic infection as the result of an inefficient immune response. A murine study model involving the injection of LPS is how the role of CB1 and CB2 during sepsis was discovered. Where the activation of CB1 is concerned, this allows the good functioning of innate immunity parameters, e.g., CB1-deficient mice are unable to develop fever, have a lower expression of TLR4 in the liver and spleen when compared to wild-type (WT) mice, and their peritoneal macrophages do not secrete proinflammatory cytokines [32].

Concerning CB2, a study performed on CB2 knockout mice revealed a higher mortality rate, a higher concentration of proinflammatory cytokines such as TNF-α, interleukin (IL)-6, and a higher HMGB1 level when compared to WT mice under sepsis; after administering GW405833, a CB2 agonist, the cytokines and the mortality rate were decreased [33]. Another study determined that the activation of CB2, using the agonist HU-308, can prevent additional damage during sepsis, in this case, at the intestinal level [34]. Furthermore, mice with endotoxemia (experimental sepsis induced by LPS administration) treated with the CB2 agonist URB597 and the inhibitor of the enzymes FAAH and MGL, JZL184, showed a reduced number of adherent leukocytes in the submucosal and axial veins, reducing the endothelial interaction of leukocytes and thus preventing inflammatory damage, in addition to improving intestinal capillary perfusion, an idea further reinforced when the mice were treated with the antagonist AM630, resulting in an unmodified number of leukocytes [34, 35].

CB1 is thus important in the development of an efficient innate immune response whereas CB2 prevents additional inflammatory damage during sepsis. These studies support the idea that the ECS could be used as an effective therapeutic target in sepsis treatment.

Table 1. Effect of cannabinoids on bacteria

Infectious agent	Treatment/situation	Effect observed	Reference
In vitro			
B. subtilus *B. pumilus* *S. aureus* *M. flavus* *P. vulgaris* *B. bronchioseptica*	*C. sativa* extracts: ethanolic and petroleum ether extracts	Antimicrobial activity	30
S. aureus (several strains)	THC, CBD, CBG, CBC, or CBN	Potent antibacterial activity	6
B. suis	SR141617A	Bactericidal effect due to a prolonged phosphorylation of the transcription factor CREB within macrophages	51
In vivo			
LPS injection	Knockout mice to:		
	CB1	Unable to develop fever; lower expression of TLR4 in liver and spleen; peritoneal macrophages do not secrete proinflammatory cytokines	32
	CB2	Higher mortality rate; higher concentration of proinflammatory cytokines (TNF-α, IL-6 and HMGB1 levels)	33
		Prevents intestinal damage during sepsis	34
	HU-308, URB597, and JZL184	Prevent inflammatory damage by: – reducing the number of adherent leukocytes and endothelial interaction of leukocytes – improving intestinal capillary perfusion	34, 35
L. pneumophila	THC	Increases mortality by:	
		– reducing protective Th1 response	48
		– inhibiting DC functions	41
		– inducing the excessive mobilization of acute-phase cytokines in a receptor-dependent mechanism.	43
		Higher *Legionella* CFU/mg in the lungs; increased levels of IL-1, IL-6, and TNF-α	44
	SR141716A and SR144528	Higher *Legionella* CFU/mg in the lungs; increased levels of IL-1, IL-6, and TNF-α.	44
L. monocytogenes	Marijuana extract or THC	Suppresses resistance to infection	40
S. pneumoniae	HU-211	Reduces brain damage	54
Clinical case			
F. nucleatum	Positive toxicology screening for cannabis	Immunosuppression, which led to a rapid brain death	41
S. pneumoniae	Long-term CBD administration	Reduces neurological damage	54

Staphylococcus aureus

S. aureus is capable of causing serious infections in humans such as bloodstream infections and pneumonia, or bone and joint infections. It can be spread by direct contact with an infected person, in droplets dispersed by sneezing or coughing, or by touching contaminated objects.

Marijuana and Infections. In the early 1980s, a study reported that the acute inhalation of marijuana smoke impaired the pulmonary antibacterial defense system of rats infected with *S. aureus* in a dose-dependent manner [36]. A similar model of marijuana smoke inhalation in mice, in a subacute schema, resulted in a higher necrotic index when compared to control mice [37].

Marijuana Derivatives and Infection Control. C. sativa is a potential source of the natural compounds capable of controlling bacterial infections by exhibiting antibiotic resistance. Appendino et al. [6] investigated the antibacterial profile of the cannabinoids THC, CBD, CBG, CBC, and CBN, a selection of their carboxylic precursors (precannabinoids), and synthetic positional isomers, using a panel of clinically relevant *S. aureus* strains: EMRSA-15, one of the main epidemic methicillin-resistant strains; SA-1199B, a multidrug-resistant strain overexpressing the NorA efflux mechanism (the best characterized antibiotic efflux pump in this species); RN4220, a macrolide-resistant strain; XU212, a tetracycline-resistant strain overexpressing the TetK efflux pump; and ATCC25923, a standard laboratory strain. These cannabinoids showed a strong antibacterial activity against the tested methicillin-resistant *S. aureus* strains [6], suggesting that some cannabinoids could be a reliable option for the treatment of antibiotic-resistant *S. aureus* (Table 1).

Legionella pneumophila

Several studies have indicated that the activation of the ECS during *L. pneumophila* infection is what facilitates its virulence. *L. pneumophila* is an intracellular gram-negative bacterium causing Legionnaire's disease. *Legionella* bacteria are mainly found in water. Cough, high fever, muscle aches, headaches, and shortness of breath are the common symptoms, beginning 2–10 days after exposure; diagnosis can be difficult due to the symptoms being similar to those of other forms of pneumonia. People >50 years of age have a higher risk of developing this disease, as do smokers, people with any lung disease (e.g., emphysema and chronic obstructive pulmonary disease), cancer, diabetes, or kidney failure, or, in general, those with a suppressed immune system [38].

Host resistance to *L. pneumophila* depends on the activation of proinflammatory cytokines and T helper type 1 (Th1) immunity, a rapid increase in serum levels of IL-12 and interferon gamma (IFN-γ), and splenic IL-12Rβ2 expression [39]. The Th1 response regulates cell-mediated immunity, controlling intracellular pathogens. Th1 cells are induced by IL-12, concomitant to IFN-γ induction. The Th2 response regulates humoral immunity, characterized by IL-4 initiation followed by the production of IL-5 and IL-13, and B cell activation, to produce certain antibody isotypes [39]. In this context, it is well known that cannabinoids suppress Th1 immunity in a variety of animal models challenged with bacterial infections, including *L. pneumophila* infection [40, 41]. THC-increased mortality is caused by a reduced protective Th1 response. For instance, when experimental animals were treated with THC a day before infection with *L. pneumophila*, this resulted in an increased lethality index [42]. It has been suggested that THC facilitates death by inducing the excessive mobilization of acute-phase cytokines [43]. The administration of CP 55,940 (a synthetic eCB), at a dose of 6 mg/kg 1 day before and 1 day after the sublethal infection of mice with *L. pneumophila*, resulted in around 50% mortality, higher *Legionella* CFU/mg in the lungs, and increased levels of IL-1, IL-6, and TNF-α [44]. This evidence leads us to conclude that ECS activation with either THC or CP 55,940 increases the likelihood of death in an *L. pneumophila*-infected host.

As previously described in the model using THC and *L. pneumophila*-infected mice, Th1 cytokine levels are diminished during a challenge infection whereas Th2 cytokines are increased [39–42]. It is well known that Th1 polarization is inhibited by increased IL-4, GATA3, and NF-κB activation, and increased prostaglandin and glucocorticoids. Interestingly, THC-induced activation of both CB1 and CB2 causes the release of glucocorticoids and prostaglandin E_2, suppressing Th1 polarization. Newton et al. [45] injected *L. pneumophila* or THC alone into mice, observing that THC induced a rapid rise in serum corticosterone; however, the injection of both agents actually significantly augmented corticosterone production, proving that THC directly increased the level of this hormone in *L. pneumophila*-infected mice. Pretreatment with the CB1 antagonist, SR141716A, had no effect on the THC-induced corticosterone response; however, treatment with the CB2 antagonist, SR144528, increased serum corticosterone levels, suggesting that although THC significantly augments the mobilization of serum corticosterone and prostaglandins, the increased levels do not account for the drug-induced suppression of Th1 activity [45].

After *L. pneumophila* infection, the dendritic cells (DCs) produce high levels of IL-12p40. Interestingly, one proposed mechanism by which THC suppresses Th1 immunity is the inhibition of IFN-γ production and DC function concomitant with lower IL-12p40 secretion [41, 46], and the expression of costimulatory MHC class II, CD86, and CD40. The polarized expression of molecules such as the Notch ligand and Delta4 has been observed in response to *L. pneumophila* infection [46]. Both Notch ligands, Jagged1 and Delta4 (Th2- and Th1-polarizing molecules, respectively), were induced in DCs after *L. pneumophila* infection; however, *L. pneumophila*-infected mice treated with THC showed a significant suppression of Delta4 expression, but there was

little effect on Jagged1, suggesting that Th1 polarization is induced by the Delta4 ligand [46]. GPCRs have also been shown to increase Jagged ligand expression and to polarize Th2 [47]. Interestingly, cannabinoid receptors are coupled to Gi, and it is possible that these types of receptors might suppress Th1 by inhibiting the Delta4 ligands [41, 46].

Blocking ECS activation through CB1 or CB2 antagonists (SR141716A and SR144528, respectively) attenuates the effect of THC on Th1-promoting cytokines, such as IFN-γ and IL-12, indicating that cannabinoid receptors are involved in this response [48]. The role of CB1 and CB2 in the shift from Th1 to Th2 immunity is linked to the suppression of serum IL-12 and IFN-γ in *L. pneumophila*-infected mice. However, it has been found that treatment with THC induces the suppression of splenic IL-12Rβ2 expression, mediated by CB1 but not by CB2. Regarding molecular mechanisms, it has been shown that THC increases GATA-3 and Jagged1 mediated by CB2, and that THC treatment also increases the NF-κB level in the spleen and decreases the Delta4 in the DCs of infected mice. THC thus shifts to a nonprotective Th2 response, by suppressing IL-12Rβ2 through CB1, and by increasing IL-4, GATA-3, NF-κB, and Jagged1 via a mechanism that, at least partly, involves CB2 [39].

Listeria monocytogenes

Listeriosis is caused by the facultative and opportunistic intracellular gram-positive bacterium *Listeria monocytogenes*, which can be transmitted through contaminated sources such as refrigerated foods, vegetables, prepared meat products, and unpasteurized milk. These bacteria can grow in cold temperatures and can cause meningoencephalitis and/or septicemia in adults and newborn infants, as well as spontaneous abortion during early pregnancy. Newborn infants, pregnant women, the elderly, and immune-compromised individuals are among those with a higher risk of developing listeriosis. Little information on the interaction between the ECS and *L. monocytogenes* is currently available (Table 1); however, it has been reported that treating *L. monocytogenes*-infected mice with marijuana extract or THC markedly suppressed resistance to bacterial infection, an effect that can be compared to flumethasone, a potent immunosuppressive steroid [49]. It would be interesting to conduct additional studies on the role of ECS components in this infection, as they could reveal information on the innate and adaptive immune response to intracellular organisms such as *L. monocytogenes*.

Fusobacterium nucleatum

Fusobacterium nucleatum is a microorganism that can cause periodontal diseases, soft-tissue abscesses, pulmonary and intra-abdominal infections, and, very rarely, intracerebral infections. There is also a report of a previously healthy 25-year-old man with a cerebellar abscess caused by *F. nucleatum* that resulted in rapid brain death, that correlated with a positive toxicological screening for cannabis and amphetamines. This was a rare case for 2 reasons: (1) *F. nucleatum* is a strictly anaerobic microorganism, and, in most cases, aerobic pathogens such as *Neisseria meningitides* and *Streptococcus pneumoniae* are thought to be responsible for meningitis or brain abscesses; and (2) only 6% of brain abscesses caused by bacteria arise from infection by *Fusobacterium* spp. [50]. Once again, these data suggest an immune suppression induced by cannabinoids that may have played an important role in an unusual clinical course.

Brucella suis

Brucella suis is a gram-negative bacterium affecting pigs, and causes inflammatory chronic infections in the gonads, causing abortions, or the birth of weak or dead piglets, orchitis, and other gonad afflictions, resulting in elevated economic loss. There is the potential for humans who are in direct contact with the diseased animals to become infected. The CB1 antagonist, SR141716A, induces a protecting effect by inhibiting bacterial replication within infected macrophages in a dose-dependent manner (10–500 nM). Even a 1-nM concentration can achieve a bactericidal effect [51] due to the activation of protein kinase A mediated by AMPc, resulting in a prolonged phosphorylation of the transcription factor CREB, and thus impairing an essential pathway for *B. suis* survival within macrophages [52].

Streptococcus pneumoniae

Little is known about the role of the ECS in pneumococcal meningitis, a bacterial infection affecting the meninges and spinal cord, with lethality established in approximately 50% of untreated cases [53]. There are several bacteria associated with meningitis, *S. pneumoniae* being one of them. An experimental model of pneumococcal meningitis caused by *S. pneumoniae* in rats determined that the synthetic cannabinoid HU-211 reduced brain damage when administered in combination with ceftriaxone [54]. Permanent neurological damage is a major problem in pneumococcal meningitis survivors; such effects can be attenuated with long-term CBD administration; however, this effect is also accompanied by

reduced proinflammatory cytokines such as TNF-α in the frontal cortex (the mechanisms of this are unknown) [55]. The little information available concedes that cannabinoids can reduce neurological damage, but more information is necessary in this regard.

Viral Infections

Hepatitis C

Hepatitis C, a liver disease caused by its namesake virus (HCV), affects approximately 150 million people globally, a significant number of whom are chronically infected and will eventually develop liver cirrhosis or cancer [53], and can also develop metabolic disorders such as insulin resistance and steatosis. Although the moderate use of cannabis may help treatment adherence in patients with hepatitis C [56], because it stabilizes weight loss and nausea [57], long-term daily use has been associated with fibrosis progression [58]. ECS activation by the CB1 agonist ACEA promotes HCV replication in hepatocyte cultures. CB1 upregulation and high levels of 2-AG during hepatic diseases have been documented [59]. Further studies on the role of the ECS during HCV infection are needed. Table 2 summarizes the in vitro and in vivo studies on this virus and the use of different cannabinoids.

Herpes

Caused by the herpes simplex virus (HSV), herpes has been described as 2 types: HSV-1 transmitted by oral contact and mainly causing orolabial herpes, and HSV-2 transmitted through sexual contact with an infected person, causing genital herpes. The WHO has estimated that 400 million people worldwide are currently infected with HSV-2 [53].

In the late 1970s, a report suggested that cannabinoids had the capacity to suppress host resistance to HSV [49]. Based on this, Cabral et al. [60, 61] evaluated the effect of THC on HSV-2 infections. Their studies in vitro, using virus-infected Vero cells pretreated for 24 h with THC, showed a higher extracellular incidence of the virus that correlated with the dissolution of the cellular membrane, and inhibited the synthesis, maturation, and cellular transport of specific HSV-2 glycoproteins [62] and macrovacuoles in the cytoplasm that contained virus aggregates. Their results suggest that treatment with cannabinoids facilitates the exit of the virus from infected cells [63], thereby facilitating viral dispersion. In addition, THC has been found to inhibit macrophage-extrinsic anti-HSV activity [64]. Experiments in vivo, using mice and guinea pigs, reported that THC decreased host resistance to HSV-2 vaginal infection, as observed by: (1) the greater frequency and severity of genital lesions, (2) higher mortality, and (3) higher virus titers in vaginal secretions and reduced IFN titers [63, 65, 66], indicating that cannabinoids induce a decreased resistance to HSV-2 (Table 2).

In another context, there is an association between HSV and Kaposi sarcoma, known as Kaposi sarcoma-associated herpes virus (KSHV), that causes Kaposi sarcoma in individuals with HIV. KSHV is very persistent in immune-suppressed hosts, promoting tumor growth. The lack of efficacious therapies has precipitated the use of compounds like CBD, a nonpsychoactive cannabinoid shown to induce apoptosis in endothelial cells infected with KSVH, as well as inhibiting endothelial growth factors, e.g., viral GPCR (vGPCR), chemokine growth-regulated protein α (GRO-α), vascular endothelial growth factor receptor (VEGFR)-3, and VEGF-C [67].

Retroviruses

People suffering from HIV/AIDS are known to use marijuana more frequently, seeking to improve their appetite, decrease nausea, or control pain; however, there are some consequences that should be considered in this regard. As we have discussed throughout this review, THC suppresses cellular immune functions; therefore, we expect to see further impairment in HIV-infected individuals; for example, animal models have demonstrated that NK cell activity becomes suppressed at high THC doses [68]. A hybrid model based on human peripheral-blood leukocytes implanted into SCID mice (the huPBL-SCID model) revealed that, in the presence of THC, HIV replication was increased 50-fold in the systemic viral load; although there was no difference in the percentage of CD4+ T cells, the expression of CCR5 and CXCR4 (chemokine receptors, both essential coreceptors for HIV infection) was increased, and the number of IFN-γ-producing cells was decreased [69]. In other cases, the negative effects produced by infection, such as by HSV, are enhanced by the administration of THC. When there is coinfection, such as by the Friend leukemia virus, these effects are even greater than the individual effect, i.e., specifically, the rate of infection development and mortality are increased [67]. On the other hand, the activation of CB2 could be an alternative in active antiretroviral therapy, as it can attenuate neurocognitive disorders associated with HIV infection by inhibiting viral replication, regulate inflammation by reducing the permeability of the hematoencephalic barrier and leukocyte infiltration, and suppress the activity of neurotoxic proteins (e.g., Tat

Table 2. Effect of cannabinoids on viruses

Infectious agent	Treatment/situation	Effect observed	Reference
In vitro			
HCV	ACEA	Promotes virus replication by: – upregulation of CB1 expression – high levels of 2-AG	46
HSV	THC	Higher quantities of extracellular virus	47, 48
HIV	AEA and 2-AG	Suppress proinflammatory cytokine production and increase anti-inflammatory cytokines in the cytotoxicity produced by HIV-1 Tat protein in the retina	61
In vivo			
HSV	THC	Higher mortality in mice and pigs from vaginal infection	50, 52, 53
Retroviruses			
HIV	THC	Increases HIV replication, besides the expression of CCR5 and CXCR4 chemokine receptors; reduces CD4+ T cells and IFN-γ-producing cells	56
		Suppresses NK cell activity	55
SIV	THC	Reduces thymic cellularity and enhances apoptosis, through CB1 and CB2 activation	57
		Reduces CB1 and CB2 levels in the hippocampus and MCP-1	58
		Decreases early mortality in male macaques	59
Influenza virus	THC	Increases viral loads by: – higher hemaglutinin 1 expression – diminished CD4+ and CD8+ lymphocyte and macrophage recruitment into the lungs	77
Theiler's virus	WIN 55,212–2, ACEA, or JWH-015	Promotes remyelination	81
	WIN 55,212-2	Inhibits the expression of adhesion molecules ICAM-1 and VCAM-1	80
		Reduces CD4+CD25+Foxp3– T cells activation in the CNS and increases regulatory CD4+CD25+Foxp3+ T cell activation	86
	AEA	Inhibition of VCAM-1 expression by the activation of CB1	83
	CBD	Reduces CCL2 and CCL5 expression and reduces leukocyte infiltration in the brain	84
	THC and CBD	Suppress Th17 response	87, 88
Ex vivo			
HSV	CBD	Produces apoptosis in endothelial cells infected with KSHV	54

and HIV-1gp120), thereby decreasing neuronal damage [70]. It also prevents Tat from promoting monocyte migration through the hematoencephalic barrier [71].

Development of the Immune System and eCBs

There are critical stages in perinatal development. The administration of cannabinoids during this period would compromise the function of the immune system, e.g., gestational exposure to THC using SR141716A and AM630 as CB1 and CB2 antagonists, respectively, reduces thymic cellularity in fetuses and produces higher rates of apoptosis in thymocytes. Both effects are mediated by the activation of CB1 and CB2. Immune function, tested with the HIV-1 p17/p24/gp120 protein in adult mice exposed prenatally to THC, revealed that these animals exhibited a lower T cell proliferation rate as well as lower amounts of specific antibodies against HIV-1 p17/p24/gp120, suggesting that prenatal cannabis exposure can lead to a less efficient immune system in adulthood, increasing the risk of infectious diseases [72].

Studies on male macaques infected with simian immunodeficiency virus (SIV) have reported that chronic THC use did not affect the viral load in the plasma, but that there were reduced levels of CB1 and CB2 in the hippocampus that correlated with the decreased expression of the proinflammatory cytokine, monocyte chemoattrac-

tant protein-1 (MCP-1). Treatment with the cannabinoid decreased early mortality, however [72, 74]. Interestingly, this effect is gender-dependent, as female macaques in the same condition showed that THC treatment did not protect them from early mortality [75].

Last but not least, eCBs seem to play an important role in the treatment of certain HIV-related pathologies, such as vision problems due to an increased inflammatory response associated with the HIV-1 Tat protein. The use of the eCBs, AEA and 2-AG, to control Tat-induced cytotoxicity in retinal cells resulted in the suppression of the production of proinflammatory cytokines such as TNF-α, IFN-γ, IL-6, and IL-12p70, and increased production of anti-inflammatory cytokines such as TGF-β and IL-10 has been suggested. These effects were associated with the MAPK pathway [76] (Table 2).

Influenza

The administration of THC could be harmful for a host infected with the influenza virus. As reported in studies on mice, THC administration after an immune challenge with influenza virus A/PR/8 resulted in increased viral loads, higher hemagglutinin 1 expression, and diminished CD4+ and CD8+ lymphocyte and macrophage recruitment into the lungs [77]. Some of these effects were observed in an opposite manner when CB1 and CB2 knockout mice were infected, i.e., showing increased CD4+ lymphocyte recruitment, IFN-γ levels, and lung inflammation, higher than in control WT mice [78]. Other immune parameters affected include cytokine secretion by CD4+ T cells and NK cells, besides a lower overall percentage of subpopulations of antigen-presenting cells present in the lungs of infected mice [79]. The observed results demonstrate that THC administration diminishes the immune response against the influenza virus.

Multiple Sclerosis

An experimental model of encephalomyelitis, induced by infection with Theiler's virus, serves as a model for the study of MS, the most common human chronic demyelinating disease. Clinical deficits described in infected mice include progressive impaired motor coordination, incontinence, and paralysis associated with axonal loss and demyelination [80], and correlating with high levels of the vascular cell adhesion molecule-1 protein (VCAM-1) which mediates the adhesion of cells such as lymphocytes, eosinophils, monocytes, and basophils to the vascular endothelium.

Concerning the specific case of MS, its characteristic infiltration of autoreactive lymphocytes from the systemic compartment into the brain makes the study of this disease of particular interest. MS is not a disease caused by a virus per se, but the model for studying it requires the use of a virus to induce the disease. This is the reason why we mention studies using the model of Theiler's murine encephalomyelitis virus-induced demyelinating disease (TMEV-IDD) with what is known about the ECS, providing an idea about what might be happening during a viral infection.

The use of cannabinoids has been suggested as a potential therapeutic agent in the treatment of MS; as was reported in 2003, the cannabinoids WIN 55,212–2, ACEA, or JWH-015 promoted remyelination in TMEV-infected mice, also reducing the number of CD4+-infiltrated T cells into the spinal cord, and showing morphology similar to that after the vehicle treatment [81]. A few years later, Mestre et al. [80] observed that the treatment with the cannabinoid agonist WIN 55,212–2 after virus infection also inhibited the expression of adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1) and VCAM-1, by the activation of nuclear receptors inhibiting the PPARγ rather than by the activation of CB1 or CB2. Moreover, the synthetic cannabinoid resulted in lower perivascular CD4+ T lymphocyte infiltrates and microglial response; despite these results, the response against the virus was not completely abolished in animals exposed to WIN 55,212–2. On the other hand, additional studies reported increased cyclo-oxygenase-2 and prostaglandin E_2 expression through the activation of CB1 and CB2 [82]. Similar to the report on WIN 55,212–2, other studies on the role of the eCB, AEA, showed that the inhibition of VCAM-1 expression induced by AEA in brain endothelial cell cultures is mediated by the activation of CB1, and that the lack of CB1 exacerbates neuroinflammation [83]. TMEV-IDD is also known to upregulate the expression of the chemokines, CCL2 and CCL5, in the spinal cord of infected mice; such chemokines are important in the recruitment of inflammatory cells to the CNS. When these mice were treated with CBD, the expression of CCL2 and CCL5 was reduced, correlating with reduced leukocyte infiltration in the brain [84].

MS is considered as an autoimmune disease, and, knowing that lymphocytic cells have CB1 and CB2, how cytokines might be involved in the disease has been addressed in other studies. In addition, serum levels of IFN-γ, IL-10, IL-12, or C-reactive protein in MS patients have not been reported to have any influence on the development of the disease [85]. Nevertheless, a study by Arevalo-Martin et al. [86] performed in vivo on mice found that the use of WIN 55,212–2 as a CB1/CB2 agonist

Table 3. Effect of cannabinoids on parasites

Infectious agent	Treatment/situation	Effect observed	Reference
In vitro			
D. discoideum	THC or CBD	Inhibits proliferation	62
N. fowleri	THC	Inhibits growth, prevents enflagellation and encystment	63
H. vermiformis *W. magna*	2-AG, AEA, or 2-O-acyl glycerol	Inhibits growth	64
T. cruzi	WIN 55,212	Inhibits invasion of cardiac myoblasts Increases parasitemia	70
M. incognita	*C. sativa* extract	Nematicide activity	72
In vivo			
A. castellanii	THC	Inhibits growth Exacerbates brain infection by inhibiting macrophage functions	65–67 68
T. brucei brucei	*C. sativa* extract	Reduces parasitemia	69
M. incognita	*C. sativa* extract	Nematicide activity	72
P. berghei ANKA	CBD + artesunate CB2 knockout mice	Prevents cognitive deficiency associated with malaria A higher survival rate due to a reduced: – parasite load in brain – expression of TNF-α and IFN-γ – hematoencephalic barrier disruption – mononuclear cell infiltrate – CD8+ lymphocyte count	100 101
S. japonicum	Mice infected without any treatment	Shows higher expression of both cannabinoid receptors in hepatic tissue	102

restored tolerance to a myelin self-antigen, ameliorating the disease in the long term. They demonstrated that this therapeutic effect correlated with a decreased activation of CD4+CD25+Foxp3– T cells in the CNS and increased the activation of regulatory CD4+CD25+Foxp3+ T cells, suggesting a good alternative for the treatment of MS.

The potential use of cannabinoids in the treatment of MS also involves the reduced synthesis and secretion of IL-17 by THC and CBD, thereby suppressing the Th17 response [87] which is commonly increased in patients with inflammatory autoimmune pathologies such as MS [88].

Parasitic Infections

Protozoa

Protozoa studies in vitro have shown the negative effect of THC over some free-living amoebae. For example, THC and CBD inhibit the proliferation and differentiation of *Dictyostelium discoideum* in culture [89]. Vero cell cultures of *Naegleria fowleri* (which causes primary amoebic meningoencephalitis) with 20 μg/mL THC added resulted in delayed growth, preventing flagellation and encystment but with no effect on motility, suggesting that macromolecular synthesis is inhibited by cannabinoids, either directly or indirectly [90]. In another study in vitro, free-living *Acanthamoeba castellanii*, *Hartmannella vermiformis*, and *Willaertia magna* were exposed to 2-AG, AEA, or 2-O-acyl glycerol, resulting in growth inhibition [91]. Although these results may seem promising for use as an effective therapeutic alternative, studies in vivo report the opposite effect, such as in the case of *Acanthamoeba* (Table 3). Mice infected with this amoeba and treated with THC presented with exacerbated brain infection [92, 93], partly due to THC exposure which inhibits macrophage chemotactic response [94] and cell contact-dependent activation [95], suggesting an explanation for why these cases presented with higher mortality rates than the controls [94].

Table 4. Effect of cannabinoids on fungi

Infectious agent	Treatment/situation	Effect observed	Reference
In vitro			
Candida	*C. sativa* extracts	Fungicidal activity	25
	4-terpenyl cannabinolate	Fungicidal activity	76
In vivo			
Candida	Cannabis use	Increases the prevalence of oral candidiasis	73
	THC	Suppresses immunity: – decreases survival of mice – decreases IFN-γ and IL-12p40 levels – increases fungal burden in the kidneys, spleen, brain, and liver	77
Clinical case			
Aspergillus	Contaminated marijuana cigarettes	In immunocompromised hosts: – complicates medical conditions – causes death	74 75

Chagas disease is caused by the protozoan *Trypanosoma cruzi*, transmitted by insects of the *Triatominae* subfamily. The WHO estimates that between 6 and 7 million people are infected worldwide, mainly in Latin America, and the disease causes chronic cardiac, digestive, and neurological disorders [53]. In 1994, Nok et al. [96] reported that rats infected with *Trypanosoma brucei brucei* and treated with *C. sativa* extract showed lower levels of parasitemia. Tests in vitro of the synthetic cannabinoid R–(+)–WIN 55,212 effect on *T. cruzi* showed that the cannabinoid inhibited the invasion of cardiac myoblasts, and, interestingly, there was colocalization of CB1 and the attached/invading *T. cruzi* in the host cell membrane. Studies in vivo showed that cannabinoid treatment actually increased parasitemia, although the mortality rate remained unaffected and cardiac inflammation was reduced [97] (Table 3).

The effect of cannabinoids on parasitic infections caused by nematodes has not yet been studied (Table 3); however, cannabis has been unconsciously used by humans as an antihelminthic [98]. The available studies on nematodes such as *Meloidogyne incognita*, a parasite affecting plants, revealed that *C. sativa* extracts possess nematicide activity [99]. However, there is no experimental evidence available to show an association between ECS components and nematodes of veterinary and/or human importance, let alone how the ECS may be participating in the course of these infections.

Plasmodium berghei

In 2015, the WHO reported 212 million cases of malaria, which caused the death of 429,000 people [53]. *Plasmodium* is the parasite responsible for malaria, a disease characterized by acute fever and the potential development of cerebral malaria, which can be fatal due to the rupture of the hematoencephalic barrier and brain inflammation. CBD, along with the antimalarial drug artesunate, is able to increase the survival rate of mice infected with *Plasmodium berghei* ANKA, and can prevent cognitive deficiency associated with the infection [100]. Interestingly, another study demonstrated that CB2 activation had no beneficial effect in an experimental murine model for cerebral malaria, as CB2 knockout mice presented with a higher survival rate due to a lower parasite load in the brain and lower expression of proinflammatory cytokines such as TNF-α and IFN-γ, in addition to lower hematoencephalic barrier disruption [101]. The mononuclear cell infiltrate was also lower, with fewer CD8+ lymphocytes, in contrast with CD11b+ cells which were found in a higher proportion. This suggests that CB2 modulates the traffic of immune cells, and that the use of antagonists for this receptor could be used as a potential therapeutic strategy against cerebral malaria.

Flatworms

Mice infected with the flatworm *Schistosoma japonicum* showed higher expression of both cannabinoid receptors in their hepatic tissue, unlike tissue from noninfected mice, in which the expression of CB1 and CB2, and also AEA, was almost undetectable, suggesting that eCBs are involved in the development of hepatic fibrosis induced by schistosomiasis in addition to ECS activation during infection, in this case by *S. japonicum* [102]. This mechanism is partly due the CB1 activation in hepatic

stellate cells and depending on O_2^- production by NAPDH oxidase, and suggests the blockage of CB1 being employed as a therapeutic alternative in the prevention and treatment of hepatic cirrhosis or infection with *Schistosoma* [103].

Fungal Infections

It is well known that the use of cannabis increases the prevalence of oral candidiasis [104], and that marijuana cigarettes may be contaminated with *Aspergillus*, in which case, their consumption leads to complicated medical conditions [105] including death [106]. On the other hand, the possible fungicide effect of compounds isolated from *C. sativa* has been under evaluation [30, 107], testing the effects of THC, other cannabinoids, or any component of the ECS in general, on infections caused by fungi, using *Candida* spp. as experimental agents (Table 4). The first study reported, concerning the effect of chronic administration of systemic THC on secondary infection resistance by *Candida albicans*, showed that the THC treatment suppressed the immune system in mice, revealing considerably decreased serum IFN-γ and IL-12p40, accompanied by decreased survival and increased fungal burden in the kidneys, spleen, brain, and liver [108]. The effects that the ECS components may be exerting on fungal infections are just beginning to be elucidated.

Concluding Remarks

It is well known that the immune system interacts with the nervous, immune, and endocrine systems, now considered as the neuroimmunoendocrine network. In this sense, ECS activation could be considered an important factor in the study of an effective or deficient immune response against infectious diseases. It should be highlighted that ECS activation might also present complex interactions during the course of an infection.

In this review, the in vitro evidence we have presented suggests that contact with cannabinoid compounds can affect different types of infectious agents, by allowing their replication or by eliminating them. This supports the idea of existing cannabinoid receptors infecting pathogens and that their activation may be responsible for previously mentioned effects, pointing to a new biological function of ECS activation. The immune system is responsible for dealing with foreign agents and their clearance, but, when the ECS is activated, the final result is sometimes different from what would be expected, i.e., the survival of infectious agents within the host.

In the case of bacteria, in vitro and in vivo tests present opposite effects, meaning that while in vitro studies showed cannabinoid compounds exerting antibacterial effects [6, 30, 54], in vivo tests showed increased host mortality. In the case of infection with *L. pneumophila*, this effect is due to immune system malfunction, caused by a compromised Th1 protective response [37] or because macrophage functions are inhibited [41], thereby supporting the notion that ECS activation contributes to the function of the immune system. Interestingly, when LPS was injected into mice, the results were similar to the results reported in vitro, because the lack of cannabinoid receptors induced an ineffective immune response [32, 33].

Similarly, in the case of viral infections, the contact of viral particles with cannabinoid compounds makes them capable of negatively modulating some immune response parameters. During HIV infection, there is a reduction in CD4+ T cells and IFN-γ concentration [69]. During SIV infection, the activity of NK cells is inhibited [68], resulting in increased host mortality [63, 65, 66], and, in an influenza virus infection, the viral load is also increased [77]. In the studies in vitro, different cannabinoids increased HCV [59] and HSV replication [60, 61]. On the other hand, the use of cannabinoids during an infection with Theiler's virus, an experimental model of MS, showed that cannabinoid agents such as WIN 5,212–2, ACEA, and JWH-015 may be good therapeutic targets for treating MS due to the fact that they promote remyelination [81].

Interestingly, in the case of parasites, the effects of cannabinoids in vitro and in vivo are similar. Parasites in contact with different cannabinoids had inhibited proliferation [89], growth [90, 91], and invasion [97], and there were also nematicide effects [99], except for *T. cruzi* and the agonist WIN 55,212–2, which increase parasitemia but also inhibit the invasion of cardiac myoblasts [97]. Similarly, studies in vivo show that ECS activation by THC or *C. sativa* extracts inhibits parasite growth [92–94], parasitemia [96], and there is also nematicidal activity [99], except for *A. castellani*, where THC administration inhibits macrophage functions, causing exacerbated brain infection.

It is important to point out that, in the report on *P. berghei* ANKA, the treatment with CBD in addition to the antimalarial drug artesunate prevented cognitive deficiencies associated with malaria [100]. These results may indicate that, where parasitic infections are concerned,

cannabinoid compound treatments are able to damage the parasites, and in some cases, when given together with parasitic agents, can prevent collateral damage in parasitic infections, with some exceptions (depending on the etiological agent).

There is scant information on ECS activation during fungal infections, with the available information allowing us to say that, under in vitro conditions, cannabinoid compounds have antifungal activity [30, 107], but that, in the host, the use of cannabis is associated with a high prevalence of oral candidiasis [104]. ECS activation is an important factor for this condition, present among cannabis users. When mice were infected with *Candida*, it caused decreased host survival because it suppressed an effective immune response [108]. However, too few studies exist to be able to make a generalization concerning the role of ECS activation during fungal infections.

Further studies to elucidate the role of ECS activation in relation to infectious diseases are necessary because: (1) infectious diseases are common; it is known that >2 billion people are infected with helminths, and (2) cannabinoid receptors are distributed throughout the body. A clear case for the importance of conducting these studies is that the immune system is responsible for eliminating pathogens and the cannabinoid receptors are present in the immune cells.

Acknowledgements

J.M.M. was supported by grant #IN-208715 from the Programa de Apoyo a Proyectos de Investigación e Innovación Tecnológica (PAPIIT) from Dirección General de Asuntos del Personal Académico (DGAPA), Universidad Nacional Autónoma de México (U.N.A.M.) and grant 176803 from the Programa de Fondos Sectoriales CB-SEP, Consejo Nacional de Ciencia y Tecnología (CONACyT). R.H.C. is a PhD student at the Programa de Doctorado en Ciencias Biomédicas, UNAM, and has a scholarship from CONACyT.

Disclosure Statement

The authors declare no conflicts of interest.

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