Cannabis and Cannabis Extracts: Greater Than the Sum of Their Parts?

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SUMMARY. A central tenet underlying the use of botanical remedies is that herbs contain many active ingredients. Primary active ingredients may be enhanced by secondary compounds, which act in beneficial synergy. Other herbal constituents may mitigate the side effects of dominant active ingredients. We reviewed the literature concerning medical cannabis and its primary active ingredient, Δ^9-tetrahydrocannabinol (THC). Good evidence shows that secondary compounds in cannabis may enhance the beneficial effects of THC. Other cannabinoid and non-cannabinoid compounds in herbal cannabis or its extracts may reduce THC-induced anxiety, cholinergic deficits, and immunosuppression. Cannabis terpenoids and flavonoids may also increase cerebral blood flow, enhance cortical activity, kill respiratory pathogens, and provide anti-inflammatory activity. *[Article copies available for a fee from The Haworth Document Delivery Service: 1-800-342-9678. E-mail address: <getinfo@haworthpressinc.com> Website: <http://www.HaworthPress.com>*

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KEYWORDS. Cannabis, marijuana, THC, cannabinoids, phytocannabinoids, cannabidiol, cannabichromene, cannabibigerol, tetrahydrocannabivarin, terpenoids, essential oils, flavonoids, herbal medicine, medicinal plants, herbal synergy

INTRODUCTION

Cannabis is an herb; it contains hundreds of pharmaceutical compounds (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, cannabis has been characterized as a "synergistic shotgun," in contrast to Marinol® (Δ^9-tetrahydrocannabinol, THC), a synthetic, single-ingredient "silver bullet" (McPartland and Pruitt 1999).

Mechoulam et al. (1972) suggested that other compounds present in herbal cannabis might influence THC activity. Carlini et al. (1974) determined that cannabis extracts produced effects "two or four times greater than that expected from their THC content." Similarly, Fairbairn and Pickens (1981) detected the presence of unidentified "powerful synergists" in cannabis extracts causing 330% greater activity in mice than THC alone.

Other compounds in herbal cannabis may ameliorate the side effects of THC. Whole cannabis causes fewer psychological side effects than synthetic THC, seen as symptoms of dysphoria, depersonalization, anxiety, panic reactions, and paranoia (Grinspoon and Bakalar 1997). This difference in side effect profiles may also be due, in part, to differences in administration: THC taken by mouth undergoes "first pass metabolism" in the small intestine and liver, to 11-hydroxy THC; the metabolite is more psychoactive than THC itself (Browne and Weissman 1981). Inhaled THC undergoes little first-pass metabolism, so less 11-hydroxy THC is formed. Thus, "smoking cannabis is a satisfactory expedient in combating fatigue, headache and exhaustion, whereas the oral ingestion of cannabis results chiefly in a narcotic effect which may cause serious alarm" (Walton 1938, p. 49).

Respiratory side effects from inhaling cannabis smoke may be ameliorated by both cannabinoid and non-cannabinoid components in cannabis. For instance, throat irritation may be diminished by anti-inflammatory agents, mutagens in the smoke may be mitigated by antimutagens, and bacterial contaminants in cannabis may be annulled by antibiotic compounds (McPartland and Pruitt 1997). The pharmaceutically active compounds in cannabis that enhance beneficial THC activity and reduce side effects are relatively unknown. The pur-

pose of this paper is to review the biochemistry and physiological effects of those other compounds.

MATERIALS AND METHODS

MEDLINE (1966-2000) was searched using MeSH keywords: cannabinoids, marijuana, tetrahydrocannabinol. AGRICOLA (1990-1999) was searched using the keywords cannabis, hemp, and marijuana. Phytochemical and ethnobotanical databases were searched via the Agricultural Research Service webpage <http://www.ars-grin.gov/~ngrlsb/>. All reports were scanned for supporting bibliographic citations; antecedent sources were retrieved to the fullest possible extent. Data validity was assessed by source (peer-reviewed article vs. popular press), identification methodology (analytical chemistry vs. clinical history) and the frequency of independent observations.

RESULTS AND DISCUSSION

Turner et al. (1980) listed over 420 compounds in cannabis. Sparacino et al. (1990) listed 200 additional compounds in cannabis smoke. We will highlight six cannabinoids beyond THC, a dozen-odd terpenoids, three flavonoids, and one phytosterol. Other non-cannabinoids with proven pharmacological activity include poorly characterized glycoproteins, alkaloids, and compounds that remain completely unidentified (Gill et al. 1970).

CANNABINOIDS

Mechoulam and Gaoni (1967) defined "cannabinoids" as a group of C_{21} terpenophenolic compounds uniquely produced by cannabis. The subsequent development of synthetic cannabinoids (e.g., HU-210) has blurred this definition, as has the discovery of endogenous cannabinoids (e.g., anandamide), defined as "endocannabinoids" by DiMarzo and Fontana (1995). Thus, Pate (1999) proposed 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).

Cannabidiol (CBD) is the next-best studied phytocannabinoid after THC (Figure 1). The investigation of CBD by marijuana researchers is rather paradoxical, considering its concentrations are notably lower in drug varieties of cannabis than in fiber cultivars (Turner et al. 1980).

CBD possesses sedative properties (Carlini and Cunha, 1981), and a clinical trial showed that it reduces the anxiety and other unpleasant psychological side effects provoked by pure THC (Zuardi et al. 1982). CBD modulates the pharmacokinetics of THC by three mechanisms: (1) it has a slight affinity for cannabinoid receptors (Ki at CB1 = 4350 nM, compared to THC = 41 nM, Showalter et al. 1996), and it signals receptors as an antagonist or reverse agonist (Petitet et al. 1998), (2) CBD may modulate signal transduction by perturbing the fluidity of neuronal membranes, or by remodeling G-proteins that carry intracellular signals downstream from cannabinoid receptors, and (3) 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 unmetabolized THC (Browne and Weissman 1981), and four times more immunosuppressive (Klein et al. 1987).

CBD provides antipsychotic benefits (Zuardi et al. 1995). It increases dopamine activity, serves as a serotonin uptake inhibitor, and enhances norepinephrine activity (Banerjee et al. 1975; Poddar and Dewey 1980). CBD protects neurons from glutamate toxicity and serves as an antioxidant, more potently than ascorbate and α-tocopherol (Hampson et al. 1998). Auspiciously, CBD does *not* decrease acetylcholine (ACh) activity in the brain (Domino 1976; Cheney et al. 1981). THC, in contrast, reduces hippocampal ACh release in rats (Carta et al. 1998), and this correlates with loss of short-term memory consolidation. In the hippocampus THC also inhibits *N*-methyl-D-aspartate (NMDA) receptor activity (Misner and Sullivan 1999; Shen and Thayer 1999), and NMDA synaptic transmission is crucial for memory consolidation (Shimizu et al. 2000). CBD, unlike THC, does not dampen the firing of hippocampal cells (Heyser et al. 1993) and does not disrupt learning (Brodkin and Moerschbaecher 1997).

Consroe (1998) presented an excellent review of CBD in neurological disorders. In some studies, it ameliorates symptoms of Huntington's disease, such as dystonia and dyskinesia. CBD mitigates other dystonic conditions, such as torticollis, in rat studies and uncontrolled human studies. CBD functions as an anticonvulsant in rats, on a par with phenytoin (Dilantin®, a standard antiepileptic drug).

CBD demonstrated a synergistic benefit in the reduction of intestinal motility in mice produced by THC (Anderson, Jackson, and Chesher 1974). This may be an important component of observed benefits of cannabis in inflammatory bowel diseases.

The CBD in cannabis smoke may explain why inhaling it causes less airway irritation and inflammation than inhalation of pure THC (Tashkin et al. 1977). CBD imparts analgesia (more potently than THC), it inhibits erythema (much more than THC), it blocks cyclooxygenase (COX) activity with a greater max-

imum inhibition than THC, and it blocks lipoxygenase (the enzyme that produces asthma-provoking leukotrienes), again more effectively than THC (Evans 1991). Mice with inflammatory collagen-induced arthritis (a mouse model for rheumatoid arthritis) were given oral CBD (5 mg/kg per day) and showed clinical improvement, and the treatment effectively blocked progression of the arthritis (Malfait et al. 2000).

CBD reportedly has little or no effect on the immune system (reviewed by Klein et al. 1998), although the mouse arthritis study by Malfait et al. (2000) showed CBD decreases the production of tumor necrosis factor (TNF) and Interferon-gamma (IFN-γ), which are two immunomodulatory cytokines described later. CBD actually kills bacteria and fungi, with greater potency than THC (Klingeren and Ham 1976; ElSohly et al. 1982; McPartland 1984). Thus, cannabis may have less microbial contamination than other herbs, an important consideration for immunocompromised individuals (McPartland and Pruitt 1997).

Cannabinol (CBN) is the degradation product of THC (Turner et al. 1980), and is found most often in aged cannabis products (Figure 1). CBN potentiates the effects of THC in man (Musty et al. 1976), yet it antagonizes the effects of THC in mice (Formukong et al. 1988). Studies reporting CBN's effects upon norepinephrine and dopamine also conflict–CBN may have negligible effects on these biogenic amines (Banerjee et al. 1975), enhance their release (Poddar and Dewey 1980), or decrease their release (Dalterio et al. 1985). CBN increases plasma concentrations of follicle-stimulating hormone, and enhances the production of testicular testosterone (Dalterio et al. 1985). CBN shares some characteristics with CBD; for example, it has anti-convulsant activity (Turner et al. 1980) and anti-inflammatory activity (Evans et al. 1991).

CBN has affinity for CB_1 receptors (Ki at CB1 = 308 nM) and signals as an agonist (Showalter et al. 1996). Further down the signal transduction cascade, it stimulates the binding of GTP-γ-S (Petitet et al. 1998), but with half the efficacy of THC; when CBN is added to THC, the effects are not significantly additive. CBN has a three-fold greater affinity for CB_2 receptors (Ki = 96 nM) (Showalter et al. 1996), thus it may affect cells of the immune system more than the central nervous system (Klein et al. 1998). CBN modulates thymocytes (Herring and Kaminski 1999) by attenuating the activity of the c-AMP response element-binding protein (CREB), nuclear factor κB (NF-κB), and interleukin-2 (IL-2). IL-2 is regulated by activator protein-1 (AP-1) transcription factor, a complex of c-Fos and c-Jun proteins (Foletta et al. 1998); CBN inhibits the expression of these proteins in splenocytes, via decreased activation of ERK MAP kinases (Faubert and Kaminski 2000).

Cannabichromene (CBC) is the fourth major cannabinoid, found predominantly in tropical *Cannabis* spp. strains (Figure 1). Until the mid-1970s, CBC was frequently misidentified as CBD, because CBC and CBD have nearly the

same retention times in gas chromatography. Like CBD, CBC decreases inflammation (Wirth et al. 1980) and provides analgesic effects (Davis and Hatoum 1983). CBC inhibits prostaglandin synthesis *in vitro*, but less potently than CBD or THC (Burstein et al. 1973). CBC exhibits strong antibacterial activity and mild antifungal activity, superior to THC and CBD in most instances (ElSohly et al. 1982). Unlike CBD, CBC has no effect on cytochrome P450 enzymes (Kapeghian et al. 1983), nor does it function as an anticonvulsant in rats (Davis and Hatoum 1983).

The molecular affinity of CBC for cannabinoid receptors has not been measured. In mice, CBC causes hypothermia, sedation, and synergizes the depressant effects of hexobarbital (Hatoum et al. 1981). CBC also sedates dogs and decreases muscular coordination in rats, but causes no cannabimimetic activity in monkeys and people (Turner et al. 1980). In rats, the co-administration of CBC with THC potentiates THC changes in heart rate, but does not potentiate THC's hypotensive effects (O'Neil et al. 1979). Co-administration of CBC lowers the LD_{50} dose of THC in mice (Hatoum et al. 1981).

Cannabigerol (CBG) is the biosynthetic precursor of CBC, CBD, and THC, and is present only in minor amounts (Figure 1). CBG has been called "inactive" when compared to THC, but CBG has slight affinity for CB_1 receptors, approximately the same as CBD (Devane et al. 1988). In rat brains, CBG inhibits the uptake of serotonin and norepinephrine, less effectively than CBD and THC, but CBG inhibits GABA uptake more effectively than CBD and THC (Banerjee et al. 1975). CBG acts as an analgesic (more potently than THC), it inhibits erythema (much more than THC), and it blocks lipoxygenase, again more effectively than THC (reviewed by Evans 1991).

CBG has antibacterial properties (Mechoulam and Gaoni 1965). Its activity against gram-positive bacteria, mycobacteria, and fungi is superior to that of THC, CBD, and CBC (ElSohly et al. 1982). CBG inhibits the growth of human oral epitheloid carcinoma cells (Baek et al. 1998).

Delta-8-THC (Δ^8-THC) is an isomer of delta-9-THC; it differs only by the location of the double bond in the cyclohexal "C" ring. The Ki of Δ^8-THC is 126 nM (Compton et al. 1993), and this loosely correlates with human studies, which show Δ^8-THC is less psychoactive than Δ^9-THC (Hollister 1974). The chemical stability of Δ^8-THC and its relative ease of synthesis compared to Δ^9-THC, have made Δ^8-THC the template for the development of two important synthetic derivatives, the extremely potent psychoactive CB_1 agonist, HU-210 (Mechoulam and Ben-Shabat 1999), and the non-psychoactive antiemetic and neuroprotectant, HU-211 (dexanabinol) (Achiron et al. 2000; Biegon and Joseph 1995; Gallily et al. 1997). Δ^8-THC was employed clinically in an important study (Abrahamov and Mechoulam 1995) in which 8 children with hematological malignancies were treated with the drug over the course of 8 months at a dose of 18 mg/m^2 to treat chemotherapy-associated

nausea and vomiting. Interestingly, not only was this agent uniformly effective as an antiemetic, but it was also free of psychoactive effects in this age range (2-13 years).

Tetrahydrocannabivarin (THCV) is a propyl analogue of Δ^9-THC, primarily appearing in *indica* and *afghanica* varieties of cannabis, such as hashish from Nepal (Merkus 1971), dagga from South Africa (Boucher et al. 1977), and in plants cultivated from seeds from Zambia (Pitts et al. 1992) (Figure 1). THCV is only 20-25% as psychoactive as Δ^9-THC (Hollister 1974). It has a quicker onset of action than Δ^9-THC (Gill et al. 1970), and is of briefer duration (Clarke 1998). THCV may be clinically effective in migraine treatment (Personal communication, HortaPharm, November 2000). Kubena and Barry (1972) suggested THCV synergizes the effects of THC, but did not hypothesize a mechanism. As a legal fine point, this analogue is not controlled in the Netherlands, and is not specified in the USA as a Schedule I drug, but would likely be considered illegal under the Controlled Substance Analogue Enforcement Act of 1986 (Public Law 99-570). THCV is of interest from a medical-legal standpoint in that is has been suggested as a biochemical marker of illicit cannabis use, since it is not a metabolite of Marinol® (synthetic THC) (ElSohly et al. 1999).

TERPENOIDS

The unique smell of cannabis does not arise from cannabinoids, but from over 100 terpenoid compounds (Turner et al. 1980). Terpenoids derive from repeating units of isoprene (C_5H_8), such as monoterpenoids (with C_{10} skeletons), sesquiterpenoids (C_{15}), diterpenoids (C_{20}), and triterpenoids (C_{30}). The final structure of terpenoids ranges from simple linear chains to complex polycyclic molecules, and they may include alcohol, ether, aldehyde, ketone, or ester functional groups. These compounds are easily extracted from plant material by steam distillation or vaporization. This distillate is called the *essential oil* or *volatile oil* of the plant. A range of researchers cite different yields of essential oil from different types of cannabis: Martin et al. (1961) cited yields of 0.05-0.11% essential oil from fresh, green leaves and flowers of mixed male and female plants, from feral hemp growing in Canada. Nigram et al. (1965) yielded 0.1% essential oil from fresh, whole, male plants from Kashmir. Malingré et al. (1973) yielded 0.12% essential oil from fresh leaves of "strain X" obtained from birdseed in the Netherlands. Ross and ElSohly (1996) yielded 0.29% essential oil from fresh marijuana buds, reputed to be the Afghani variety "Skunk #1." Drying the plant material led to a loss of water content and net weight, concentrating the essential oil to 0.80% in buds that had been dried at room temperature for one week (Ross and ElSohly 1966).

Field-cultivated cannabis yields about 1.3 liter of essential oil per metric ton of freshly harvested plant material (Mediavilla and Steinemann 1997). Preventing pollination increases the yield of essential oil–18 l/ha in sinsemilla crops, versus 8 l/ha in pollinated crops (Meier and Mediavilla 1998). The composition of terpenoids varies between strains of cannabis (Mediavilla and Steinemann 1997), and varies between harvest dates (Meier and Mediavilla 1998).

Many terpenoids vaporize near the same temperature as THC, which boils at 157°C (see Figures 1-2). Terpenoids are lipophilic and permeate lipid membranes. Many cross the blood-brain barrier (BBB) after inhalation (Buchbauer et al. 1993; Nasel et al. 1994).

Meschler and Howlett (1999) discussed several mechanisms by which terpenoids modulate THC activity. For instance, terpenoids may bind to cannabinoid receptors. Thujone, from *Artemisia absinthium*, has a weak affinity for CB_1 receptors (Ki at CB_1 = 130,000 nM). Terpenoids might 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 also act on other receptors and neurotransmitters. Some terpenoids act as serotonin uptake inhibitors (as does Prozac®), enhance norepinephrine activity (as do tricyclic antidepressants), increase dopamine activity (as do monoamine oxidase inhibitors and bupropion), and augment GABA (as do baclofen and the benzodiazepines). Recently, strong serotonin activity at the $5\text{-}HT_{1A}$ and $5\text{-}HT_{2a}$ receptors has been demonstrated (Russo et al. 2000; Russo 2001) that may support synergistic contributions of terpenoids on cannabis-mediated pain and mood effects. Further studies are in progress to identify the most active terpenoid components responsible, and whether synergism of the components is demonstrable.

The essential oil of cannabis is traditionally employed as an anti-inflammatory in the respiratory and digestive tracts without known contraindications at physiological dosages (Franchomme and Pénoël 1990). The essential oil of black pepper, *Piper nigrum*, has a composition of terpenes that is qualitatively quite similar to that of cannabis (Lawless 1995). It has often been claimed anecdotally, that smoked cannabis may substitute for nicotine in attempts at smoking cessation. Aside from cannabinoid influences, current evidence supports this contention based on terpene content and its activity. A recent study has shown that inhalation of black pepper essential oil vapor significantly reduced withdrawal symptoms and anxiety in tobacco smokers (Rose and Behm 1994). Interestingly, the authors posited not a central biochemical mechanism,

FIGURE 1. Phytocannabinoids

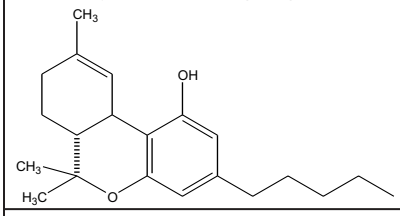
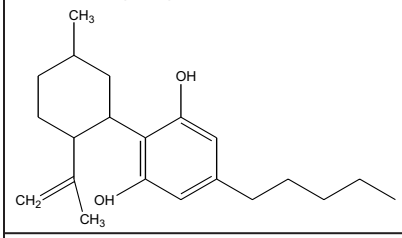
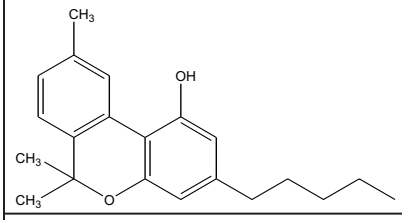
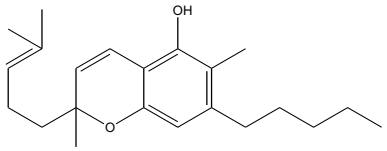
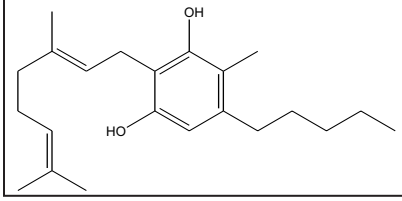
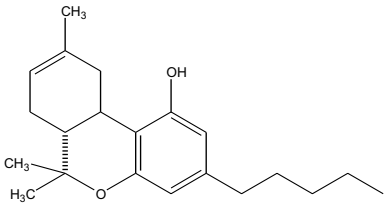
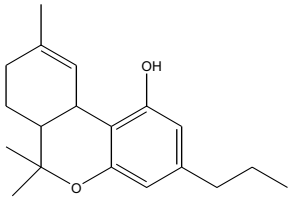
Structure*	**Concentration†** (% dry weight)	**Boiling Point °C§**	**Properties**
Δ-9-tetrahydrocannabinol (THC) 	0.1-25%	157	Euphoriant Analgesic Antiinflammatory Antioxidant Antiemetic
cannabidiol (CBD) 	0.1-2.89%	160-180	Anxiolytic Analgesic Antipsychotic Antiinflammatory Antioxidant Antispasmodic
cannabinol (CBN) 	0.0-1.6%	185	Oxidation breakdown product Sedative Antibiotic
cannabichromene (CBC) 	0.0-0.65%	220	Antiinflammatory Antibiotic Antifungal
cannabigerol (CBG) 	0.03-1.15%	MP 52	Antiinflammatory Antibiotic Antifungal

FIGURE 1 (continued)

Structure*	**Concentration†** (% dry weight)	**Boiling Point °C§**	**Properties**
Δ-8-tetrahydrocannabinol (Δ-8-THC) 	0.0-0.1%	175-178	Resembles Δ-9-THC Less psychoactive More stable Antiemetic
tetrahydrocannabivarin (THCV) 	0.0-1.36%	< 220	Analgesic Euphoriant

*Structures of constituents obtained from Bissett and Wichtl 1994; British Medical Association 1997; Buckingham 1992; Iversen 2000; Tisserand and Balacs 1995; Turner et al. 1980.

†Concentrations of constituents (v/w or w/w) were calculated from various sources. Cannabinoid concentrations (presented as a range, including cannabinoids and cannabinoidic acids) were primarily obtained from Small, 1979; Veszki et al., 1980; Fournier et al., 1987; and Pitts et al., 1992. Terpenoid data (presented as maximum values) were calculated from Ross and El Sohly, 1996; and Mediavilla and Steinemann, 1997. Flavonoid data came from Paris et al., 1976; and Barrett et al., 1986.

§Boiling/melting points (MP) recorded at atmospheric pressure (760 mmHg) unless otherise noted; values obtained from various sources, primarily Buckingham, 1992; Guenther, 1948; Parry, 1918; and Mechoulam (personal communication, April 2001).

but rather a peripheral one assuming physical cues of bronchial sensation as operative in the origin of the benefit. The true scope of the essential oil benefits in this context may be quite a bit broader.

Pate (1994), McPartland (1997), and McPartland, Clarke and Watson (2000), have reviewed the pesticidal properties of cannabis attributable to its terpenoid content. The essential oil of *Eugenia dysenterica* was recently demonstrated to have significant inhibitory effects on *Cryptococcus neoformans* strains isolated from HIV patients with cryptococcal meningitis (Costa et al. 2000). Key components of that oil were common to cannabis: β-caryophyllene, α-humulene, α-terpineol, and limonene.

Additionally, monoterpenes such as those abundant in cannabis resin have been suggested to: (1) inhibit cholesterol synthesis, (2) promote hepatic en-

FIGURE 2. Terpenoid essential oil components of cannabis.

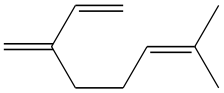
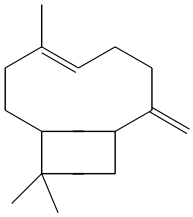
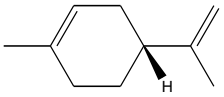
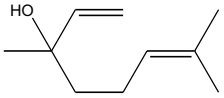
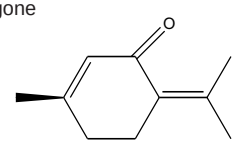
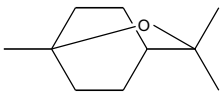
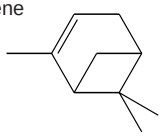
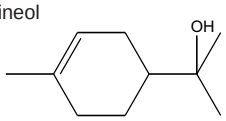
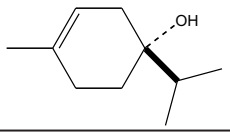
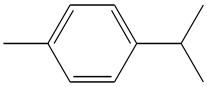
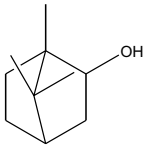
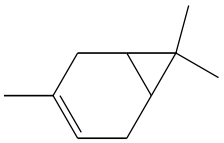
Cannabis Constituent Structure*	**Concentration†**	**Boiling Point °C§**	**Properties**
β-myrcene 	0.47%	166-168	Analgesic Antiinflammatory Antibiotic Antimutagenic
β-caryophyllene 	0.05%	119	Antiinflammatory Cytoprotective (gastric mucosa) Antimalarial
d-limonene 	0.14%	177	Cannabinoid agonist? Immune potentiator Antidepressant Antimutagenic
linalool 	0.002%	198	Sedative Antidepressant Anxiolytic Immune potentiator
pulegone 	0.001%	224	Memory booster? AChE inhibitor Sedative Antipyretic
1,8-cineole (eucalyptol) 	> 0.001%	176	AChE inhibitor Increases cerebral blood flow Stimulant Antibiotic Antiviral Antiinflammatory Antinociceptive
α-pinene 	0.04%	156	Antiinflammatory Bronchodilator Stimulant Antibiotic Antineoplastic AChE inhibitor

FIGURE 2 (continued)

Cannabis Constituent Structure*	Concentration†	Boiling Point °C§	Properties
α-terpineol 	0.02%	217-218	Sedative Antibiotic AChE inhibitor Antioxidant Antimalarial
terpineol-4-ol 	0.0004%	209	AChE inhibitor Antibiotic
p-cymene 	0.0004%	177	Antibiotic Anticandidal AChE inhibitor
borneol 	0.008%	210	Antibiotic
Δ-3-carene 	0.004%	168	Antiinflammatory

zyme activity to detoxify carcinogens, (3) stimulate apoptosis in cells with damaged DNA, and (4) inhibit protein isoprenylation implicated in malignant deterioration (Jones 1999).

Myrcene, specifically β-myrcene, a noncyclic monoterpene, is the most abundant terpenoid produced by cannabis (Ross and ElSohly 1996; Mediavilla and Steinemann 1997). It also occurs in high concentrations in hops (*Humulus lupulus*) and lemongrass (*Cymbopogon citratus*). Myrcene is a potent analgesic, acting at central sites that are antagonized by naloxone (Rao et al. 1990). Myrcene also works via a peripheral mechanism shared by CBD, CBG, and CBC–by blocking the inflammatory activity of prostaglandin E_2 (Lorenzetti et al. 1991). This activity is expressed by other terpenoids in cannabis smoke,

such as carvacrol, which is more potent than THC or CBG (Burstein et al. 1975). The activity of many terpenoids may be cumulative: unfractionated cannabis essential oil exhibits greater antiinflammatory activity than its individual constituents, suggesting synergy (Evans et al. 1987).

Myrcene also synergizes the antibiotic potency of other essential oil components, against *Staphylococcus aureus, Bacillus subtilis, Pseudomonas aeruginosa*, and a specific strain of *Escherichia coli* (Onawunmi et al. 1984). Myrcene inhibits 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 and Pruitt 1997). After aflatoxin B_1 is metabolized by P450 2B1, it becomes extremely hepatocarcinogenic. Myrcene blocks this metabolism, as do other terpenoids in cannabis, including limonene, α-pinene, α-terpinene, and citronellal (De Oliveira et al. 1997).

β-Caryophyllene is the most common sesquiterpenoid in cannabis (Mediavilla and Steinemann 1997). It is the main component of copaiba balsam, from *Copaifera* spp. (Lawless 1995), which is a popular oral and topical anti-inflammatory agent in Brazil (Basile et al. 1988). The latter authors were able to demonstrate anti-inflammatory effects of the oleoresin in rats comparable to phenylbutazone, in reduction of granuloma formation. A decreased vascular permeability to injected histamine was also observed.

A gastric cytoprotective effect of β-caryophyllene was demonstrated in rats against challenge with absolute ethanol and hydrochloric acid (Tambe et al. 1996). This benefit was noted without influence on gastric acid or pepsin secretion. The authors suggested this agent as clinically safe, and potentially useful. Campbell et al. (1997) have demonstrated a moderate antimalarial effect against two strains of *Plasmodium falciparum* by an essential oil rich in β-caryophyllene and α-terpineol.

Limonene is a monocyclic monoterpenoid and a major constituent of citrus rinds (Tisserand and Balacs 1995). It finds extensive use as a solvent and in the perfumery and flavor industries. Because of limonene's widespread occurrence and application, its biological activity is well known. Limonene is highly absorbed by inhalation and quickly appears in the bloodstream (Falk-Flilipsson et al. 1993). According to Ross and ElSohly (1996), limonene is the second most common terpenoid in an unidentified cultivar of cannabis.

Limonene may have a low-affinity interaction with cannabinoid receptors (Meschler and Howlett 1999). Studies of long-term inhalation of lemon fragrance (predominately limonene) have demonstrated inhibition of thymic involution in stress-induced immunosuppression in mice (Ortiz de Urbina et al. 1989).

Limonene was the primary component of the essential oil mixture employed by Komori et al. (1995), in their clinical study of immune function and depressive states in humans. The key result of this experiment was the ability to markedly reduce the dosage of, or even eliminate the need for, synthetic antidepressant drugs.

As mentioned in the myrcene section, limonene protects against aflatoxin B_1-induced cancer by inhibiting the hepatic metabolism of the promutagen to its active form. Limonene also blocks this process at two earlier steps by inhibiting the growth of *Aspergillus* fungi and inhibiting their production of aflatoxins (Greene-McDowelle et al. 1999). Limonene and other terpenoids suppress the growth of many species of fungi and bacteria, demonstrated in hundreds of published studies (reviewed by McPartland 1997).

Limonene blocks the carcinogenesis induced by benz[α]anthracene (Crowell 1999), a component of the "tar" generated by the combustion of herbal cannabis. Thus, this terpenoid may reduce the harm caused by inhaling cannabis smoke. Limonene blocks carcinogenesis by multiple mechanisms. It detoxifies carcinogens by inducing Phase II carcinogen-metabolizing enzymes (Crowell 1999). It selectively inhibits the isoprenylation of Ras proteins, thus blocking the action of mutant *ras* oncogenes (Hardcastle et al. 1999). It induces redifferentiation of cancer cells (by enhancing expression of transforming growth factor β1 and growth factor II receptors), and it induces apoptosis of cancer cells (Crowell 1999). Orally administered limonene is currently undergoing Phase II clinical trials in the treatment of breast cancer (Vigushin et al. 1998); it also protects against lung, liver, colon, pancreas, and skin cancers (Vigushin et al. 1998; Crowell 1999; Setzer et al. 1999).

Linalool is a noncyclic monoterpenoid, commonly extracted from lavender (*Lavandula* spp.), rose (*Rosa* spp.), and neroli oil (from *Citrus aurantium*). It usually constitutes 5% or less of cannabis essential oil (Ross and ElSohly 1996). Linalool nevertheless exhibits strong biological activity. Buchbauer et al. (1993) assayed the sedative effects of over 40 terpenoids upon *inhalation* by mice; linalool was the most powerful, reducing mouse motility 73% after 1 hour of inhalation. The study demonstrated that other terpenoids found in cannabis, such as citronellol and α-terpineol, are also deeply sedating upon inhalation, even in low concentrations. Furthermore, combinations of these terpenoids (e.g., neroli oil) are synergistic in their sedative effects. These terpenoids may mitigate the anxiety provoked by pure THC. Inhalation of such terpenoids also provides antidepressant effects (Komori et al. 1995).

Reducing anxiety and depression will improve immune function via the neuroendocrine system, by damping down the hypothalamic-pituitary-adrenal (HPA) axis. Hence, inhalation of terpenoids reduces the secretion of HPA stress hormones (e.g., corticosterone), and normalizes CD4-CD8 ratios (Komori et al. 1995). By a similar mechanism, terpenoids in *Ginkgo biloba* inhibit

corticosterone secretion by attenuating corticotropin-releasing factor (CRF) expression (Marcihac et al. 1998). CRF not only induces corticosterone secretion via the HPA axis, it is also associated with anxiety. Rodríguez de Fonseca et al. (1996) showed that the psychoactive cannabinoid HU-210 caused a release of CRF. Thus, the terpenoids act synergistically with non-psychoactive CBD, which may decrease CRF by inhibiting IFN-γ (Malfait et al. 2000).

Pulegone, a monocyclic monoterpenoid, is a minor constituent of cannabis (Turner et al. 1980). Higher concentrations of pulegone are found in rosemary (*Rosmarinus officinalis*), "the herb of remembrance." Pulegone may alleviate a major side effect of THC–loss of short-term memory consolidation. THC causes acetylcholine (ACh) deficits in the hippocampus. Hippocampal ACh deficits are also seen in people with Alzheimer's disease. Alzheimer's patients can be treated with tacrine (Cognex®), a drug that increases ACh activity by inhibiting acetylcholinesterase (AChE). Indeed, tacrine has blocked THC-induced memory loss behavior in rats. Pulegone exhibits the same activity as tacrine, that of AChE inhibition (Miyazawa et al. 1997). Other terpenoids in cannabis also provide AChE inhibition, including limonene, limonene oxide, α-terpinene, γ-terpinene, terpinen-4-ol, carvacrol, l-and d-carvone, 1,8-cineole, *p*-cymene, fenchone, and pulegone-1,2-epoxide (Perry et al. 1996; McPartland and Pruitt 1999). The beneficial effects of AChE inhibitors, however, are decreased in individuals carrying the E4 subtype of the apolipoprotein E gene, ApoE E4 (Poirier et al. 1995). Pulegone has also demonstrated significant sedative and antipyretic properties in a study in rats (Ortiz de Urbina et al. 1989).

1,8-Cineole, a bicyclic monoterpenoid, is a minor constituent of cannabis and the major aromatic found in *Eucalyptus* species. 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, much as the ginkgolides in *Ginkgo biloba* (Russo 2000). Similarly, cerebral blood flow increases after inhaling cannabis smoke, and this increase is *not* related to plasma levels of THC (Mathew and Wilson 1993).

A stimulatory effect on rat locomotion was demonstrated employing a 1,8-cineole-rich essential oil of rosemary with a terpene profile similar to that of cannabis (Kovar et al. 1987). Blood levels correlated with the degree of stimulation observed. Antinociceptive and anti-inflammatory effects of 1,8-cineole were demonstrated at high doses in rats, using carrageenan rat paw and cotton pellet-induced granuloma models (Santos and Rao 2000). An analgesic effect of an essential oil was demonstrated in another animal study, and correlated with the 1,8-cineole concentration (Aydin et al. 1999).

1,8-Cineole demonstrated antibacterial activity against *Bacillus subtilis*, and antifungal properties against *Trichophyton mentagrophytes*, *Cryptococcus neoformans*, and *Candida albicans* (Hammerschmidt et al. 1993). In subse-

quent assays, this essential oil component was cidal against *Candida albicans* and *Escherichia coli*, and bacteriostatic against *Staphylococcus aureus* (Carson and Riley 1995). In a rat study, 1,8-cineole prevented the sexual transmission of *Herpes simplex* virus type 2 (HSV-2). HSV-2 is a frequently comorbid condition with HIV, and its prevention has been suggested as one method of lowering HIV transmission risks (Gwanzura et al. 1998).

Perry et al. (2000) demonstrated that 1,8-cineole was an inhibitor of human erythrocyte acetylcholinesterase, but that an essential oil of *Salvia lavandulaefolia* containing 1,8-cineole and other terpenoids produced a synergistic inhibition of acetylcholinesterase that suggested utility in the clinical treatment of Alzheimer's disease. A similar mechanism may operate in cannabis essential oil with the same components.

α-Pinene, a bicyclic monoterpenoid, was effective in prevention of acute inflammation in a carrageenan-induced plantar edema model (Gil et al. 1989). A pharmacokinetics study of inhaled α-pinene in humans demonstrated 60% uptake, and a relative bronchodilation effect (Falk et al. 1990). After 1 hour of inhalation, α-pinene produced a 13.8% increase in mouse motility measures (Buchbauer et al. 1993). α-Pinene has inhibited acetylcholinesterase in a variety of assays (Perry et al. 1996; McPartland and Pruitt 1999), suggesting utility in the clinical treatment of Alzheimer's disease. The antibiotic properties of α-pinene, α-terpineol, and terpinen-4-ol have been demonstrated against *Staphylococcus aureus, S. epidermidis* and *Propionibacterium acnes* (Raman et al. 1995). α-Pinene and its isomer β-pinene were both cytotoxic *in vitro* against Hep-G2 (human hepatocellular carcinoma) and Sk-Mel-28 (human melanoma) tumor cell lines (Setzer et al. 1999).

α-Terpineol, terpinen-4-ol, and 4-terpineol are three closely related monoterpenoids. Inhalation of α-terpineol reduced mouse motility 45% (Buchbauer et al. 1993). Burits and Bucar (2000) demonstrated that 4-terpineol exhibits "respectable" radical scavenging and antioxidant properties. Terpinen-4-ol, α-terpineol, and α-pinene demonstrated dose-dependent antibiotic properties against *Staphylococcus aureus, S. epidermidis* and *Propionibacterium acnes* (Raman et al. 1995). Similar studies have demonstrated antimicrobial activity against a wide range of pathogenic organisms, excluding *Pseudomonas* (Carson and Riley 1995). Campbell et al. (1997) have demonstrated a moderate antimalarial effect against two strains of *Plasmodium falciparum* by an essential oil with major α-terpineol and α-caryophyllene components.

Cymene, or *p*-cymene, a monoterpenoid, is active against *Bacterioides fragilis, Candida albicans*, and *Clostridium perfringens* (Carson and Riley 1995).

Borneol, a bicyclic monoterpenoid, was tested in walnut oil as an external treatment for purulent otitis media (Liu 1990), where it proved to be 98% effective ($P < 0.001$), to a greater degree than neomycin, and without toxicity.

Δ^3-Carene, a bicyclic monoterpenoid, was effective in prevention of acute inflammation in a carrageenan-induced plantar edema model (Gil et al. 1989).

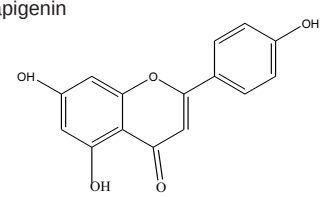
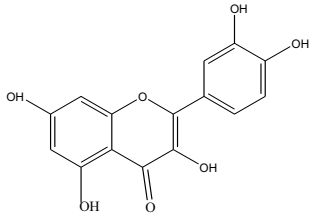
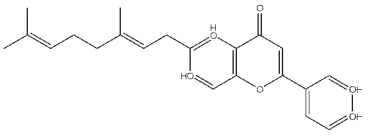
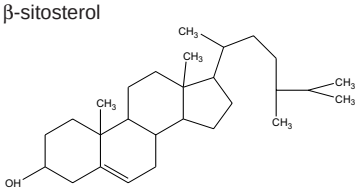
FLAVONOIDS

Flavonoids are aromatic, polycyclic phenols. Cannabis produces about 20 of these compounds, as free flavonoids and conjugated glycosides (Turner et al. 1980). Paris et al. (1976) estimated that cannabis leaves consist of 1% flavonoids. Some flavonoids are volatile, lipophilic, permeate membranes, and apparently retain pharmacological activity in cannabis smoke (Sauer et al. 1983). Flavonoids may modulate the pharmacokinetics of THC, via a mechanism shared by CBD, the inhibition of P450 3A11 and P450 3A4 enzymes. Naringenin, a flavonoid in grapefruit juice, also inhibits these enzymes, thus blocking the metabolism of cyclosporine, caffeine, benzodiazepines, and calcium antagonists (Fuhr 1998). Two related enzymes, P450 3A4 and P450 1A1, metabolize environmental toxins from procarcinogens to their activated forms. Thus, P450-suppressing compounds serve as chemoprotective agents, shielding healthy cells from the activation of benzo[α]pyrene and aflatoxin B_1 (Offord et al. 1997), which are two procarcinogens potentially found in cannabis smoke (McPartland and Pruitt 1997).

Apigenin is a flavone found in nearly all vascular plants (Figure 3). It exerts a wide range of biological effects, including many properties shared by terpenoids and cannabinoids. Apigenin is the primary anxiolytic agent found in chamomile, *Matricaria recutita*, (reviewed in Russo 2000). It selectively binds with high affinity to central benzodiazepine receptors, which are located in α- and β-subunits of $GABA_A$ receptors (Salgueiro et al. 1997); this anxiolytic activity is not associated with the unwanted side effects caused by synthetic benzodiazepines, such as muscular relaxation, amnesia, and sedation.

Apigenin inhibits the production of tumor necrosis factor-alpha (TNF-α), a cytokine primarily expressed by monocytes and macrophages (Gerritsen et al. 1995). TNF-α induces and maintains inflammation, a pathological condition in rheumatoid arthritis and multiple sclerosis. THC decreases TNF-α, probably by a nonreceptor-mediated mechanism (Burnette-Curley and Cabral 1995), although one study suggested THC might induce TNF-α (Shivers et al. 1994). Either way, apigenin provides beneficial suppression of TNF-α, whether in concert with THC or counteracting THC.

FIGURE 3. Flavonoid and phytosterol components of cannabis.

Cannabis Constituent Structure*	Concentration†	Boiling Point °C§	Properties
apigenin 	> 0.1%	178	Anxiolytic Antiinflammatory Estrogenic
quercetin 	> 0.1%	250	Antioxidant Antimutagenic Antiviral Antineoplastic
cannflavin A 	0.02%	182	COX inhibitor LO inhibitor
β-sitosterol 	?	134	Antiinflammatory 5-α-reductase inhibitor

Apigenin and other flavonoids interact with estrogen receptors, and appear to be the primary estrogenic agents in cannabis smoke (Sauer et al. 1983). Although apigenin has a high affinity for estrogen receptors (especially β-estrogen receptors), it has low estrogenic activity; apigenin actually inhibits estradiol-induced proliferation of breast cancer cells (Wang and Kurzer 1998).

Quercetin is a flavonol found in nearly all vascular plants, including cannabis (Turner et al. 1980). Quercetin is a potent antioxidant; by some measures more potent than ascorbic acid, α-tocopherol, and BHT (Gadow et al. 1997). Combinations of quercetin and other antioxidants work synergistically (Hud-

son and Mahgoub 1981). The antioxidant potential of quercetin and other flavonoids should be tested against CBD, another potent antioxidant (Hampson et al. 1998). Perhaps flavonoids can induce chemical reduction of CBD, effectively recycling CBD as an antioxidant. Flavonoids block free radical formation at several steps: by scavenging superoxide anions (in both enzymatic and non-enzymatic systems), by quenching intermediate peroxyl and alkoxyl radicals, and by chelating iron ions, which catalyze many Fenton reactions leading to free radical formation (Musonda and Chipman 1998).

Free radicals activate NF-κB, a transcription factor protein that induces the expression of oncogenes, inflammation, and apoptosis. Quercetin arrests the formation of NF-κB, by blocking the PKC-induced phosphorylation of an inhibitory subunit of NF-κB called IκB (Musonda and Chipman 1998), consequently quercetin hinders carcinogenesis and inflammatory diseases. 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 thus inhibits hepatic carcinoma (McPartland 1996). These flavonoids may synergize with CBN, which also downregulates NF-κB (Herring and Kaminski 1999), thereby counteracting the effects of THC, which may increase NF-κB activity (Daaka et al. 1997).

Cannflavin A is one of a pair of prenylated flavones apparently unique to cannabis (Barrett et al. 1986). The yield of cannflavin A is 0.02% of dry herb. This compound is a potent inhibitor of prostaglandin E_2 in human rheumatoid synovial cells, with an IC_{50} of 31 ng/ml, about 30 times more potent than aspirin in that system (Barrett et al. 1986). Cannflavin A inhibits cyclooxygenase (COX) enzymes and lipoxygenase (LO) enzymes more potently than THC (Evans et al. 1987). However, these assays were done with alcohol-extracted cannflavin; we question whether cannflavin is sufficiently volatile. Other phenols related to flavonoids are volatile and apparently retain pharmacological activity in cannabis smoke, such as eugenol and *p*-vinylphenol (Burstein et al. 1976).

β-Sitosterol was demonstrated in significant concentrations in the red oil extract of cannabis (Fenselau and Hermann 1972). In animal assays, this phytosterol reduced acute inflammation 65% and chronic edema 40.6% (Gomez et al. 1999). This agent has been the subject of most interest as the active ingredient of *Serenoa repens*, the saw palmetto, and *Urtica dioica*, the nettle, wherein β-sitosterol acts as a 5-α-reductase inhibitor. In numerous trials (Wilt et al. 1998; McPartland and Pruitt 2000), standardized extracts of saw palmetto have proven equivalent or superior to finasteride in treatment of benign prostatic hyperplasia.

CONCLUSIONS

Does the body absorb non-cannabinoids in physiologically relevant concentrations? In the absence of experimental data, we can estimate, using limonene as an example of AChE inhibition. According to Ross and ElSohly (1996), fresh, female flowering tops consist of 0.29% essential oil. Air drying of female flowering tops decreases their moisture content (MC) from approximately 85% MC to 15% MC, with a concomitant loss in water weight (McPartland and Pruitt 1997). Although some essential oil is volatilized and lost in the drying process, the remaining terpenoids become concentrated. The concentration of essential oil in air-dried cannabis is 0.8%, and limonene consists of 17.2% of the essential oil (Ross and ElSohly 1996). Thus, air-dried cannabis consists of 0.14% limonene; therefore a 500 mg cannabis cigarette (which is half the size of a standard tobacco cigarette) would contain 0.7 mg limonene. If we assume the systemic bioavailability of limonene from smoking cannabis is 18%, the same as THC (Ohlsson et al. 1980), then 0.13 mg would be absorbed. Distributing this dose evenly in the total body water of a 70 kg man, without metabolism or sequestration, would produce a maximum tissue concentration of 1.3 μM. This concentration is an order of magnitude below the IC_{50} concentration of limonene's inhibition of AChE (Miyazawa et al. 1997). Hence, limonene *must* synergize with other AChE inhibitors in order to be effective.

Vaporizer technology may improve the bioavailability of limonene and other compounds, which volatilize around the same temperature as THC (see Figures 1-3). Vaporizers are smoking apparati that heat cannabis to 185°C (365°F), which vaporizes THC but is below the ignition point of combustible plant material. Vaporized cannabis emits a thin gray vapor, whereas combusted cannabis produces a thick smoke. Thus, vaporizers deliver a better cannabinoid-to-tar ratio than cigarettes or water pipes (Gieringer 1996). In a recent study, traces of THC were vaporized at temperatures as low as 140°C (284°F) and the majority of THC vaporized by 185°C (365°F); benzene and other carcinogenic vapors did not appear until 200°C (392°F), and cannabis combustion occurred around 230°C (446°F) (Gieringer 2001).

Concerning bioavailability, it should be mentioned that cannabis compounds need not be absorbed systemically through the lungs to produce CNS activity. Inhaled compounds may reach receptors in the olfactory bulb, sending mood-altering messages via olfactory nerves directly to the limbic region and hippocampus. This route may be responsible for some sedative effects of terpenoids upon inhalation (Buchbauer et al. 1993).

The paucity of research concerning non-THC synergists in cannabis is periodically criticized (Mechoulam et al. 1972; McPartland and Pruitt 1999; Russo 2000). We have highlighted several cannabinoids, terpenoids, and flavonoids

that deserve further attention regarding their contributions to the effects of clinical cannabis. Most of the data we present here is based on *in vitro* experiments or animal studies. Clearly the next step should involve human clinical trials of each constituent, alone, or in combination with THC, or combined with a cocktail of cannabis compounds.

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