ISSN 0975-6299 Vol 3/Issue 1/Jan – Mar 2012

International Journal of Pharma and Bio Sciences

RESEARCH ARTICLE PHARMACOLOGY

MARIJUANA (CANNABIS): IT'S ILLUSION AND INFORMATION

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ABSTRACT

The present article deals with the pharmacognosy, pharmacology and many other aspects about the plant marijuana that is well known as cannabis. The above plant has been through many legal and medical issues all round the world. The use of this plant in medical purposes has been a long time hot topic in our fraternity. The plant has been blamed to have an addiction causing character. On the other hand, It has also been supported to have a good and accepted pharmacological activity by literature and practical users. Marijuana was first used for medical purpose in Britain in the mid-nineteenth century by O'Shaughnessy, a surgeon in army. In India the above plant has been used in wide range of medical condition such as rabies, epilepsy, muscle spasms and for pain relief. This article is a sincere effort to bring forward the possible information about the plant, its chemical constituents and uses. The plant has been in talk for long time regarding the use and legal aspect and so detailed information regarding it should be necessary.

KEY WORDS

Marijuana, Cannabis, Pharmacognosy, Pharmacology, Uses.

INTRODUCTION

The plant Cannabis produces medicinal important compounds. The breeding of cannabis is looking as the future prospect for the production of many medicines. The above plant has been one among the oldest to be important in various aspects such as fiber, cloths, food for both animal and humans and the most is its medicinal values. *Cannabis* is an annual crop plant propagated from seed and grows vigorously when provided an open sunny location with light well-drained soil, ample nutrients, and water. *Cannabis* can reach up to 5 m (16 ft.) in height in a 4- to 8-month spring-to autumn growing season. In India it is cultivated all over the country and it commonly occurs in waste grounds, along road side, often becoming gregarious along the irrigation channels of gardens. Seeds usually germinate in 3–7 days. During the first 2–3 months of growth, juvenile plants respond to increasing day length with a more vigorous vegetative growth characterized by an increasing number of leaflets on each leaf [1- 4]. The above plants in Ayurveda is used for Hallucinogenic, hypnotic, sedative, analgesic, anti-inflammatory,Hemp derivatives are suggested for treating glaucoma and as an antiemetic in cancer chemotherapy. All variants produce initial excitement followed by depression [1].

Figure no. 01
Mature female cannabis plant.

Scientific classification

Kingdom	:	Plantae
Phylum	:	Magnoliophyta
Class	:	Magnoliopsida
Order	:	Rosales
Family	:	Cannabaceae
Genus	:	*Cannabis*
Species	:	*C. sativa*
Synonym	:	*Cannabis sativa* L.

Phytochemical constituents and chemistry

The *Cannabis* plant consists of an enormous variety of chemicals. So far, 66 cannabinoids have been identified. They are divided into 10 subclasses. The description are as follows.

1. Cannabigerol (CBG) type: CBG was the first cannabinoid identified, and its precursor cannabigerolic acid (CBGA) was shown to be the first biogenic cannabinoid formed in the plant. Propyl side-chain analogs and a monomethyl ether derivative are other cannabinoids of this group (5, 6).
2. Cannabichromene (CBC) type: Five CBC-type cannabinoids, mainly present as C5-analogs, have been identified.
3. Cannabidiol (CBD) type: CBD was isolated in 1940, but its correct structure was first elucidated in 1963 by Mechoulam and Shvo. Seven CBD-type cannabinoids with C1 to C5 side chains have been described. CBD and its corresponding acid CBDA are the most abundant cannabinoids in fiber-type *Cannabis* (industrial hemp). Isolated in 1955, CBDA was the first discovered cannabinoid acid (7, 8).
4. Δ^9-Tetrahydrocannabinol (THC) type: Nine THC-type cannabinoids with C1 to C5 side chains are known. The major biogenic precursor is the THC acid A, whereas THC acid B is present to a much lesser extent. THC is the main psychotropic principle; the acids are not psychoactive. THC (6a,10a-*trans*-6a,7,8,10a-tetrahydro-6,6,9- trimethyl-3-pentyl-6H-dibenzo[*b,d*]pyran-1-ol) was first isolated in 1942, but the correct structure assignment by Gaoni and Mechoulam took place in 1964 *(9, 10)*.
5. Δ^8-THC type: Δ^8-THC and its acid precursor are considered as THC and THC acid artifacts, respectively. The 8,9 double-bond position is thermodynamically more stable than the 9,10 position. Δ^8-THC is approx 20% less active than THC.
6. Cannabicyclol (CBL) type: Three cannabinoids characterized by a five-atom ring and C1-bridge instead of the typical ring A are known: CBL, its acid precursor, and the C3 side-chain analog. CBL is known to be a heat-generating artifact from CBC.
7. Cannabielsoin (CBE) type: Among the five CBE-type cannabinoids, which are artifacts formed from CBD, are CBE and its acid precursors A and B.
8. Cannabinol (CBN) and Cannabinodiol (CBND) types: Six CBN- and two CBND-type cannabinoids are known. With ring A aromatized, they are oxidation artifacts of THC and CBD, respectively. Their concentration in *Cannabis* products depends on age and storage conditions. CBN was first named in 1896 by Wood et al and its structure elucidated in 1940 (11, 12).
9. Cannabitriol (CBT) type: Nine CBT-type cannabinoids have been identified, which are characterized by additional OH substitution. CBT itself exists in the form of both isomers and the racemate, whereas two isomers (9-a- and 9-b-hydroxy) of CBTV were identified. CBDA tetrahydrocannabitriol ester (ester at 9-hydroxy group) is the only reported ester of any naturally occurring cannabinoids.
10. Miscellaneous types: Eleven cannabinoids of various unusual structure, e.g., with a furano ring (dehydrocannabifuran, cannabifuran), carbonyl function (cannabichromanon, 10- oxo-δ-6a-tetrahydrocannabinol), or tetrahydroxy substitution (cannabiripsol), are known.

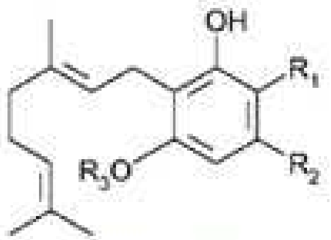

Figure no 02
Structure of cannabigerol class.

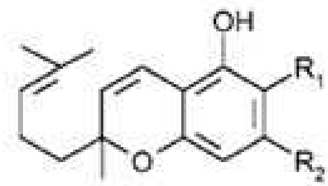

Figure no. 03
Cannabichromene class.

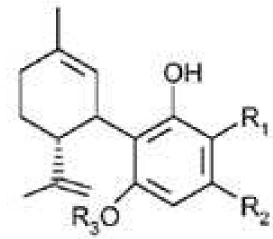

Figure no. 04
Cannabidiol class.

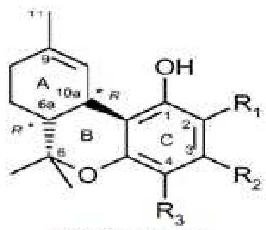

Figure no. 05
Δ^9-Tetrahydrocannabinol class.

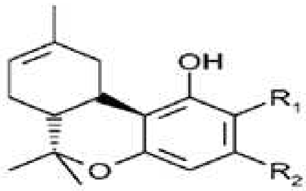

Figure no. 06
Δ^8-THC class.

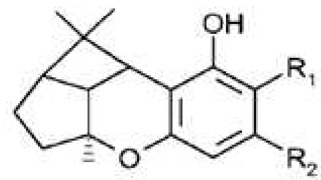

Figure no. 07
Cannabicyclol class.

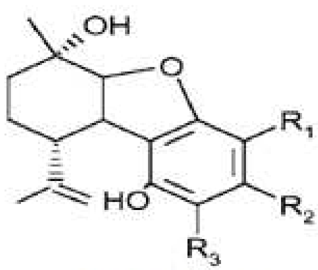

Figure no. 08
Cannabielsoin class.

Figure no. 09
Cannabinol and Cannabinodiol.

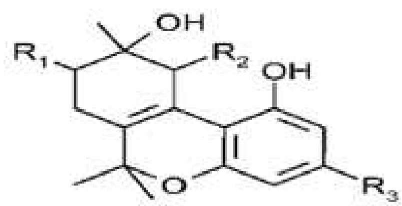

Figure no. 10
Cannabitriol class.

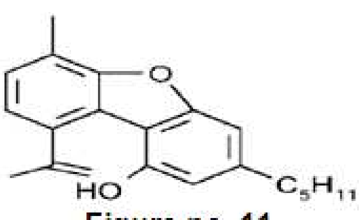

Figure no. 11
Dihydrocannabifurane.

Table no. 01
Pharmacological action of the above classes.

S.no.	Cannaboids subclass	Pharmacological activity
1.	Cannabigerol	Antibiotic, Antifungal, Analgesic, Anti-inflammatory.
2.	Cannabichromene	Antibiotic, Antifungal, Analgesic, Anti-inflammatory.
3.	Cannabidiol	Antibiotic, Anxiolytic, Antipsychotic, Antispasmodic, Analgesic.
4.	Δ^9-TCH	Euphoriant, Antioxidant, Antiemetic, Analgesic, Antiinflammotary.
5.	Δ^8-THC	Similar to the activity of Δ^9-TCH class but less potent.
6.	Cannabicyclol	……………………
7.	Cannabinol and Cannabinodiol	Anticonvulsant, Sedative, Antibiotic.
8.	Cannabitriol	…………………………

The typical scent of *Cannabis* results from about 140 different terpenoids. Isoprene units (C5H8) form monoterpenoids (C10 skeleton), sesquiterpenoids (C15), diterpenoids (C20), and triterpenoids (C30). Terpenoids may be acyclic, monocyclic, or polycyclic hydrocarbons with substitution patterns including alcohols, ethers, aldehydes, ketones, and esters. The essential oil (volatile oil) can easily be obtained by steam distillation or vaporization.

Cannabis sativa L. is one of the rare psychotropic plants in which the central nervous system activity is not linked to particular alkaloids. However, two spermidine- type alkaloids have been identified among the more than 70 nitrogen- containing constituents. Other nitrogenous compounds found are the quartenary bases choline, trigonelline, muscarine, isoleucine betaine, and neurine. Five lignanamide derivatives have been isolated, including cannabisin A, B, C, and D.

Common sugars are the predominant constituents of this class. Thirteen monosacharides (fructose, galactose, arabinose, glucose, mannose, rhamnose, etc.), two disaccharides (sucrose, maltose), and five polysaccharides (raffinose, cellulose, hemicellulose, pectin, xylan) have been identified so far. In addition, 12 sugar alcohols and cyclitols (mannitol, sorbitol, glycerol, inositol, quebrachitol, etc.) and two amino sugars (galactosamine, glucosamine) were found. Twenty-three commonly occurring flavonoids have been identified in *Cannabis*, existing mainly as C-/O- and *O*-glycosides of the flavon- and flavonol-type aglycones apigenin, luteolin, quercetin, and kaempferol . Orientin, vitexin, luteolin-7-*O*-glucoside, and apigenin-7-*O*-glucoside were the major flavonoid glycosides present in low-THC *Cannabis* cultivars [13-17]. The cannflavins A and B are unique to *Cannabis.* A total of 33 different fatty acids, mainly unsaturated fatty acids, have been identified in the oil of *Cannabis* seeds.

Marijuana smoking and related pharmacology

The study of the complication and the pharmacology of marijuana smoking were determined by parameter related to *MARIJUANA SMOKE CONDENSATE* (MSC) [18]. Various analytical parameters of blended marijuana (i.e., ash, hexane solubles, nitrate, reducing sugars, citric acid, malic acid, oxalic acid, potassium, sodium, calcium, magnesium, cadmium, chromium, and Δ^9-tetrahydrocannabinol) and marijuana cigarettes (average weight, average moisture content, static burning rate, fire zone temperature at 15- and 55-mm marks) were determined.

- ***Behavior Activity***

Male Swiss-Webster mice were used for all studies, and all administrations were via the tail vein. The acidic fraction was essentially inactive in a general activity screen at doses of 5 and 25 mg/kg. A dose of 125 mg/kg caused a nonspecific depression of behavioral and neurological parameters with little effect on autonomic function. The basic fraction also showed little activity in a general pharmacological screen at doses of 5, 10, and 20 mg/kg. Incidence of defecation and urination was also reduced at doses of 17 and 29 mg/kg. The polar-neutral fraction lowered body position, impaired motor coordination, and induced hypothermia at 30 and 60 minutes postinjection at a dose of 200 mg/kg. Both the acidic and polar-neutral fractions altered the activity of Δ9-THC when administered with that compound. Doses of 5.6 mg/kg acidic fraction and 7.4 mg/kg polarneutral fraction prolonged the hypothermia induced by 1 mg/kg Δ9-THC, while not affecting body temperature when administered alone. The basic fraction, however, did not alter body temperature when given alone or in combination with Δ9-THC. A subsequent study on the basic fraction of MSC obtained from Mexican marijuana (0.8% Δ9-THC) was evaluated in mice [19] looking at behavioral, neurological, and autonomic effects. This fraction administered by intravenous route (tail vein) at doses of 5, 10, and 20 mg/kg caused impairment of visual placing, increase in tail pinch response, decrease in tail evaluation, and induction of piloerection.

- ***Mutagenicity***

The well known carcinogen benzo[*a*]pyrene was present in MSC by a 70% higher amount than in TSC. It was suggested that the pyrolysis products of Δ9-THC and other cannabinoids are major contributors to the formation of polynuclear aromatic hydrocarbons. MSC was shown to be mutagenic in strain TA 98 of the Ames Salmonella/microsome test [20, 21], a short term bioassay that estimates the mutagenic potential of some chemicals. The mutagens in MSCs required liver enzymes to be activated. The authors concluded that the basic fraction accounted for 76% of the recovered mutagenic activity.

Yet another study was carried out using *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538, both with and without metabolic activation. No mutagenic activity was detected in the methylene chloride extracts of marijuana and tobacco, but all the smoke condensates exhibited mutagenicity with metabolic activation.

- ***Pulmonary hazards***

The pulmonary effects associated with smoking marijuana and tobacco were examined in men (mean age 31.5 ± 7.1 years) by quantification of the relative burden to the lung of insoluble particulates (tar) and carbon monoxide from the smoke of similar quantities of marijuana and tobacco [22]. Fifteen subjects who had smoked both marijuana and tobacco habitually for the previous 5 years were included in this study. Each subject’s blood carboxyhemoglobin level before and after smoking and the amount of tar inhaled and deposited in the respiratory tract from the smoke of a single filter-tipped tobacco cigarette (900–1200 mg) and marijuana cigarettes (741– 985 mg) containing 0.004% or 1.24% Δ9-THC were measured. Compared with smoking tobacco, smoking marijuana was associated with a nearly fivefold increment in the blood carboxyhemoglobin level, an approximate threefold increase in the amount of tar inhaled, and retention in the respiratory tract of one third more inhaled tar ($p < 0.001$). Significant differences were also noted in the dynamics of smoking marijuana and tobacco, among them an approximately two-thirds larger puff volume, a one-third greater depth of inhalation, and a fourfold longer breath-holding time with marijuana than with tobacco ($p < 0.001$). These results may account for previous findings that smoking only a few marijuana cigarettes a day (without tobacco) has the same effect on the prevalence and chronic respiratory symptoms [23] and the extent of tracheobronchial epithelial histopathology [24] as smoking more than 20 tobacco cigarettes a day (without marijuana). These observations justify concern about the potential adverse pulmonary effects resulting from the long-term smoking of only a few marijuana cigarettes a day.

Interaction with Estrogen Receptor

Intraperitoneal administration of marijuana resin and smoke condensate to rat in doses of 10 and 20 mg/kg (in maize oil) affected their estrous cycle [25]. Estrous was shortened with doses of both the resin and the smoke condensate, whereas diestrous was lengthened with the 20 mg/kg dose of the resin and both the 10 and 20 mg/kg doses of the smoke condensate. In addition, the administration of 20 mg/kg of either the resin or the smoke condensate resulted in a lengthening of the postestrous cycle.

Inhibition of Dihydrotestosterone Binding to the Androgen Receptor

MSC and two constituents of Cannabis, Δ9-THC and cannabinol, were tested for their ability to interact with the androgen receptor in rat prostate cytosol [26]. The above-mentioned materials competitively inhibited the specific binding of dihydrotestosterone to the androgen receptor with a dissociation constant (Ki) of 2.1 × 10–7 M for CBN, 2.6 × 10–7 M for Δ9-THC, and 5.8 × 10–7 M for MSC. The data indicate that the antiandrogenic effects associated with marijuana use result, at least in part, from inhibition of androgen action at the receptor level.

Hunger and Appetite

Earlier marijuana was believed to stimulate hunger, suggesting that it might be used for anorexia nervosa. Although it is common knowledge that cannabis stimulates hunger, very little research has been accomplished over subsequent years. The statement was supported by administered 9-aza-cannabinol to sheep intravenously and found that feeding behavior increased.
along with a decrease in gastric secretion [27,28].

Anxiety

It seems that the preponderance of the data suggest that these compounds are anxiolytic. Agonists, on the other hand, seem to have biphasic effects: low doses seem to be anxiolytic, high doses anxiogenic. In addition, it seems that the context is important. Further research is needed to sort out the differences among various studies, but it is clear that both antagonists and agonists on the CB1 receptor have anxiolytic properties [29].

Depression

In a study of normal object the result was found to have a positive correlation on the depression scale of the Minnesota Multiphase Personality Inventory with feelings of euphoria after smoking marijuana; while there was no correlation between anxiety (hysteria scale) and somatic concerns (hypochondriasis scale) with feeling euphoric, suggesting an antidepressive effect from marijuana use. In a survey of 128 patients in Germany, it was reported that 12% used marijuana for relief of depression [30, 31].

Schizophrenia

Animal Studies were conducted to evaluate the effects of CBD and haloperidol in a model that predicts antipsychotic activity in rats. Apomorphine induces stereotyped sniffing and biting. Both drugs decreased the frequency of these behaviors. CBD did not induce catalepsy, even at very high doses, although haloperidol induced catalepsy. The authors conclude that CBD has a pharmacological profile similar to the atypical antipsychotic drugs [32]. In the first, ibotenic acid lesions of the hippocampus were made in neonatal rats, which results in a brain degeneration pattern similar to that observed in schizophrenics as well as abnormal play behavior in an anxiety-provoking environment. In a second model, ketamine-induced enhancement of prepulse inhibition was tested. In both of these tests, SR141716 reversed the abnormal behavior. These findings in animal models are consistent with the hypothesis that CB1 receptor antagonists have antipsychotic activity [33].

Human studies conducted for the evaluation of Schizophrenia

A study was conducted using 95 schizophrenics who had used cannabis in the last year. They found lower scores in the schizophrenics on delusions and alogia scales of Andreasen's Scales for the Assessment of Positive and Negative Symptoms, suggesting that cannabis may affect the negative symptoms of schizophrenia [34]. In a sample of community-based mentally ill patients, *it* reported fewer hospital admissions and fewer symptoms of anxiety, depression, and insomnia among users preferring marijuana [35].

Alcohol Dependence

A study conducted for the evaluation of alcohol dependency resulted that CBD, Δ^9-THC, and clonidine reduced body tremor and audiogenic seizures during alcohol withdrawal in C57Bl6J mice forced to become alcohol tolerant on a liquid diet containing alcohol. Equivalent reductions in tremors and seizures were found with clonidine [36].

Cannabis and Analgesia

CB1 receptors are found on peripheral nerves [37], and injection of anandamide into tissues swollen from carageenan-induced inflammation has shown to reduce pain in rats [38]. Evidence shows that THC and cannabinoids prevent pain transmission when injected directly into the spinal cord, the brainstem, or even the thalamus [39]. CB1 receptors are very dense in specific layers of the dorsal horn of the spinal cord, where peripheral sensory afferents synapse with second-order neurons to transmit pain to higher centers [40, 41].

Cannabis and addiction

A typical *Cannabis* high starts with tingling of the body and head, progresses to dizziness and a quickening of mental associations with sharpened senses, heightened perception, increased appetite, and a distortion of the sense of time, causing it to go faster, and ends with calm, drowsiness, and eventually sleep [42]. CB1 receptors are central to the intoxicating effects, as evidenced by the blockade of those effects by rimonabant [43]. Dopamine plays a major role in reward, and most drugs abused directly increase dopamine levels in the mesocorticolimbic pathways involved with reinforcement and pleasure [44].

Cannabis and cardio vascular effect

In humans, the acute administration of cannabinoids causes marked tachycardia and a small increase in blood pressure, whereas in chronic users, hypotension and bradycardia are generally noted [45,46].

Cannabis and immune modulation

Immune/inflammatory responses are at the basis of a number of pathological conditions. CB1 are mainly found centrally and mediate

analgesic effects of cannabinoids. CB2 receptors are mainly found on cells of the immune system, such as macrophages, T-lymphocytes, and natural killer cells [47]. High doses of cannabinoids suppress immune responses, whereas low doses cause metabolic stimulation of lymphocytes (48,49). The mechanism of immunomodulation by cannabinoids is still unclear, but evidence suggests that CB2 receptors mediate most of these effects, with downregulation of mast cells and granulocytes and reduced cytokine release, although VR1 receptors may be implicated (50)

CONCLUSION

The above plant and its byproducts both have a long list of use and activity. The issue regarding the use of the plant is facing great deal of debate in terms of the fact of abuse and addiction. Yet it seems to have a promising result and potency on many disorders. Modes of action of the constituent extracted from the plant at receptor level are to be verified yet. Inspite of the debate and legal issues, the research have to be conducted so that the fruitful use of the flora could be gifted to man kind. The article was an effort to bring out the good aspects of plant gifted by nature and criticized by mankind.

REFERENCES

1. Khare , C. P., Indian medicinal plants, An illustrated dictionary, p-116.
2. Mahmoud A. ElSohly, Marijuana and cannabis, Humana Press Inc, 2007.
3. Musty, R. E. (2004) Natural cannabinoids: interactions and effects, in *The Medicinal Use of Cannabis and the Cannabinoids* (Guy, G. W., Whittle, B. A., and Robson, R. J., eds.), Pharmaceutical Press, London, pp.165–204.
4. Clarke, R. C. (1981) *Marijuana Botany*, Berkeley: Ronin Publishing.
5. Gaoni, Y. and Mechoulam, R. (1964) The structure and synthesis of cannabigerol, a new hashish constituent, in *Proc. Chem. Soc.*, London, p. 82.
6. Shoyama, Y., Yagi, M., Nishioka, I., and Yamauchi, T. (1975) Biosynthesis of cannabinoid acids. *Phytochemistry* 14, 2189–2192.
7. Adams, R., Hunt, M., and Clark, J. (1940) Structure of cannabidiol, a product isolated from the marihuana extract of Minnesota wild hemp. I. *J. Am. Chem. Soc.* 62, 196–199.
8. Mechoulam, R. and Shvo, Y. (1963) Hashish—I. The structure of cannabidiol. *Tetrahedron* 19, 2073–2078.
9. Wollner, H., Matchett, J., Levine, J., and Loewe, S. (1942) Isolation of a physiologicallyactive tetrahydrocannabinol from Cannabis sativa resin. *J. Am. Chem. Soc.* 64, 26–29.
10. Gaoni, Y. and Mechoulam, R. (1964) Isolation, structure and partial synthesis of an active constituent of hashish. *J. Am. Chem. Soc.* 86, 1646–1647.
11. Wood, T., Spivey, W., and Easterfield, T. (1896) XL. Charas. The resin of Indian hemp. *J. Chem. Soc.* 69, 539.
12. Adams, R., Baker, B., and Wearn, R. (1940) Structure of cannabinol III. Synthesis of cannabinol, 1-hydroxy-3-n-amyl-6,6,9-trimethyl-6-dibenzopyran. *J. Am. Chem. Soc.* 62,2204–2207.
13. McPartland, J. and Mediavilla, V. (2002) Noncannabinoid components, in *Cannabis and Cannabinoids—Pharmacology, Toxicology, and Therapeutic Potential* (Grotenhermen, F., and Russo, E., eds.), Haworth Press, New York, pp. 401–409.
14. Vanhoenacker, G., Van Rompaey, P., De Keukeleire, D., and Sandra, P. (2002) Chemotaxonomic features associated with flavonoids of cannabinoid-free cannabis (Cannabis sativa subsp. sativa L.) in relation to hops (Humulus lupulus L.). *Nat. Prod. Lett.* 16, 57–63.
15. Barrett, M. L., Scutt, A. M., and Evans, F. J. (1986) Cannflavin A and B, prenylated

flavones from Cannabis sativa L. *Experientia* 42, 452–453.

16. Barrett, M. L., Gordon, D., and Evans, F. J. (1985) Isolation from Cannabis sativa L. of cannflavin—a novel inhibitor of prostaglandin production. *Biochem. Pharmacol.* 34, 2019–2024.
17. Leson, G., Pless, P., and Roulac, J. (1999) *Hemp Foods and Oils for Health*, Hemptech, Sebastopol, CA.
18. Patel, A. R. and Gori, G. B. (1975) Preparation and monitoring of marijuana smoke condensate samples. *Bull. Narc.* 27, 47–54.
19. Johnson, J. M., Lemberger, L., Novotny, M., Forney, R. B., Dalton, W. S., and Maskarinec, M. P. (1984) Pharmacological activity of the basic fraction of marijuana whole smoke condensate alone and in combination with Δ^9-tetrahydrocannabinol in mice. *Tox. Appl. Pharm.* 72, 440–448.
20. Busch, F. W., Seid, D. A., and Wei, E. T. (1979) Mutagenic activity of marihuana smoke condensates. *Cancer Lett.* 6, 319–324.
21. Wehner, F. C., Van Rensburg, S. J., and Theil, P. G. (1980) Mutagenic activity of marihuana and Transkei tobacco smoke condensates in the Samonella / microsome assay. *Mutat. Res.* 77, 135–142.
22. Wu, T. C., Tashkin, D. P., Djahed, B., and Rose, J. E. (1988) Pulmonary hazards of smoking marijuana as compared with tobacco. *N. Engl. J. Med.* 318, 347–351.
23. Tashkin, D. P., Coulson, A. H., and Clark, V. A. (1987) Respiratory and lung function in habitual heavy smokers of marijuana alone, smokers of marijuana and tobacco, smokers of tobacco alone, and non-smokers. *Am. Rev. Respir. Dis.* 135, 209–216.
24. Gong, H., Fliegel, S., Tashkin, D. P., and Barbers, R. G. (1987) Tracheobronchial changes in habitual, heavy smokers of marijuana with and without tobacco. *Am. Rev. Respir. Dis.* 136, 142–149.
25. Lares, A., Ochoa, Y., Bolanos, A., Aponte, N., and Montenegro, M. (1981) Effects of the resin and smoke condensate of *Cannabis sativa* on the oestrous cycle of the rat. *Bull.Narc.* 33, 55–61.
26. Purohit, V., Ahluwahlia, B. S., and Vigersky, R. A. (1980) Marihuana inhibits dihydrotestosterone binding to the androgen receptor. *Endocrinology* 107, 848–850.
27. Donovan, M. (1845) On the physical and medicinal qualities of Indian hemp *(Cannabis indica)*; with observations on the best mode of administration, and cases illustrative of its powers. *Dublin J. Med. Sci.* 26, 368–402, 459–461.
28. Van Den Broek, G. W., Robertson, J., Keim, D. A., and Baile, C. A. (1979) Feeding and depression of abomasal secretion in sheep elicited by elfazepam and 9-aza-cannabinol. *Pharmacol. Biochem. Behav*. 11, 51–56.
29. Musty, R. E. (2005) Cannabinoids and anxiety, in *Cannabinoids as Therapeutics* (Mechoulam, R., ed.), Birkhauser Verlag, Basel, pp. 141–148.
30. Musty, R. E. (1988) Individual differences as predictors of marihuana phenomenology, in *Marihuana: An International Research Report* (Chesher, G., Consroe, P., and Musty, R., eds.), Australian Government Publishing Service, Canberra, pp. 201–207.
31. Schnelle, M., Grotenhermen, F., Reif, M., and Gorter, R. W. (1999) Ergebnisse einer standardisierten Umfrage zur medizinischen Verwendung von Cannabisprodukten im deutschen Sprachraum [Results of a standardized survey on the medical use of cannabis products in the German-speaking area]. *Forsch. Komplementarmed. Suppl*. 3, 28–36.
32. Zuardi, A. W., Rodrigues, J. A., and Cunha, J. M. (1991) Effects of cannabidiol in animal models predictive of antipsychotic activity. *Psychopharmacology* 104, 260–264.
33. Musty, R. E., Deyo, R. A., Baer, J. L., Darrow, S. M., and Coleman, B. (2000) Effects of SR141716A on animal models of depression. 2000 Symposium on the Cannabinoids,

International Cannabinoid Research Society, Burlington, VT, p. 109.
34. Peralta, V. and Cuesta, M. J. (1992) Influence of cannabis abuse on schizophrenic psychopathology. *Acta Psychiatr. Scand.* 85,127–130.
35. Warner, R., Taylor, D., Wright, J., et al. (1994) Substance use among the mentally ill: prevalence, reasons for use, and effects on illness. *Am. J. Orthopsychiatry* 64, 30–39.
36. Musty, R.E. (1984) Possible anxiolytic effects of cannabidiol, in *The Cannabinoids* (Agurell, S., Dewey, W., and Willette, R., eds.), Academic Press, New York, pp. 829–844.
37. Hohmann, A. G. and Herkenham, M. (1999) Cannabinoid receptors undergo axonal flow in sensory nerves. *Neuroscience* 92(4), 1171–1175.
38. Richardson, J. D., Kilo, S., and Hargreaves, K. M. (1998) Cannabinoids reduce hyperalgesia and inflammation via interaction with peripheral CB1 receptors. *Pain* 75, 111–119.
39. Pertwee, R. G. (2001) Cannabinoid receptors and pain. *Prog. Neurobiol.* 63, 569–611.
40. Drew, L. J., Harris, J., Millns, P. J., Kendall, D. A., and Chapman, V. (2000) Activation of spinal cannabinoid 1 receptors inhibits C-fibre driven hyperexcitable neuronal responses and increases [35S]GTPγS binding in the dorsal horn of the spinal cord of noninflamed and inflamed rats. *Eur. J. Neurosci.* 12, 2079–2086.
41. Hohmann, A. G. and Herkenham, M. (1998) Regulation of cannabinoid and mu opioid receptors in rat lumbar spinal cord following neonatal capsaicin treatment. *Neurosci. Lett.* 252, 13–16.
42. Iversen, L. (2003) Cannabis and the brain. *Brain* 126, 1252–1270.
43. Huestis, M. A., Gorelick, D. A., Heishman, S. J., et al. (2001) Blockade of effects of smoked marijuana by the CB1-selective cannabinoid receptor antagonist SR141716. *Arch. Gen. Psychiatry* 58, 322–328.
44. Wise, R. A. (1987) The role of reward pathways in the development of drug dependence. *Pharmacol. Ther.* 35, 227–263.
45. Benowitz, N. L., Rosenberg, J., Rogers, W., Bachman, J., and Jones, R. T. (1979) Cardiovascular effects of intravenous delta-9-tetrahydrocannabinol: autonomic nervous mechanisms. *Clin. Pharmacol. Ther.* 25, 440–446.
46. Tsou, K., Brown, S., Sanudo-Pena, M.C., Mackie, K., and Walker, J.M (1998) Immunohistochemical distribution of cannabinoid CB1 receptors in the rat central nervous system. *Neurosci.* 83(2), 393–411.
47. Klein, T. W., Newton, C., and Friedman, H. (1998) Cannabinoid receptors and immunity. *Immunol. Today* 19(8), 373–381.
48. Berdyshev, E.V., Boichot, E., Germain, N., Allain, N., Anger, J. P., and Lagente, V. (1997) Influence of fatty acid ethanolamides and Δ9-tetrahydrocannabinol on cytokine and arachidonate release by mononuclear cells. *Eur. J. Pharmacol.* 330, 231–240.
49. Zhu, L. X., Sharma, S., Stolina, M., et al. (2000) Δ9-Tetrahydrocannabinol inhibits antitumor immunity by a CB2 receptor-mediated, cytokine-dependent pathway. *J. Immunol.* 165, 373–380.
50. Hwang, S. W. and Oh, U. (2002) Hot channels in airways: pharmacology of the vanilloid receptor. *Curr. Opin. Pharmacol.* 2, 235–242.