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CANNABINOIDS AND AUTOIMMUNE DISEASES: A SYSTEMATIC REVIEW

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ABSTRACT
Cannabinoids have shown to have a variety effects on body systems. Through CB1 and CB2 receptors, amongst other, they exert an effect by modulating neurotransmitter and cytokine release. Current research in the role of cannabinoids in the immune system shows that they possess immunosuppressive properties. They can inhibit proliferation of leucocytes, induce apoptosis of T cells and macrophages and reduce secretion of pro-inflammatory cytokines. In mice models, they are effective in reducing inflammation in arthritis, multiple sclerosis, have a positive effect on neuropathic pain and in type 1 diabetes mellitus. They are effective as treatment for fibromyalgia and have shown to have anti-fibrotic effect in scleroderma. Studies in human models are scarce and not conclusive and more research is required in this field. Cannabinoids can be therefore promising immunosuppressive and anti-fibrotic agents in the therapy of autoimmune disorders.
1. Introduction

Cannabinoids are diverse chemical compounds that can bind to receptors of our endocannabinoid system. Cannabinoids can be endocannabinoids, when produced by our own body, phytocannabinoids, present naturally in the plant Cannabis sativa [1,2], and synthetic cannabinoids. The most well-known cannabinoid is ∆9-tetrahydrocannabinol (∆9-THC), the main constituent of cannabis. Nabilone, a synthetic analogue of ∆9-THC has been licensed for medical use [2]. Endocannabinoid system and the physiological effects of cannabinoids have been widely studied in the past decades. Cannabinoids are believed to have immunomodulatory effects and therefore their potential role as an autoimmune/inflammatory treatment has been extensively investigated. Herewith, we revise the properties and the effects of cannabinoids on autoimmune disorders known so far.

2. The Endocannabinoid System

2.1 Cannabinoid Receptor Agonists

Cannabinoids receptor agonists are very heterogeneous and can be divided into four groups according to the difference in their chemical structure. These are classical, non-classical, aminoalkylindole and eicosanoid compounds groups. [1,2]

Briefly, the classical group consists of phytocannabinoids (∆9-THC, cannabinol) and their synthetic analogues. The eicosanoid group are mostly endocannabinoids, produced by our own cells. These are arachidonylethanolamide (anandamide), O-arachidonylethanolamine (virodhamine), 2-arachidonoyl glycerol and 2-arachidonylglycerol ) and several synthetic analogues of anandamide. The two other groups, non-classical and aminoalkylindole consist of synthetic cannabinoids. (See Table 1)

Cannabinoids act on the two main receptors of the endocannabinoid system, CB1 and CB2 receptors. Every endocannabinoid agonist has a different affinity for the receptors. For example,
Δ9-THC has a higher affinity for CB1 receptor and the phytocannabinoid cannabinol is an agonist without marked CB1/CB2 selectivity. (Fig 1)

2.2 Cannabinoid RECEPTORS

2.2.1 CB1 and CB2 receptors

There are two types of cannabinoid receptor that have been mostly identified and studied. These are CB1 and CB2 receptors. They belong to a class of cell membrane receptors under the G protein-coupled receptor superfamily and consist of seven transmembrane spanning domains. The effect of binding is variable from partial agonism, functional selectivity to inverse agonism and all play important roles in determining the cellular response to specific cannabinoid receptor ligands.

2.2.2 Mechanism of action of CB1 and CB2 receptors

Both, CB1 and CB2 receptors produce their effects through heterotrimeric G_{i/o} proteins coupled to them. CB1 receptor activated exhibits its effects mainly through activation of G alpha i/o. Binding of CB1 to its agonist leads to inhibition of the production of adenylate cyclase enzyme. Consequently, the binding between CB1 and its ligands decrease the intracellular cAMP levels and an increase the mitogen-activated protein kinase (MAP kinase). In some cases CB1 receptor activation may be coupled to G_s proteins, which stimulate adenylate cyclase-cAMP. [3,4]

CB1 and CB2 receptors are also coupled to a variety of ion channels in the cell membrane, which are the positively influenced inwardly rectifying potassium channels (=Kir or IRK) and the calcium channels. These channels are activated when there is a cAMP dependent interaction between the receptor and the molecules such as protein kinase A (PKA), protein kinase C (PKC), Raf-1, ERK, JNK, p38, c-fos, c-jun, and others. [5]

In case of CB1, activation can produce a subsequent decrease of Ca2+ entry into the cell, without involvement of cAMP, which is the requirement for neurotransmitter release. The overall effect
is a decrease in the neurotransmitter release. CB\textsubscript{1} receptor is therefore a pre-synaptic receptor that modulates neurotransmitter release when activated in a dose-dependent manner [6].

CB\textsubscript{1} and CB\textsubscript{2} cannabinoid receptors also act to regulate the phosphorylation and activation of different members of the family of mitogen-activated-protein kinases (MAPKs), including extracellular signal regulated kinase-1 and -2 (ERK1/2), p38 MAPK and c-Jun N-terminal kinase (JNK). MAPK, in turn controls gene expression related to cell proliferation, motility, adhesion and apoptosis as well as glucose metabolism [6].

CB\textsubscript{1} and CB\textsubscript{2} receptors produce their effects through the stimulation by their agonists.

(endogenous/ exogenous/ synthetic). After release, agonist molecules are rapidly deactivated by uptake into cells and metabolized. Metabolism of anandamide and 2-AG occurs by either enzymatic hydrolysis with a help of fatty acid amide hydrolase enzyme (FAAH) [7,8] or other metabolic processes, including hydrolysis of 2-AG by monoglyceride lipase [9].

The mechanism is summarized in Figure 2.

2.2.3 Distribution of cannabinoid receptors:

CB\textsubscript{1} receptors are expressed by central and peripheral neurons and also by some non-neuronal cells [1,2, 10]. Within the central nervous system, the distribution pattern of CB\textsubscript{1} receptors is heterogeneous and can be related to their function. CB\textsubscript{1} receptors are densely distributed in cerebral cortex, hippocampus, caudate-putamen, substantia nigra pars reticulata, globus pallidus, entopeduncular nucleus and cerebellum, as well as in other areas of the brain and spinal cord.

They process or modulate nociceptive information. Distribution within the central nervous system might be related to CB\textsubscript{1} receptor agonists' ability to impair cognition and memory, to alter the control of motor function and to produce anti nociception [1, 10, 11,12].

Some CB\textsubscript{1} receptors are located on central and peripheral nerve terminal, where they modulate the release of excitatory and inhibitory neurotransmitters when activated [1, 2]. CB\textsubscript{2} receptors are expressed mainly on immune cells [2, 10] and have a role in immunomodulation.
Both, CB1 and CB2 receptors share the ability to modulate the release of chemical messengers. By acting on CB1 receptors, cannabinoids interact with a multitude neurotransmitters at the CNS and can modulate their release. [13]. CB2 control the release of inflammatory cytokines, regulating the immune system.

2.3 Other cannabinoid receptors of the endocannabinoid system. Cannabinoid Non-CB1 Non-CB2 receptors

2.3a Vanilloid receptors:
One of the non CB1/CB2 receptors described, with binding capacity to cannabinoids is TRPV1 receptor, also called capsaicin receptor. It is a non-selective cation channel that is present on sensory neurons in tissues such as skin, heart, blood vessels and lung. TRPV1 receptors are found mainly in the nociceptive neurons of the peripheral nervous system, but they have also been described in many other tissues, including the central nervous system. TRPV1 is involved in the transmission and modulation of pain (nociception) [35,14,15] through sensory primary afferent and perivascular neurons. It has been shown that activation of TRPV1 by the endogenous cannabinoid anandamide leads to a release of substance P (SP) and of calcitonin gene-related (CGRP), which have allogenic and local vasodilatory and pro-inflammatory effects, as well as beneficial actions such as cardio protection and anti-hypertensive effects. [16-22]

2.3b Non-CB1, Non-CB2, non-Vanilloid receptors.

It has been shown by successive experiments that many biological effects of the cannabinoids are not reversed by CB1 / CB2 antagonists. Additional receptor pathways, including the peroxisome proliferator-activated receptors (PPARs), G-protein receptor 55 (GPR55) as well as nicotin, 5-HT3 and adenosine A2A receptors, have been involved in cannabinoid signal transduction. [23,24]

2.3c Allosteric sites for cannabinoids

Apart from different receptors, there is an evidence for the presence of allosteric sites for anandamide and other cannabinoids on several non-cannabinoid receptors [1,26]. These are 5-HT2
receptors [27], 5-HT3 receptors [28,29,30,31], α1-adrenoceptors, M1 and M4 muscarinic receptors [32] and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) GLUA1 and GLUA3 glutamate receptors [33,34] The biological consequences of occupation of the proposed allosteric sites on 5-HT2 receptors (by HU-210) and on M1 and M4 receptors (by anandamide, methanandamide and SR141716A) have not been determined yet.[1]

2.4 Effects of cannabinoids on body systems. (See Table 2)

The effects of cannabinoids include analgesia, muscle relaxation, immunosuppression, anti-inflammation, anti-allergic effects, sedation, improvement of mood, stimulation of appetite, anti-emesis, lowering of intraocular pressure, bronchodilation, neuroprotection and antineoplastic effects. [36]

2.4a Cannabinoids and the Central Nervous System (CNS):

Cannabinoids interact with different neurotransmitters and neuromodulators [36–39], among them acetylcholine, dopamine, α-aminobutyric acid (GABA), histamine, serotonin, glutamate, norepinephrine, prostaglandins and opioid peptides. Some effects of THC of the body can be explained by these interactions. For example, tachycardia and hypo salivation with dry mouth [40,41] are mediated by the effects of THC on the release and turn-over of acetylcholine [40]. The antiemetic properties of cannabinoid are explained by interactions with serotonin [42]. Therapeutic effects in movement and spastic disorders could be ascribed in part to interactions with GABAergic, glutamergic and dopaminergic transmitters systems [43,44].

Neuroprotective cannabinoid effects observed in animal studies are based on inhibition of excessive glutamate production, inhibition of calcium influx into cells and the anti-oxidant properties which reduce damage caused by oxygen radicals and modulation of vascular tone [36, 45-47]. The use of cannabinoids as a treatment of stroke and brain injury is therefore being investigated.

2.4b Cannabinoids and the circulatory system:
Stimulating the endocannabinoid system with THC leads to tachycardia [36,48] and increased cardiac output, cardiac labor and oxygen demand [49]. It can also produce peripheral vasodilation and orthostatic hypotension [50,51] mediated by central inhibition of the sympathicus system, by activation of CB1 receptors [54]. It has been shown that endocannabinoids can be synthesized by vascular endothelium, circulating macrophages and platelets [52] and the subsequent activation of vascular cannabinoid CB1 receptors can decrease vascular resistance in the coronary arteries and the brain [53]

2.4c Cannabinoids, appetite and eating

Endocannabinoids control appetite though leptin signaling pathway in the hypothalamus [55]. Leptin downregulates food intake by upregulating appetite-reducing neuropeptides and downregulating appetite-stimulating factors. In animal model, reduced levels of leptin were associated with elevated levels of endocannabinoids in the hypothalamus [55]. Cannabinoid antagonists have been tried to treat obesity but a selective loss of positive emotional memory in healthy volunteers was noted. [62]

Rest of the effects on osteoarticular, digestive, reproductive, ocular and immune system are resumed in Table 2.

3. Endocannabinoid System and its potential role in medicine

Several studies about cannabinoids system and their possible actions in medical purposes have been done in the last decades. Cannabinoids have multiple physiological effects. Hence, modulation of endocannabinoids system, with agonists and antagonists, have been broadly studied as potential novel treatments for different diseases. For example, Anandamide could increase food intake in rats [63] and has been approved to increase weight in cancer and HIV+ patients, while the antagonist SR-141716A inhibits the intake of food [64, 65, 66], being a potential anti-obesity treatment, acting probably in the CB1 receptor in the hypothalamus [67]. They were already shown to be effective in many medical conditions listed in Table 3.
4. How cannabinoids are consumed

Cannabinoids can be consumed in several ways. However, the pharmacokinetics of Δ9-THC is different in each manner [68]. Possible forms of administration are listed in Table 4, with their advantages and limitations to being used for medical purposes. The most well-known and used way of administration of cannabinoids is inhaling.

5. Cannabinoids and the immune system

Immune cells express CB1 and CB2 receptors and can synthesize, secrete, transport and catabolize cannabinoids [69-73]. The expression of cannabinoids receptors is different in each immune cell. They are expressed, from the most abundant to the less extensive, on B cells, natural killer cells (NK), monocytes, neutrophils, CD8 leucocytes and CD4 leucocytes. The level of expression also depends on the immune stimulation and on the activation state of the cell [74].

In mice, deficiency in the Fatty Acid Amide Hydrolase (FAAH), anandamide-catabolizing enzyme, elevates the levels of anandamide (an endocannabinoid) in the CNS and periphery. Increased levels of anandamide attenuate inflammatory responses, suggesting that the endocannabinoids are physiologically involved in dampening the immune system [75-77].

The evidences that endocannabinoid system has probably immunomodulatory effects generated the theory that exogenous cannabinoids might also have immunosuppressive effects, being a potential novel therapy to autoimmune and inflammatory disease. Since then, several studies about this association have been published. [71, 78-80].

Δ9-THC can modulate Th1/Th2 balance by enhancing Th2 and suppressing Th1 immune responses [81-84]. Although, the psychoactive effects of Δ9-THC limit its potential as a therapy. Cannabidiol, on the other hand, has low affinity for the CB1 and CB2 receptors, resulting in no psychoactive effects [85,86]. Besides, Cannabidiol is well tolerated without side effects when chronically administered to humans [87, 88].
Cannabinoids were shown, *in vivo* and *in vitro*, to exert their immunosuppressive properties through 4 main pathways: induction of apoptosis, inhibition of cell proliferation, inhibition of cytokines and chemokines production and induction of regulatory T cells (T regs) [89].

### 5.1 Cannabinoids induce apoptosis

Anandamide was shown to induce apoptosis in mitogen-induced T and B human lymphocytes, human neuroblastoma CHP100 cells and lymphoma U937 cells, depending on the dose [90, 91]. It was also observed that Δ9-THC can trigger apoptosis in murine macrophages and T cells, through regulation of BCl2 and caspase activity [92].

However, there is no demonstration of cannabinoids inducing apoptosis *in vivo*, perhaps because apoptosis detection *in vivo* is difficult since the apoptotic cells are rapidly and efficiently cleared through phagocytes [89].

Δ9-THC injection in C57BL/6 mice (10 mg/kg body weight) was demonstrated to decrease the cellularity in the spleen and thymus, affecting several cell populations such as T cells, B cells and macrophages. [93]. When administered at a lower concentration (10 µM), Δ9-THC only induced AnnexinV + cells, which is indicative of early apoptotic cells, but at higher concentrations (20 µM), the splenocytes had both AnnexinV and PI positive, which represent late apoptotic as well as necrotic cells.

Δ9-THC may affect more intensively naive lymphocyte than activated lymphocytes. Levels of apoptosis were shown to be greater in cultures treated only with THC, when compared to the cultures that contained Δ9-THC and mitogen [93]. In the same study, it was noticed that activated lymphocytes can down-regulate the expression of CB2, decreasing their sensitivity to Δ9-THC.
Administration of CB2 antagonists block ∆9-THC-induced apoptosis in lymphocytes and thymocytes, while CB1 antagonists failed to show a significant effect, what suggest that ∆9-THC induces apoptosis via CB2 receptors [93].

Cannabidiol was also demonstrated to induce apoptosis in a time-and-dose dependent manner on CD4+ and CD8+ T cell populations, on murine thymocytes and on EL-4 cells. Cannabidiol lead to apoptosis by producing reactive oxygen species (ROS) and activating caspase 8 and caspase 3. [94]

5.2 Cannabinoids inhibit immune cell proliferation

While low doses of ∆9-THC stimulate T cell, high doses of ∆9-THC inhibited responses to LPS, T cell mitogens and anti-CD3 antibody in both human and mice in vitro studies [95]. This bi-phasic role of cannabinoids has also been shown on B cells: a study demonstrated increased B cell proliferation in response to ∆9-THC [96], and, on the other hand, another study showed decreased B cells response to LPS after cannabinoid treatment [95].

∆9-THC could suppress immune functions and increase susceptibility to infections in experimental models. The precise mechanism by which ∆9-THC suppress the immunity is still unclear. The inhibition of lymphocytes proliferation in those cultures might be induced through direct effects on immune cells, and not in CB1 and CB2, once it still observed in presence of CB1 and CB2 antagonists [97]. ∆9-THC can also decreased proliferation of thymocytes. This effect was shown to happen by inhibiting the calcium stabilization within the cell [98]. Low doses of anandamide were also able to inhibited proliferation of T and B lymphocytes after mitogen stimulation [90].

5.3 Cannabinoids inhibit cytokine and chemokine production and inflammatory cells migration

Cannabidiol inhibits IL1, IL12, TNF alfa and interferon-gama (INF-g) cytokine release by peripheral blood mononuclear cells, and enhances production of the Th2-associated cytokines, IL-4
and IL-10 [99]. Cannabidiol can also reduce prostaglandin E2 and tissue cyclooxygenase (COX) activity [P61]. ∆9-THC also changes destructive TH1 immunity to protective TH2 immunity, but less effectively than Cannabidiol [70, 100-104].

Cannabinoids can regulate monocytes differentiation to M1 or M2 macrophage phenotypes, as well as their ability to produce cytokines, chemokines and other immune mediators [105-112].

The responses to cannabinoids in the immune system are different in people who usually use consume cannabis and in the ones that are not. Phytocannabinoids can inhibit monocyte migration in individuals exposed to cannabis more than twice a week (non-naïve), while they do not affect subjects that never tried or that were not exposed in the past 3 years (naïve) [113]. In this study, endocannabinoids and synthetic cannabinoids had no effect in both groups. The authors also demonstrated that monocytes isolated from cannabis non-naïve subjects expressed fourfold higher amounts of CB1 receptor mRNA than cannabis naïve subjects, whereas CB2 receptor mRNA remained unchanged between the two cohorts. These results show that the sensitivity of monocytes isolated from non-naïve subjects to phytocannabinoids correlates with enhanced expression of CB1 receptors.

∆9-THC was also shown to have immunosuppressive effects in Legionella pneumophila (Lp) infected dendritic cells. When the dendritic cells were pretreated with ∆9-THC, the immunization potential of Lp-loaded cells in mice was suppressed. ∆9-THC suppressed IL-12p40 production by the dendritic cells and inhibited expression of maturation markers such as MHCII, CD86, and CD40 [114].

5.4 Cannabinoids induct regulatory T cells

∆9-THC can increase the number of Foxp3+ Treg cells. In a ConA-induced hepatitis model, ∆9-THC was able to alleviate liver damage, it was not only by increasing levels of apoptosis in activated T cells, but also by inducing Treg cells to inhibit the cytokines induced in vivo by ConA.
More studies are still needed, but it suggests that Treg cells, unlike other T cells, may be resistant to apoptosis induced by Δ9-THC and may suppress the activation of T cells that eventually escape from apoptosis. [89, 115]

5.5 Other cannabinoids immunomodulatory effects

Cannabis and certain cannabinoid receptor ligands have the ability to suppress serum immunoglobulin (Ig) levels [69, 70, 116]. Δ9-THC reduces B cell numbers while decreases IgG and IgM levels [116]. Although, this effect is controversial: some authors believe that there are no changes in B cell levels [117].

Cannabinoid receptor ligands can suppress spreading and phagocytosis, cytolysis, cytokine production, and antigen presentation in mouse peritoneal macrophages [118-124]. They also suppress, in vivo and in vitro, NK cells and cytotoxic effector functions. [125-127].

5.6 Cannabinoids as pro-inflammatory molecules?

Despite all these data, some studies suggest that cannabinoids could also have pro-inflammatory effects. [128,129]: promoting allergic reactions [130]; releasing inflammatory mediators through CB1 receptors in mast cells [129], increasing B cell proliferation [95].

The key to understand the role of cannabinoids in immunomodulation is to stress that their effects depend on the type of cannabinoid, on the type of cells that they are acting on and on the doses administrated. In optimal concentrations, cannabinoids can induce apoptosis in immune cells, alleviating inflammatory responses and protecting the host from acute and chronic inflammation. Thus, they can be beneficial when an immune suppression is necessary. Additional research is still needed to validate these studies in humans through clinical trials.

The effects of the three main cannabinoids that could be beneficial to autoimmune diseases are summarized in Fig 4.
6. Effects of cannabinoids in autoimmune disorders

6.1 Cannabinoids in Multiple Sclerosis (MS)

MS is a chronic neuroinflammatory autoimmune demyelinating disease of the human central nervous system, mediated by T lymphocytes. The inflammatory process leads to BBB disruption, causing swelling, activation of macrophages, and further production of cytokines and “cytotoxic” proteins such as metalloproteinases.

In mice model of MS (Experimental Autoimmune Encephalomyelitis (EAE)) it has been shown that CB1 receptors play an important role in the control of neuroinflammation. Mice deficient in CB1 tolerate inflammatory and exitotoxic insults poorly and develop substantial neurodegeneration following immune attack [131].

THC has been reported to inhibit neurodegeneration in the EAE model by reducing inflammatory cytokines and to reduce the associated induced elevated level of glutamate in cerebrospinal fluid [132]. Glutamate, the major excitatory neurotransmitter in the cerebral cortex, has been implicated in neurodegenerative disease when present at high levels.

Studies in the CB1 knockout mice showed greater susceptibility to neurofilament damage, caspase 3 activation as well as greater dephosphorylation of a neurofilament H epitope, considered as a marker of axonal damage during chronic relapsing EAE. [133] Collectively, the data suggested that signaling through CB1 conferred neuroprotection during EAE.

Studies have also shown that CB1 receptor activation exhibited down-regulatory responses in the motor regions of CNS system where they were expressed and could explain the improvement in motor symptoms such as spasticity, tremor, and ataxia of mice and human models treated with CB1 agonists.[134] Rolipram, an inhibitor of type IV phosphodiesterase that suppresses EAE in different species, has been found to attenuate clinical decline, reduce motor inhibition, and normalize CB1 gene expression in the basal ganglia of EAE rats [135]. EAE rats also have been reported to exhibit changes in endocannabinoid levels presenting decreased levels of
anandamide and 2-AG in motor related regions such as the striatum and midbrain as well as in other brain regions. [135].

CB2-selective agonists such as RWJ400065 have not shown to inhibit spasticity. However, CB2-deficient T lymphocytes in the CNS during EAE exhibit reduced levels of apoptosis, a higher rate of proliferation, and increased production of inflammatory cytokines resulting in severe clinical disease. In addition, selective glial expression of both, CB1, CB2, and FAAH has been reported as associated with MS, supporting a role for the endocannabinoid system in the pathogenesis and/or evolution of this disease [136].

Endogenous cannabinoid, anandamide plays an important role in controlling the inflammatory process during the course of MS progression. It was demonstrated that treatment with the selective anandamide uptake inhibitor UCM707 during established disease resulted in a significant improvement in motor function. UCM707 was able to reduce microglial activation, diminish MHC class II antigen expression, decrease cellular infiltrates in the spinal cord, and decrease the production of the pro-inflammatory cytokines TNF-α, IL-1β, and IL-6. The endocannabinoid system is highly activated during CNS inflammation and anandamide protects neurons from inflammatory damage through a CB1/CB2-mediated rapid induction of microglial mitogen-activated protein kinase phosphatase-1 (mpk-1) [137].

Studies in humans are scarce. Recently the results of a clinical trial have been published where the effect of (9)-tetrahydrocannabinol was tried in 498 patients with primary or secondary progressive MS, 1-year evidence of disease progression and baseline EDSS 4.0–6.5. No differences were found in the rate of progression of MS in both groups although lower than expected progression rates might have affected the ability to detect clinical change. [138]

Nevertheless, there is sufficient data to suggest symptomatic improvement when cannabinoid treatment is used in MS patients. Studies done in patients with MS with the aim to see the effect of THC on spasticity and pain proved long-term symptomatic improvement of spasticity and relief of pain. [139-141]
6.2 Cannabinoids in Rheumatoid Arthritis.

Joint diseases, inflammatory and degenerative, all share a pathological feature which is the loss of articular cartilage. In osteoarthritis and rheumatoid arthritis (RA), there is an increased cartilage breakdown. It is induced by an increased production of inflammatory cytokines, particularly IL-1 and tumor necrosis factor (TNF) produced by the articular chondrocytes or cells of the synovium [142]. The overall result is an increase in metalloproteinases (MMPs) particularly MMP-3 and MMP-13, which are responsible for cartilage destruction.

Cannabinoids were shown to have anti-inflammatory effects and reduce to joint damage in animal models of arthritis [143-145]. According to in vitro studies, cannabinoids reduce cytokine production by RA fibroblasts as well as the release of matrix metalloproteinases (MMPs) from fibroblast-like synovial cells [146-148]. Cannabinoids have also shown to reduce interleukin 1 (IL-1) induced proteoglycan and collagen degradation in bovine cartilage, thus reducing cartilage extracellular matrix (ECM) breakdown [149].

Studies have been performed with synthetic cannabinoid WIN-55,212-2 mesylate (WIN-55). It is an agonist of CB1, CB2 receptors and also has an ability to activate other receptors including peroxisome proliferator activated receptors alpha and gamma (PPARa and g) [150-152]. It was proved that WIN-55 can reduce the gene and protein expression of MMP-3 and MMP-13 in the presence of IL-1b, suggesting that cannabinoids may have potential in terms of arthritis therapy. It also significantly reduces the gene expression of TIMP-1 and TIMP-2 tissue inhibitors of matrix metalloproteinases to below basal levels. [153]

Similar results were obtained with a selective CB2R agonist (HU-308) in vitro. Pre-treatment with HU-308 inhibited IL-1β-induced proliferation of cultured RA fibroblast-like synoviocytes. The agonist also decreased the production of proinflammatory cytokines (IL-6 specifically) and of matrix metalloproteinases that are thought to be involved in cartilage erosion (MMP3 and MMP13.) In another study non-psychoactive cannabinoid ajulemic acid (AJA) reduced MMP-1,
MMP-3 and MMP-9 release from fibroblast like synovial cells stimulated with IL-1α and TNFα [148]. In vivo, AJA has also been shown to reduce the severity of adjuvant-induced arthritis [144]. When a novel synthetic cannabinoid acid, Hebrew University– 320 (HU-320) was administered to a mouse model of arthritis, inhibition of mouse macrophages TNF production was observed. The authors also noticed reduction of reactive oxygen intermediates and suppression of the rise in serum TNF level following endotoxin challenge. [153]

All these data suggests that cannabinoids have anti-inflammatory properties and should be considered as a treatment for inflammatory arthritis. There are no studies in humans up to date on the use of cannabinoids reducing inflammation in RA and further studies are needed to prove that.

There are however, studies which have shown that cannabinoids are efficient in the treatment of pain associated with RA. There is evidence that endocannabinoid system plays an important role in the peripheral regulation of nociception [154,155]. CB1R present on nociceptor terminals may mediate the anti-nociceptive and anti-inflammatory actions of locally produced N-arachidonoyl ethanolamine through its inhibitory influence on the release of excitatory neuropeptides [155] CB1R and CB2R are also expressed in the dorsal root ganglia, and their stimulation at this level also decreases nociceptive transmission [156,157]. At the central level, the endocannabinoid system controls nociception through CB1R located at spinal and supraspinal levels [158] Pharmacological studies have suggested a peripheral endocannabinoid basal activity that modulates nociceptor activity in osteoarthritic joints [159]. CB1R and CB2R mRNA and protein, were found in synovial biopsies deriving from total knee arthroplasty of advanced osteoarthritis and rheumatoid arthritis patients [160] Both, anandamide (AEA) and 2-arachidonoylglycerol (2-AG) were detected in the synovial fluid of these patients, but not in healthy volunteers, providing further evidence for a functional endocannabinoid system in osteoarthritic joints [160] Spinal cord levels of AEA, 2-AG and their synthesizing enzymes were also increased in the rat model of os-
teoarthritis [161] All these findings provide evidence for both peripheral and central adaptive changes involving the endocannabinoid system during osteoarthritis.

Studies on human models are scarce and contradictory. A recent review article on the effect of cannabinoid nabiximol on chronic pain in rheumatic diseases shows that there is a low-quality evidence suggesting that cannabinoids may be associated with improvements in pain and sleep quality in RA. Measures of morning pain at rest, sleep quality and a global disease activity score showed improvement, but measures of pain intensity were unchanged [162]. However, Savitex (dronabinol) is sometimes used to reduce pain in inflammatory joint disease- [163]

6.3 Cannabinoids in Scleroderma:

Cannabinoid receptors CB1 and CB2 were found to be over-expressed in scleroderma fibroblasts compared with healthy fibroblasts. A study was carried out to see the effect of WIN55,212-2, CB1 CB2 agonist on the production of collagen. It was demonstrated that WIN55,212-2 induced inhibition of type I collagen as well as procollagen type I PIP supernatant levels, which was also associated with changes in skin fibrosis [164]. The reduction in type 1 collagen production was accompanied by a decrease in levels of growth factors involved in the fibrotic process, TGF-beta and its downstream mediator CTGF. There was also an inhibition of fibroblast trans differentiation and inhibition of the over-expressed IL-6 in scleroderma cultures, known to be involved in scleroderma pathogenesis [165].

The agonist WIN55,212-2 also significantly increased the number of scleroderma fibroblasts undergoing apoptosis. These observations are consistent with the anti-proliferative effect of cannabinoids. [166]. No toxicity of WIN55,212-2 on cell cultures was found. However, the anti-fibrogenic effect of WIN55,212-2 did not seem to be mediated by the ‘classic’ cannabinoid receptors CB1 and CB2 and it was proposed that ERK signaling pathways may be involved. [167]

Further studies have shown that additional receptor pathways, including the transient receptor potential vanilloid type-1 (TRPV1), the peroxisome proliferator-activated receptors (PPARs), G-protein receptor 55 (GPR55) as well as nicotine, 5-HT3 and adenosine A2A receptors are in-
volved in cannabinoid signal transduction.[168,169] Oral administration of Ajulemic Acid (AjA), a non-psychoactive synthetic analogue of tetrahydrocannabinol able to bind the peroxisome proliferator-activated receptor-γ (PPAR-γ) prevented the development of skin fibrosis, and reduced skin thickness nearly to control levels. At the biological level it produced dose dependent reduction of procollagen and 5 TGF-β [170]. According to these observations, the stimulation of peroxisome proliferator-activated receptor-γ (PPAR-γ) could have an anti-fibrotic effect and cannabinoids should be studied as a potential anti fibrotic treatment.

6.4 Cannabis in Type 1 Diabetes

In type 1 diabetes mellitus, the insulin-pancreatic b-cells are destroyed, most probably, mediated by CD4 Th1 and CD8 T lymphocytes [171,172]. During insulitis, the initial lesion of this disease, leukocytes, especially lymphocytes, surround and infiltrate the islets [173].

Cannabidiol treatment of 6 to 12 week-old Non-Obese-Diabetes (NOD) mice was shown to significantly reduce the incidence of diabetes (from 86% in non-treated control mice to 30% in mice treated with cannabidiol). The plasma levels of INF-gama and TNF-alfa were reduced too, as well as other TH1 cytokines. The production of IL4 and IL10 (TH2 cytokines), on the other hand, was increased. When histological examination of the pancreatic islets was done, cannabidiol treated mice revealed significantly reduced insulitis. Therefore, cannabinoids can inhibit or at least delay destructive insulitis and TH1 associated cytokine in NOD mice. [99]

Despite the fact that cannabinoid could prevent diabetes type 1 in NOD young mice, it was not demonstrated to ameliorate diabetes after onset or around onset time. Thus, the same authors repeated the experiment with cannabidiol treatment, this time with 11 to 14 week-old NOD mice. They observed amelioration of diabetes manifestations: while the untreated and the emulsifier-treated group had 86% and 100%, respectively, of diabetes incidence at the end of the treatment; the group treated with cannabidiol had only 32%. Histological examination of the pancreas of cannabidiol treated mice revealed more intact islets than in the controls [174].
It was suggested that cannabidiol could have a role in prevention of human type 1 diabetes. However, it depends on the mechanism of the anti-autoimmune properties of this molecule. The main issue is to determine if it is a non-specific immunosuppressive agent or if it deviates Th1 to the response. If it is a non-specific immunosuppression mechanism, it requires lifelong treatment. Long-term therapy causes substantial potential risks, including possible enhanced susceptibility to opportunistic infection and increased risk of malignancy. Diabetes also has longstanding consequences, but they can be reduced with intensive insulin therapy aimed at normalizing glucose levels [175], what makes cannabinoid therapy need to be carefully evaluated before using in humans. On the other hand, if cannabidiol is causing the deviation from Th1 to Th2, it could be used to prevent diabetes in early on-set patients, before complete beta-cells destruction, and maybe in high risk individuals. Once the autoimmune response is deviated from a destructive Th1 response to a protective Th2 response, cannabidiol therapy is no longer required, eliminating the concern regarding long-term safety issues. [99]

Cytokines released by macrophages have a critical immunomodulatory role in skewing the immune response to either Th1 or Th2 [176]. Administration of IL-12 to macrophage-depleted NOD mice is known to initiate the disease [177]. Cannabidiol was shown to significantly reduce macrophage IL-12 production. [174] By reducing IL12, it induces TH2 differentiation and also reduces INF-g production. INF-g, that potentiates IL12 effects, activates cytotoxic T cells and stimulates macrophages to produce TNF-alfa, IL1 and IL6, besides nitrogen free radicals. Those molecules are associated with beta cells destruction [178-180]. Therefore, cannabidiol suppression of macrophage IL-12 production could inhibit Th1-mediated autoimmunity [99].

At onset of diabetes most patients have approximately 10% functional beta cells, evidenced by residual c-peptide secretion. Approximately 50% of patients diagnosed with type 1 diabetes will enter a “honeymoon” remission phase of diabetes and remain insulin independent within the first year of diagnosis [99]. These patients have sufficient residual beta cells to maintain normoglycemia and insulin independence, so they could be candidates for immunomodulation therapy.
Studies are still needed to prove if a Th1/Th2 shift actually happens in humans, and if it occurs, it really provides long-term protection from disease without other interventions.

6.5. Cannabis and Inflammatory Bowel Diseases

Cannabis has been widely used to cure disturbances and inflammation of the bowel. The mechanisms involved are still unclear, but probably include peripheral actions on CB1 and CB2 and may also include central actions [181].

Many animal experiments studies of cannabinoids possible therapy in colitis have been done in the last decade. Most of them showed reduced inflammation with cannabinoid agonists, while cannabinoid antagonists or cannabinoid receptor knockout increased inflammation [182-189]. Recently, studies with human colitis patients are underway.

Cannabinoids receptors are differentially expressed in human IBD, indicating a cannabinoid regulatory role in the disease progress [104, 190, 192].

Anandamide and its synthesizing enzyme are decreased in Ulcerative Colitis (UC), and the expression of CB2 receptors and of enzymes responsible for synthesis and degradation of 2-Arachidonoylglycerol are increased [193]. It suggests that cannabinoids can ameliorate the IBD. There are CB1 and CB2 receptors located at the colonic epithelium, so cannabinoids might enhance epithelial wound closure in the colon [194]. The activation of CB2 also leads to apoptosis and decreased proliferation of T cells in colitis, and diminishes the recruitment of neutrophils, T cells and macrophages to the inflamed colon [195].

The endocannabinoid system can also control gut motility and secretion, by CB receptors located in the enteric nervous system [192, 196]. These CB1 receptors can protect the bowels from the hyper stimulation that happen during IBD. By this mechanism, THC may improve IBD symptoms, mainly diarrhea, besides controlling the inflammation [196-198].
The possible central effect would be the reduction in pain sensation and relief of nausea, induced by stimulation on CB1 present in the central nervous system. This theory is supported by the fact that one study with peripherally restricted CB1 and CB2 agonist was too weak to improve colitis [199].

In a prospective placebo-controlled study with 21 Crohn Disease patients [200], cannabis induced clinical remission in 50% of patients. 80% of the participants had nonresponse or intolerance to anti–TNF-alfa. Although, the improvement was only symptomatic, with no induction of remission comparing to placebo. When patients discontinued the cannabis therapy, relapses were noticed in 2 weeks. Other cohort study of patients with IBD using cannabis [201] also reported that the patients perceive that it improved abdominal pain. Patients with UC, in particular, reported cannabis to improve diarrhea.

In another observational study [202], this time with 30 patients with Crohn’s disease, medical cannabis was associated with improvement in disease activity and reduction in the use of other medications was reported.

Usually, 25% to 38% of operated Crohn’s disease patients require a second operation within 5 years [203], but in a retrospective cohort study [204] only 2 of 15 patients (13%) who had surgery before cannabis consumption required surgery while consuming cannabis. Studies are still needed, but this one suggested that the use of cannabis reduces the need for surgery.

Some patients with UC and CD also use cannabis to enhance appetite [205]. In a study of 13 patients using cannabis for 3 months, a statistically significant increase in the subject’s weight was observed [206]. They also presented improvement in the disease activity index, perception of general health status, and ability to perform daily activities.
There is evidence that cannabinoids treatment could have beneficial effects on IBD. However, further research is required before it can be established which cannabinoid to use, in what dose and in which administration mode [202].

6.6. Cannabis in neuropathic pain

Neuropathic pain is a disease of peripheral or central nervous system. It happens when peripheral nerves, spinal cord, or brain are injured or the sensory system functions in the wrong way. There are many causes such as underlying pathological process (e.g., neuropathy) and catastrophic injury (e.g., stroke or spinal cord injury) [207]. The treatment for neuropathic pain is a difficult field, because in randomized clinical trials, less than half of patients report clinically meaningful pain relief from pharmacotherapy, most of them, just partial relief [208]. Because of that, and due to the studied anti-inflammatory potential of cannabis, a lot of studies about cannabinoid therapy to neuropathic pain have been performed [209].

Chronic pain is associated with the worst quality of life as compared with other chronic diseases such as chronic heart, lung or kidney disease, and what's more, is associated with a higher risk of suicide [210, 211]. A systematic review about cannabis in chronic non-cancer pain, especially in neuropathic pain, [212] selected 18 randomized control trials demonstrating a modest analgesic effect of cannabinoids in chronic pain.

A recent qualitative systematic review [213] stated that new safe and effective agonists at the cannabinoid receptors may dissociate therapeutic effects from psychotropic effects. For example, 1′,1′Dimethylheptyl-Δ8-tetrahydrocannabinol-11-oic acid (CT-3) is a synthetic analog of THC-11-oic acid, one of the endogenous transformation products of THC. It was shown to be a potent anti-inflammatory, analgesic and antiallodynic agent with no psychoactive properties in preclinical studies [214].
The exact neurobiological mechanism of action of cannabinoids is still unclear. Some studies claim that they work by binding to CB1 and in the intracellular peroxisome proliferator–activated receptor γ (PPARγ), which is directly associated to anti-inflammatory and antitumor effects [213-215]. Other studies suggest that there is an inhibition of eicosanoid synthesis and down-regulation of COX2 [216].

In order to examine the analgesic efficacy and safety of CT-3 in chronic neuropathic pain in humans, a randomized placebo-controlled double-blind crossover trial was preformed [217]. There were 28 patients with examination consistent with chronic neuropathic pain for at least 6 months with hyperalgesia and allodynia. They analyzed visual analog scale (VAS) and verbal rating scale scores for pain. It was observed that the VAS values in the CT-3 sequence, measured 3 hours after intake of study drug, differed significantly from those in the placebo–CT-3 sequence (11.54 [14.16] vs 9.86 [21.43]; P = .02). Although 8 hours after intake of the drug, the pain scale differences between groups were less marked.

In two different trials, patients with HIV peripheral neuropathy in cannabinoid therapy showed reduction in the pain (46-52%) compared to 18-24% in the placebo groups [218, 219]. This type of pain is notoriously resistant to other treatments normally used for neuropathic pain, which emphasize the importance of these study. [220]

Another group [221] made a human experimental model of neuropathic pain using intradermal injection of capsaicin in healthy volunteers and tested the efficacy of different doses of THC as a therapy. Low dose cigarettes (2% THC) had no analgesic value, while high dose (8% THC) cigarettes were associated with reports of an increase in pain. On the other hand, the medium dose of cannabis cigarettes (4% THC) produced significant analgesia.

A randomized double-blind placebo-controlled trial published in 2014, [207] compared medium dose (3.53% THC) to low dose (1.29% THC) cannabis, to see if the analgesia was sufficient in the low doses. The purpose was that if it as effective as the medium dose, it should be used pre-
ferentially, to avoid side effects. Both provided statistically significant 30% reductions in pain intensity when compared to placebo.

In a crossover trial with 23 patients with post-traumatic or post-surgical neuropathic pain [222], it was given 4 different doses of THC to the patients (0%, 2.5%, 6% and 9.4%) for four 14-days periods. It was inhale through a pipe three times a day for the first 5 days, followed by 9 days washout period, in each cycle. The pain intensity was measured daily by a numeric rating scale. They also analyzed the effects on mood, sleep and quality of life. The average daily pain measured was lower on the pre-specified primary contrast of 9.4% to 0% (5.4 to 6.1 respectively). Individuals who received 9.4% THC demonstrated improved ability to fall asleep and quality of sleep, when compared to the 0% THC group. There was no differences in mood or in quality of life.

All those studies showed that modulating the cannabinoid system can help patients with neuropathic pain, not only by relieving their pain, but also by improving their sleeping skills. Further long-term safety and efficacy are still needed.

6.7 Fibromyalgia:

FM is characterized by chronic widespread pain and elevated response to pressure which is perceived as pain. Other symptoms include tiredness, morning stiffness, sleep and emotional disturbances as well as cognitive dysfunction [223]. The pathophysiology of the disorder is not known. Several mechanisms have been proposed including central sensitization, suppression of descending inhibitory pathways, excessive activity of glial cells, abnormalities of neurotransmitter release as well as abnormal response to stress. [224]. Currently, the treatment is based on the relief of symptoms but poor results are achieved. The participation of the endocannabinoid system in multiple physiological functions such as pain modulation, stress response system, neuroendocrine regulation and cognitive functions amongst others, is well known [225]... It was suggested that clinical endocannabinoid deficiency may underlie the hyperalgesic tender muscle
points of this condition and play an important part in etiopathology of myofascial pain syndrome – fibromyalgia [226,227].

Some studies provide data that cannabinoids can prove to be an effective treatment of fibromyalgia symptoms. One retrospective study of fibromyalgia affected patients who were chronic users of cannabis, analyzed the effect of smoked, oral and combined cannabis on symptoms and the quality of life. A significant reduction of pain and stiffness, enhancement of relaxation, and an increase in somnolence and feeling of wellbeing were observed in cannabis users. Furthermore, mental health component summary score was significantly higher (p=0.05) in cannabis users than in non-users [228].

Some data suggests the beneficial effect on sleep in fibromyalgia patients. Nabilone had shown to be effective in improving sleep in patients with FM and was well tolerated. Low-dose nabilone given once daily at bedtime may be considered as an alternative to amitriptyline treatment. [229]

7. Adverse Effects of Cannabis

Due to the extend distribution of its receptors, cannabis are known to have many side effects. The most important ones are listed in Table 5.

In a systematic study [230], 8371 adverse events related to medical cannabinoid use were reported, 4779 of which were reported in 23 randomized controlled trials and 3592 in 8 observational studies.

Patients in cannabinoid therapy presented twice the incidence of severe adverse events than control groups. Respiratory (16.5%), gastrointestinal (16.5%) and nervous system disorders (15.2%) were the most frequently reported categories of serious adverse events among those assigned to cannabinoids, whereas nervous system disorders (30%) were the most frequently reported among
controls. The events considered severe side effect were: dyspnea, pneumonia, pleural effusion, lower respiratory tract infection and pulmonary embolism; vomiting, diarrhea, gastroenteritis, abdominal pain, constipation, duodenal ulcer; relapse of multiple sclerosis, convulsions.

15 deaths were also reported among cannabinoid users against 3 deaths in the control group, although these results did not prove to be statistically significant. [230]

The incidence rate of non-serious adverse events was significantly higher among subjects assigned to cannabinoid therapy than among controls, dizziness being the most frequent non-serious adverse event among cannabinoid-exposed participants.

8. Conclusion

Cannabinoids are potent inflammatory modulators and in several animal studies, *in vivo* and *in vitro*, they have shown to have an immunosuppressive effect.

However, human studies are still few.

Models of multiple sclerosis, rheumatoid arthritis, scleroderma and type 1 diabetes evidenced clinical improvement as well as biochemical and/or histological anti-inflammatory changes. Inflammatory bowel disease, neuropathic pain and fibromyalgia were studied in human subjects and improvement of pain, positive effect on sleep and better quality of life were noted. In ulcerative colitis there were less diarrhea symptoms after cannabinoid administration.

Certain types of cannabinoids, like cannabidiol, have low affinity to CB1 and CB2. Others, such as certain synthetic cannabinoids, have higher affinity for CB2 receptor. However, they do produce immunomodulatory effect without being psychoactive. Therefore, they have a potential in research, as a possible therapy for autoimmune diseases.

Nevertheless, cannabis are known to have many adverse effects, including memory impairment. THC is related to a decrease in gray matter volume and lower IQ levels. It can also trigger some
psychiatric disorders. Because of the THC stimulation of dopaminergic pathways involved in drug addiction, it can lead to dependence and drug abuse.

Further studies are required. How cannabinoids should be consumed, their optimal doses and which type of cannabinoids would be more effective, with fewer side effects still remain as questions to be answered.
Table 1. Cannabinoids receptor agonists groups and its components. [1,2]

<table>
<thead>
<tr>
<th>Classical</th>
<th>Non-Classical</th>
<th>Aminoalkylin-dole</th>
<th>Eicosanoid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phytocannabinoids:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• $\Delta 9$-THC</td>
<td>• Bicyclic and tricyclic analogues of $\Delta 9$-THC that lack a pyran ring:</td>
<td>• WIN5</td>
<td>Endocannabinoids:</td>
</tr>
<tr>
<td>• $\Delta 8$-THC</td>
<td></td>
<td>512</td>
<td>• Anandamide</td>
</tr>
<tr>
<td>• Cannabinol</td>
<td>• P5594</td>
<td></td>
<td>• Virodhamine</td>
</tr>
<tr>
<td>Synthetic cannabinoids:</td>
<td>• CP47</td>
<td></td>
<td>• 2-arachidonoyl glycerol (2-AG)</td>
</tr>
<tr>
<td>• HU-210</td>
<td>• CP55</td>
<td></td>
<td>Synthetic analogues of anandamide:</td>
</tr>
<tr>
<td>• JWH-133</td>
<td>244</td>
<td></td>
<td>• $R$-(+)-methanandamide</td>
</tr>
<tr>
<td>• L-759633</td>
<td>• HU-308</td>
<td></td>
<td>• Arachidonyl-2-chloroethylamide (ACEA)</td>
</tr>
<tr>
<td>• L-759656</td>
<td></td>
<td></td>
<td>• Arachidonylecyclopropylamide (AC-PA)</td>
</tr>
<tr>
<td>• L-</td>
<td></td>
<td></td>
<td>• O-689</td>
</tr>
</tbody>
</table>


nantradol

- Desacetyl-l-nantradol.
Table 2: Effects of Cannabinoids in the Human Body

<table>
<thead>
<tr>
<th>Body System</th>
<th>Effect</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS</td>
<td>Anti-emetic; neuroprotective, nociception. Sedating. Simpaticomimethic</td>
<td>[40]</td>
</tr>
<tr>
<td>Circulatory</td>
<td>Tachycardia, increased cardiac output</td>
<td>[49,50,51,53,54]</td>
</tr>
<tr>
<td></td>
<td>Vasodilation and orthostatic hypotension</td>
<td></td>
</tr>
<tr>
<td>Appetite and eating</td>
<td>Stimulation by leptin inhibition</td>
<td>[55]</td>
</tr>
<tr>
<td>Osteoarticular</td>
<td>Bone formation</td>
<td>[56]</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Inhibition of motility and gastric secretion</td>
<td>[57,58]</td>
</tr>
<tr>
<td>Reproductive system</td>
<td>Minor changes in hormone levels, no effect when tolerance is reached.</td>
<td>[51,59]</td>
</tr>
<tr>
<td></td>
<td>Decrease in sperm count without functional impairment</td>
<td></td>
</tr>
<tr>
<td>Ocular</td>
<td>Vasodilation. Decrease intraocular pressure</td>
<td>[60,61]</td>
</tr>
<tr>
<td>Immune system</td>
<td>Inmunosupression, immunomodulation</td>
<td>[69-73]</td>
</tr>
</tbody>
</table>
Table 3: Medical conditions in which cannabinoids were shown to be effective.

<table>
<thead>
<tr>
<th>Medical condition</th>
<th>Effect</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic pain in cancer</td>
<td>Improve pain</td>
<td>231, 232</td>
</tr>
<tr>
<td>Post-operative and trauma pain</td>
<td>Improve pain</td>
<td>233</td>
</tr>
<tr>
<td>Chemotherapy induced nausea and vomiting</td>
<td>Improve symptoms of nausea and vomiting</td>
<td>234-239</td>
</tr>
<tr>
<td>Cancer cachexia and HIV disease</td>
<td>Improve appetite and increasing weight in</td>
<td>240-243</td>
</tr>
<tr>
<td>Spasticity, movement disorders and dystonia</td>
<td>Improve symptoms</td>
<td>244-246</td>
</tr>
<tr>
<td>Gastro-intestinal conditions (gastric ulcers,</td>
<td>Improve symptoms, pain and increase life quality</td>
<td>191, 247</td>
</tr>
<tr>
<td>irritable bowel syndrome, ulcerative colitis,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crohn’s disease, secretory diarrhea, paralytic ileus and gastroesophageal reflux disease</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 4: How cannabinoids can be consumed: advantages and limitations.

<table>
<thead>
<tr>
<th>Administration form</th>
<th>Advantages</th>
<th>Limitations</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cutaneous absorption by adhesives impregnated by herbs</td>
<td>No need to eat or inhale</td>
<td>Takes too long to act.</td>
<td>248</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No clinical applications.</td>
<td></td>
</tr>
<tr>
<td>Oral absorption</td>
<td>No need to inhale.</td>
<td>Increased bioavailability by presence of food in the stomach and gastric acid partial destruction.</td>
<td>249, 250</td>
</tr>
<tr>
<td></td>
<td>Onset of action after 30-60 minutes.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Peak of action 2-3 hours after ingestions</td>
<td>Psychoactive effects due to conversion of Δ9-THC to 11-hydroxy-THC in the liver (9-10 times more psychoactive than Δ9-THC)</td>
<td></td>
</tr>
<tr>
<td>Administration form</td>
<td>Advantages</td>
<td>Limitations</td>
<td>References</td>
</tr>
<tr>
<td>---------------------------------------------</td>
<td>----------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------</td>
<td>------------</td>
</tr>
<tr>
<td>Intravenous administration (bolus or infusion)</td>
<td>No need to eat or inhale. Fast absorption (goes directly to the systemic circulation)</td>
<td>Needs a vehicle to permits aqueous administration due to cannabis low water solubility.</td>
<td>248, 251</td>
</tr>
<tr>
<td>Rectal administration (suppositories)</td>
<td>No need to eat or inhale. Fast absorption (goes directly to the systemic circulation)</td>
<td>Irregular absorption</td>
<td>251</td>
</tr>
<tr>
<td>Inhaling administration - smoking (cigarettes, pipes)</td>
<td>Peak of action in 20-30 minutes after smoking High intensity and short duration of action (2-3 hours)</td>
<td>Needs combustion (can lead to lung lesions). Plasma levels depending on volume and respiratory rate.</td>
<td>252</td>
</tr>
<tr>
<td>Administration form</td>
<td>Advantages</td>
<td>Limitations</td>
<td>References</td>
</tr>
<tr>
<td>---------------------</td>
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</tbody>
</table>
| Inhaling administration - vaporizer (portable dispositive that boils the cannabis herbs, creating a vapor that can be inhale without combustion) | No need for combustion  
Peak of action as fast as intravenous injection (due to its high liposolubility, it crosses rapidly the alveolar membrane reaching the blood through pulmonary capillaries) | Plasma levels depending on volume and respiratory rate. | 248, 253 |
Table 5: Side effects of cannabinoids in each system.

<table>
<thead>
<tr>
<th>Effects</th>
<th>Examples:</th>
<th>References</th>
</tr>
</thead>
</table>


<table>
<thead>
<tr>
<th>Effects</th>
<th>Examples:</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuropsychiatric effects</td>
<td>Dysphoric mood alterations like anxiety, panic.</td>
<td>230, 254-262</td>
</tr>
<tr>
<td></td>
<td>Psychosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sedation</td>
<td></td>
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<tr>
<td></td>
<td>Impaired global and prospective memory, verbal immediate and delayed recall and visual recognition.</td>
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</tr>
<tr>
<td></td>
<td>Convulsion</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lower IQ (depending on age at onset)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Decrease in gray matter volume in the medial temporal cortex, temporal pole, parahippocampal gyrus, left insula, and orbitofrontal cortex</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Increased appetite.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Drug Addiction</td>
<td></td>
</tr>
<tr>
<td>Effects</td>
<td>Examples:</td>
<td>References</td>
</tr>
<tr>
<td>-------------------------</td>
<td>---------------------------------------------------------------------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>Immune system effects</td>
<td>Increase incidences of common infectious diseases</td>
<td>230, 259, 260, 263-270</td>
</tr>
<tr>
<td></td>
<td>Increase susceptibility to viral infections such as herpes simplex virus,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Listeria monocytogenes, Staphylococcus albus, Treponema pallidum and</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Legionella pneumophila</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Allergies to cannabis (rare): contact urticaria and rhino conjunctivitis</td>
<td></td>
</tr>
<tr>
<td>Vascular system</td>
<td>Syncope</td>
<td>259, 260</td>
</tr>
<tr>
<td></td>
<td>Transient ischemic attack</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stroke</td>
<td></td>
</tr>
<tr>
<td>Effects</td>
<td>Examples:</td>
<td>References</td>
</tr>
<tr>
<td>---------------------------</td>
<td>----------------------------------------------</td>
<td>------------</td>
</tr>
<tr>
<td><strong>Respiratory system</strong></td>
<td>Chronic respiratory irritation</td>
<td>230, 267</td>
</tr>
<tr>
<td></td>
<td>Inflammatory changes in respiratory tract</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Suppression in responsiveness to infectious disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dyspnea</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pneumonia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pleura effusion</td>
<td></td>
</tr>
<tr>
<td><strong>Gastrointestinal system</strong></td>
<td>Vomiting</td>
<td>230</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diarrhea</td>
<td></td>
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<tr>
<td></td>
<td>Gastroenteritis</td>
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<td>Abdominal pain</td>
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<td>constipation</td>
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<td>Duodenal ulcer</td>
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Figure 1: Cannabinoids agonists and antagonists

The table resumes the most important cannabinoid agonists and antagonists. AEA and 2-AG are endogenous agonists and D9-tetrahydrocannabinol (D9-THC), the main psychoactive cannabis component is an exogenous agonist. Together with synthetic derivatives (HU 210, HU 308, CP 55,940, etc.), they are the compounds most frequently used as pharmacologic tools.
Both CB1 and CB2 cannabinoid receptors are associated with G proteins. Activation of these receptors leads to inhibition of adenylyl cyclase activity and activation of the different MAPK cascades. In addition, the CB1 cannabinoid receptor negatively regulates voltage-gated Ca2+ channels and positively regulates inwardly rectifying K+ channels. CB1 receptor can also induce elevation of intracellular free Ca2+ through activation of phospholipase C (PLC). Cannabinoid-mediated inhibition of protein kinase A (PKA) leads to inhibition of gene expression through a decrease in cAMP. It also results in activation of MAPK cascades related to cell survival/apoptosis. These signaling pathways are directly related to the variety of functions regulated by cannabinoid receptors.
Fig 3. Action of cannabinoids at the presynaptic terminal.

Cannabinoid agonists such as THC, 2-Ag and AEA bind to CB1 receptors, causing change in intracellular Ca2+ and K+ level. This in turn leads to neurotransmitter release inhibition at the presynaptic neuron. Cannabinoids are destroyed at the postsynaptic neuron by FAAH enzyme and the metabolites are recycled.
Figure 4: Benefit effects of cannabinoids in autoimmune diseases.

(a) Δ9-tetrahydrocannabinol

- Suppresses IL12 production, inhibits expression of maturation markers (MCHII, CD86 and CD40)
- Induces apoptosis, decreases proliferation, decreases IgG and IgM levels production
- Suppresses Th1
- Enhances Th2
- Induces apoptosis, decreases proliferation, increases the number of FoxP3+ T regs cells
- Induces apoptosis

(b) Cannabidiol

- Induces apoptosis in CD4+ and CD8+ T cells
- Inhibits release of IL1, IL12, TNF-α and ING-g
- Enhance production of IL4 and IL10

(c) Anandamide

- Induces apoptosis
- Damper the immune system
- Induces apoptosis
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