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. Δ⁹-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
degradate 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
depth 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](https://doi.org/10.3390/medicines20152251).

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.”


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.


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 ∆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. ∆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  

Δ⁹-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-arachidonoylglcerol (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, Δ⁹-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  

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 Δ⁹-THC, i.e. CB₁ and CB₂ 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. 5HT₁₅) [18, 19, and 28], adenosine uptake [37], nuclear receptors of the PPAR family (i.e. PPAR-γ) [38, 39] and many other pharmacological targets...”


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

1. The psychoactive phytocannabinoid Δ⁹-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 Δ⁹-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 neuroprotective properties of CBD (such as protection from brain damage produced by different types of cytotoxic insults) do not involve CB1 or CB2 receptor 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 NFκB (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. NFκB 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 Δ9-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.


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.”


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


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 Δ⁹-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 Δ⁹-THC analgesic effects are significantly decreased in mice lacking α3-GlyR, but not in mice lacking CB₁ and CB₂ 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, Δ⁹-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.”

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.”


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.


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.


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. Cannabissins are a group of lignans found in Cannabis seeds and roots. They have free radical scavenging anti-oxidative and anti-cancer activity.


http://www.eurekaselect.com/154874/article
# Phytocannabinoid Pharmacology Table

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

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5-HT, 5-hydroxytryptamine (serotonin); AEA, arachidonylethanolamide (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

Geranyl Pyrophosphate + Olivetolic Acid

CBGA → CBG

CBDA, THCA → CBNA

CBD, THC → CBN

To access a fully-interactive version of this schematic please go to:
http://www.heavensenthemp.com/our_research/HSHPhytocannabinoidBiosynthesisDiagram.pdf
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*).
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.

RETURN TO DIAGRAM
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.
**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:

\[
\text{geranyl diphosphate} + 2,4\text{-dihydroxy-6-pentyibenzoate diphosphate} \rightleftharpoons \text{cannabigerolate}
\]
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.
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 $\alpha_2$-adrenergic receptor agonist, moderate affinity 5-HT$_{1A}$ receptor antagonist, and low affinity CB$_1$ receptor antagonist.
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:

\[
\text{cannabigerolate} + O_2 \rightarrow \text{cannabidiolate} + H_2O
\]
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), Tetrahydrocannabinolic 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.
**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.
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.

Reduction

Oxidant + e− → Product
(Gain of Electrons) (Oxidation Number Decreases)

Oxidation

Reductant → Product + e−
(Loss of Electrons) (Oxidation Number Increases)
CBNA (Cannabinolic Acid)

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

Decarboxylation is a chemical reaction that removes a carboxyl group and releases carbon dioxide (CO\textsubscript{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\textsubscript{2} to a compound. Enzymes that catalyze decarboxylations are called decarboxylases or, the more formal term, carboxy-lyases.

\[
\begin{align*}
\text{R-CO-OH} & \quad \rightarrow \quad \text{R-H} + \text{O=C=O} \\
\end{align*}
\]
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.
**THC - Tetrahydrocannabinol**

Tetrahydrocannabinol, abbreviated THC, is one of at least 113 cannabinoids identified in cannabis. THC is the principal psychoactive constituent of cannabis. With chemical name, \((-\text{trans-}\Delta^9\text{-tetrahydrocannabinol})\), the term THC also refers to cannabinoid isomers.

Like most pharmacologically-active secondary metabolites of plants, THC is a lipid found in cannabis, assumed to be involved in the plant's self-defense, putatively against insect predation, ultraviolet light, and environmental stress.
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).\[1\] 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.
THCA synthase

Tetrahydrocannabinolic acid (THCA) synthase (full name $\Delta^1$-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 Cannabis 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.
## Terpenoid Pharmacology Table

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

<table>
<thead>
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<td>De Oliveira AC, Ribeiro-Pinto LF, Paumgartten JR</td>
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Understanding the Complexity of Healing Hemp
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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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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
Alpha Bisabolol

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


**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.


**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.


**Cannabinoid Synergy**
CBG, CBD

[RETURN TO TERPENOID LIST](#)
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.


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


**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


**Anti-cancer**

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


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.

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.


Cannabinoid Synergy

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

RETURN TO TERPENOID LIST
Beta Caryophyllene

Beta-caryophyllene exhibits 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 an 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
- 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

Anti-oxidant

Anti-inflammatory

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/](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3070571/)

Cannabinoid Synergy
Analgesic - CBG, CBD

RETURN TO TERPENOID LIST
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.


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

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.


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.


RETURN TO TERPENOID LIST
Caryophyllene oxide

Caryophyllene oxide is an oxygenated terpenoid, usually a metabolic byproduct 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.


Anticoagulant

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


Cannabinoid Synergy

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

RETURN TO TERPENOID LIST
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**


**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*.


RETURN TO TERPENOID LIST
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**


**Anti-inflammatory**


**Anti-oxidant**


**Anti-cancer**


**Anti-asthma**


RETURN TO TERPENOID LIST
Geraniol

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

**Analgesic**


**Anti-fungal**


**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.


**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.


**Anti-inflammatory**

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

RETURN TO TERPENOID LIST

Humulene

Antibacterial

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


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.


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.


Cannabinoid synergy

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

RETURN TO TERPENOID LIST
Limonene

Antidepressant/Anti-anxiety


Anti-inflammatory


Anti-cancer


Cannabinoid synergy

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

RETURN TO TERPENOID LIST
Linalool

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

**Anti-inflammatory**

**Analgesic**

**Anticonvulsant**

**Sedative**

**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.


**Cannabinoid Synergy**

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

[RETURN TO TERPENOID LIST](#)
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**


**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.


**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.


**Cannabinoid Synergy**

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

RETURN TO TERPENOID LIST
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**


**Antiprotozoan**


**Cannabinoid Synergy**

THC, CBN – sedative

**RETURN TO TERPENOID LIST**
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**


**Antifungal**

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


**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.


**RETURN TO TERPENOID LIST**
Terpinolene

Antibacterial

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


Anti-oxidant


Sedative

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


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.


**RETURN TO TERPENOID LIST**
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 an anti-inflammatory, lowering the levels of inflammatory markers in macrophages.

**Insect Repellent**


**Anti-inflammatory**


**RETURN TO TERPENOIDS LIST**

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# Terpene Chart

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