

## Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects

[Ethan B Russo](#)

GW Pharmaceuticals, Salisbury, Wiltshire, UK

Ethan Russo, MD, 20402 81st Avenue SW, Vashon, WA 98070, USA. E-mail: [ethanrusso@comcast.net](mailto:ethanrusso@comcast.net)

Received 2010 Nov 19; Revised 2010 Dec 29; Accepted 2011 Jan 12.

[Copyright](#) British Journal of Pharmacology © 2011 The British Pharmacological Society

This article has been [cited by](#) other articles in PMC.

### Abstract

[Go to:](#) [Go to:](#)

Tetrahydrocannabinol (THC) has been the primary focus of cannabis research since 1964, when Raphael Mechoulam isolated and synthesized it. More recently, the synergistic contributions of cannabidiol to cannabis pharmacology and analgesia have been scientifically demonstrated. Other phytocannabinoids, including tetrahydrocannabivarin, cannabigerol and cannabichromene, exert additional effects of therapeutic interest. Innovative conventional plant breeding has yielded cannabis chemotypes expressing high titres of each component for future study. This review will explore another echelon of phytotherapeutic agents, the cannabis terpenoids: limonene, myrcene,  $\alpha$ -pinene, linalool,  $\beta$ -caryophyllene, caryophyllene oxide, nerolidol and phytol. Terpenoids share a precursor with phytocannabinoids, and are all flavour and fragrance components common to human diets that have been designated Generally Recognized as Safe by the US Food and Drug Administration and other regulatory agencies. Terpenoids are quite potent, and affect animal and even human behaviour when inhaled from ambient air at serum levels in the single digits  $\text{ng}\cdot\text{mL}^{-1}$ . They display unique therapeutic effects that may contribute meaningfully to the entourage effects of cannabis-based medicinal extracts. Particular focus will be placed on phytocannabinoid-terpenoid interactions that could produce synergy with respect to treatment of pain, inflammation, depression, anxiety, addiction, epilepsy, cancer, fungal and bacterial infections (including methicillin-resistant *Staphylococcus aureus*). Scientific evidence is presented for non-cannabinoid plant components as putative antidotes to intoxicating effects of THC that could increase its therapeutic index. Methods for investigating entourage effects in future experiments will be proposed. Phytocannabinoid-terpenoid synergy, if proven, increases the likelihood that an extensive pipeline of new therapeutic products is possible from this venerable plant.

### LINKED ARTICLES

This article is part of a themed issue on Cannabinoids in Biology and Medicine. To view the other articles in this issue visit <http://dx.doi.org/10.1111/bph.2011.163.issue-7>

**Keywords:** cannabinoids, terpenoids, essential oils, THC, CBD, limonene, pinene, linalool, caryophyllene, phytotherapy

Cannabis has been a medicinal plant of unparalleled versatility for millennia ([Mechoulam, 1986](#); [Russo, 2007; 2008](#)), but whose mechanisms of action were an unsolved mystery until the discovery of tetrahydrocannabinol (THC) ([Gaoni and Mechoulam, 1964a](#)), the first cannabinoid receptor, CB<sub>1</sub> ([Devane \*et al.\*, 1988](#)), and the endocannabinoids, anandamide (arachidonylethanolamide, AEA) ([Devane \*et al.\*, 1992](#)) and 2-arachidonoylglycerol (2-AG) ([Mechoulam \*et al.\*, 1995](#); [Sugiura \*et al.\*, 1995](#)). While a host of phytocannabinoids were discovered in the 1960s: cannabidiol (CBD) ([Mechoulam and Shvo, 1963](#)), cannabigerol (CBG) ([Gaoni and Mechoulam, 1964b](#)), cannabichromene (CBC) ([Gaoni and Mechoulam, 1966](#)), cannabidivarin (CBDV) ([Vollner \*et al.\*, 1969](#)) and tetrahydrocannabivarin (THCV) ([Gill \*et al.\*, 1970](#)), the overwhelming preponderance of research focused on psychoactive THC. Only recently has renewed interest been manifest in THC analogues, while other key components of the activity of cannabis and its extracts, the cannabis terpenoids, remain understudied ([McPartland and Russo, 2001b](#); [Russo and McPartland, 2003](#)). The current review will reconsider essential oil (EO) agents, their peculiar pharmacology and possible therapeutic interactions with phytocannabinoids. Nomenclature follows conventions in [Alexander \*et al.\* \(2009\)](#).

Phytocannabinoids and terpenoids are synthesized in cannabis, in secretory cells inside glandular trichomes ([Figure 1](#)) that are most highly concentrated in unfertilized female flowers prior to senescence ([Potter, 2004; Potter, 2009](#)). Geranyl pyrophosphate is formed as a precursor via the deoxyxylulose pathway in cannabis ([Fellermeier \*et al.\*, 2001](#)), and is a parent compound to both phytocannabinoids and terpenoids ([Figure 2](#)). After coupling with either olivetolic acid or divarinic acid, pentyl or propyl cannabinoid acids are produced, respectively, via enzymes that accept either substrate ([de Meijer \*et al.\*, 2003](#)), a manifestation of Mechoulam's postulated 'Nature's Law of Stinginess'. Although having important biochemical properties in their own right, acid forms of phytocannabinoids are most commonly decarboxylated via heat to produce the more familiar neutral phytocannabinoids ([Table 1](#)). Alternatively, geranyl pyrophosphate may form limonene and other monoterpenoids in secretory cell plastids, or couple with isopentenyl pyrophosphate in the cytoplasm to form farnesyl pyrophosphate, parent compound to the sesquiterpenoids, that co-localizes with transient receptor potential vanilloid receptor (TRPV) 1 in human dorsal root ganglion, suggesting a role in sensory processing of noxious stimuli ([Bradshaw \*et al.\*, 2009](#)), and which is the most potent endogenous ligand to date on the G-protein coupled receptor (GPR) 92 ([Oh \*et al.\*, 2008](#)).

[Table 1](#)  
Phytocannabinoid activity table



[Figure 1](#)  
Cannabis capitata glandular (EBR by permission of Bedrocan BV, Netherlands).



[Figure 2](#)  
Phytocannabinoid and cannabis terpenoid biosynthesis.

An obvious question pertains to the chemical ecology of such syntheses that require obvious metabolic demands on the plant ([Gershenzon, 1994](#)), and these will be considered.

Is cannabis merely a crude vehicle for delivery of THC? Might it rather display herbal synergy ([Williamson,](#)

[2001](#)) encompassing potentiation of activity by active or inactive components, antagonism (evidenced by the ability of CBD to reduce side effects of THC; [Russo and Guy, 2006](#)), summation, pharmacokinetic and metabolic interactions? Recently, four basic mechanisms of synergy have been proposed ([Wagner and Ulrich-Merzenich, 2009](#)): (i) multi-target effects; (ii) pharmacokinetic effects such as improved solubility or bioavailability; (iii) agent interactions affecting bacterial resistance; and (iv) modulation of adverse events. Cannabis was cited as an illustration.

Could phytocannabinoids function analogously to the endocannabinoid system (ECS) with its combination of active and ‘inactive’ synergists, first described as an entourage ([Ben-Shabat et al., 1998](#)), with subsequent refinement ([Mechoulam and Ben-Shabat, 1999](#)) and qualification (p. 136): ‘This type of synergism may play a role in the widely held (but not experimentally based) view that in some cases plants are better drugs than the natural products isolated from them’. Support derives from studies in which cannabis extracts demonstrated effects two to four times greater than THC ([Carlini et al., 1974](#)); unidentified THC antagonists and synergists were claimed ([Fairbairn and Pickens, 1981](#)), anticonvulsant activity was observed beyond the cannabinoid fraction ([Wilkinson et al., 2003](#)), and extracts of THC and CBD modulated effects in hippocampal neurones distinctly from pure compounds ([Ryan et al., 2006](#)). Older literature also presented refutations: no observed differences were noted by humans ingesting or smoking pure THC versus herbal cannabis ([Wachtel et al., 2002](#)); pure THC seemed to account for all tetrad-type effects in mice ([Varvel et al., 2005](#)); and smoked cannabis with varying CBD or CBC content failed to yield subjective differences combined with THC ([Ilan et al., 2005](#)). Explanations include that the cannabis employed by Wachtel yielded 2.11% THC, but with only 0.3% cannabinol (CBN) and 0.05% CBD ([Russo and McPartland, 2003](#)), and Ilan's admission that CBN and CBD content might be too low to modulate THC. Another factor is apparent in that terpenoid yields from vaporization of street cannabis were 4.3–8.5 times of those from US National Institute on Drug Abuse cannabis ([Bloor et al., 2008](#)). It is undisputed that the black market cannabis in the UK ([Potter et al., 2008](#)), Continental Europe ([King et al., 2005](#)) and the USA ([Mehmedic et al., 2010](#)) has become almost exclusively a high-THC preparation to the almost total exclusion of other phytocannabinoids. If – as many consumers and experts maintain ([Clarke, 2010](#)) – there are biochemical, pharmacological and phenomenological distinctions between available cannabis ‘strains’, such phenomena are most likely related to relative terpenoid contents and ratios. This treatise will assess additional evidence for putative synergistic phytocannabinoid-terpenoid effects exclusive of THC, to ascertain whether this botanical may fulfil its promise as, ‘a neglected pharmacological treasure trove’ ([Mechoulam, 2005](#)).

## **Phytocannabinoids, beyond THC: a brief survey**

[Go to:](#)   [Go to:](#)

---

Phytocannabinoids are exclusively produced in cannabis (*vide infra* for exception), but their evolutionary and ecological *raison d'être* were obscure until recently. THC production is maximized with increased light energy ([Potter, 2009](#)). It has been known for some time that CBG and CBC are mildly antifungal ([ElSohly et al., 1982](#)), as are THC and CBD against a cannabis pathogen ([McPartland, 1984](#)). More pertinent, however, is the mechanical stickiness of the trichomes, capable of trapping insects with all six legs ([Potter, 2009](#)). Tetrahydrocannabinolic acid (THCA) and cannabichromenic acid ([Morimoto et al., 2007](#)), as well as cannabidiolic acid and cannabigerolic acid (CBGA; [Shoyama et al., 2008](#)) produce necrosis in plant cells. Normally, the cannabinoid acids are sequestered in trichomes away from the flower tissues. Any trichome breakage at senescence may contribute to natural pruning of lower fan leaves that otherwise utilize energy that the plant preferentially diverts to the flower, in continued efforts to affect fertilization, generally in vain when subject to human horticulture for pharmaceutical production. THCA and CBGA have also proven to be insecticidal in their own right ([Sirikantaramas et al., 2005](#)).

Over 100 phytocannabinoids have been identified ([Brenneisen, 2007](#); [Mehmedic et al., 2010](#)), but many are

artefacts of analysis or are produced in trace quantities that have not permitted thorough investigation. The pharmacology of the more accessible phytocannabinoids has received excellent recent reviews ([Pertwee et al., 2007](#); [Izzo et al., 2009](#); [De Petrocellis and Di Marzo, 2010](#); [De Petrocellis et al., 2011](#)), and will be summarized here, with emphasis on activities with particular synergistic potential.

THC ([Table 1](#)) is the most common phytocannabinoid in cannabis drug chemotypes, and is produced in the plant via an allele co-dominant with CBD ([de Meijer et al., 2003](#)). THC is a partial agonist at CB<sub>1</sub> and cannabinoid receptor 2 (CB<sub>2</sub>) analogous to AEA, and underlying many of its activities as a psychoactive agent, analgesic, muscle relaxant and antispasmodic ([Pacher et al., 2006](#)). Additionally, it is a bronchodilator ([Williams et al., 1976](#)), neuroprotective antioxidant ([Hampson et al., 1998](#)), antipruritic agent in cholestatic jaundice ([Neff et al., 2002](#)) and has 20 times the anti-inflammatory power of aspirin and twice that of hydrocortisone ([Evans, 1991](#)). THC is likely to avoid potential pitfalls of either COX-1 or COX-2 inhibition, as such activity is only noted at concentrations far above those attained therapeutically ([Stott et al., 2005](#)).

CBD is the most common phytocannabinoid in fibre (hemp) plants, and second most prevalent in some drug chemotypes. It has proven extremely versatile pharmacologically ([Table 1](#)) ([Pertwee, 2004](#); [Mechoulam et al., 2007](#)), displaying the unusual ability to antagonize CB<sub>1</sub> at a low nM level in the presence of THC, despite having little binding affinity ([Thomas et al., 2007](#)), and supporting its modulatory effect on THC-associated adverse events such as anxiety, tachycardia, hunger and sedation in rats and humans ([Nicholson et al., 2004](#); [Murillo-Rodriguez et al., 2006](#); [Russo and Guy, 2006](#)). CBD is an analgesic ([Costa et al., 2007](#)), is a neuroprotective antioxidant more potent than ascorbate or tocopherol ([Hampson et al., 1998](#)), without COX inhibition ([Stott et al., 2005](#)), acts as a TRPV1 agonist analogous to capsaicin but without noxious effect ([Bisogno et al., 2001](#)), while also inhibiting uptake of AEA and weakly inhibiting its hydrolysis. CBD is an antagonist on GPR55, and also on GPR18, possibly supporting a therapeutic role in disorders of cell migration, notably endometriosis ([McHugh et al., 2010](#)). CBD is anticonvulsant ([Carlini and Cunha, 1981](#); [Jones et al., 2010](#)), anti-nausea ([Parker et al., 2002](#)), cytotoxic in breast cancer ([Ligresti et al., 2006](#)) and many other cell lines while being cytoprotective for normal cells ([Parolaro and Massi, 2008](#)), antagonizes tumour necrosis factor-alpha (TNF- $\alpha$ ) in a rodent model of rheumatoid arthritis ([Malfait et al., 2000](#)), enhances adenosine receptor A<sub>2A</sub> signalling via inhibition of an adenosine transporter ([Carrier et al., 2006](#)), and prevents prion accumulation and neuronal toxicity ([Dirikoc et al., 2007](#)). A CBD extract showed greater anti-hyperalgesia over pure compound in a rat model with decreased allodynia, improved thermal perception and nerve growth factor levels and decreased oxidative damage ([Comelli et al., 2009](#)). CBD also displayed powerful activity against methicillin-resistant *Staphylococcus aureus* (MRSA), with a minimum inhibitory concentration (MIC) of 0.5–2  $\mu\text{g}\cdot\text{mL}^{-1}$  ([Appendino et al., 2008](#)). In 2005, it was demonstrated that CBD has agonistic activity at 5-hydroxytryptamine (5-HT)<sub>1A</sub> at 16  $\mu\text{M}$  ([Russo et al., 2005](#)), and that despite the high concentration, may underlie its anti-anxiety activity ([Resstel et al., 2009](#); [Soares Vde et al., 2010](#)), reduction of stroke risk ([Mishima et al., 2005](#)), anti-nausea effects ([Rock et al., 2009](#)) and ability to affect improvement in cognition in a mouse model of hepatic encephalopathy ([Magen et al., 2009](#)). A recent study has demonstrated that CBD 30  $\text{mg}\cdot\text{kg}^{-1}$  i.p. reduced immobility time in the forced swim test compared to imipramine ( $P < 0.01$ ), an effect blocked by pre-treatment with the 5-HT<sub>1A</sub> antagonist WAY100635 ([Zanelati et al., 2010](#)), supporting a prospective role for CBD as an antidepressant. CBD also inhibits synthesis of lipids in sebocytes, and produces apoptosis at higher doses in a model of acne (*vide infra*). One example of CBD antagonism to THC would be the recent observation of lymphopenia in rats (CBD 5  $\text{mg}\cdot\text{kg}^{-1}$ ) mediated by possible CB<sub>2</sub> inverse agonism ([Ignatowska-Jankowska et al., 2009](#)), an effect not reported in humans even at doses of pure CBD up to 800 mg ([Crippa et al., 2010](#)), possibly due to marked interspecies differences in CB<sub>2</sub> sequences and signal transduction. CBD proved to be a critical factor in the ability of nabiximols oromucosal extract in successfully treating intractable cancer pain patients unresponsive to opioids

(30% reduction in pain from baseline), as a high-THC extract devoid of CBD failed to distinguish from placebo ([Johnson et al., 2010](#)). This may represent true synergy if the THC–CBD combination were shown to provide a larger effect than a summation of those from the compounds separately ([Berenbaum, 1989](#)).

CBC ([Table 1](#)) was inactive on adenylate cyclase inhibition ([Howlett, 1987](#)), but showed activity in the mouse cannabinoid tetrad, but only at 100 mg·kg<sup>-1</sup>, and at a fraction of THC activity, via a non-CB<sub>1</sub>, non-CB<sub>2</sub> mechanism ([DeLong et al., 2010](#)). More pertinent are anti-inflammatory ([Wirth et al., 1980](#)) and analgesic activity ([Davis and Hatoum, 1983](#)), its ability to reduce THC intoxication in mice ([Hatoum et al., 1981](#)), antibiotic and antifungal effects ([ElSohly et al., 1982](#)), and observed cytotoxicity in cancer cell lines ([Ligresti et al., 2006](#)). A CBC-extract displayed pronounced antidepressant effect in rodent models ([Deyo and Musty, 2003](#)). Additionally, CBC was comparable to mustard oil in stimulating TRPA1-mediated Ca<sup>++</sup> in human embryonic kidney 293 cells (50–60 nM) ([De Petrocellis et al., 2008](#)). CBC recently proved to be a strong AEA uptake inhibitor ([De Petrocellis et al., 2011](#)). CBC production is normally maximal, earlier in the plant's life cycle ([de Meijer et al., 2009a](#)). An innovative technique employing cold water extraction of immature leaf matter from selectively bred cannabis chemotypes yields a high-CBC 'enriched trichome preparation' ([Potter, 2009](#)).

CBG ([Table 1](#)), the parent phytocannabinoid compound, has a relatively weak partial agonistic effect at CB<sub>1</sub> (K<sub>i</sub> 440 nM) and CB<sub>2</sub> (K<sub>i</sub> 337 nM) ([Gauson et al., 2007](#)). Older work supports gamma aminobutyric acid (GABA) uptake inhibition greater than THC or CBD ([Banerjee et al., 1975](#)) that could suggest muscle relaxant properties. Analgesic and anti-erythemic effects and the ability to block lipoxygenase were said to surpass those of THC ([Evans, 1991](#)). CBG demonstrated modest antifungal effects ([ElSohly et al., 1982](#)). More recently, it proved to be an effective cytotoxic in high dosage on human epithelioid carcinoma ([Baek et al., 1998](#)), is the next most effective phytocannabinoid against breast cancer after CBD ([Ligresti et al., 2006](#)), is an antidepressant in the rodent tail suspension model ([Musty and Deyo, 2006](#)) and is a mildly anti-hypertensive agent ([Maor et al., 2006](#)). Additionally, CBG inhibits keratinocyte proliferation suggesting utility in psoriasis ([Wilkinson and Williamson, 2007](#)), it is a relatively potent TRPM8 antagonist for possible application in prostate cancer ([De Petrocellis and Di Marzo, 2010](#)) and detrusor over-activity and bladder pain ([Mukerji et al., 2006](#)). It is a strong AEA uptake inhibitor ([De Petrocellis et al., 2011](#)) and a powerful agent against MRSA ([Appendino et al., 2008](#); *vide infra*). Finally, CBG behaves as a potent  $\alpha$ -2 adrenoreceptor agonist, supporting analgesic effects previously noted ([Formukong et al., 1988](#)), and moderate 5-HT<sub>1A</sub> antagonist suggesting antidepressant properties ([Cascio et al., 2010](#)). Normally, CBG appears as a relatively low concentration intermediate in the plant, but recent breeding work has yielded cannabis chemotypes lacking in downstream enzymes that express 100% of their phytocannabinoid content as CBG ([de Meijer and Hammond, 2005](#); [de Meijer et al., 2009a](#)).

THCV ([Table 1](#)) is a propyl analogue of THC, and can modulate intoxication of the latter, displaying 25% of its potency in early testing ([Gill et al., 1970](#); [Hollister, 1974](#)). A resurgence of interest accrues to this compound, which is a CB<sub>1</sub> antagonist at lower doses ([Thomas et al., 2005](#)), but is a CB<sub>1</sub> agonist at higher doses ([Pertwee, 2008](#)). THCV produces weight loss, decreased body fat and serum leptin concentrations with increased energy expenditure in obese mice ([Cawthorne et al., 2007](#); [Riedel et al., 2009](#)). THCV also demonstrates prominent anticonvulsant properties in rodent cerebellum and pyriform cortex ([Hill et al., 2010](#)). THCV appears as a fractional component of many southern African cannabis chemotypes, although plants highly predominant in this agent have been produced ([de Meijer, 2004](#)). THCV recently demonstrated a CB<sub>2</sub>-based ability to suppress carageenan-induced hyperalgesia and inflammation, and both phases of formalin-induced pain behaviour via CB<sub>1</sub> and CB<sub>2</sub> in mice ([Bolognini et al., 2010](#)).

CBDV ([Table 1](#)), the propyl analogue of CBD, was first isolated in 1969 ([Vollner et al., 1969](#)), but formerly received little investigation. Pure CBDV inhibits diacylglycerol lipase [50% inhibitory concentration (IC<sub>50</sub>) 16.6

$\mu\text{M}$ ] and might decrease activity of its product, the endocannabinoid, 2-AG ([De Petrocellis et al., 2011](#)). It is also anticonvulsant in rodent hippocampal brain slices, comparable to phenobarbitone and felbamate ([Jones et al., 2010](#)).

Finally, CBN is a non-enzymatic oxidative by-product of THC, more prominent in aged cannabis samples ([Merzouki and Mesa, 2002](#)). It has a lower affinity for CB<sub>1</sub> (K<sub>i</sub> 211.2 nM) and CB<sub>2</sub> (K<sub>i</sub> 126.4 nM) ([Rhee et al., 1997](#)); and was judged inactive when tested alone in human volunteers, but produced greater sedation combined with THC ([Musty et al., 1976](#)). CBN demonstrated anticonvulsant ([Turner et al., 1980](#)), anti-inflammatory ([Evans, 1991](#)) and potent effects against MRSA (MIC 1  $\mu\text{g}\cdot\text{mL}^{-1}$ ). CBN is a TRPV2 (high-threshold thermosensor) agonist (EC 77.7  $\mu\text{M}$ ) of possible interest in treatment of burns ([Qin et al., 2008](#)). Like CBG, it inhibits keratinocyte proliferation ([Wilkinson and Williamson, 2007](#)), independently of cannabinoid receptor effects. CBN stimulates the recruitment of quiescent mesenchymal stem cells in marrow (10  $\mu\text{M}$ ), suggesting promotion of bone formation ([Scutt and Williamson, 2007](#)) and inhibits breast cancer resistance protein, albeit at a very high concentration (IC<sub>50</sub> 145  $\mu\text{M}$ ) ([Holland et al., 2008](#)).

### Cannabis terpenoids: neglected entourage compounds?

[Go to:](#)   [Go to:](#)

Terpenoids are EO components, previously conceived as the quintessential fifth element, ‘life force’ or spirit ([Schmidt, 2010](#)), and form the largest group of plant chemicals, with 15–20 000 fully characterized ([Langenheim, 1994](#)). Terpenoids, not cannabinoids, are responsible for the aroma of cannabis. Over 200 have been reported in the plant ([Hendriks et al., 1975; 1977; Malingre et al., 1975; Davalos et al., 1977; Ross and ElSohly, 1996; Mediavilla and Steinemann, 1997; Rothschild et al., 2005; Brenneisen, 2007](#)), but only a few studies have concentrated on their pharmacology ([McPartland and Pruitt, 1999; McPartland and Mediavilla, 2001a; McPartland and Russo, 2001b](#)). Their yield is less than 1% in most cannabis assays, but they may represent 10% of trichome content ([Potter, 2009](#)). Monoterpenes usually predominate (limonene, myrcene, pinene), but these headspace volatiles ([Hood et al., 1973](#)), while only lost at a rate of about 5% before processing ([Gershenzon, 1994](#)), do suffer diminished yields with drying and storage ([Turner et al., 1980; Ross and ElSohly, 1996](#)), resulting in a higher relative proportion of sesquiterpenoids (especially caryophyllene), as also often occurs in extracts. A ‘phytochemical polymorphism’ seems operative in the plant ([Franz and Novak, 2010](#)), as production favours agents such as limonene and pinene in flowers that are repellent to insects ([Nerio et al., 2010](#)), while lower fan leaves express higher concentrations of bitter sesquiterpenoids that act as anti-feedants for grazing animals ([Potter, 2009](#)). Evolutionarily, terpenoids seem to occur in complex and variable mixtures with marked structural diversity to serve various ecological roles. Terpenoid composition is under genetic control ([Langenheim, 1994](#)), and some enzymes produce multiple products, again supporting Mechoulam's ‘Law of Stinginess’. The particular mixture of mono- and sesquiterpenoids will determine viscosity, and in cannabis, this certainly is leveraged to practical advantage as the notable stickiness of cannabis exudations traps insects ([McPartland et al., 2000](#)), and thus, combined with the insecticidal phytocannabinoid acids ([Sirikantaramas et al., 2005](#)), provides a synergistic mechano-chemical defensive strategy versus predators.

As observed for cannabinoids, terpenoid production increases with light exposure, but decreases with soil fertility ([Langenheim, 1994](#)), and this is supported by the glasshouse experience that demonstrates higher yields if plants experience relative nitrogen lack just prior to harvest ([Potter, 2004](#)), favouring floral over foliar growth. EO composition is much more genetically than environmentally determined, however ([Franz and Novak, 2010](#)), and while cannabis is allogamous and normally requires repeat selective breeding for maintenance of quality, this problem may be practically circumvented by vegetative propagation of high-performance plants under controlled environmental conditions (light, heat and humidity) ([Potter, 2009](#)), and such techniques have proven to provide notable consistency to tight tolerances as Good Manufacturing Practice for any pharmaceutical would require

([Fischedick et al., 2010](#)).

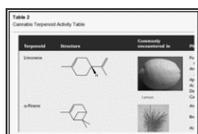
The *European Pharmacopoeia*, Sixth Edition (2007), lists 28 EOs ([Pauli and Schilcher, 2010](#)). Terpenoids are pharmacologically versatile: they are lipophilic, interact with cell membranes, neuronal and muscle ion channels, neurotransmitter receptors, G-protein coupled (odorant) receptors, second messenger systems and enzymes ([Bowles, 2003](#); [Buchbauer, 2010](#)). All the terpenoids discussed herein are Generally Recognized as Safe, as attested by the US Food and Drug Administration as food additives, or by the Food and Extract Manufacturers Association and other world regulatory bodies. Germane is the observation ([Adams and Taylor, 2010](#)) (p. 193), ‘With a high degree of confidence one may presume that EOs derived from food are likely to be safe’. Additionally, all the current entries are non-sensitizing to skin when fresh ([Tisserand and Balacs, 1995](#); [Adams and Taylor, 2010](#)), but may cause allergic reactions at very low rates when oxidized ([Matura et al., 2005](#)). For additional pharmacological data on other common cannabis terpenoids not discussed herein (1,8-cineole, also known as eucalyptol, pulegone,  $\alpha$ -terpineol, terpineol-4-ol,  $\rho$ -cymene, borneol and  $\Delta$ -3-carene), please see [McPartland and Russo \(2001b\)](#).

Are cannabis terpenoids actually relevant to the effects of cannabis? Terpenoid components in concentrations above 0.05% are considered of pharmacological interest ([Adams and Taylor, 2010](#)). Animal studies are certainly supportive ([Buchbauer et al., 1993](#)). Mice exposed to terpenoid odours inhaled from ambient air for 1 h demonstrated profound effects on activity levels, suggesting a direct pharmacological effect on the brain, even at extremely low serum concentrations (examples: linalool with 73% reduction in motility at  $4.22 \text{ ng}\cdot\text{mL}^{-1}$ , pinene 13.77% increase at trace concentration, terpineol 45% reduction at  $4.7 \text{ ng}\cdot\text{mL}^{-1}$ ). These levels are comparable to those of THC measured in humans receiving cannabis extracts yielding therapeutic effects in pain, or symptoms of multiple sclerosis in various randomized controlled trials (RCTs) ([Russo, 2006](#); [Huestis, 2007](#)). Positive effects at undetectable serum concentrations with orange terpenes (primarily limonene, 35.25% increase in mouse activity), could be explainable on the basis of rapid redistribution and concentration in lipophilic cerebral structures. A similar rationale pertains to human studies ([Komori et al., 1995](#)), subsequently discussed. Limonene is highly bioavailable with 70% human pulmonary uptake ([Falk-Filipsson et al., 1993](#)), and a figure of 60% for pinene with rapid metabolism or redistribution ([Falk et al., 1990](#)). Ingestion and percutaneous absorption is also well documented in humans ([Jäger et al., 1992](#)): 1500 mg of lavender EO with 24.7% linalool (total 372 mg) was massaged into the skin of a 60 kg man for 10 min, resulting in a peak plasma concentration of  $100 \text{ ng}\cdot\text{mL}^{-1}$  at 19 min, and a half-life of 13.76 min in serum ([Jäger et al., 1992](#)). EO mixtures (including limonene and pinene) also increase permeation of estradiol through mouse skin ([Monti et al., 2002](#)).

Government-approved cannabis supplied to patients in national programmes in the Netherlands and Canada is gamma-irradiated to sterilize coliform bacteria, but the safety of this technique for a smoked and inhaled product has never been specifically tested. Gamma-radiation significantly reduced linalool titres in fresh cilantro ([Fan and Sokorai, 2002](#)), and myrcene and linalool in orange juice ([Fan and Gates, 2001](#)).

D-limonene, common to the lemon and other citrus EOs ([Table 2](#)), is the second most widely distributed terpenoid in nature ([Noma and Asakawa, 2010](#)), and is the precursor to other monoterpenoids ([Figure 2](#)) through species-specific synthetic schemes. Unfortunately, these pathways have not yet been investigated in cannabis. The ubiquity of limonene serves, perhaps, as a demonstration of convergent evolution that supports an important ecological role for this monoterpene. Studies with varying methodology and dosing in citrus oils in mice suggest it to be a powerful anxiolytic agent ([Carvalho-Freitas and Costa, 2002](#); [Pultrini Ade et al., 2006](#)), with one EO increasing serotonin in the prefrontal cortex, and dopamine (DA) in hippocampus mediated via  $5\text{-HT}_{1A}$  ([Komiya et al., 2006](#)). Compelling confirmatory evidence in humans was provided in a clinical study ([Komori et al., 1995](#)), in which hospitalized depressed patients were exposed to citrus fragrance in ambient air, with subsequent normalization of Hamilton Depression Scores, successful discontinuation of antidepressant medication in 9/12

patients and serum evidence of immune stimulation (CD4/8 ratio normalization). Limonene also produces apoptosis of breast cancer cells, and was employed at high doses in Phase II RCTs ([Vigushin et al., 1998](#)). Subsequent investigation in cancer treatment has centred on its immediate hepatic metabolite, perillic acid, which demonstrates anti-stress effects in rat brain ([Fukumoto et al., 2008](#)). A patent has been submitted, claiming that limonene effectively treats gastro-oesophageal reflux ([Harris, 2010](#)). Citrus EOs containing limonene proved effective against dermatophytes ([Sanguinetti et al., 2007](#); [Singh et al., 2010](#)), and citrus EOs with terpenoid profiles resembling those in cannabis demonstrated strong radical scavenging properties ([Choi et al., 2000](#)). As noted above, limonene is highly bioavailable ([Falk-Filipsson et al., 1993](#)), and rapidly metabolized, but with indications of accumulation and retention in adipose tissues (e.g. brain). It is highly non-toxic (estimated human lethal dose 0.5–5 g·kg<sup>-1</sup>) and non-sensitizing ([Von Burg, 1995](#))



[Table 2](#)  
Cannabis Terpenoid Activity Table

β-Myrcene is another common monoterpene in cannabis ([Table 2](#)) with myriad activities: diminishing inflammation via prostaglandin E-2 (PGE-2) ([Lorenzetti et al., 1991](#)), and blocking hepatic carcinogenesis by aflatoxin ([De-Oliveira et al., 1997](#)). Interestingly, myrcene is analgesic in mice, but this action can be blocked by naloxone, perhaps via the α-2 adrenoreceptor ([Rao et al., 1990](#)). It is non-mutagenic in the Ames test ([Gomes-Carneiro et al., 2005](#)). Myrcene is a recognized sedative as part of hops preparations (*Humulus lupulus*), employed to aid sleep in Germany ([Bisset and Wichtl, 2004](#)). Furthermore, myrcene acted as a muscle relaxant in mice, and potentiated barbiturate sleep time at high doses ([do Vale et al., 2002](#)). Together, these data would support the hypothesis that myrcene is a prominent sedative terpene in cannabis, and combined with THC, may produce the ‘couch-lock’ phenomenon of certain chemotypes that is alternatively decried or appreciated by recreational cannabis consumers.

α-Pinene is a bicyclic monoterpene ([Table 2](#)), and the most widely encountered terpene in nature ([Noma and Asakawa, 2010](#)). It appears in conifers and innumerable plant EOs, with an insect-repellent role. It is anti-inflammatory via PGE-1 ([Gil et al., 1989](#)), and is a bronchodilator in humans at low exposure levels ([Falk et al., 1990](#)). Pinene is a major component of *Sideritis* spp. ([Kose et al., 2010](#)) and *Salvia* spp. EOs ([Ozek et al., 2010](#)), both with prominent activity against MRSA (*vide infra*). Beyond this, it seems to be a broad-spectrum antibiotic ([Nissen et al., 2010](#)). α-Pinene forms the biosynthetic base for CB<sub>2</sub> ligands, such as HU-308 ([Hanus et al., 1999](#)). Perhaps most compelling, however, is its activity as an acetylcholinesterase inhibitor aiding memory ([Perry et al., 2000](#)), with an observed IC<sub>50</sub> of 0.44 mM ([Miyazawa and Yamafuji, 2005](#)). This feature could counteract short-term memory deficits induced by THC intoxication (*vide infra*).

D-Linalool is a monoterpene alcohol ([Table 2](#)), common to lavender (*Lavandula angustifolia*), whose psychotropic anxiolytic activity has been reviewed in detail ([Russo, 2001](#)). Interestingly, linalyl acetate, the other primary terpene in lavender, hydrolyses to linalool in gastric secretions ([Bickers et al., 2003](#)). Linalool proved sedating to mouse activity on inhalation ([Buchbauer et al., 1991](#); [Jirovetz et al., 1992](#)). In traditional aromatherapy, linalool is the likely suspect in the remarkable therapeutic capabilities of lavender EO to alleviate skin burns without scarring ([Gattafosse, 1993](#)). Pertinent to this, the local anaesthetic effects of linalool ([Re et al., 2000](#)) are equal to those of procaine and menthol ([Ghelardini et al., 1999](#)). Another explanation would be its ability to produce hot-plate analgesia in mice ( $P < 0.001$ ) that was reduced by administration of an adenosine A<sub>2A</sub> antagonist ([Peana et al., 2006](#)). It is also anti-nociceptive at high doses in mice via ionotropic glutamate receptors ([Batista et al., 2008](#)). Linalool demonstrated anticonvulsant and anti-glutamatergic activity ([Elisabetsky et al., 1995](#)), and reduced seizures as part of *Ocimum basilicum* EO after exposure to pentylenetetrazole,

picrotoxin and strychnine ([Ismail, 2006](#)). Furthermore, linalool decreased  $K^+$ -stimulated glutamate release and uptake in mouse synaptosomes ([Silva Brum et al., 2001](#)). These effects were summarized ([Nunes et al., 2010](#), p. 303): ‘Overall, it seems reasonable to argue that the modulation of glutamate and GABA neurotransmitter systems are likely to be the critical mechanism responsible for the sedative, anxiolytic and anticonvulsant properties of linalool and EOs containing linalool in significant proportions’. Linalool also proved to be a powerful anti-leishmanial agent ([do Socorro et al., 2003](#)), and as a presumed lavender EO component, decreased morphine opioid usage after inhalation versus placebo ( $P = 0.04$ ) in gastric banding in morbidly obese surgical patients ([Kim et al., 2007](#)).

$\beta$ -Caryophyllene ([Table 2](#)) is generally the most common sesquiterpenoid encountered in cannabis ([Mediavilla and Steinemann, 1997](#)), wherein its evolutionary function may be due to its ability to attract insect predatory green lacewings, while simultaneously inhibiting insect herbivory ([Langenheim, 1994](#)). It is frequently the predominant terpenoid overall in cannabis extracts, particularly if they have been processed under heat for decarboxylation ([Guy and Stott, 2005](#)). Caryophyllene is common to black pepper (*Piper nigrum*) and Copaiba balsam (*Copaifera officinalis*) ([Lawless, 1995](#)). It is anti-inflammatory via PGE-1, comparable in potency to the toxic phenylbutazone ([Basile et al., 1988](#)), and an EO containing it was on par with etodolac and indomethacin ([Ozturk and Ozbek, 2005](#)). In contrast to the latter agents, however, caryophyllene was a gastric cytoprotective ([Tambe et al., 1996](#)), much as had been claimed in the past in treating duodenal ulcers in the UK with cannabis extract ([Douthwaite, 1947](#)). Caryophyllene may have contributed to antimalarial effects as an EO component ([Campbell et al., 1997](#)). Perhaps the greatest revelation regarding caryophyllene has been its demonstration as a selective full agonist at CB<sub>2</sub> (100 nM), the first proven phytocannabinoid beyond the cannabis genus ([Gertsch et al., 2008](#)). Subsequent work has demonstrated that this dietary component produced anti-inflammatory analgesic activity at the lowest dose of 5 mg·kg<sup>-1</sup> in wild-type, but not CB<sub>2</sub> knockout mice ([Gertsch, 2008](#)). Given the lack of attributed psychoactivity of CB<sub>2</sub> agonists, caryophyllene offers great promise as a therapeutic compound, whether systemically, or in dermatological applications such as contact dermatitis ([Karsak et al., 2007](#)). Sensitization reactions are quite rare, and probably due to oxidized product ([Skold et al., 2006](#)).

Nerolidol is a sesquiterpene alcohol with sedative properties ([Binet et al., 1972](#)), present as a low-level component in orange and other citrus peels ([Table 2](#)). It diminished experimentally induced formation of colon adenomas in rats ([Wattenberg, 1991](#)). It was an effective agent for enhancing skin penetration of 5-fluorouracil ([Cornwell and Barry, 1994](#)). This could be a helpful property in treating fungal growth, where it is also an inhibitor ([Langenheim, 1994](#)). It seems to have anti-protozoal parasite control benefits, as a potent antimalarial ([Lopes et al., 1999](#); [Rodrigues Goulart et al., 2004](#)) and anti-leishmanial agent ([Arruda et al., 2005](#)). Nerolidol is non-toxic and non-sensitizing ([Lapczynski et al., 2008](#)).

Caryophyllene oxide ([Table 2](#)) is a sesquiterpenoid oxide common to lemon balm (*Melissa officinalis*), and to the eucalyptus, *Melaleuca stypheloides*, whose EO contains 43.8% ([Farag et al., 2004](#)). In the plant, it serves as an insecticidal/anti-feedant ([Bettarini et al., 1993](#)) and as broad-spectrum antifungal in plant defence ([Langenheim, 1994](#)). Analogously, the latter properties may prove therapeutic, as caryophyllene oxide demonstrated antifungal efficacy in a model of clinical onychomycosis comparable to ciclopiroxalamine and sulconazole, with an 8% concentration affecting eradication in 15 days ([Yang et al., 1999](#)). Caryophyllene oxide is non-toxic and non-sensitizing ([Opdyke, 1983](#)). This agent also demonstrates anti-platelet aggregation properties *in vitro* ([Lin et al., 2003](#)). Caryophyllene oxide has the distinction of being the component responsible for cannabis identification by drug-sniffing dogs ([Stahl and Kunde, 1973](#)).

Phytol ([Table 2](#)) is a diterpene ([McGinty et al., 2010](#)), present in cannabis extracts, as a breakdown product of chlorophyll and tocopherol. Phytol prevented vitamin A-induced teratogenesis by inhibiting conversion of retinol to a harmful metabolite, all-*trans*-retinoic acid ([Arnhold et al., 2002](#)). Phytol increased GABA expression via

inhibition of succinic semialdehyde dehydrogenase, one of its degradative enzymes ([Bang et al., 2002](#)). Thus, the presence of phytol could account for the alleged relaxing effect of wild lettuce (*Lactuca sativa*), or green tea (*Camellia sinensis*), despite the latter's caffeine content.

## Selected possibilities for phytocannabinoid-terpenoid synergy

[Go to:](#) [Go to:](#)

---

### Cannabis and acne

AEA simulates lipid production in human sebocytes of sebaceous glands at low concentrations, but induces apoptosis at higher levels, suggesting that this system is under ECS control ([Dobrosi et al., 2008](#)). CBD 10–20  $\mu\text{M}$  did not affect basal lipid synthesis in SZ95 sebocytes, but did block such stimulation by AEA and arachidonate ([Biro et al., 2009](#)). Higher doses of CBD (30–50  $\mu\text{M}$ ) induced sebocyte apoptosis, which was augmented in the presence of AEA. The effect of CBD to increase  $\text{Ca}^{++}$  was blocked by ruthenium red, a TRP-inhibitor. RNA-mediated silencing of TRPV1 and TRPV3 failed to attenuate CBD effects, but experiments did support the aetiological role of TRPV4, a putative regulator of systemic osmotic pressure (T. Bíró, 2010, pers. comm.). Given the observed ability of CBD to be absorbed transcutaneously, it offers great promise to attenuate the increased sebum production at the pathological root of acne.

Cannabis terpenoids could offer complementary activity. Two citrus EOs primarily composed of limonene inhibited *Propionibacterium acnes*, the key pathogen in acne (MIC 0.31  $\mu\text{L}\cdot\text{mL}^{-1}$ ), more potently than triclosan ([Kim et al., 2008](#)). Linalool alone demonstrated an MIC of 0.625  $\mu\text{L}\cdot\text{mL}^{-1}$ . Both EOs inhibited *P. acnes*-induced TNF- $\alpha$  production, suggesting an adjunctive anti-inflammatory effect. In a similar manner, pinene was the most potent component of a tea-tree eucalyptus EO in suppression of *P. acnes* and *Staph* spp. in another report ([Raman et al., 1995](#)).

Considering the known minimal toxicities of CBD and these terpenoids and the above findings, new acne therapies utilizing whole CBD-predominant extracts, via multi-targeting ([Wagner and Ulrich-Merzenich, 2009](#)), may present a novel and promising therapeutic approach that poses minimal risks in comparison to isotretinoin.

### MRSA

[Go to:](#) [Go to:](#)

---

MRSA accounted for 10% of cases of septicaemia and 18 650 deaths in the USA in 2005, a number greater than that attributable to human immunodeficiency virus/acquired immunodeficiency syndrome ([Bancroft, 2007](#)). Pure CBD and CBG powerfully inhibit MRSA (MIC 0.5–2  $\mu\text{g}\cdot\text{mL}^{-1}$ ) ([Appendino et al., 2008](#)).

Amongst terpenoids, pinene was a major component of *Sideritis erythrantha* EO that was as effective against MRSA and other antibiotic-resistant bacterial strains as vancomycin and other agents ([Kose et al., 2010](#)). A *Salvia rosifolia* EO with 34.8% pinene was also effective against MRSA (MIC 125  $\mu\text{g}\cdot\text{mL}^{-1}$ ). The ability of monoterpenoids to enhance skin permeability and entry of other drugs may further enhance antibiotic benefits ([Wagner and Ulrich-Merzenich, 2009](#)).

Given that CBG can be produced in selected cannabis chemotypes ([de Meijer and Hammond, 2005](#); [de Meijer et al., 2009a](#)), with no residual THC as a possible drug abuse liability risk, a whole plant extract of a CBG-chemotype also expressing pinene would seem to offer an excellent, safe new antiseptic agent.

## Psychopharmacological applications: depression, anxiety, insomnia, dementia and addiction

[Go to:](#) [Go to:](#)

---

Scientific investigation of the therapeutic application of terpenoids in psychiatry has been hampered by methodological concerns, subjective variability of results and a genuine dearth of appropriate randomized controlled studies of high quality ([Russo, 2001](#); [Bowles, 2003](#); [Lis-Balchin, 2010](#)). The same is true of

phytocannabinoids ([Fride and Russo, 2006](#)). Abundant evidence supports the key role of the ECS in mediating depression ([Hill and Gorzalka, 2005a,b](#)), as well as anxiety, whether induced by aversive stimuli, such as post-traumatic stress disorder ([Marsicano et al., 2002](#)) or pain ([Hohmann et al., 2005](#)), and psychosis ([Giuffrida et al., 2004](#)). With respect to the latter risk, the presence of CBD in smoked cannabis based on hair analysis seems to be a mitigating factor reducing its observed incidence ([Morgan and Curran, 2008](#)). A thorough review of cannabis and psychiatry is beyond the scope of this article, but several suggestions are offered with respect to possible therapeutic synergies operative with phytocannabinoids-terpenoid combinations. While the possible benefits of THC on depression remain controversial ([Denson and Earleywine, 2006](#)), much less worrisome would be CBD- or CBG-predominant preparations. Certainly the results obtained in human depression solely with a citrus scent ([Komori et al., 1995](#)), strongly suggest the possibility of synergistic benefit of a phytocannabinoid-terpenoid preparation. Enriched odour exposure in adult mice induced olfactory system neurogenesis ([Rochefort et al., 2002](#)), an intriguing result that could hypothetically support plasticity mechanisms in depression ([Delgado and Moreno, 1999](#)), and similar hypotheses with respect to the ECS in addiction treatment ([Gerdeman and Lovinger, 2003](#)). Phytocannabinoid-terpenoid synergy might theoretically apply.

The myriad effects of CBD on 5-HT<sub>1A</sub> activity provide a strong rationale for this and other phytocannabinoids as base compounds for treatment of anxiety. Newer findings, particularly imaging studies of CBD in normal individuals in anxiety models ([Fusar-Poli et al., 2009; 2010; Crippa et al., 2010](#)) support this hypothesis. Even more compelling is a recent randomized control trial of pure CBD in patients with social anxiety disorder with highly statistical improvements over placebo in anxiety and cognitive impairment ([Crippa et al., 2011](#)). Addition of anxiolytic limonene and linalool could contribute to the clinical efficacy of a CBD extract.

THC was demonstrated effective in a small crossover clinical trial versus placebo in 11 agitated dementia patients with Alzheimer's disease ([Volicer et al., 1997](#)). THC was also observed to be an acetylcholinesterase inhibitor in its own right, as well as preventing amyloid  $\beta$ -peptide aggregation in that disorder ([Eubanks et al., 2006](#)). Certainly, the anti-anxiety and anti-psychotic effects of CBD may be of additional benefit ([Zuardi et al., 1991; 2006; Zuardi and Guimaraes, 1997](#)). A recent study supports the concept that CBD, when present in significant proportion to THC, is capable of eliminating induced cognitive and memory deficits in normal subjects smoking cannabis ([Morgan et al., 2010b](#)). Furthermore, CBD may also have primary benefits on reduction of  $\beta$ -amyloid in Alzheimer's disease ([Iuvone et al., 2004; Esposito et al., 2006a,b](#)).

Psychopharmacological effects of limonene, pinene and linalool could putatively extend benefits in mood in such patients.

The effects of cannabis on sleep have been reviewed ([Russo et al., 2007](#)), and highlight the benefits that can accrue in this regard, particularly with respect to symptom reduction permitting better sleep, as opposed to a mere hypnotic effect. Certainly, terpenoids with pain-relieving, anti-anxiety or sedative effects may supplement such activity, notably, caryophyllene, linalool and myrcene.

The issue of cannabis addiction remains controversial. Some benefit of oral THC has been noted in cannabis withdrawal ([Hart et al., 2002; Haney et al., 2004](#)). More intriguing, perhaps, are claims of improvement on other substance dependencies, particularly cocaine ([Labigalini et al., 1999; Dreher, 2002](#)). The situation with CBD is yet more promising. CBD and THC at doses of 4 mg·kg<sup>-1</sup> i.p. potentiated extinction of cocaine- and amphetamine-induced conditioned place preference in rats, and CBD produced no hedonic effects of its own ([Parker et al., 2004](#)). CBD 5 mg·kg<sup>-1</sup>·d<sup>-1</sup> in rats attenuated heroin-seeking behaviour by conditioned stimuli, even after a lapse of 2 weeks ([Ren et al., 2009](#)). A suggested mechanism of CBD relates to its ability to reverse changes in  $\alpha$ -amino-3-hydroxyl-5-methyl-4-isoxazole-propionate glutamate and CB<sub>1</sub> receptor expression in the nucleus accumbens induced by heroin. The authors proposed CBD as a treatment for heroin craving and addiction relapse. A recent study demonstrated the fascinating result that patients with damage to the insula due

to cerebrovascular accident were able to quit tobacco smoking without relapse or urges ([Naqvi et al., 2007](#)), highlighting this structure as a critical neural centre mediating addiction to nicotine. Further study has confirmed the role of the insula in cocaine, alcohol and heroin addiction ([Naqvi and Bechara, 2009](#); [Naqvi and Bechara, 2010](#)). In a provocative parallel, CBD 600 mg p.o. was demonstrated to deactivate functional magnetic resonance imaging (fMRI) activity in human volunteers in the left insula versus placebo ( $P < 0.01$ ) without accompanying sedation or psychoactive changes ([Borgwardt et al., 2008](#)), suggesting the possibility that CBD could act as a pharmaceutical surrogate for insular damage in exerting an anti-addiction therapeutic benefit. Human studies have recently demonstrated that human volunteers smoking cannabis with higher CBD content reduced their liking for drug-related stimuli, including food ([Morgan et al., 2010a](#)). The authors posited that CBD can modulate reinforcing properties of drugs of abuse, and help in training to reduce relapse to alcoholism. A single case report of a successful withdrawal from cannabis dependency utilizing pure CBD treatment was recently published ([Crippa et al., 2010](#)).

Perhaps terpenoids can provide adjunctive support. In a clinical trial, 48 cigarette smokers inhaling vapour from an EO of black pepper (*Piper nigrum*), a mint-menthol mixture or placebo ([Rose and Behm, 1994](#)). Black pepper EO reduced nicotine craving significantly ( $P < 0.01$ ), an effect attributed to irritation of the bronchial tree, simulating the act of cigarette smoking, but without nicotine or actual burning of material. Rather, might not the effect have been pharmacological? The terpenoid profile of black pepper suggests possible candidates: myrcene via sedation, pinene via increased alertness, or especially caryophyllene via CB<sub>2</sub> agonism and a newly discovered putative mechanism of action in addiction treatment.

CB<sub>2</sub> is expressed in dopaminergic neurones in the ventral tegmental area and nucleus accumbens, areas mediating addictive phenomena ([Xi et al., 2010](#)). Activation of CB<sub>2</sub> by the synthetic agonist JWH144 administered systemically, intranasally, or by microinjection into the nucleus accumbens in rats inhibited DA release and cocaine self-administration. Caryophyllene, as a high-potency selective CB<sub>2</sub> agonist ([Gertsch et al., 2008](#)), would likely produce similar effects, and have the advantage of being a non-toxic dietary component. All factors considered, CBD, with caryophyllene, and possibly other adjunctive terpenoids in the extract, offers significant promise in future addiction treatment.

### **Taming THC: cannabis entourage compounds as antidotes to intoxication**

[Go to:](#) [Go to:](#)

Various sources highlight the limited therapeutic index of pure THC, when given intravenously ([D'Souza et al., 2004](#)) or orally ([Favrat et al., 2005](#)), especially in people previously naïve to its effects. Acute overdose incidents involving THC or THC-predominant cannabis usually consist of self-limited panic reactions or toxic psychoses, for which no pharmacological intervention is generally necessary, and supportive counselling (reassurance or 'talking down') is sufficient to allow resolution without sequelae. CBD modulates the psychoactivity of THC and reduces its adverse event profile ([Russo and Guy, 2006](#)), highlighted by recent results above described. Could it be, however, that other cannabis components offer additional attenuation of the less undesirable effects of THC? History provides some clues.

In 10th century Persia, Al-Razi offered a prescription in his *Manafi al-agdhiya wa-daf madarri-ha* (p. 248), rendered ([Lozano, 1993](#), p. 124; translation EBR) '– and to avoid these harms {from ingestion of cannabis seeds or hashish}, one should drink fresh water and ice or eat any acid fruits'. This concept was repeated in various forms by various authorities through the ages, including ibn Sina ([ibn Sina \(Avicenna\), 1294](#)), and Ibn al-Baytar ([ibn al-Baytar, 1291](#)), until O'Shaughnessy brought Indian hemp to Britain in 1843 ([O'Shaughnessy, 1843](#)). Robert Christison subsequently cited lemon ([Figure 3A](#)) as an antidote to acute intoxication in numerous cases ([Christison, 1851](#)) and this excerpt regarding morning-after residua ([Christison, 1848](#)) (p. 973):



**Figure 3**

Ancient cannabis antidotes. (A) Lemon (*Citrus limon*). (B) Calamus plant root (*acorus calamus*). (C) Pine nuts (*Pinus* spp.). (D) Black pepper (*Piper nigrum*).

*Next morning there was an ordinary appetite, much torpidity, great defect and shortness of memory, extreme apparent protraction of time, but no peculiarity of articulation or other effect; and these symptoms lasted until 2 P.M., when they ceased entirely in a few minutes after taking lemonade.*

Literary icons on both sides of the Atlantic espoused similar support for the citrus cure in the 19th century, notably Bayard Taylor after travels in Syria ([Taylor, 1855](#)), and Fitzhugh Ludlow after his voluntary experiments with ever higher cannabis extract doses in the USA ([Ludlow, 1857](#)). The sentiment was repeated by [Calkins \(1871\)](#), who noted the suggestion of a friend in Tunis that lemon retained the confidence of cure of overdoses by cannabis users in that region. This is supported by the observation that lemon juice, which normally contains small terpenoid titres, is traditionally enhanced in North Africa by the inclusion in drinks of the limonene-rich rind, as evidenced by the recipe for *Agua Limón* from modern Morocco ([Morse and Mamane, 2001](#)). In his comprehensive review of cannabis in the first half of the 20th century, Walton once more supported its prescription ([Walton, 1938](#)).

Another traditional antidote to cannabis employing *Acorus calamus* ([Figure 3B](#)) is evident from the Ayurvedic tradition of India ([Lad, 1990](#), p. 131):

*Calamus root is the best antidote for the ill effects of marijuana. . . . if one smokes a pinch of calamus root powder with the marijuana, this herb will completely neutralize the toxic side effects of the drug.*

This claim has gained credence, not only through force of anecdotal accounts that abound on the Internet, but with formal scientific case reports and scientific analysis ([McPartland et al., 2008](#)) documenting clearer thinking and improved memory with the cannabis–calamus combination, and with provision of a scientific rationale: calamus contains beta-asarone, an acetylcholinesterase inhibitor with 10% of the potency of physostigmine ([Mukherjee et al., 2007](#)). Interestingly, the cannabis terpenoid,  $\alpha$ -pinene, also has been characterized as a potent inhibitor of that enzyme ([Miyazawa and Yamafuji, 2005](#)), bolstering the hypothesis of a second antidote to THC contained in cannabis itself. Historical precedents also support pinene in this pharmacological role.

In the first century, Pliny wrote of cannabis in his *Natural History, Book XXIV* ([Pliny, 1980](#), p. 164):

*The gelotophyllis [‘leaves of laughter’ = cannabis] grows in Bactria and along the Borysthenes. If this be taken in myrrh and wine all kinds of phantoms beset the mind, causing laughter which persists until the kernels of pine-nuts are taken with pepper and honey in palm wine.*

Of the components, palm wine is perhaps the most mysterious. Ethanol does not reduce cannabis intoxication ([Mello and Mendelson, 1978](#)). However, ancient wines were stored in clay pots or goatskins, and required preservation, usually with addition of pine tar or terebinth resin (from *Pistacia* spp.; [McGovern et al., 2009](#)). Pine tar is rich in pinene, as is terebinth resin (from *Pistacia terebinthus*; [Tsokou et al., 2007](#)), while the latter also contains limonene ([Duru et al., 2003](#)). Likewise, the pine nuts ([Figure 3C](#)) prescribed by Pliny the Elder harbour pinene, along with additional limonene ([Salvadeo et al., 2007](#)). Al-Ukbari also suggested pistachio nuts as a cannabis antidote in the 13th century ([Lozano, 1993](#)), and the ripe fruits of *Pistacia terebinthus* similarly contain pinene ([Couladis et al., 2003](#)). The black pepper ([Figure 3D](#)), might offer the mental clarity afforded by pinene,

sedation via myrcene and helpful contributions by  $\beta$ -caryophyllene. The historical suggestions for cannabis antidotes are thus supported by modern scientific rationales for the claims, and if proven experimentally would provide additional evidence of synergy ([Berenbaum, 1989](#); [Wagner and Ulrich-Merzenich, 2009](#)).

## Conclusions and suggestions for future study

[Go to:](#) [Go to:](#)

Considered ensemble, the preceding body of information supports the concept that selective breeding of cannabis chemotypes rich in ameliorative phytocannabinoid and terpenoid content offer complementary pharmacological activities that may strengthen and broaden clinical applications and improve the therapeutic index of cannabis extracts containing THC, or other base phytocannabinoids. Psychopharmacological and dermatological indications show the greatest promise.

One important remaining order of business is the elucidation of mono- and sesquiterpenoid biosynthetic pathways in cannabis, as has been achieved previously in other species of plants ([Croteau, 1987](#); [Gershenzon and Croteau, 1993](#); [Bohlmann et al., 1998](#); [Turner et al., 1999](#); [Trapp and Croteau, 2001](#)).

Various cannabis component combinations or cannabis extracts should be examined via high throughput pharmacological screening where not previously accomplished. Another goal is the investigation of the biochemical targets of the cannabis terpenoids, along with their mechanisms of action, particularly in the central nervous system. Possible techniques for such research include radio-labelling of select agents in animals with subsequent necropsy. On a molecular level, investigation of terpenoid changes to phytocannabinoid signal transduction and trafficking may prove illuminating. While it is known that terpenoids bind to odorant receptors in the nasal mucosa ([Friedrich, 2004](#)) and proximal olfactory structures ([Barnea et al., 2004](#)), it would be essential to ascertain if direct effects in limbic or other cerebral structures are operative. Given that farnesyl pyrophosphate is a sesquiterpenoid precursor and the most potent endogenous agonist yet discovered for GPR92 ([McHugh et al., 2010](#)), *in silico* studies attempting to match minor cannabinoids and terpenoids to orphan GPCRs may prove fruitful. Behavioural assays of agents in animal models may also provide clues. Simple combinations of phytocannabinoids and terpenoids may demonstrate synergy as antibiotics if MICs are appreciable lowered ([Wagner and Ulrich-Merzenich, 2009](#)). Ultimately, fMRI and single photon emission computed tomography studies in humans, with simultaneous drug reaction questionnaires and psychometric testing employing individual agents and phytocannabinoid-terpenoid pairings via vaporization or oromucosal application, would likely offer safe and effective methods to investigate possible interactions and synergy.

Should positive outcomes result from such studies, phytopharmaceutical development may follow. The development of zero-cannabinoid cannabis chemotypes ([de Meijer et al., 2009b](#)) has provided extracts that will facilitate discernment of the pharmacological effects and contributions of different fractions. Breeding work has already resulted in chemotypes that produce 97% of monoterpenoid content as myrcene, or 77% as limonene (E. de Meijer, pers. comm.). Selective cross-breeding of high-terpenoid- and high-phytocannabinoid-specific chemotypes has thus become a rational target that may lead to novel approaches to such disorders as treatment-resistant depression, anxiety, drug dependency, dementia and a panoply of dermatological disorders, as well as industrial applications as safer pesticides and antiseptics. A better future via cannabis phytochemistry may be an achievable goal through further research of the entourage effect in this versatile plant that may help it fulfil its promise as a pharmacological treasure trove.

## Acknowledgments

[Go to:](#) [Go to:](#)

The author offers appreciation to the following individuals, who provided materials and/or consultation: David Potter, Etienne de Meijer, John McPartland, David Watson, Rob Clarke, Indalecio Lozano, Tamas Biró, José Crippa, Roger Pertwee, Colin Stott, Vincenzo Di Marzo, Luciano De Petrocellis, Patrick McGovern, John Riddle

and Elisaldo Carlini. Most of all, I would like to thank Raphael Mechoulam for his example, guidance, friendship, a life of good works and for listening to many ‘crazy ideas’.

## Glossary

[Go to:](#) [Go to:](#)

---

### Abbreviations

2-AG	2-arachidonoylglycerol
5-HT	5-hydroxytryptamine (serotonin)
AD	antidepressant
AEA	arachidonoylethanolamide (anandamide)
AI	anti-inflammatory
AMPA	$\alpha$ -amino-3-hydroxyl-5-methyl-4-isoxazole-propionate
Ca <sup>++</sup>	calcium ion
CB <sub>1</sub> /CB <sub>2</sub>	cannabinoid receptor 1 or 2
CBC	cannabichromene
CBCA	cannabichromenic acid
CBD	cannabidiol
CBDA	cannabidiolic acid
CBDV	cannabidivarin
CBG	cannabigerol
CBGA	cannabigerolic acid
CBGV	cannabigerivarin
CNS	central nervous system
COX	cyclo-oxygenase
DAGL	diacylglycerol lipase
ECS	endocannabinoid system
EO	essential oil
FAAH	fatty acid amidohydrolase
FDA	US Food and Drug Administration
FEMA	Food and Extract Manufacturers Association

fMRI	functional magnetic resonance imaging
GABA	gamma aminobutyric acid
GPCR	G-protein coupled receptor
GPR	G-protein coupled receptor
HEK	human embryonic kidney
IC <sub>50</sub>	50% inhibitory concentration
i.p	intraperitoneal
MAGL	monoacylglycerol lipase
MIC	minimum inhibitory concentration
MS	multiple sclerosis
NGF	nerve growth factor
NIDA	US National Institute on Drug Abuse
PG	prostaglandin
PTSD	post-traumatic stress disorder
RCT	randomized clinical trial
SPECT	single photon emission computed tomography
SSADH	succinic semialdehyde dehydrogenase
Sx	symptoms
T <sub>1/2</sub>	half-life
TCA	tricyclic antidepressant
THC	tetrahydrocannabinol
THCA	tetrahydrocannabinolic acid
THCV	tetrahydrocannabivarin
TNF- $\alpha$	tumour necrosis factor-alpha, TRPV, transient receptor potential vanilloid receptor

### Conflict of Interest

[Go to:](#) [Go to:](#)

The author is a Senior Medical Advisor to GW Pharmaceuticals and serves as a consultant.

### Supporting Information

[Go to:](#) [Go to:](#)

Teaching Materials; Figs 1–3 as PowerPoint slide.

[Click here to view.](#) (458K, pptx)

## References

Go to: Go to:

Adams TB, Taylor SV. Safety evaluation of essential oils: a constituent-based approach. In: Baser KHC, Buchbauer G, editors. *Handbook of Essential Oils: Science, Technology, and Applications*. Boca Raton, FL: CRC Press; 2010. pp. 185–208.

Alexander SP, Mathie A, Peters JA. Guide to Receptors and Channels (GRAC), 4th edition. *Br J Pharmacol*. 2009;158(Suppl 1):S1–254. [[PMC free article](#)] [[PubMed](#)]

Appendino G, Gibbons S, Giana A, Pagani A, Grassi G, Stavri M, et al. Antibacterial cannabinoids from *Cannabis sativa*: a structure-activity study. *J Nat Prod*. 2008;71:1427–1430. [[PubMed](#)]

Arnhold T, Elmazar MM, Nau H. Prevention of vitamin A teratogenesis by phytol or phytanic acid results from reduced metabolism of retinol to the teratogenic metabolite, all-trans-retinoic acid. *Toxicol Sci*. 2002;66:274–282. [[PubMed](#)]

Arruda DC, D'Alexandri FL, Katzin AM, Uliana SR. Antileishmanial activity of the terpene nerolidol. *Antimicrob Agents Chemother*. 2005;49:1679–1687. [[PMC free article](#)] [[PubMed](#)]

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. *Arch Pharm Res*. 1998;21:353–356. [[PubMed](#)]

Bancroft EA. Antimicrobial resistance: it's not just for hospitals. *JAMA*. 2007;298:1803–1804. [[PubMed](#)]

Banerjee SP, Snyder SH, Mechoulam R. Cannabinoids: influence on neurotransmitter uptake in rat brain synaptosomes. *J Pharmacol Exp Ther*. 1975;194:74–81. [[PubMed](#)]

Bang MH, Choi SY, Jang TO, Kim SK, Kwon OS, Kang TC, et al. Phytol, SSADH inhibitory diterpenoid of *Lactuca sativa*. *Arch Pharm Res*. 2002;25:643–646. [[PubMed](#)]

Barnea G, O'Donnell S, Mancina F, Sun X, Nemes A, Mendelsohn M, et al. Odorant receptors on axon termini in the brain. *Science*. 2004;304:1468. [[PubMed](#)]

Basile AC, Sertie JA, Freitas PC, Zanini AC. Anti-inflammatory activity of oleoresin from Brazilian *Copaifera*. *J Ethnopharmacol*. 1988;22:101–109. [[PubMed](#)]

Batista PA, Werner MF, Oliveira EC, Burgos L, Pereira P, Brum LF, et al. Evidence for the involvement of ionotropic glutamatergic receptors on the antinociceptive effect of (-)-linalool in mice. *Neurosci Lett*. 2008;440:299–303. [[PubMed](#)]

Ben-Shabat S, Fride E, Sheskin T, Tamiri T, Rhee MH, Vogel Z, et al. An entourage effect: inactive endogenous fatty acid glycerol esters enhance 2-arachidonoyl-glycerol cannabinoid activity. *Eur J Pharmacol*. 1998;353:23–31. [[PubMed](#)]

Berenbaum MC. What is synergy? *Pharmacol Rev*. 1989;41:93–141. [[PubMed](#)]

Bettarini F, Borgonovi GE, Fiorani T, Gagliardi I, Caprioli V, Massardo P, et al. Antiparasitic compounds from East African plants: isolation and biological activity of anonaine, matricarianol, canthin-6-one, and

caryophyllene oxide. *Insect Sci Appl.* 1993;14:93–99.

Bickers D, Calow P, Greim H, Hanifin JM, Rogers AE, Saurat JH, et al. A toxicologic and dermatologic assessment of linalool and related esters when used as fragrance ingredients. *Food Chem Toxicol.* 2003;41:919–942. [[PubMed](#)]

Binet L, Binet P, Miocque M, Roux M, Bernier A. Recherches sur les propriétés pharmacodynamiques (action sédative et action spasmolytique) de quelques alcools terpeniques aliphatiques. *Ann Pharm Fr.* 1972;30:611–616. [[PubMed](#)]

Biro T, Olah A, Toth BI, Czifra G, Zouboulis CC, Paus R. Proceedings 19th Annual Conference on the Cannabinoids. Pheasant Run, St. Charles, IL: International Cannabinoid Research Society; 2009. Cannabidiol as a novel anti-acne agent? Cannabidiol inhibits lipid synthesis and induces cell death in human sebaceous gland-derived sebocytes; p. 28.

Bisogno T, Hanus L, De Petrocellis L, Tchilibon S, Ponde DE, Brandi I, et al. Molecular targets for cannabidiol and its synthetic analogues: effect on vanilloid VR1 receptors and on the cellular uptake and enzymatic hydrolysis of anandamide. *Br J Pharmacol.* 2001;134:845–852. [[PMC free article](#)] [[PubMed](#)]

Bisset NG, Wichtl M. *Herbal Drugs and Phytopharmaceuticals: A Handbook for Practice on A Scientific Basis.* 3rd edn. Boca Raton, FL: Medpharm Scientific Publishers; Stuttgart; CRC Press; 2004.

Bloor RN, Wang TS, Spanel P, Smith D. Ammonia release from heated ‘street’ cannabis leaf and its potential toxic effects on cannabis users. *Addiction.* 2008;103:1671–1677. [[PubMed](#)]

Bohlmann J, Meyer-Gauen G, Croteau R. Plant terpenoid synthases: molecular biology and phylogenetic analysis. *Proc Natl Acad Sci USA.* 1998;95:4126–4133. [[PMC free article](#)] [[PubMed](#)]

Bolognini D, Costa B, Maione S, Comelli F, Marini P, Di Marzo V, et al. The plant cannabinoid Delta9-tetrahydrocannabivarin can decrease signs of inflammation and inflammatory pain in mice. *Br J Pharmacol.* 2010;160:677–687. [[PMC free article](#)] [[PubMed](#)]

Borgwardt SJ, Allen P, Bhattacharyya S, Fusar-Poli P, Crippa JA, Seal ML, et al. Neural basis of Delta-9-tetrahydrocannabinol and cannabidiol: effects during response inhibition. *Biol Psychiatry.* 2008;64:966–973. [[PubMed](#)]

Bowles EJ. *The Chemistry of Aromatherapeutic Oils.* 3rd edn. Crow's Nest, NSW: Allen & Unwin; 2003.

Bradshaw HB, Lee SH, McHugh D. Orphan endogenous lipids and orphan GPCRs: a good match. *Prostaglandins Other Lipid Mediat.* 2009;89:131–134. [[PMC free article](#)] [[PubMed](#)]

Brenneisen R. Chemistry and analysis of phytocannabinoids and other *Cannabis* constituents. In: Elsohly M, editor. *Marijuana and the Cannabinoids.* Totowa, NY: Humana Press; 2007. pp. 17–49.

Buchbauer G. Biological activities of essential oils. In: Baser KHC, Buchbauer G, editors. *Handbook of Essential Oils: Science, Technology, and Applications.* Boca Raton, FL: CRC Press; 2010. pp. 235–280.

Buchbauer G, Jirovetz L, Jager W, Dietrich H, Plank C. Aromatherapy: evidence for sedative effects of the essential oil of lavender after inhalation. *Z Naturforsch [C]* 1991;46:1067–1072. [[PubMed](#)]

Buchbauer G, Jirovetz L, Jager W, Plank C, Dietrich H. Fragrance compounds and essential oils with sedative effects upon inhalation. *J Pharm Sci.* 1993;82:660–664. [[PubMed](#)]

Calkins A. *Opium and the Opium-Appetite: with Notices of Alcoholic Beverages, Cannabis Indica, Tobacco and*

Coca, and Tea and Coffee, in Their Hygienic Aspects and Pathologic Relationships. Philadelphia, PA: J.B. Lippincott; 1871.

Campbell WE, Gammon DW, Smith P, Abrahams M, Purves TD. Composition and antimalarial activity in vitro of the essential oil of *Tetradenia riparia*. *Planta Med*. 1997;63:270–272. [[PubMed](#)]

Carlini EA, Cunha JM. Hypnotic and antiepileptic effects of cannabidiol. *J Clin Pharmacol*. 1981;21(Suppl):417S–427S. [[PubMed](#)]

Carlini EA, Karniol IG, Renault PF, Schuster CR. Effects of marijuana in laboratory animals and in man. *Br J Pharmacol*. 1974;50:299–309. [[PMC free article](#)] [[PubMed](#)]

Carrier EJ, Auchampach JA, Hillard CJ. Inhibition of an equilibrative nucleoside transporter by cannabidiol: a mechanism of cannabinoid immunosuppression. *Proc Natl Acad Sci USA*. 2006;103:7895–7900. [[PMC free article](#)] [[PubMed](#)]

Carvalho-Freitas MI, Costa M. Anxiolytic and sedative effects of extracts and essential oil from *Citrus aurantium* L. *Biol Pharm Bull*. 2002;25:1629–1633. [[PubMed](#)]

Cascio MG, Gauson LA, Stevenson LA, Ross RA, Pertwee RG. Evidence that the plant cannabinoid cannabigerol is a highly potent alpha2-adrenoceptor agonist and moderately potent 5HT1A receptor antagonist. *Br J Pharmacol*. 2010;159:129–141. [[PMC free article](#)] [[PubMed](#)]

Cawthorne MA, Wargent E, Zaibi M, Stott C, Wright S. Proceedings 17th Annual Symposium on the Cannabinoids. Saint-Sauveur, QC: International Cannabinoid Research Society; 2007. The CB1 antagonist, delta-9-tetrahydrocannabivarin (THCV) has anti-obesity activity in dietary-induced obese (DIO) mice; p. 141.

Choi HS, Song HS, Ukeda H, Sawamura M. Radical-scavenging activities of citrus essential oils and their components: detection using 1,1-diphenyl-2-picrylhydrazyl. *J Agric Food Chem*. 2000;48:4156–4161. [[PubMed](#)]

Christison R. *A Dispensatory Or Commentary on the Pharmacopoeias of Great Britain and the United States*. Philadelphia, PA: Lea and Blanchard; 1848.

Christison A. On the natural history, action, and uses of Indian hemp. *Monthly J Med Sci Edinburgh, Scotland*. 1851;13:26–45. 117-121.

Clarke RC. *Hashish!* 2nd edn. Los Angeles, CA: Red Eye Press; 2010.

Comelli F, Bettoni I, Colleoni M, Giagnoni G, Costa B. Beneficial effects of a *Cannabis sativa* extract treatment on diabetes-induced neuropathy and oxidative stress. *Phytother Res*. 2009;23:1678–1684. [[PubMed](#)]

Cornwell PA, Barry BW. Sesquiterpene components of volatile oils as skin penetration enhancers for the hydrophilic permeant 5-fluorouracil. *J Pharm Pharmacol*. 1994;46:261–269. [[PubMed](#)]

Costa B, Trovato AE, Comelli F, Giagnoni G, Colleoni M. The non-psychoactive cannabis constituent cannabidiol is an orally effective therapeutic agent in rat chronic inflammatory and neuropathic pain. *Eur J Pharmacol*. 2007;556:75–83. [[PubMed](#)]

Couladis M, Ozcan M, Tzakou O, Akgul A. Comparative essential oil composition of various parts of the turpentine tree (*Pistacia terebinthus*) growing wild in Turkey. *J Sci Food Agric*. 2003;83:136–138.

Crippa JA, Zuardi AW, Hallak JE. [Therapeutical use of the cannabinoids in psychiatry] *Rev Bras Psiquiatr*. 2010;32(Suppl 1):S56–S66. [[PubMed](#)]

- Crippa JA, Derenusson GN, Ferrari TB, Wichert-Ana L, Duran F, Marti NSRO, et al. Neural basis of anxiolytic effects of cannabidiol (CBD) in generalized social anxiety disorder: a preliminary report. *J Psychopharmacol*. 2011;25:121–130. [[PubMed](#)]
- Croteau R. Biosynthesis and catabolism of monoterpenoids. *Chem Rev*. 1987;87:929–954.
- De Oliveira AC, Ribeiro-Pinto LF, Paumgartten JR. *In vitro* inhibition of CYP2B1 monooxygenase by beta-myrcene and other monoterpenoid compounds. *Toxicol Lett*. 1997;92:39–46. [[PubMed](#)]
- D'Souza DC, Perry E, MacDougall L, Ammerman Y, Cooper T, Wu YT, et al. The psychotomimetic effects of intravenous delta-9-tetrahydrocannabinol in healthy individuals: implications for psychosis. *Neuropsychopharmacology*. 2004;29:1558–1572. [[PubMed](#)]
- Davalos SD, Fournier G, Boucher F, Paris M. [Contribution to the study of Mexican marihuana. Preliminary studies: cannabinoids and essential oil (author's transl)] *J Pharm Belg*. 1977;32:89–99. [[PubMed](#)]
- Davis WM, Hatoum NS. Neurobehavioral actions of cannabichromene and interactions with delta 9-tetrahydrocannabinol. *Gen Pharmacol*. 1983;14:247–252. [[PubMed](#)]
- De Oliveira AC, Ribeiro-Pinto LF, Paumgartten JR. In vitro inhibition of CYP2B1 monooxygenase by beta-myrcene and other monoterpenoid compounds. *Toxicol Lett*. 1997;92:39–46. [[PubMed](#)]
- De Petrocellis L, Di Marzo V. Non-CB1, non-CB2 receptors for endocannabinoids, plant cannabinoids, and synthetic cannabimimetics: focus on G-protein-coupled receptors and transient receptor potential channels. *J Neuroimmune Pharmacol*. 2010;5:103–121. [[PubMed](#)]
- De Petrocellis L, Vellani V, Schiano-Moriello A, Marini P, Magherini PC, Orlando P, et al. Plant-derived cannabinoids modulate the activity of transient receptor potential channels of ankyrin type-1 and melastatin type-8. *J Pharmacol Exp Ther*. 2008;325:1007–1015. [[PubMed](#)]
- De Petrocellis L, Ligresti A, Moriello AS, Allara M, Bisogno T, Petrosino S, et al. Effects of cannabinoids and cannabinoid-enriched *Cannabis* extracts on TRP channels and endocannabinoid metabolic enzymes. *Br J Pharmacol*. 2011 DOI: 10.1111/j.1476-5381.2010.0166.x. [[PMC free article](#)] [[PubMed](#)]
- Delgado P, Moreno F. Antidepressants and the brain. *Int Clin Psychopharmacol*. 1999;14(Suppl 1):S9–16. [[PubMed](#)]
- DeLong GT, Wolf CE, Poklis A, Lichtman AH. Pharmacological evaluation of the natural constituent of *Cannabis sativa*, cannabichromene and its modulation by Delta(9)-tetrahydrocannabinol. *Drug Alcohol Depend*. 2010;112:126–133. [[PMC free article](#)] [[PubMed](#)]
- Denson TF, Earleywine M. Decreased depression in marijuana users. *Addict Behav*. 2006;31:738–742. [[PubMed](#)]
- Devane WA, Dysarz FA, 3rd, Johnson MR, Melvin LS, Howlett AC. Determination and characterization of a cannabinoid receptor in rat brain. *Mol Pharmacol*. 1988;34:605–613. [[PubMed](#)]
- Devane WA, Hanus L, Breuer A, Pertwee RG, Stevenson LA, Griffin G, et al. Isolation and structure of a brain constituent that binds to the cannabinoid receptor. *Science*. 1992;258:1946–1949. [[PubMed](#)]
- Deyo R, Musty R. Proceedings 2003 Symposium on the Cannabinoids. Cornwall, ON: International Cannabinoid Research Society; 2003. A cannabichromene (CBC) extract alters behavioral despair on the mouse tail suspension test of depression; p. 146.
- Dirikoc S, Priola SA, Marella M, Zsuzger N, Chabry J. Nonpsychoactive cannabidiol prevents prion

- accumulation and protects neurons against prion toxicity. *J Neurosci.* 2007;27:9537–9544. [[PubMed](#)]
- Dobrosi N, Toth BI, Nagy G, Dozsa A, Geczy T, Nagy G, et al. Endocannabinoids enhance lipid synthesis and apoptosis of human sebocytes via cannabinoid receptor-2-mediated signaling. *FASEB J.* 2008;22:3685–3695. [[PubMed](#)]
- Douthwaite AH. Choice of drugs in the treatment of duodenal ulcer. *Br Med J.* 1947;2:43–47. [[PMC free article](#)] [[PubMed](#)]
- Dreher M. Crack heads and roots daughters: the therapeutic use of cannabis in Jamaica. *J Cannabis Therap.* 2002;2:121–133.
- Duru ME, Cakir A, Kordali S, Zengin H, Harmandar M, Izumi S, et al. Chemical composition and antifungal properties of essential oils of three Pistacia species. *Fitoterapia.* 2003;74:170–176. [[PubMed](#)]
- Elisabetsky E, Marschner J, Souza DO. Effects of Linalool on glutamatergic system in the rat cerebral cortex. *Neurochem Res.* 1995;20:461–465. [[PubMed](#)]
- ElSohly HN, Turner CE, Clark AM, ElSohly MA. Synthesis and antimicrobial activities of certain cannabichromene and cannabigerol related compounds. *J Pharm Sci.* 1982;71:1319–1323. [[PubMed](#)]
- Esposito G, De Filippis D, Carnuccio R, Izzo AA, Iuvone T. The marijuana component cannabidiol inhibits beta-amyloid-induced tau protein hyperphosphorylation through Wnt/beta-catenin pathway rescue in PC12 cells. *J Mol Med.* 2006a;84:253–258. [[PubMed](#)]
- Esposito G, De Filippis D, Maiuri MC, De Stefano D, Carnuccio R, Iuvone T. Cannabidiol inhibits inducible nitric oxide synthase protein expression and nitric oxide production in beta-amyloid stimulated PC12 neurons through p38 MAP kinase and NF-kappaB involvement. *Neurosci Lett.* 2006b;399:91–95. [[PubMed](#)]
- Eubanks LM, Rogers CJ, Beuscher AE, 4th, Koob GF, Olson AJ, Dickerson TJ, et al. A molecular link between the active component of marijuana and Alzheimer's disease pathology. *Mol Pharm.* 2006;3:773–777. [[PMC free article](#)] [[PubMed](#)]
- Evans FJ. Cannabinoids: the separation of central from peripheral effects on a structural basis. *Planta Med.* 1991;57:S60–S67. [[PubMed](#)]
- Fairbairn JW, Pickens JT. Activity of cannabis in relation to its delta'-trans-tetrahydro-cannabinol content. *Br J Pharmacol.* 1981;72:401–409. [[PMC free article](#)] [[PubMed](#)]
- Falk AA, Hagberg MT, Lof AE, Wigaeus-Hjelm EM, Wang ZP. Uptake, distribution and elimination of alpha-pinene in man after exposure by inhalation. *Scand J Work Environ Health.* 1990;16:372–378. [[PubMed](#)]
- Falk-Filipsson A, Lof A, Hagberg M, Hjelm EW, Wang Z. d-limonene exposure to humans by inhalation: uptake, distribution, elimination, and effects on the pulmonary function. *J Toxicol Environ Health.* 1993;38:77–88. [[PubMed](#)]
- Fan X, Gates RA. Degradation of monoterpenes in orange juice by gamma radiation. *J Agric Food Chem.* 2001;49:2422–2426. [[PubMed](#)]
- Fan X, Sokorai KJ. Changes in volatile compounds of gamma-irradiated fresh cilantro leaves during cold storage. *J Agric Food Chem.* 2002;50:7622–7626. [[PubMed](#)]
- Farag RS, Shalaby AS, El-Baroty GA, Ibrahim NA, Ali MA, Hassan EM. Chemical and biological evaluation of the essential oils of different Melaleuca species. *Phytother Res.* 2004;18:30–35. [[PubMed](#)]

- Favrat B, Menetrey A, Augsburger M, Rothuizen L, Appenzeller M, Buclin T, et al. Two cases of 'cannabis acute psychosis' following the administration of oral cannabis. *BMC Psychiatry*. 2005;5:17. [[PMC free article](#)] [[PubMed](#)]
- Fellermeier M, Eisenreich W, Bacher A, Zenk MH. Biosynthesis of cannabinoids. Incorporation experiments with (13)C-labeled glucoses. *Eur J Biochem*. 2001;268:1596–1604. [[PubMed](#)]
- Fischedick JT, Hazekamp A, Erkelens T, Choi YH, Verpoorte R. Metabolic fingerprinting of *Cannabis sativa* L., cannabinoids and terpenoids for chemotaxonomic and drug standardization purposes. *Phytochem*. 2010;71:2058–2073. [[PubMed](#)]
- Formukong EA, Evans AT, Evans FJ. Analgesic and antiinflammatory activity of constituents of *Cannabis sativa* L. *Inflammation*. 1988;12:361–371. [[PubMed](#)]
- Franz C, Novak J. Sources of essential oils. In: Baser KHC, Buchbauer G, editors. *Handbook of Essential Oils: Science, Technology, and Applications*. Boca Raton, FL: CRC Press; 2010. pp. 39–82.
- Fride E, Russo EB. Neuropsychiatry: Schizophrenia, depression, and anxiety. In: Onaivi E, Sugiura T, Di Marzo V, editors. *Endocannabinoids: The Brain and Body's Marijuana and beyond*. Boca Raton, FL: Taylor & Francis; 2006. pp. 371–382.
- Friedrich RW. Neurobiology: odorant receptors make scents. *Nature*. 2004;430:511–512. [[PubMed](#)]
- Fukumoto S, Morishita A, Furutachi K, Terashima T, Nakayama T, Yokogoshi H. Effect of flavour components in lemon essential oil on physical or psychological stress. *Stress Health*. 2008;24:3–12.
- Fusar-Poli P, Allen P, Bhattacharyya S, Crippa JA, Mechelli A, Borgwardt S, et al. Modulation of effective connectivity during emotional processing by Delta9-tetrahydrocannabinol and cannabidiol. *Int J Neuropsychopharmacol*. 2010;13:421–432. [[PubMed](#)]
- Fusar-Poli P, Crippa JA, Bhattacharyya S, Borgwardt SJ, Allen P, Martin-Santos R, et al. Distinct effects of {delta}9-tetrahydrocannabinol and cannabidiol on neural activation during emotional processing. *Archiv Gen Psychiatr*. 2009;66:95–105. [[PubMed](#)]
- Gaoni Y, Mechoulam R. Isolation, structure and partial synthesis of an active constituent of hashish. *J Am Chem Soc*. 1964a;86:1646–1647.
- Gaoni Y, Mechoulam R. The structure and function of cannabigerol, a new hashish constituent. *Proc Chem Soc*. 1964b;1:82.
- Gaoni Y, Mechoulam R. Cannabichromene, a new active principle in hashish. *Chem Commun*. 1966;1:20–21.
- Gattefosse R-M. *Gatefosse's Aromatherapy*. Essex, MD: C.W. Daniel; 1993.
- Gauson LA, Stevenson LA, Thomas A, Baillie GL, Ross RA, Pertwee RG. Proceedings 17th Annual Symposium on the Cannabinoids. Saint-Sauveur, QC: International Cannabinoid Research Society; 2007. Cannabigerol behaves as a partial agonist at both CB1 and CB2 receptors; p. 206.
- Gerdeman GL, Lovinger DM. Emerging roles for endocannabinoids in long-term synaptic plasticity. *Br J Pharmacol*. 2003;140:781–789. [[PMC free article](#)] [[PubMed](#)]
- Gershenzon J. Metabolic costs of terpenoid accumulation in higher plants. *J Chem Ecol*. 1994;20:1281–1328. [[PubMed](#)]

Gershenzon J, Croteau R. Terepenoid Biosynthesis: the basic pathway and formation of monoterpenes, sesquiterpenes, and diterpenes. In: Moore TS, editor. *Lipid Metabolism in Plants*. Boca Raton, FL: CRC Press; 1993. pp. 339–388.

Gertsch J. Anti-inflammatory cannabinoids in diet: towards a better understanding of CB(2) receptor action? *Commun Integr Biol*. 2008;1:26–28. [[PMC free article](#)] [[PubMed](#)]

Gertsch J, Leonti M, Raduner S, Racz I, Chen JZ, Xie XQ, et al. Beta-caryophyllene is a dietary cannabinoid. *Proc Natl Acad Sci USA*. 2008;105:9099–9104. [[PMC free article](#)] [[PubMed](#)]

Ghelardini C, Galeotti N, Salvatore G, Mazzanti G. Local anaesthetic activity of the essential oil of *Lavandula angustifolia*. *Planta Med*. 1999;65:700–703. [[PubMed](#)]

Gil ML, Jimenez J, Ocete MA, Zarzuelo A, Cabo MM. Comparative study of different essential oils of *Bupleurum gibraltarium* Lamarck. *Pharmazie*. 1989;44:284–287. [[PubMed](#)]

Gill EW, Paton WD, Pertwee RG. Preliminary experiments on the chemistry and pharmacology of cannabis. *Nature*. 1970;228:134–136. [[PubMed](#)]

Giuffrida A, Leweke FM, Gerth CW, Schreiber D, Koethe D, Faulhaber J, et al. Cerebrospinal anandamide levels are elevated in acute schizophrenia and are inversely correlated with psychotic symptoms. *Neuropsychopharmacol*. 2004;29:2108–2114. [[PubMed](#)]

Gomes-Carneiro MR, Viana ME, Felzenszwalb I, Paumgarten FJ. Evaluation of beta-myrcene, alpha-terpinene and (+)- and (-)-alpha-pinene in the Salmonella/microsome assay. *Food Chem Toxicol*. 2005;43:247–252. [[PubMed](#)]

Guy GW, Stott CG. The development of Sativex- a natural cannabis-based medicine. In: Mechoulam R, editor. *Cannabinoids As Therapeutics*. Basel: Birkhäuser Verlag; 2005. pp. 231–263.

Hampson AJ, Grimaldi M, Axelrod J, Wink D. Cannabidiol and (-)Delta9-tetrahydrocannabinol are neuroprotective antioxidants. *Proc Natl Acad Sci USA*. 1998;95:8268–8273. [[PMC free article](#)] [[PubMed](#)]

Haney M, Hart CL, Vosburg SK, Nasser J, Bennett A, Zubarán C, et al. Marijuana withdrawal in humans: effects of oral THC or divalproex. *Neuropsychopharmacol*. 2004;29:158–170. [[PubMed](#)]

Hanus L, Breuer A, Tchilibon S, Shiloah S, Goldenberg D, Horowitz M, et al. HU-308: a specific agonist for CB(2), a peripheral cannabinoid receptor. *Proc Natl Acad Sci USA*. 1999;96:14228–14233. [[PMC free article](#)] [[PubMed](#)]

Harris B. Phytotherapeutic uses of essential oils. In: Baser KHC, Buchbauer G, editors. *Handbook of Essential Oils: Science, Technology, and Applications*. Boca Raton, FL: CRC Press; 2010. pp. 315–352.

Hart CL, Haney M, Ward AS, Fischman MW, Foltin RW. Effects of oral THC maintenance on smoked marijuana self-administration. *Drug Alcohol Depend*. 2002;67:301–309. [[PubMed](#)]

Hatoum NS, Davis WM, Elsohly MA, Turner CE. Cannabichromene and delta 9-tetrahydrocannabinol: interactions relative to lethality, hypothermia and hexobarbital hypnosis. *Gen Pharmacol*. 1981;12:357–362. [[PubMed](#)]

Hendriks H, Malingré TM, Batterman S, Bos R. Mono- and sesqui-terpene hydrocarbons of the essential oil of *Cannabis sativa*. *Phytochem*. 1975;14:814–815.

Hendriks H, Malingré TM, Batterman S, Bos R. Alkanes of the essential oil of *Cannabis sativa*. *Phytochem*.

1977;16:719–721.

Hill MN, Gorzalka BB. Is there a role for the endocannabinoid system in the etiology and treatment of melancholic depression? *Behav Pharmacol.* 2005a;16:333–352. [[PubMed](#)]

Hill MN, Gorzalka BB. Pharmacological enhancement of cannabinoid CB1 receptor activity elicits an antidepressant-like response in the rat forced swim test. *Eur Neuropsychopharmacol.* 2005b;15:593–599. [[PubMed](#)]

Hill AJ, Weston SE, Jones NA, Smith I, Bevan SA, Williamson EM, et al. Delta-Tetrahydrocannabinol suppresses in vitro epileptiform and in vivo seizure activity in adult rats. *Epilepsia.* 2010;51:1522–1532. [[PubMed](#)]

Hohmann AG, Suplita RL, Bolton NM, Neely MH, Fegley D, Mangieri R, et al. An endocannabinoid mechanism for stress-induced analgesia. *Nature.* 2005;435:1108–1112. [[PubMed](#)]

Holland ML, Allen JD, Arnold JC. Interaction of plant cannabinoids with the multidrug transporter ABCB1 (MRP1) *Eur J Pharmacol.* 2008;591:128–131. [[PubMed](#)]

Hollister LE. Structure-activity relationships in man of cannabis constituents, and homologs and metabolites of delta9-tetrahydrocannabinol. *Pharmacol.* 1974;11:3–11. [[PubMed](#)]

Hood LV, Dames ME, Barry GT. Headspace volatiles of marijuana. *Nature.* 1973;242:402–403. [[PubMed](#)]

Howlett AC. Cannabinoid inhibition of adenylate cyclase: relative activity of constituents and metabolites of marijuana. *Neuropharmacol.* 1987;26:507–512. [[PubMed](#)]

Huestis MA. Human Cannabinoid Pharmacokinetics. *Chem Biodivers.* 2007;4:1770–1804. [[PMC free article](#)] [[PubMed](#)]

ibn al-Baytar. *Kitab al-Yami' li-mufradat al-adwiya wa-l-agdiya.* Egypt: Bulaq; 1291.

ibn Sina (Avicenna) *Al-Qanun fi l-tibb (Canon of medicine)* Egypt: Bulaq; 1294.

Ignatowska-Jankowska B, Jankowski M, Glac W, Swiergel AH. Cannabidiol-induced lymphopenia does not involve NKT and NK cells. *J Physiol Pharmacol.* 2009;60(Suppl 3):99–103. [[PubMed](#)]

Ilan AB, Gevins A, Coleman M, ElSohly MA, de Wit H. Neurophysiological and subjective profile of marijuana with varying concentrations of cannabinoids. *Behav Pharmacol.* 2005;16:487–496. [[PubMed](#)]

Ismail M. Central properties and chemical composition of *Ocimum basilicum* essential oil. *Pharm Biol.* 2006;44:619–626.

Iuvone T, Esposito G, Esposito R, Santamaria R, Di Rosa M, Izzo AA. Neuroprotective effect of cannabidiol, a non-psychoactive component from *Cannabis sativa*, on beta-amyloid-induced toxicity in PC12 cells. *J Neurochem.* 2004;89:134–141. [[PubMed](#)]

Izzo AA, Borrelli F, Capasso R, Di Marzo V, Mechoulam R. Non-psychoactive plant cannabinoids: new therapeutic opportunities from an ancient herb. *Trends Pharmacol Sci.* 2009;30:515–527. [[PubMed](#)]

Jäger W, Buchbauer G, Jirovetz L, Fritzer M. Percutaneous absorption of lavender oil from a massage oil. *J Soc Cosmet Chem.* 1992;43:49–54. Jan/Feb.

Jirovetz L, Buchbauer G, Jäger W, Woidich A, Nikiforov A. Analysis of fragrance compounds in blood samples of mice by gas chromatography, mass spectrometry, GC/FTIR and GC/AES after inhalation of sandalwood oil.

Biomed Chromatogr. 1992;6:133–134. [[PubMed](#)]

Johnson JR, Burnell-Nugent M, Lossignol D, Ganae-Motan ED, Potts R, Fallon MT. Multicenter, double-blind, randomized, placebo-controlled, parallel-group study of the efficacy, safety, and tolerability of THC:CBD extract and THC extract in patients with intractable cancer-related pain. *J Pain Symptom Manage.* 2010;39:167–179. [[PubMed](#)]

Jones NA, Hill AJ, Smith I, Bevan SA, Williams CM, Whalley BJ, et al. Cannabidiol displays antiepileptiform and antiseizure properties in vitro and in vivo. *J Pharmacol Exp Ther.* 2010;332:569–577. [[PMC free article](#)] [[PubMed](#)]

Karsak M, Gaffal E, Date R, Wang-Eckhardt L, Rehnelt J, Petrosino S, et al. Attenuation of allergic contact dermatitis through the endocannabinoid system. *Science.* 2007;316:1494–1497. [[PubMed](#)]

Kavia R, De Ridder D, Constantinescu C, Stott C, Fowler C. Randomized controlled trial of Sativex to treat detrusor overactivity in multiple sclerosis. *Mult Scler.* 2010;16:1349–1359. [[PubMed](#)]

Kim JT, Ren CJ, Fielding GA, Pitti A, Kasumi T, Wajda M, et al. Treatment with lavender aromatherapy in the post-anesthesia care unit reduces opioid requirements of morbidly obese patients undergoing laparoscopic adjustable gastric banding. *Obes Surg.* 2007;17:920–925. [[PubMed](#)]

Kim SS, Baik JS, Oh TH, Yoon WJ, Lee NH, Hyun CG. Biological activities of Korean Citrus obovoides and Citrus natsudaoidai essential oils against acne-inducing bacteria. *Biosci Biotechnol Biochem.* 2008;72:2507–2513. [[PubMed](#)]

King LA, Carpentier C, Griffiths P. Cannabis potency in Europe. *Addiction.* 2005;100:884–886. [[PubMed](#)]

Komiya M, Takeuchi T, Harada E. Lemon oil vapor causes an anti-stress effect via modulating the 5-HT and DA activities in mice. *Behav Brain Res.* 2006;172:240–249. [[PubMed](#)]

Komori T, Fujiwara R, Tanida M, Nomura J, Yokoyama MM. Effects of citrus fragrance on immune function and depressive states. *Neuroimmunomodulation.* 1995;2:174–180. [[PubMed](#)]

Kose EO, Deniz IG, Sarikurkcu C, Aktas O, Yavuz M. Chemical composition, antimicrobial and antioxidant activities of the essential oils of *Sideritis erythrantha* Boiss. and Heldr. (var. *erythrantha* and var. *cedretorum* P.H. Davis) endemic in Turkey. *Food Chem Toxicol.* 2010;48:2960–2965. [[PubMed](#)]

Labigalini E, Jr, Rodrigues LR, Da Silveira DX. Therapeutic use of cannabis by crack addicts in Brazil. *J Psychoactive Drugs.* 1999;31:451–455. [[PubMed](#)]

Lad V. *Ayurveda: the Science of Self-Healing: A Practical Guide.* Milwaukee, WI: Lotus Light Publications; 1990.

Langenheim JH. Higher plant terpenoids: a phytocentric overview of their ecological roles. *J Chem Ecol.* 1994;20:1223–1279. [[PubMed](#)]

Lapczynski A, Bhatia SP, Letizia CS, Api AM. Fragrance material review on nerolidol (isomer unspecified) *Food Chem Toxicol.* 2008;46(Suppl 11):S247–S250. [[PubMed](#)]

Lawless J. *The Illustrated Encyclopedia of Essential Oils : the Complete Guide to the Use of Oils in Aromatherapy and Herbalism.* Shaftesbury, Dorset, [England]; Rockport, MA: Element; 1995.

Ligresti A, Moriello AS, Starowicz K, Matias I, Pisanti S, De Petrocellis L, et al. Antitumor activity of plant cannabinoids with emphasis on the effect of cannabidiol on human breast carcinoma. *J Pharmacol Exp Ther.*

2006;318:1375–1387. [[PubMed](#)]

Lin WY, Kuo YH, Chang YL, Teng CM, Wang EC, Ishikawa T, et al. Anti-platelet aggregation and chemical constituents from the rhizome of *Gynura japonica*. *Planta Med.* 2003;69:757–764. [[PubMed](#)]

Lis-Balchin M. Aromatherapy with essential oils. In: Baser KHC, Buchbauer G, editors. *Handbook of Essential Oils: Science, Technology, and Applications*. Boca Raton, FL: CRC Press; 2010. pp. 549–584.

Lopes NP, Kato MJ, Andrade EH, Maia JG, Yoshida M, Planchart AR, et al. Antimalarial use of volatile oil from leaves of *Viola surinamensis* (Rol.) Warb. by Waiapi Amazon Indians. *J Ethnopharmacol.* 1999;67:313–319. [[PubMed](#)]

Lorenzetti BB, Souza GE, Sarti SJ, Santos Filho D, Ferreira SH. Myrcene mimics the peripheral analgesic activity of lemongrass tea. *J Ethnopharmacol.* 1991;34:43–48. [[PubMed](#)]

Lozano I. *Estudios Y Documentos Sobre La Historia Del Cáñamo Y Del Hachís En El Islam Medieval* doctoral Dissertation. Granada: Universidad de Granada; 1993.

Ludlow FH. *The Hasheesh Eater: Being Passages Form the Life of A Pythagorean*. New York: Harper; 1857.

McGinty D, Letizia CS, Api AM. Fragrance material review on phytol. *Food Chem Toxicol.* 2010;48(Suppl 3):S59–S63. [[PubMed](#)]

McGovern PE, Mirzoian A, Hall GR. Ancient Egyptian herbal wines. *Proc Natl Acad Sci USA.* 2009;106:7361–7366. [[PMC free article](#)] [[PubMed](#)]

McHugh D, Hu SS, Rimmerman N, Juknat A, Vogel Z, Walker JM, et al. N-arachidonoyl glycine, an abundant endogenous lipid, potently drives directed cellular migration through GPR18, the putative abnormal cannabidiol receptor. *BMC Neurosci.* 2010;11:44. [[PMC free article](#)] [[PubMed](#)]

McPartland J. Pathogenicity of *Phomopsis ganjae* on *Cannabis sativa* and the fungistatic effect of cannabinoids produced by the host. *Mycopathologia.* 1984;87:149–153.

McPartland JM, Pruitt PL. Side effects of pharmaceuticals not elicited by comparable herbal medicines: the case of tetrahydrocannabinol and marijuana. *Altern Ther Health Med.* 1999;5:57–62. [[PubMed](#)]

McPartland JM, Mediavilla V. Non-cannabinoids in cannabis. In: Grotenhermen F, Russo EB, editors. *Cannabis and Cannabinoids*. Binghamton, NY: NY: Haworth Press; 2001a. pp. 401–409.

McPartland JM, Russo EB. Cannabis and cannabis extracts: greater than the sum of their parts? *J Cannabis Therap.* 2001b;1:103–132.

McPartland JM, Clarke RC, Watson DP. *Hemp Diseases and Pests: Management and Biological Control*. Wallingford: CABI; 2000.

McPartland JM, Blanchon DJ, Musty RE. Cannabimimetic effects modulated by cholinergic compounds. *Addict Biol.* 2008;13:411–415. [[PubMed](#)]

Magen I, Avraham Y, Ackerman Z, Vorobiev L, Mechoulam R, Berry EM. Cannabidiol ameliorates cognitive and motor impairments in mice with bile duct ligation. *J Hepatol.* 2009;51:528–534. [[PubMed](#)]

Malfait AM, Gallily R, Sumariwalla PF, Malik AS, Andreakos E, Mechoulam R, et al. The nonpsychoactive cannabis constituent cannabidiol is an oral anti-arthritic therapeutic in murine collagen-induced arthritis. *Proc Natl Acad Sci USA.* 2000;97:9561–9566. [[PMC free article](#)] [[PubMed](#)]

- Malingre T, Hendriks H, Batterman S, Bos R, Visser J. The essential oil of *Cannabis sativa*. *Planta Med*. 1975;28:56–61. [[PubMed](#)]
- Maor Y, Gallily R, Mechoulam R. Symposium on the Cannabinoids. Tihany, Hungary: International Cannabinoid Research Society; 2006. The relevance of the steric factor in the biological activity of CBD derivatives—a tool in identifying novel molecular target for cannabinoids; p. 1.
- Marsicano G, Wotjak CT, Azad SC, Bisogno T, Rammes G, Cascio MG, et al. The endogenous cannabinoid system controls extinction of aversive memories. *Nature*. 2002;418:530–534. [[PubMed](#)]
- Matura M, Skold M, Borje A, Andersen KE, Bruze M, Frosch P, et al. Selected oxidized fragrance terpenes are common contact allergens. *Contact Dermatitis*. 2005;52:320–328. [[PubMed](#)]
- de Meijer E. The breeding of cannabis cultivars for pharmaceutical end uses. In: Guy GW, Whittle BA, Robson P, editors. *Medicinal Uses of Cannabis and Cannabinoids*. London: Pharmaceutical Press; 2004. pp. 55–70.
- de Meijer EPM, Hammond KM. The inheritance of chemical phenotype in *Cannabis sativa* L. (II): cannabigerol predominant plants. *Euphytica*. 2005;145:189–198.
- de Meijer EP, Bagatta M, Carboni A, Crucitti P, Moliterni VM, Ranalli P, et al. The inheritance of chemical phenotype in *Cannabis sativa* L. *Genetics*. 2003;163:335–346. [[PMC free article](#)] [[PubMed](#)]
- de Meijer EPM, Hammond KM, Micheler M. The inheritance of chemical phenotype in *Cannabis sativa* L. (III): variation in cannabichromene proportion. *Euphytica*. 2009a;165:293–311.
- de Meijer EPM, Hammond KM, Sutton A. The inheritance of chemical phenotype in *Cannabis sativa* L. (IV): cannabinoid-free plants. *Euphytica*. 2009b;168:95–112.
- Mechoulam R. The pharmacohistory of *Cannabis sativa*. In: Mechoulam R, editor. *Cannabinoids As Therapeutic Agents*. Boca Raton, FL: CRC Press; 1986. pp. 1–19.
- Mechoulam R. Plant cannabinoids: a neglected pharmacological treasure trove. *Br J Pharmacol*. 2005;146:913–915. [[PMC free article](#)] [[PubMed](#)]
- Mechoulam R, Ben-Shabat S. From gan-zi-gun-nu to anandamide and 2-arachidonoylglycerol: the ongoing story of cannabis. *Nat Prod Rep*. 1999;16:131–143. [[PubMed](#)]
- Mechoulam R, Shvo Y. Hashish-I. The structure of cannabidiol. *Tetrahedron*. 1963;19:2073–2078. [[PubMed](#)]
- Mechoulam R, Ben-Shabat S, Hanus L, Ligumsky M, Kaminski NE, Schatz AR, et al. Identification of an endogenous 2-monoglyceride, present in canine gut, that binds to cannabinoid receptors. *Biochem Pharmacol*. 1995;50:83–90. [[PubMed](#)]
- Mechoulam R, Peters M, Murillo-Rodriguez E, Hanus LO. Cannabidiol – recent advances. *Chem Biodivers*. 2007;4:1678–1692. [[PubMed](#)]
- Mediavilla V, Steinemann S. Essential oil of *Cannabis sativa* L. strains. *J Intl Hemp Assoc*. 1997;4:82–84.
- Mehmedic Z, Chandra S, Slade D, Denham H, Foster S, Patel AS, et al. Potency trends of delta(9)-THC and other cannabinoids in confiscated cannabis preparations from 1993 to 2008. *J Forensic Sci*. 2010;55:1209–1217. [[PubMed](#)]
- Mello NK, Mendelson JH. Marijuana, alcohol, and polydrug use: human self-administration studies. *NIDA Res Monogr*. 1978;20:93–127. [[PubMed](#)]

- Merzouki A, Mesa JM. Concerning kif, a Cannabis sativa L. preparation smoked in the Rif mountains of northern Morocco. *J Ethnopharmacol.* 2002;81:403–406. [[PubMed](#)]
- Mishima K, Hayakawa K, Abe K, Ikeda T, Egashira N, Iwasaki K, et al. Cannabidiol prevents cerebral infarction via a serotonergic 5-hydroxytryptamine1A receptor-dependent mechanism. *Stroke.* 2005;36:1077–1082. [[PubMed](#)]
- Miyazawa M, Yamafuji C. Inhibition of acetylcholinesterase activity by bicyclic monoterpenoids. *J Agric Food Chem.* 2005;53:1765–1768. [[PubMed](#)]
- Monti D, Chetoni P, Burgalassi S, Najarro M, Saettone MF, Boldrini E. Effect of different terpene-containing essential oils on permeation of estradiol through hairless mouse skin. *Int J Pharm.* 2002;237:209–214. [[PubMed](#)]
- Morgan CJ, Curran HV. Effects of cannabidiol on schizophrenia-like symptoms in people who use cannabis. *Br J Psychiatry.* 2008;192:306–307. [[PubMed](#)]
- Morgan CJ, Freeman TP, Schafer GL, Curran HV. Cannabidiol attenuates the appetitive effects of Delta 9-tetrahydrocannabinol in humans smoking their chosen cannabis. *Neuropsychopharmacology.* 2010a;35:1879–1885. [[PMC free article](#)] [[PubMed](#)]
- Morgan CJ, Schafer G, Freeman TP, Curran HV. Impact of cannabidiol on the acute memory and psychotomimetic effects of smoked cannabis: naturalistic study. *Br J Psychiatry.* 2010b;197:285–290. [[PubMed](#)]
- Morimoto S, Tanaka Y, Sasaki K, Tanaka H, Fukamizu T, Shoyama Y, et al. Identification and characterization of cannabinoids that induce cell death through mitochondrial permeability transition in Cannabis leaf cells. *J Biol Chem.* 2007;282:20739–20751. [[PubMed](#)]
- Morse K, Mamane D. *The Scent of Orange Blossoms : Sephardic Cuisine from Morocco.* Berkeley, CA: Ten Speed Press; 2001.
- Mukerji G, Yiangou Y, Corcoran SL, Selmer IS, Smith GD, Benham CD, et al. Cool and menthol receptor TRPM8 in human urinary bladder disorders and clinical correlations. *BMC Urol.* 2006;6:6. [[PMC free article](#)] [[PubMed](#)]
- Mukherjee PK, Kumar V, Mal M, Houghton PJ. In vitro acetylcholinesterase inhibitory activity of the essential oil from Acorus calamus and its main constituents. *Planta Med.* 2007;73:283–285. [[PubMed](#)]
- Murillo-Rodriguez E, Millan-Aldaco D, Palomero-Rivero M, Mechoulam R, Drucker-Colin R. Cannabidiol, a constituent of Cannabis sativa, modulates sleep in rats. *FEBS Lett.* 2006;580:4337–4345. [[PubMed](#)]
- Musty R, Deyo R. Symposium on the Cannabinoids. Tihany: International Cannabinoid Research Society; 2006. A cannabigerol extract alters behavioral despair in an animal model of depression; p. 32. Proceedings June 26.
- Musty RE, Karniol IG, Shirikawa I, Takahashi RN, Knobel E. Interactions of delta-9-tetrahydrocannabinol and cannabiniol in man. In: Braude MC, Szara S, editors. *The Pharmacology of Marihuana.* Vol. 2. New York: Raven Press; 1976. pp. 559–563.
- Naqvi NH, Bechara A. The hidden island of addiction: the insula. *Trends Neurosci.* 2009;32:56–67. [[PMC free article](#)] [[PubMed](#)]
- Naqvi NH, Bechara A. The insula and drug addiction: an interoceptive view of pleasure, urges, and decision-making. *Brain Struct Funct.* 2010;214:435–450. [[PMC free article](#)] [[PubMed](#)]
- Naqvi NH, Rudrauf D, Damasio H, Bechara A. Damage to the insula disrupts addiction to cigarette smoking.

Science. 2007;315:531–534. [[PMC free article](#)] [[PubMed](#)]

Neff GW, O'Brien CB, Reddy KR, Bergasa NV, Regev A, Molina E, et al. Preliminary observation with dronabinol in patients with intractable pruritus secondary to cholestatic liver disease. *Am J Gastroenterol*. 2002;97:2117–2119. [[PubMed](#)]

Nerio LS, Olivero-Verbel J, Stashenko E. Repellent activity of essential oils: a review. *Bioresour Technol*. 2010;101:372–378. [[PubMed](#)]

Nicholson AN, Turner C, Stone BM, Robson PJ. Effect of delta-9-tetrahydrocannabinol and cannabidiol on nocturnal sleep and early-morning behavior in young adults. *J Clin Psychopharmacol*. 2004;24:305–313. [[PubMed](#)]

Nissen L, Zatta A, Stefanini I, Grandi S, Sgorbati B, Biavati B, et al. Characterization and antimicrobial activity of essential oils of industrial hemp varieties (*Cannabis sativa* L.) *Fitoterapia*. 2010;81:413–419. [[PubMed](#)]

Noma Y, Asakawa Y. Biotransformation of monoterpenoids by microorganisms, insects, and mammals. In: Baser KHC, Buchbauer G, editors. *Handbook of Essential Oils: Science, Technology, and Applications*. Boca Raton, FL: CRC Press; 2010. pp. 585–736.

Nunes DS, Linck VM, da Silva AL, Figueiro M, Elisabetsky E. Psychopharmacology of essential oils. In: Baser KHC, Buchbauer G, editors. *Handbook of Essential Oils: Science, Technology, and Applications*. Boca Raton, FL: CRC Press; 2010. pp. 297–314.

O'Shaughnessy WB. Indian hemp. *Prov Med J Retrospect Med Sci*. 1843;5:397–398.

Oh DY, Yoon JM, Moon MJ, Hwang JI, Choe H, Lee JY, et al. Identification of farnesyl pyrophosphate and N-arachidonylglycine as endogenous ligands for GPR92. *J Biol Chem*. 2008;283:21054–21064. [[PMC free article](#)] [[PubMed](#)]

Opdyke DLJ. Caryophyllene oxide. *Food Chem Toxicol*. 1983;21:661–662.

Ozek G, Demirci F, Ozek T, Tabanca N, Wedge DE, Khan SI, et al. Gas chromatographic-mass spectrometric analysis of volatiles obtained by four different techniques from *Salvia rosifolia* Sm., and evaluation for biological activity. *J Chromatog*. 2010;1217:741–748. [[PubMed](#)]

Ozturk A, Ozbek H. The anti-inflammatory activity of *Eugenia caryophyllata* essential oil: an animal model of anti-inflammatory activity. *Eur J Gen Med*. 2005;2:159–163.

Pacher P, Batkai S, Kunos G. The endocannabinoid system as an emerging target of pharmacotherapy. *Pharmacol Rev*. 2006;58:389–462. [[PMC free article](#)] [[PubMed](#)]

Parker LA, Mechoulam R, Schlievert C. Cannabidiol, a non-psychoactive component of cannabis and its synthetic dimethylheptyl homolog suppress nausea in an experimental model with rats. *Neuroreport*. 2002;13:567–570. [[PubMed](#)]

Parker LA, Burton P, Sorge RE, Yakiwchuk C, Mechoulam R. Effect of low doses of Delta(9)-tetrahydrocannabinol and cannabidiol on the extinction of cocaine-induced and amphetamine-induced conditioned place preference learning in rats. *Psychopharmacol (Berl)* 2004;175:360–366. [[PubMed](#)]

Parolaro D, Massi P. Cannabinoids as potential new therapy for the treatment of gliomas. *Expert Rev Neurother*. 2008;8:37–49. [[PubMed](#)]

Pauli A, Schilcher H. *In vitro* antimicrobial activities of essential oils monographed in the European

- Pharmacopoeia 6th Edition. In: Baser KHC, Buchbauer G, editors. Handbook of Essential Oils: Science, Technology, and Applications. Boca Raton, FL: CRC Press; 2010. pp. 353–548.
- Peana AT, Rubattu P, Piga GG, Fumagalli S, Boatto G, Pippia P, et al. Involvement of adenosine A1 and A2A receptors in (-)-linalool-induced antinociception. *Life Sci.* 2006;78:2471–2474. [[PubMed](#)]
- Perry NS, Houghton PJ, Theobald A, Jenner P, Perry EK. In-vitro inhibition of human erythrocyte acetylcholinesterase by salvia lavandulaefolia essential oil and constituent terpenes. *J Pharm Pharmacol.* 2000;52:895–902. [[PubMed](#)]
- Pertwee RG. The pharmacology and therapeutic potential of cannabidiol. In: DiMarzo V, editor. *Cannabinoids*. Dordrecht: Kluwer Academic Publishers; 2004. pp. 32–83.
- Pertwee RG, Thomas A, Stevenson LA, Ross RA, Varvel SA, Lichtman AH, Martin BR, Razdan RK. The psychoactive plant cannabinoid, Delta9-tetrahydrocannabinol, is antagonized by Delta8- and Delta9-tetrahydrocannabivarin in mice *in vivo*. *Br J Pharmacol.* 2007;150:586–594. [[PMC free article](#)] [[PubMed](#)]
- Pertwee RG. The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: delta9-tetrahydrocannabinol, cannabidiol and delta9-tetrahydrocannabivarin. *Br J Pharmacol.* 2008;153:199–215. [[PMC free article](#)] [[PubMed](#)]
- Pliny. *Natural History, Books XXIV-XXVII. Vol. 7.* Cambridge, MA: Harvard University Press; 1980.
- Potter D. Growth and morphology of medicinal cannabis. In: Guy GW, Whittle BA, Robson P, editors. *Medicinal Uses of Cannabis and Cannabinoids*. London: Pharmaceutical Press; 2004. pp. 17–54.
- Potter DJ. The propagation, characterisation and optimisation of *Cannabis sativa* L. as a phytopharmaceutical. 2009. PhD, King's College, London, 2009.
- Potter DJ, Clark P, Brown MB. Potency of delta 9-THC and other cannabinoids in cannabis in England in 2005: implications for psychoactivity and pharmacology. *J Forensic Sci.* 2008;53:90–94. [[PubMed](#)]
- Pultrini Ade M, Galindo LA, Costa M. Effects of the essential oil from *Citrus aurantium* L. in experimental anxiety models in mice. *Life Sci.* 2006;78:1720–1725. [[PubMed](#)]
- Qin N, Neepser MP, Liu Y, Hutchinson TL, Lubin ML, Flores CM. TRPV2 is activated by cannabidiol and mediates CGRP release in cultured rat dorsal root ganglion neurons. *J Neurosci.* 2008;28:6231–6238. [[PubMed](#)]
- Rahn EJ, Hohmann AG. Cannabinoids as pharmacotherapies for neuropathic pain: from the bench to the bedside. *Neurotherapeutics.* 2009;6:713–737. [[PMC free article](#)] [[PubMed](#)]
- Raman A, Weir U, Bloomfield SF. Antimicrobial effects of tea-tree oil and its major components on *Staphylococcus aureus*, *Staph. epidermidis* and *Propionibacterium acnes*. *Lett Appl Microbiol.* 1995;21:242–245. [[PubMed](#)]
- Rao VS, Menezes AM, Viana GS. Effect of myrcene on nociception in mice. *J Pharm Pharmacol.* 1990;42:877–878. [[PubMed](#)]
- Re L, Barocci S, Sonnino S, Mencarelli A, Vivani C, Paolucci G, et al. Linalool modifies the nicotinic receptor-ion channel kinetics at the mouse neuromuscular junction. *Pharmacol Res.* 2000;42:177–182. [[PubMed](#)]
- Ren Y, Whittard J, Higuera-Matas A, Morris CV, Hurd YL. Cannabidiol, a nonpsychotropic component of cannabis, inhibits cue-induced heroin seeking and normalizes discrete mesolimbic neuronal disturbances. *J Neurosci.* 2009;29:14764–14769. [[PMC free article](#)] [[PubMed](#)]

- Resstel LB, Tavares RF, Lisboa SF, Joca SR, Correa FM, Guimaraes FS. 5-HT<sub>1A</sub> receptors are involved in the cannabidiol-induced attenuation of behavioural and cardiovascular responses to acute restraint stress in rats. *Br J Pharmacol.* 2009;156:181–188. [[PMC free article](#)] [[PubMed](#)]
- Rhee MH, Vogel Z, Barg J, Bayewitch M, Levy R, Hanus L, et al. Cannabinol derivatives: binding to cannabinoid receptors and inhibition of adenylyl cyclase. *J Med Chem.* 1997;40:3228–3233. [[PubMed](#)]
- Riedel G, Fadda P, McKillop-Smith S, Pertwee RG, Platt B, Robinson L. Synthetic and plant-derived cannabinoid receptor antagonists show hypophagic properties in fasted and non-fasted mice. *Br J Pharmacol.* 2009;156:1154–1166. [[PMC free article](#)] [[PubMed](#)]
- Rocheffort C, Gheusi G, Vincent JD, Lledo PM. Enriched odor exposure increases the number of newborn neurons in the adult olfactory bulb and improves odor memory. *J Neurosci.* 2002;22:2679–2689. [[PubMed](#)]
- Rock EM, Limebeer CL, Mechoulam R, Parker LA. Proceedings 19th Annual Symposium on the Cannabinoids. St. Charles, IL: International Cannabinoid Research Society; 2009. Cannabidiol (the non-psychoactive component of cannabis) may act as a 5-HT<sub>1A</sub> auto-receptor agonist to reduce toxin-induced nausea and vomiting; p. 29.
- Rodrigues Goulart H, Kimura EA, Peres VJ, Couto AS, Aquino Duarte FA, Katzin AM. Terpenes arrest parasite development and inhibit biosynthesis of isoprenoids in *Plasmodium falciparum*. *Antimicrobial Agents Chemother.* 2004;48:2502–2509. [[PMC free article](#)] [[PubMed](#)]
- Rose JE, Behm FM. Inhalation of vapor from black pepper extract reduces smoking withdrawal symptoms. *Drug Alcohol Depend.* 1994;34:225–229. [[PubMed](#)]
- Ross SA, ElSohly MA. The volatile oil composition of fresh and air-dried buds of *Cannabis sativa*. *J Nat Prod.* 1996;59:49–51. [[PubMed](#)]
- Rothschild M, Bergstrom G, Wangberg S-A. *Cannabis sativa*: volatile compounds from pollen and entire male and female plants of two variants, Northern Lights and Hawaiian Indica. *Bot J Linn Soc.* 2005;147:387–397.
- Russo EB. *Handbook of Psychotropic Herbs: A Scientific Analysis of Herbal Remedies for Psychiatric Conditions*. Binghamton, NY: Haworth Press; 2001.
- Russo EB. The solution to the medicinal cannabis problem. In: Schatman ME, editor. *Ethical Issues in Chronic Pain Management*. Boca Raton, FL: Taylor & Francis; 2006. pp. 165–194.
- Russo EB. History of cannabis and its preparations in saga, science and sobriquet. *Chem Biodivers.* 2007;4:2624–2648. [[PubMed](#)]
- Russo EB, Guy GW. A tale of two cannabinoids: the therapeutic rationale for combining tetrahydrocannabinol and cannabidiol. *Med Hypotheses.* 2006;66:234–246. [[PubMed](#)]
- Russo EB, McPartland JM. Cannabis is more than simply Delta(9)-tetrahydrocannabinol. *Psychopharmacol (Berl)* 2003;165:431–432. [[PubMed](#)]
- Russo EB, Burnett A, Hall B, Parker KK. Agonistic properties of cannabidiol at 5-HT<sub>1a</sub> receptors. *Neurochem Res.* 2005;30:1037–1043. [[PubMed](#)]
- Russo EB, Guy GW, Robson PJ. Cannabis, pain, and sleep: lessons from therapeutic clinical trials of Sativex, a cannabis-based medicine. *Chem Biodivers.* 2007;4:1729–1743. [[PubMed](#)]
- Russo EB, Jiang HE, Li X, Sutton A, Carboni A, del Bianco F, et al. Phytochemical and genetic analyses of

- ancient cannabis from Central Asia. *J Exp Bot.* 2008;59:4171–4182. [[PMC free article](#)] [[PubMed](#)]
- Ryan D, Drysdale AJ, Pertwee RG, Platt B. Differential effects of cannabis extracts and pure plant cannabinoids on hippocampal neurones and glia. *Neurosci Lett.* 2006;408:236–241. [[PubMed](#)]
- Salvadeo P, Boggia R, Evangelisti F, Zunin P. Analysis of the volatile fraction of ‘Pesto Genovese’ by headspace sorptive extraction (HSSE) *Food Chem.* 2007;105:1228–1235.
- Sanguinetti M, Posteraro B, Romano L, Battaglia F, Lopizzo T, De Carolis E, et al. In vitro activity of Citrus bergamia (bergamot) oil against clinical isolates of dermatophytes. *J Antimicrob Chemother.* 2007;59:305–308. [[PubMed](#)]
- Schmidt E. Production of essential oils. In: Baser KHC, Buchbauer G, editors. *Handbook of Essential Oils: Science, Technology, and Applications.* Boca Raton, FL: CRC Press; 2010. pp. 83–120.
- Scutt A, Williamson EM. Cannabinoids stimulate fibroblastic colony formation by bone marrow cells indirectly via CB2 receptors. *Calcif Tissue Int.* 2007;80:50–59. [[PubMed](#)]
- Shoyama Y, Sugawa C, Tanaka H, Morimoto S. Cannabinoids act as necrosis-inducing factors in Cannabis sativa. *Plant Signal Behav.* 2008;3:1111–1112. [[PMC free article](#)] [[PubMed](#)]
- Silva Brum LF, Emanuelli T, Souza DO, Elisabetsky E. Effects of linalool on glutamate release and uptake in mouse cortical synaptosomes. *Neurochem Res.* 2001;26:191–194. [[PubMed](#)]
- Singh P, Shukla R, Prakash B, Kumar A, Singh S, Mishra PK, et al. Chemical profile, antifungal, antiaflatoxic and antioxidant activity of Citrus maxima Burm. and Citrus sinensis (L.) Osbeck essential oils and their cyclic monoterpene, DL-limonene. *Food Chem Toxicol.* 2010;48:1734–1740. [[PubMed](#)]
- Sirikantaramas S, Taura F, Tanaka Y, Ishikawa Y, Morimoto S, Shoyama Y. Tetrahydrocannabinolic acid synthase, the enzyme controlling marijuana psychoactivity, is secreted into the storage cavity of the glandular trichomes. *Plant Cell Physiol.* 2005;46:1578–1582. [[PubMed](#)]
- Skold M, Karlberg AT, Matura M, Borje A. The fragrance chemical beta-caryophyllene-air oxidation and skin sensitization. *Food Chem Toxicol.* 2006;44:538–545. [[PubMed](#)]
- Soares Vde P, Campos AC, Bortoli VC, Zangrossi H, Jr, Guimaraes FS, Zuardi AW. Intra-dorsal periaqueductal gray administration of cannabidiol blocks panic-like response by activating 5-HT1A receptors. *Behavioural Brain Res.* 2010;213:225–229. [[PubMed](#)]
- do Socorro SRMS, Mendonca-Filho RR, Bizzo HR, de Almeida Rodrigues I, Soares RM, Souto-Padron T, et al. Antileishmanial activity of a linalool-rich essential oil from Croton cajucara. *Antimicrob Agents Chemother.* 2003;47:1895–1901. [[PMC free article](#)] [[PubMed](#)]
- Stahl E, Kunde R. Die Leitsubstanzen der Haschisch-Suchhunde. *Kriminalistik: Z Gesamte Kriminal Wiss Prax.* 1973;27:385–389.
- Stott CG, Guy GW, Wright S, Whittle BA. Symposium on the Cannabinoids. Clearwater, FL: International Cannabinoid Research Association; 2005. The effects of cannabis extracts Tetranabinex and Nabidiolex on human cytochrome P450-mediated metabolism; p. 163. June 27.
- Sugiura T, Kondo S, Sukagawa A, Nakane S, Shinoda A, Itoh K, et al. 2-Arachidonoylglycerol: a possible endogenous cannabinoid receptor ligand in brain. *Biochem Biophys Res Commun.* 1995;215:89–97. [[PubMed](#)]
- Tambe Y, Tsujiuchi H, Honda G, Ikeshiro Y, Tanaka S. Gastric cytoprotection of the non-steroidal anti-

inflammatory sesquiterpene, beta-caryophyllene. *Planta Med.* 1996;62:469–470. [[PubMed](#)]

Taylor B. *The Lands of the Saracens*. New York: G.P. Putnam & Sons; 1855.

Thomas A, Stevenson LA, Wease KN, Price MR, Baillie G, Ross RA, et al. Evidence that the plant cannabinoid delta-9-tetrahydrocannabinol is a cannabinoid CB1 and CB2 antagonist. *Br J Pharmacol.* 2005;146:917–926. [[PMC free article](#)] [[PubMed](#)]

Thomas A, Baillie GL, Phillips AM, Razdan RK, Ross RA, Pertwee RG. Cannabidiol displays unexpectedly high potency as an antagonist of CB1 and CB2 receptor agonists in vitro. *Br J Pharmacol.* 2007;150:613–623. [[PMC free article](#)] [[PubMed](#)]

Tisserand R, Balacs T. *Essential Oil Safety: A Guide for Health Care Professionals*. Edinburgh: Churchill Livingstone; 1995.

Trapp SC, Croteau RB. Genomic organization of plant terpene synthases and molecular evolutionary implications. *Genet.* 2001;158:811–832. [[PMC free article](#)] [[PubMed](#)]

Tsokou A, Georgopoulou K, Melliou E, Magiatis P, Tsitsa E. Composition and enantiomeric analysis of the essential oil of the fruits and the leaves of *Pistacia vera* from Greece. *Molecules.* 2007;12:1233–1239. [[PubMed](#)]

Turner CE, Elsohly MA, Boeren EG. Constituents of *Cannabis sativa* L. XVII. A review of the natural constituents. *J Nat Prod.* 1980;43:169–234. [[PubMed](#)]

Turner G, Gershenzon J, Nielson EE, Froehlich JE, Croteau R. Limonene synthase, the enzyme responsible for monoterpene biosynthesis in peppermint, is localized to leucoplasts of oil gland secretory cells. *Plant Physiol.* 1999;120:879–886. [[PMC free article](#)] [[PubMed](#)]

do Vale TG, Furtado EC, Santos JG, Jr, Viana GS. Central effects of citral, myrcene and limonene, constituents of essential oil chemotypes from *Lippia alba* (Mill.) n.e. Brown. *Phytomed.* 2002;9:709–714. [[PubMed](#)]

Varvel SA, Bridgen DT, Tao Q, Thomas BF, Martin BR, Lichtman AH. Delta9-tetrahydrocannabinol accounts for the antinociceptive, hypothermic, and cataleptic effects of marijuana in mice. *J Pharmacol Exp Ther.* 2005;314:329–337. [[PubMed](#)]

Vigushin DM, Poon GK, Boddy A, English J, Halbert GW, Pagonis C, et al. Phase I and pharmacokinetic study of d-limonene in patients with advanced cancer. Cancer Research Campaign Phase I/II Clinical Trials Committee. *Cancer Chemother Pharmacol.* 1998;42:111–117. [[PubMed](#)]

Volicer L, Stelly M, Morris J, McLaughlin J, Volicer BJ. Effects of dronabinol on anorexia and disturbed behavior in patients with Alzheimer's disease. *Int J Geriatr Psychiatry.* 1997;12:913–919. [[PubMed](#)]

Vollner L, Bieniek D, Korte F. [Hashish. XX. Cannabidivarin, a new hashish constituent] *Tetrahedron Lett.* 1969;3:145–147. [[PubMed](#)]

Von Burg R. Toxicology update. Limonene. *J Appl Toxicol.* 1995;15:495–499. [[PubMed](#)]

Wachtel SR, ElSohly MA, Ross RA, Ambre J, de Wit H. Comparison of the subjective effects of delta9-tetrahydrocannabinol and marijuana in humans. *Psychopharmacol.* 2002;161:331–339. [[PubMed](#)]

Wagner H, Ulrich-Merzenich G. Synergy research: approaching a new generation of phytopharmaceuticals. *Phytomed.* 2009;16:97–110. [[PubMed](#)]

Walton RP. *Marihuana, America's New Drug Problem. A Sociologic Question with Its Basic Explanation*

Dependent on Biologic and Medical Principles. Philadelphia, PA: J.B. Lippincott; 1938.

Wattenberg LW. Inhibition of azoxymethane-induced neoplasia of the large bowel by 3-hydroxy-3,7,11-trimethyl-1,6,10-dodecatriene (nerolidol) Carcinogen. 1991;12:151–152. [[PubMed](#)]

Wilkinson JD, Williamson EM. Cannabinoids inhibit human keratinocyte proliferation through a non-CB1/CB2 mechanism and have a potential therapeutic value in the treatment of psoriasis. *J Dermatol Sci*. 2007;45:87–92. [[PubMed](#)]

Wilkinson JD, Whalley BJ, Baker D, Pryce G, Constanti A, Gibbons S, et al. Medicinal cannabis: is delta9-tetrahydrocannabinol necessary for all its effects? *J Pharm Pharmacol*. 2003;55:1687–1694. [[PubMed](#)]

Williams SJ, Hartley JP, Graham JD. Bronchodilator effect of delta1-tetrahydrocannabinol administered by aerosol of asthmatic patients. *Thorax*. 1976;31:720–723. [[PMC free article](#)] [[PubMed](#)]

Williamson EM. Synergy and other interactions in phytomedicines. *Phytomed*. 2001;8:401–409. [[PubMed](#)]

Wirth PW, Watson ES, ElSohly M, Turner CE, Murphy JC. Anti-inflammatory properties of cannabichromene. *Life Sci*. 1980;26:1991–1995. [[PubMed](#)]

Xi Z-X, Peng X-Q, Li X, Zhang H, Li JG, Gardner EL. Proceedings 20th Annual Symposium on the Cannabinoids. Lund: International Cannabinoid Research Society; 2010. Brain cannabinoid CB2 receptors inhibit cocaine self-administration and cocaine-enhanced extracellular dopamine in mice; p. 32.

Yang D, Michel L, Chaumont JP, Millet-Clerc J. Use of caryophyllene oxide as an antifungal agent in an in vitro experimental model of onychomycosis. *Mycopathologia*. 1999;148:79–82. [[PubMed](#)]

Zanelati TV, Biojone C, Moreira FA, Guimaraes FS, Joca SR. Antidepressant-like effects of cannabidiol in mice: possible involvement of 5-HT1A receptors. *Br J Pharmacol*. 2010;159:122–128. [[PMC free article](#)] [[PubMed](#)]

Zuardi AW, Guimaraes FS. Cannabidiol as an anxiolytic and antipsychotic. In: Mathre ML, editor. *Cannabis in Medical Practice: A Legal, Historical and Pharmacological Overview of the Therapeutic Use of Marijuana*. Jefferson, NC: McFarland; 1997. pp. 133–141.

Zuardi AW, Rodrigues JA, Cunha JM. Effects of cannabidiol in animal models predictive of antipsychotic activity. *Psychopharmacol*. 1991;104:260–264. [[PubMed](#)]

Zuardi AW, Crippa JA, Hallak JE, Moreira FA, Guimaraes FS. Cannabidiol, a Cannabis sativa constituent, as an antipsychotic drug. *Braz J Med Biol Res*. 2006;39:421–429. [[PubMed](#)]