REVIEW

On the Pharmacological Properties of Δ^9-Tetrahydrocannabinol (THC)

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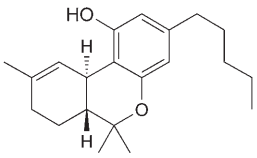
Cannabis is one of the first plants used as medicine, and the notion that it has potentially valuable therapeutic properties is a matter of current debate. The isolation of its main constituent, Δ^9-tetrahydrocannabinol (THC), and the discovery of the endocannabinoid system (cannabinoid receptors CB_1 and CB_2 and their endogenous ligands) made possible studies concerning the pharmacological activity of cannabinoids. This paper reviews some of the most-important findings in the field of THC pharmacology. Clinical trials, anecdotal reports, and experiments employing animal models strongly support the idea that THC and its derivatives exhibit a wide variety of therapeutic applications. However, the psychotropic effects observed in laboratory animals and the adverse reactions reported during human trials, as well as the risk of tolerance development and potential dependence, limit the application of THC in therapy. Nowadays, researchers focus on other therapeutic strategies by which the endocannabinoid system might be modulated to clinical advantage (inhibitor or activator of endocannabinoid biosynthesis, cellular uptake, or metabolism). However, emerging evidence highlights the beneficial effects of the whole cannabis extract over those observed with single components, indicating cannabis-based medicines as new perspective to revisit the pharmacology of this plant.

1. Introduction. – Marijuana has been used in medicine for millennia, but it was not until 1964 that Δ^9-tetrahydrocannabinol (THC)[1]), its major psychoactive component, was isolated in pure form and its structure was elucidated [1]. Emerging evidence supports a role of the endocannabinoid system in a wide variety of physiological and pathophysiological processes. This suggests that, at present, it is difficult to state which are the functions, if at all, in which endocannabinoids and their receptors are not involved. THC exerts a wide variety of biological effects by mimicking endogenous substances, *i.e.*, the endocannabinoids anandamide and 2-arachidonoylglycerol, which activate specific cannabinoid receptors (CB_1, particularly abundant in the central and peripheral nervous system, and CB_2, mainly expressed in the immune system). Consequently, cannabis and its derivatives promise an almost infinite array of cannabis-based drug therapies. The present review summarizes the recent advances in some selected pharmacological aspects of THC in terms of its therapeutic potential.

2. Anti-Inflammatory Effect. – A series of papers published more than 30 years ago [2–4] demonstrated the potent anti-inflammatory actions of a crude marijuana extract,

[1]) Systematic name: (6a*R*,10a*R*)-6a,7,8,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6*H*-dibenzo[*b*,*d*]pyran-1-ol.



Δ^9-Tetrahydrocannabinol (THC)

of THC, and of the non-psychoactive cannabis constituents, cannabidiol and cannabinol, in the carrageenan-induced paw-edema model of acute inflammation in rats. In these studies, THC proved 80 times more potent than aspirin, and twice as potent as hydrocortisone. In the mid-1980s, it was shown that mouse cells treated with THC produced decreased levels of interferons (IFN-α and IFN-β) after stimulation with LPS [5][6], providing the first evidence that cannabinoids might modulate cytokine production. Their suppression of pro-inflammatory cytokine and chemokine production indicates that cannabinoids might have anti-inflammatory effects and could, therefore, be used for the treatment of chronic inflammatory diseases. Apart from suppressing the production of some cytokines, THC has been shown to increase the production of other cytokines (including TNF, IL-1, IL-6, and IL-10), when administered together with bacteria or other antigens [7][8]. The non-psychotropic cannabidiol shares with THC many of these effects, suggesting that THC and cannabidiol have complex lineage- and derivative-specific effects on cytokines, consistent with previous animal studies. These effects, while of potential benefits in some inflammatory/autoimmune diseases, may worsen HIV infection, tumorigenesis, and allergic inflammation in the lung. The main obstacle to the therapeutic employment of THC as an anti-inflammatory agent, however, are its potent psychoactive effects.

Consequently, *Burstein*'s group suggested a class of cannabinoids, the so-called 'carboxy THCs', as therapeutic agents since they are free of cannabimimetic central-nervous-system (CNS) activity [9]. Cannabinoid acid includes all the carboxylic acid metabolites of the cannabinoids, and their synthetic analogues. The principal metabolite in this series, THC-11-oic acid was found effective when orally administered (20–40 mg/kg) in animal models of inflammation [10][11]. THC-11-oic acid also suppresses both the cyclooxygenase and lipoxygenase activities of cells in tissue culture [10]. However, more potent activity is needed for clinical use. It is known that modifications of the pentyl side chain of THC increase its potency [12]. In particular, extending the chain length to seven C-atoms and introducing branching close to the benzene ring leads to compounds with potencies that are 50 to 100 times greater than that of THC proper. This strategy was employed by the same group to design the structure of 1′,1′-dimethylheptyl-THC-11-oic acid, also known as ajulemic acid (AjA) [13], which showed potent anti-inflammatory action in several animal models [9]. AjA also suppresses 5-lipoxygenase and cyclooxygenase-2 activities, but unlike the non-steroidal anti-inflammatory drugs currently used, AjA is not ulcerogenic [14], and, most importantly, it is devoid of psychotropic effects. It has been shown [15] that oral administration of AjA at a dose of 0.1 mg/kg, three times weekly, significantly reduces the severity of adjuvant-induced polyarthritis in rats; particularly, AjA reduces clinical inflammation (joint redness and swelling) only modestly, but prevents joint cartilage and bone damage.

Cannabinoid acids, including AjA, exhibit only modest affinity for either cannabinoid receptor, CB_1 or CB_2, suggesting that, although possible, it is unlikely that the effects of AjA are mediated by either of these receptors. These effects may be rather due to differential effects of AjA on IL-1β and TNFα. A Phase-1, single-center, double-blind, randomized, placebo-controlled study of AjA was recently performed [16].

In conclusion, although current studies suggest that THC, and especially THC derivatives devoid of psychoactivity, may prove useful alternatives to some current therapeutic agents in treating a variety of human inflammatory disorders in the future, a thorough evaluation of the immunomodulatory effects of cannabinoids needs to be undertaken. The observation that expression of cannabinoid receptors on T- and B-cells is altered in habitual marijuana smokers [17] suggests that exposure to inhaled THC exerts biologic consequences on the immune system. Animal models demonstrate a clear pattern of immune regulation in response to THC, including impairment in the ability to generate antigen-specific T-cells, suppression of Th1-biasing cytokines (IFN-γ and IL-12), enhancement of Th2-biasing cytokines (IL-4 and IL-10), and a resulting shift in the balance of activated Th1 and Th2 cells [18]. The same pattern of T-cell responses occurs when human cells are activated in the presence of THC *in vitro*, and these immunologic sequalae may contribute to epidemiologic reports linking marijuana use to opportunistic infections, AIDS, and respiratory-tract cancer. Additional studies are needed at all levels of research to further substantiate and understand the complex role that endogenous cannabinoids and exogenous THC play on human immune function. More information is needed about the regulation and expression of cannabinoid receptors on different subsets of human immune cells and their response to different types of activation and to acute and chronic exposure to THC. In addition to cytokines, the production of other pro-inflammatory mediators has been shown to be affected by THC, including nitric oxide (NO) and prostaglandin E2, as reported in a study performed on J774 macrophages [19].

3. Neurodegenerative Diseases and Neuroprotection. – 3.1. *Neuroprotection*. Within the brain, CB_1 receptors are present at high densities on presynaptic terminals of glutamatergic and GABAergic synapses [20][21]. Consistent with this location, it has been suggested that activation of CB_1 receptors suppresses the presynaptic release of both excitatory and inhibitory neurotransmitters, including excess glutamate involved in excitotoxicity. Drugs that attenuate glutamatergic synaptic transmission show promise as therapeutic agents for neurodegenerative disorders, as discussed in the following sections. The potential neuroprotective properties of THC are of particular interest because this compound fails to completely block glutamatergic synaptic transmission, as reported in a very elegant study [22]; so it does not cause discernible side effects peculiar of drugs that completely block glutamatergic synaptic transmission. The neuroprotective actions of THC and other cannabinoids were first examined in rat cortical-neuron cultures exposed to toxic levels of the excitatory neurotransmitter glutamate by *Hampson et al.* [23], who demonstrated that both cannabidiol and THC protect equally well against neurotoxicity mediated by *N*-methyl-D-aspartate receptors, 2-amino-3-(4-butyl-3-hydroxyisoxazol-5-yl)propanoic acid receptors, or kainate receptors. Furthermore, the neuroprotection observed with cannabidiol and THC was unaffected by cannabinoid-receptor antagonists, indicating that there is no dependence on cannabinoid receptor.

Another evidence supporting the CB_1-independent neuroprotective effect of THC was obtained by *Marsicano et al.* [24], who found that alteration of CB_1-receptor expression using knockout animals, or gene transfer in the HT22 cell line, did not influence the protecting effect of THC against hydrogen peroxide (H_2O_2) toxicity *in vitro*. Conversely, another study showed that THC reduces neuronal injury in neonatal rats injected intracerebrally with the Na^+/K^+-ATPase inhibitor ouabain to elicit excitotoxicity. In particular, in the acute phase, THC reduced the volume of cytotoxic edema by 22%. After seven days, 36% less neuronal damage was observed in treated rats compared with control animals. Co-administration of the CB_1 cannabinoid-receptor antagonist SR141716 prevented the neuroprotective actions of THC, indicating that CB_1 receptors are involved in the protection to neurons elicited by THC [25]. Moreover, *El-Remessy et al.* [26] investigated the neuroprotective effect of THC in a model of NMDA-induced retinal toxicity. In this model, the effect of THC was partially, although not completely, blocked by the CB_1 antagonist SR141716A. Therefore, it appears that, under some circumstances, THC exerts neuroprotective effects exclusively through non-receptor-mediated antioxidant properties, while in other models or other cell types stimulation of CB_1 receptors by THC can produce neuroprotection. Such differences may be related to the cell type or model system, and to differences in the toxic events employed.

A more recent study reported that THC produces a potent neuroprotective effect in AF 5 cells (a useful *in vitro* model to investigate neuroprotective and toxic mechanisms of antioxidants and drugs able to block glutamatergic neurotoxicity), which appears to be mediated by antioxidant properties and is independent of the cannabinoid receptor CB_1 [27]. However, in the same study, THC produced toxic effects in AF 5 cells at higher concentrations; especially, THC produced a toxic effect at doses that were about two- to three-fold higher than those that were neuroprotective. Because the toxic effect of THC at higher doses is mediated by CB_1-receptor activation, development of neuroprotective antioxidant cannabinoids lacking CB_1-receptor efficacy may be the most useful route for the application of cannabinoids in preventing neurodegenerative disorders related to oxidative stress or excitotoxicity. In this context, many experimental setups showed that cannabinoid neurotoxicity, particularly by THC, resides side by side with neuroprotection. In addition, the same study [27] reported that prolonged exposure to THC desensitized the CB_1-mediated inhibition of synaptic activity and diminished the neuroprotection afforded by the drug. The effects of agonist efficacy and receptor desensitization on neuronal survival are important factors to consider when modulating cannabinoid-receptor signaling.

3.2. *Multiple Sclerosis.* The first study exploring the potential of THC in the treatment of multiple sclerosis (MS) dated from 1989 [28], and employed the experimental autoimmune encephalomyelitis (EAE) as animal model of MS. This study reported that THC-treated animals had either no clinical signs or only mild signs of MS, with delayed onset and survival greater than 95%. In addition, examination of the CNS tissue revealed a marked reduction of inflammation in the THC-treated animals. Later, a more stable and less psychoactive THC analogue, Δ^8-THC, was found to reduce the incidence and severity of neurological deficit in the same animal model [29].

The mechanisms involved in THC-induced amelioration of MS remain not completely understood, even though an inhibition of glutamate release through the

CB_1 receptors in the CNS, in particularly the spinal cord of EAE animals, has been recently reported [30]. Prior to 2002, few clinical data were available to indicate whether cannabis extracts may be beneficial in humans. However, in the last years, results of several placebo-controlled clinical trials of orally administered cannabinoids have been published, and these cast doubt on the efficacy of THC in objectively reducing spasticity in MS (for a review, see [31]). The preparations studied were smoked marijuana and hashish, oral THC in capsule form, oral extracts of cannabis administered in capsules or as sublingual spray and containing THC, cannabidiol, or a combination of the two, as well as oral nabilone. The results of these clinical trials are mixed: in a few cases, patients reported an improvement in spasticity, muscle spasms, pain, sleep quality, tremors, and general condition. The authors reported the absence of beneficial effects of cannabinoids on spasticity, estimated by means of the *Ashworth* scale, while noting after the fact the limitations of this scale in measuring the highly complex symptoms of spasticity. However, they observed an objective improvement in mobility with oral THC. By contrast, it has been claimed that cannabis extracts that contain approximately equal concentrations of THC and cannabidiol, a natural cannabinoid that does not act on the CB_1 receptor, can produce a statistically and clinically significant reduction in spasticity [32][33], although this claim has yet to be thoroughly validated. Nonetheless, results of preclinical trials also lend support to the hypothesis that the endogenous cannabinoid system may be involved in the regulation of spasticity and pain related to MS.

In conclusion, it is still questionable whether THC, and cannabinoids in general, are superior to existing, conventional medications for the treatment of spasticity and pain. In the case of spasticity, there are too few controlled clinical trials to draw any reliable conclusion at this stage. In the case of pain, as discussed in more detail below, most of the available trials suggest that cannabinoids are not superior to existing treatments; however, few trials have examined chronic-pain syndromes that are relevant to MS. A further issue will be whether synthetic cannabinoids should be used in preference to cannabis itself. THC, as a broad-spectrum cannabinoid-receptor agonist, will activate both the CB_1 and CB_2 receptors. Synthetic cannabinoids, which target specific cannabinoid-receptor subtypes in specific parts of the CNS, are likely to be of more therapeutic use than THC itself.

3.3. *Amyotrophic Lateral Sclerosis.* Only one paper reported that treatment with THC was effective, when administered either before or after onset of signs in the amyotrophic-lateral-sclerosis mouse model performed with hSOD(G93A) transgenic mice. Administration at the onset of tremors delayed motor impairment and prolonged survival in THC-treated mice, when compared to vehicle controls. *In vitro*, THC was extremely effective at reducing oxidative damage in spinal-cord cultures and exerted anti-excitotoxic effect. These cellular mechanisms may underlie the presumed neuroprotective effect in amyotrophic lateral sclerosis [34].

3.4. Tourette *Syndrome.* The *Gilles de la Tourette* syndrome (TS) is a neurobehavioral disorder associated with motor and vocal tics, and a spectrum of behavioral and cognitive features. Anecdotal reports [35–38] and controlled studies performed by *Muller-Vahl* and co-workers [39–41] provide evidence that marijuana and THC, respectively, are effective in the treatment of tics and behavioral problems in TS, with no detrimental effect on neuropsychological performance. However, larger and longer-

duration controlled studies are recommended to provide more information on the adverse-effect profile of THC in patients suffering from TS. Concerning the mechanism of action, an involvement of the central CB_1-receptor system in TS pathology has been suggested; the central cannabinoid receptor gene encoding CB_1 was recently systematically screened by single-strand-conformation-polymorphism (SSCP) analysis and sequencing. It was concluded that genetic variations of the CB_1 gene are not a plausible explanation for the clinically observed relation between the cannabinoid system and TS [42]. At present, it remains unclear whether herbal cannabis, different natural or synthetic cannabinoid CB_1-receptor agonists, or agents that interfere with the inactivation of endocannabinoids may have the best adverse-effect profile in TS.

3.5. Parkinson's *Disease*. The first evidence for a neuroprotective action of THC in an animal model of *Parkinson*'s disease, an adult-onset neurodegenerative disorder characterized by preferential loss of the dopaminergic neurons of the *substantia nigra pars compacta*, was reported by *Fernandez-Ruiz* and co-workers [43], who evaluated whether the *in vivo* administration of THC reduces the neurodegeneration produced by a unilateral injection of 6-hydroxydopamine, a toxin currently used to generate parkinsonism in laboratory animals, into the medial forebrain bundle. The results are compatible with a potential neuroprotective action of THC against the progressive degeneration of nigrostriatal dopaminergic neurons occurring in *Parkinson*'s disease. In fact, THC chronic treatment produced a significant recovery in the impairment of dopaminergic transmission caused by the toxin, likely indicating a reduction of dopaminergic cell death. Interestingly, this recovery seemed to be persistent and irreversible, since the interruption of chronic THC treatment did not result in a relapse of the dopaminergic injury. However, the fact that the same neuroprotective effects were elicited by cannabidiol, a plant-derived cannabinoid with negligible affinity for the cannabinoid receptors, suggests a major involvement of CB_1-receptor-independent mechanisms, possibly based on the antioxidative properties of both compounds and/or the effects associated with their well-known anti-inflammatory activities. The observation that cannabidiol was equivalent to THC in reducing dopaminergic injury in *Parkinson*'s disease supports the assumption that cannabidiol would be more advantageous for a potential neuroprotectant therapy in this disease, since it can be used at higher doses and for longer times compared to THC, due to its lack of psychoactivity and the lack of tolerance after prolonged treatments. In spite of this animal-model result of *Parkinson*'s disease, the only clinical trial performed in the United Kingdom, using 19 patients suffering from *Parkinson*'s disease and levodopa-induced dyskinesia, showed that the oral administration of a cannabis extract (2.5 mg of THC and 1.25 mg of cannabidiol per capsule) resulted in no objective or subjective improvement in parkinsonism or dyskinesias [44].

4. Antitumor Effect. – In 1975, *Munson et al.* discovered that *Lewis* lung adenocarcinoma growth was retarded by the oral administration of THC [45]. In spite of the promising results from this early study, further investigations in this area were not reported until a few years ago, when *Guzman*'s group demonstrated that THC induced apoptosis in C6.9 glioma cells, as determined by DNA fragmentation and loss of plasma-membrane asymmetry [46]. One year later, THC was also found active in human prostate cancer cells PC-3 [47]. In addition, both reports suggested that the pro-

apoptotic effect induced by THC in tumor cell lines was cannabinoid-receptor-independent. *In vivo* studies were then performed, showing that intratumoral administration of THC induced a considerable regression of malignant gliomas in *Wistar* rats and in mice [48]. Other groups also started work in this field, and today, a wide array of cancer cell lines that are affected is known, and some mechanisms involved have been elucidated. Particularly, it has been established that THC stimulates the activity of proteins that are downstream of the activation of p21ras, that are the mitogen-activated protein kinases [49], and that the apoptotic effect of THC on glioma cells is mediated by sustained ceramide synthesis and extracellular signal-regulated kinase (ERK)-dependent pathways [48][50].

In addition to apoptosis and inhibition of proliferation, THC might exert its antitumor effects by inhibiting tumor angiogenesis and metastasis, even if this effect has been demonstrated employing synthetic CB_1 agonists [51]. A recent report shows that THC is able to block the progression of breast cancer cell cycle *via* CB_2 receptors [52]. Of interest, non-tumor mammary epithelial cells were rather insensitive to THC, suggesting that the compound demonstrates selectivity for tumor cells [52]. Conversely, another study indicated that THC may enhance breast cancer cell growth under certain circumstances. In that study, the authors showed a direct association between the degree of sensitivity of a tumor to THC and the level of cannabinoid-receptor expression [53]. Other studies have shown that THC may induce proliferation of tumor cells *in vitro* [54] and *in vivo* [55]. Thus, THC has antiproliferative effect in tumors expressing cannabinoid receptors, whereas those with low or no expression suffer increased growth and metastasis due to THC-induced suppression of the antitumor immune response [53].

Recently, some results were reported from the first clinical study aimed at the evaluation of the antitumor effect of THC upon intracranial administration [56]. The study indicated that THC delivery was safe and could be achieved without overt psychoactive effects. Median survival of the cohort from the beginning of cannabinoid administration was 24 weeks (95% confidence interval: 15–33). THC inhibited tumor-cell proliferation *in vitro* and decreased tumor-cell Ki67 immunostaining, when administered to two patients [56].

In conclusion, further research on products is required and the precise mechanism of antitumor action needs to be clarified in more detail. The assessment of which intercellular factors and processes are modulated by cannabinoids in tumors and which tumors are sensitive or resistant to cannabinoids, and why this is so, will lead us closer to understand how these compounds can be used in therapy. In fact, in spite of the favorable drug-safety profiles, the use of cannabinoids in medicine, however, is limited by their psychoactive effects, and so cannabinoid-based therapies that are devoid of unwanted side effects are being designed.

5. Cancer Palliation. – The best-established palliative effect of THC in cancer patients is the inhibition of chemotherapy-induced nausea and vomiting. Today, THC capsules containing dronabinol (*Marinol®*) or its synthetic analogue nabilone (*Cesamet®*) are approved for this purpose. Other potential palliative effects of cannabinoids in cancer patients include appetite stimulation and pain inhibition (see below). The location of CB_1 receptors in cholinergic nerve terminals of the myenteric

plexus of the stomach, duodenum, and colon accounts for the THC-induced inhibition of digestive-tract motility, whereas the presence of CB_1 receptors in the brainstem might have a role in THC-induced control of emesis. THC has been found active in animal models of vomiting (for a review, see [57]).

Since these early studies, several clinical trials have compared the effectiveness of THC with placebo or with another anti-emetic drug [58–60]. Although THC showed anti-emetic efficacy, the comparisons of oral THC with existing anti-emetic agents generally indicated that THC was at least as effective as prochlorperazine [58–60]. In a well-controlled study, THC completely controlled emesis in only 13% of patients *vs.* 47% of those who received metoclopramide. THC achieved major control of vomiting in 27% of patients compared with 73% of the comparator group. Nabilone has shown greater anti-emetic efficacy than THC. In fact, nabilone turned out to be significantly superior to prochlorperazine, domperidone, and alizapride for treating nausea and vomiting associated with cancer chemotherapy. The results led *Health Canada* to approve the marketing of this product, which was introduced under the commercial name *Cesamet*® in 1982. Nonetheless, the efficacy of nabilone and dronabinol as anti-emetic agents is eclipsed by the high and sometimes severe incidence of their undesirable reactions. On the other hand, since these trials, more-effective anti-emetic drugs have been developed, and THC should be compared alone and in combination with these new anti-emetics, such as the selective serotonin 5-HT3-receptor antagonist ondansetron and the selective substance P/neurokinin-1-receptor antagonist aprepitant. Interestingly, cannabinoids are relatively effective in preventing nausea and emesis in patients during the delayed phase of chemotherapy-induced emesis. Further studies will be required to establish which patients and what types of cancer chemotherapy are suited to cannabinoid use for the prevention of nausea and emesis. THC and cannabinoids in general could help unresponsive patients, or may be used as adjuvant treatment to enhance the effects of existing anti-emetics.

Chemotherapy is often associated to anorexia that might ultimately lead to massive weight loss, which is an important risk factor for morbidity and mortality in cancer. On the basis of the well-established role of the endocannabinoid system in the regulation of feeding behavior, it is not surprising that many studies have reported that THC has a stimulatory effect on appetite and increases food intake in animals [61]. Since CB_1 receptors are expressed in the brain, the usual view is that THCs centrally control appetite; however, CB_1 receptors present in nerve terminals [62] and adipocytes [63][64] might also participate in the regulation of feeding behavior. Anecdotal information from cannabis smokers, but especially a series of clinical trials, supported the appetite-stimulating properties of THC [62][65]. In particular, dronabinol has been registered for use in the USA as an appetite stimulant in patients with AIDS-related wasting disease on the basis of evidence from clinical trials [66][67]. In cancer patients, at least three Phase-II clinical trials indicated a relation between increased appetite and the prevention of body-weight loss following THC treatment [65][68]. Further research should elucidate the clinical relevance of cannabinoids for cancer anorexia. For example, the efficacy/safety ratio of different regimens of cannabinoid administration should be evaluated (sublingual or inhaled cannabinoids may allow better titration of THC compounds).

6. Analgesic Effect. – CB_1 Cannabinoid receptors are found in tissue sites associated with the transmission and processing of nociceptive information (spinal cord, thalamus, periaqueductal grey, rostro-ventromedial medulla, dorsal-root ganglia, afferent-fiber terminals). These are the putative cellular targets responsible for mediating the analgesic effect of THC and, in general, of cannabinoids.

THC has been tested in a wide range of antinociceptive assays. It has been demonstrated effective in producing antinociception in both phasic (*e.g.*, tail-flick and hot-plate tests) and tonic (*e.g.*, stretching) nociceptive tests. In the early studies, the potency of THC varied widely from study to study, but there is general agreement that it is potent in blocking nociceptive stimuli. Its potency actually compared quite favorably to that of morphine in several studies. Actually, there are a wide range of animal models of acute pain [69–79] in which THC exhibits antinociceptive activity, when administered orally, systemically, or directly into the brain or spinal cord (*Table 1*). As shown in *Table 2*, THC also exhibits antinociceptive activity in animal models of tonic pain/hyperalgesia [80–87].

Table 1. *Studies Evaluating the Analgesic Effect of THC in Animal Models of Acute Pain*

Test	Species	Route[a])	Reference
Hot plate	mouse	i.p.	[69]
Hot plate	mouse	p.o.	[70]
Hot plate	mouse	s.c.	[71]
Tail-flick	mouse	i.p.	[69]
Tail-flick	mouse	i.v., i.p., p.o.	[72]
Tail-flick	mouse	s.c.	[73]
Tail-flick	mouse	i.v.	[74]
Tail-flick	rat	i.p.	[75]
Stretching	mouse	i.p.	[69]
Stretching	mouse	s.c.	[74]
Stretching	mouse	i.v.	[74]
Randall–Selitto paw pressure	mouse	p.o.	[76]
Flinch jump	rat	s.c.	[77]
Electrically stimulated sciatic nerve	rabbit	not provided	[69]
Tooth pulp	dog	i.v.	[78]
Skin-twitch reflex	dog	i.v.	[79]

[a]) Abbreviations: i.p., intraperitoneal; i.v., intravenous; p.o., per oral; s.c., subcutaneous.

There is no doubt that THC induces antinociception in animal models of both acute and tonic pain, at least in part, through the activation of CB_1 receptors. The first evidence is that the antinociceptive potencies of spinally injected THC correlate negatively with its lipid solubility, suggesting that, in spite of its high lipophilicity, THC does not induce antinociception by interacting with membrane phospholipids through non-receptor-mediated mechanisms. In addition, the selective CB_1-receptor antagonist SR141716 was found to prevent the antinociceptive effects of THC [88–91]. Moreover, antinociceptive responses to THC are absent or markedly attenuated in CB_1 knockout mice. Particularly, *Ledent et al.* [92], and *Zimmer et al.* [93] have reported that, in the hot-plate test, THC-induced antinociception is detectable in wild-type but not in CB_1-

Table 2. *Studies Evaluating the Analgesic Effect of THC in Animal Models of Tonic/Chronic Pain*

Test	Species	Route[a])	Reference
Abdominal stretch test (phenylbenzoquinone into *peritoneum*)	mouse	i.v., s.c., p.o.	[80–82]
Abdominal stretch test (phenylbenzoquinone into *peritoneum*)	mouse	i.t.	[83]
Abdominal stretch test (phenylbenzoquinone into *peritoneum*)	rat, cat	s.c.	[81]
Acetic or formic acid into *peritoneum*	mouse	i.v., s.c., p.o.	[81]
Freund's adjuvant into hind paw (i.p.)	rat	i.p.	[84]
Formalin into hind paw (i.p.)	rat	p.o.	[85]
Capsaicin (s.c.)	rhesus monkey	s.c. (to tail)	[86]
Loose ligation of sciatic nerve	rat	i.t.	[87]

[a]) Abbreviations: i.p., intraperitoneal; i.v., intravenous; p.o., per oral; s.c., subcutaneous; i.t., intrathecal.

receptor knockout mice. They have also found that, in CB_1 knockout mice, THC-induced antinociception in the warm-water tail-withdrawal test is strongly reduced [92]. Interestingly, *Zimmer et al.* [93] also found that, in their knockout mice, THC fully retained its ability to induce antinociception in the tail-flick test, a possible indication that this effect is not mediated exclusively by CB_1 receptors. An important aspect of the analgesic property of THC is the finding that THC can interact synergistically with opioid-receptor agonists in the production of antinociception. THC administered intrathecally (i.t.) has been shown to release endogenous opioids, which stimulate both δ- and κ-opioid receptors [94–96]. A time correlation between antinociception and increased dynorphin levels suggests that these endogenous opioids interact with the δ- and κ-opioid receptors to mediate the antinociceptive effect of THC [97][98]. Another report [99] demonstrated that five-day treatment with THC produced increases in both prodynorphin and proenkephalin gene expression in rat spinal cord, and other studies demonstrate that THC-induced analgesia is reduced in prodynorphin knockout animals [100].

Cannabinoid–opioid interactions not only underlie synergy in acute analgesia, but persist after chronic drug administration. After short-term treatment in mice with low doses of THC and morphine in combination, there is an avoidance of tolerance to the opioid, without compromising the antinociceptive effect [101]. While high doses of THC are analgesic, they can be accompanied by adverse effects. Low doses of oral THC have no analgesic effects, and in mice, no behavioral changes have been observed. Thus, these low doses could safely be administered in combination with opioids such as morphine, without increasing detrimental side effects. The administration of low doses of THC in conjunction with low doses of morphine seems to be an alternative regimen that reduces the need to escalate opioid dose while increasing opioid potency.

Concerning neuropathic pain, there is only one report showing the antihyperalgesic effect of THC, when intrathecally administered to rats with neuropathic pain [87]; conversely, a clinical study performed on eight patients with refractory neuropathic pain administered with oral THC to a maximum daily dosage of 25 mg showed no benefit of THC in pain and quality of life [102].

An important type of chronic pain with therapeutic need is cancer pain. Almost half of all patients with cancer experience moderate to severe pain. Chronic cancer pain usually has a nociceptive component, which originates from inflammatory reactions around the sites of injury, and a neuropathic component, which results from damage to the nervous system. There are some human data to support the effectiveness of THC in alleviating pain associated with cancer. In particular, oral THC (5–20 mg) was found to have an analgesic effect when compared with placebo in ten patients with pain related to advanced cancer [103]. In this study, a dose–response relation was shown for analgesia, but also for adverse effects. In a further study by the same group, oral THC (10 mg) was found to be about equipotent to codeine (60 mg), and THC (20 mg) was about equipotent to codeine (120 mg) [104].

In conclusion, human studies indicated insufficient evidence to support the introduction of THC into widespread clinical practice for pain management, although the absence of evidence of effect is not the same as the evidence of absence of effect. New safe and effective agonists at the cannabinoid receptor may dissociate therapeutic from psychotropic effects and make randomized comparisons in neuropathic pain and spasticity worthwhile. In this context, there is growing evidence supporting the therapeutic usage of whole extracts in pain; such natural compounds might offer various advantages over the employment of pure cannabinoids. The most significant example is *Sativex*®, containing THC/CBD in a 1:1 ratio, and *GW-2000-02*, containing primarily THC, for the relief of pain from brachial-plexus avulsion, a human model of central neuropathic pain and pain associated with multiple sclerosis (for a review, see [105]).

7. Conclusions. – The available pharmacological data have provided evidence that cannabis, and THC in particular, have a potential for clinical use. The accomplishment of a greater number of controlled clinical trials makes it possible to affirm that THC exhibits an interesting therapeutic potential as anti-emetic, appetite stimulant in debilitating diseases (cancer and AIDS), analgesic, as well as in the treatment of multiple sclerosis and *Tourette*'s syndrome. Also, THC and other plant constituents exhibit interesting neuroprotective properties. However, further clinical trials, well-designed, carefully executed, and powered for efficacy, are essential to clearly define the role of THC-based medicines in all these pathologies.

Not all the observed effects with cannabis can be ascribed to THC alone, other plant constituents may significantly modulate its action. A standardized extract of the herb may be, therefore, more beneficial in practice, and clinical-trial protocols have been drawn up to assess this. Moreover, apart from the smoking aspect (smoking cannabis is associated with significant risks of lung cancer and other respiratory dysfunction), the safety profile of cannabis is fairly good. Natural materials are highly variable and multiple components need to be standardized to ensure reproducible effects. Pure natural and synthetic compounds do not have disadvantages, but may not have the overall therapeutic effect of the herb.

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