Phytopharmacology

Inforesights Publishing

Cannabinoids: Pharmacological profile of promising molecules

Vikram Lohar*, Arvind Singh Rathore

Department of Pharmacology, Faculty of Pharmaceutical Sciences, Jodhpur National University, Narnadi, Jodhpur, Rajasthan, India.

*Corresponding author: lohar.vikram@gmail.com; Phone: +917737596989

Received: 2 August 2012, **Revised**: 7 September 2012, **Accepted**: 9 September 2012

Abstract

Cannabinoid research has gained remarkable interest in the past ten years after the discoveries of endogenous compounds with cannabimimetic activity and identification of their molecular targets, CB1 and CB2 receptors. Subsequently, attention has focused on putative therapeutic applications of cannabinoids. The non-psychotropic cannabidiol (CBD), some analogues of natural cannabinoids and their metabolites, antagonists at the cannabinoid receptors and modulators of the endogenous cannabinoid system are also promising candidates for clinical research and therapeutic uses. There is evidence that besides the two cannabinoid receptor subtypes cloned so far additional cannabinoid receptor subtypes and vanilloid receptors are involved in the complex physiological functions of the cannabinoid system that include motor coordination, memory procession, control of appetite, pain modulation and neuroprotection. Properties of cannabinoids that might be of therapeutic use include analgesia, asthma, atherosclerosis, dystonia, epilepsy, digestive diseases, gliomas, hepatitis C, Huntington's disease, leukemia, skin tumors, methicillin-resistant *Staphylococcus aureus* (MRSA), Parkinson's disease, muscle relaxation, immunosuppression, anti-inflammation, anti-allergic effects, sedation, improvement of mood, stimulation of appetite, anti-emesis, lowering of intraocular pressure, and bronchodilation effects. Although the results of cannabinoid research and clinical trials with cannibinergic compounds have been confusing, the vast therapeutic potential of these compounds are only just beginning to be appreciated.

Keywords: Cannabinoids, Cannabis, Therapeutic potential, Tetrahydrocannabinol

Introduction

For centuries preparations of *Cannabis sativa* L. (marijuana) have been used for both medical and recreation purposes. The therapeutic potential of this drug was documented as early as the fourth century B.C. The Chinese have used marijuana for the treatment of malaria, constipation, rheumatic pains, absent-mindedness, and female disorders. Interest in cannabis and its active constituents, Cannabinoids, as therapeutic agents is a recent phenom-enon (Kulkarni et al., 2001).

Cannabis, also known as marijuana (sometimes spelled "marihuana") among many other names, refers to any number of preparations of the *Cannabis* plant intended for use as a psychoactive drug. According to the United Nations, cannabis "is the most widely used illicit substance in the world." The typical herbal form of cannabis consists of the flowers and subtending leaves and stalks of mature pistillate of female plants. The resinous form of the drug is known as hashish (or merely as 'hash').

Medical cannabis (also referred to as medical marijuana) is the use of cannabis and its constituent cannabinoids such as THC as a physician-recommended form of medicine or herbal therapy. The *Cannabis* plant from which the cannabis drug is derived has a long history of medicinal use, with evidence dating back to 2,737 BC. Although the extent of the medicinal value of cannabis has been disputed, and despite the opposition to research and use put forward by most national governments, it does have several well-documented beneficial effects. Among these are: the amelioration of nausea and vomiting, stimulation of hunger in chemotherapy and AIDS patients, lowered intraocular eye pressure (shown to be effective for treating glaucoma), as well as gastrointestinal illness. Its effectiveness as an analgesic has been suggested (and disputed), as well.

In a 2002 review of medical literature, medical cannabis was shown to have established effects in the treatment of nausea, vomiting, premenstrual syndrome, unintentional weight loss, insomnia, and lack of appetite. Other "relatively well-confirmed" effects were in the treatment of "spasticity, painful conditions, especially neurogenic pain, movement disorders, asthma, [and] glaucoma".

Preliminary findings indicate that cannabis-based drugs could prove useful in treating inflammatory bowel disease, migraines, fibromyalgia, and related conditions. Medical cannabis has also been found to relieve certain symptoms of multiple sclerosis and spinal cord injuries by exhibiting antispasmodic and muscle-relaxant properties as well as stimulating appetite.

Other studies have shown cannabis or cannabinoids may be useful in treating alcohol abuse, amyotrophic lateral sclerosis, collagen-induced arthritis, asthma, atherosclerosis, bipolar disorder, colorectal cancer, depression, dystonia, epilepsy, digestive diseases, gliomas, hepatitis C, Huntington's disease, leukemia, skin tumors, methicillin-resistant *Staphylococcus aureus* (MRSA), Parkinson's disease, pruritus, post-traumatic stress disorder (PTSD), sickle-cell disease, sleep apnea, and anorexia nervosa. Controlled research on treating Tourette syndrome with a synthetic version of tetrahydrocannabinol (brand name Marinol), the main psychoactive chemical found in cannabis, showed the patients taking Marinol had a beneficial response without serious adverse effects; other studies have shown that cannabis "has no effects on tics and increases the individuals inner tension". Case reports found that marijuana helped reduce tics, but validation of these results requires longer, controlled studies on larger samples (Net reference 2012).

The medicinal value of marijuana and hashish (derivatives of the plant *Cannabis sativa)* has been recognised world-wide for thousands of years. However, not until the identification of the major psychoactive component in cannabis, Δ9-tetrahydrocannabinol (Δ9-THC), in 1964, was the research of cannabinoids stimulated and obtained a firm footing. The subsequent synthesis of high-affinity cannabinoid ligands enabled the discoveries of two spe-

cific cannabinoid receptors, CB1 and CB2, which mediate the pharmacological effects of cannabinoids in the central nervous system (CNS) and the peripheral nervous system (PNS). The ongoing, long-delayed elucidation of the biochemistry and the physiology of the endogenous cannabinoid system (ECS) have led to the discoveries of five endogenous cannabinoids; arachidonoylethanolamide (AEA), 2-arachidonoyl glycerol (2-AG), 2-arachidonyl glyceryl ether (noladin ether), *O*arachidonoylethanolamine (virodhamine) and *N*-arachidonoyl dopamine (NADA) as well as the enzymes metabolising endogenous cannabinoids. (Walker et al., 2002)

Biology of cannabinoids

The acute effects of cannabis use are well recognized; it induces a psychoactive, mildly euphoric, relaxing intoxication or "high", which leads to slight changes in psychomotor and cognitive function. In some limited cases, cannabis can also induce unpleasant effects including anxiety, panic, and paranoia, and very rarely it may lead to acute psychosis involving delusions and hallucinations.Frequent users may develop an amotivational syndrome. Cannabis also induces an increase in heart rate, a lowering of blood pressure due to vasodilatation (which causes the classic "red eye"), appetite stimulation (known as "the munchies"), dry mouth, and dizziness. These may be thought of as adverse effects but all are due to a basic biology, which is now beginning to be understood.

The cannabis plant (*Cannabis sativa*) contains many compounds, but Δ9-tetrahydrocannabinol (THC) is the main psychoactive ingredient. THC breaks down to produce cannabinol and was identified—along with cannabidiol (the main non-psychoactive component)—in the 1940s. However, THC was not isolated, synthesised, and stereochemically defined until the 1960s. THC is concentrated in the flowering head of the female plant and selective growing in the past 5–10 years has substantially increased THC content from 1–3% THC in the "flowerpower" era to 6–13% and above. Thus, current users of cannabis may have very different experiences to those of the past. Cannabis may contain over 60 "classical" cannabinoid (tricyclic dibenzopyran) compounds and some, such as cannabidiol, may modulate the response to THC. How these different compounds act has only started to become clear in the past decade (Baker et al., 2003).

Pharmacology of Cannabinoids

Two separate cannabis receptors have been identified (CB1 and CB2), which were cloned in 1990 and 1993, respectively. Both receptors are coupled to G proteins and their activation leads to an inhibition of adenyl cyclase, decreased production of cAMP and modulation of the ion channel activity. At the cellular level, cannabinoids act through CB receptors to hyperpolarise neurones by closing voltage-dependent calcium channels and by activating potassium channels. CB1 receptors are distributed widely throughout the central nervous system (CNS) and the peripheral nervous system (PNS). They are present in their greatest concentration around the hippocampus, cortex, olfactory areas, basal ganglia, cerebellum and spinal cord. This pattern accounts for the effects of cannabinoids on memory, emotion, cognition and movement. Increased levels of CB1 receptors are found in the peri-aqueductal grey matter (PAG) and dorsal horn of the spinal cord, regions involved in the modulation of

nociceptive transmission. CB1 receptors are sparse in the brainstem, which may explain the lack of respiratory depression associated with the administration of these compounds. CB2 receptors are located peripherally and are closely linked with cells in the immune system, predominantly the spleen and macrophages (Kumar et al., 2001).

Mechanism of action

The majority of THC effects are mediated through agonistic actions at cannabinoid receptors. Some non-CB mediated effects of THC and synthetic derivatives have also been described, e.g. some effects on the immune system, some neuroprotective effects, and anti-emetic effects. It is possible that several effects previously thought to be non-receptor mediated are mediated by cannabinoid receptor subtypes that have not yet been identified. The majority of THC effects are mediated through agonistic actions at cannabinoid receptors.

Some non-CB mediated effects of THC and synthetic derivatives have also been described, e.g. some effects on the immune system, some neuroprotective effects, and anti-emetic effects. It is possible that several effects previously thought to be non-receptor mediated are mediated by cannabinoid receptor subtypes that have not yet been identified. The mode of action of cannabidiol is not fully understood and several mechanisms have been proposed:

1. CBD acts as antagonist at the central CB1 receptor and was able to inhibit several CB1 mediated THC effects. CBD considerably reduced the receptor activation of a potent classical CB1 receptor agonist.
2. CBD stimulates the vanilloid receptor type 1 (VR1) with a maximum effect similar in efficacy to that of capsaicin.
3. CBD inhibits the uptake and hydrolysis of the endocannabinoid anandamide, thus increasing its concentration (Grotenhermen et al., 2004).

Classification of Ligands That Bind to Cannabinoid Receptors

Classical Cannabinoids

The compounds in this group consist of dibenzopyran derivatives and are either plant-derived cannabinoids or synthetic analogues of these. Notable examples are:

- (–)-Δ9-THC, which binds equally well to CB1 and CB2 receptors and behaves as a partial agonist at both of these receptor types. It has even less efficacy at CB2 than at CB1 receptors and, indeed, has been reported in one CB2 bioassay system to behave as an antagonist.

- (–)-Δ8-THC, which resembles Δ9-THC both in its affinities for CB1 and CB2 receptors and in its CB1 receptor efficacy.

- (–)-11-hydroxy-Δ8-THC-dimethylheptyl (HU 210), which has efficacies at CB1 and CB2 receptors that match those of CP 55,940 and WIN 55,212-2 (see below) and

affinities for CB1 and CB2 receptors that exceed those of many other cannabinoids. It is a particularly potent cannabinoid receptor agonist and its pharmacological effects in vivo are exceptionally long-lasting. The enhanced affinity and efficacy shown by HU 210 at cannabinoid receptors can be largely attributed to the replacement of the pentyl side chain of Δ8-THC with a dimethylheptyl group.

Nonclassical Cannabinoid

The compounds in this group were developed by a Pfizer research team. They are quite similar in structure to classical cannabinoids, consisting as they do of bicyclic and tricyclic analogues of Δ9-THC that lack a pyran ring. The most widely used nonclassical cannabinoid is CP 55,940, which has CB1 and CB2 affinities in the low nanomolar range and exhibits relatively high efficacy at both of these receptor types.

Aminoalkylindole

The prototype of this group is WIN 55,212-2, which was discovered by a Sterling Winthrop research team and is widely used in cannabinoid research. The structure of WIN 55,212-2 bears no resemblance to that of classical, nonclassical or eicosanoid cannabinoids. Indeed, there is evidence that it binds differently to the CB1 receptor than classical and nonclassical cannabinoids, albeit it in a manner that still permits mutual displacement between WIN 55,212-2 and non-aminoalkylindole cannabinoids at CB1 binding sites. Like CP 55,940, WIN 55,212-2 exhibits relatively high efficacy at CB1 and CB2 receptors and possesses CB1 and CB2 affinities in the low nanomolar range. However, in contrast to CP 55,940, it has slightly greater affinity for CB2 than for CB1 receptors.

Eicosanoid

The prototypic and most investigated members of this group are the endocannabinoids, anandamide and 2-arachidonylglycerol.

- Anandamide binds marginally more readily to CB1 than to CB2 receptors and, when protected from enzymic hydrolysis, exhibits a CB1 affinity similar to that of (-)-Δ9-THC. It also resembles (–)-Δ9-THC in behaving as a partial agonist at CB1 and CB2 receptors and in exhibiting lower CB2 than CB1 efficacy.

- 2-Arachidonylglycerol has been found in several investigations to have affinities for CB1 and CB2 receptors similar to those of anandamide but to exhibit higher CB1 and CB2 efficacy than anandamide. In one recent investigation, however, performed with human CB1 receptorcontaining tissue, this endocannabinoid was found to lack both detectable CB1 receptor efficacy at concentrations of up to 10 μM and any significant CB1 receptor affinity (Ki > 10 μM) (Pertwee et al., 2010, Steffens et al., 2005, Howlett et al 2002, Pertwee et al., 1999, Bayewitch et al., 1995)

Preclinical data: rationale for clinical applications

The lack of appropriate animal models with the complexity of the human brain hampers the study of the behavioural effects of these compounds. Therefore, most experimental

studies have concentrated on measurable physiological effects, and, as a result, the understanding of the underlying biology is improving. Most claims made by patients suggest that cannabis may be useful in symptom management and there is now experimental support for the clinical investigation of cannabis in the control of pain and spasticity in multiple sclerosis (MS). We will concentrate on these areas in order to highlight potential therapeutic uses. Various preclinical studies on cannabis plants and their parts were done and having strong evidence for Abortifacient activity, Alkaline phosphatase stimulation, Aminopyrene-N-demethylase induction, Angiotensinconverting enzyme inhibition, Anti-anaphylactic activ-ity, Anti-androgenic effect, Antibacterial activity, Anticonvulsant activity, Anti-estroge-nic effect, Antifertility effect, Antifungal activity, Antiglaucomic activity, Antigonadotropin eff-ect, Anti-inflammatory activity, Antispasmodic activity, Antispermatogenic effects of Canna-bis. (Table 1) These are strong evidence for therapeutic uses of Cannabinoids (Ross IA et al., 2005, Agnihotri PK et al., 1992, Dixit VP et al., 1977, Sethi SN et al., 1989, Dha ML et al., 1968, Cutler MG et al., 1975, Duncan AC et al., 1999, Kataoka M et al., 1995, Mendelson JH et al., 1978, Fournier G et al., 1978, Rousinov KS et al., 1966, Chakravarty I et al., 1980, Kostellow AB et al., 1980, Dabby V et al., 1985, Green KC et al., 1981, Dixit VP et al., 1981, Formukong EA et al., 1988, Segelman AB et al., 1974, Montour JL et al., 1981, Kubena RK et al., Carlini EA et al., Dhar ML et al., 1968, Dalterio S et al., 1982, Dixit VP et al., 1977).

Table 1. Preclinical studies data for Cannabinoids**.**

Activity	Part/Extract	Study On/ Amount	Route of Administration
Abortifacient activity	Alcohol extract of the dried leaf	Rats at a dose of 125 mg/kg	Intragastrically
Alkaline phosphatase stimulation	Ethanol (95%) extract of the dried resin	Toads at a dose of 10 mg/day for 14 days	Intraperitoneally
Aminopyrene-N-demethylase induction	Ethanol (95%) extract of the dried aerial parts	Rats at a dose of 2 mg/kg for 15 days	Intraperitoneally
Analgesic activity	Ethanol (50%) extract of the entire plant	Mice at a dose of 250 mg/kg,	Intraperitoneally
Anaphrodisiac effect	Tincture of the resin	Male mice at a dose of 12.5 mg/kg	Intraperitoneally
Angiotensin-converting enzyme inhibition	Ethanol (100%) extract of the dried leaf	At a concentration of 333.3g/mL produced weak activity	-------
Anti-anaphylactic activity	Water extract of the dried fruit	Rat Leuk-RBL concentration of 1 g/mL	-------
Anti-androgenic effect	Ethanol (95%) extract of the aerial parts,	Castrated mice at a dose of 2 mg/animal	Intraperitoneally
Antibacterial activity	Essential oil	*Staphylococcus aureus* and *Streptococcus faecalis*, minimum inhibitory concentration (MIC) 0.5 mg/mL	-------
Anticonvulsant activity	Ethanol (95%) extract of the entire plant	Subcutaneously to male mice and rats at a dose of 2–4 mL/kg	Subcutaneously
Anti-estrogenic effect	Petroleum ether extract of the dried leaf	female rats at a dose equivalent to 10 mg/kg tetrahydrocannabinol (THC) on 11–21 days of age	Intraperitoneally

Antifertility effect	Petroleum ether extract of the entire plant	Female mice at doses of 75 mg/kg and 150 mg/kg	Gastric intubation
Antifungal activity	Ethanol (50%) extract of the dried leaf	*Rhizoctonia solani*, mycelia	-------
Antiglaucomic activity	Water extract of the dried entire plant	Rhesus monkeys and rabbits at a dose of 0.01 □□g/animal	Intravenously
Antigonadotropin effect	Ethanol (80%) extract of the dried aerial parts	Male langurs at a dose of 14 mg/kg daily for 90 days	Intragastrically
Anti-inflammatory activity	Petroleum ether and ethanol (95%) extracts of the dried aerial parts	Mice at a dose of 100 g/ear	Applied externally
Antispasmodic activity	Ethanol (50%) extract of the entire plant	Guinea pig ileum	-------
Antispermatogenic effect	Ethanol (80%) extract of the dried aerial parts	Langurs at a dose of 14 mg/kg daily for 90 days	Intragastrically
	Ethanol (95%) extract of the dried aerial parts	Mice at a dose of 2 mg/animal daily for 45 days	Intraperitoneally
Barbiturate potentiation	Flavonoid fraction of the leaf	Mice	Intraperitoneally
Carcinogenic activity	Dried leaf	Rats of both sexes at a dose of 7 mg/kg/week	Intraperitoneally
Central nervous system depressant activity.	Fluidextract of the aerial parts	Rats at a dose of 25 mg/kg	Intraperitoneally
Cataleptic effect	Petroleum ether extract of the dried entire plant	Guinea pigs at a dose of 100 mg/kg	Intraperitoneally
DNA synthesis inhibition	Ethanol (95%) extract of the dried resin	Toads at a dose of 10 mg/ day for 14 days	Intraperitoneally
Estrous cycle disruption effect	Petroleum ether extract of the dried aerial	Mice and rats at doses of 1 and 5 mg/animal, respectively, for 64 days	Intraperitoneally
Follicle-stimulating hormone release inhibition	Ethanol (95%) extract of the dried resin	toads at a dose of 10 mg/day for 14 days	Intraperitoneally
Hepatotoxic activity	Ethanol (95%) extract of the dried resin,	Toads at a dose of 10 mg/ day for 14 days	Intraperitoneally
Hypoglycemic activity	Ethanol (95%) extract of the dried leaf	Rabbits, produced an increase, followed by a gradual decrease, in blood sugar levels	Gastric intubation
Hypotensive activity	Ethanol (50%) extract of the entire plant	Dogs at a dose of 50 mg/kg, was active	Intravenously
Mutagenic activity	Petroleum ether extract of the dried leaf	Male mice at a dose of 50 mg/kg	Gastric intubation
Protein synthesis inhibition	Ethanol (95%) extract of the dried resin	Toads at a dose of 10 mg/day for 14 days	Intraperitoneally

Therapeutic uses of Cannabinoids

The activation of the cannabinoid system through THC and other phytocannabinoids, synthetic cannabinoids and endocannabinoids causes numerous actions that have been extensively reviewed. Additional non-receptor mediated effects effects have come into focus as well. Some effects of cannabinoid receptor agonists show a biphasic behavior in dependency of dose, e.g. low doses of anandamide stimulated phagocytosis and stimulated behavioral activities in mice while high doses decreased activities and caused inhibitory effects on immune functions. Nonpsychotropic phytocannabinoids exert multiple pharmacological actions in the

central nervous system and in the periphery. Among these compounds, CBD has been more thoroughly investigated. CBD effects (e.g. analgesic/anti-inflammatory, antioxidant, neuroprotective and pro-apoptotic) might predict possible future use for the treatment of pain, neurodegenerative disorders, ischemia and cancer. Many effects of CBD (e.g. anxiolytic, antiinflammatory, neuroprotective, anti-ischemic) follow a bell-shaped dose–response curve, suggesting that dose is a key factor in CBD pharmacology. Effects of cannabinoids are summarized in Table 2.

Cannabinoid and vanilloid receptor effects as well as non-receptor mechanisms are explored, such as the capability of THC and CBD to act as anti-inflammatory substances independent of cyclo-oxygenase (COX) inhibition. CBD is demonstrated to antagonise some undesirable effects of THC including intoxication, sedation and tachycardia, while contributing analgesic, antiemetic, and anti-carcinogenic properties in its own right. In modern clinical trials, this has permitted the administration of higher doses of THC,

Table 2. Summary of the effects of cannabinoids

Pharmacological effect	Description
Psychological effects	Euphoria, dysphoria, anxiety, depersonalisation, aggravation of psychotic states
Effects on perception	Heightened sensory perception, distortion of space and time sense, misperceptions, hallucinations
Sedative effects	Generalised CNS depression, drowsiness, sleep, additive effect with other CNS depressants
Effects on cognition and psychomotor performance	Fragmentation of thoughts, mental clouding, memory impairment, global impairment of performance
psychomotor performance	Fragmentation of thoughts, mental clouding, memory impairment, global impairment of performance
Effects on motor function	Increased motor activity followed by inertia and incoordination, ataxia, dysarthria, tremulousness, weakness, muscle twitching
Analgesic effects	Similar in efficacy to codeine
Anti-emetic effects	In acute doses; effect reversed with larger doses or chronic use Increased appetite
Tolerance	To most behavioural and somatic effects including the `high' with chronic use
Dependence, abstinence syndrome	Rarely observed but has been produced experimentally following prolonged intoxication
Cardiorespiratory system Heart rate	Tachycardia with acute dosage; bradycardia with chronic use
Peripheral circulation	Vasodilatation, conjunctival redness, postural hypotension
Cardiac output	Increased output and myocardial oxygen demand
Cerebral blood flow	Increased acutely, decreased with chronic use
Ventilation	Small doses stimulate, larger doses depress
Bronchodilation	Coughing, but tolerance develops

Table 3: Effects of tetrahydrocannabinol (THC) and cannabidiol (CBD).

Effect	THC	CBD
Receptor/Non-Receptor Effects		
CB1 (CNS/PNS receptors)	++	±
CB2 (peripheral receptors	+	±
Vanilloid (TRPV1) receptors	-	-
Anti-inflammatory	+	+
COX-1, COX-2 inhibition	-	-
Immunomodulatory	+	+
CNS Effects		
Anticonvulsant	+	++
Muscle relaxant	++	+
Antinociceptive	++	+
Psychotropic	++	-
Anxiolytic	±	++
Antipsychotic	-	++
Neuroprotective antioxidant	+	++
Antiemetic	++	+
Sedation	+	-
Agitation (Alzheimer disease)	+	-
Tic reduction (Tourette syndrome)	+	**?**
Opiate withdrawal reduction	+	**?**
Migraine treatment	+	+
Bipolar disease	+	**?**
Dystonia		+
Parkinsonian symptoms	+	**?**
Withdrawal symptoms to other drugs (reduction)	+	+
Motor neurone disease (ALS) (increased survival, function)	+	+
Cardiovascular Effects		
Bradycardia	-	+
Tachycardia	+	-
Hypertension	+	-
Hypotension	-	+
Appetite/Gastrointestinal		
Appetite	+	-
GI motility (slowed)	++	+
Anti-Carcinogenesis		
Glioma (apoptosis)	+	+
Glioma cell migration	--	+
Ophthalmological		
Intra-ocular pressure (reduced)	++	+
Night vision	+	-

providing evidence for clinical efficacy and safety for cannabis based extracts in treatment of spasticity, central pain and lower urinary tract symptoms in multiple sclerosis, as well as sleep disturbances, peripheral neuropathic pain, brachial plexus avulsion symptoms, rheumatoid arthritis and intractable cancer pain (Russo et al., 2006). Effects of tetrahydrocannabinol (THC) and cannabidiol (CBD) are summarized in Table 3.

Cannabinoids might serve as therapeutic treatment for disorders that have neurological failure at these regions, since activation of the ECS is found to modulate the release of a few neurotransmitters. Cannabinoids are currently also considered as neuroprotective agents. This review will briefly summarize present knowledge of the ECS and the potential therapeutic usefulness of cannabinoids as a treatment for certain neurological disorders (Table 4).

As we learn more about the pharmacological activities of compounds in cannabis and their biological targets outside the cannabinoid system, varieties of cannabis might be tailored to different diseases or used in combination with known drugs. Whatever the future holds, there are many challenges to be overcome before we view cannabinoids as routine medicine in neurological disorders.

The challenge now is to continue investigations into the physiological and pathophysiological roles of the endocannabinoid system and to identify and implement the best strategies for exploiting what emerges from this research, in the clinic. Another important objective is to extend current knowledge about the pharmacology, firstly of endocannabinoids, and secondly of cannabinoid receptors and their exogenous agonists, inverse agonists and neutral antagonists when these are administered acutely or chronically. It will also be important to characterize proposed non-CB1, non-CB2, non-TRPV1 targets for cannabinoids more comp-

Table 4: Effects of Cannabinoids on Synaptic Function.

Region (Neurotransmiter)	Modulatory action	CB1 containing cell	Endocannabinoids	Effect
Hippocampus (Glutamate)	↓release	Glutamatergic CA3 and CA1 neurons	Anandamide 2-arachidonylglycerol	↓LTP
--- (Ach)	↓release	Cholinergic neurons	As above	↓Learning and memory
Cerebellum (Glutamate)	Inhibition of P/Q type Ca2+ channel	Gluatamatergic granule cell	Anandamide	↓motor coordination neuroprotection
Cortex (Glutamate)	As above	Cortical molecular layers	Anandamide 2-arachidonylglycerol	↓memory and motor behavior neuroprotection
Spinal cord (Glutamate)	Inhibition of NMDA receptor mediated actions	Neurons of dorsal horn	2-arachidonylglycerol	Antinociception
Basal ganglia and substantia nigra (GABA)	↓uptake	GABAergic striatonigral and striatopallidal neurons	Anandamide	↓locomotor activity, catalepsy
--- (DA)	↓synthesis/release/ action	DAergic nigrostriatal neurons	As above	↓locomotor activity
--- (DA)	Potentiation	As above	As above	Contralateral turning
Hypothalamus (DA)	Potentiation	DAergic neurons of the tubero-infundibular system	No evidence	↓prolactin release

receptor allosteric sites more fully, to seek out and explore the pharmacology of any as yet unidentified endocannabinoids or phar-macological targets for cannabinoids, to follow-up early indications that cannabinoid recept-ors may exist as homodimers or form heterodimers or oligomers with one or more other class of coexpressed receptor and to continue the task of exploring the pharmacology of plant can-nabinoids.

Conflicts of Interest:

The authors declare no conflict of interest.

References

Agnihotri PK, Singh RK, Sethi SN. (1992). Fototoxic effects of crude alcoholic Cannabis sativa extract in rats. *Fitoterapia* 63, 489–492.

Baker D, Pryce G, Giovannoni G, Thompson AJ. (2003). The therapeutic potential of cannabis. *Lancet Neurology* 2, 291–298.

Bayewitch *et al.* (1996). *J Biol Chem* 271, 9902-99055.

Carlini EA, Gagliardi RA. (1970). Comparison of the pharmacological actions of crude extracts of Olmedioperebia calophyllum and Cannabis sativa. *Ancad Bras Cienc* 42, 409–412.

Cutler MG, Mackintosh JH, Chance MRA. (1975). Cannabis resin and sexual behaviour in the laboratory mouse. *Psychopharmacologia* 45, 129.

Chakravarty I, Sengupta D. (1980). Effect of cannabis extract on uterine phosphatase activities in prepubertal rats. *IRCS Med Sci Biochem* 8, 25.

Dabby V. (1985). Acute pancreatitis after marijuana smoking: Is there a relationship? *The journal of the American Medical Association* 253, 1791.

Dalterio S, Badr F, Bartke A, Mayfield D. (1982). Cannabinoids in male mice: Effects on fertility and spermatogenesis. *Science* 216, 315–316.

Dha ML, Dhar MM, Mehrotra BN, Ray C. (1968). Screening of Indian plants for biological activity. Part I. *Indian J Exp Biol* 6, 232–247.

Dixit VP, Jain HC, Verma OP, Sharma AN. (1977). Effects of cannabis extract on the testicular function of the toad Bufo andersonii Boulenger. *Indian J Exp Biol* 15, 555–556.

Dixit VP. (1981). Effects of Cannabis sativa extract on testicular function of Presbytis entellus. *Planta Med* 41, 288–294.

Duncan AC, Jager AK, Van Staden J. (1999). Screening of Zulu medicinal plants for angiotensin converting enzyme (ACE) inhibitors. *J Ethnopharmacol* 68, 63–70.

Fournier G, Paris MR, Fourniat MC, Quero AM. (1978). Bacteriostatic effect of essential oil from Cannabis sativa. *Ann Pharm Fr* 36, 603.

Formukong EA, Evans AT, Evans FJ. (1988). Analgesic and anti-inflammatory activity of constituents of Cannabis sativa L. *Inflammation (NY)* 12, 361–371.

Green KC, Symonds M, Elijah DR, Zalkow LH, Deutsch HM, Bowman KA, Morgan TR. (1981). Water soluble marihuana-derived material: Pharmacological actions in rabbit and primate. *Curr Eye Res* 1, 599–608.

Grotenhermen F. (2004). Pharmacology of Cannabinoids. Neuroendocrinology Letters 25, 14-25.

Howlett AC, Barth F, Bonner TI, Cabral G, Casellas P, Devane WA, Felder CC, Herkenham M, Mackie K, Martin BR, Mechoulam R, Pertwee RG. (2002). International Union of Pharmacology XXVII: Classification of cannabinoid receptors. *Pharmacol Rev* 54, 161-202.

Ross IA. (2005). Medicinal Plants of the World. Humana Press Inc. pp 29-94.

Kataoka M, Takagaki Y. (1995). Effect of the crude drugs (standards of natural drugs not in the J. P. XII) on beta-hexosaminidase release from rat basophilic leukemia (RBL-2H3) cells. *Nat Med* 49, 346–349.

Kostellow AB, Ziegler D, Kunar J, Fujimoto GI, Morrill GA. (1980). Effect of cannabinoids on estrous cycle, ovulation, and reproduction capacity of female A/J mice. *Pharmacology* 21, 68–75.

Kubena RK, Barry H, Selegman AB, Theiner M, Farnsworth NR. (1972). Biological and chemical evaluation of a 43-year old sample of cannabis fluidextract. *J Pharm Sci* 61, 144–145.

Kulkarni SK, Ninan I. (2001). Current Concepts in Cannabinoid Pharmacology. *Indian Journal of Pharmacology* 33, 170-184.

Kumar RN, Chambers WA, Pertwee RG. (2001)Pharmacological actions and therapeutic uses of cannabis and cannabinoids. *Anaesthesia* 56, 1059-1068.

Mendelson JH, Ellingboe J, Kuehnle JC, Mello NK. (1978). Effects of chronic marihuana use on integrated plasma testosterone and luteinizing hormone levels. *J Pharmacol Exp Ther* 207, 611–617.

Montour JL, Dutz W, Harris LS. (1981). Modification of radiation carcinogenesis by marihuana. *Cancer* 47, 1279–1285.

Pertwee RG. (2010). Cannabinoid Receptor Ligands. Tocris Bioscience Scientific Review Series. *Tocris Reviews* No. 27.

Pertwee RG. (1999). Pharmacology of cannabinoid receptor ligands. *Curr Med Chem* 6, 635 -664.

Rousinov KS, Athanasova-Shopova S. (1966). Experimental screening of the anticonvulsive activity of certain plants used in popular medicine in Bulgaria. *C R Acad Bulg Sci* 19, 333–336.

Russo E, Guy GW. (2006). A tale of two cannabinoids: The therapeutic rationale for combining tetrahydrocannabinol and cannabidiol. *Medical Hypotheses* 66, 234–246.

Segelman AB, Segelman FP, Sofia RD, Star AE. (1974). Some pharmacological effects of certain cannabinoid free marijuana extracts. *Lloydia* 37, 645A.

Sethi SN, Agnihotri PK, Srivastava S. (1989). Aminopyrine-n-demethylase activity of rat liver after administration of crude cannabis extract. *Indian J Med Res* 90, 36–38.

Steffens M, Zentner J, Honegger J, Feuerstein TJ. (2005). Binding affinity and agonist activity of putative endogenous cannabinoids at the human neocortical CB_1 receptor. Biochem Pharmacol 69, 169–178.

Walker JM, Krey JF, Chu CJ, Huang SM. (2002). Endocannabinoids and related fatty acid derivatives in pain modulation. *Chem Phys Lipids* 121, 159-72.

