Understanding the Complexity of Healing Hemp

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The Conundrum of Scientifically Evaluating Cannabis (Drug & Fiber Types of Hemp)

It is important to accept the challenges and limitations of trying to scientifically "prove" how natural hemp – containing near 500 chemical entities – affects the human body. One would be hard pressed to describe precisely how hemp influences our health, as natural compounds often impact different individuals in unique ways.

The mainstream pharmaceutical model of health intervention has developed a pattern of reducing complex causes of human illness to a singular diagnosis. That diagnosis, the theory submits, provides a clearly defined entity that can be targeted by a precisely matched drug. *Clinical experiences with cannabis suggest, however, that in general, this may not be the best approach.* When the numerous biologically active ingredients in hemp go to work concurrently (creating confounding variables), it becomes virtually impossible to scientifically describe what causes what.

Human clinical outcome studies that employ biologically active substances prepared in biocompatible ways and containing different chemical variations, tend to provide more real and usable information from the standpoint of holistic and preventive medicine. It's unfortunate that institutions who conduct the preponderance of Cannabis research are significantly funded by and therefore tied to pharmaceutical entities that support their business model by isolating and testing single active ingredients for patent and marketing purposes. It will be a great step forward for humanity when average citizens communicate the need for medicine to shift from a focus on controlling late-stage illnesses using pharmaceutical drugs (including its attendant anxiety, suffering, and astronomical costs) to a more rational and affordable approach of *genuine* preventive care.

It can be argued that in order to better understand healing hemp there is no alternative but to present information relating to the characterization of its individual compounds that, for purposes of study, have been chemically manipulated, isolated, and synthesized. As an example of an unintended consequence of this approach, the preponderance of scientific literature citing experimental results of terpenoids found in Cannabis is scientifically misleading because the terpenoids in question are most often derived from other medicinal plants and are part of complex terpenoid mixtures. Even more noteworthy is the fact that the molecular biology of Cannabis has been elucidated predominantly (in vitro) in cell cultures and (in vivo) in genetically engineered mice. As long as we remain cognizant of the innumerable scientific deficiencies and the limitations of rodent experimentation and single compound analysis, we can nevertheless gain useful insights from information that has been gleaned from hundreds of scientific studies.

Primary metabolites in plants are compounds that are synthesized for essential functions such as growth and development. They include carbohydrates, fats (lipids), proteins, nucleic acids, structural components such as cellulose, and pigments such as chlorophyll. Unfortunately these are minimally discussed with respect to the healing characteristics of hemp.

Fiber and psychoactive varieties of Cannabis/hemp contain an enormous range of healing chemicals that are technically referred to as **"secondary metabolites" (SM)**. They are bioactive natural compounds – generally low in molecular weight – that have a broad array of properties. The key SM in hemp are: phytocannabinoids (e.g. Δ^9-THC and CBD), terpenes (including well known terpenoids of essential oils), and polyphenols (including more than 20 flavonoids such as notable cannflavones: cannflavin A, B, and C.)

Secondary metabolites serve as defense compounds against microbes, other plants, and grazing animals, and, of profound importance, as cellular signaling agents. In the latter function, their cellular targets often include

proteins, biomembranes, and nucleic acids. SM may also specifically target ion channels, ion pumps, enzymes that degrade neurotransmitters, or elements of the cytoskeleton (e.g. tubulin or microtubules).

Proteins (which function as enzymes and receptors) are the most common cellular targets of SM. When proteins become engaged by SM, their 3D conformation can be changed, and they may no longer be able to bind with signaling molecules (ligands) or substrates. If this should occur, body homeostasis is affected, and there can be deep implications relating to gene expression. Humans can benefit when their unhealthy genes are blocked. It can also be beneficial for people when unhealthy microbes in the human body are disabled by SM.

How Can Hemp Possess Such Vast Healing Properties?

Until the last few years, many Cannabis research articles focused substantially on describing CB1 and CB2 receptors in our body's endocannabinoid system, trying to elucidate how exogenous (external) hemp cannabinoids, THC and CBD, might be interacting with those endogenous (native, internal) receptors to cause therapeutic effects.

A better understanding of how Cannabis' phytocannabinoids transmit their regulating information to our body is as important as ever, because our body requires instruction on a cellular level for all of its functions. When cell receptors are not working optimally, our body's essential control information is blocked, and our health suffers. So at this point I believe it will be useful for readers who would like a greater understanding of the pharmacological and biological activity of Cannabis to review a condensed explanation of Cannabis Compounds & Their Action In Humans.

Michael Wink wrote an authoritative review article that examined a broad range of plant secondary metabolites in use as herbal medicines (along with the implications of their interactions). Referring to his exhaustive review of scientific literature, Wink states that: "In most cases it was almost impossible to define a single SM which could explain the bioactivity of the extract or its application in traditional [natural] medicine. It is likely that the activity of an extract can be due to synergistic interactions of several SM which cannot be detected when single compounds are evaluated alone."

Michael Wink, **Modes of Action of Herbal Medicines and Plant Secondary Metabolites,** Medicines 2015, 2, p. 251-286

The importance of the last sentence of this quote cannot be over-emphasized. Many respected Cannabis researchers and clinicians ascribe true significance to the way in which varied Cannabis secondary metabolites act synchronously (often additively) to achieve their broad therapeutic reach. Appreciation of this concept gave rise in 1998/99 to the term "entourage effect" (coined by renowned Cannabis researchers, Ben-Shabat & Mechoulam), that is also described academically as the "ensemble effect".

Only in recent years has Cannabis investigation moved away from research focused primarily on the characteristics of either psychoactive THC (in drug strains of the herb) or non-psychoactive CBD (most prominent in fiber strains or so-called "industrial hemp"). Finally, the importance of more hemp secondary metabolites is gaining recognition.

Biological Action of the Secondary Metabolites of Cannabis

Click below on each of the secondary metabolites to link to details of its properties:

Phytocannabinoids

I. **Phytocannabinoid Pharmacology Table**

II. **Schematic of Phytocannabinoid Biosynthesis**

III. **Phytocannabinoid Function Pie Chart**

Terpenoids

I. **Terpenoid Pharmacology Table**

II. **Cannabis Terpenoid Characteristics**

III. **Terpene Chart**

Phenolics

I. **Cannabis Compounds & Their Action in Humans (Phenolics)**

Cannabis Compounds and Their Actions in Humans

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Introduction

When Cannabis' signaling molecules (ligands) enter the human body, they exert **just a part** of their profound influence by interacting with receptors in the endocannabinoids system (eCS). The eCS is one of the supreme body-regulating systems, and depends on two types of receptors (CB1 & CB2) located throughout the human body. The eCS is involved in a variety of physiological activities including metabolic processes, such as lipolysis, glucose metabolism, and energy balance, as well as regulation of cognitive processes, brain reward systems, appetite, pain-sensation, mood, and memory.

> Oier Aizpurua-Olaizola et al. **Targeting the endocannabinoid system: future therapeutic strategies.** Drug Discovery Today v.22, issue 1, January 2017, pp 105-110 https://www.ncbi.nlm.nih.gov/pubmed/27554802

A novice attempting to understand how hemp's healing compounds exert profound therapeutic influence can become confused by the preponderance of hemp literature presented to the lay public, which largely depicts CB1 receptors in the brain being influenced by psychoactive Δ^9-THC. One might naturally wonder how Cannabis compounds influence CB2 receptors, and in particular, what role non-psychoactive Cannabidiol (CBD), which clearly demonstrates highly therapeutic properties, plays in these interactions. Until recently there has been a dearth of information in this area.

A "deeper dive" beyond the common descriptions found in the literature of currently-available hemp products reveals that hemp engages other important signaling pathways. Other compounds found within hemp, specifically terpenoids and phenolics, involve completely different mechanisms of interaction with the human body. Some of those interactions, along with more commonly encountered information relating to cannabinoids and phytocannabinoids, are described below.

Cannabinoids

A. Cannabinoid/Phytocannabinoid interactions with CB1 and CB2 receptors

Cannabinoid cell membrane receptors are activated by three major groups of fat-soluble signaling molecules:

a. Our body's own endocannabinoids that are produced in our brain by a part of our limbic system;
b. Plant (phyto)cannabinoids that derive principally from Cannabis species, e.g. Δ^9-THC and Cannabidiol (CBD), although CBD reacts weakly with CB1 and CB2 receptors;
c. Synthetic cannabinoids manufactured to investigate the functioning of the eCS.

CB1 receptors are found in the brain (especially in the substantia nigra, the basal ganglia, limbic system, hippocampus and cerebellum) but also occur in the peripheral nervous system, liver, thyroid, uterus, bones and testicular tissue.

CB2 receptors are found in immune cells (e.g. leukocytes, various populations of T and B lymphocytes, monocytes/macrophages, dendritic cells, mast cells, microglia in the brain, Kupffer cells in the liver, astrocytes, etc.), the gastrointestinal system, and to some extent in the brain and peripheral nervous system. They have a function in keratinocytes. Also these receptors play a role in relieving pain.

> Zerrin Atakan **Cannabis:A complex plant: different compounds and different effects on individuals.** Adv Psychopharmacol (2012) 2(6) 241–254. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3736954/

Δ^9-THC is a signaling compound (ligand) that is defined as a moderate partial agonist (stimulator) of CB1 and CB2 receptors. In the human body the natural ligands for CB1 and CB2 receptors are, respectively, called *N*-arachidonoyl-ethanolamine (anandamide) and 2-arachidonoylglycerol (2-AG). They are G protein-coupled receptors–GPCR's.

> **GPCR's interact with G proteins in the plasma (cell) membrane and work like a switch — turning on or turning off communication from outside the cell. It is a very complex process with many intermediary steps.**

Hemp's psychoactive phytocannabinoid, Δ^9-THC, mimics the action of our body's natural endocannabinoid, anandamide, that significantly stimulates CB1 receptors in the brain, producing a sense of euphoria/wellbeing.

Hemp's most notable non-psychoactive phytocannabinoid, CBD, is a ligand that acts as a weak agonist (stimulator) of CB1 and CB2 receptors. It has been found "to inhibit cellular uptake of the endogenous CB1 ligand, anandamide [therefore prolonging the life of its influence in the body], and directly affecting endocannabinoids' tone."

> Paula Morales, Dow P. Hurst, Patricia H. Reggio **Molecular Targets of the Phytocannabinoids-A Complex Picture.** Prog Chem Org Nat Prod. 2017; 103: 103–131. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5345356/

Fernandez-Ruiz and co-authors write in the article abstract referenced below:

> "CBD acts in some experimental models as an anti-inflammatory, anticonvulsant, anti-oxidant, anti-emetic, anxiolytic and antipsychotic agent, and is therefore a potential medicine for the treatment of neuroinflammation, epilepsy, oxidative injury, vomiting and nausea, anxiety and schizophrenia, respectively. The neuroprotective potential of CBD, based on the combination of its anti-inflammatory and anti-oxidant properties, is of particular interest and is presently under intense preclinical research in numerous neurodegenerative disorders…."

The researchers succinctly address the complex action of CBD as follows:

> "The therapeutic properties of CBD do not appear to be exerted by the activation of key targets within the endocannabinoid system for plant-derived cannabinoids like Δ^9-THC, i.e. CB_1 and CB_2 receptors. CBD has in general negligible activity at these cannabinoid receptors [2], so it has been generally assumed that most of its pharmacological effects are not *a priori* pharmacodynamic in nature and related to the activation of specific signaling pathways, but related to its innate

chemical properties… that enables CBD to have an important anti-oxidant action [2]." … "However, the anti-oxidant profile of CBD, as well as the few effects it exerts through targets within the endocannabinoid system in certain pathophysiological conditions, cannot completely explain all of the many pharmacological effects of CBD, prompting a need to seek out possible targets for this phytocannabinoid outside the endocannabinoid system. There is, indeed, already evidence that CBD can affect serotonin receptors (i.e. $5HT_{1A}$) [18, 19, and 28], adenosine uptake [37], nuclear receptors of the PPAR family (i.e. PPAR-γ) [38, 39] and many other pharmacological targets…"

Fernández-Ruiz J, Sagredo O, Pazos MR, García C, Pertwee R, Mechoulam R, Martínez-Orgado J. **Cannabidiol for neurodegenerative disorders: important new clinical applications for this phytocannabinoid?** Br J Clin Pharmacol. 2013 Feb;75(2):323-33 https://www.ncbi.nlm.nih.gov/pubmed/22625422

The important "take away" from the matter of how phytocannabinoids in hemp provide therapeutic benefits to the human body is:

1. The psychoactive phytocannabinoid Δ^9-THC mimics the action of our endocannabinoid, anandamide, in the central nervous system, and clearly influences CB1 and CB2 receptors and their metabolic pathways with many beneficial attendant physical responses (notably as a powerful neuroprotective anti-oxidant).

2. The non-psychoactive phytocannabinoid, Cannabidiol (CBD) reduces some of the adverse effects of Δ^9-THC. It has minimal effects on the G protein-coupled receptors, CB1 and CB2, but especially interacts with other receptors and physiological targets.

Later in the above-referenced article the authors discuss the fact that although the pronounced neuro-protective properties of CBD (such as protection from brain damage produced by different types of cytotoxic insults) do not involve CB_1 or CB_2receptor activation, they do "normalize glutamate homeostasis [71, 72], reduce oxidative stress [73, 77] and attenuate glial activation and the occurrence of local inflammatory events [74, 78]."

The most complete picture of the huge therapeutic reach of healing hemp includes an appreciation of:

- Phytocannabinoids' influence not only CB1 and CB2 receptors, but also other receptor types.
- How other phytochemicals in hemp such as terpenoids and polyphenols synergistically deliver their therapeutic input in an additive manner (described forthcoming).

CBD and other phytocannabinoid secondary metabolites deliver powerful healing effects due in part to interaction with gene transcription factors including PPARs (Peroxisome Proliferator-Activated Receptors) and proteins NFkB (nuclear factor KB). In the former case they are important therapeutic targets for metabolic dysfunction (e.g. glucose and lipid dysregulation), and additionally improve histone and DNA methylation, that altogether reduces inflammation. NFkB plays an important role in control of inflammation as well.

B. Phytocannabinoid interactions with PPARs (Peroxisome Proliferator-Activated Receptors)

PPAR's are nuclear hormone receptors that control the transcription of target genes. It is not clear how PPAR's are activated. Recent findings have shown that one of several possible mechanisms may be the experimentally observed transport of Δ^9-THC and CBD to the interior of the cell by fatty acid binding proteins (FABPs). Once phytocannabinoids are proximate to the nucleus they could trigger activation of PPARα and PPARγ isoforms, resulting in antiproliferative, anti-inflammatory, neuroprotective, antinociceptive, and metabolic effects. There is a therapeutic potential, therefore, for the treatment of cancer, cardiovascular or neurodegenerative disorders, as well as pathologies such as diabetes, and obesity. This is an exciting prospect from the standpoint of nutrigenomics.

> Paula Morales, Dow P. Hurst, Patricia H. Reggio **Molecular Targets of the Phytocannabinoids-A Complex Picture.** Prog Chem Org Nat Prod. 2017; 103: 103–131. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5345356/

Tyagi and co-authors provide the following useful information:

The "PPAR family of nuclear receptors plays a major regulatory role in energy homeostasis and metabolic function."… "Activation of PPAR-α reduces triglyceride level and is involved in regulation of energy homeostasis."…

"*In vivo* and *In vitro* studies demonstrate that PPAR-α plays a central role in lipid and lipoprotein metabolism, and thereby decreases dyslipidemia associated with metabolic syndrome. In the fasting state, PPAR-α is activated by adipose-derived FAs [fatty acids], thereby enhancing the generation of ketone bodies through FA oxidation in liver and peripheral blood mononuclear cells."

"PPAR-γ is a ligand-dependent transcription factor and a member of the nuclear receptor superfamily. Acting as sensors of hormones, vitamins, endogenous metabolites, and xenobiotic compounds, the nuclear receptors control the expression of a very large number of genes.

"PPAR-δ/β is expressed in skeletal muscle, adipocytes, macrophages, lungs, brain, and skin. It promotes FA metabolism and suppresses macrophage derived inflammation.

"PPAR-δ has been noted to reduce the expression of inflammatory mediators and adhesion molecules, suggesting their potential role in attenuating atherogenesis."

> Sandeep Tyagi, Paras Gupta, Arminder Singh Saini, Chaitnya Kaushal, and Saurabh Sharma **The peroxisome proliferator-activated receptor: A family of nuclear receptors role in various diseases** J Adv Pharm Technol Res. 2011 Oct-Dec; 2(4): 236–240. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3255347/

C. Phytocannabinoid potential interactions with NF-kB (nuclear factor-kappaB)

NF-kappaB proteins respond to many different stimuli, and regulate a broad range of genes involved in cellular responses to: immune, inflammatory, stress, proliferative and apoptotic (programmed cell death) events. They act like a switch, turning inflammation "on" or "off". If they are imbalanced and overactive they can sustain inflammation and impede healing of chronic conditions. Under circumstances where they are "positively" activated, they can, for example, induce p53 tumor suppressor following DNA damage or oncogene (cancer) activation.

Campbell KJ, Perkins ND. **Regulation of NF-kappaB function.** Biochem Soc Symp. 2006;(73):165-80. https://www.ncbi.nlm.nih.gov/pubmed/16626297

In one study investigating the anti-tumor mechanisms of Cannabidiol in breast cancer, researchers found that cannabidiol's positive performance involves inhibition of activation of NF-kB signaling pathways.

Elbaz, Mohamad et al, **Modulation of the tumor microenvironment and inhibition of EGF/EGFR pathway: Novel anti-tumor mechanisms of Cannabidiol in breast cancer.** Science Direct, 19 January 2015. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4387115/

D. Phytocannabinoid potential interactions with glycine receptors (GlyR)

Morales and colleagues state: "Glycine receptors mediate synaptic inhibitory neurotransmission involved in crucial physiological and pathological processes. …" "The anti-inflammatory and antinociceptive [pain-countering] properties of phytocannabinoids are in part mediated by their ability to target glycine receptors. Different cannabinoids, including Δ^9-THC and CBD, can potentiate glycine currents in native neurons, hippocampus, amygdala or spinal cord. …*In vivo* studies in a rodent model have also demonstrated that CBD and Δ^9-THC analgesic effects are significantly decreased in mice lacking α3-GlyR, but not in mice lacking CB_1 and CB_2 receptors. Therefore, these receptors likely contribute to the therapeutic effects of phytocannabinoids in the treatment of inflammatory and neuropathic pain."

E. Phytocannabinoid potential interactions with transient receptor potential channels (TRP channels)

Further quoting from Morales and colleagues: TRP channels are "membrane proteins [that] modulate ion entry mediating a variety of neural signaling processes. They are involved in numerous physiological functions such as temperature sensation, smell, taste, vision, pressure or pain perception among others."… "Increasing data regarding cannabinoid interactions with these receptors has prompted some research groups to consider certain TRP channels as the "ionotropic cannabinoid receptors". Therefore, these receptors represent potentially attractive targets for the therapeutic use of phytocannabinoids in the treatment of sensory, inflammatory or dermatological pathologies." CBD, CBN, CBG, CBC, Δ^9-THCV, and CBDV are agonists of the TRPV1 channel which "is widely expressed in brain and sensory neurons (mainly in dorsal root and trigeminal ganglia), being involved in pain, nociception, and temperature sensing among other physiological and pathological conditions." Additional studies investigating expression of other TRP channels "highlight the therapeutic potential of phytocannabinoids for the treatment of diseases such as gastrointestinal inflammation."

Paula Morales, Dow P. Hurst, Patricia H. Reggio Molecular Targets of the Phytocannabinoids-A Complex Picture. Prog Chem Org Nat Prod. 2017; 103: 103–131. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5345356/

Terpenes/Terpenoids

The terms, terpene and terpenoid, are frequently used interchangeably, although in actuality, terpenoids are produced from terpenes when they are oxidized or undergo rearrangement of their carbon skeleton. Terpenes basically occur in the fresh, green plant and once it has dried the compounds become terpenoids. Most scientific literature refers to terpenoids in Cannabis, so that convention is used here.

Terpenoids are what we associate with the essential oils of fragrant plants such as pine, lavender, and unknown to most people, the flowering tops of industrial hemp that is used for medicine. The most commonly recognized benefit of terpenoids is that they are broadly anti-microbial and anti-inflammatory. Both drug type and fiber/industrial hemp varieties contain a rich complement of nearly the same terpenoids–just varying in relative proportions.

Referring to terpenoids at the beginning of the authoritative text, *Natural Terpenoids as Messengers,* the authors write: "No other group of metabolites shows such diversity, with so many functions, and [is] produced by so many organisms…" "What makes terpenoids most interesting is the fact that they have a role in the regulation of…signal transduction, and as such can exert a profound effect on cell growth, differentiation, apoptosis [programmed cell death] and multiplication." "Terpenoids and other isoprenoids have important functions as messengers…within organisms, within organs and within the cell body, in particular between the cell surface and the cell nucleus." … "They can influence cell stage and mitosis, resulting in changes in morphology and differentiation." "Terpenoid end products … can interfere with gene expression, or more directly, act as key enzyme regulators."

Harrewijin, P. et al, **Natural Terpenoids As Messengers**, Kluwer Academic Publishers, Norwell, MA USA 2001

Due to the fact that terpenoids are lipophilic (are attracted to lipids), they have an affinity for biomembranes which function to prevent leakage of cellular contents into extracellular space, but also control the influx of material into the cell. If terpenoids come into contact with a pathogenic organism in the human body, the pathogen can be destroyed by increasing its cell membrane permeability. That is one reason essential oils show such strong antimicrobial and cytotoxic activities. Many terpenoids are even effective defense against membrane-enclosed viruses. Terpenoids can also modulate the activity of ion channels in the human body. For example, essential oil of mint affects calcium channels and the motility of smooth muscle cells in the intestines. Cannabis essential oils are also anti-spasmodic.

Michael Wink, **Modes of Action of Herbal Medicines and Plant Secondary Metabolites,** Medicines 2015, 2, p. 251-286

In summary, terpenoids are enormously important directors and communicators in living systems. When their communication capability is combined with *classical* phytocannabinoids – the unique signaling chemicals that occur only in the Cannabis plant – the capacity to "turn on" communication within the human body, thereby influencing body systems regulation, is increased manyfold.

Virtually all terpenoid scientific citations that are available refer to studies that were done with purified terpenoids or terpenoids derived from plants other than Cannabis (medical or industrial/fiber hemp), so from a scientific standpoint we cannot draw for certain a parallel conclusion as to the action of terpenoids

from Cannabis. From a clinical perspective in natural medicine, however, the action of individual terpenoids seems to apply quite generically. It would appear that the way in which terpenoids combine with cannabinoids in hemp makes them even more therapeutic.

Phenolics (polyphenols)

Polyphenols exhibit a broad range of pharmacological actions, including antimicrobial, antiviral, antioxidant, anti-inflammatory, sedative, and wound-healing properties.

Van Wyk, B.-E.; Wink, M. **Medicinal Plants of the World**; Timber Press: Portland, OR, USA, 2004.

A. Flavonoid phenolics

Flavonoids are hydroxylated phenolic substances, and are one of the largest groups of natural compounds. They are spread widely throughout the plant kingdom. They have well recognized health benefits including modulation of inflammation (e.g. regulation of enzymes such as lipoxygenase and cyclooxygenase), detoxification of carcinogens, and cancer prevention. Their antioxidant effects are mediated by their functional hydroxyl groups that scavenge free radical and/or chelate metal ions. When flavonoids enter the human body they are conjugated in the liver by glucuronidation, sulfation, or methylation or metabolized to smaller phenolic compounds.

Currently 26 flavonoids have been identified in Cannabis.

Interesting flavonoids unique to Cannabis are canniflavones. They are better known as cannflavins A, B, & C. Cannflavin A has a strong anti-leishmanial activity with moderate anti-oxidant activity. Cannflavins B & C possess strong anti-inflammatory flavonoid features, and moderate anti-leishmanial activity. (Leishmaniasis is caused by protozoan Leishmania parasites which are transmitted by the bite of infected female phlebotomine sandflies. This infection affects the skin, mucous membranes, and internal organs. The latter is the most serious.)

Canniprene is another highly bioactive phenol from Cannabis with pronounced anti-inflammatory activity in its inhibition of 5-LO and PGES-1.

B. Stilbenoids

Denbinobin is a stilbenoid and member of a small group of phenolic compounds found in a Cannabis chemotype called Carma. It may have promise for human health in that it has shown antiretroviral activity and the ability to promote apoptosis in human leukemia cell cultures.

C. Lignans

Lignans are a class of phenylpropanoids found in the woody tissue of plants. Cannabisins are a group of lignans found in Cannabis seeds and roots. They have free radical scavenging anti-oxidative and anti-cancer activity.

Federica Pollastro et al. **Cannabis Phenolics and their Bioactivities** Current Medicinal Chemistry, 2017, 24, 1-26
http://www.eurekaselect.com/154874/article

RETURN TO MAIN PAPER

Phytocannabinoid Pharmacology Table

After Russo, EB. British Journal of Pharmacology (2011) 163 1344–1364

Phytocannabinoid	Selected Pharmacology Action	References	Complementary Terpenoid(s)
delta-9 – THC delta-9 – tetrahydrocannabinol	antiinflammatory/antioxidant	Hampson AJ, Grimaldi M, Axelrod J, Wink D (1998). Cannabidiol and (-)Delta9-tetrahydrocannabinol are neuroprotective antioxidants. Proc Natl Acad Sci USA 95: 8268–8273. **https://www.ncbi.nlm.nih.gov/pubmed/9653176**	Limonene et al.
	Muscle relaxant	Kavia R, De Ridder D, Constantinescu C, Stott C, Fowler C (2010). Randomized controlled trial of Sativex to treat detrusor overactivity in multiple sclerosis. Mult Scler 16: 1349–1359. **https://www.ncbi.nlm.nih.gov/pubmed/20829244**	potentially Linalool
	↓ Seizures. Alzheimer disease	Volicer L, Stelly M, Morris J, McLaughlin J, Volicer BJ (1997). Effects of dronabinol on anorexia and disturbed behavior in patients with Alzheimer's disease. Int J Geriatr Psychiatry 12: 913–919. **https://www.ncbi.nlm.nih.gov/pubmed/9309469** Eubanks LM, Rogers CJ, Beuscher AE 4th, Koob GF, Olson AJ, Dickerson TJ et al. (2006). A molecular link between the active component of marijuana and Alzheimer's disease pathology. Mol Pharm 3: 773–777. **https://www.ncbi.nlm.nih.gov/pubmed/17140265**	Limonene, pinene, linalool
	Analgesic via CB1 and CB2	Rahn EJ, Hohmann AG (2009). Cannabinoids as pharmacotherapies for neuropathic pain: from the bench to the bedside. Neurotherapeutics 6: 713–737. **https://www.ncbi.nlm.nih.gov/pubmed/19789075**	Various
Cannabidiol – CBD	Anti-inflammatory /antioxidant	Hampson et al., (1998) op,cit.	Limonene et al.
	Anti-anxiety via 5-HT1A	Russo EB, Burnett A, Hall B, Parker KK (2005). Agonistic properties of cannabidiol at 5-HT-1a receptors. Neurochem Res 30: 1037–1043**.** **https://www.ncbi.nlm.nih.gov/pubmed/16258853**	Linalool, limonene
	Anticonvulsant	Jones NA, Hill AJ, Smith I, Bevan SA, Williams CM, Whalley BJ, et al. (2010). Cannabidiol displays antiepileptiform and antiseizure properties in vitro and in vivo. J Pharmacol Exp Ther 332: 569–577. **https://www.ncbi.nlm.nih.gov/pubmed/19906779**	Linalool
	Cytotoxic versus breast cancer	Ligresti A, Moriello AS, Starowicz K, Matias I, Pisanti S, De Petrocellis L et al. (2006). Antitumor activity of plant cannabinoids with emphasis on the effect of cannabidiol on human breast carcinoma. J Pharmacol Exp Ther 318: 1375–	Limonene

Phytocannabinoid	Selected Pharmacology Action	References	Complementary Terpenoid(s)
		1387. https://www.ncbi.nlm.nih.gov/pubmed/16728591	
	↑ adenosine A2A signalling	Carrier EJ, Auchampach JA, Hillard CJ (2006). Inhibition of an equilibrative nucleoside transporter by cannabidiol: a mechanism of cannabinoid immunosuppression. Proc Natl Acad Sci USA 103: 7895–7900. https://www.ncbi.nlm.nih.gov/pubmed/16672367	Linalool
	Effective versus MRSA	Appendino G, Gibbons S, Giana A, Pagani A, Grassi G, Stavri M et al. (2008). Antibacterial cannabinoids from Cannabis sativa: a structure-activity study. J Nat Prod 71: 1427–1430. https://www.ncbi.nlm.nih.gov/pubmed/18681481	Pinene
	Decreases sebum/sebocytes	Biro T, Olah A, Toth BI, Czifra G, Zouboulis CC, Paus R (2009). Cannabidiol as a novel anti-acne agent? Cannabidiol inhibits lipid synthesis and induces cell death in human sebaceous gland-derived sebocytes. Proceedings 19th Annual Conference on the Cannabinoids. International Cannabinoid Research Society: Pheasant Run, St. Charles, IL, p. 28. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4151231/	Pinene, limonene, linalool
	Treatment of addiction	Russo, EB. British Journal of Pharmacology (2011) 163 1344–1364 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3165946/	Caryophyllene
Cannabichromene – CBC	Anti-inflammatory /analgesic	Davis WM, Hatoum NS (1983). Neurobehavioral actions of cannabichromene and interactions with delta 9-tetrahydrocannabinol. Gen Pharmacol 14: 247–252. https://www.ncbi.nlm.nih.gov/pubmed/6301931	Various
	Antifungal	ElSohly HN, Turner CE, Clark AM, ElSohly MA (1982). Synthesis and antimicrobial activities of certain cannabichromene and cannabigerol related compounds. J Pharm Sci 71: 1319–1323. https://www.ncbi.nlm.nih.gov/pubmed/7153877	Caryophyllene oxide
	AEA uptake inhibitor	De Petrocellis L, Ligresti A, Moriello AS, Allara M, Bisogno T, Petrosino S et al. (2011). Effects of cannabinoids and cannabinoid-enriched Cannabis extracts on TRP channels and endocannabinoid metabolic enzymes. Br J Pharmacol DOI:10.1111/j.1476-5381.2010.0166.x https://www.ncbi.nlm.nih.gov/pubmed/21175579	Unknown
	Antidepressant in rodent model	Deyo R, Musty R (2003). A cannabichromene (CBC) extract alters behavioral despair on the mouse tail suspension test of depression. Proceedings 2003 Symposium on the	Limonene

Phytocannabinoid	Selected Pharmacology Action	References	Complementary Terpenoid(s)
		Cannabinoids. International Cannabinoid Research Society: Cornwall, ON, p. 146.	
Cannabigerol – CBG	TRPM8 antagonist prostate cancer	De Petrocellis L, Ligresti A, Moriello AS, Allara M, Bisogno T, Petrosino S et al. (2011). Effects of cannabinoids and cannabinoid-enriched Cannabis extracts on TRP channels and endocannabinoid metabolic enzymes. Br J Pharmacol DOI:10.1111/j.1476-5381.2010.0166.x **https://www.ncbi.nlm.nih.gov/pubmed/21175579**	Cannabis terpenoids
	GABA uptake inhibitor	Banerjee SP, Snyder SH, Mechoulam R (1975). Cannabinoids: influence on neurotransmitter uptake in rat brain synaptosomes. J Pharmacol Exp Ther 194: 74–81. **https://www.ncbi.nlm.nih.gov/pubmed/168349**	Phytol, linalool
	Anti-fungal	ElSohly HN, Turner CE, Clark AM, ElSohly MA (1982). Synthesis and antimicrobial activities of certain cannabichromene and cannabigerol related compounds. J Pharm Sci 71: 1319–1323. **https://www.ncbi.nlm.nih.gov/pubmed/7153877**	Caryophyllene oxide
	Antidepressant rodent model	Musty R, Deyo R (2006). A cannabigerol extract alters behavioral despair in an animal model of depression. Proceedings June 26; Symposium on the Cannabinoids. International Cannabinoid Research Society: Tihany, p. 32.	Limonene
	5-HT1A antagonism	Cascio MG, Gauson LA, Stevenson LA, Ross RA, Pertwee RG (2010). Evidence that the plant cannabinoid cannabigerol is a highly potent alpha2-adrenoceptor agonist and moderately potent 5HT1A receptor antagonist. Br J Pharmacol 159: 129–141.**https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2823359/**	Limonene
	Analgesic, a-2 adrenergic blockade	**(above reference)**	Various
	↓ keratinocytes in psoriasis	Wilkinson JD, Williamson EM (2007). 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 45: 87–92. **https://www.ncbi.nlm.nih.gov/pubmed/17157480**	adjunctive role?
	Effective versus MRSA	Appendino G, Gibbons S, Giana A, Pagani A, Grassi G, Stavri M et al. (2008). Antibacterial cannabinoids from Cannabis sativa: a structure-activity study. J Nat Prod 71:	Pinene

Phytocannabinoid	Selected Pharmacology Action	References	Complementary Terpenoid(s)
		1427–1430. https://www.ncbi.nlm.nih.gov/pubmed/18681481	
	Antiinflammatory	Bolognini D, Costa B, Maione S, Comelli F, Marini P, Di Marzo V, et al. (2010). The plant cannabinoid Delta9-tetrahydrocannabivarin can decrease signs of inflammation and inflammatory pain in mice. Br J Pharmacol 160: 677–687. https://www.ncbi.nlm.nih.gov/pubmed/20590571	Caryophyllene et al. . . .
	Anti-hyperalgesic	(see previous row)	(see previous row)
Tetrahydrocannabivarin – THCV	Treatment of metabolic syndrome	Cawthorne MA, Wargent E, Zaibi M, Stott C, Wright S (2007). The CB1 antagonist, delta-9-tetrahydrocannabivarin (THCV) has anti- oebesity activity in dietary-induced obese (DIO) mice. Proceedings 17th Annual Symposium on the Cannabinoids. International Can- nabinoid Research Society: Saint-Sauveur, QC, p. 141.	Unknown
	Anticonvulsant	Hill AJ, Weston SE, Jones NA, Smith I, Bevan SA, Williamson EM et al. (2010). Delta-Tetrahydrocannabivarin suppresses in vitro epileptiform and in vivo seizure activity in adult rats. Epilepsia 51: 1522–1532. https://www.ncbi.nlm.nih.gov/pubmed/20196794	Linalool
	Inhibits diacylglycerol lipase	De Petrocellis L, Ligresti A, Moriello AS, Allara M, Bisogno T, Petrosino S et al. (2011). Effects of cannabinoids and cannabinoid-enriched Cannabis extracts on TRP channels and endocannabinoid metabolic enzymes. Br J Pharmacol DOI:10.1111/j.1476-5381.2010.0166.x https://www.ncbi.nlm.nih.gov/pubmed/21175579	Unknown
Cannabidivarin – CBDV	Anticonvulsant in hippocampus	Hill AJ, Weston SE, Jones NA, Smith I, Bevan SA, Williamson EM et al. (2010). Delta-Tetrahydrocannabivarin suppresses in vitro epileptiform and in vivo seizure activity in adult rats. Epilepsia 51: 1522–1532. https://www.ncbi.nlm.nih.gov/pubmed/20196794	Linalool
Cannabinol – CBN	Sedative	Musty RE, Karniol IG, Shirikawa I, Takahashi RN, Knobel E (1976). Interactions of delta-9-tetrahydrocannabinol and cannabinol in man. In: Braude MC, Szara S (eds). The Pharmacology of Marihuana, Vol. 2. Raven Press: New York, pp. 559–563.	Nerolidol, myrcene

Phytocannabinoid	Selected Pharmacology Action	References	Complementary Terpenoid(s)
	Effective versus MRSA	Appendino G, Gibbons S, Giana A, Pagani A, Grassi G, Stavri M et al. (2008). Antibacterial cannabinoids from Cannabis sativa: a structure-activity study. J Nat Prod 71: 1427–1430. https://www.ncbi.nlm.nih.gov/pubmed/18681481	Pinene
	TRPV2 agonist for burns	Qin N, Neeper MP, Liu Y, Hutchinson TL, Lubin ML, Flores CM (2008). TRPV2 is activated by cannabidiol and mediates CGRP release in cultured rat dorsal root ganglion neurons. J Neurosci 28: 6231–6238. https://www.ncbi.nlm.nih.gov/pubmed/18550765	Linalool

5-HT, 5-hydroxytryptamine (serotonin); AEA, arachidonoylethanolamide (anandamide); AI, anti-inflammatory; CB1/CB2, cannabinoid receptor 1 or 2; GABA, gamma aminobutyric acid; TRPV, transient receptor potential vanilloid receptor; MRSA, methicillin-resistant Staphylococcus aureus; Sx, symptoms.

THC, tetrahydrocannabinol; THCA, tetrahydrocannabinolic acid; THCV,Tetrahydrocannabivarin, CBC, cannabichromene; CBCA, cannabichromenic acid; CBD, cannabidiol; CBDA, cannabidiolic acid; CBDV, cannabidivarin; CBG, cannabigerol;

CBGA, cannabigerolic acid; CBGV, cannabigerivarin

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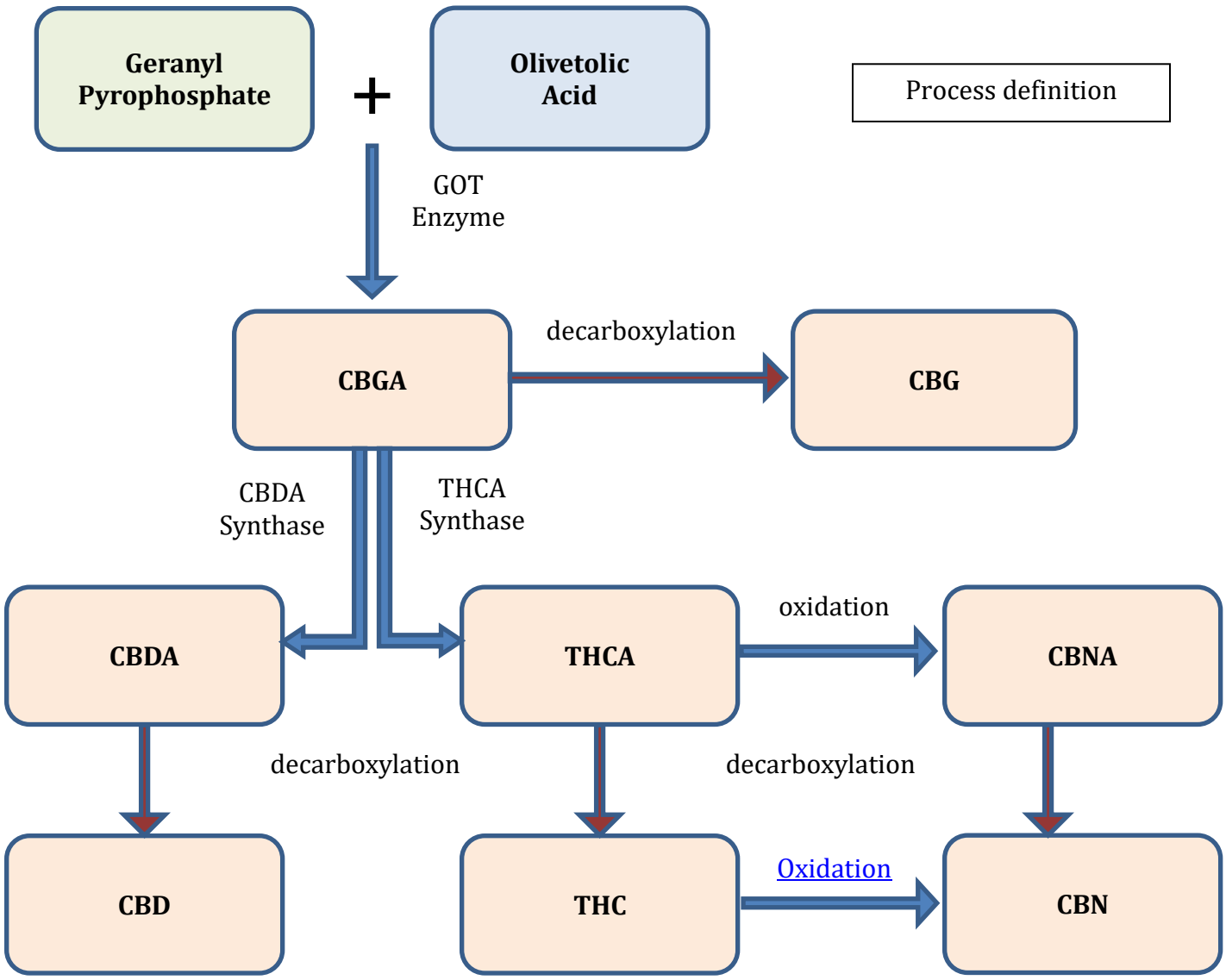
Schematic of Phytocannabinoid Biosynthesis



To access a fully-interactive version of this schematic please go to :

http://www.heavensenthemp.com/our_research/HSHPhytocannabinoidBiosynthesisDiagram.pdf

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Phytocannabinoid Biosynthesis - Process Definition

This process has three basic steps:

- *Binding*,
- *Prenylation*
- *Cyclization*

On a molecular level, the process includes the following:

1. Nanoscale macromolecules called enzymes literally grab (bind) to one or two small molecules (substrates)
2. These substrates then attach to each other (*prenylation,* catalytic chemical conversion of the substrates), and then
3. They pass the small molecule (transformed substrate) down an assembly line to another enzyme that produces sequential changes to the small molecule (*cyclization*).

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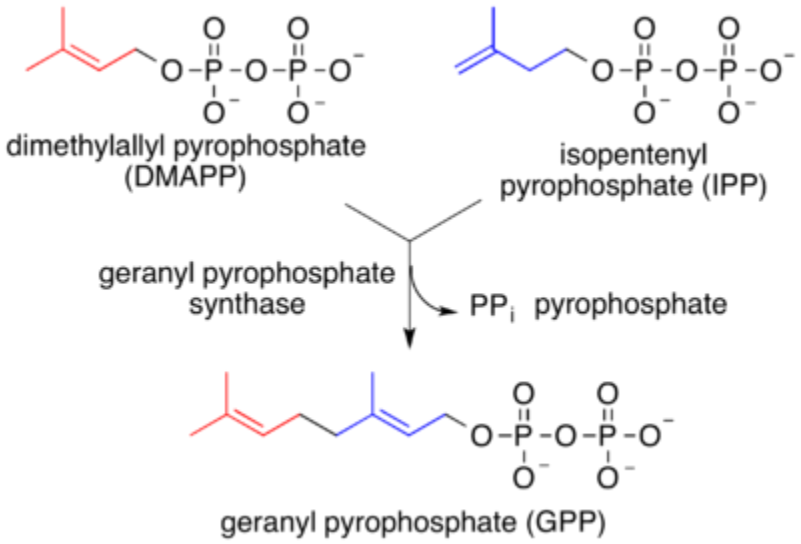
Geranyl Pyrophosphate

Geranyl pyrophosphate (**GPP**), also known as **geranyl diphosphate** (**GDP**), is an intermediate in the HMG-CoA reductase pathway used by organisms in the biosynthesis of farnesyl pyrophosphate, geranylgeranyl pyrophosphate, cholesterol, terpenes and terpenoids. 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



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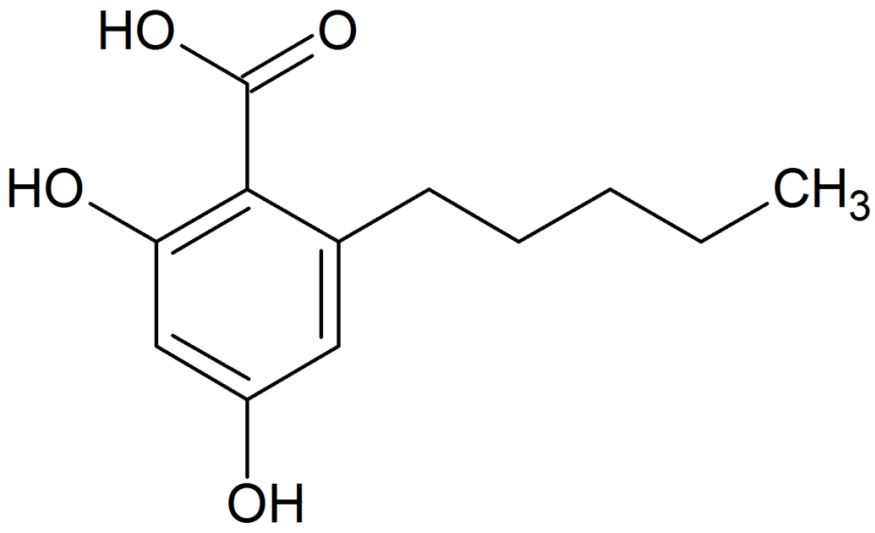
Olivetolic Acid

A member of the class of benzoic acids that is salicylic acid in which the hydrogens *ortho*- and *para*- to the carboxy group are replaced by a pentyl and a hydroxy group, respectively.



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GOT - Geranyl Pyrophosphate: Olivetolic Acid geranylTransferase

GOT is the first enzyme in the biosynthesis of cannabinoids. It can be detected in extracts of young leaves of *Cannabis sativa*. The enzyme accepts geranylpyrophosphate (GPP) and to a lesser degree also nerylpyrophosphate (NPP) as a cosubstrate. It is, however, specific for olivetolic acid; its decarboxylation product olivetol is inactive as a prenyl acceptor.

This enzyme catalyzes the following chemical reaction:

genaryl diphosphate + 2,4-dihydroxy-6-pentyibenzoate $\rightleftharpoons$ diphosphate + cannabigerolate

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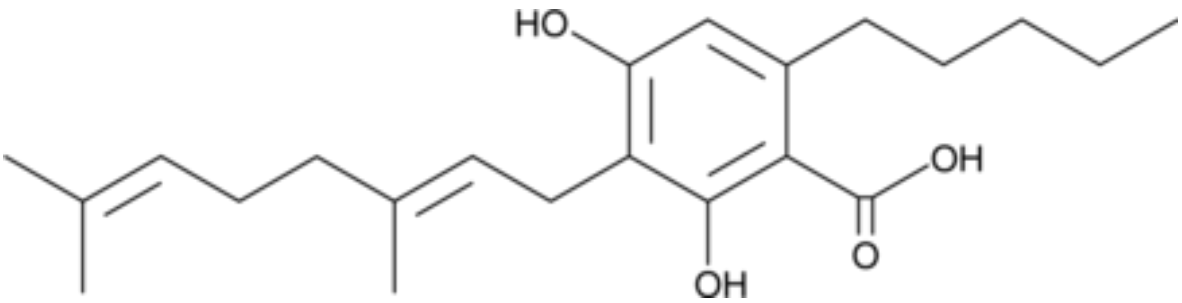
Cannabigerolic Acid (CBGA)

Cannabigerolic acid is a non-psychoactive phytocannabinoid. It is found in the *Cannabis* genus of plants, and is a precursor to the three major branches of cannabinoids: tetrahydrocannabinolic acid, cannabidiolic acid, and cannabichromenic acid. CBGA reportedly has efficacy in treatment of cancer and schizophrenia.



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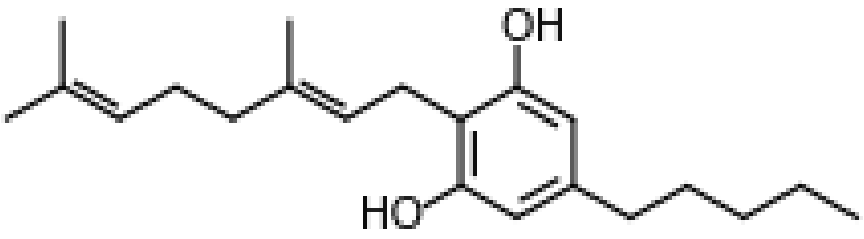
Cannabigerol (CBG)

Cannabigerol (**CBG**) is a non-intoxicating cannabinoid found in the *Cannabis* genus of plants, as well as certain other plants including *Helichrysum umbraculigerum*. CBG is the non-acidic form of cannabigerolic acid (CBGA), the parent molecule ("mother cannabinoid") from which many other cannabinoids are made. By the time most strains of cannabis reach maturity, most of the CBG has been converted into other cannabinoids, primarily tetrahydrocannabinol (THC) or cannabidiol (CBD), usually leaving somewhere below 1% CBG in the plant.
CBG has been found to act as a high affinity α_2-adrenergic receptor agonist, moderate affinity 5-HT_{1A} receptor antagonist, and low affinity CB_1 receptor antagonist.



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Cannabidiolic Acid Synthase (CBDA synthase)

Cannabidiolic acid synthase (*CBDA synthase*) is an enzyme with systematic name *cannabigerolate:oxygen oxidoreductase (cyclizing, cannabidiolate-forming)*.
It is an oxidoreductase found in *Cannabis sativa* that catalyses the formation of cannabidiolate, carboxylated precursor of cannabidiol.
Cannabidiolic acid synthase catalyses the production of cannabidiolate predominantly from cannabigerolate by stereospecific oxidative cyclization of the geranyl group of cannabigerolic acid according to the following chemical reaction:

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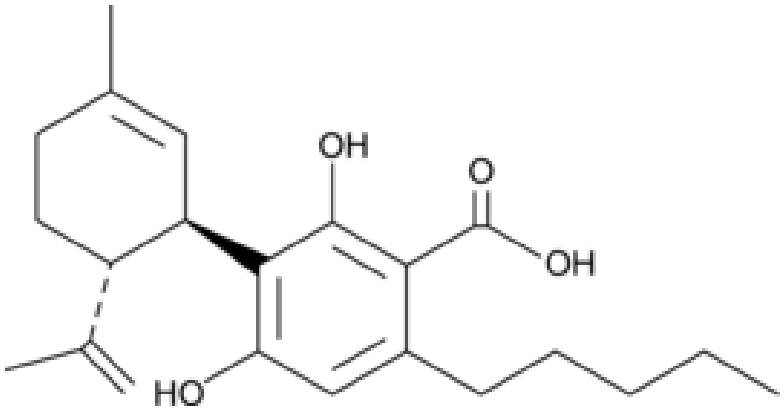
Cannabidiolic Acid (CBDA)

Cannabidiolic Acid (CBDa) is one of the four possible outcomes of Cannabigerolic acid (CBGa) being processed into cannabigerol (CBG), Cannabichromic acid (CBCa), Tetrahydrocannabibolic acid (THCa), and CBDa.

Until recently, CBDa was thought to be a minor cannabinoid and only be a small part of the overall cannabinoid profile. Higher amounts have been seen in ruderalis strains and recent hybrids like Cannatonic C-6 and ACDC have elevated levels of CBDa at potentially higher levels than THCa. Just like THCa, when heated up CBDa decarboxylates; as THCa becomes THC, so CBDa becomes CBD. Like CBD, CBDa is not psychoactive. It appears to have anti-emetic effects as well as anti-proliferative effects, making it ideal for fighting cancer. It also has been shown to be an anti-inflammatory and to possess anti-bacterial properties.



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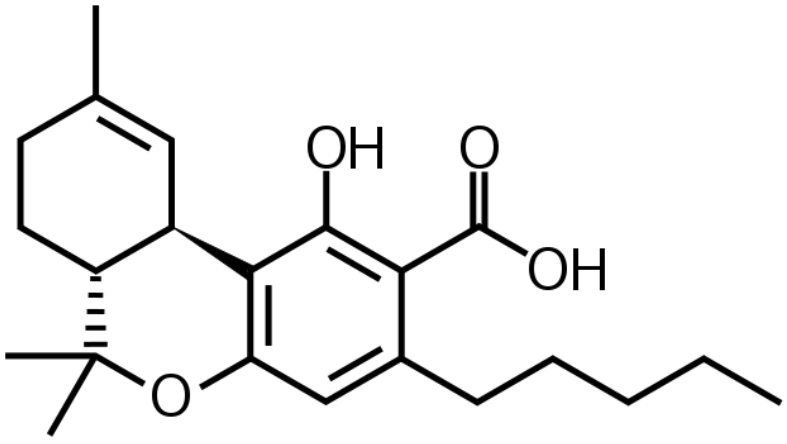
Tetrahydrocannabinolic Acid - THCA

Tetrahydrocannabinolic acid (**THCA**, **2-COOH-THC**; conjugate base **tetrahydrocannabinolate**) is a precursor of tetrahydrocannabinol (THC), the active component of cannabis.

THCA is found in variable quantities in fresh, undried cannabis, but is progressively decarboxylated to THC with drying, and especially under intense heating such as when cannabis is smoked or cooked into cannabis edibles. THCA is often the majority constituent in cannabis resin concentrates, such as [hashish] and hash oil, when prepared from high-THC cannabis plant material, frequently comprising between 50% and 90% by weight.



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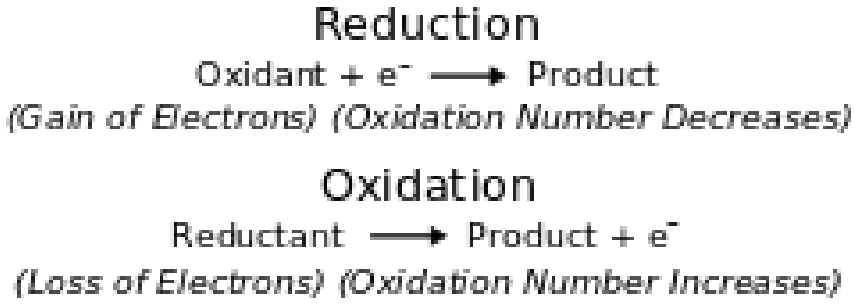
Oxidation

Oxidation is the loss of electrons during a reaction by a molecule, atom or ion. In cannabis, oxidation typically takes place through exposure to air and/or heat, as well as from the passage of time.

Oxidation occurs when the oxidation state of a molecule, atom or ion is increased. The opposite process is called reduction, which occurs when there is a gain of electrons or the oxidation state of an atom, molecule, or ion decreases.



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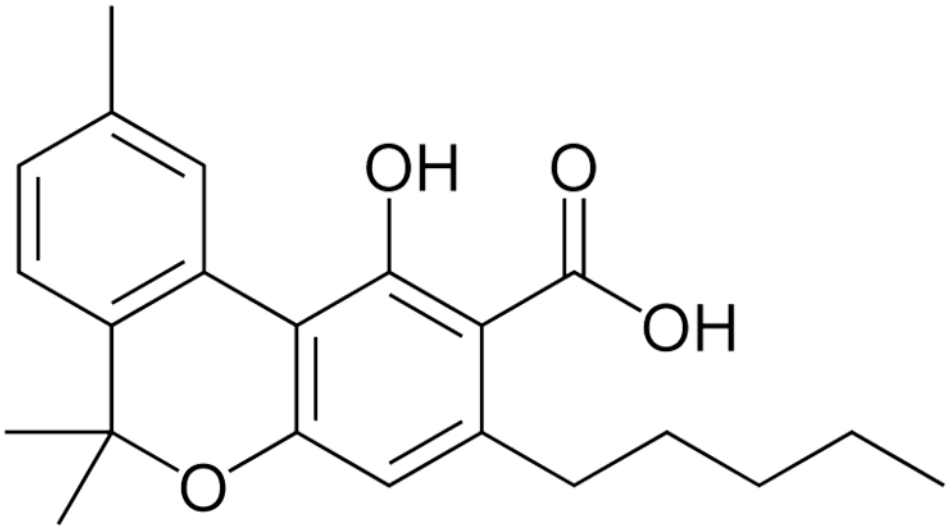
CBNA (Cannabinolic Acid)

THCA can degrade into CBNA (Cannabinolic Acid) via oxidation, and CBNA can be converted to CBN via decarboxylation.



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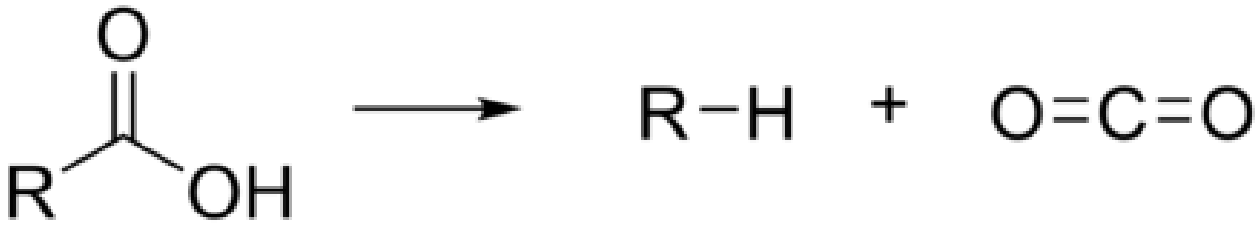
Decarboxylation

Decarboxylation is a chemical reaction that removes a carboxyl group and releases carbon dioxide(CO_2). Usually, decarboxylation refers to a reaction of carboxylic acids, removing a carbon atom from a carbon chain. The reverse process, which is the first chemical step in photosynthesis, is called carboxylation, the addition of CO_2 to a compound. Enzymes that catalyze decarboxylations are called decarboxylases or, the more formal term, carboxy-lyases.



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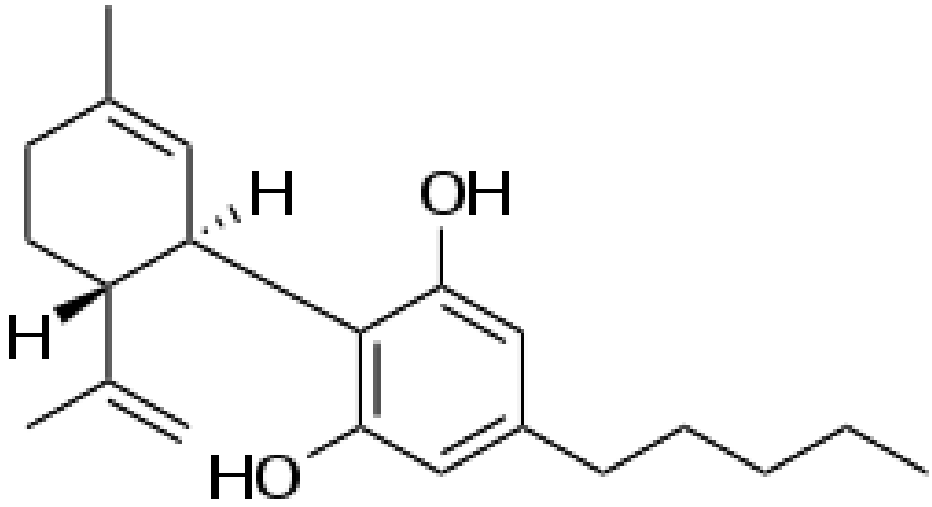
CBD - Cannabidiol

Cannabidiol (CBD) is one of the naturally occurring cannabinoids found in cannabis plants. It is a 21-carbon terpenophenolic compound which is formed following decarboxylation from a cannabidiolic acid precursor. It is a non-psychoactive phytocannabinoid, and it appears to have a remarkably safe and effective profile for use in humans.



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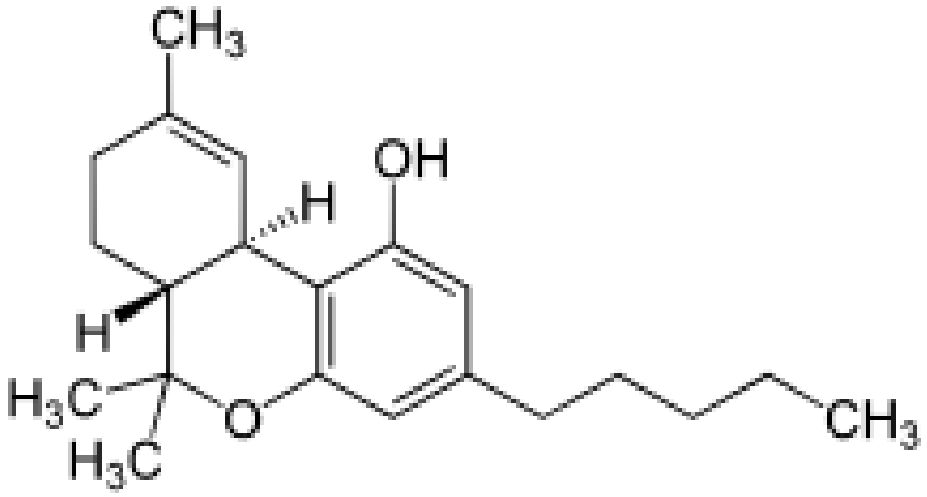
THC - Tetrahydrocannabinol

Tetrahydrocannabinol, abbreviated **THC**, is one of at least 113 cannabinoids identified in cannabis. THC is the principal psychoactiveconstituent of cannabis. With chemical name, **(–)-*trans*-Δ⁹-tetrahydrocannabinol**, the term *THC* also refers to cannabinoid isomers.

Like most pharmacologically-active secondary metabolites of plants, THC is a *lipid* found in cannabis,[10] assumed to be involved in the plant's self-defense, putatively against insect predation, ultraviolet light, and environmental stress.



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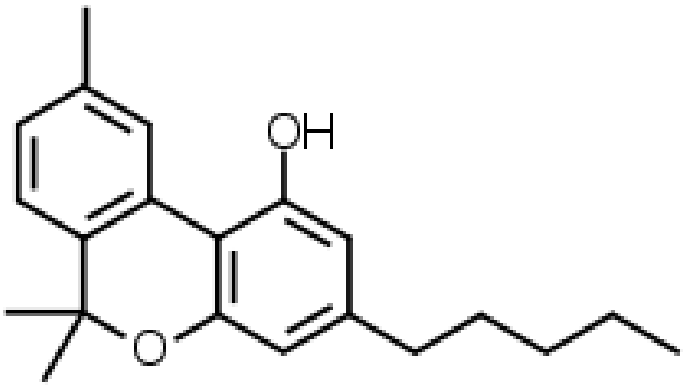
CBN - Cannabinol

Cannabinol (**CBN**) is a non-psychoactive cannabinoid found only in trace amounts in *Cannabis*, and is mostly found in aged *Cannabis.* Pharmacologically relevant quantities are formed as a metabolite of tetrahydrocannabinol (THC).[CBN acts as a partial agonist at the CB_1 receptors, but has a higher affinity to CB_2 receptors; however, it has lower affinities relative to THC. Degraded or oxidized cannabis products, such as low-quality baled cannabis and traditionally produced hashish, are high in CBN, but modern production processes minimize the formation of CBN. Cannabinol has been shown to have analgesic properties. CBN is formed by decarboxylation of CBNA.



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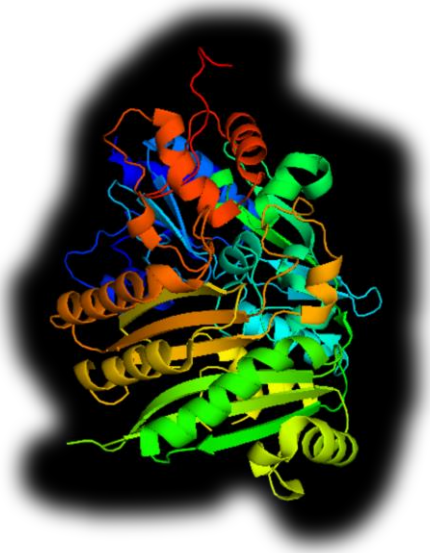
THCA synthase

Tetrahydrocannabinolic acid (THCA) synthase (full name Δ^1-*tetrahydrocannabinolic acid synthase*) is an enzyme responsible for catalyzing the formation of THCA from cannabigerolic acid (CBGA). THCA is the direct precursor of tetrahydrocannabinol (THC), the principal psychoactive component of cannabis, which is produced from various strains of *Cannibis sativa*. Therefore, THCA synthase is considered to be a key enzyme controlling cannabis psychoactivity. Polymorphisms of THCA synthase result in varying levels of THC in Cannabis plants, resulting in "drug-type" and "fiber-type" *C. sativa* varieties.



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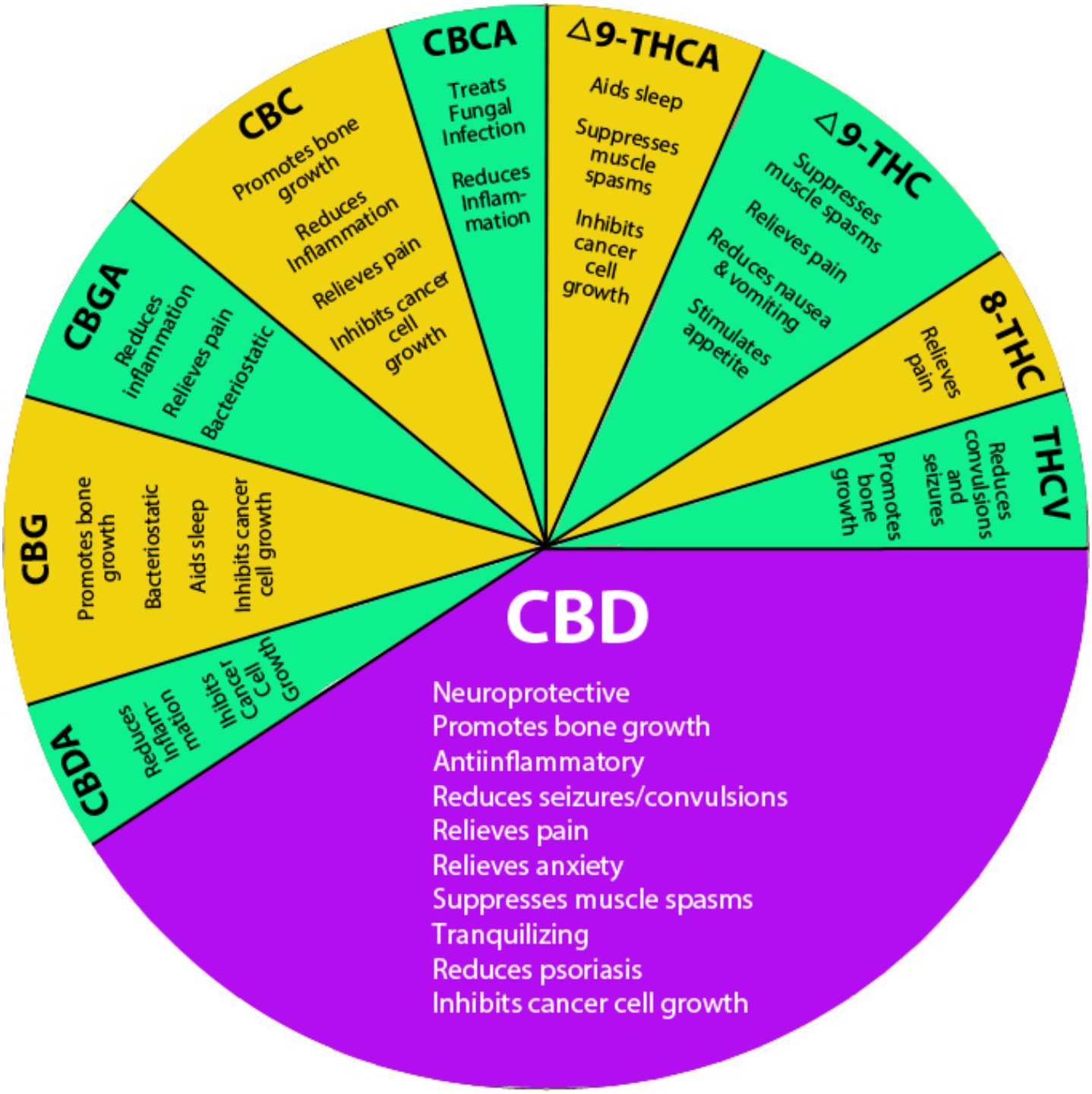
Phytocannabinoid Functions Pie Chart



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Terpenoid Pharmacology Table

After Russo, EB. British Journal of Pharmacology (2011) 163 1344–1364

Terpenoid	Selected Pharmacology Action	References	Complementary Terpenoid(s)
Limonene	Potent antidepressant/ immunostimulant via inhalation	Komori T, Fujiwara R, Tanida M, Nomura J, Yokoyama MM (1995). Effects of citrus fragrance on immune function and depressive states. Neuroimmunomodulation 2: 174–180. https://www.ncbi.nlm.nih.gov/pubmed/8646568	CBD
	Anxiolytic	Carvalho-Freitas MI, Costa M (2002). Anxiolytic and sedative effects of extracts and essential oil from Citrus aurantium L. Biol Pharm Bull 25: 1629–1633; https://www.ncbi.nlm.nih.gov/pubmed/12499653 Pultrini Ade M, Galindo LA, Costa M (2006). Effects of the essential oil from Citrus aurantium L. in experimental anxiety models in mice. Life Sci 78: 1720–1725. https://www.ncbi.nlm.nih.gov/pubmed/16253279 via 5-HT1A Komiya M, Takeuchi T, Harada E (2006). Lemon oil vapor causes an anti-stress effect via modulating the 5-HT and DA activities in mice. Behav Brain Res 172: 240–249. https://www.ncbi.nlm.nih.gov/pubmed/16780969	CBD
	Apoptosis of breast cancer cells	Vigushin DM, Poon GK, Boddy A, English J, Halbert GW, Pagonis C et al. (1998). 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 42: 111–117. https://www.ncbi.nlm.nih.gov/pubmed/9654110	CBD, CBG
	Active against acne bacteria	Kim SS, Baik JS, Oh TH, Yoon WJ, Lee NH, Hyun CG (2008). Biological activities of Korean Citrus obovoides and Citrus natsudaidai essential oils against acne-inducing bacteria. Biosci Biotechnol Biochem 72: 2507–2513. https://www.ncbi.nlm.nih.gov/pubmed/18838824	CBD
	Active against Dermatophytes	Sanguinetti M, Posteraro B, Romano L, Battaglia F, Lopizzo T, De Carolis E et al. (2007). In vitro activity of Citrus bergamia (bergamot) oil against clinical isolates of dermatophytes. J Antimicrob Chemother 59: 305–308;	CBG

Terpenoid	Selected Pharmacology Action	References	Complementary Terpenoid(s)
		https://academic.oup.com/jac/article/59/2/305/725087 Singh P, Shukla R, Prakash B, Kumar A, Singh S, Mishra PK et al. (2010). Chemical profile, antifungal, antiaflatoxigenic and antioxidant activity of Citrus maxima Burm. and Citrus sinensis (L.) Osbeck essential oils and their cyclic monoterpene, DL-limonene. Food Chem Toxicol 48: 1734–1740. https://www.ncbi.nlm.nih.gov/pubmed/20385194	
	Active against Gastro-oesophageal reflux	Harris B (2010). Phytotherapeutic uses of essential oils. In: Baser KHC, Buchbauer G (eds). Handbook of Essential Oils: Science, Technology, and Applications. CRC Press: Boca Raton, FL, pp.315–352.	THC
alpha-Pinene	Anti-inflammatory via PGE-1	Gil ML, Jimenez J, Ocete MA, Zarzuelo A, Cabo MM (1989). Comparative study of different essential oils of Bupleurum gibraltaricum Lamarck. Pharmazie 44: 284–287. https://www.ncbi.nlm.nih.gov/pubmed/2772005	CBD
	Bronchodilatory in humans	Falk AA, Hagberg MT, Lof AE, Wigaeus-Hjelm EM, Wang ZP (1990). Uptake, distribution and elimination of alpha-pinene in man after exposure by inhalation. Scand J Work Environ Health 16: 372–378. https://www.ncbi.nlm.nih.gov/pubmed/2255878	THC
	Acetylcholinesterase inhibitor, aiding memory	Perry NS, Houghton PJ, Theobald A, Jenner P, Perry EK (2000). In-vitro inhibition of human erythrocyte acetylcholinesterase by salvia lavandulaefolia essential oil and constituent terpenes. J Pharm Pharmacol 52: 895–902. https://www.ncbi.nlm.nih.gov/pubmed/10933142	THC?, CBD
beta-Myrcene	Blocks inflammation via PGE-2	Lorenzetti BB, Souza GE, Sarti SJ, Santos Filho D, Ferreira SH (1991). Myrcene mimics the peripheral analgesic activity of lemongrass tea. J Ethnopharmacol 34: 43–48. https://www.ncbi.nlm.nih.gov/pubmed/1753786	CBD
	Analgesic, antagonized by naloxone	Rao VS, Menezes AM, Viana GS (1990). Effect of myrcene on nociception in mice. J Pharm Pharmacol 42: 877–878. https://www.ncbi.nlm.nih.gov/pubmed/1983154	CBD, THC
	Blocks hepatic	De Oliveira AC, Ribeiro-Pinto LF, Paumgartten JR	THC, CBD, CBG

Terpenoid	Selected Pharmacology Action	References	Complementary Terpenoid(s)
	carcinogenesis by aflatoxin	(1997). In vitro inhibition of CYP2B1 monooxygenase by beta-myrcene and other monoterpenoid compounds. Toxicol Lett 92: 39–46. https://www.ncbi.nlm.nih.gov/pubmed/9242356	
Linalool	Anti-anxiety	Russo EB (2001). Handbook of Psychotropic Herbs: A Scientific Analysis of Herbal Remedies for Psychiatric Conditions. Haworth Press: Binghamton, NY.	CBD, CBG?
	Sedative on inhalation in mice	Buchbauer G, Jirovetz L, Jager W, Plank C, Dietrich H (1993). Fragrance compounds and essential oils with sedative effects upon inhalation. J Pharm Sci 82: 660–664. https://www.ncbi.nlm.nih.gov/pubmed/8331544	THC
	Local anesthetic	Re L, Barocci S, Sonnino S, Mencarelli A, Vivani C, Paolucci G et al. (2000). Linalool modifies the nicotinic receptor-ion channel kinetics at the mouse neuromuscular junction. Pharmacol Res 42: 177–182. https://www.ncbi.nlm.nih.gov/pubmed/10887049	THC
	Analgesic via adenosine A2A	Peana AT, Rubattu P, Piga GG, Fumagalli S, Boatto G, Pippia P et al. (2006). Involvement of adenosine A1 and A2A receptors in (-)-linalool-induced antinociception. Life Sci 78: 2471–2474.	CBD
	Anticonvulsant/anti-glutamate	Elisabetsky E, Marschner J, Souza DO (1995). Effects of Linalool on glutamatergic system in the rat cerebral cortex. Neurochem Res 20: 461–465. europepmc.org/abstract/med/16343551	CBD, THCV, CBDV
	Potent anti-leishmanial	do Socorro S Rosa Mdo S, et al. Antileishmanial activity of a linalool-rich essential oil from Croton cajucara. Antimicrob Agents Chemother. 2003. https://www.ncbi.nlm.nih.gov/m/pubmed/12760864/	?
beta-Caryophyllene	Antiinflammatory via PGE-1 –	Basile AC, Sertie JA, Freitas PC, Zanini AC (1988). Anti-inflammatory activity of oleoresin from	CBD

Terpenoid	Selected Pharmacology Action	References	Complementary Terpenoid(s)
	comparable to phenylbutazone	Brazilian Copaifera. J Ethnopharmacol 22: 101–109. https://www.ncbi.nlm.nih.gov/pubmed/3352280	
	Gastric cytoprotective	Tambe Y, Tsujiuchi H, Honda G, Ikeshiro Y, Tanaka S (1996). Gastric cytoprotection of the non-steroidal anti-inflammatory sesquiterpene, beta-caryophyllene. Planta Med 62: 469–470. https://www.ncbi.nlm.nih.gov/pubmed/9005452	THC
	Anti-malarial	Campbell WE, Gammon DW, Smith P, Abrahams M, Purves TD (1997). Composition and antimalarial activity in vitro of the essential oil of Tetradenia riparia. Planta Med 63: 270–272. https://www.ncbi.nlm.nih.gov/pubmed/9225614	?
	Selective CB2 agonist (100 nM)	Gertsch J, Leonti M, Raduner S, Racz I, Chen JZ, Xie XQ et al. (2008). Beta-caryophyllene is a dietary cannabinoid. Proc Natl Acad Sci USA 105: 9099–9104. https://www.ncbi.nlm.nih.gov/pubmed/18574142	THC
	Treatment of pruritus?	Karsak M, Gaffal E, Date R, Wang-Eckhardt L, Rehnelt J, Petrosino Set al. (2007). Attenuation of allergic contact dermatitis through the endocannabinoid system. Science 316: 1494–1497. https://www.ncbi.nlm.nih.gov/pubmed/17556587	THC
	Treatment of addiction?	Xi Z-X, Peng X-Q, Li X, Zhang H, Li JG, Gardner EL (2010). Brain cannabinoid CB2 receptors inhibit cocaine self-administration and cocaine-enhanced extracellular dopamine in mice. Proceedings 20thAnnual Symposium on the Cannabinoids. International Cannabinoid Research Society: Lund, p. 32.	CBD
Caryophyllene Oxide	Decreases platelet aggregation	Lin WY, Kuo YH, Chang YL, Teng CM, Wang EC, Ishikawa T et al. (2003). Anti-platelet aggregation and chemical constituents from the rhizome of Gynura japonica. Planta Med 69: 757–764. https://www.ncbi.nlm.nih.gov/pubmed/14531028	THC

Terpenoid	Selected Pharmacology Action	References	Complementary Terpenoid(s)
	Antifungal in onychomycosis comparable to ciclopiroxolamine and sulconazole	Yang D, Michel L, Chaumont JP, Millet-Clerc J (1999). Use of caryophyllene oxide as an antifungal agent in an in vitro experimental model of onychomycosis. Mycopathologia 148: 79–82. https://www.ncbi.nlm.nih.gov/pubmed/11189747	CBC,CBG
	Insecticidal/ anti-feedant	Bettarini F, Borgonovi GE, Fiorani T, Gagliardi I, Caprioli V, Massardo P et al. (1993). Antiparasitic compounds from East African plants: isolation and biological activtiry of anonaine, matricarianol, canthin-6-one, and caryophyllene oxide. Insect Sci Appl 14: 93–99. https://www.cambridge.org/core/journals/international-journal-of-tropical-insect-science/article/antiparasitic-compounds-from-east-african-plants-isolation-and-biological-activity-of-anonaine-matricarianol-canthin6one-and-caryophyllene-oxide/C56257E480BE	THCA, CBGA
Nerolidol	Sedative	Binet L, Binet P, Miocque M, Roux M, Bernier A (1972). Recherches sur les proprietes pharmcodynamiques (action sedative et action spasmolytique) de quelques alcools terpeniques aliphatiques. Ann Pharm Fr 30: 611–616. https://tigerprints.clemson.edu/cgi/viewcontent.cgi?article=2327&context=all_theses	THC, CBN
	Skin penetrant	Cornwell PA, Barry BW (1994). Sesquiterpene components of volatile oils as skin penetration enhancers for the hydrophilic permeant 5-fluorouracil. J Pharm Pharmacol 46: 261–269. https://www.ncbi.nlm.nih.gov/pubmed/8051608	–
	Potent antimalarial	Lopes NP, Kato MJ, Andrade EH, Maia JG, Yoshida M, Planchart AR et al. (1999). Antimalarial use of volatile oil from leaves of Virola surinamensis (Rol.) Warb. by Waiapi Amazon Indians. J Ethnopharmacol 67: 313–319. https://www.sciencedirect.com/journal/journal-of-ethnopharmacology/vol/67/issue/3	?
	Anti-leishmanial activity	Arruda DC, D'Alexandri FL, Katzin AM, Uliana SR (2005).	?

Terpenoid	Selected Pharmacology Action	References	Complementary Terpenoid(s)
		Antileishmanial activity of the terpene nerolidol. Antimicrob Agents Chemother 49: 1679–1687. https://www.ncbi.nlm.nih.gov/pubmed/15855481	
Phytol	Prevents Vitamin A teratogenesis	Arnhold T, Elmazar MM, Nau H (2002). 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 66: 274–282. https://www.ncbi.nlm.nih.gov/pubmed/11896294	–
	↑GABA via SSADH inhibition	Bang MH, Choi SY, Jang TO, Kim SK, Kwon OS, Kang TC et al. (2002). Phytol, SSADH inhibitory diterpenoid of Lactuca sativa. Arch Pharm Res 25: 643–646. https://link.springer.com/article/10.1007/BF02976937	CBG

5-HT, 5-hydroxytryptamine (serotonin); AD, antidepressant; AI, anti-inflammatory; CB1/CB2, cannabinoid receptor 1 or 2; GABA, gamma aminobutyric acid;PGE-1/PGE-2, prostaglandin E-1/prostaglandin E-2; SSADH, succinic semialdehyde dehydrogenase.

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Cannabis Terpenoid Characteristics

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MEDICAL HERBALIST

Important Notice

Many of the following scientific citations involve *in vivo* studies that frequently subject laboratory animals to the terror of mutilation or other equally horrible experimental conditions. It should be obvious that such suffering can produce powerful neuroendocrine effects that can, in turn, muddy the validity of experimental results. Despite the fact that this approach typically makes only gross physiological responses measurable, institutional science systematically ignores the phenomenon. This position tends to compromise true scientific integrity to the point that mainstream science abdicates its right to label as "unscientific" the progressive and ingenious clinical techniques that are employed in non-pharmaceutically aligned holistic and preventive medicine. In fact, these techniques yield usable information *based on humans in real world living conditions* as to the effects of experimental therapeutic substances.

When safe whole plant herbal extracts (such as those derived from Cannabis) are evaluated in human holistic clinical practice, it is possible to gain insights as to potential beneficial effects based on patient response. That is the essence of clinical outcome studies. Unknown to most, however, is the fact that advanced level practitioners, using special techniques from refined alternative medicine disciplines, are able to perform *pre-administration* screening procedures with potential therapeutic preparations to assess their *real time* relative benefits. This can substantially aid selection of products for dispensing. Pooled consensus results from collaborating practitioners who are appropriately trained in these kinds of test systems can provide truly useful information. This writer has participated in such endeavors, evaluating herbal and nutritional substances since 1978.

The key component of physiological functioning is cell signaling. This process can be measured on a gross level via pharmaceutical test systems, but these systems can frequently deliver many conflicting results. Cell signaling also takes place on a subtle, profoundly important level that involves the complexities of quantum biology, but the instrumentation to measure this process and provide reproducible information does not yet exist in the mainstream.

When the human body comes in contact with a potentially therapeutic substance, however, it can provide its own real-time "read out" in terms of: subtle changes in pulse (oriental medicine pulse diagnosis); changes in acupuncture meridian activity (measured by highly variable electrodermal screening instruments); or neuromuscular reflexive changes (best measured by practitioners thoroughly trained in applied kinesiology muscle testing.)

An article exploring the rational use of alternative medicine test systems mentioned above to advance knowledge in potential applications of different chemovars of Cannabis (prepared by various extraction methods) will be forthcoming from this writer.

(The following information is derived from www.terpene.info , and is edited and annotated.)

Terpenoids found in Cannabis

- **alpha bisabolol**
- **alpha pinene**
- **beta caryophyllene**
- **borneol**
- **caryophyllene oxide**
- **delta3 carene**
- **eucalyptol**
- **geraniol**
- **humulene**
- **limonene**
- **linalool**
- **myrcene**
- **nerolidol**
- **ocimene**
- **terpinolene**
- **valencene**

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Alpha Bisabolol

Anti-mutagenic /Anti-oxidant

Antimutagenicity of alpha-Bisabolol (BISA) could be mediated by an inhibitory effect on the metabolic activation of promutagens.

> Gomes-Carneiro MR et al. **Evaluation of mutagenic and antimutagenic activities of alpha-bisabolol in the Salmonella/microsome assay.** Mutat Res. 2005 Aug 1;585(1-2):105-12. https://www.ncbi.nlm.nih.gov/pubmed/15936245

Anti-bacterial

Alpha-bisabolol in combination with other companion terpenoids exhibited a strong anti-Campylobacter activity without adversely affecting the fermentation potential of chicken-caeca microflora.

> Kurekci C, **Antimicrobial activity of essential oils and five terpenoid compounds against Campylobacter jejuni in pure and mixed culture experiments.** Int J Food Microbiol 2013 Sep 16;166(3):450-7 https://www.ncbi.nlm.nih.gov/pubmed/24041998

Analgesic/Neuroprotectant

Bisabolol reversibly and in a concentration dependent manner inhibits acetylcholine-induced receptor mediated currents. Testing in this system suggests a neuroprotective and potential anti-parkinsonian action.

> Nurulain S., **Inhibitory actions of bisabolol on α7-nicotinic acetylcholine receptors.** Neuroscience. 2015 Oct 15;306:91-9
>
> https://www.ncbi.nlm.nih.gov/pubmed/26283025

Cannabinoid Synergy

CBG, CBD

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Alpha pirene

Anti-inflammatory

In mice induced to express acute pancreatitis, alpha-pinene treatment reduced histological damage and myeloperoxidase activity in the pancreas and lungs. Furthermore, alpha-pinene pretreatment reduced the production of pancreatic tumor necrosis factor (TNF)-alpha, interleukin (IL)-1beta, and IL-6 during acute pancreatitis. In vitro, alpha-pinene inhibited cerulein-induced cell death and cytokine production in isolated cerulein-treated pancreatic acinar cells. This could point to alpha-pinene possibly having beneficial effects with pancreatic cancer and potentially diabetes.

> Bae GS, et al. **Protective effects of alpha-pinene in mice with cerulein-induced acute pancreatitis.** Life Sci. 2012 Oct 29;91(17-18):866-71 https://www.ncbi.nlm.nih.gov/pubmed/22982349

It has been shown that alpha pinene has anti-inflammatory effects in human chondrocytes, thus exhibiting potential antiosteoarthritic activity.

> Ruffino AT. Anti-inflammatory and Chondroprotective Activity of (+)-α-Pinene: Structural and Enantiomeric Selectivity. J Nat Prod. 2014 Feb 28;77(2):264-9 https://www.ncbi.nlm.nih.gov/pubmed/24455984

Anti-bacterial

The effectiveness of eugenol, b-pinene and a-pinene in inhibiting the growth of potential infectious endocarditis causing gram-positive bacteria was evaluated. Pinene exhibited toxic effects against Staphylococcus aureus, S. epidermidis, Streptococcus pneumoniae and S. pyogenes

> Aristides Medeiros Leite, et al. **Inhibitory effect of b-pinene, a-pinene and eugenol on the growth of potential infectious endocarditis causing Gram-positive bacteria** Rev. Bras. Cienc. Farm. vol.43 no.1 São Paulo Jan./Mar. 2007 http://www.scielo.br/scielo.php?script=sci_arttext&pid=S1516-93322007000100015

Anti-cancer

Alpha-pinene arrested carcinoma cell growth and demonstrates potentially useful antitumor properties.

> Chen WQ, et al. **Inhibitory Effects of α-Pinene on Hepatoma Carcinoma Cell Proliferation.** Asian Pac J Cancer Prev. 2014;15(7):3293-7. https://www.ncbi.nlm.nih.gov/pubmed/24815485

Mice placed in an environment enriched with a-pinene demonstrated reduced melanoma growth, and tumor volume of the mice was about 40% smaller than that in the control mice. In another study, alpha-pinene was identified as an active anti-proliferative compound on liver cancer BEL-7402 cells using the MTT assay.

> Kusuhara M **Fragrant environment with α-pinene decreases tumor growth in mice.** Biomed Res. 2012 Feb;33(1):57-61 https://www.ncbi.nlm.nih.gov/pubmed/22361888

Memory-enhancer

Alpha pinene has been shown to be an uncompetitive reversible inhibitor of red blood cell acetylcholinesterase in vitro. The essential oil of sage having, camphor, 1,8-cineole, bornyl acetate, alpha pinene and several other terpenes in much smaller concentrations were exposed to human cells. Since many memory-enhancing and dementia drugs are based on inhibiting cholinesterase to enhance cholinergic activity, it is thought that alpha pinene may act as an effective supplement for such conditions.

Miyazawa M. **Inhibition of Acetylcholinesterase Activity by Bicyclic Monoterpenoids.** J Agric Food Chem. 2005 Mar 9;53(5):1765-8 https://www.ncbi.nlm.nih.gov/pubmed/15740071

Cannabinoid Synergy

Anti-inflammatory - CBD
Bronchodilator - THC
Memory enhancer - CBD
Anti-bacterial - CBN, CBG

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Beta Caryophyllene

Beta-caryophyllene exibits antioxidant properties by preventing lipid oxidation and scavenging free radicals. It activates several receptors in the body, including CB2, which among phytocannabinoids is usually activated most by CBD. Its analgesic properties arise from its ability to regulate neuroinflammation and thermal hyperalgesia. As and anti-inflammatory, beta-caryophyllene has been proven to mediate kidney inflammation and its side effects. In addition, beta-caryophyllene has been shown to be gastric-protective.

Analgesic

Ghelardini C. et al. **Local anaesthetic activity of β-caryophyllene.** Farmaco. 2001 May-Jul;56(5-7):387-9 https://www.ncbi.nlm.nih.gov/pubmed/11482764

Klauke AL et al. **The cannabinoid CB2 receptor-selective phytocannabinoid beta-caryophyllene exerts analgesic effects in mouse models of inflammatory and neuropathic pain.** Eur Neuropsychopharmacol. 2014 Apr;24(4):608-20. https://www.ncbi.nlm.nih.gov/pubmed/24210682

Anti-oxidant

Calleja MA et al. **The antioxidant effect of β-caryophyllene protects rat liver from carbon tetrachloride-induced fibrosis by inhibiting hepatic stellate cell activation.** Br J Nutr. 2013 Feb 14;109(3):394-401. https://www.ncbi.nlm.nih.gov/pubmed/22717234

Anti-inflammatory

Horváth B et al. **β-Caryophyllene ameliorates cisplatin-induced nephrotoxicity in a cannabinoid 2 receptor-dependent manner.** Free Radic Biol Med. 2012 Apr 15;52(8):1325-33 https://www.ncbi.nlm.nih.gov/pubmed/22326488

Colitis-protective

Endocannabinoid receptor CB2 is upregulated in inflamed colons of patients with colitis. β-Caryophyllene demonstrates in IEC-6 cell line mice that it modulates CB2 and PPARγ receptors, leading to the inhibition of proinflammatory cytokines and inflammatory cell influx, and inhibits nuclear factor NFκB. The authors conclude, "Taken together, the present findings strongly suggest that BCP [β-Caryophyllene] could constitute an attractive and apparently safe molecule for development of new anti-inflammatory drugs with therapeutic potential for use in treatment of human IBDs, such as ulcerative colitis and Crohn's disease."

Allisson Freire Bento et al. **β-Caryophyllene Inhibits Dextran Sulfate Sodium-Induced Colitis in Mice through CB2 Receptor Activation and PPARγ Pathway.** Am J Pathol. 2011 Mar; 178(3): 1153–1166. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3070571/

Cannabinoid Synergy

Analgesic - CBG, CBD

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Borneol

Analgesic

In a study using cultured bovine chromaffin cells, borneol was found to inhibit acetylcholine-mediated effects and to have more powerful effects that lidocaine, a commonly used anesthetic.

> Tae-JuPark, et al. **Inhibition of acetylcholine-mediated effects by borneol** Biochemical Pharmacology Volume 65, Issue 1 January 2003, Pages 83-90 https://www.ncbi.nlm.nih.gov/pubmed/12473382

Anticoagulant

Borneol demonstrates anticoagulant effects in arteriolar and venous test systems and in prothrombin over time in blood samples. In a related study, reduced levels of pro-inflammatory mediators were also seen.

> Yan-Hong Li et al, The Antithrombotic Effect of Borneol Related to Its Anticoagulant Property
>
> Am. J. Chin. Med. **36**, 719 (2008). http://www.worldscientific.com/doi/abs/10.1142/S0192415X08006181

Antifungal

Borneol was found to broadly inhibit plant fungi in the genus, Colletotrichum, and demonstrated significant antimycobacterial activity against Mycobacterium intracellulare. Borneol was found to be **non-selective** at inhibiting growth and development of reproductive stroma of the plant pathogens Colletotrichum acutatum, Colletotrichum fragariae, and Colletotrichum gloeosporioides. There was also significant antimycobacterial activity observed against Mycobacterium intracellulare.

> Nurhayat Tabanca, et al. **Chemical Composition and Antifungal Activity of Salvia macrochlamys and Salvia recognita Essential Oils.** *J. Agric. Food Chem.*, 2006, *54* (18), pp 6593–6597 http://pubs.acs.org/doi/abs/10.1021/jf0608773

Anti-inflammatory

The release of pro-inflammatory interleukins from human fibroblasts was reduced more than 50% by exposure to borneol and companion essential oils.

Anti-cancer

Borneol has the remarkable property of increasing absorption of therapeutic compounds. Borneol was shown to help increase the cellular uptake of two anti-cancer natural compounds selenocysteine and bisdemethoxycurcumin in liver cancer cells, and reduced cancer cell growth through the triggering of apoptotic cell death.

> Jianping Chen, et al. **Natural borneol enhances bisdemethoxycurcumin-induced cell cycle arrest in the G2/M phase through up-regulation of intracellular ROS in HepG2 cells.** Food & Function. Issue 3, 2015
> http://pubs.rsc.org/en/content/articlelanding/2015/fo/c4fo00807c - !divAbstract
>
> Zhang, Q, et al. Improved blood-brain barrier distribution: effect of borneol on the brain pharmacokinetics of kaempferol in rats by in vivo microdialysis sampling. Journal of Ethnopharmacology, Volume 162**, 13 March 2015, Pages 270-277**
> https://www.sciencedirect.com/journal/journal-of-ethnopharmacology/vol/162

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Caryophyllene oxide

Caryophyllene oxide is an oxygenated terpenoid, usually a metabolic by product of caryophyllene. Its use as an antifungal is highly effective with certain species. In addition, caryophyllene oxide has also been indicated as an anticoagulant.

Antifungal

Caryophyllene oxide is commonly used as a preservative in food, drugs, and cosmetics. Its antifungal activity has been compared to ciclopiroxolamine and sulconazole, mainly used in onychomycosis treatment and dermatophytes.

Yang D, et al. **Use of caryophyllene oxide as an antifungal agent in an in vitro experimental model of onychomycosis.** Mycopathologia. 1999 Nov;148(2):79-82. https://www.ncbi.nlm.nih.gov/pubmed/11189747

Anticoagulant

Caryophyllene oxide isolated from the rhizome of Formosan Gynura japonica was shown to exhibit significant anti-platelet aggregation activity in vitro.

Lin WY et al. **Anti-platelet aggregation and chemical constituents from the rhizome of Gynura japonica**. Planta Med. 2003 Aug;69(8):757-64. https://www.ncbi.nlm.nih.gov/pubmed/14531028

Cannabinoid Synergy

Antifungal - CBC, CBG
Anticoagulant - THC
Insecticidal - THCA, CBGA

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Delta 3 Carene

Carene has shown ability to help differentiate and stimulate calcium production in bone cells. It is also effective as a toxin for mosquitos.

Bone growth

Jeong JG et al. **Low concentration** of **3-carene stimulates** the **differentiation** of**mouse osteoblastic MC3T3-E1 subclone 4 cells**. Phytother Res. 2008 Jan;22(1):18-22. https://www.ncbi.nlm.nih.gov/pubmed/17685387

Insecticide

Brazilian pepper oil, its main constituent being carene, was proven to be as an insecticide for S. Aegypti, yet safe for other aquatic organisms. The terpene was also shown to be a repellant as well in a separate study. The synergistic effect of coumarins, flavonoids and terpenes from the Lippia javanica extract had an additive effect on the repellency. One more study also inferred the toxicity of carene on two other human disease vector mosquitoes, Cx. quinquefasciatus and An. gambiae.

Nzira L et al. **Lippia javanica (Burm F) Spreng: its general constituents and bioactivity on mosquitoes**. Trop Biomed. 2009 Apr;26(1):85-91. https://www.ncbi.nlm.nih.gov/pubmed/19696732

EJ Kweka et al. **Insecticidal activity of the essential oil from fruits and seeds of Schinus terebinthifolia Raddi against African malaria vectors**. Parasit Vectors. 2011 Jul 5;4:129. https://www.ncbi.nlm.nih.gov/pubmed/21729280

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Eucalyptol

Research suggests eucalyptol may contribute to treatment of Alzheimer's, as it lowered the inflammation caused by amyloid beta plaques. Eucalyptol is also an anti-inflammatory for sinuses and the digestive system. As an antioxidant, eucalyptol is effective at preventing lipid oxidation. In addition, eucalyptol has been effective in battling leukemia and colon cancer cells. Eucalyptol is also an ingredient in asthma remedies.

Alzheimer's

Khan A et al. **1,8-cineole (eucalyptol) mitigates inflammation in amyloid Beta toxicated PC12 cells: relevance to Alzheimer's disease**. Neurochem Res. 2014 Feb;39(2):344-52. https://www.ncbi.nlm.nih.gov/pubmed/24379109

Anti-inflammatory

Santos FA et al. **1,8-cineole (eucalyptol)**, a **monoterpene oxide attenuates**the **colonic damage** in **rats** on **acute TNBS-colitis**. Food Chem Toxicol. 2004 Apr;42(4):579-84. https://www.ncbi.nlm.nih.gov/pubmed/15019181

Lima PR et al. **1,8-cineole(eucalyptol) ameliorates cerulein-induced acute pancreatitis via modulation** of **cytokines**, **oxidative stress** and **NF-κB activity** in **mice**. Life Sci. 2013 Jul 10;92(24-26):1195-201. https://www.ncbi.nlm.nih.gov/pubmed/23702424

Kehrl W et al. **Therapy for Acute Nonpurulent Rhinosinusitis With Cineole: Results of a Double-Blind, Randomized, Placebo-Controlled Trial.** Laryngoscope. 2004 Apr;114(4):738-42. https://www.ncbi.nlm.nih.gov/pubmed/15064633

Santos FA et al. **Antiinflammatory and antinociceptive effects of 1,8-cineole a terpenoid oxide present in many plant essential oils**. Phytother Res. 2000 Jun;14(4):240-4. https://www.ncbi.nlm.nih.gov/pubmed/10861965

Anti-oxidant

Cho KH et al.**1,8-cineole protected human lipoproteins from modification by oxidation and glycation and exhibited serum lipid-lowering and anti-inflammatory activity in zebrafish.** BMB Rep. 2012 Oct;45(10):565-70. https://www.ncbi.nlm.nih.gov/pubmed/23101510

Anti-cancer

Moteki H et al. **Specific induction** of **apoptosis** by **1,8-cineole** in **two human leukemia cell lines**, **but not** a in **human stomach cancer cell line**. Oncol Rep. 2002 Jul-Aug;9(4):757-60. https://www.ncbi.nlm.nih.gov/pubmed/12066204

Murata S et al. **Antitumor effect of 1, 8-cineole against colon cancer**. Oncol Rep. 2013 Dec;30(6):2647-52. https://www.ncbi.nlm.nih.gov/pubmed/24085263

Anti-asthma

Juergens UR et al. **Inhibitory activity of 1,8-cineol (eucalyptol) on cytokine production in cultured human lymphocytes and monocytes**. Pulm Pharmacol Ther. 2004;17(5):281-7. https://www.ncbi.nlm.nih.gov/pubmed/15477123

Worth H et al.**Patients with asthma benefit from concomitant therapy with cineole: a placebo-controlled, double-blind trial.** J Asthma. 2012 Oct;49(8):849-53. https://www.ncbi.nlm.nih.gov/pubmed/22978309

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Geraniol

Geraniol is anti-inflammatory and is toxic to bacteria and certain fugi. It is a topical drug delivery enhancer.

Analgesic

Santos, PL et al., **Preparation, Characterization, and Pharmacological Activity of Cymbopogon winterianus Jowitt ex Bor (Poaceae) Leaf Essential Oil of β-Cyclodextrin Inclusion Complexes.** Evid Based Complement Alternat Med. 2015;2015:502454. Epub 2015 Jul 13. https://www.ncbi.nlm.nih.gov/pubmed/26246838

Anti-fungal

Leite MC, **Investigating the antifungal activity and mechanism(s) of geraniol against Candida albicans strains.** Med Mycol. 2015 Apr;53(3):275-84 http://www.ncbi.nlm.nih.gov/pubmed/25480017

Kpoviessi S., et al. **Chemical composition, cytotoxicity and in vitro antitrypanosomal and antiplasmodial activity of the essential oils of four Cymbopogon species from Benin.** J Ethnopharmacol. 2014;151(1):652-9 http://www.ncbi.nlm.nih.gov/pubmed/24269775

Anti-bacterial

Geraniol and companion essential oils have been confirmed to be toxic against several bacteria species. Nerolidol, thymol, eugenol and geraniol inhibited growth of the pathogens Escherichia coli O157:H7(VT), Clostridium difficile DSM1296, Clostridium perfringens DSM11780, Salmonella typhimurium 3530 and Salmonella enteritidis S1400 at a half-maximal inhibitory concentration (IC(50)) varying from 50 to 500 ppm.

Thapa D, et al. **Sensitivity of pathogenic and commensal bacteria from the human colon to essential oils.** Microbiology. 2012 Nov;158 (Pt 11):2870-7. https://www.ncbi.nlm.nih.gov/pubmed/22878397

Solorzano-Santos F. et al. **Essential oils from aromatic herbs as antimicrobial agents. Curr Opin Biotechnol.** 2012 Apr;23(2):136-41. https://www.ncbi.nlm.nih.gov/pubmed/21903378

Topical Drug Enhancer

Geraniol with other essential oils co-applied with a couple of topical drugs was concluded to enhance skin penetration in delivering medicines in laboratory mice.

Godwin DA, **Influence of drug lipophilicity on terpenes as transdermal penetration enhancers.** Drug Dev Ind Pharm. 1999 Aug;25(8):905-15. https://www.ncbi.nlm.nih.gov/pubmed/10434134

Anti-inflammatory

Geraniol, and geranylgeraniol were effective in preventing inflammation in mice induced by the chemical alendronate-muramyldipeptide. This suggests a possibly effective treatment for mevalonate kinase deficiency (MKD) in humans.

Marcuzzi A, et al. **Natural isoprenoids are able to reduce inflammation in a mouse model of mevalonate kinase deficiency.** Pediatr Res. 2008 Aug;64(2):177-82. https://www.ncbi.nlm.nih.gov/pubmed/18391837

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Humulene

Antibacterial

Geraniol, and geranylgeraniol were effective in preventing inflammation in mice induced by the chemical alendronate-muramyldipeptide. This suggests a possibly effective treatment for mevalonate kinase deficiency (MKD) in humans.

Marcuzzi A, et al. **Natural isoprenoids are able to reduce inflammation in a mouse model of mevalonate kinase deficiency.** Pediatr Res. 2008 Aug;64(2):177-82. https://www.ncbi.nlm.nih.gov/pubmed/18391837

Anti-inflammatory

Humulene was shown to be a good anti-inflammatory across a wide range of inflammatory markers. Its effects were comparable to dexamethasone in rat and mouse models. Humulene has been shown to have rapid onset and relatively good absorption with both oral and topical administration routes. In airway allergic inflammatory routes, humulene was shown to be effective orally or through aerosol.

Chaves JS. **Pharmacokinetics and tissue distribution of the sesquiterpene alpha-humulene in mice.** Planta Med. 2008 Nov;74(14):1678-83 *https://www.ncbi.nlm.nih.gov/pubmed/18951339*

Fernandes ES. **Anti-inflammatory effects of compounds alpha-humulene and (-)-trans-caryophyllene isolated from the essential oil of Cordia verbenacea.** Eur J Pharmacol. 2007 Aug 27;569(3):228-36. Epub 2007 May 22. *https://www.ncbi.nlm.nih.gov/pubmed/17559833*

Alexandre P Rogerio. **Preventive and therapeutic anti-inflammatory properties of the sesquiterpene α-humulene in experimental airways allergic inflammation.** Br J Pharmacol. 2009 Oct; 158(4): 1074–1087. *https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2785529/*

Anti-cancer

Humulene was shown to be potent against several solid tumor cell lines. The molecular mechanism involves generation of reactive oxygen species, or free radicals, that deplete natural antioxidants in the tumor cells. Humulene was also shown to work synergistically with beta-caryophyllene in delivering the molecule to cancer cells, thus increasing the cytotoxicity of humulene on several cancer cell lines.

Legault J. **Antitumor activity of balsam fir oil: production of reactive oxygen species induced by alpha-humulene as possible mechanism of action.** Planta Med. 2003 May;69(5):402-7. https://www.ncbi.nlm.nih.gov/pubmed/12802719

Legault J. **Potentiating effect of beta-caryophyllene on anticancer activity of alpha-humulene, isocaryophyllene and paclitaxel**. J Pharm Pharmacol. 2007 Dec;59(12):1643-7. https://www.ncbi.nlm.nih.gov/pubmed/18053325

Tundis R. **In vitro cytotoxic effects of Senecio stabianus Lacaita (Asteraceae) on human cancer cell lines.** Nat Prod Res. 2009;23(18):1707-18. https://www.ncbi.nlm.nih.gov/pubmed/19921589

Cannabinoid synergy

Anti-fungal - CBC, CBG
Anti-coagulant - THC
Insecticidal - THCA, CBGA

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Limonene

Antidepressant/Anti-anxiety

Burr, R. L. **Limonene attenuates anxiogenic- and depression-like effects of corticotropin-releasing factor in mice**. Pharmtechmedica, 1(6), 214-220. 2. (2007).

Anti-inflammatory

Hirota R et al. **Anti-inflammatory Effects of Limonene from Yuzu (Citrus junos Tanaka) Essential Oil on Eosinophils** J Food Sci. 2010 Apr;75(3):H87-92. https://www.ncbi.nlm.nih.gov/pubmed/20492298

Anti-cancer

Crowell PL **Antitumorigenic effects of limonene and perillyl alcohol against pancreatic and breast cancer**. Adv Exp Med Biol. 1996;401:131-6. https://www.ncbi.nlm.nih.gov/pubmed/8886131

Crowell PL et al. **Chemoprevention and therapy of cancer by d-limonene.** Crit Rev Oncog. 1994;5(1):1-22. https://www.ncbi.nlm.nih.gov/pubmed/7948106

Cannabinoid synergy

CBD,CBG,CBN - anti-cancer
CBG- anti-depressant

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Linalool

Linalool is a terpenoid with a unique pathway allowing it to act on the opioidergic and cholinergic systems to relieve pain. Linalool also acts as an anticonvulsant, having similar effects to diazepam.

Anti-inflammatory

Peana AT et al. **Anti-inflammatory activity of linalool and linalyl acetate constituents of essential oils**. Phytomedicine. 2002 Dec;9(8):721-6. https://www.ncbi.nlm.nih.gov/pubmed/12587692

Analgesic

Peana AT et al. (-)-**Linalool produces antinociception in two experimental models of pain**. Eur J Pharmacol. 2003 Jan 26;460(1):37-41. https://www.ncbi.nlm.nih.gov/pubmed/12535857

Anticonvulsant

de Sousa DP **Anticonvulsant activity of the linalool enantiomers and racemate**: **investigation of chiral influence**. Nat Prod Commun. 2010 Dec;5(12):1847-51. https://www.ncbi.nlm.nih.gov/pubmed/21299105

Sedative

Cline M et al. Investigation of the anxiolytic effects of linalool, a lavender extract, in the male Sprague-Dawley rat. AANA J. 2008 Feb;76(1):47-52. https://www.ncbi.nlm.nih.gov/pubmed/18323320

Anti-anxiety

Linalool was shown to possess anxiolytic properties without any side effects, showing promising potential use in treatment of anxiety disorders. Linalool was evaluated on 4-week ICR mice using an open field test, a light-dark test and an elevated plus maze test. The measurements of monoamines in the brain showed decreased serotonin, dopamine, and norepinephrine, which is commonly seen in animal models exhibiting anxiolytic effects.

Bing-HoCheng et al. **Evaluation of anxiolytic potency of essential oil and *S*-(+)-linalool from *Cinnamomum osmophloeum* ct. linalool leaves in mice** Journal of Traditional and Complementary Medicine Volume 5, Issue 1, January 2015, Pages 27-34 https://www.sciencedirect.com/science/article/pii/S222541101400008X

Cannabinoid Synergy

Anti-anxiety - CBG
Sedative - CBN,THC
Analgesic - CBD
Anticonvulsant - CBD, CBDV, THCV

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Myrcene

Myrcene is a monoterpene and an important precursor to many terpenes. Myrcene is hypothesised to help compounds enter cells through enhancing membrane permeation. It is also noted to have antioxidant effects with mutagenic compounds. Another benefit to myrcene is its ability to relax muscles and induce sleep.

Analgesic

Lorenzetti BB et al. **Myrcene mimics the peripheral analgesic activity of lemongrass tea.** J Ethnopharmacol. 1991 Aug;34(1):43-8. https://www.ncbi.nlm.nih.gov/pubmed/1753786

Sedative

Myrcene was explored as a sedative in the mouse model. Muscle relaxation was seen as observed through the rota rod test. In addition there was an increase in sleeping time by 2.6x.

Lorenzetti BB et al. **Myrcene mimics the peripheral analgesic activity of lemongrass tea.** J Ethnopharmacol. 1991 Aug;34(1):43-8. https://www.ncbi.nlm.nih.gov/pubmed/1753786

T. Gurgel do Vale et al. Central effects of citral, myrcene and limonene, constituents of essential oil chemotypes from*Lippia alba* (Mill.) N.E. Brown Phytomedicine **Volume 9, Issue 8, 2002, Pages 709-714** https://www.sciencedirect.com/science/article/pii/S0944711304701786

Antioxidant

The effects of myrcene were evaluated through the activity of liver microsomes. The potent inhibitory effects on cytochrome p450 suggest that myrcene could also interfere with the metabolism of xenobiotics which are substrates for the isoenzyme.

De-Oliveira AC et al. **In vitro inhibition of CYP2B1 monooxygenase by beta-myrcene and other monoterpenoid compounds**. Toxicol Lett. 1997 Jun 16;92(1):39-46. https://www.ncbi.nlm.nih.gov/pubmed/9242356

Cannabinoid Synergy

Analgesic - CBD, THC
Sedative - THC, CBN
Anti-oxidant - CBD, CBG

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Nerolidol

This terpenoid acts as a toxin to harmful protozoa like malaria and leishmaniasis. Furthermore, nerolidol aids drug delivery through the skin.

Topical Drug Enhancer

Barry BW et al. **Sesquiterpene components of volatile oils as skin penetration enhancers for the hydrophilic permeant 5-fluorouracil.** Cornwell PA(1), J Pharm Pharmacol. 1994 Apr;46(4):261-9. https://www.ncbi.nlm.nih.gov/pubmed/8051608

Antiprotozoan

Lopes NP et al. **Antimalarial use of volatile oil from leaves of Virola surinamensis (Rol.) Warb. by Waiãpi Amazon Indians.** J Ethnopharmacol. 1999 Nov 30;67(3):313-9. https://www.ncbi.nlm.nih.gov/pubmed/10617066

Arruda DC et al. Antileishmanial activity of the terpene nerolidol. Antimicrob Agents Chemother. 2005 May;49(5):1679-87. https://www.ncbi.nlm.nih.gov/pubmed/15855481

Cannabinoid Synergy

THC, CBN – sedative

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Ocimene

Ocimene exhibits anti-inflammatory effects in white blood cell through a variety of pathways. Antifungal effects are also seen with human specific Candida species. Very interestingly, ocimene showed specificity and effectiveness against SARS virus.

Anti-inflammatory

Kim MJ et al.**Chemical composition and anti-inflammation activity of essential oils from Citrus unshiu flower**. Nat Prod Commun. 2014 May;9(5):727-30. https://www.ncbi.nlm.nih.gov/pubmed/25026734

Antifungal

Ocimene has been shown to be toxic to against Candida albicans. This effect was seen with Ferulago carduchorum essential oil.

Golfakhrabadi F et al. Biological Activities and Composition of Ferulago carduchorum Essential Oil. J Arthropod Borne Dis. 2014 Jul 16;9(1):104-15. eCollection 2015 Jun. https://www.ncbi.nlm.nih.gov/pubmed/26114148

Antiviral

The essential oil of Laurus nobilis was evaluated on the SARS virus. Ocimene was noted to be a major constituent of the oil. The oil demonstrated a selectivity index of 4.16.

Loizzo MR et al. **Phytochemical analysis and in vitro antiviral activities of the essential oils of seven Lebanon species**. Chem Biodivers. 2008 Mar;5(3):461-70. https://www.ncbi.nlm.nih.gov/pubmed/18357554

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Terpinolene

Antibacterial

Terpinolene has been shown to be toxic against, Bacillus subtilis, Staphylococcus aureus, Staphylococcus epidermidis and Escherichia coli.

Eftekhar F et al. **Essential oil composition and antimicrobial activity of Diplotaenia damavandica**. Z Naturforsch C. 2005 Nov-Dec;60(11-12):821-5. https://www.ncbi.nlm.nih.gov/pubmed/16402540

Habibi Z et al. **Chemical composition and antibacterial activity of essential oil of Heracleum rechingeri Manden from Iran**. Nat Prod Res. 2010 Jul;24(11):1013-7. https://www.ncbi.nlm.nih.gov/pubmed/20552523

Carson CF et al. **Antimicrobial activity of the major components of the essential oil of Melaleuca alternifolia.** J Appl Bacteriol. 1995 Mar;78(3):264-9. https://www.ncbi.nlm.nih.gov/pubmed/7730203

Anti-oxidant

Turkez H et al. **Genotoxic and oxidative damage potentials in human lymphocytes after exposure to terpinolene in vitro**. Cytotechnology. 2015 May;67(3):409-18. https://www.ncbi.nlm.nih.gov/pubmed/24590926

Grassmann J et al. **The monoterpene terpinolene from the oil of Pinus mugo L**. in**concert** with **alpha-tocopherol** and **beta-carotene effectively prevents oxidation** of **LDL**. Phytomedicine. 2005 Jun;12(6-7):416-23. https://www.ncbi.nlm.nih.gov/pubmed/16008117

Sedative

Nasal transmission of terpinolene was concluded to induce sleep in mice. Oral administration may prove more potent.

Ito K et al. **The sedative effect of inhaled terpinolene in mice and its structure-activity relationships**. J Nat Med. 2013 Oct;67(4):833-7. https://www.ncbi.nlm.nih.gov/pubmed/23339024

Anti-cancer

A key protein involved in progressing cancers, RAC-alpha serine/threonine-protein kinase, was shown to be reduced in leukemia cells with the treatment of terpinolene. Also brain cancer cells were shown to be significantly affected by the terpenoid as well, and no signs of genetic damage were seen in the normal cells.

Okumura N et al. **Terpinolene, a component of herbal sage**,**downregulates AKT1 expression in K562 cells**. Oncol Lett. 2012 Feb;3(2):321-324. https://www.ncbi.nlm.nih.gov/pubmed/22740904

Aydin E et al. **Anticancer and antioxidant properties of terpinolene in rat brain cells.** Arh Hig Rada Toksikol. 2013 Sep;64(3):415-24. https://www.ncbi.nlm.nih.gov/pubmed/24084350

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Valencene

This terpenoid has been shown to repel ticks and mosquitoes at lesser concentrations than DEET and without the toxicity to humans. Valencene has been shown to be and anti-inflammatory, lowering the levels of inflammatory markers in macrophages.

Insect Repellent

Panella NA et al. **Use of novel compounds for pest control: insecticidal and acaricidal activity of essential oil components from heartwood of Alaska yellow cedar**. J Med Entomol. 2005 May;42(3):352-8. https://www.ncbi.nlm.nih.gov/pubmed/15962787

Dietrich G et al. **Repellent activity of fractioned compounds from Chamaecyparis nootkatensis essential oil against nymphal Ixodes scapularis** (**Acari: Ixodidae**). J Med Entomol. 2006 Sep;43(5):957-61. https://www.ncbi.nlm.nih.gov/pubmed/17017233

Anti-inflammatory

Tsoyi K et al. (+)-**Nootkatone** and (+)-**valencene** from **rhizomes** of **Cyperus rotundus increase survival rates** in **septic mice due** to **heme oxygenase-1 induction**. J Ethnopharmacol. 2011 Oct 11;137(3):1311-7. https://www.ncbi.nlm.nih.gov/pubmed/21843620

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Terpene Chart

Terpene	a-pinene	Beta-Caryophyllene	Borneol	Caryophyllene Oxide	Cineol	Citronellol	Humulene	Limonene	Linalool	Myrcene	Nerolidol	Phytol	Terpinolene
Property													
Analgesic													
Anorectic													
Anti-anxiety													
Anti-bacterial													
Anti-Cancer													
Anti-Depressant													
Anti-Fungal													
Anti-Inflammatory													
Anti-Insomnia													
Anti-Ischemic													
Anti-Septic													
Anti-Spasmodic													
Bronchodilator													

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