PRESENTATION FOR NOVA-INSTITUTE "ONLINE PROCEEDINGS"
Third International Symposium: Bioresource Hemp.
13-16 September 2000, Wolfsburg, Germany

Advantages of polypharmaceutical herbal *Cannabis* compared to single-ingredient, synthetic tetrahydrocannabinol

John McPartland
Vermont Alternative Medicine/AMRITA
53 Washington Street Ext.
Middlebury, VT 05753 USA

Introduction

In the United States, marijuana (*Cannabis sativa,* possibly also *Cannabis indica* and *Cannabis afghanica*) is classified by the Drug Enforcement Administration (DEA) as a prohibited Schedule I drug ("no currently accepted medical use"). As a substitute for marijuana, the DEA approved dronabinol (Marinol®). Dronabinol is synthetic delta-9-tetrahydrocannabinol (Δ^9-THC). It is formulated in a capsule, designed for oral administration. Because Δ^9-THC is the primary psychoactive ingredient in both Dronabinol and marijuana, the DEA considers Dronabinol equal to marijuana in effectiveness, for the treatment of nausea, vomiting, and anorexia.

But Dronabinol and marijuana are not equal, according to many reports (Grinspoon & Bakalar 1997). Many patients report that marijuana has better therapeutic activity than Dronabinol, and that marijuana has less side effects than Dronabinol. Dronabinol often causes psychological "overdose" reactions, symptoms such as dysphoria, depersonalization, anxiety, panic reactions, and paranoia.

Route of administration

These side effects may be secondary to the drug's route of administration — Dronabinol is formulated as a capsule for oral administration. Swallowing THC leads to first-pass metabolism by the liver, resulting in approximately equal amounts of THC and its 11-hydroxy metabolite in the blood stream (Perez-Reyes & Wall, 1981). The metabolite, 11-hydroxy-THC, is about 4 times more psychoactive

than THC (Browne & Weissman 1981). Other studies cite different multipliers, in a range from 2 to 17. In contrast, when THC is inhaled as marijuana, it avoids first-pass metabolism by the liver. Very little of inhaled THC is converted to 11-hydroxy-THC (Perez-Reyes & Wall 1981).

Swallowed THC is poorly absorbed (approximately 6-15%), and its absorption is very erratic, due to low water solubility (Ohlsson *et al.* 1980). The absorption varies on a day-to-day basis, depending on the state of the patient's digestive system. Hence, an identical dose may be insufficient one day and overpowering the next day. Furthermore, swallowed THC has a slow onset of action (60-90 minutes, compared to as many seconds for inhaled THC), which makes it difficult to self-titrate. Lastly, oral administration may be difficult for patients who are anorexic, nauseous, or vomiting. Such patients find it much easier to inhale marijuana than to hold down a capsule.

Polypharmacy and synergy

The most obvious difference between marijuana and Dronabinol is polypharmacy. Marijuana is a herbal medicine and it contains hundreds of ingredients besides THC (Turner *et al.* 1980). Herbalists contend that polypharmaceutical herbs provide two advantages over single-ingredient synthetic drugs: 1) therapeutic effects of the primary active ingredients in herbs may be *synergized* by other compounds, and 2) side effects of the primary active ingredients may be *mitigated* by other compounds. Thus, marijuana has been characterized as a "synergistic shotgun," in contrast to Dronabinol, a synthetic, single-ingredient "silver bullet" (McPartland & Pruitt 1999).

Mechoulam *et al.* (1972) suggested that THC activity may be influenced by other compounds present in herbal marijuana. Carlini *et al.* (1974) determined that marijuana produced effects "two or four times greater than that expected from its THC content." Similarly, Fairbairn & Pickens (1981) detected the presence of unidentified "powerful synergists" in *Cannabis* extracts, causing 330% greater activity in mice than THC alone.

The "powerful synergists" may be compounds related to THC, a group of chemicals called the cannabinoids. Mechoulam & Gaoni (1967) defined "cannabinoids" as a group of C_{21} terpenophenolic compounds uniquely produced by *Cannabis*. Due to the subsequent development of synthetic

cannabinoids (e.g., HU-210), and the discovery of endogenous cannabinoids (e.g., anandamide), Pate (1999) coined the term "phytocannabinoids" to designate the C_{21} compounds produced by *Cannabis.* Phytocannabinoids exhibit very low mammalian toxicity, and mixtures of cannabinoids are *less toxic* than pure THC (Thompson *et al.* 1973).

Cannabinoids bind to cannabinoid receptors in our bodies, and cause what are called receptor-mediated effects. Various cannabinoids differ in their ability to bind to receptors; this ability is called binding affinity. In the laboratory, binding affinity is measured as "Ki" -- the smaller the Ki value, the more powerful the binding affinity (reviewed by Felder & Glass 1998). Δ^9-THC has the lowest Ki value, measured at 41 nM for the CB1 receptor (Showalter *et al.* 1996), so Δ^9-THC has the strongest binding affinity. In experiments with rats, cats, and humans, binding affinity correlates with drug potency.

Some varieties of marijuana contain significant amounts of Δ^8-THC, which is nearly identical to Δ^9-THC, except for a shift of one double bond. This shift changes the Ki of Δ^8-THC to 126 nM (Showalter *et al.* 1996). The decrease in Δ^8-THC binding ability correlates with behavioral studies in rats, which show Δ^8-THC is two or three times less potent than Δ^9-THC. Tetrahydrocannabivarin (THCV) is similar to Δ^9-THC, except for a shortened side chain. THCV appears in *indica* and *afghanica* varieties of *Cannabis.* THCV is weaker than Δ^9-THC in animal studies, but it works faster than THC (Gill *et al.* 1970). Its binding affinity awaits measurement. Kubena & Barry (1972) suggested THCV synergizes with Δ^9-THC, but they did not hypothesize a mechanism. Cannabichromene (CBC) is a major component in most marijuana varieties. Nevertheless, its binding affinity has not been measured. In rats, the coadministration of CBC with THC potentiates THC changes in heart rate, but not blood pressure (O'Neil *et al.* 1979). Cannabinol (CBN) is the degradation product of THC (Turner *et al.* 1980). CBN potentiates the effects of THC in man (Musty *et al.* 1976). Cannabigerol (CBG) is the biosynthetic precursor to CBC and THC. CBG has been called "inactive" when compared to THC, but CBG has slight affinity for CB1 receptors, approximately the same amount as cannabidiol (Devane *et al.* 1988).

Alleviating THC-induced anxiety

Polypharmaceutical herbs may contain compounds that decrease the side effects of their primary active ingredients. Some cannabinoids decrease the side effects of THC. For example, cannabidiol (CBD) possesses sedative properties (Carlini & Cunha 1981), and a clinical trial showed that CBD reduces the anxiety and other unpleasant psychological side effects provoked by pure THC (Zuardi *et al.* 1982).

CBD modulates the pharmacokinetics of THC by at least four mechanisms: 1) CBD binds to cannabinoid receptors (Ki at CB1 = 4350 nM, Showalter *et al.* 1996), but it acts the opposite of THC — CBD signals receptors as an antagonist or reverse agonist (Petitet *et al.* 1998). 2) CBD may modulate THC signal transduction by perturbing the fluidity of neuronal membranes. 3) CBD may remodel G-proteins that carry intracellular signals downstream from cannabinoid receptors. 4) Last but not least, CBD is a potent inhibitor of cytochrome P450 3A11 metabolism, thus it blocks the hydroxylation of THC to its 11-hydroxy metabolite (Bornheim *et al.,* 1995). The 11-hydroxy metabolite is four times more psychoactive than THC (Browne & Weissman, 1981), and four times more immunosuppressive (Klein *et al.* 1987).

CBD, CBN, and CBG may affect anxiety and depression by modulating other neurotransmitters (reviewed by McPartland & Pruitt 1999). The cannabinoids can act as serotonin uptake inhibitors (the same mechanism as Prozac®), enhance norepinephrine activity (similar to tricyclic antidepressants), increase dopamine activity (similar to monoamine oxidase inhibitors), and augment GABA (like baclofen and benzodiazepines). CBD provides antipsychotic benefits (Zuardi *et al.* 1995).

Terpenoids in marijuana may also alleviate THC-induced anxiety. Terpenoids are volatile compounds that provide the unique smell of marijuana. *Cannabis* produces over 100 terpenoids, many of which vaporize around the same temperature as THC. Terpenoids are lipophilic and permeate lipid membranes. Many cross the blood-brain barrier (BBB) after inhalation. Buchbauer *et al.* (1993) assayed the sedative effects of over 40 essential oils upon inhalation; many of the most sedative compounds are found in marijuana, including linalool, citronellol, and α-terpineol.

Meschler & Howlett (1999) discussed several mechanisms by which terpenoids modulate THC activity: Some terpenoids may dock at cannabinoid receptors, such as thujone (Ki at CB1 = 130,000 nM). Terpenoids may modulate the affinity of THC for its own receptor — by sequestering THC, by perturbing annular lipids surrounding the receptor, or by increasing the fluidity of neuronal membranes. Further

downstream, terpenoids may alter the signal cascade by remodeling G-proteins. Terpenoids may alter the pharmacokinetics of THC by changing the BBB; *Cannabis* extracts are known to cause a significant increase in BBB permeability (Agrawal *et al.* 1989).

Terpenoids may affect anxiety and depression by modulating the activity of serotonin, norepinephrine, dopamine, and GABA (reviewed by McPartland & Pruitt 1999). Some terpenoids may decrease anxiety by attenuating corticotropin-releasing factor (CRF) expression (Marcihac *et al.* 1998). CRF is associated with anxiety; cannabinoids cause a release of CRF (Rodríguez de Fonseca *et al.* 1996).

Flavonoids are aromatic, polycyclic phenols. *Cannabis* produces about 20 of these compounds (Turner *et al.* 1980). Many flavonoids are volatile, lipophilic, and permeate membranes. Some flavonoids, such as apigenin, apparently retain pharmacological activity in marijuana smoke (Sauer *et al.* 1983). Apigenin is a powerful anxiolytic agent. It is the primary active ingredient in chamomile, *Matricaria recutita* (Russo 2000). Apigenin selectively binds with high affinity to central benzodiazepine receptors, which are located on $GABA_A$ receptors (Salgueiro *et al.* 1997).

Mitigating memory loss

THC disrupts short-term memory, primarily by decreasing acetylcholine activity in the brain, especially in the hippocampus (Carta *et al.,* 1998). Terpenoids may ameliorate THC-induced short-term memory loss. Cholinergic deficits in people with Alzheimer's disease are treated with tacrine (Cognex®). Tacrine increases acetylcholine activity by inhibiting acetylcholinesterase. Tacrine has blocked THC-mediated memory loss behavior in rats (Brown 1971). Terpenoids in marijuana that inhibit acetylcholinesterase include limonene, limonene oxide, α-terpinene, γ-terpinene, terpinen-4-ol, carvacrol, l- and d-carvone, 1,8-cineole, p-cymene, fenchone, pulegone, and pulegone-1,2-epoxide (reviewed by McPartland & Russo 2000).

Separate studies show the inhalation of 1,8-cineole increases cerebral blood flow and enhances cortical activity (Nasel *et al.* 1994). Brain function is enhanced by administering terpenoids that improve cerebral blood flow, such as the ginkgolides in *Ginkgo biloba.* Similarly, cerebral blood flow increases after

the inhalation of marijuana, and the increase is *not* related to plasma levels of THC (Mathew & Wilson 1993).

Ameliorating immunosuppression

THC receptors are present in white blood cells, and affect the immune system (Bouaboula *et al.* 1993). This is a critical discovery, because THC is frequently prescribed for immunocompromised individuals. Initial studies that characterized THC as a noxious immune-*suppressing* drug (e.g., Nahas *et al.* 1974) have not been substantiated in subsequent studies (White *et al.* 1975; Lau *et al.* 1976; Rachelfsky *et al.* 1977). THC is now considered an *immunomodulator,* capable of either enhancing or suppressing the function of T lymphocytes, B lymphocytes, natural killer cells, macrophages, and the cytokine network (Klein *et al.* 1998). The immunosuppresive effects of THC may be modulated by other constituents present in marijuana (McPartland & Pruitt 1997).

Reducing anxiety and depression will improve immune function via the neuroendocrine axis. Hence, inhalation of terpenoids reduces stress hormone secretion (such as corticosterone), and normalizes CD4 -CD8 ratios (Komori *et al.* 1995). Terpenoids inhibit corticosterone secretion by attenuating corticotropin-releasing factor (CRF) expression (Marcihac *et al.,* 1998), so terpenoids undo the effects of cannabinoids, which cause an increase of CRF (Rodríguez de Fonseca *et al.,* 1996).

Mollifying mutagenesis

Our immune system protects us from mutagens and carcinogens. Studies that suggested THC was mutagenic/carcinogenic (Nahas & Latour 1992) have been discredited (Christie & Chesher 1994). In fact, THC induces apoptosis in carcinogenic cells (Galve-Roperh *et al.,* 2000), as do other cannabinoids (Baek *et al.,* 1998). Nevertheless, the burning of marijuana creates mutagenic "tar compounds" in marijuana smoke, such as benz[a]anthracene, benzo[a]pyrene, napthalene and cresol (Sparacino *et al.* 1990).

Terpenoids may again come to the rescue. Limonene blocks the carcinogenesis induced by benz[a]anthracene (Crowell 1999), via multiple mechanisms: Limonene detoxifies carcinogens by inducing Phase II carcinogen-metabolizing enzymes; limonene inhibits the isoprenylation of Ras proteins,

thus blocking mutant *ras* oncogenes; limonene induces redifferentiation of cancer cells by enhancing expression of transforming growth factor β1 and growth factor II receptors; and limonene induces apoptosis of cancer cells (Crowell 1999). Orally administered limonene is currently undergoing Phase II clinical trials in the treatment of breast cancer; it also protects against lung, colon, pancreas, and skin cancers. Limonene is highly absorbed by inhalation and quickly appears in the bloodstream (Falk-Filipsson *et al.* 1993).

Flavonoids may also come to the rescue. Quercetin arrests the formation of NF-κB, a transcription factor protein that induces the expression of oncogenes (Musonda & Chipman 1998). NF-κB also plays a role in the activation of HIV-1 (Greenspan 1993), so quercetin may hinder the replication of that virus. In a similar fashion, silymarin (a flavonoid produced by milk thistle, *Silybum marianum*) impedes NF-κB-induced replication of the hepatitis C virus, and inhibits THFα-induced hepatic carcinoma (McPartland 1996). These flavonoids may synergize with CBN, which also downregulates NF-κB (Herring & Kaminski, 1999), thereby counteracting the effects of THC, which increases NF-κB activity (Daaka *et al.*, 1997).

Mollifying mutagenesis, part II

Limonene, myrcene, and other terpenoids inhibit cytochrome P450 2B1, an enzyme implicated in the metabolic activation of promutagens (De Oliveira *et al.*, 1997). Aflatoxin B_1 is a promutagen produced by *Aspergillus flavus* and *Aspergillus parasiticus,* two fungal contaminants of moldy marijuana (reviewed by McPartland & Pruitt 1997). After aflatoxin B_1 is metabolized by P450 2B1, it becomes extremely hepatocarcinogenic. The terpenoids block this metabolism of the promutagen to its active form. Limonene and myrcene also protect us from fungal contaminants at an earlier step -- they inhibit the production of aflatoxins by *Aspergillus* fungi (Greene-McDowelle *et al.*, 1999). Many terpenoids and cannabinoids are antifungal and antibacterial; they suppress the growth of fungal and bacterial contaminants, as demonstrated in hundreds of published studies (reviewed by McPartland, 1997).

Decreasing inflammation

Experiments have found that inhaling aerosolized THC causes more throat and airway irritation than inhaling marijuana smoke (Tashkin *et al.,* 1977). The CBD in marijuana smoke may explain the difference. CBD imparts analgesia (more potently than THC), CBD inhibits erythema (much more than THC), CBD blocks cyclooxygenase (COX) activity with a greater maximum inhibition than THC, and CBD blocks lipoxygenase (the enzyme that produces asthma-provoking leukotrienes), again more effectively than THC (reviewed by Evans, 1991). CBD also serves as an antioxidant, more potently than ascorbate and α-tocopherol (Hampson *et al.,* 1998).

Although THC has anti-inflammatory properties (Burstein *et al.,* 1973), CBD, CBN, CBG, CBC, and cannabidiolic acid are more potent prostaglandin inhibitors than THC (Burstein *et al.,* 1973, Evans 1991). Unique flavonoids in marijuana (the cannaflavins) are equipotent to cannabinoids in prostaglandin inhibition (Barett *et al.,* 1986). Other flavonoids, such as apigenin and quercetin, also exhibit potent anti-prostaglandin activity. Apigenin specifically inhibits tumor necrosis factor (TNF)-induced inflammation (Gerritsen *et al.,* 1995), possibly mitigating the effects of THC, which increases TNF activity. Quercetin is a potent antioxidant; by some measures more potent than ascorbic acid, α-tocopherol, and BHT (Gadow *et al.,* 1997). The antioxidant potential of quercetin should be tested against CBD; perhaps quercetin can reduce CBD, effectively recycling CBD as an antioxidant.

Eugenol, carvacrol, and *p*-vinylphenol surpass the cannabinoids in prostaglandin inhibition (Burstein *et al.,* 1975). In the final analysis, crude *Cannabis* oil inhibits prostaglandins more effectively on a weight basis than individual constituents, suggesting synergy (Evans *et al.,* 1987).

Conclusions

We hypothesize several mechanisms whereby the polypharmacy present in marijuana may serve to synergize the beneficial effects of THC. The many compounds in *Cannabis* may also mitigate the side effects of THC, as well as some side effects of inhaling smoke. Of course, polypharmacy also has drawbacks. Western medical science has made great advances by studying the effects of single active ingredients on disease processes, which is impossible in the analysis of whole herbs. Herbal compounds are much more difficult to standardize than single ingredients. Standardization reduces the natural

variability that makes accurate dosing difficult in crude herbal preparations. A British pharmaceutical firm, GW Pharmaceuticals, has been given a license to grow 20,000 marijuana plants in England. A Dutch plant-breeding corporation, HortaPharm, provided GW with standardized strains of *Cannabis* that contain primarily one cannabinoid. Extracts of single-cannabinoid plants will be blended to defined chemical compositions. *Cannabis* varieties with different terpenoid profiles are being investigated in Switzerland (Mediavilla & Steinemann, 1997). The future looks bright.

Cited References

Agrawal AK, Kumar P, Gulati A, Seth PK. Cannabis-induced neurotoxicity in mice: effects on cholinergic (muscarinic) receptors and blood brain barrier permeability. *Res Commun Subst Abuse* 1989; 10:155-168.

Baek SH, Kim YO, Kwag JS, Choi KE, Jung WY, Han DS. Boron trifluoride etherate on silica-A modified Lewis acid reagent (VII). Antitumor activity of cannabigerol against human oral epitheloid carcinoma cells. *Archives of Pharmacal Research* 1998; 21:353-6.

Barrett ML, Scutt AM, Evans FJ. Cannaflavin A and B, prenylated flavones from *Cannabis sativa* L. *Experientia* 1986; 42:452-453.

Bornheim LM, Kim KY, Li J, Perotti BY, Benet LZ. Effect of cannabidiol pretreatment on the kinetics of tetrahydrocannabinol metabolites in mouse brain. *Drug Metabolism & Disposition* 1995 23:825-31.

Brown H. Some anticholinergic-like behavioural effects of trans (-)-delta-8 tetrahydrocannabinol. *Psychopharmacologia.* 1971; 21:294-301.

Browne RG, Weissman A. Discriminative stimulus properties of delta 9-tetrahydrocannabinol: mechanistic studies. *J. Clinical Pharmacology.* 1981; 21(8-9 Suppl):227S-234S.

Buchbauer G, Jirovetz L, Jäger W, Plank C, Dietrich H. Fragrance compounds and essential oils with sedative effects upon inhalation. *J. Pharmaceut Sci.* 1993; 82:660-664.

Burstein S, Levin E, Varanelli C. Prostaglandins and *Cannabis*—II. Inhibition of biosynthesis by the naturally occurring cannabinoids. *Biochemical Pharmacology* 1973; 22:2905-2910.

Burstein S, Varanelli C, Slade LT. Prostaglandins and *Cannabis*—III. Inhibition of biosynthesis by essential oil components of marihuana. *Biochemical Pharmacology* 1975; 24:1053-1054.

Carlini EA, Karniol IG, Renault PF, Schuster CR. Effects of marihuana in laboratory animals and man. *Br. J. Pharmacol.* 1974; 50:299-309.

Carlini EA, Cunha JM. Hypnotic and antiepileptic effects of cannabidiol. *J Clin. Pharmacol.* 1981; 21:417S-427S.

Carta G, Nava F, Gessa GL. Inhibition of hippocampal acetylcholine release after acute and repeated •9-tetrahydrocannabinol in rats. *Brain Research* 1998; 809:1-4.

Christie MJ, Chesher GB. The human toxicity of marijuana: a critique of a review by Nahas and Latour. *Drug & Alcohol Review* 1994; 13:209-216.

Crowell PL. Prevention and therapy of cancer by dietary monoterpenes. *J. Nutrition* 1999; 129:775S-778S.

Daaka Y, Zhu W, Friedman H, Klein TW. Induction of interleukin-2 receptor α gene by •9-tetrahydrocannabinol is mediated by nuclear factor κB and CB1 cannabinoid receptor. *DNA and Cell Biology* 1997; 16:301-309.

Devane WA, Dysarz FA, Johnson MR, Melvin LS, Howlett AC. Determination and characterization of a cannabinoid receptor in rat brain. *Molecular Pharmacol.* 1988; 34:605-613.

De Oliverira AC, Ribeiro-Pinto LF, Paumgartten JR. In vitro inhibition of CYP2B1 monooxygenase by beta-myrcene and other monoterpenoid compounds. *Toxicology Letters* 1997; 92:39-46.

Evans FJ. Cannabinoids: the separation of central from peripheral effects on a structural basis. *Planta Medica.* 1991; 57 (Suppl 1):S60-S67.

Evans AT, Formukong EA, Evans FJ. Actions of cannabis constituents on enyzmes of arachidonate metabolism: anti-inflammatory potential. *Biochem. Pharmacol.* 1987; 36:2035-2037.

Fairbairn JW, Pickens JT. Activity of *Cannabis* in relation to its •-tetrahydrocannabinol content. *Br. J. Pharmacol.* 1981; 72:401-409.

Falk-Filipsson A, Löf, Hagberg M, Hjelm EW, Wang Z. *d*-Limonene exposure to humans by inhalation: uptake, distribution, elimination, and effects on the pulmonary function. *J. Toxicology Environ. Health* 1993; 38:77-88.

Felder CC, Glass M. Cannabinoid receptors and their endogenous agonists. *Annu Rev Pharmacol Toxicol* 1998; 38:179-200.

Gadow A von, Joubert E, Hansmann CF. Comparison of the antioxidant activity of aspalathin with that of other plant phenols of rooibos tea (*Aspalathus linearis*), α-tocopherol, BHT, and BHA. *J. Agric. Food Chem.* 1997; 45:632-638.

Galve-Roperh I, Sánchez C, Cortés ML, Gómez del Pulgar T, Izquierdo M, Guzmán M. Anti-tumoral action of cannabinoids: involvement of sustained ceramide accumulation and extracellular signal-regulated kinase activation. *Nature Medicine* 2000; 3:313-319

Gerritsen ME, Carley WW, Ranges GE, Shen C-P, Phan SA, Ligon GF, Perry CA. Flavonoids inhibit cytokine-induced endothelial cell adhesion protein gene expression. Am J Path 1995; 147:278-292.

Gill EW, Paton WDM, Pertwee RG. Preliminary experiments on the chmistry and pharmacology of *Cannabis. Nature* 1970; 228:134-136.

Greene-McDowelle DM, Ingber B, Wright MS, Zeringue HJ, Bhatnagar D, Cleveland TE. The effects of selected cotton-leaf volatiles on growth, development and aflatoxin production of *Aspergillus parasiticus. Toxicon* 1999; 37:883-893.

Greenspan HC. The role of reactive oxygen species, antioxidants and phytopharmaceuticals in human immunodeficiency virus activity. *Medical Hypotheses* 1993; 40:85-92.

Grinspoon L, Bakalar JB. *Marihuana, the Forbidden Medicine,* revised edition. New Haven, CT: Yale University Press, 1997.

Hampson AJ, Grimaldi M, Axelrod J, Wink D. Cannabidiol and (-) Δ9-tetrahydrocannabinol are neuroprotective antioxidants. *Proc. Natl. Acad. Sci. USA* 1998; 95:8268-73.

Herring AC, Kaminski NE. Cannabinol-mediated inhibition of nuclear factor-κB, cAMP response element-binding protein, and interleukin-2 secretion by activated thymocytes. *J. Pharma. Exp. Therap.* 1999; 291:1156-1163.

Klein TW, Newton C, Friedman H. Inhibition of natural killer cell function by marijuana components. J Toxicol Environ Health 1987; 20:321-32.

Klein TW, Friedman H, Specter S. Marijuana, immunity and infection. *J Neuroimmunology.* 1998; 83:102-115.

Kubena RK, Barry H. Stimulus characteristics of marihuana components. *Nature* 1972; 235:397-398.

Lau RJ, Tubergen DG, Barr M, Domino EF, Benowitz N, Jones RT. Phytohemagglutnin-induced lymphocyte transformation in humans receiving delta-9-tentrahydrocannabinol. *Science* 1976; 192:805-807.

Marcihac A, Dakine N, Bourhim N, Guillaume V, Grino M, Drieu K, Oliver C. Effect of chronic administration of *Ginkgo biloba* extract or kinkgolide on the hypothalamic-pituitary-adrenal axis in the rat. *Life Sciences* 1998; 62:2329-2340.

Mathew RJ, Wilson WH. Acute changes in cerebral blood flow after smoking marijuana. *Life Sciences* 1993; 52:757-767.

McPartland JM. Viral hepatitis treated with *Phyllanthus amarus* and milk thistle (*Silybum marianum*): a case report. *Complementary Medicine International* 1996; 3(2):40-42.

McPartland JM. *Cannabis* as a repellent crop and botanical pesticide. *Journal International Hemp Association* 1997; 4(2):89-94.

McPartland JM, Pruitt PP. Medical marijuana and its use by the immunocompromised. *Alternative Therapies* 1997; 3(3):39-45.

McPartland JM, Pruitt PP. Side effects of pharmaceuticals not elicited by comparable herbal medicines: the case of tetrahydrocannabinol and marijuana. *Alternative Therapies* 1999; 5(4):57-62.

McPartland JM, Russo E. *Cannabis* and cannabis extracts: greater than the sum of their parts? *J. Cannabis Therapeutics* 2000, accepted for publication.

Mechoulam R, Gaoni Y. Recent advances in the chemistry of hashish. *Fortschr. Chem. Organ. Natur..* 1967; 25:175-213.

Mechoulam R, Ben-Zvi Z, Shani A, Zemler H, Levy S. Cannabinoids and Cannabis activity. In: *Cannabis and its Derivatives*. Paton WDM, Crown J, eds. London: Oxford University Press, 1972:1-13.

Mediavilla V, Steinemann S. Essential oil of *Cannabis sativa* L. strains. *J. International Hemp Assoc.* 1997; 4(2):82-84.

Meschler JP, Howlett AC. Thujone exhibits low affinity for cannabinoid receptors but fails to evoke cannabimimetic responses. *Pharm. Biochem. Behav.* 1999; 62:473-480.

Musonda CA, Chipman JK. Quercetin inhibits hydrogen peroxide-induced NF-κB DNA binding activity and DNA damage in HepG2 cells. *Carcinogenesis* 1998; 19:1583-1589.

Musty RE, Karniol IG, Shirakawa I, Takahshi N, Knobel E. Interactions of Δ^9-THC and cannabinol in man. In *The Pharmacology of Marihuana,* MC Braude and S. Szara, eds. Raven Press, NY. Vol. 2:559-563.

Nahas GG, Suciu-Foca N, Armand JP, Hsu J, Morishima A. Inhibition of cellular mediated immunity in marijuana smokers. *Science* 1974; 183:419-420.

Nahas G, Latour C. The human toxicity of marijuana. *Medical Journal Australia* 1992; 156:495-497.

Nasel C, Nasel B, Samec P, Schindler E, Buchbauer G. Functional imaging of effects of fragrances on the human brain after prolonged inhalation. *Chemical Senses* 1994; 19:359-364.

Ohlsson A, Lindgren JE, Wahlen A, Agurell S, Hollister LE, Gillespie HK. Plasma Δ9-tetrahydrocannabinol concentrations and clinical effects after oral and intravenous administration and smoking. *Clinical Pharm. Therapeutics* 1980; 28:409-416.

O'Neil JD, Dalton WS, Forney RB. The effect of cannabichromene on mean blood pressure, heart rate, and respiration rate responses to tetrahydrocannabinol in the anesthetized rat. *Toxicology Applied Pharmacology* 1979; 49:265-270.

Pate D. *Anandamide structure-activity relationships and mechanisms of action on intraocular pressure in the normotensive rabbit model*. PhD thesis, 1999, University of Kuopio, Finland, 99 pp.

Perez-Reyes M, Wall ME. The metabolism of delta-9-tetrahydrocannabinol and related cannabinoids in man. *J. Clin. Pharmacol..* 1981; 21:178S-189S.

Petitet F, Jeantaud B, Imperato A, Dubroeucq MC. Complex pharmacology of natural cannabinoids: evidence for partial agonist activity of Δ^9-tetrahydrocannabinol and antagonist activity of cannabidiol on rat brain cannabinoid receptors. *Life Sciences.* 1998; 63:PL1-6.

Rachelfsky GS, Opedz G. Normal lymphocyte function in the presence of delta-9-THC. *Clin. Pharm. Therapeutics* 1977; 21:44-46.

Rodríguez de Fonseca F, Rubio P, Menzaghi F, Merlo-Pich E, Rivier J, Koob GF, Navarro M. Corticotropin-releasing factor (CRF) antagonist (D-Phe^{12}, Nle^{21}, C$^{\alpha}$MeLeu^{37}]CRF attenuates the acute

actions of the highly potent cannabinoid receptor agonist HU-210 on defensive-withdrawal behavior in rats. *J. Pharmac. Exp. Therap.* 1996; 276:56-64.

Russo EB. *Handbook of Psychotropic Herbs.* Haworth Press, New York, 2000, 329 pp.

Salgueiro JB, Ardenghi P, Dias M, Ferreira MBC, Izquierdo I, Medina JH. Anxiolytic natural and synthetic flavonoid ligands of the central benzodiazepine receptor have no effect on memory tasks in rats. *Pharmacol. Biochem. Behav*. 1997; 58:887-891.

Sauer MA, Rifka SM, Hawks RL, Cutler GB, Loriaux DL. Marijuana: interaction with the estrogen receptor. *J. Pharmacol. Exp. Ther.* 1983; 224:404-407.

Showalter VM, Compton DR, Martin BR, Abood ME. Evaluation of binding in a transfected cell line expressing a peripheral cannabinoid receptor (CB2): identification of cannabinoid receptor subtype selective ligands. *J. Pharm. Exp. Therap.* 1996; 278:989-999.

Sparacino CM, Hyldburg PA, Hughes TJ. Chemical and biological analysis of marijuana smoke condensate. *NIDA Research Monograph* 1990; 99:121-140.

Tashkin DP, Reiss S, Shapiro BJ, Calvarese B, Olsen JL, Lodge JW. Bronchial effects of aerosolized Δ9-tetrahydrocannabinol in healthy and asthmatic subjects. *Amer Rev Respiratory Dis* 1977; 115:57-65.

Thompson GR, Rosenkrantz H, Schaeppi UH, Braude MC. Comparison of acute oral toxicity of cannabinoids in rats, dogs and monkeys. *Toxicology & Applied Pharmacology* 1973; 25:363-373.

Turner CE, Elsohly MA, Boeren EG. Constituents of *Cannabis sativa* L. XVII. A review of the natural constituents. *J. Natural Prod.* 1980; 43:169-304.

White SC, Brin SC, Janicki BW. Mitogen-induced blastogenic responses of lymphocytes from marijuana smokers. *Science* 1975; 188:71-72.

Zuardi AW, Shirakawa I, Finkelfarb E, Karniol IG. Action of cannabidiol on the anxiety and other effects produced by Δ^9-THC in normal subjects. *Psychopharmacology.* 1982; 76:245-250.

Zuardi AW, Morais SL, Guimarães FS, Mechoulam R. Antipsychotic effect of cannabidiol. *J Clin. Psychiatry.* 1995; 56:485-486.