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

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**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 (Δ⁹-THC). It is formulated in a capsule, designed for oral administration. Because Δ⁹-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 C21 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). ∆9-THC has the lowest Ki value, measured at 41 nM for the CB1 receptor (Showalter et al. 1996), so ∆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 ∆8-THC, which is nearly identical to ∆9-THC, except for a shift of one double bond. This shift changes the Ki of ∆8-THC to 126 nM (Showalter et al. 1996). The decrease in ∆9-THC binding ability correlates with behavioral studies in rats, which show ∆8-THC is two or three times less potent than ∆9-THC. Tetrahydrocannabivarin (THCV) is similar to ∆9-THC, except for a shortened side chain. THCV appears in indica and afghanica varieties of Cannabis. THCV is weaker than ∆8-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 ∆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 immunosuppressive 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 (Marchac et al., 1998), so terpenoids undo the effects of cannabinoids, which cause an increase of CRF (Rodriguez 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 B1 is a promutagen produced by Aspergillus flavus and Aspergillus parasiticus, two fungal contaminants of moldy marijuana (reviewed by McPartland & Pruitt 1997). After aflatoxin B1 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.

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