Introduction to Cannabis Science

A Primer for Healthcare Professionals, Students, and the Cannabis Curious

By Timothy Byars

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For Rebecca.
You are my compass, my courage, my captain.

Introduction

As of August 2021, there are eighteen states (plus the District of Columbia, the Commonwealth of the Northern Mariana Islands, and Guam) with legislation that regulates adult use cannabis, 37 states (plus the District of Columbia, Guam, the U.S. Virgin Islands, and Puerto Rico) with legislation to regulate medical cannabis, and 14 states with legislation to regulate high CBD/low Δ9-THC cannabis products. Currently, only 2 states (Idaho and Nebraska) allow no form of legal medical cannabis. Despite that the overwhelming majority of states allow some form of medical cannabis, it remains illegal at the federal level and defined as a Schedule I drug. The changes at the state level represent a dramatic shift in public opinion and support for legal cannabis access.

With the rapid increase in legal access, patients are using cannabis to manage a multitude of symptoms, such as pain, anxiety, sleep, depression, nausea, vomiting, and appetite loss. In many cases, patients know more about using cannabis as a medicine than their healthcare professional (HCP). Unfortunately, most patients receive guidance and instruction from industry retail workers and manufacturers, most of whom have no medical background and many of whom have little cannabis education.

Despite decades-long prohibition, cannabis remains the most widely used and most widely available illegal substance in the world.[1] The number of individuals who have tried cannabis is estimated to be ten times greater than those who have tried cocaine, opiates, and other internationally regulated drugs. Global patient use is estimated at 2.7-4.9%.[2] A recent survey suggested that, in the U.S., approximately 1 in 7 individuals have tried cannabis.[3]

People are using cannabis. It's imperative that healthcare professionals, students, and consumers understand the science behind the effects of cannabis and cannabinoid products. This book is a primer for readers who want to understand the foundational science of the cannabis plant, from the molecular structure of the plant's compounds to the analytical methods used to test samples for potency and toxins.

Chapter 1: Cannabis Botany, Paleobotany, and Ethnobotany

Humans have been using cannabis for medical, textile, and spiritual uses for a very long time. In fact, hemp cord found in pottery in the area of modern-day Taiwan was dated at 10,000 BCE.[4] Agriculture is a fairly recent invention—the practice is only about 10,000 years old—and it is the basis for modern civilization. Carl Sagan, in 1977, suggested that *cannabis* might have been the first domesticated crop, and was possibly instrumental to the development of civilization itself.[5]

Based on archaeobotanical data and the synthesis of subfossil pollen, researchers estimate that the cannabis plant diverged from a common ancestor (with hops) nearly 30 million years ago.[6] Since then, it has distributed to every continent during the last two millennia (yes, even to Antarctica),[7] and while its taxonomy is hotly disputed, the cannabis diaspora has produced a genetically diverse plant.

This diversity is evident in the plant's morphology. The height of a cannabis plant, the leaf shape and color, the density of the plant's inflorescence, the density and type of trichomes, the quality of the fiber, the flowering time and yield—these combinations of attributes suggest scores of unique phenotypes—and the molecular study of cannabis plants in the past decade have confirmed a genetic diversity among plant types.

The previous consensus was that cannabis likely originated in central Asia, possibly on the Tibetan Plateau (this hypothesis is supported by fossil pollen analysis completed in 2019).[8] However, in 2021 a team of researchers from the University of Lausanne in Switzerland used DNA sequencing and molecular analysis to study 110 genomes of *Cannabis sativa L*. and concluded that the origin of our modern-day domesticated cannabis originated in East Asia and China.[9]

What seems evident is that cannabis originated from a desert-like environment and the plant evolved with mechanisms necessary to survive in dry and hot environments. In fact, many botanical features of cannabis are also common to other desert plants. For example, trichomes are common among desert plants because they help plants conserve water by stabilizing the air surrounding the plant. Trichomes prevent the desert air from direct contact with the surface of a plant's leaves and reduce the rate at which a plant loses water.[10] In the cannabis plant, the trichomes contain (among other compounds) the phytocannabinoids. THCa, one of the most common phytocannabinoids in raw cannabis, is likely another evolutionary adaptation to a desert environment—protecting cannabis plants from UV light.

> ***Keywords:*** Cannabinoids, terpenes, flavonoids, and other compounds are produced by cannabis plants and stored as resin in *trichomes*, which are microscopic mushroom-shaped protuberances that form on the flowers, the stems, leaves, and stalk of cannabis plants. The trichomes that form on the stalk, stems, and leaves of cannabis plants are different than those that form on the flowers—they are shaped differently and they do not contain the number or diversity of chemical compounds as those found on flower trichomes—there are far fewer trichomes on the leaves, stalk, and stems than on the flowers. For example, the trichomes on the flowers contain approximately 18 times the amount of cannabinoids than those found on the leaves and stalks.[11]

Exposure to sunlight is, of course, essential for photosynthesis. The spectrum of light produced by the sun, however, contains types of radiation that are destructive to plants. Natural selection favored plants that evolved with protections from this destructive light. One defense that plants developed is a chemical shield, which functions in a manner similar to the pigmentation of human skin.[12]

Ultraviolet rays are classified by their wavelength and grouped into three broad categories: UVA, UVB, and UVC. UVC light (short wave UV rays) are highly damaging to all living things, but this part of the light spectrum is filtered by the Earth's ozone layer. At high levels, UVB (medium wave UV rays) can cause damage to humans and plant cells (these are rays of light that are responsible, for example, for sunburns on skin). The ability of cannabis plants to produce secondary metabolites likely contributes to their ability to defend themselves

from destructive UVB radiation. Flavonoids, for example, absorb UVB light and prevent it from penetrating into plant tissue. The acidic cannabinoid THCA also absorbs UVB radiation, contributing to the chemical shield that cannabis plants produce to shield them from UV light.[13]

> ***Keywords:*** Secondary metabolites are organic compounds produced by bacteria, fungi, or plants that are not directly involved in the growth, development, or reproduction of the organism. Secondary metabolites often mediate ecological interactions to produce selective. For example, secondary metabolites can improve a plant's defense against herbivores or pests. While some secondary metabolites are toxic, others can be used as medicines, flavorings, pigments, and drugs.[14]

In geographical areas where there exist high levels of ultraviolet radiation exposure—such as high-altitude and tropical environments—the existence of THCA in a cannabis plant's trichomes possibly conferred an evolutionary advantage to plant lineages that produced THCA in abundance. And, it appears that THCA not only protects the cannabis plant from UV light, but UVB light increases the *production* of THCa. When cannabis is exposed to UVB, the plant produces specific chemicals that, through a series of enzymatic reactions, eventually produce Olivetolic acid. Olivetolic acid is the precursor to CBGa. A single enzyme, the THCA synthase enzyme, converts CBGa into THCa.[15]

In fact, researchers have confirmed that UV radiation increases the yield of THCa. Cannabis researchers exposed cannabis plants to increased amounts of ultraviolet radiation[16] and discovered that increasing UVB radiation produced an increase of the THCA by 28%.

Modern cannabis growers have manipulated this evolutionary trait to produce plants with higher potencies. Growers can purchase high pressure sodium and metal halide lights (both of which generate UVB light) and supplement their primary light sources with the judicious use of UVB rays to produce higher amounts of THCA in the plant material and higher potency Δ9-THC flowers and products.[17]

Cannabis Taxonomy

Taxonomy is the science of naming, describing, and classifying plants, animals, and microorganisms. The earliest formal botanical taxonomies of cannabis suggested multiple species. In 1542, Leonhart Fuchs was among the first

Botanist Carl Linnaeus

botanists to apply the name *Cannabis sativa*, over 200 years before Carl Linnaeus formalized botanical system with binomial names. The specimen that Linnaeus collected and named *Cannabis sativa L.* was likely from Sweden and the plant's morphology is consistent with hemp stock of northern Europe—with loose, airy inflorescences and with few sessile glandular and capitate stalked glandular trichomes.[18]

Thirty years after Linnaeus named *C. sativa L.*, French naturalist Jean-Baptiste Lamarck identified *Cannabis indica* (plants originating in India) as a different species. In addition to being smaller than Linnaeus' plant, Lamarck's plant had multiple distinct morphological attributes, including velvety bracts, dense trichomes, and different leaf structures.[19]

More modern species assignation (Small and Cronquist) recognizes a single species with two subspecies: *C. sativa subsp. sativa* and *C. sativa subsp. indica*. Other botanists consider these *C. sativa* and *C. indica* to be of different species, with some recognizing a third species, *Cannabis ruderalis*. Dr. Ethan Russo—a board-certified neurologist, psychopharmacology researcher, author, and prominent cannabis expert—states that the issue, to this day, remains "fraught with great debate."[20] The following table describes the taxonomic classification of cannabis:[21]

Category	**Taxon**
Domain	Eukarya
Kingdom	Plantae—Plants
Subkingdom	Tracheobionta—Vascular plants
Superdivision	Spermatophyta—Seed plants
Division	Magnoliophyta—Flowering plants
Class	Magnoliopsida—Dicotyledons
Subclass	Hamamelididae
Order	Urticales
Family	Cannabaceae
Genus	*Cannabis*
Species	*Cannabis sativa L.*

Adding to the confusion, the terms “Sativa” and “Indica” are often used in common vernacular to organize cannabis types into two broad categories and to suggest that—in general—these categories predict the overall effects of products within each group. Dr. John M. McPartland—cannabis researcher, author, and prominent cannabis expert—notes that “Sativa” and “Indica” have very little relationship with the formal taxonomic categories *Cannabis sativa* and *Cannabis indica* and the vernacular use of “Sativa” and “Indica” simply sows confusion.[22]

Russo notes that the best approach is “eschew the irreconcilable taxonomic debate as an unnecessary distraction and…emphasize that only biochemical and pharmacological distinctions between Cannabis accessions are relevant.” [23] McPartland agrees, stating, “Categorizing Cannabis as either ‘Sativa’ and ‘Indica’ has become an exercise in futility. Ubiquitous interbreeding and hybridization renders (*sic*) their distinction meaningless.”[24]

If the usefulness of cannabis plant identification is to predict some attribute about the plant’s effects, the best method is to understand the plant’s cannabinoid and terpene profiles. Today, no morphological aspects can predict a plant’s effects—not the height of the plant, its leaf shape or color or thickness, and certainly not whether the plant is labeled “Indica” or “Sativa”.

Researchers, manufacturers, retailers, and consumers are beginning to recognize new nomenclature based on a plant’s chemotype. The chemotype profile categorization with Type I, Type II, Type III plant types is a good start, as it broadly combines chemovars with high Δ9-THC, combinations of Δ9-THC and CBD, and high CBD, respectively. This system can be expanded to account for chemovars bred with other dominant cannabinoids (such CBG and CBC) or with very few cannabinoids (bred for fiber or manufacturing).

The biochemical assay of a plant is incomplete, however, if it includes only cannabinoid content. The system must also account for terpene profiles to help consumers make informed decisions.[25] Chemotype categories should include subcategories to identify dominant terpenes to enable consumers to anticipate the effects of a plant (or product) and to enable clinicians to make more informed recommendations for patients. For example, case studies have demonstrated that clinicians using cannabis extracts with high levels of linalool saw greater efficacy in the treatment of epilepsy than when using extracts absent of this terpene.[26]

As the research continues to mature, chemotypes with specific cannabinoid, terpene, and even flavonoid profiles can be matched to specific diseases and conditions for efficacy and safety.

Cannabis Morphology

Cannabis plants are dioecious (male and female flowers develop on separate plants) but can occasionally also be monoecious, where the male and female flowers develop on a single plant (these are hermaphroditic plants, which is how growers can obtain feminized seeds).

On the female plant, the stigmas will begin to protrude from the intersections of the stem and leaves—these are intersections are called nodes. A female plant (if not cropped during the vegetation growth stage) will grow a single main flower cluster and multiple secondary clusters. The main cluster is called the cola and it is large, heavy, and densely covered in trichomes.

All female flowers each contain a single ovule, which are surrounded by bracts. The bracts are small leaves that surround the reproductive cells. If a plant is exposed to pollen, the bracts surround and protect the seed pod. The bracts have the densest covering of capitate-stalked trichomes, in which the plant synthesizes and stores the highest concentrations of cannabinoids, terpenes, flavonoids, and other compounds. A female plant's collection of bracts comprises most of the weight of a cannabis flower.

Each female flower includes two stigmas that extend from a single ovule. Stigmas are thin hairs that are approximately one quarter to one half inch in length, and can be white, yellowish, red, or purple. Stigmas catch pollen from male plants. This collection of female reproductive parts—the two stigmas and the ovule—is called the pistil. If a female flower is pollinated, it can produce up to 150 seeds. An entire cola might contain hundreds of seeds, and a small plant might bear many thousands of seeds.[27]

You can identify a male cannabis plant at about 6 weeks of growth. In a male plant, sacs will begin to appear at the intersections of the stem and leaves (the nodes). These sacs, which contain pollen, eventually grow into large bell-shaped clusters. A single male flower can produce 350,000 pollen grains.[28] Wind carries male pollen to female plants. Two studies provide some indication of the distances that cannabis pollen can traverse to pollinate female plants, one measuring pollen drift across a 3 to 7.5 mile range, and the second measuring pollen drift up to 30 miles.[29] Bees can collect cannabis pollen but the plant did not

Figure 1 Hand-drawn Botanical Illustration of Cannabis

evolve to attract bees and bees do not generally contribute to cannabis pollination.[30]

A study in 2000[31] measured the airborne pollen counts in Midwest states during August. Researchers noted that 36% of the total airborne pollen count was cannabis pollen. Given that this was well before cannabis legalization in the Midwest, the pollen likely came from wild fields or from illicit fields where male plants were not culled.

Male plants do produce cannabinoids and terpenes, though far less than the amount produced by female flowers. Trichomes on males are mostly in the areas where pollen is produced, but trichomes are also produced on the small leaves.[32] Male plants, then, do have some therapeutic value. Growers can use the smaller leaves to make raw juices, teas, and extracts (the fan leaves and stems likely contain too much chlorophyll and might impart a bitterness or a hay flavor).

In general, cannabis plants have palmately compound leaves with 3 to 13 veined, serrated leaflets. Plants that originated in dry areas—the Middle East, Afghanistan, northwestern Pakistan, Turkestan, Uzbekistan, and northwest China, which are plants that have been described as a Wide Leaf Drug (WLD) biotype[33]—are typically shorter in height and bushier with leaves that tend to be broader, thicker, and colored a deep green.[34] Plants that originated in India,

including descendants in Southeast Asia, Africa, and the Americas—plants that have been described as Narrow Leaf Drug (NLD) biotypes—excel in humid environments. These plants have slender leaves that are light green in color and these biotypes tend to include greater numbers of leaves than WLD plants.[35]

Regardless of the origin, all cannabis fan leaves collect light for photosynthesis and help regulate metabolic function. A protective, waxy film called the cuticle covers each leaf's epidermis, a single layer of cells that forms the boundary between the plant and its external environment. Beneath this layer of cells are two types of mesophyll cells: palisade cells, in which chloroplasts absorb most of the light energy used by the leaf;[36] and spongy mesophyll cells, in which pores called stomata regulate gas and water exchange. Each stoma can open and close to conserve moisture and to regulate metabolic function.[37]

Cannabis fan leaves are large leaves that appear along the length of the stem and provides sites for photosynthesis. These leaves appear on both male and female plants. Sugar leaves are much smaller than fan leaves. These are single-bladed leaves that appear on cannabis flowers. Sugar leaves are coated with trichomes, which give the leaves a frosted appearance, and can be used to make edibles, juice, teas, or concentrates.

Cannabis leaves can be covered in capitate-sessile glandular, bulbous glandular, and non-glandular trichomes.

Trichomes

Cannabis trichomes are fine outgrowths or appendages that are produced on the surface of cannabis plants and contain flavonoids, cannabinoids, terpenes, and other resinous compounds that give cannabis plants their unique characteristics.

Capitate-Stalked Trichomes

There are three types of trichomes: bulbous, capitate-sessile, and capitate-stalked:

- Bulbous trichomes are microscopic bulbs that cover the entire plant.
- Capitate-sessile trichomes are slightly larger than bulbous trichomes and appear on the underside of the sugar leaves and fan leaves.
- Capitate-stalked trichomes are mushroom shaped with a stalk and head. These are visible on the surface of cannabis flowers.

In addition to storing the secondary metabolites, trichomes also reflect radiation, reduce the surface temperature of the plant, and reduce water loss. Trichomes also protect the plant from insects.

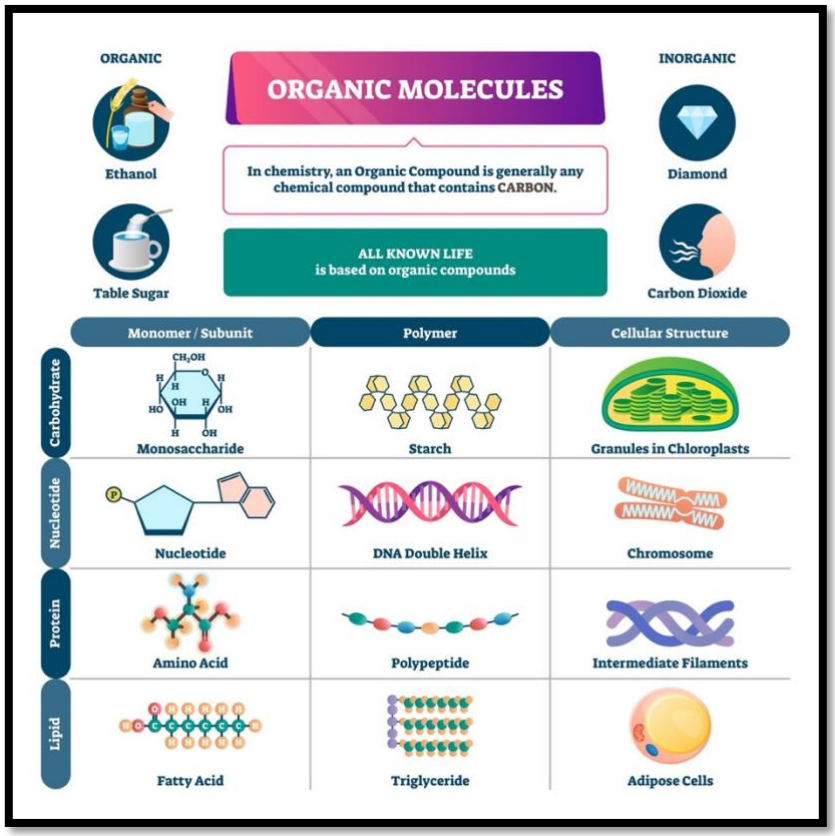
Inorganic and Organic Compounds

In biochemistry, there are a number of different compounds essential to the structure and function of human life. Very broadly, these compounds can be categorized as organic and inorganic, which are considered the two main disciplines in chemistry.

Organic compounds include carbon and hydrogen atoms. Behind only oxygen, carbon is the second most abundant element in the human body. Hydrogen is the third most abundant element in the human body. These compounds are associated with living organisms and include fats, proteins,

enzymes, and hydrocarbons. Many organic compounds always oxygen, such as table sugar ($C_{12}H_{22}O_{11}$) and ethanol (C_2H_6O).[38]

Inorganic compounds lack the combination of carbon and hydrogen atoms. Water, salts, acids, and bases are all examples of inorganic compounds. These compounds can, however, contain *either* carbon atoms *or* hydrogen atoms. For example, water is an inorganic compound (H_2O—water compounds contain hydrogen atoms but no carbon atoms). And, carbon dioxide is also an inorganic compound (CO_2—carbon dioxide contains carbon atoms but no hydrogen atoms). Diamond, which is pure carbon, is also considered an inorganic compound.



The cannabis plant includes over 400 organic compounds, including phytocannabinoids, terpenes, and flavonoids.

Chapter 2: Cannabinoids, Terpenes, and Flavonoids

A cannabinoid is a chemical compound that influences cannabinoid receptors in cells to affect neurotransmitter release**.** *Cannabinoid* is a general term that can refer to any of the following:

- *Phytocannabinoids* are cannabinoids produced by cannabis plants and which contribute to the therapeutic properties of cannabis plants. Cannabis flowers secrete resin that contains over 100 unique phytocannabinoids. Two of the best-known and well-studied phytocannabinoids are Tetrahydrocannabinol (Δ9-THC) and Cannabidiol (CBD). The chemical compounds in cannabis absorb into the bloodstream and distribute to cell receptor sites throughout the body. While phytocannabinoids are from cannabis, there exist other medical herbs—such as Echinacea—that have cannabimimetic effects and that can interact with cannabinoid receptors, inhibit endocannabinoid uptake, and otherwise interact with the endocannabinoid system.[39]
- *Endocannabinoids* are cannabinoids produced in the nervous systems and in the immune systems of humans and animals (the prefix *endo-* means internal or within). The two most well understood of these molecules are called anandamide (AEA) and 2-arachidonoylglycerol (2-AG). Endocannabinoids are discussed in detail later in this book.
- *Synthetic* cannabinoids are cannabinoids made from a chemical synthesis to imitate phytocannabinoids and endocannabinoids. The prescription drugs Dronabinol, Nabilone, and Rimonabant all include synthetically made, isolated cannabinoids.

This book uses the more generic term, *cannabinoid*, when referring to any of these subcategories, except when a more specific term is required for clarity.

Phytocannabinoids

Phytocannabinoids are cannabinoids that occur naturally in plants (the prefix *phyto-* indicates that a thing pertains to or is derived from plants). While phytocannabinoids are isolated from cannabis plants, compounds with similar attributes and mechanisms (called *cannabimimetics*) are produced in other flowering plants, liverworts, and fungi. In this book, phytocannabinoids refer to cannabinoids produced by cannabis plants, although readers should understand that a phytocannabinoid can be any plant-derived natural product capable of directly interacting with cannabinoid receptors or that shares a chemical similarity with cannabinoids.[40]

Phytocannabinoids are *secondary metabolites*, which are organic molecules that are not essential for the growth, development, or reproduction of an organism. These metabolites help organisms survive and thrive in their surroundings. Plants are unable to locomote. To defend themselves, plants can synthesize secondary metabolites that are antimicrobial, antiherbivore, or that can both attract and repel insects. Secondary metabolites are classified into four major classes: terpenoids, phenolic compounds, alkaloids, and sulfur compounds.[41] Humans use secondary metabolites as medicines, flavorings, pigments, and drugs.[42]

Phytocannabinoids from cannabis are hydrophobic, lipophilic molecules. They are soluble in fat and they dissolve in solvents such as ethanol or methanol. Because phytocannabinoids are lipid-soluble, they can access areas of the brain that many neurotransmitters cannot reach.

The actual number of phytocannabinoids that have been identified is not clearly defined, but the consensus is that over 113 different cannabinoids have been isolated from cannabis alone. These phytocannabinoids are classified into distinct types: cannabigerols (CBG), cannabichromenes (CBC), cannabidiols (CBD), Δ9-trans-tetrahydrocannabinols (Δ9-THC), Δ8-trans-tetrahydrocannabinols (Δ8-THC), cannabicyclols (CBL), cannabielsoins (CBE), cannabinols (CBN), cannabinodiols (CBND), cannabitriols (CBT), and additional miscellaneous cannabinoids. The most abundant cannabinoids in cannabis plants are Δ9-THC, CBD, CBC, and CBG, in combination with their respective acid forms (Δ9-THCa, CBDA, CBCa, and CBGa).[43]

One difference among phytocannabinoids is the extent to which they are psychologically active. Some phytocannabinoids are psychoactive to varying degrees, although not all of them create the type of euphoria typically associated with psychoactivity. Some phytocannabinoids are psychoactive but non-impairing, meaning that they do not create the kind of psychoactivity that impairs a consumer's mental processes or motor functions.

> ***Keywords:*** The suffix *-phobic* generally refers to a fear or aversion to something. The term *hydrophobic* is a tendency to repel water or failure to mix with water. The suffix *-philic* denotes a fondness for something. The term *lipophilic* is a tendency to combine with or to dissolve in lipids or fats. Cannabinoids generally fail to mix well or dissolve in water but do mix well and dissolve in fats.

Phytocannabinoid Water Solubility and Lipophilicity

Cannabinoids are highly lipophilic and have low solubility in water, and these attributes can be predicted by studying each compound's chemical structure. We know that cannabinoids are lipids—they readily dissolve in fats and alcohol. Lipophilicity can be predicted based on the prevalence of hydrocarbons in a compound—lipids are non-polar and tend to contain hydrocarbons while water-soluble compounds are polar and tend to include hydroxy groups.

> ***Keywords:*** *Hydroxy groups* are molecular entities that contain an oxygen bonded to a hydrogen and are represented by the formula OH.

Cannabinoids have lipophilic attributes because of the non-polar characteristics of the carbon-carbon and carbon-hydrogen bonds in hydrocarbon chains.[44] Nonpolar molecules have no separation of electron charges and no positive or negative poles—the electrical charges of nonpolar molecules are evenly distributed across the molecule. Conversely, polar molecules (these are molecules that are water soluble) have one side with a positive electrical charge and an opposite side with a negative electrical charge.[45]

Polarity has profound effects on the physical properties of the compounds, including solubility, boiling point, and melting point. Nonpolar substances are very soluble in nonpolar solvents and have relatively low boiling and melting points. Polar molecules have high solubility in water and higher boiling and melting points.[46]

Compounds become more water soluble when they contain two or more hydroxy groups.[47] CBD has 2 hydroxy groups and Δ9-THC includes only a single hydroxy group, suggesting that CBD is more water soluble than Δ9-THC. Research investigating the permeability of cannabinoids in human skin suggest that CBD can absorb into the skin more effectively than Δ8-THC by a factor of 10.[48] However, despite the two hydroxy groups in CDB, the hydrocarbon attributes dominate as the hydroxy groups are not enough to compensate for the number of nonpolar hydrocarbons.

Of course, humans are mostly water and water solubility facilitates absorption (the movement of a drug from the site of administration into the bloodstream). Absorption is a critical consideration in drug development because a compound must be absorbed to produce pharmacodynamic effects.[49] The lipophilic attributes of cannabinoids predict the challenges faced when administering cannabinoid medicines, especially when cannabinoids are consumed orally.

Drugs that have high absorption rates and good bioavailability are typically:

- Soluble in water.
  Cannabinoids are hydrophobic and have poor water solubility.
- Stable to hydrolysis.
  Both CBD and Δ9-THC are resistant to hydrolysis (hydrolysis refers to chemical reactions in which a molecule of water ruptures one or more chemical bonds).[50]
- Stable to oxidation, both in the atmosphere and within the body via metabolism.
  Cannabinoids are very prone to oxidation (both in atmosphere and in metabolism) because they include hydroxy groups on the benzene rings. Cannabinoids readily decompose when exposed to heat, light, or air.[51]

Based on these attributes, it's no surprise that oral bioavailability of cannabinoids is very low—between 4% and 12%.[52] To address this issue, some manufactures are attempting to create cannabinoid molecules that are more water soluble. For example, some companies are using existing nanoemulsion technology to produce products that are water-compatible and that can be mixed into beverages in varied concentrations. Manufacturers claim that these products have very fast onset (in some cases, onset comparable to inhalation) and very

high bioavailability (some industry advocates suggest a bioavailability of up to 75%).[53]

Additionally, there are now companies who are genetically modifying cannabis plants (by inserting enzymes) to make cannabinoids more water soluble and less toxic to the plant.[54] For example, companies are looking for methods to produce cannabinoids outside of the trichomes to substantially increase the cannabinoid yield. Water solubility facilitates a simpler extraction process and produces cannabinoids that have broader uses in the market.

> ***Keywords:*** *Oxidation* is a chemical reaction that facilitates the movement of electrons from one substance to another. When a substance loses electrons (or when a substance loses a hydrogen atom) that substance is oxidized. The process of oxidation is called *oxidation* because it was historically associated with changes to chemical substances that occur with the addition of oxygen (oxygen is highly reactive and easily binds with most other elements—for example, some metals rust when exposed to water and the oxygen in the atmosphere).[55] The definition of oxidation now includes other types of reactions that might not include oxygen. When Δ9-THC oxidizes (when the molecule is exposed to light, heat, and air) the molecule loses four hydrogen atoms. The molecular formula for Δ9-THC is $C_{21}H_{30}O_2$. When the molecule loses four hydrogen atoms, the molecular formula becomes $C_{21}H_{26}O_2$, which is the molecular formula for CBN.

Phytocannabinoid Biosynthesis

Cannabis plants are biological factories that produce hundreds of different chemical compounds. The production process of complex molecules in living organisms or cells is called *biosynthesis*.

Biosynthesis is a multi-step process where simple compounds are modified, converted, or joined together to form more complex compounds. To facilitate these transformations, biological systems have mechanisms to catalyze reactions—including enzymes that can initiate and facilitate chemical reactions—and the energy required to drive these reactions to completion.[56]

> ***Keywords:*** A *catalyst* is a substance that increases the rate of a chemical reaction. For example, enzymes often serve as catalysts during the transformation of compounds in biosynthesis.

Cannabis plants extract CO_2 out of atmosphere and use the CO_2 to form sugar. Then, the plant uses those sugars, through multiple enzymatic conversions, to eventually create two compounds called geranyl pyrophosphate and olivetolic acid. These two compounds react, and when catalyzed by an enzyme, they produce cannabigerolic acid (CBGa). When geranyl pyrophosphate combines with divarinolic acid and is catalyzed by an enzyme, the plant produces cannabigerovarin acid (CBGVA).

Decarboxylation converts CBGA into CBG. The following enzymes convert CBGA into acidic cannabinoids:

- Cannabichromenic acid synthase creates CBCA.
- Cannabidiolic acid synthase creates CBDA.
- Tetrahydrocannabinolic acid synthase creates Δ9-THCA.

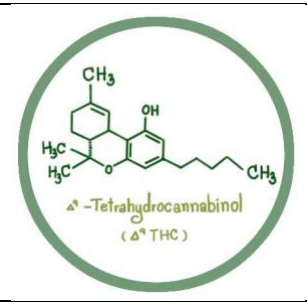
Decarboxylation converts CBGVA into CBGV. The following enzymes convert CBGVA into varin cannabinoids:

- Cannabichromevarinic acid synthase creates CBCVA.
- Cannabidivarinic acid synthase creates CBDVA.
- Tetrahydrocannabivarinic acid synthase creates THCVA.

Δ9-Tetrahydrocannabinol (Δ9 THC)

Δ9-Tetrahydrocannabinol (Δ9-THC, pronounced *delta-nine THC*) is the substance primarily responsible for the psychoactive effects of cannabis and is the cannabinoid typically most abundant in Type I chemovars when cannabis is burned or cooked. Δ9-THC can produce euphoric effects, and can alter behavior, consciousness, mood, and perception. Many chemovars[57] of cannabis have been selectively bred to contain a high Δ9-THC content.

The biological precursor to Δ9-THC is THCA. The biological precursor to THCA is CBGA. Tetrahydrocannabinolic acid synthase is an enzyme that converts CBGA into THCA. Heat and time work to decarboxylate the THCA into Δ9-THC. When Δ9-THC oxidizes, it forms CBN.

Molecular Formula	$C_{21}H_{30}O_2$	
Molecular Weight	314.45 g/mol	

Δ9-THC is the most well-studied cannabinoid in cannabis. As of August 2021, Cannakeys (a platform that facilitates access to published science and aggregated critical data) lists over 160 completed clinical trials with Δ9-THC and human subjects. [58] A simple keyword search for clinical trials using the terms, "Delta 9 THC" returns over 500 search results. These studies[59] suggest that Δ9-THC can provide multiple therapeutic benefits and might help treat nausea,[60] some types of pain,[61] [62] [63] [64] [65] appetite loss,[66] [67] [68] [69] [70] [71], insomnia,[72] anxiety,[73] inflammation,[74] [75] post-traumatic stress,[76] Tourette's syndrome, [77] and some types of cancers.[78] [79] [80] [81] [82]

Δ9-THC is not a COX-1 or COX-2 inhibitor (except at concentrations far above those attained therapeutically) and does not cause the type of mucosal damage, ulceration, and gastrointestinal tract complications as do non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen or aspirin.[83]

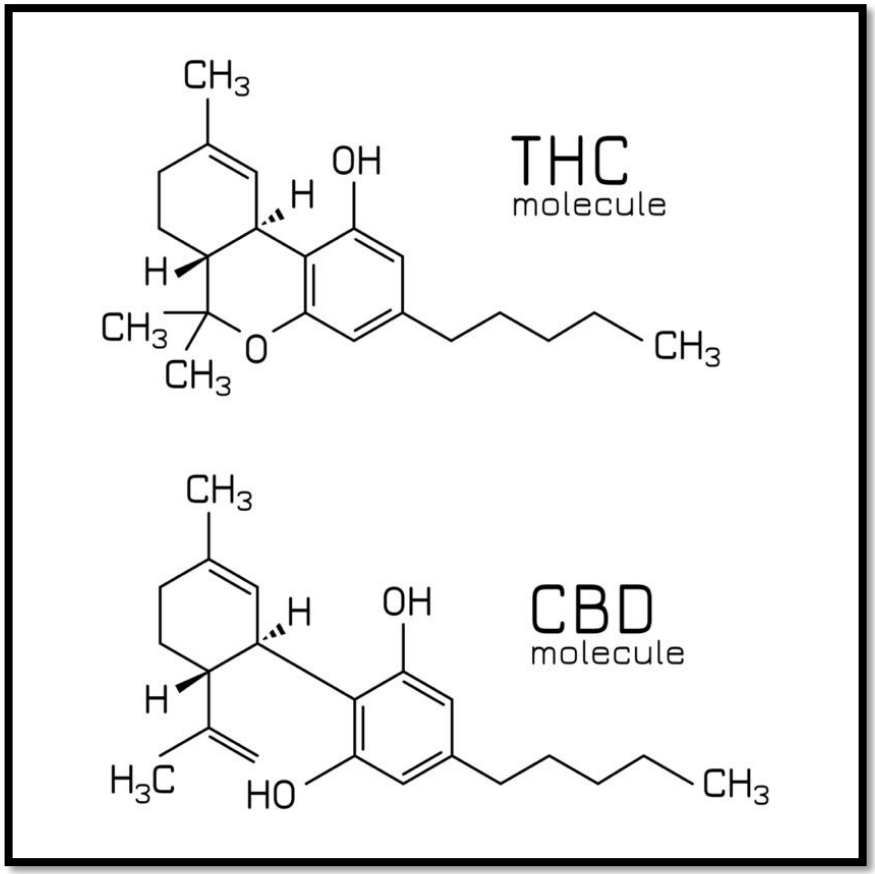
Keywords: *Cyclooxygenase* (COX) is an enzyme. There are two types of COX enzymes: COX-1 and COX-2. Both enzymes can promote inflammation, pain, and fever. However, COX-1 enzymes also facilitate the production of cells that promote normal blood clotting and that protect the stomach and intestinal lining. Medications that can inhibit the production of COX enzymes can help relieve inflammation and pain. For example, nonsteroidal anti-inflammatory drugs (NSAIDs), such as aspirin and ibuprofen, provide relief by inhibiting COX enzymes. Drugs that selectively target only COX-2 enzymes can reduce the risk of mucosal damage, ulcers, and gastrointestinal tract damage associated with COX-1 inhibition.

Δ9-THC can also produce adverse side effects. These adverse effects are dose dependent and more prevalent at higher doses. The most common side

effects are increased heart rate, increased appetite, and fatigue, but other side effects include dizziness, decreased blood pressure and body temperature, forgetfulness, and anxiety. At very high doses Δ9-THC can produce paranoia and hallucinations.

Δ9-THC Isomers

CBD and Δ8-THC (each discussed later) are both isomers of Δ9-THC and have the same chemical formula. Both compounds have 5-carbon alkyl side chains and both have benzene rings (an alkyl functional group that contains only carbon and hydrogen atoms that are arranged in a chain). And while there are some fundamental differences in their structures (for example, Δ9-THC has a



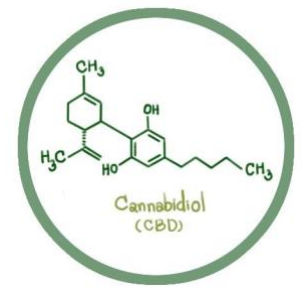
FCBD and Δ8-THC (each discussed later) are both isomers of Δ9-THC.

closed cyclic ring where CBD contains a second hydroxy group; Δ9-THC has a double bond at the carbon 9 position and Δ8-THC has a double bond at the carbon 8 position),[84] these compounds are so similar that it's possible to convert CBD or Δ8-THC into Δ9-THC. In fact, in 1940 chemist Roger Adams published a method for converting CBD to Δ9-THC and by 1949 he had synthesized a catalog of Δ9-THC analogs, which were the first synthetic cannabinoids.[85] [86]

> ***Keywords:*** An *isomer* refers to each of at least two molecules that have the same constituent atoms but that have different arrangements of atoms—such as different bonding, shape, or orientation of atoms.

Cannabidiol (CBD)

Cannabidiol (CBD) is a non-impairing and the second most abundant cannabinoid in cooked or heated Type I cannabis chemovars and is typically the most abundant cannabinoid in cooked or heated Type III chemovars. The biological precursor to CBD is CBDA, and the biological precursor to CBDA is CBGA. CBGA is converted into CBDA by a synthase enzyme. Heat and time work to decarboxylate CBDA into CBD.

Molecular Formula	$C_{21}H_{30}O_2$	
Molecular Weight	314.47 /mol	

Studies suggest that CBD has neuroprotective effects that are more potent than Vitamins C and E.[87] Studies also suggest that CBD demonstrates some anticancer properties[88] [89] [90] [91] and further research suggests that CBD can kill some cancer without impacting normal, healthy cells.[92] [93] [94] Also, some studies suggest that CBD has antibacterial properties, exhibiting exceptional efficacy against MRSA (MRSA, or *methicillin-resistant Staphylococcus aureus*, is a bacterium that causes infections and that fails to respond to conventional antibiotics).[95] Additional studies[96] suggest that CBD might help treat nausea and vomiting,[97] seizure activity,[98] psychosis disorders[99], inflammatory disorders,[100]

anxiety and depression disorders.[101] A purified form of CBD is FDA-approved in the United States for the treatment of with tuberous sclerosis complex and two rare forms of pediatric epilepsy (Lennox–Gastaut syndrome and Dravet syndrome).[7] This medication is sold under the brand name Epidiolex.

CBD is often referred to as a *non-psychoactive* cannabinoid. However, CBD can be used to treat psychotic disorders, anxiety, and depression, and a substance that can relieve anxiety, depression, and psychosis is, in fact, a mood-altering substance, even if it doesn't necessarily produce euphoria. It's more accurate to state that CBD is not psychoactive in same manner as Δ9-THC.[102]

> ***Keywords:*** *Neuroprotection* refers to mechanisms that protect the nervous system from damage caused by injuries (such as damage from a stroke) or from disease (such as damage from Parkinson's or Alzheimer's disease). Cannabinoids, including CBD, might protect the central nervous system against further nerve damage and slow down the degeneration of nerve cells in patients suffering from these conditions and disease.

Hemp-Derived CBD

Hemp is legally defined in the United States as cannabis that contains less than 0.3% Δ9-THC by dry weight. These plants and their derivatives are regulated in the United States very differently—and much less rigorously—than cannabis plants that contain greater than 0.3% Δ9-THC. Consequently, there exists now a very large marketplace for hemp-derived CBD products (as well as products with other hemp-derived cannabinoids, such as CBN and CBG).

All cannabis plants are bioaccumulators—they readily absorb nutrients, metals, and toxins from the soil. In fact, one underrated but well-established use of industrial hemp, for example, is for land reclamation and remediation. A study[103] conducted in China suggested that hemp plants are good biodiesel crop candidates for phytoremediation in soil contaminated by cadmium. For over two decades, industrial hemp has been planted near the abandoned Chernobyl nuclear power plant in Pripyat, Ukraine to help reduce soil toxicity.[104]

Unfortunately, when hemp plants are sourced from unregulated markets, they can be riddled with heavy metals, mold, bacteria, pesticides, and other contaminants, which can block receptors and cause any number of health issues.

All flower-derived cannabis products sold in licensed dispensaries must undergo rigorous testing. Patients can obtain the test results to verify that they've

been tested for mold, bacteria, pesticides, and metals. Patients can also verify the terpene and cannabinoid content.

Hemp-derived cannabis products, however, are regulated in the U.S as diet supplement—you can buy hemp-derived CBD products from a gas station, a health food store, or on the internet (in many states, the one place where you *cannot* buy hemp-derived products is from a cannabis dispensary). The FDA is not authorized to review dietary supplement products for safety and efficacy before they reach the marketplace. Many of these products offer no assurances about efficacy, do not list ingredients, and do not provide any testing results.

By February 2016, the FDA had tested 24 products that claimed to contain CBD. Only two of the 24 CBD products contained the amount of CBD claimed on product labels (more specifically, eleven of the products did not list the amount on the label, eight failed outright, and three others failed but were close to the stated amount).[105] These results were duplicated in another study published in JAMA in 2017.[106]

The Agricultural Improvement Act of 2018 (also known as the Farm Bill) was signed into law on 20 December 2018.[107] This bill included language that effectively removed hemp from the Controlled Substances Act (CSA). That same day, former Food and Drug Administration (FDA) Commissioner, Scott Gottlieb, issued a statement to clarify the agency's role in regulating products containing cannabis and cannabis-derived compounds.

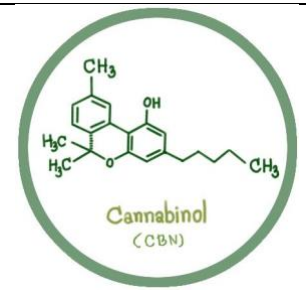
According to Gottlieb, while hemp is no longer an illegal substance under federal law, all products containing cannabis or cannabis-derived compounds are subject to the same regulatory authority as any other FDA-regulated product. With the growing public interest in CBD, the FDA will continue to monitor products marketed with drug claims and will require such products to be approved by the FDA for the intended use. Gottlieb also stated:

> "It's unlawful under the FD&C Act to introduce food containing added CBD or THC into interstate commerce, or to market CBD or THC products as, or in, dietary supplements, regardless of whether the substances are hemp-derived…Under the FD&C Act, it's illegal to introduce drug ingredients like these into the food supply, or to market them as dietary supplements."

Despite the passing of the Agricultural Improvement Act of 2018 bill, CBD remains a Schedule I drug.[108]

Cannabinol (CBN)

Cannabinol (CBN) is a cannabinoid that mostly occurs as a result of Δ9-THC degradation after prolonged exposure to heat and storage. CBN rarely exceeds 1% of the total weight in dried cannabis flower.

Molecular Formula	$C_{21}H_{26}O_2$	
Molecular Weight	314.47 /mol	

Unlike most other cannabinoids, CBN is not produced by an enzyme synthesis of CBGA or CBGV. Rather, CBN is the product of degradation of THCA and decarboxylation of CBNA:[109]

- When exposed to heat or UV light, CBNA converts to CBN. The precursor to CBNA is THCa—with prolonged exposure to air, THCA can lose hydrogen molecules and oxidize into CBNA.
- The chemical formula for CBN is nearly identical to that of Δ9-THC—CBN has four fewer hydrogen atoms. It is the loss of these atoms during exposure to air, when oxidation occurs, that produces CBN.[110]

CBN is a weak partial agonist at the CB_1 and CB_2 receptors, with a higher affinity for CB_2 receptors. Studies[111] suggest that CBN might help treat pain,[112] [113] [114] inflammation, appetite issues,[115] some types of cancer,[116] bacterial infections,[117] and autoimmune diseases.[118]

Claims that CBN has sedative effects are common on the Internet. For example, one prominent testing lab once claimed that the consumption of 2.5mg to 5mg of CBN has the same level of sedation as a mild pharmaceutical sedative, with a relaxed body sensation similar to 5mg to 10mg of diazepam.

Michael Tagen, Ph.D., provides an excellent summary of the CBN studies that are publicly available,[119] none of which conclusively demonstrates or even suggests that CBN has sedating effects. In fact, there exists only one study that suggests CBN might contribute to a drugged or drowsy effect. This study,[120] from

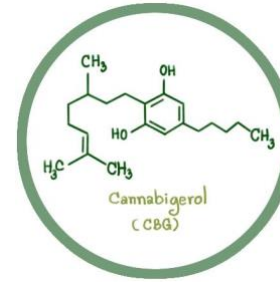
1975, included only 5 participants, combined CBN with THC, and included no consistent dose-response. These researchers stated, "With combined drug treatment, volunteers reported feeling more drugged, drunk, dizzy, and drowsy than under the THC condition alone." [121] It should be noted that the volunteers, in combination with CBN, were given Δ9-THC doses between 12.5-25mg. The sedative effects can likely be attributed to Δ9-THC.

Tagen suggests that, because aged cannabis seems more sedative, there now exists a prevailing misconception that CBN is a sedative. Of course, other ingredients (he suggests oxidized terpenes as one example) might contribute to the sedative effect of aged cannabis.

Cannabigerol (CBG)

Cannabigerol (CBG) is a non-impairing cannabinoid and is the biological precursor to many other cannabinoids. Two compounds—geranyl pyrophosphate and olivetolic acid—are catalyzed by an enzyme to produce cannabigerolic acid (CBGA).

Different enzymes then convert CBGA into one of the acidic cannabinoids. When exposed to heat or UV light, decarboxylation converts CBGA into CBG.

Molecular Formula	$C_{21}H_{32}O_2$	
Molecular Weight	316.5 g/mol	

CBG is present in higher concentrations in developing cannabis plants. CBG is not typically found in high concentrations in dried or cured cannabis plants, except in industrial hemp varieties.[122]

In-vitro studies looking at the affinity and efficacy of CBG at the cannabinoid receptors suggest that CBG is a partial agonist at the orthosteric binding site of CB_2, which might explain CBG's anti-inflammatory properties. Its binding affinity to CB_1 is less clear, but researchers have predicted that CBG is a

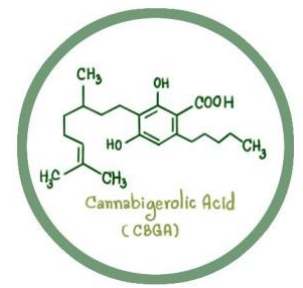
negative allosteric modulator at CB_1 because CBG seems to inhibit some CB_1 agonist signaling.[123]

Studies[124] [125] suggest that CBG might inhibit the progression of some cancers in mice, and help prevent some cancers. A very old study[126] suggested that CBG might be effective at treating skin melanoma cells. Another studies[127] [128] suggest that CBG might have potential for treating pain, anxiety, and sleep, and might help amplify the effects of antidepressants.[129]

Studies also suggest that the anti-inflammatory properties of CBG might help mitigate symptoms in patients with intestinal bowel disease.[130] Other studies suggest that CBG might have therapeutic potential for the treatment of glaucoma[131] and psoriasis.[132] Finally, one study using a synthetic CBG derivative suggested that CBG can stimulate the growth of new brain cells.[133]

Cannabigerolic Acid (CBGA)

Cannabigerolic Acid (CBGA) is a non-impairing cannabinoid and is the biological precursor to many other cannabinoids. Two compounds—geranyl pyrophosphate and olivetolic acid—are catalyzed by an enzyme to produce cannabigerolic acid (CBGA). Different enzymes then convert CBGA into one of the acidic cannabinoids. When exposed to heat or UV light, decarboxylation converts CBGA into CBG.

Molecular Formula	$C_{21}H_{32}O_2$	
Molecular Weight	316.5 g/mol	

Compared with other cannabinoids, there exists very little research exploring the therapeutic properties of CBGA. As of early 2021, there are no clinical trials with human subjects and fewer than ten studies looking specifically at CBGA as a novel therapeutic agent.[134] A computer simulation study suggested that CBGA might activate peroxisome proliferator activated receptors (PPARs, which help regulate homeostasis and metabolic function). PPAR receptor dysfunction can contribute to diabetes and dyslipidemia (dyslipidemia is an

abnormal level of fats in the blood, which increase the risk of heart disease). Activation of PPAR receptors helps the body metabolize lipids and might help treat dyslipidemia and type 2 diabetes.[135]

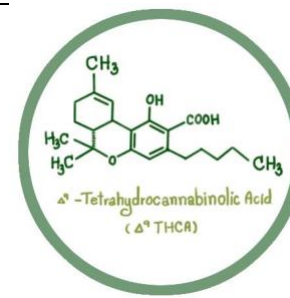
A study in mice suggested that a derivative of CBGA might have neuroprotective properties in inflammatory models of Parkinson's disease, potentially by activating peroxisome proliferator-activated receptor-γ (PPAR-γ).[136]

In one in-vitro study, researchers compared the efficacy of commercially available toothpastes with a number of cannabinoids (including CBGA) and determined that the cannabinoids were more effective in reducing the bacterial colony count in dental plaques. Dental plaque is a complex biofilm that contains millions of bacteria that forms on the teeth and causes cavities, bad breath, bleeding gums, tooth decay, and tooth loss. Another study suggested that CBGA might help kill colon cancer cells and prevent the growth and proliferation of polyps.[137]

> ***Keywords:*** In vitro (Latin for *in the glass*) describes a study that is performed outside of a living organism—these studies are performed in a lab in test tubes and petri dishes. In vivo describes research that is performed with or within a living organism. In silico experiments are completed in a computer simulation.

Tetrahydrocannabinolic Acid (THCA)

Tetrahydrocannabinolic acid (THCA) is the most abundant cannabinoid in most raw Type I cannabis chemovars. THCA is a non-impairing biological precursor for Δ9-THC. Tetrahydrocannabinolic acid synthase is an enzyme that converts CBGa into THCA. When THCA is exposed to heat or to prolonged UV light, it loses a molecule of carbon dioxide to form Δ9-THC.

Molecular Formula	$C_{22}H_{30}O_4$	
Molecular Weight	358.5 g/mol	

THCA is a potent antagonist at the TRPM8 receptor[138] and an agonist at TRPV2 and TRPA1. Some research suggests that THCA has limited ability to cross the blood brain barrier and instead works mostly through peripheral mechanisms.[139]

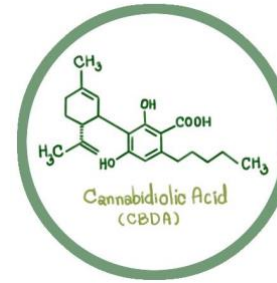
Compounds become more water-soluble when they contain two or more hydroxy groups[140] and THCA has two hydroxy groups, whereas Δ9-THC includes only a single hydroxy group. Research suggests that THCA is more water-soluble than Δ9-THC,[141] [142] [143] [144] so consumers might be able to use lower doses of THCA to achieve symptom relief, which reduces cost and the risk of potential adverse side effects.

Studies[145] suggest that THCA can provide multiple therapeutic benefits and might help treat neurodegenerative disease,[146] nausea,[147] inflammation,[148] some types of cancer,[149] [150] some types of pain,[151] and muscle spasms.[152]

Researchers at GW Pharmaceuticals suggest that THCA has little affinity or efficacy at the CB_1 receptor or at the CB_2 receptor and therefore has no cannabimimetic effects.[153] However, researchers also found, because of the instability of THCA, the presence of Δ9-THC in THCA is nearly unavoidable,[154] and that repeated exposure to heat and light makes it difficult to study THCA without complicating it with Δ9-THC. Finally, researchers suggest that THCA has limited ability to cross the blood brain barrier and instead works mostly through peripheral mechanisms.[155]

Cannabidiolic Acid (CBDA)

Cannabidiolic acid (CBDA) is an acidic cannabinoid and the most prominent cannabinoid in raw Type III (CBD-dominant) chemovars. CBDA is the biological precursor to CBD. The biological precursor to CBDA is CBGA. When CBDA is exposed to heat or to prolonged UV light, it loses a molecule of carbon dioxide to form CBD.

Molecular Formula	$C_{22}H_{30}O_4$	
Molecular Weight	314.45 g/mol	

There is currently limited scientific information on the pharmacology and toxicology of CBDA. The data that is available suggests that CBDA might be effective at helping to treat nausea and vomiting,[156] especially anticipatory nausea, for which there exists no current treatment. Anticipatory nausea is a condition of psychological nausea and vomiting and is believed to be a learned response to chemotherapy.[157] [158]

Studies also suggest that CBDA might also help treat inflammation, as CBDA is a COX-2 inhibitor and might have similar effects as non-steroidal anti-inflammatory drugs.[159]

Finally, some research suggests that CBDa might be effective at treating some types of cancer, as COX-2 activity is also involved the metastasis of cancer cells and regular consumption of COX inhibitors might lower the rates of cancer, especially for colorectal cancer.[160] Research also suggests that CBDA, as a COX-2 inhibitor, might reduce cancer cell proliferation, promote the natural death of diseased cells, and reduce the blood supply required for tumor growth.[161] For example, one study suggested that CBDA inhibits migration of a specific type of invasive breast cancer cell,[162] preventing these cancer cells from growing and dividing. A second study[163] suggested that CBDA can mitigate the spread of cancerous cells, which is especially critical in breast cancer, where metastases are responsible for 90% of breast cancer-related deaths.[164]

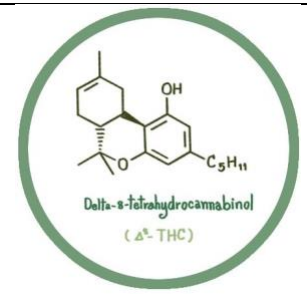
Δ8-Tetrahydrocannabinol (Δ8-THC)

Δ8-THC is a naturally occurring cannabinoid compound found in very low levels in cannabis plants. Like other cannabinoids, Δ8-THC is very lipophilic—it's fat-loving. And, like other cannabinoids, Δ8-THC is an extremely viscous and colorless oil at room temperature.

Tetrahydrocannabinolic acid synthase is an enzyme that converts CBGA into THCA. Heat and time work to decarboxylate the THCA into Δ9-THC. Δ9-THC

is oxidized into Δ8-THC. As an isomer of Δ9-THC, Δ8-THC is subtly different than Δ9-THC. The isomerization of Δ8-THC increases the chemical stability of Δ8-THC, which can lengthen the compound's shelf life and enable the compound to resist further oxidation.[165]

Δ8-THC is an isomer of Δ9-THC. An isomer refers to each of at least two molecules that have the same constituent atoms but that have different arrangements of atoms—these molecules might have different bondings of atoms, different molecular shapes, or different orientations of atoms.

Molecular Formula	$C_{21}H_{30}O_2$	
Molecular Weight	314.5 g/mol	

Δ8-THC binds to the CB_1 and CB_2 receptors but has impairing and psychoactive effects that are much more mild and tolerable than those produced by Δ9-THC. [166] One study suggested that Δ8-THC has about two-thirds of the potency of Δ9-THC.[167] The National Cancer Institute suggests that Δ8-THC provides relief from nausea, pain and anxiety, as well as neuroprotection for the aging brain.[168]

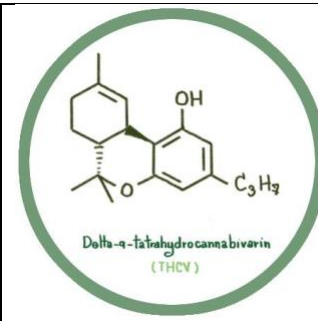
A study[169] with 8 pediatric patients with cancer were given Δ8-THC to test whether Δ8-THC would prevent vomiting from chemotherapy. The patients were treated with a variety of anticancer drug protocols. Researchers found that the children could be administered doses of Δ8-THC that were considerably higher than the doses of Δ9-THC generally administered to adult cancer patients, and without the occurrence of major side effects (5-10 mg/m2 of Δ9-THC for adult patients versus 18 mg/m2 of Δ8-THC used in the study with pediatric patients). Success rates were 100%, regardless of the cancer protocol used. The total number of treatments was 480 (the 8 patients were treated during a 2-year period). Researchers concluded that the complete success in preventing chemotherapy-induced vomiting suggested that Δ8-THC might offer a new, inexpensive antiemetic agent in pediatric cancer chemotherapy. To date, no follow-up studies have been conducted.

A study completed in 1975[170] at the National Cancer Institute found that Δ8-THC (as well as Δ9-THC and CBN) had the ability to stop tumor growth. Another study suggested that low doses (.001mg/kg) of Δ8-THC caused increased food consumption and tendency to improve cognitive function, without the side effects typically associated with Δ9-THC.

These studies suggest that low doses of Δ8-THC can help treat nausea, eating disorders, and cachexia.[171]

Tetrahydrocannabivarin (THCV)

Tetrahydrocannabivarin (THCV) is a naturally occurring cannabinoid compound found in very low levels in cannabis plants, though modern breeding techniques have produced plants with increasing amounts of THCV by dry weight. Uniquely, THCV is an agonist and an antagonist at CB_1 receptors, depending on the concentration[172] (at low concentrations, THCV is an antagonist at CB_1; at high concentrations, THCv can act as an agonist at CB_1 and produce mild psychoactivity).

Molecular Formula	$C_{19}H_{26}O_2$	
Molecular Weight	286.41 g/mol	

The biological precursor to THCV is THCVA. THCVA is decarboxylated with heat or UV light to create THCV. To date, THCV is the only cannabinoid that is an antagonist at CB_1 (some cannabinoids, of course, are negative allosteric modulators at CB_1. Ligand types—such as negative and positive allosteric modulators—are discussed later in this book).

Recall that Δ9-THC has a 5-carbon alkyl side chain. THCV has a shorter alky side chain containing only 3-carbons. The shorter side chain of THCV might suggest why THCV has lower binding affinity to CB_1 (longer side chains increase cannabinoid receptor binding affinity).[173]

Cannabis chemovars with high levels of THCV are sometimes referred to as *diet weed*, as the antagonism of the CB_1 receptor can suppress appetite.[174] In fact, a small, double-blind study suggested that THCV might be used as an appetite suppressant and as novel therapeutic to help treat obesity.[175] Low levels of THCV in common chemovars might account for the results of two national surveys that illustrate how cannabis users tend to have lower prevalence of obesity than nonusers.[176] A different study[177] suggested that cannabis use is associated with smaller waist circumferences and lower BMIs (body mass index, which is measure of body fat based on height and weight). Cannabinoids, and especially THCV, might also impact the manner in which the body produces insulin. Insulin is a hormone made in the pancreas that helps control blood sugar levels by facilitating the absorption of glucose from your food into the cells in your organs and tissues. Your body uses this glucose of energy. A study suggested that cannabis users have lower insulin resistance and lower fasting insulin levels.[178] [179] The correlation between cannabis and lower body mass and lower insulin resistance suggests that cannabis users might be less inclined to develop diabetes (high fasting insulin levels is a predictor of diabetes). In fact, a double-blind, placebo-controlled study suggested that patients with type 2 diabetes and dyslipidemia might be able to improve glycemic control with THCV.[180]

Another study suggested that THCV might delay the onset of and decrease the intensity of dyskinesia, which is characterized by involuntary and erratic movements of the face, arms, or legs. Dyskinesia is an adverse side effect of some Parkinson's disease medications.[181]

> ***Keywords:*** In a *double-blind, placebo-controlled clinical trial*, participants are randomly assigned to an experimental group (these patients receive the treatment) or to a control group (these patients receive a placebo). Neither the researchers nor the patients know to which group the patients are assigned.

Synthetic Cannabinoids

Synthetic cannabinoids are human-designed molecules that bind to cannabinoid receptors. The broad use of the term *synthetic cannabinoid* can create confusion. The term can refer to man-made cannabinoids that have traditionally been used in research settings. And, the term can refer to the FDA-approved synthetic cannabinoid medications such as dronabinol and nabilone. Finally, the term can refer to illicit market designer drugs such as K2 and Spice.

To fully understand the story of synthetic cannabinoids, you must understand drug synthesis. And to fully understand drug synthesis (including the synthesis of cannabinoids) you should have some understanding of chemistry, which is mostly outside the scope of this book.

We can, however, address some fundamental concepts. Typically, there are 3 methods used to produce cannabinoid extracts:

- Plant-based extraction
  This is the process where phytochemicals are extracted directly from harvested plant material. While this is the most commonly used method of cannabinoid production, plant-based extraction methods are beyond the scope of this book and is not discussed at any depth, except to provide points of comparison with synthetic production.
- Chemical synthesis
- Biosynthesis

Chemical synthesis and biosynthesis can be discussed collectively under the umbrella term, *synthetic production*.

Chemical compounds are comprised of atoms, connected by chemical bonds. Typically, the synthetic production of a specific compound will require chemists to break some of those existing bonds and form new bonds. Synthesis of a complex molecule (such as a cannabinoid) includes a considerable and varied number of required reactions (often, each step of the process focuses on the reaction of a single chemical bond).

Chemists can use different methods to cause a reaction. For example, some bonds can be influenced simply by applying heat. Some bonds respond to the exposure to ultraviolet light, others react to electric currents. Essentially, chemists attempt to mimic the processes that occur in nature to construct chemical compounds through these controlled reactions.[182] Both chemical synthesis and biosynthesis are processes where controlled chemical reactions using two or more agents are combined to produce a desired compound. So, no plant material is required here. Essentially, these cannabinoids are created in a laboratory.

Chemical synthesis involves two or more non-biological (non-living) compounds, combined in a controlled chemical reaction to create a desired output. Chemists start with two or more materials, usually they combine the material with a catalyst to accelerate the process, and they create a more complex output as a result of the reaction. And they can perfect this process to

create desired end products in large quantities, in short periods of time, and with identical chemical structures to their naturally occurring analogs.

Broadly, *biosynthesis* refers to reactions that occur in a living organism (typically reactions that convert simple structures into more complex structures). Biological systems have mechanisms to catalyze reactions—including enzymes that can initiate and facilitate chemical reactions—and the energy required to drive these reactions to completion.[183] Biosynthesis in the context of synthetic cannabinoid production refers to the use of biological (or living) organisms as agents in a controlled chemical reaction, again, to yield the desired output (in this context, the desired cannabinoids). Biosynthesis differs from chemical synthesis in that one of the inputs used in the chemical reaction is a living, biological organism. Usually, the input is a simple organism, such as a bacteria, fungus (such as a yeast), or algae.

These living organisms serve as an engine for the chemical reaction because they produce their own enzymes to catalyze the reaction. A simple example of biosynthesis is the process for alcohol production:

- Sugar from grains or fruits is combined with water and yeast
- The yeast metabolizes the sugar (it processes the sugar for energy) in the fermentation process
- The by-product of the metabolism is carbon dioxide and alcohol

This is a simple process with inputs that are naturally available. You cannot produce compounds as complex as cannabinoids, however, using only naturally produced inputs. To produce cannabinoids using biosynthetic processes, you must start with a biological organism that has been genetically engineered—changes are made to the organism so that it's cells produce the enzymes required to create the desired by-product. The genetic modification hijacks the organism's natural chemical processes to create the desired output. DNA modification, of course, is difficult, expensive, and requires years of research and development to perfect.

This field of research—the engineering and modification of biological organisms, systems, and processes—is called *synthetic biology*. This field is changing the manner in which commercial compounds are produced—not only cannabinoids but also pharmaceuticals, consumables, industrial items, and wellness products.

Currently, chemical synthesis and biosynthesis are both commonly used in the pharmaceutical industry for the production of drugs. For example, yeast

fermentation is used to biosynthesize insulin. And aspirin—or acetyl salicylic acid—is now produced synthetically (initially it was derived from chemicals found in the bark of willow trees).

To put a final point on the chemistry of the synthetic production of cannabinoids, let's consider a very basic description of how cannabis plants produce cannabinoids. Cannabis plants extract CO2 out of atmosphere and use the CO2 to form sugar. Then, the plant uses those sugars, through a number of different enzymatic conversions, to eventually create CBGA or CBGV. CBGA and CBGV are the biological precursors to most cannabinoids.

The processes involved in reactions to convert glucose to CBGa, however, are complex. When determining how to synthesize cannabinoids, chemists must determine how to replicate these steps starting with either non-organic or living molecules or determine where in this series of steps they can insert some genetic material to subsequently produce the same process to create the biological precursor to cannabinoids.

Synthetic Cannabinoids for Research

Western chemists began to explore the chemistry of cannabinoids in the late 1800s and early 1900s. Thomas Wood, W. T. Spivey, and Thomas Easterfield began the work of identifying CBN from an alcohol extraction of cannabis.[184] Their research was confirmed by British chemist Robert Cahn, who confirmed and published the structure of CBN in 1940.

The American chemist Roger Adams was the first to isolate and synthesize a cannabinoid. Adams was a well-known and respected chemist and, as the Department Head of Chemistry at the University of Illinois between 1926 to 1954, he greatly influenced graduate education in America—he taught over 250 Ph.D. students and postgraduate students. He also served the U.S. as a scientist at the highest levels during World War I and World War II.

In 1939—just two years after the Marijuana Tax Act was passed by Congress—Adams received a Treasury Department license to work with cannabis oil at his lab. Shortly thereafter, he and his team first identified CBD in 1940,[185] and secured a patent for isolating CBD in 1942.[186]

Adams was also the first to identify and synthesize Δ9-THC, but he wasn't able to isolate Δ9-THC directly from the cannabis plant. He knew there must exist a psychoactive cannabinoid and he assumed (quite accurately, it turns out) the molecular makeup of the cannabinoid, but the technology required to isolate Δ9-THC from the plant (which was later used by Raphael Mechoulam) wasn't

available to Rogers. Instead, he synthesized Δ9-THC by converting the molecular structure of other cannabinoids, principally CBD.[187] In fact, in 1940, Adams published a method for converting CBD to Δ9-THC and by 1949, he had synthesized a catalog of Δ9-THC analogs, which were the first artificial cannabinoids.[188] [189] Adams would eventually publish 27 studies on cannabis in the American Journal of Chemistry. To this day, chemists still use his system to measure potency in cannabis, which is now called the *Adams scale*.

> ***Keywords:*** *Isolation* is a separation technique in which we can obtain a purified compound. Therefore, the key difference between *extraction* and *isolation* is that extraction is a technique in which we can separate a compound from a mixture whereas isolation is a technique we use to purify the extracted compound.[190]

Cannabinoids that were initially synthesized for use in research are named for the person who first synthesized them or after the institution or company where they originated. For example, JWH cannabinoids are named after John W. Huffman; AM cannabinoids for Alexandros Makriyannis; HU cannabinoids after Hebrew University in Jerusalem; and CP compounds after Carl Pfizer.[191]

The structures and stereochemistry of CBD and Δ9-THC were further elucidated in Raphael Mechoulam's laboratory—CBD in 1963 and Δ9-THC in 1964. Research into the therapeutic potential of individual cannabinoids began shortly after in the 1970s when a number of studies and anecdotal reports suggested that Δ9-THC might suppress pain. In 1979, a team working at the pharmaceutical company Pfizer developed a synthetic Δ9-THC called CP-47,497, which is structurally similar to Δ9-THC and in animal models exerted analgesic, motor depressant, anticonvulsant, and hypothermic effects. In 1982, Pfizer's scientists (Weissman, Milne, and Melvin) published their research on CP-47,497.[192] The research program was eventually terminated, but another synthetic cannabinoid developed by Pfizer, CP55940, would eventually help other researchers discover the CB_1 receptor (CP55940 was made radioactive and was used to detect binding sites).[193]

> ***Keywords:*** *Elucidation* is the process of determining the chemical structure of a compound. Identifying how a molecule's atoms are arranged in space can enable chemists to predict its pharmacodynamic

effects, how the molecule might react with other molecules, the boiling point of the molecule, and which substances might metabolize the molecule. Today, this process is facilitated by nuclear magnetic resonance spectroscopy, a technology that was initially discovered in the late 1930's but not available to working chemists until much later.

A team at Eli Lilly and Company developed another synthetic cannabinoid—nabilone—and began publishing results in the mid-1970s.[194] In 1985, the FDA approved nabilone to mitigate chemotherapy-induced nausea and vomiting (Eli Lilly withdrew nabilone for approval, citing commercial reasons). Valeant Pharmaceuticals would eventually acquire the rights from Lilly in 2004 and Valeant now sells the product under the brand name Cesamet, a capsule administered orally. In other countries, nabilone is approved for use as an antiemetic, to treat glaucoma, spasticity in MS, cachexia, and as an adjunct analgesic for neuropathic pain.

Beginning in 1984, John W. Huffman and his team of researchers at Clemson University began synthesizing cannabinoids, specifically looking for medicinal properties similar to Δ9-THC. Over twenty years, Huffman's team developed over 400 synthetic cannabinoids that would be used to study cannabis pharmacology, providing researchers with a better understanding of endocannabinoids and cannabinoid receptors.[195]

In 1985, the FDA approved dronabinol (brand name is Marinol) for the treatment of nausea and vomiting associated with cancer chemotherapy. Dronabinol is a capsule with synthetic Δ9-THC in sesame oil and is administered orally. In 1992, the FDA approved dronabinol for the treatment of anorexia associated with weight loss in patients with AIDS.[196] Dronabinol was approved as a Schedule II drug in 1985 and was moved to Schedule III in 1999.[197]

In 1988, Raphael Mechoulam and his team at the Hebrew University in Jerusalem created HU-210. Similar to Δ9-THC, HU-210 is a potent analgesic and a potent anti-inflammatory. And, HU-210 can reduce the build-up of beta amyloid proteins in the brain, which has been associated with the onset of Alzheimer's disease. [198] More recently, Mechoulam's team at the Hebrew University of Jerusalem announced a synthetic cannabinoid acid molecule—HU580, which is a CBDA methyl ester molecule—that suggests greater stability and higher potency compared to phytocannabinoids.

There now exist hundreds of synthetic cannabinoids in five general categories (based on their molecular structure), and more chemical analogues

continue to be created, many intended to subvert the legal regulations on earlier generations of synthetic cannabinoids.

FDA-Approved Prescription Medications

The following synthetic cannabinoids are currently available to patients through prescriptions (not all of them, however, are available in the U.S.). It should be noted that the availability of these cannabinoid medications have not led to any illicit market demand or addiction treatment issues, despite being available by prescription for decades:[199]

- Dronabinol (sold in the U.S. under the brand name Marinol) is a synthetic cannabinoid similar to the structure of Δ9-THC and is suspended in sesame oil. Dronabinol is approved for the treatment of anorexia in AIDS patients, and nausea and vomiting associated with cancer chemotherapy who have failed conventional treatment. Dronabinol was approved in 1985 and is a Schedule III drug.[200] Syndros is a dronabinol oral solution with the same clinical indications as Marinol but is a Schedule II drug.[201]
- Nabilone (sold in the U.S. under the brand name Cesamet) is another synthetic cannabinoid that is similar to the structure to Δ9-THC. Nabilone is approved for nausea and vomiting in chemotherapy patients who have not responded to the standard of care for anti-emetics. Nabilone is a Schedule II drug.[202]

Note: Two medications are not included in this list, as they are not medications made from synthetic cannabinoids. Epidiolex is a purified form of CBD that is FDA-approved in the United States for the treatment of with tuberous sclerosis complex and two rare forms of pediatric epilepsy (Lennox–Gastaut syndrome and Dravet syndrome).[7] Nabiximols (sold throughout the world under the brand name Sativex) is a 1:1 Δ9-THC and CBD (2.7mg Δ9-THC and 2.5mg CBD) oral mucosal spray derived from whole-plant the cannabis plants. Nabiximols has been approved in 25 countries for multiple sclerosis spasticity but is not currently approved in the United States.[203]

Prescription Medication Examples: Dronabinol and Nabilone

Dronabinol is a naturally occurring compound that can be extracted from cannabis and is an isomer of Δ9-THC—in fact, dronabinol is the main and most active isomer of Δ9-THC in cannabis.[204] However, the term *dronabinol* not only refers to this naturally occurring substance, but can also (and more commonly)

refer to a completely synthetic substance with no natural source, or to a synthetically modified substance derived from a molecule extracted from a natural source (for example, chemists can extract Δ9-THC from plant material by chromatography and then synthetically convert it to dronabinol).[205]

Dronabinol is a yellow resinous oil that is viscous at room temperature, hardens under refrigerated conditions, and is insoluble in water. Consequently, dronabinol is typically formulated in sesame oil.[206] The chemical structure of dronabinol is nearly indistinguishable from Δ9-THC.

When using standard drug manufacturing processes to chemically produce dronabinol, chemists can eliminate the need to obtain the material by extraction from natural sources. Creating a pure, synthetic dronabinol facilitates the study of its pharmacological effects (study that is adversely impacted by variations in the potency and availability of plant material) and enables accurate and reproducible dosages of the active ingredient.[207]

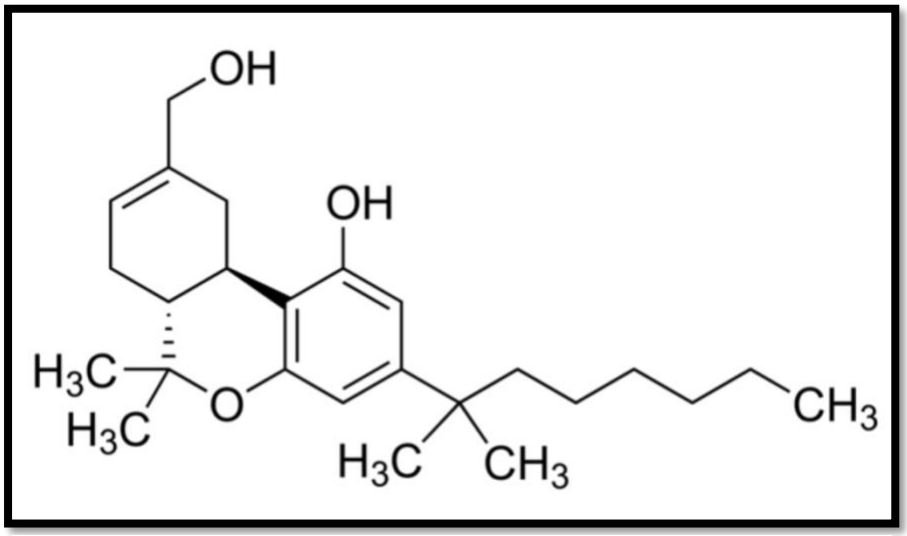
In its synthetic form, Dronabinol is FDA approved for treatment of anorexia associated with weight loss in patients with HIV/AIDS, and for nausea and vomiting associated with cancer chemotherapy (in patients who failed to respond to conventional prescription medications). It is marketed as Marinol (as a gel capsule) or Syndros (as a liquid version of dronabinol).

Nabilone (marketed as Cesamet) is a synthetic analog of Δ9-THC and is FDA-approved in the United States for chemotherapy-induced nausea and vomiting (also only for patients who failed to respond to conventional antiemetic treatments). Unlike dronabinol, the chemical structure of nabilone includes functional groups that make these isomers somewhat distinct from Δ9-THC.

For example, where Δ9-THC has a methyl group at the C-11 position, nabilone has a double oxygen bond (a ketone group). Synthetic Δ9-THC analogues with a hydroxy group at C-11 tend to exhibit enhanced activity at CB_1 (11-OH-THC, for example, is much more potent than Δ9-THC and has higher affinity at CB_1).[208] Also, nabilone has a 7-carbon side alkyl chain and this chain has two attached methyl groups (CH_3 groups). Δ9-THC has a 5-carbon side alkyl chain with no attached methyl groups. The length of the side alkyl chain is believed to influence a compound's pharmacodynamic effects. For example, synthetic cannabinoids such as HU-210 and CP55940—both of which have 7-carbon side alkyl chains—demonstrate far higher affinity to CB_1 receptors than Δ9-THC and are far more potent than Δ9-THC.[209] As expected, nabilone has a much smaller K_d value at CB_1

(1.84) than does Δ9-THC (53.3), [210] suggesting that nabilone has a binding affinity at CB_1 that is nearly 30 times stronger than Δ9-THC.

In fact, until recently, it was thought that all naturally forming cannabinoids were limited to, at most, 5-carbon side alkyl chains. However, in December 2019, a team of Italian researchers announced the discovery of two



HU-210 with a 7-Carbon Side Alkyl Chain

new cannabinoids: THCP (tetrahydrocannabiphorol) and CBDP (cannabidiphorol), both of which exhibit a 7-carbon side alkyl chain. [211] THCP binds to the CB_1 receptor (in vitro) in manner similar to that of CP55940, a potent full agonist at CB_1.

Keywords: *Dissociation constant*—which is written as K_d and pronounced *kay dee*—measures the strength of a binding between a protein (such as a cannabinoid receptor) and a ligand (such as a cannabinoid like Δ9-THC). The strength of the binding is referred to as binding affinity and is measured by the K_d value. The smaller the K_d value, the greater the binding affinity of the ligand to its target. That's the reason why 11-OH-THC has a smaller K_d value than Δ9-THC at the CB_1 receptor. 11-OH-THC has a stronger binding affinity at CB_1 than does Δ9-THC, and consequently has a smaller K_d value.

The Future of Synthetic Cannabinoids

Of course, cannabis plants are metabolic factories that produce scores of different molecular compounds. Which begs the question: if cannabis plants are so prolific at naturally producing compounds, why do we need synthetic cannabinoids?

Initially, synthetic cannabinoids were developed for research, as legal restrictions limited the availability of plant-derived cannabinoids and forced researchers to develop similar compounds. More recently, businesses see profit-related reasons for developing synthetic cannabinoids.

From a commercial perspective, the goal is to produce cannabinoids cheaply, efficiently, and reliably. Achieving these results can be difficult to do by conventional plant cultivation, for multiple reasons. Cannabinoid production is not optimized during plant production—cannabis plants produce cannabinoids only during a specific phase of growth, and those cannabinoids are concentrated only in the unfertilized female flower. During most of the plant growth phase, the plant produces no cannabinoids at all. Furthermore, cannabinoids are stored only in trichomes because they are fat-soluble and cannot exist in the other aqueous parts of the plant (in fact, in their natural state, cannabinoids are toxic to cannabis plants). And, when the plant matures, an extraction process is required to isolate the cannabinoids and remove all of the unwanted material, such as chlorophylls, plant lipids, and waxes. While producers are getting more savvy about extraction, it remains an inefficient process.

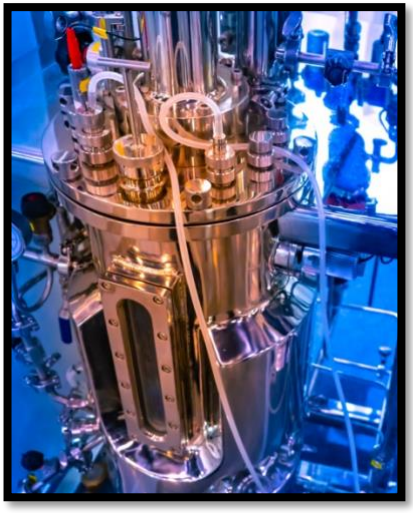


Figure 2 The future of cannabis?

While the start-up costs of biomanufacturing are high, soon the cost of mass-producing synthetic cannabinoids in a bioreactor will likely be far cheaper than traditional cannabis plant farming. Cannabis cultivation, especially at commercial scale, is land and capital intensive. Greenhouses and indoor grow facilities at commercial scale can cost tens of millions of dollars. Also, biomanufacturing enables a consistency that is impossible to replicate in plants, is not influenced by weather or pests, and requires less energy than indoor cannabis-grown plants. And, importantly, synthetic

cannabinoids can be patented. Companies are reticent to invest in the research and development of a therapeutic substance if there are no guarantees that their intellectual property will be protected.

From a pharmacology perspective, synthetic cannabinoids offer researchers an opportunity to improve the potency, affinity, and efficacy of cannabinoids. For example, many companies are looking to develop a cannabinoid that has very high affinity at the CB_2 receptor but low affinity at the CB_1 receptor, which would help consumers benefit from the therapeutic properties of CB_2 activation (such as anti-inflammation and pain mitigation) while avoiding the side effects of CB_1 activation—specifically, psychoactivity.

From a medical perspective, synthetic approaches to cannabinoids can help facilitate the creation of products that include cannabinoids that rarely occur naturally or that are difficult to extract, offering new therapeutic possibilities. In fact, some companies are creating completely new cannabinoid-like molecules not found in nature. Remember that there have been over 100 identified cannabinoids, many of which have already demonstrated therapeutic possibilities. However, many of these minor cannabinoids are understudied because of their rarity in natural plant production. Mass produced synthetic versions of CBG, CBC, THCV, Δ8-THC, CBN, and other cannabinoids will provide new opportunities for research, product development, and novel approaches to treating disease

The future of *medical* cannabis (and possibly all commercial cannabis) is likely tied to genetic engineering. Some companies are now employing genetic engineering to create more efficient alternatives to cannabis plants by using genetically enhanced microorganisms to produce cannabinoids. There are currently multiple companies working in either the chemical synthesis or biosynthesis space. A good example of a company operating in the chemical synthesis space is Noramco (they're in Delaware). They are one of the largest manufacturers of controlled substances in the world, and they supply major global pharmaceutical companies with compounds produced at their FDA, DEA and Health Canada-approved facilities. Basically, they are a wholesale manufacturer and supplier of drugs.

Noramco currently makes pharmaceutical grade, synthetically-derived CBD with 99.5% purity, which typically meets the threshold for "THC-free" products. Noramco has existing agreements to supply CBD to companies for the sale of pharmaceuticals in both Canada and Mexico. Noramco also produces nabilone and dronabinol.

In the biosynthesis space, there are also currently a number of companies who are attempting to produce cannabinoids from yeast, bacteria, and algae. Each company is developing a propriety process which includes the introduction of genetic material to enable an organism to produce the chemical reactions necessary for cannabinoid production.

For example, in September of 2018, the Cronos Group, which is a global cannabinoid research, technology, and product development company announced a partnership with Ginkgo Bioworks in Boston to develop cannabinoids from yeast fermentation. InMed Pharmaceuticals—they're located in Vancouver and they focus on the development of cannabinoid-derived pharmaceuticals—is developing a biosynthetic manufacturing process using fermentation with the genetically modified E. coli bacteria. They intend to use these cannabinoids for the production of their drugs.

Additionally, there are now companies who are genetically modifying the plant itself to produce cannabinoids from shoot to tip, thereby boosting yield. For example, companies are looking for methods to produce cannabinoids outside of the trichomes to substantially increase the cannabinoid yield. Companies are also adding enzymes into plants to make cannabinoids more water soluble and less toxic to the plant. Water solubility facilitates a simpler extraction process and produces cannabinoids that have broader uses in the market.

The primary benefits of chemical and biosynthetic manufacturing are commercial scalability, precision and purity (even for rare cannabinoids), repeatability, and consistency. Given the pace at which the industry is moving, given the demand for products and the advancements in new product development, it's predictable that the industry will see a significant increase in demand for cannabinoid extracts and isolates. And, in many sectors, the demand will not be limited to quantity—some of the demand will require better standards of quality, production, and specificity, especially when considering derivative products—products in which cannabinoids are used as an ingredient, such as beverages, foods, and wellness products.

Consider, for example, Coca Cola, McDonalds, or any large-scale corporation. When they introduce cannabinoids into a product, they will likely not want to source natural cannabinoids. Rather, these corporations will require massive amounts of product, they'll want the exact same product every time with no variables and will insist on consistency and purity. Research and pharmaceutical products will require even higher standards of production and

consistency. The demand required by these markets will likely be met by synthetically produced cannabinoids.

Illicit Market Synthetic Cannabinoids

You might be thinking: *what does any of this have to do with illicit market products such as Spice and K2?* Remember John Huffman, professor emeritus of chemistry at Clemson University in South Carolina? Recall that Huffman began researching synthetic cannabinoids in the late 1980s and early 1990s, focusing on synthesizing new compounds that would activate the CB_1 and CB_2 receptors. Huffman and his colleagues eventually created more than 400 new compounds and, naturally, they published their research, formulas, and conclusions in peer-reviewed journals.

In 2008, John Huffman received a message from a German blogger, who sent Huffman an article from the German magazine *Der Spiegel* about a man who was using a JWH compound (JWH-018) as a recreational intoxicant. Hoffman would subsequently learn multiple commercial products based on his compounds started appearing in Europe in 2006 after Huffman had published a paper describing how to make the compounds. "JWH-018 can be made by a halfway decent undergraduate chemistry major," said Huffman, "in three steps using commercially available materials."

Typically, the packaging for these products—sometimes referred to as synthetic marijuana—lists only natural herbs as ingredients and are often labeled "not intended for human consumption" (language that is presumably used to obfuscate the intended use and to provide the flimsiest of legal protections). Early products were marketed as incense, herbal blends, and potpourri and with names such as Spice Silver, Spice Gold, Spice Diamond, Yucatan Fire and Smoke, AKB-48, and 2NE1 (the names of a popular Japanese girl band and a South Korean girl band, respectively). These products were often combinations of herbs that included Egyptian (or blue) lotus, lion's ear, honeyweed, beach bean, or maconha brava, and many claimed that these mixtures produced cannabis-like effects.

Testing would reveal that these products also contained synthetic cannabinoids, including multiple compounds created by Huffman, compounds initially invented by Pfizer, Mechoulam, and scores of other synthetic cannabinoids. Because many of these compounds are structurally distinct from Δ9-THC, they were not initially included in the U.S. Controlled Substances Act. They provided an alternative for people who wanted to avoid the legal consequences of cannabis use or for people who needed to pass a drug test[212]

(the DEA has since closed this loophole, however, by stating that all synthetically derived tetrahydrocannabinols remain Schedule I controlled substances, and specifically addresses *synthetic marijuana*, which the DEA describes as a mixture of plant material sprayed with synthetic psychoactive chemicals).

There are hundreds of these products now available commercially. And, new and inventive methods for consuming them continue to appear. In one case, prisoners in Great Briton were receiving pictures drawn by children that had a synthetic cannabinoid mixture sprayed onto them. After receiving the pictures, the inmates would smoke the paper.

As discussed earlier, there exist FDA-approved synthetic cannabinoid medications that are currently being prescribed by doctors to patients. What's different about the illicit market substances?

First, the adverse effects of any synthetic cannabinoid can be much more severe than those associated with phytocannabinoids. Δ9-THC is a partial agonist at CB_1 and CB_2 and does not activate the receptors to the fullest extent. Most synthetic cannabinoids, however, are full agonists with high affinity at the CB_1 and CB_2 cannabinoid receptors. [213] [214] Full agonists can create higher risks of very severe adverse effects. For example, HU-210 is highly potent at cannabinoid receptors when compared to Δ9-THC. When studied in primates, researchers determined that HU-210 has a longer duration of action than Δ9-THC because HU-210 has a slow rate of dissociation from cannabinoid receptors. In fact, the duration is so long it's called *pseudo-irreversible*. When administered intravenously, HU-210 demonstrated a duration of 1-2 days, whereas Δ9-THC demonstrated a duration about approximately five hours.[215]

Researchers have also performed intraventricular administration (this is direct administration into the brain) of HU-210—this route produces effects that can last for at least 24 hours. Based on the duration noted collectively for intravenous and intraventricular administration, researchers speculate that the prolonged duration of HU-210 is not a product of an active metabolite (in the same manner, for example, as Δ9-THC and its metabolite 11-OH-THC), but rather from greater agonist efficacy at CB_1.

There might be a few different reasons why synthetic cannabinoids have higher binding affinity to CB_1. For example, several synthetic cannabinoids have a 7-carbon side chain. Δ9-THC has a 5-carbon side chain. The length of the side chain is believed to influence a compound's pharmacodynamic effects. For example, synthetic cannabinoids such as HU-210 and CP55940—both of which have 7-carbon side chains—demonstrate far higher affinity to CB_1 receptors than

Δ9-THC and are far more potent than Δ9-THC.[216] It's suggested that nabilone has a binding affinity at CB_1 that is nearly 30 times stronger than Δ9-THC. It's suggested that HU-210 has between 100-800 times the potency of Δ9-THC.

> **Keywords:** *Affinity* can be defined as the extent to which a drug binds to receptors at any given drug concentration and the firmness with which the drug binds to the receptor. *Potency* is a measure of necessary amount of the drug to produce an effect

Other possibilities for the high-binding affinity exist. For example, Δ9-THC has a methyl group (CH_3) at the carbon 11 (C-11) position, but nabilone has a double oxygen bond at C-11. Synthetic Δ9-THC analogues with a double oxygen bond or a hydroxy group (an OH) attached at C-11 tend to exhibit enhanced activity at CB_1 (11-OH-THC is an example of a molecule with a hydroxy group at C-11, and 11-OH-THC has higher affinity at CB_1 than Δ9-THC).[217]

In 2013, a National Forensic Service in South Korea reported that 90% of all seized synthetic cannabinoids were fluorinated (whereas no fluorinated synthetic cannabinoids were reported in 2010). Fluorinated synthetic cannabinoids are 2-5 times more potent at CB_1 receptors than unfluorinated analogues. An example of a fluorinated synthetic cannabinoid is AB-FUBINACA, which was developed by Pfizer in 2009 as a potential pain medication. It was discovered in synthetic cannabinoid products in Japan in 2012. This cannabinoid is responsible for two instances of mass overdoses involving hundreds of hospitalizations: one event in the U.S (2018, Connecticut) and one in New Zealand (also 2018, in the cities Napier and Christchurch). [218]

So, chemists continue to find methods for increasing the potency of these cannabinoids. Higher binding affinity to CB_1 can produce greater risks of adverse effects. Reported adverse effects include agitation, coma, toxic psychosis, cardiovascular problems, respiratory depression, acute kidney injury, addiction and even death (often as a result from hypothermia).

Except for a very few number of synthetic cannabinoids approved by governing bodies for patient use, these compounds were never intended to be used outside of research settings. And these products—because they are mostly circulated through the illicit market—have very little regulatory oversight. They have extremely high dosages in these illicit products. Moreover, the material that the synthetic mixture is sprayed onto is usually not safe for consumption, either.

As long as cannabis remains a criminalized Schedule I drug, people will seek alternatives—especially if they're attempting to treat conditions that impact quality of life— and they will continue to make compromises and poor choices with respect. The only logical path forward is full decriminalization and legalization at the federal level.

Terpenes

In addition to cannabinoids, cannabis plants produce compounds called terpenes, which are universally present in small amounts in living organisms and provide organisms with protection from bacteria and fungus, insects, and other environmental stresses. For example, a plant may produce specific terpenes in the flower to repel insects and produce bitter terpenes on the lower fan leaves to deter grazing animals.[219] In the cannabis industry, the term *terpene* is commonly used interchangeably with the term *terpenoid*, but there exists a subtle difference. A terpenoid is a modified terpene. For example, a terpene that is denatured by oxidation by drying and curing cannabis flowers is a terpenoid. Terpenes (or, more specifically, terpenoids) are responsible for the aroma of dried cannabis.

As a food additive, the terpenes expressed in cannabis are regarded as generally safe to use by the US Food and Drug Administration, by the Food and Extract Manufacturers Association, and by other world regulatory bodies.[220]

Some estimates suggest that there exist between 100-200 terpenes in cannabis.[221] These are compounds that are not unique to cannabis—they have been studied extensively for their own therapeutic properties. Terpenes might be the reason why consumers can report different experiences—for example, a sedating experience versus an uplifting experience—when using two cannabis chemovars with similar cannabinoid profiles.

Terpenes share a biological precursor with phytocannabinoids and display unique therapeutic effects that might contribute to the effects of cannabis-based products. Dr. Ethan Russo has suggested that terpenes can inhibit the psychoactive effects of Δ9-THC, can increase the therapeutic index of Δ9-THC, and can increase the potential of cannabis-based medicinal extracts to treat pain, inflammation, depression, anxiety, addiction, epilepsy, cancer, fungal and bacterial infections (including methicillin-resistant staphylococcus aureus). [222]

Terpene concentrations in cannabis plants can range from 1% to 10% and are concentrated in trichomes.[223] The following terpenes are those most commonly found in cannabis plants:

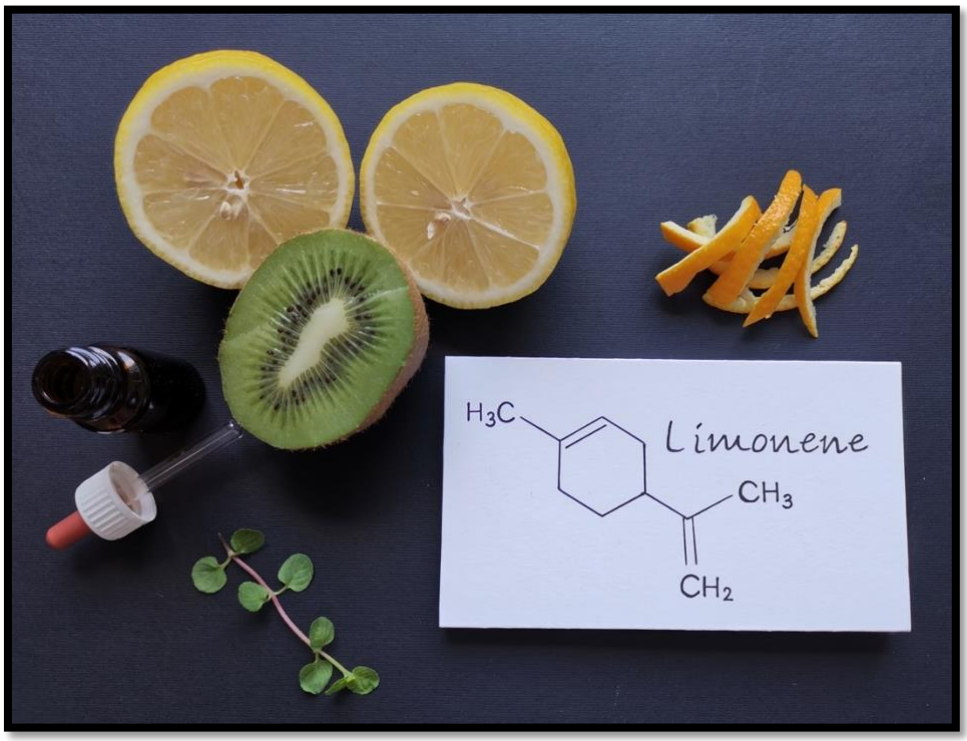
Myrcene

Myrcene (or β-myrcene) is the most prevalent terpene found in cannabis.[224] Myrcene is also found in high concentrations in sweet basil, hops, and mangoes. Myrcene produces an earthy, fruity, clove-like odor. Studies suggest that myrcene in cannabis can reduce inflammation, block carcinogenesis and inhibit cancer cell mutation, relieve pain, relax muscles, and aid sleep. In fact, it is generally agreed that myrcene, in combination with Δ9-THC, is the prominent sedative component in cannabis.[225]

Myrcene is found in high concentrations in sweet basil, hops, mangoes, and cannabis.

Limonene

Limonene is common to the lemon and other citrus fruits and is the second most widely distributed terpene in nature. Limonene is highly bioavailable and rapidly metabolized. Studies with citrus oils in mice[226] and in clinical studies with patients suffering from depression[227] suggest that limonene is a powerful anxiolytic agent. Studies also suggest that limonene might induce apoptosis of breast cancer cells and treat gastro-esophageal reflux.[228]

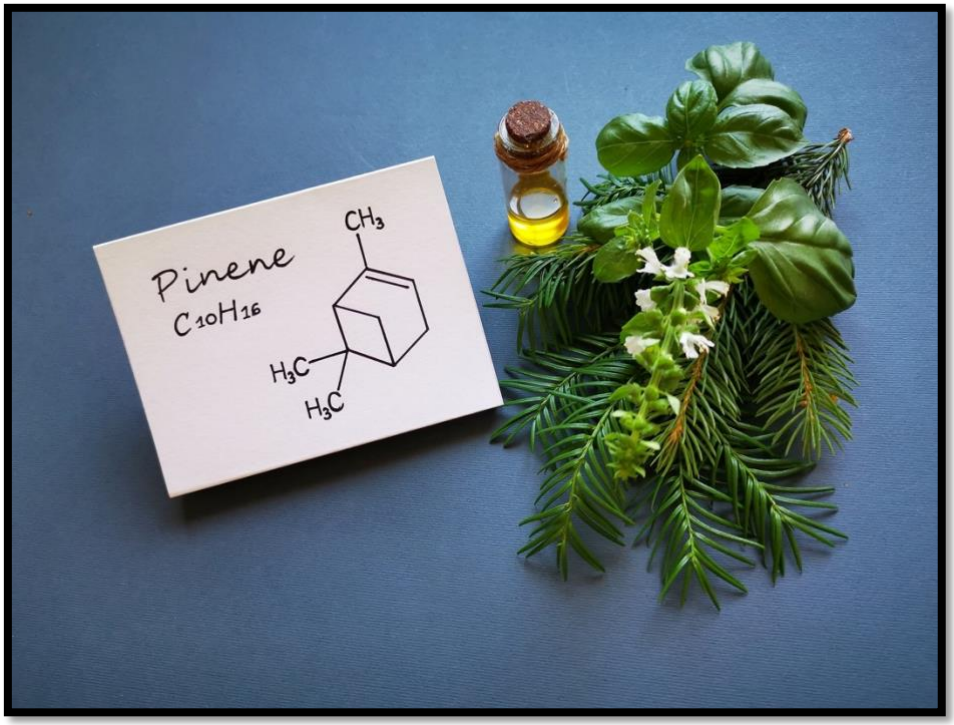


Limonene is common to lemons and other citrus fruits, and cannabis.

Pinene

Pinene is a common terpene found in cannabis, turpentine, rosemary, and is the main terpene in pine trees (in fact, pinene is responsible for the characteristic scent of pine trees). Pinene is the most widely distributed terpene in nature (possibly because it is highly repellant to insects).[229] Studies suggest that pinene is an anti-inflammatory, a bronchodilator, an antibiotic, and a memory aid

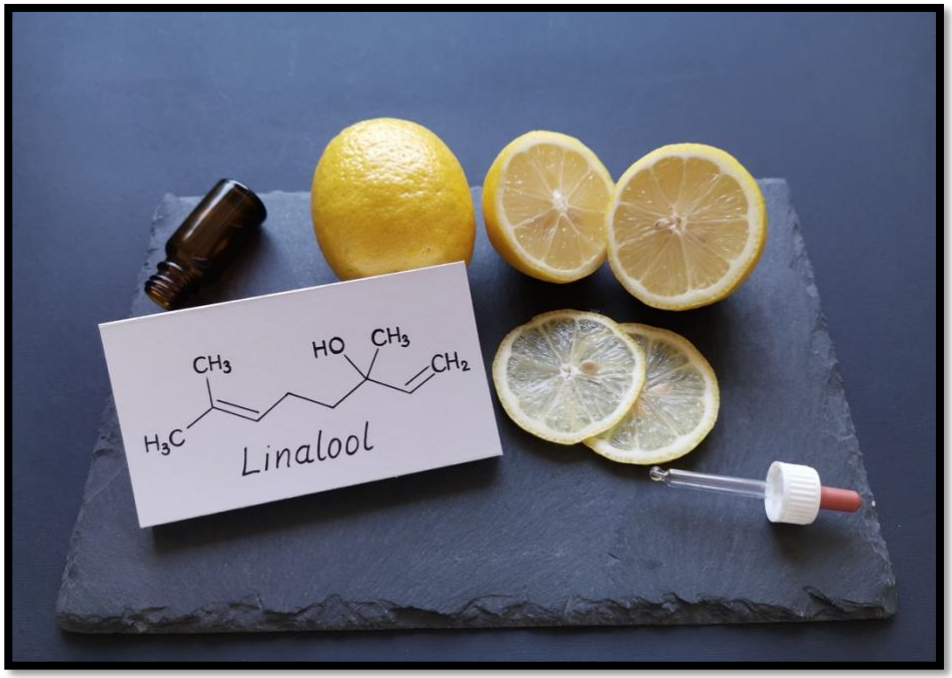
that may counteract short-term memory deficits induced by Δ9-THC intoxication.[230]



Pinene is common to cannabis, turpentine, rosemary, and is the main terpene in pine trees.

Linalool

Linalool is a common terpene in cannabis and is responsible for the scent and flavor of lavender. Linalool has long been used in aromatherapy as a sleep aid, a relaxant, and as a treatment for anxiety. Studies suggest that linalool can help treat anxiety, sleep disturbances, and seizures. As a local anesthetic, linalool might be as effective as procaine and menthol.[231] Research in rats suggests that linalool can influence cytochrome P450 activity and might influence cannabinoid metabolization.[232]

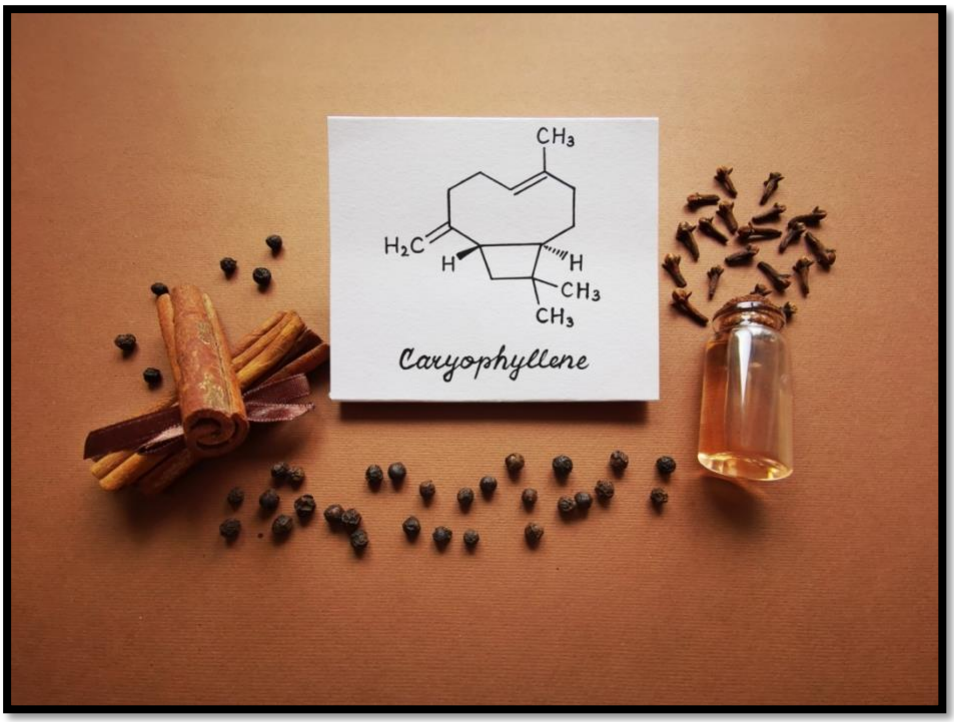


Linalool is common to citrus fruits, cannabis, and is the main scent and flavor of lavender.

β-caryophyllene

β-caryophyllene (BCP) is the terpene responsible for the spiciness of black pepper, is produced in cloves, hops, and rosemary, and is commonly found in cannabis. In fact, BCP is frequently the predominant terpene in cannabis extracts, especially in extracts that are processed under heat for decarboxylation.[233] BCP is commonly used in the cosmetic industry, and as a food preservative, additive, and flavoring. Unlike other terpenes, BCP is an agonist at the CB_2 receptor and has demonstrated affinity with other receptors that influence neuropathic pain and neurodegenerative diseases. In fact, BCP exhibits potent antioxidant and anti-inflammatory properties in multiple models of human disease,[234] [235] [236] as well as antispasmodic properties,[237] antidepressant and anxiolytic properties, [238] [239] and anti-addictive properties. [240]

Because BCP activates the CB_2 receptor and has therapeutic effects similar to those of cannabinoids, some researchers suggest that BCP should be classified as a cannabinoid rather than a terpene. In one study, BCP as an anti-inflammatory was more effective than synthetic cannabinoids.[241]



β-caryophyllene is common to black pepper, cloves, hops, rosemary, and cannabis.

Flavonoids

In addition to phytocannabinoids and terpenes, cannabis plants also produce secondary metabolites called flavonoids. Flavonoids are a diverse group of phytonutrients (plant chemicals) found in almost all fruits and vegetables. Flavonoids are partly responsible for the vivid colors in fruits and vegetables, help provide plants with protection from UV light, can help prevent oxidation of fats, help protect plants from infections, and help attract pollinating insects, among other functions.[242] [243]

Flavonoids in fruits, vegetables, seeds, flowers, and other plants are abundant in nature and have been widely studied for potential therapeutic properties, such as anticancer, anti-inflammatory, antioxidant, antiviral, antibacterial, and other properties. [244]

There are a number of different flavonoids identified in cannabis plants, including cannflavin A, cannflavin B, cannflavin C, vitexin, isovitexin, apigenin, kaempferol, quercetin, luteolin, and orientin. Flavonoids might represent nearly 3% of the dry weight of a cannabis plant and they are mostly concentrated in the flowers and leaves (no flavonoids exist in the root system or seed). Flavonoids are generally soluble in water and might contribute to the therapeutic effects of cannabis infusions in water.[245]

The most well-studied flavonoids in cannabis are cannflavin A and cannflavin B, both unique to cannabis and both first identified in the mid 1980s[246] (there is also a cannflavin C, which was first identified in 2008)[247].

- Cannflavin A displays potent anti-inflammatory and potential anticancer properties.[248] Also, cannflavin A does not significantly inhibit COX-1 nor COX-2, which might make it a novel therapeutic agent for treating inflammation while avoiding gastrointestinal bleeding, cardiovascular, and cerebrovascular adverse effects associated with COX inhibitors. [249]
- Cannflavin B also displays potent anti-inflammatory properties. Additionally, an isomer of cannflavin B suggested it might be a novel therapeutic in the treatment of pancreatic cancer. In vitro tests suggested that this flavonoid increases apoptosis and in vivo tests suggested efficacy in delaying tumor progression.[250]

Keywords: *Apoptosis* is sometimes referred to as cellular suicide. Apoptosis is the normal, protective, and programmed process of cellular destruction. It is the process that body uses to remove old, damaged, or potentially harmful cells. For example, apoptosis supports the immune system by instructing cells damaged by virus to self-destruct before the virus can spread throughout an organism. [251]

Entourage Effect

In 1998, Raphael Mechoulam and Shimon Ben-Shabat demonstrated that two esters—with no binding affinity for cannabinoid receptors—significantly potentiated the binding of the endogenous cannabinoid 2-AG at CB_1 and CB_2

receptors. They referred to this relationship as an *entourage effect* and noted that it was also observed with the esters in combination with some HU-type synthetic cannabinoids. Their paper included a suggestion that researchers investigate the effect of active components in the presence of entourage compounds to potentially observe the effects of these compounds as they might occur in nature, rather than in isolation.[252]

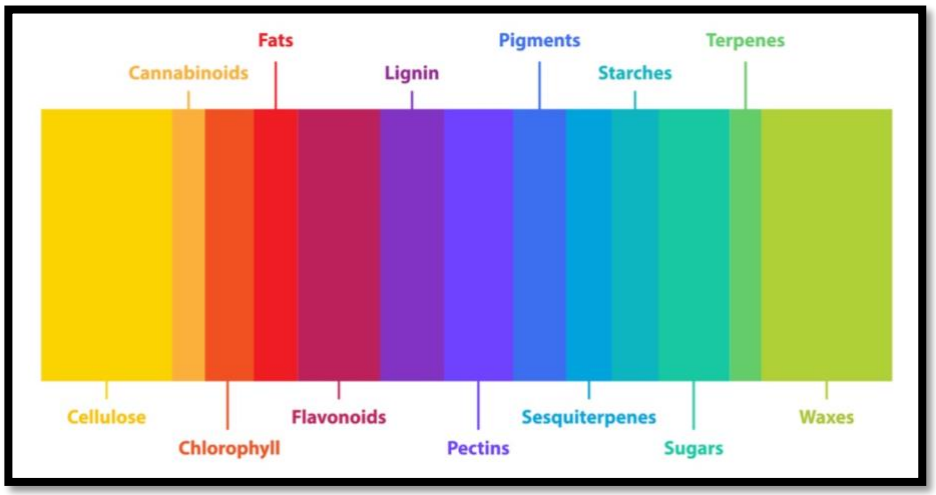
Since then, the cannabinoid industry has adopted this language to suggest that chemical compounds in cannabis can work together to produce a synergy of benefits and this synergy is now called the *entourage effect*.

There is some evidence to support this hypothesis. For example, a 2015 Israeli study[253] demonstrated that whole plant, high-CBD cannabis "is superior over [synthetic] CBD for the treatment of inflammatory conditions." Researchers reviewed available data and determined that the administration of pure CBD in preclinical studies resulted in a bell-shaped, dose-response curve, meaning that pure, isolated CBD had no therapeutic effect beyond a certain dose threshold. They then discovered that—unlike the bell-shaped dose-response curve of isolated CBD—the anti-inflammatory and anti-pain response of whole-plant CBD increased with dose, making whole plant CBD ideal for clinical use. The researchers concluded that, "It is likely that other components in the extract synergize with CBD to achieve the desired anti-inflammatory action that may contribute to overcoming the bell-shaped dose-response of purified CBD." Those other components include other phytocannabinoids, terpenes, flavonoids, amino acids, proteins, enzymes, fatty acids, and sugars.

A 2014 study in the UK demonstrated "dramatic reductions" in high-grade glioma brain cancer when Δ9-THC and CBD were used in conjunction with radiation treatment on mice. High-grade glioma brain tumor survival rates are low, and treatments remain mostly unsuccessful. The UK study demonstrated that phytocannabinoids inhibit glioma growth and neutralize oncogenic processes, such as angiogenesis, and that, when used to kill cancer cells, smaller doses of Δ9-THC with CBD were as effective as larger doses of either individual phytocannabinoid.[254]

A 2009 study[255] set out to study the "longstanding, successful use of herbal drug combinations in traditional medicine" and to determine a reason for "the pharmacological and therapeutic superiority of many of them in comparison to isolated single constituents." The study noted that whole-plant extracts can affect multiple targets in the body, can improve the absorption of active

ingredients, can overcome bacterial defenses, and can minimize adverse side effects.



The Entourage Effect proposes that compounds can produce a synergy of benefits.

In 2005, Ethan Russo and Geoffrey Guy published *A tale of two cannabinoids: The therapeutic rationale for combining Tetrahydrocannabinol and Cannabidiol* in the Journal of Medical Hypotheses and Ideas. Their research suggested that CBD enhanced the medical benefits of Δ9-THC and reduced the adverse effects. [256] For example, Russo points to data that suggests that 10 milligrams of Δ9-THC can cause acute psychosis in approximately 40 percent of consumers.[257] [258] In clinical trials conduction by GW Pharmaceuticals during the development of Sativex—an oral mucosal spray with equal parts Δ9-THC and CBD—48 milligrams of Δ9-THC (administered with a comparable amount of CBD) produced acute psychosis in only four patients out of 250 exposures.

Other data exist[259] that suggest a cannabis synergy and that support botanical drug development over isolated components, including the biosynthesis of cannabinoids using fermentation methods in yeast and micro-organisms. Furthermore, many cannabis products are artisanal in nature and are produced from whole-plant extracts. Western medicine has traditionally considered whole plant extracts as being less effective than isolated and synthesized plant compounds. The acceptable research and development process in Western medicine is to identify specific, beneficial compounds in raw plant

material, isolate those compounds, synthesize them, patent them, and monetize them for public consumption.

For example, the FDA has approved Dronabinol for human consumption. The active ingredient in Dronabinol is a synthetic version of Δ9-THC. Of course, Δ9-THC from cannabis is currently defined as a Schedule I drug. All Schedule I drugs, by definition, have no medicinal value and have the highest risk of addiction. Dronabinol is a Schedule III drug. The FDA (and the DEA) see no conflict here—they argue that Dronabinol is a safe, man-made synthesized product, and Δ9-THC is a compound in an unsafe raw material.[260]

Chapter 3: Homeostasis and the Endocannabinoid System

All living organisms regulate their internal environment to maintain the relatively narrow range of conditions required for proper cell function. For example, body temperature must be relatively close to 98.6 °F in a healthy person. Blood pH must be between 7.35 and 7.45 for a person to function normally. Blood must also approximate specific levels of systolic and diastolic pressures to remain healthy.

Human bodies work automatically and continuously to monitor these important levels and functions. The human body constantly monitors temperature, hormone levels, blood pressure, the rate of heartbeat, whether the body requires food or sleep, whether there is something building up in the bloodstream or inside of a cell. And, when something is operating outside of the right range, the body activates the necessary processes to help correct it. This maintenance of a stable internal environment is known as *homeostasis*.

Homeostasis

In biology, homeostasis is the state of steady internal, physical, and chemical conditions maintained by a living system. This state is the condition of optimal functioning for the organism, and the state considers a complex and nuanced number of systems and variables that work together to maintain health.

Consider, again, body temperature—our physical response to overheating is to sweat, which helps promote heat loss through evaporation. Flushing is also an automatic response to overheating—when we are hot, our skin turns red because blood vessels expand to bring blood close to the skin surface so that it can cool. Our physical response to cold temperatures, however, is quite different, as the body automatically reduces blood circulation to the skin. We might start to shiver, which is the result of muscles shaking in small movements, which can create warmth by expending energy. Changes in our external environment can automatically trigger an internal, physiological response that counters the change.[261]

Homeostasis is a unifying theme in anatomy and physiology—an organism's survival depends on the management of materials and energy, including the proper amounts of water, nutrients, and oxygen to create and disperse energy. In fact, one can argue that the ultimate cause of all deaths in living organisms is the extreme and irreversible loss of homeostasis.[262]

Since the early 1990s, researchers have discovered that these corrections are all part of a major physiologic system in the human body. It's called the endogenous cannabinoid system—or endocannabinoid system (ECS)—and it is our physiologic system required for maintaining homeostasis.

> **Keywords:** *Physiology* is the study of normal functions of living organisms. It refers to the study of systems. If anatomy is the study of parts, physiology is how those parts create systems and processes.

Biomolecules

In living organisms, biological molecules are organic compounds that are essential to biological processes. The term "biomolecule" is a broad description of molecules that includes proteins, carbohydrates, lipids, fatty acids, vitamins, hormones, neurotransmitters, nucleic acids, primary metabolites, and secondary metabolites. These molecules can be produced in the organism (they can be *endogenous* to the organism) or they can be produced outside of the organism (they can be *exogenous* to the organism). Most biomolecules are comprised of only four elements—oxygen, carbon, hydrogen, and nitrogen.[263]

Understanding how specific biomolecules interact in the human body is essential to the study of the endocannabinoid system. For example, phytocannabinoids and terpenes are biomolecules (they are lipids). Endocannabinoids (which are produced naturally in the human body) are also biomolecules—they are neurotransmitters that are metabolized by fatty acids (also biomolecules) and converted into metabolites (yet another type of biomolecule).

The Endocannabinoid System

The endocannabinoid system is a complex cell-signaling system that includes molecules that our bodies create on demand—these are neurotransmitters called endocannabinoids—the cell receptors that these endocannabinoids bind with, the enzymes that metabolize or degrade the cannabinoids, and the neurons and neural pathways where the

endocannabinoids, receptors, and enzymes are all co-located. There is evidence of an ECS present in all mammals, in fish, reptiles, earthworms, leeches, amphibians, birds—every animal except insects. The scientific community estimates that the ECS first began to evolve over 600 million years ago.[264] In humans, it's likely that the ECS is primarily responsible for regulating our mood, appetite, pain-sensation, memory, and sleep, among other functions.[265] [266]

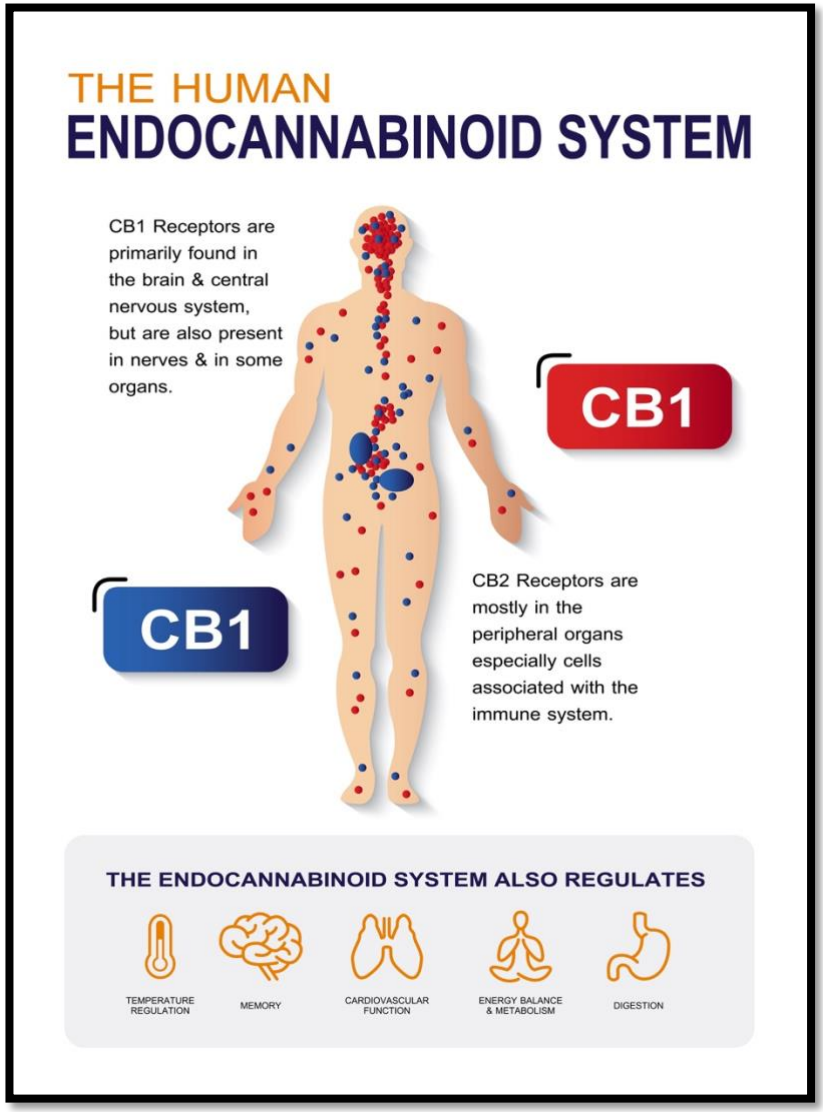
The importance of the endocannabinoid system to the regulation of so many physiological functions and processes suggests that the modulation of the ECS might provide novel therapeutic strategies for multiple medical fields, including pain management, neuroprotection, anti-inflammatory, and antibacterial fields of research.[267]

The ECS coordinates messages via cellular communication. The human body includes more than 37 trillion cells. [268] Each cell has a specific function—a specific task or set or tasks that it performs. To achieve these tasks, cells require mechanisms for letting things into and pushing things out of the cell wall. One mechanism that cells use to bring information into a cell is called a receptor. Receptors are embedded in cell membranes and act as gates. When the right type of molecule binds to a receptor, that connection can initiate a variety of cell functions.

There exist multiple receptors that are modulated by the ECS, but the most well-studied cannabinoid receptors are cannabinoid receptor 1 (CB_1) and cannabinoid receptor 2 (CB_2). These are G protein-coupled receptors that are located throughout the human body, including in the brain, organs, connective tissues, glands, and immune cells. Endocannabinoid receptors are the most common type of cell receptor in the body.[269] In fact, there are more CB_1 receptors in the brain than any other type of G protein-coupled receptor. [270]

Keywords: *G protein-coupled receptors* (GPCRs) are a large family of cell membrane receptors that bind with molecules outside the cell membrane and activate cellular responses. These receptors are long strings of amino acids that weave across the cell membrane seven times and are connected to G proteins inside of the cell membrane. Each receptor has multiple unique binding pockets and each pocket has a spectrum of affinity for specific proteins. Often, the simple analogy of a lock and key is used to describe the relationship between cell receptors (the lock) and proteins—or ligands—that bind to the receptor (the key). When some ligands dock in a binding pocket, they can act as a molecular

switches to turn on (or activate) the cell function (however, not all ligands activate the cell function). In addition to cannabinoid receptors, other



well-known GPCRs include opioid, dopamine, and serotonin receptors.[271] When a ligand binds to and activates a CB_1 receptor, the effects produced can include an increased drive to sleep and eat, a reduction of perceived pain, fear, and anxiety, a maintenance of well-being, and the promotion

of recovery during stress. CB_2 receptor activation does not produce the psychoactivity associated with CB_1 receptor activation.[272] When a ligand binds to and activates the CB_2 receptor, the effect produced is mostly the reduction of inflammation. See Cannabinoid Pharmacodynamics for more information about receptors.

Endocannabinoids

The discovery of the first cannabinoid receptor—by Allyn Howlett and William Devane in 1988—led researchers to assume the existence of a naturally occurring substance in the body that would bind to the receptor. The first endogenous cannabinoid—or endocannabinoid—was discovered in 1992 by Raphael Mechoulam in collaboration with William Devane and Lumir Hanus.

Endocannabinoids are the substances our bodies naturally make to stimulate the CB_1 and CB_2 receptors. The two most well understood of these molecules are called anandamide (AEA) and 2-arachidonoylglycerol (2-AG). These molecules have a local effect, are short-lived, and are degraded by the enzymes fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL).

Anandamide and 2-AG are not the only endocannabinoids. In fact, researchers have identified at least eight endogenous ligands that influence the endocannabinoid system, including 2-arachidonoyl glyceryl ether (noladin ether), N-arachidonoyl dopamine, O-arachidonoyl-ethanolamide (virodhamine), docosatetraenoylethanol-amide, lysophosphatidylinositol, and oleoylethanolamide.[273]

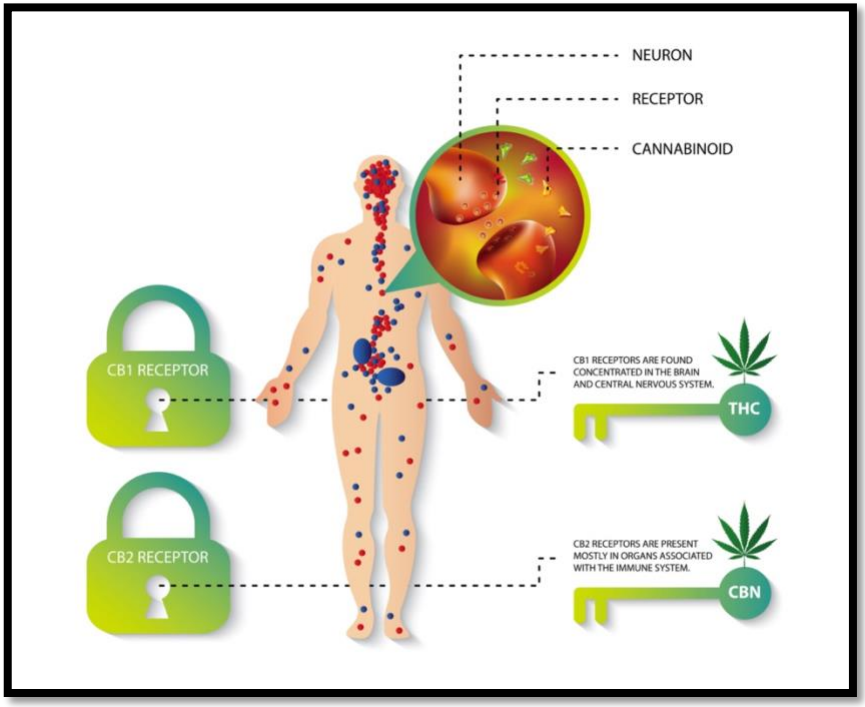
These endocannabinoids are all lipophilic ligands. Most lipophilic ligands tend to bind to receptors that are inside of the cell membrane wall. However, endocannabinoids can bind to intracellular receptors and to receptors that are embedded in the cell membrane.

Clinical Endocannabinoid Deficiency

Some research demonstrates that many diseases—especially diseases that are difficult to diagnose and treat, such as fibromyalgia, migraine, and IBS (irritable bowel syndrome)—arise from a deficiency in the ECS. Dr. Ethan Russo has named this a Clinical Endocannabinoid Deficiency, and this condition shares similarities with other human chemical deficiencies: for example, just as Parkinson's can be characterized by a lack of dopamine, and just as diabetes can be characterized by a lack of insulin, some diseases might be characterized by a deficiency in the ECS –a lack of endocannabinoids.

Researchers from the national institutes of health have stated that they believe that dysfunction in the ECS is responsible for all underlying human disease. The importance of the ECS cannot be overstated.

Because the cannabinoids in the cannabis plant are structurally and chemically similar to our endocannabinoids, they can interact with the ECS by binding with receptors in the human body. The cannabinoids produced by cannabis plants simply imitate endocannabinoids—some phytocannabinoids fit perfectly into specialized receptors found throughout the nervous and immune systems, and they can enhance the body's own ability to maintain homeostasis and health. In fact, low doses of Δ9-THC and CBD might increase endocannabinoid levels by upregulating CB_1 receptors. In one study, acute doses of Δ9-THC improved the efficacy of endogenous cannabinoids for pain relief.[274] So just as patients can use medications to supplement a dopamine deficiency or an insulin deficiency, some patients can use cannabis to treat conditions and disease caused by a clinical endocannabinoid deficiency.



Chapter 4: Intercellular Communication

In order to think, move, feel, speak, hear, or perform any human function, your cells must communicate with each other. Intercellular communication is necessary for human survival. And, to understand how endocannabinoids and phytocannabinoids exert influence on cells, it's important to have a foundational understanding of the manner in which cells communicate.

There exist two types of intercellular communication: direct communication and indirect communication. For example, some cells are physically linked together and can pass cellular material through a physical channel. This book, however, will focus mostly on indirect communication. In indirect intercellular communication, a cell produces and releases a chemical messenger which travels through the fluid between cells or through the blood stream to bind to a target cell on a cell receptor. The receptor might be embedded in the cell membrane, it might inside the cell, or it might inside the nucleus of the cell. Regardless of where the chemical messenger binds, it produces an effect on the target cell.

There are different methods for describing or classifying these chemical messengers—also called *ligands*—and understanding these classifications can help you understand the properties and effects these chemical messengers have on cells.

Ligands: Functional Classification

Ligands can be categorized according to how they function. There are four types of functional categories for ligands: paracrine, neurotransmitter, hormone, and neurohormone.

Paracrine signaling is a type of signaling that occurs over short distances. Some types of signaling can produce hormones. For example, in hormone and neurohormone signaling, a cell (an endocrine cell in hormone signaling, a neuron in neurohormone signaling) produces a ligand and that ligand is a hormone. Hormones travel through the interstitial fluid and then enter the bloodstream to

reach target cells, enabling long distance intercellular communication. This book will focus on neurotransmitter signaling.

Ligands: Chemical Classification

Ligands can be categorized according to their chemical class. The chemical class categories for ligands are: eicosanoids, amino acids, amines, peptides and proteins, steroids, and endocannabinoids. Understanding the chemical properties of a ligand can help you understand how the ligand is created, released, how it's transported to and how it binds with a target cell, and the effects the ligand will have on a target cell.

- Amino Acids are lipophobic and bind to receptors on the target cell located in the cell membrane. There exist 20 common amino acids, but only four function as neurotransmitters: glutamate, aspartate, glycine, and GABA. Amino acid ligands are created (or *synthesized* by the secreting cell) independent of any demand and stored in the secretary cell until needed.
- Amines are lipophobic and bind to receptors on the target cell located in the cell membrane. Amines can function as paracrines, neurotransmitters, or hormones. Examples of amine messengers include dopamine, serotonin, histamine, and thyroid hormones. Amine ligands are synthesized independent of any demand and stored in the secretary cell until needed.
- Peptides and proteins are lipophobic and bind to receptors on the target cell located in the cell membrane. Peptides and proteins can function as paracrines, neurotransmitters, or hormones. Peptides and protein ligands are synthesized independent of any demand and stored in the secretary cell until needed.
- Steroids are lipophilic and bind to receptors on the target cell located in the cytosol, which is the fluid inside of the cell membrane. Steroids function as hormones, and steroid ligands are synthesized on demand by the secreting cell.
- Eicosanoids are lipophilic and bind to receptors on the target cell located in the cytosol, which is the fluid inside of the cell membrane. Eicosanoids function as paracrines and eicosanoid ligands are synthesized on demand by the secreting cell. Examples of eicosanoids include prostaglandins

(which are important in the inflammatory response), and thromboxanes (which are important in blood clotting).

- Endocannabinoids are lipophilic and bind to receptors on cells located in the cell membrane. Endocannabinoid ligands function as neurotransmitters and are synthesized on demand by the secreting cell. Two examples of endocannabinoid ligands are N-arachidonoylethanolamide (more commonly referred to as anandamide), and 2-arachidonolyl glycerol (2-AG). Endocannabinoids are not considered standard neurotransmitters. First, unlike other neurotransmitters, endocannabinoids are lipids. The interstitial fluid that surrounds neurons is an aqueous solution, which does not typically facilitate intercellular communication for messengers that are hydrophobic. Also, endocannabinoids travel in a direction opposite to the normal flow chemical synaptic signaling. Typically, presynaptic neurons release neurotransmitters and the chemical messenger travels across the synapse to a postsynaptic neuron. Endocannabinoids are synthesized in and released from postsynaptic cells and travel backward across the synapse. [275]

Neurons, Neurotransmitters, and Action Potentials

Neurons are primary cells in the nervous system. Neurons have three parts: dendrites, which are branches that receive signals from other neurons; the cell body, which includes the nucleus; and the axon, which is a tail-like structure from which a neuron passes chemical signals.

In neurotransmitter cell signaling, the neuron that produces the ligand is called a presynaptic cell and the cell that receives the ligand is called the postsynaptic cell (the postsynaptic cell is typically a neuron too, but it can also a muscle or a gland). And while this type of signaling occurs between cells that are nearby, some neurons have axons that are over three feet in length, which effectively produces long distance communication.

Recall that neurotransmitters are a class of chemical messengers (the others are paracrine, hormone, and neurohormones). There are likely hundreds of types of neurotransmitters, and they are typically grouped into four categories, with each category containing neurotransmitters with similar molecular structures. Some neurotransmitters are released widely throughout the nervous system, while others are concentrated in specific areas. For example, neurotransmitters that are widely distributed include glutamate (which is the

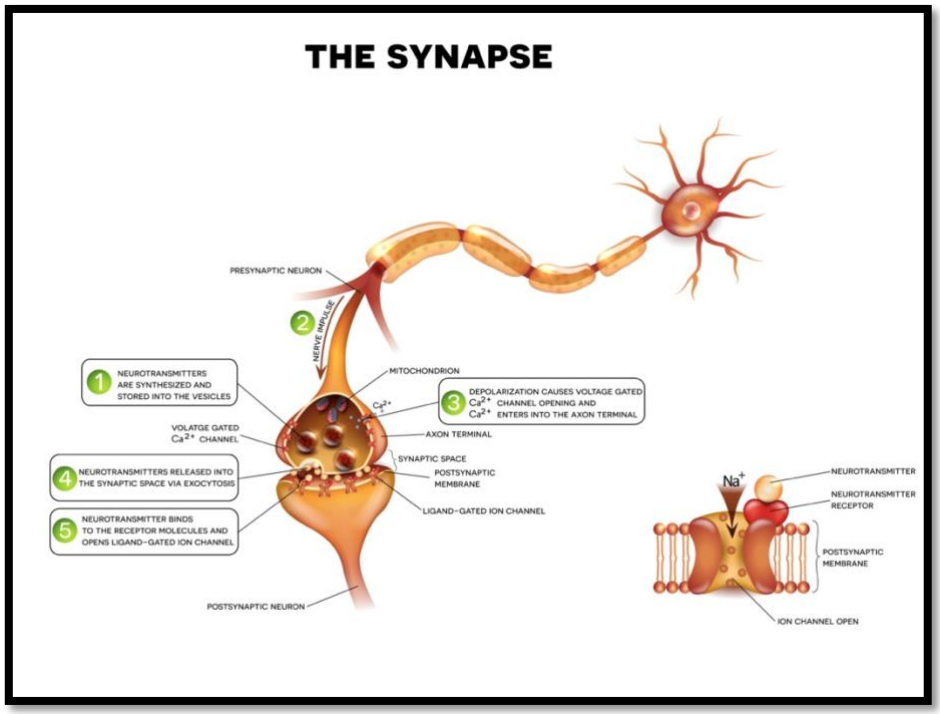
most common excitatory neurotransmitter), GABA, and glycine (the latter two neurotransmitters are the most common inhibitory neurotransmitters). All three of these neurotransmitters are involved in some manner in most functions of the nervous system.[276]

Endocannabinoids—for example, 2-AG and anandamide—are also neurotransmitters. Recall that endocannabinoids travel in a direction opposite to most other neurotransmitters, from a postsynaptic neuron to a presynaptic neuron. This type of signaling is called *retrograde signaling*.

Dendrites receive neurotransmitters from adjacent neurons and those neurotransmitters bind to G-protein-coupled receptors on the target neuron's dendrites. The binding eventually facilitates the opening of ion channels in the cell that enable charged particles to flow into and out of the cell. Functionally, the chemical signal (the neurotransmitter) is converted into an electrical signal (a group of negatively and positively charged ions). A neuron has an electric charge because of the concentrations of ions on the inside of the cell versus the concentrations of ions directly outside of the cell membrane. In its normal resting state, a neuron has a negative charge.

The branching created by dendrites can enable a single neuron to receive as many as 100,000 signals from neighboring neurons.[277] When a neurotransmitter binds to a G-protein coupled receptor, the G-protein detaches from the receptor and causes a channel to open in the cell membrane (these channels are called *ligand-gated* channels because they open when ligands bind to specific receptors). The type of channel that opens determines the type of ion that can flow through the open channel and into the cell. Typically, neurotransmitters will affect many channels simultaneously, enabling different types of ions (like sodium, potassium, and calcium ions) to flow into and out of the cell. If the signaling results in a net positive charge, the effect is called an *excitatory postsynaptic potential* (EPSP). If the signaling results in a net negative charge, the effect is called an *inhibitory postsynaptic potential* (IPSP). If enough EPSPs occur in the cell and the positive charge surpasses a specific threshold, it triggers the opening of another type of channel (these are called *voltage-gated* channels because they respond to specific changes in the charge of the cell) and these channels allow more positive ions to flow into the cell. These positively charged ions continue to enter the cell as channels open farther down the axon, causing a chain reaction. If the combined effect of these signals produces enough of a positive charge to surpass a specific threshold, the collective charge can trigger an action potential, which is an electrical signal that moves down the

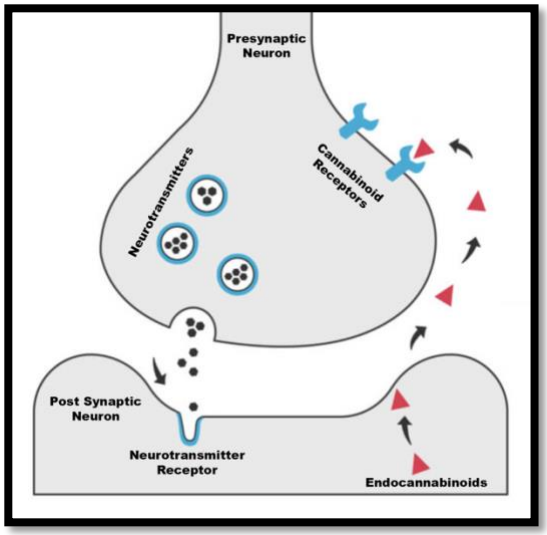
neuron's tail—the axon—and triggers the release of neurotransmitters at the end of axon to pass the signal to an adjacent neuron (sometimes this is referred to as a nerve *firing*). Neurons pass neurotransmitters as a method of communication,



but it is the action potential that ensures that the message is passed among neurons.[278] Eventually, the cell stops the positive sodium ions from flowing in and opens positive potassium channels to allow these ions to flow out. Positive ions flow out of the cell and eventually the cell returns to its normal negative charge resting state.

Retrograde Signaling

Endocannabinoids are not standard neurotransmitters. Most neurotransmitters travel in a single direction, moving from the presynaptic neuron, crossing the synapse, and then attaching to a postsynaptic neuron. The ECS communicates its messages in the opposite direction using *retrograde* signaling, which moves from a postsynaptic neuron to a presynaptic neuron. When the postsynaptic neuron is activated, fat cells present in the neuron create



Postsynaptic cells synthesize and release endocannabinoids that travel back to the presynaptic cell.

endocannabinoids, which are released from the cell and which travel backwards to the presynaptic neuron, where they attach to endocannabinoid receptors.

CB_1 receptors are present in abundance and on a variety of different cell types. Endocannabinoids are agonists at CB_1 receptors. And, endocannabinoids are generally inhibitory neurotransmitters (overall, they affect cells with a net negative charge, inhibiting the action potential). Because CB_1 receptors are present on neurons that release excitatory neurotransmitters *as well as on* neurons that release inhibitory neurons, endocannabinoid signaling can modulate the release of both types of neurotransmitters. When postsynaptic cells synthesize and release endocannabinoids that travel back to the presynaptic cell and inhibit the release of inhibitory or excitatory neurotransmitters, the postsynaptic cell is effectively influencing its own number and type of incoming signals,[279] which enables the endocannabinoid system to act as a master regulator in the body. Because endocannabinoids act on cells where neurotransmitter signaling originates, they can limit the release of neurotransmitters and influence how messages are sent, received, and processed by the cell. And while the ECS performs different tasks in different types of tissue, its overall function is to achieve homeostasis, the maintenance of a stable internal environment.

Of course, many phytocannabinoids can also bind to cannabinoid receptors and influence inhibitory and excitatory neurotransmitters. And, many cannabinoids are promiscuous—they can bind to many different types of receptors and influence neurotransmitter signaling through multiple and complex mechanisms.

Ligand Binding Types

When cannabinoids bind to G protein-coupled receptors (such as CB_1 and CB_2), they act as ligands. There are six types of ligands that can bind to a cannabinoid receptor, and these ligands can bind to different types of sites on a receptor.

The main binding site on a cannabinoid receptor is called the *orthosteric* site. A ligand docking at the main *orthosteric* site on a cell receptor enables the cell's signaling. There also exists a secondary binding site called the *allosteric* site. Ligands that bind to the allosteric site cannot directly activate a receptor, but they can increase or decrease the activity of agonists or partial agonists that bind to the orthosteric site by changing the shape of the orthosteric receptor.

Positive allosteric modulators induce signaling. Negative allosteric modulators inhibit signaling. For example, Δ9-THC binds to the main *orthosteric* site at CB_1, and CBD binds to the allosteric receptor site at CB_1. Cannabinoids that demonstrate therapeutic efficacy but that bind weakly (or not at all) to CB_1 or CB_2 receptors must bind to other receptors in the brain and body or have other mechanisms of action in the ECS.

Exogenous orthosteric site ligands (such as Δ9-THC) compete with any endogenous ligands (such as anandamide). If the affinity for the orthosteric site is high, exogenous substances can competitively block the natural ligand from binding. Allosteric substances can produce more nuanced effects than can orthosteric substances—as allosteric substances can *modulate* activity at the site. For example, while orthosteric substances complete with endogenous ligands at the main binding site, allosteric modulators can exert influence over *any* compound that is bound to orthosteric site.

Orthosteric receptor sites tend to be homogenous across families of proteins. Consequently, substances that bind to the orthosteric site of one protein are likely to bind to the orthosteric site of other receptor family proteins. While most drugs are formulated to bind to an orthosteric site, it can be difficult to design drug formulations that are highly selective at a single protein's active binding site. The influence of a substance on multiple receptor sites increases the risk of unintentional—and potentially adverse—side effects. Allosteric binding sites are less homogenous across protein families. Drug formulations that target secondary binding sites can be highly selective and might result in fewer unintentional side effects. Consequently, allosteric substances, when formulated into drugs, tend to have fewer side effects than orthosteric substances.[280]

The types of ligands that bind to orthosteric receptor cites are:[281]

- Full Agonists
  Full agonists activate a receptor to the fullest extent possible. Many synthetic cannabinoids are full agonists. Full CB_1 receptor activation is not desirable because of the frequency and severity of adverse side effects.
- Partial Agonists
  Partial agonists activate a receptor, but not to full capacity. Δ9-THC is a partial agonist at CB_1. Partial agonists and full agonists compete for the same orthosteric binding site on the CB_1 receptor.
- Neutral Antagonists
  A neutral antagonist binds to the orthosteric site but does not activate the receptor. It does, however, block agonists from binding. Neutral antagonists do nothing on their own in the absence of an agonist. CBD, at very high doses, might bind weakly to the CB_1 receptor orthosteric binding site and, in this scenario, might be a neutral antagonist.
- Inverse Agonists
  G protein-coupled receptors have *constitutive activity*—they have a baseline level of signaling activity even in the absence of an agonist. An inverse agonist not only blocks agonist binding, but also inhibits this constitutive activity.[282] The discontinued drug Rimonabant is an inverse agonist at the CB_1 receptor.

The types of ligands that bind to allosteric receptor cites are:[283]

- Positive Allosteric Modulators
  Positive allosteric modulators (PAM) bind to the allosteric site and amplify the effect of an agonist by increasing agonist binding or by increasing receptor signaling. Recall that Anandamide, Δ9-THC, and CBD are all positive allosteric modulators of glycine receptors.[284] [285] [286]
- Negative Allosteric Modulators
  Negative allosteric modulators (NAM) decrease agonist binding or receptor signaling. When it binds to the allosteric site, CBD is a negative allosteric modulator and can mitigate the adverse effects of Δ9-THC, such as lethargy and psychoactivity. [287]

Chapter 5: Cannabinoid Pharmacology

Pharmacology is the study of drug properties and their interaction with living organisms and viruses. The field of pharmacology includes multiple sub-disciplines. For example, *pharmaceutics* refers to the process of turning chemical substances into medications that can be used safely and effectively by patients. *Pharmacogenetics* is the study of genetic differences that affect individual responses to drugs. These genetic differences can be specific to enzymes, messengers, receptors, and metabolic pathways, and can impact the therapeutic effects and adverse effects experienced by an individual patient.

This book focuses on two additional sub-disciplines: *pharmacodynamics* and *pharmacokinetics.* Pharmacodynamics is the study of the biochemical, physiologic, and molecular effects of drugs on the body. This discipline includes the study of receptor binding and sensitivity, postreceptor effects, and chemical interactions. Pharmacodynamics is often described as *what a drug does to the body.* Pharmacokinetics refers to the movement of a drug into, through, and out of the body. It measures and describes the absorption, bioavailability, distribution, metabolism, and excretion of a drug. Pharmacokinetics is often described as *what the body does to a drug*.

Cannabinoid Pharmacokinetics

Pharmacokinetics refers to the overall movement of a drug into and out of the body. Pharmacokinetics is concerned with the site of absorption (determined by the route of administration); it measures the amount of the drug absorbed into and useful to the body (the bioavailability); it measures how the drug is distributed from the bloodstream and into tissues; how the body metabolizes the drug, and how (and when) the body eliminates the drug.

The manner in which a drug passes through the body depends the drug's own chemical properties as well as on a patient's physical and genetic characteristics. Aging, for example, will influence the metabolism and excretion

of many drugs—senior patients with slower metabolisms might experience the effects of a drug for longer periods than younger patients.[288]

Absorption

The route of administration determines cannabinoid absorption and bioavailability. The route of administration can also impact the probability and severity of drug interactions, with interactions more common when both drugs are taken orally (and subsequently processed through the liver). Ingested cannabinoids have higher peak liver concentrations than inhaled cannabinoids, suggesting that ingested cannabinoids can produce higher prevalence of drug interactions during first-pass metabolism.

Inhalation

During inhalation of vaporized or smoked cannabis flower or vaporized oil concentrates, there is passive diffusion into the capillaries with onset in seconds to minutes. Peak plasma concentrations of cannabinoids are attained rapidly (3–10 minutes) [289] [290] and maximum concentrations are higher compared to oral ingestion.[291] [292] The bioavailability of cannabinoids after inhalation is between 10% and 35%,[293] depending on the number of and the intervals between inhalations, the duration of inhalation, the volume inhaled, and the length of time the breath is held. Inhalation largely avoids first-pass metabolism.

Maximum cannabinoid concentration is greater in frequent smokers compared to occasional smokers, likely because frequent smokers are more efficient and skilled at smoking.[294] [295] Consumers can use a vaporizer to mitigate the respiratory risks associated with smoking cannabis and the toxins associated with combustion.[296]

CBD bioavailability after inhalation is comparable to that of Δ9-THC and the body metabolizes both compounds in a similar manner.[297] The ratio of the cannabinoids in the blood remains consistent with the ratio of these molecules in the chemovar used for inhalation. The pharmacokinetics of vaporized and smoked cannabinoids is comparable.[298]

The National Academy of Sciences, after an exhaustive review of the medical literature in 2017, stated the following: [299]

- “There is substantial evidence of a statistical association between long-term cannabis smoking and worse respiratory symptoms and more frequent chronic bronchitis.”

- "There is moderate evidence of a statistical association between cannabis smoking and improved airway dynamics with acute use, but not with chronic use."
- "There is moderate evidence of a statistical association between cannabis smoking and a higher forced vital capacity."
- "There is moderate evidence of a statistical association between the cessation of cannabis smoking and improvements in respiratory symptoms."
- "There is limited evidence of a statistical association between cannabis smoking and an increased risk of developing chronic obstructive pulmonary disease (COPD)."
- "There is no or insufficient evidence to support or refute a statistical association between cannabis smoking and hospital admissions for COPD or asthma development or asthma exacerbation."

Keywords: *First pass metabolism* (also called first pass effect) refers to the metabolism of a substance (usually taken orally) where the concentration of that substance is substantially reduced prior to reaching the blood stream. Substances taken orally must pass through the stomach and gastrointestinal tract (where acids and enzymes begin to break down and metabolize the substance), and then into the liver (where enzymes responsible for eliminating substances are concentrated).

Oromucosal Administration

Cannabis can be absorbed through the oral mucosa that lines the mouth cavity and into the bloodstream. Some sublingual (under the tongue) and buccal (between the cheek and gums) administrations can be rapidly absorbed into the oral mucosa and produce plasma concentrations higher than those of oral administrations but less than those of inhaled cannabis.[300]

Oromucosal administration can provide rapid relief, but there are few true oromucosal cannabis products on the market. Cannabinoids are fat-soluble and, in their natural state, do not absorb well into the oral mucosa. Moreover, cannabis products are often extracted into oils, and these products are not water-soluble. Consumers might expect rapid onset when using tinctures, only to wait between one and three hours for the dose to take effect. Many products marketed as tinctures will follow the pattern of ingestion, regardless of how long they are held under the tongue.

Even cannabinoid drugs that are specifically formulated for transmucosal delivery might not effectively absorb through the mucosa. For example, some research suggests that there are no statistically significant differences in maximum concentrations or time to maximum concentration between orally administered Δ9-THC and buccally administered Sativex. Sativex is an oral-mucosal spray that contains Δ9-THC and CBD, but also contains anhydrous ethanol (ethyl alcohol with a purity of at least ninety-nine percent and no added denaturants), peppermint oil, and propylene glycol. These results suggest that much of the active drug in Sativex is swallowed and the pharmacokinetics follow the pattern of ingestion.[301]

A true sublingual (a product in which the cannabinoids are formulated to be more water-soluble) absorbs rapidly into the mouth. The effects can be perceived in 15-20 minutes and can last between four and six hours.

Oral Administration

Oral administration has highly variable absorption and depends on metabolism, gut content, and genetics. Cannabinoids are highly lipophilic and have poor oral bioavailability, possibly as low as 6% [302] [303] (although some companies are beginning to offer products made from oil-in-water emulsions—such as nanoemulsions—that promise better bioavailability and faster onsets). Oral administration has extensive first-pass metabolism,[304] has peak plasma concentrations that are lower than inhalation, [305] and a variable and lengthy onset (30 minutes to 2 hours) to reach peak concentration.[306] [307] The duration of effects via oral administration can last from 5 to 8 hours.

There is some research to suggest that bioavailability of ingested cannabinoids is higher in a fed stated versus a fasted state.[308] Eating causes the gallbladder to release bile acids that help break down molecules and that increase the amount of absorption. In one study, participants who were fed a full meal prior to cannabis ingestion had a Δ9-THC absorption that was 2.8-fold higher than the rates in fasting participants and had CBD absorption rates that were 4.1-fold higher than that in fasting participants.[309]

When cannabinoid produces are ingested, the ratio of CBD to Δ9-THC can change in the body, depending on metabolism, genetic makeup, and gut content. In the study cited previously, participants experienced an absorption rate of CBD that was four-fold lower during a fasted state: CBD doesn't absorb very well on an empty stomach—neither does Δ9-THC—but Δ9-THC absorbs into the body better than CBD, and this difference in absorption can reduce the therapeutic

impact of CBD. Also, Δ9-THC is converted into 11-Hydroxy-THC. The total amount of Δ9-THC, combined with its more potent metabolite, can produce an even lower ratio of CBD to Δ9-THC.

Eating a meal before ingesting cannabis is a guideline that is less important to follow if ingesting products that contain predominantly Δ9-THC. However, consumers will feel the effects on an empty stomach earlier than they would on a full stomach (with peak affects occurring in about 90 minutes).

Transdermal Administration

The absorption of cannabinoids through transdermal administration relies on drug concentration gradients. There exists a high concentration of cannabinoids on the patch and a low concentration of cannabinoids under the skin, so the cannabinoids will begin to transfer into the area of low concentration to achieve equilibrium. Typically, transdermal products include a chemical agent enables the cannabinoids to diffuse across the aqueous layer of the skin and enter the bloodstream. This route of administration can avoid first-pass metabolism. [310] [311] With transdermal administration, the time of onset is rapid, sometimes within twenty minutes and lasting up to twelve hours with time-released applications, such as patches. Research investigating the permeability of cannabinoids in human skin suggest that CBD can absorb into the skin more effectively than Δ8-THC by a factor of 10.[312] Most cannabis transdermal producers recommend that patients apply transdermal patches to a thin layer of skin—for example, inside of the wrist, on the top of the foot, or near the ankle—to more readily access the bloodstream.

The results of one study in animals suggested that CBD could be successfully delivered through transdermal administration.[313] Another animal study suggested that transdermally administered CBD might be effective for treating inflammation and pain without any side-effects.[314] There exist few completed clinical studies that demonstrate efficacy with transdermal cannabis patches in human subjects. One study completed in 2019 suggested that transdermal CBD might be effective for treating chronic muscular pain.[315]

Topical Administration

Cannabis can be applied on the skin by topical application and can provide localized pain relief.[316] Topicals can be effective for treating localized pain, rashes, and itchy areas and they do not cause systemic side effects. Typically, the onset with topicals can occur within 20 minutes and last 2-3 hours.

Generally, CB_1 agonists can help redness and inflammation in atopic dermatitis, contact dermatitis, and psoriasis.[317] Also, cannabis topicals can help reduce arthritic pain and inflammation without side effects.[318]

Distribution

Cannabinoids rapidly distribute into well-vascularized organs (lungs, heart, brain, and liver)[319] [320] [321] with subsequent distribution into less vascularized tissue.[322] Distribution is affected by body size and by disease states.[323] With chronic use, cannabinoids accumulate in fat tissues.[324] [325] Subsequent release and redistribution [326] [327] can result in the persistence of cannabinoid activity for several weeks post-administration. [328] [329] [330] [331]

Distribution of Inhaled Cannabinoids

After inhalation, cannabinoids are rapidly absorbed from the lungs into the blood, typically within about 15 minutes. [332] Approximately 90% of cannabinoids in blood circulates in plasma and the remaining 10% circulates in red blood cells.[333] Cannabinoid bioavailability after inhalation varies depending on the depth of inhalation, the duration of inhalation, and the length of time the breath is held. Combusting cannabinoids destroys about 30% of the total cannabinoids. The bioavailability of inhaled cannabinoids is approximately 15% for occasional users and 25% for heavy users,[334] though other estimates range from 10% to 35%.[335]

Between 15-60 minutes after inhalation, cannabinoid levels in the blood rapidly decrease because the cannabinoids distribute into organs and into fat tissue. Two to four hours after inhalation, an equilibrium occurs between cannabinoid blood levels and cannabinoid levels in organs. Movement of cannabinoids continues from the blood into fat tissue (cannabinoids diffuse into fat tissue more slowly than into other tissue). Eventually, cannabinoids move from fat into the blood as the cannabinoid levels in the blood are reduced by metabolism in the liver.[336]

Distribution of Ingested Cannabinoids

Following oral ingestion of cannabinoids, absorption is slow (compared to other routes), as the plasma concentrations reach a peak within 1-3 hours.[337] Metabolism by the cytochrome P450 family of enzymes reduces cannabinoid bioavailability to a range of 4-12%.[338] After liver metabolism, cannabinoids rapidly penetrate into fat tissues and into highly vascularized tissues (including brain and muscle tissue) and there is a rapid decrease in plasma concentration.[339]

Subsequently, a slow redistribution and equilibrium of cannabinoids occurs from deep fat deposits back into the blood stream.

Metabolism[340]

In the context of drugs and therapeutic substances, metabolism refers to the chemical alteration of a drug by the body. Effectively, the body wants to break down a drug into water soluble components that it can then eliminate. The components that are the products of metabolism—called metabolites—can be inactive or active. Inactive metabolites demonstrate no therapeutic activity or toxicity. Active metabolites might produce effects similar to the original drug or they might produce a toxicity or effect very different from the original drug. Metabolites can be further metabolized before being excreted from the body in the urine or bile.[341]

The liver is the primary site for drug metabolism, especially for drugs that are orally ingested, and one family of enzymes—the cytochrome P-450 enzymes—is responsible for metabolizing most drugs. Multiple factors can influence this family of enzymes and the efficacy with which they function, including drugs, diet, health, and genetics. Our metabolic system is only partially developed at birth and enzymatic activity decreases with age. Consequently, newborns and seniors metabolize substances more slowly and less efficiently.

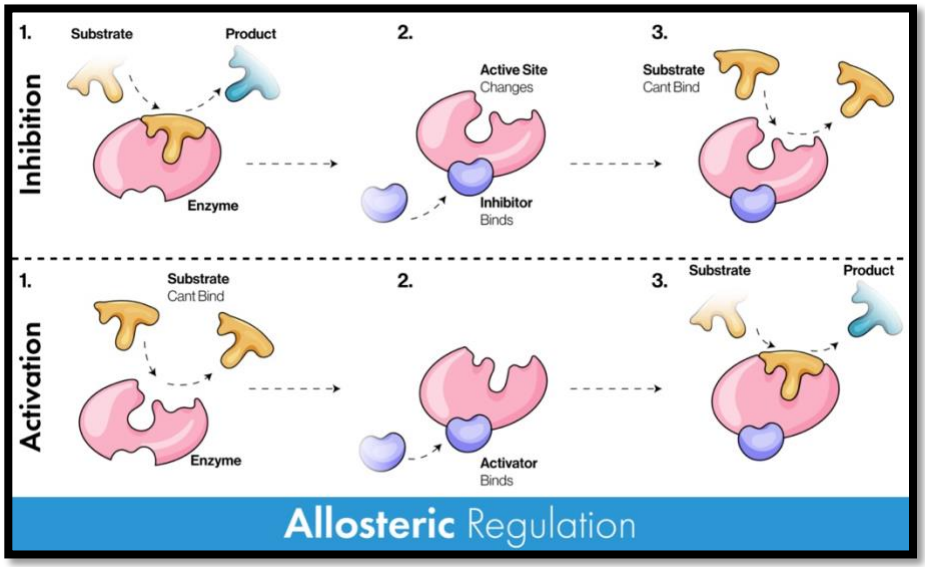
Enzymes

Enzymes are proteins comprised of amino acid chains that catalyze a reaction, meaning that enzymes accelerate the conversion of one substance (called a substrate or natural ligand) into another substance. Enzymes are responsible for metabolizing drugs—they help the body eliminate drugs.

Natural ligands bind to enzymes using a process called induced fit. When the ligand begins to bind with the enzyme, the interaction causes the enzyme's active binding site (called an *orthosteric* site) to conform more accurately with the shape of the ligand, increasing the ligand's affinity and maximizing the enzyme's ability to catalyze the reaction.[342] When the reaction is complete, the enzyme releases the product of the reaction and returns to its original state, ultimately unchanged by the reaction or by the ligand.[343]

Enzymes also have a secondary binding site—the *allosteric* site. Some molecules can induce (or increase) the reaction between a natural ligand and an enzyme by binding to the allosteric site. These molecules cause the enzyme to slightly modify the shape of the main binding site to increase affinity with the

natural ligand, thereby increasing the reaction rate.[344] Other molecules inhibit an enzyme's ability to catalyze reactions. For example, some molecules have a structure that enable the molecule to fit into an enzyme's active site, effectively blocking natural ligands from binding and forming reactions with the enzyme. Some molecules inhibit enzyme activity by binding to the secondary allosteric site. This type of inhibition is called noncompetitive allosteric inhibition (the molecule isn't competing with the natural ligand at the main orthosteric site).



Noncompetitive allosteric inhibition causes the enzyme to slightly modify the shape of the main binding site to decrease affinity with the natural ligand, thereby decreasing the reaction rate.[345]

Cytochrome P-450 Enzymes

The cytochrome P450 enzymes (cytochrome is abbreviated as *CYP* and pronounced *sip*) are a family of enzymes that metabolize drugs, meaning that these enzymes modify, detoxify, and remove drugs from the body. In humans, CYPs are heavily expressed in the liver (though they are also expressed most tissues and are also concentrated in the lungs and in the intestines), are responsible for the metabolism of most pharmaceuticals, and typically make compounds more water-soluble. CYP enzymes have been identified in viruses and

in the animal, plant, fungi, protist, bacteria, and archaea kingdoms. There are estimated to be more than 300,000 distinct CYP enzymes.[346]

Naturally occurring compounds and drugs, including cannabinoids, can *induce* or *inhibit* CYP activity. When a substance *inhibits* a CYP enzyme, that substance decreases the enzyme's activity. If that same enzyme is responsible for metabolizing a second drug, inhibiting the enzyme activity enables larger amounts of the second drug to remain in body for longer periods of time (that is, there is less of the enzyme available to metabolize the drug, so more of the second drug is available for absorption and distribution). In this scenario, more of the drug enters the bloodstream and produces greater effects. For example, compounds found in grapefruit juice can inhibit the CYP3A4 enzyme, which is responsible for metabolizing many prescription medications. If CYP3A4 enzyme is inhibited, it is not able to efficiently metabolize these drugs, and more of those drugs would make it into the bloodstream, producing an effect greater than expected.

If a substance *induces* a CYP enzyme, that substance increases the enzyme's activity. If that same enzyme is responsible for metabolizing a second drug, inducing the enzyme activity produces more of the enzyme and reduces the amount of the second drug in body (that is, there is more of the enzyme available to metabolize the drug, so less of the second drug is available for absorption and distribution). In this scenario, less of the second drug enters the bloodstream and produces less of an effect.

Typically, the induction of a CYP enzyme requires a longer period of time than the inhibition of a CYP enzyme. For example, induction might require several days before it facilitates any decreased drug effects. Conversely, inhibition of a CYP enzyme is instantaneous, which can immediately exaggerate the effects of co-administered drugs.[347] Inducers are much more rare than inhibitors.

The CYP family of enzymes are responsible for metabolizing cannabinoids. For example, if you ingest cannabinoids orally, these enzymes will determine how much of a cannabinoid reaches the bloodstream (and subsequently how strongly you feel the effects of the cannabinoid) and they will determine how fast the cannabinoid will be cleared from your body (and subsequently how long you feel the effects).[348]

The following CYP enzymes are relevant to cannabinoid metabolism. These enzymes determine how quickly your body can metabolize and eliminate cannabinoids, how effectively cannabinoids can penetrate the brain-brain

barrier, and how sensitive or tolerant you might be to the effects of cannabinoids:

CYP3A4

The CYP3A family is the most abundant subfamily of the CYP enzymes in the liver. There are at least four variants, including 3A4, 3A5, 3A7, and 3A43. CY3A4—which is highly concentrated in the liver and small intestine—is the most important of the 3A family, as it contributes to bile acid detoxification, metabolism of steroid hormones, and elimination of chemicals in food and most medicines.[349] Women seem to have higher levels of CYP3A4 activity than men, with some data suggesting twice the levels of CYP3A4 enzymes in female tissue samples as compared to male samples.[350] Genetics, gender, food, supplements, and drugs can all affect CYP3A4 metabolism.[351] [352] [353] For example, grapefruit is a potent inhibitor of intestinal CYP3A4 and can adversely interact with multiple medications.[354]

CYP3A4 metabolizes Δ9-THC and CBD.[355] CYP3A4 inhibitors can increase Δ9-THC and CBD plasma levels and can dramatically increase 11-OH-THC plasma levels and cause adverse effects.[356] The CYP3A4 variant *22 eliminates cannabinoids less efficiently. People with this allele will experience stronger effects and longer durations of action when using cannabis. [357]

Research[358] [359] suggests that cannabinoids do not influence CYP3A4 activity, though CBD and some terpenes might be weak inhibitors.[360] [361]

CYP2C9

CYP2C9 is the primary enzyme responsible for the metabolism of approximately 100 therapeutic drugs, including blood thinners and some nonsteroidal anti-inflammatory drugs.[362] While this enzyme metabolizes both Δ9-THC and CBD, it is the primary enzyme for the metabolism of Δ9-THC into 11-OH-THC.[363]

Over 70 variant alleles have been identified for CYP2C9.[364] Many of these polymorphisms are associated with reduced enzyme activity and CYP2CP allele variants typically demonstrate decreased drug metabolism. [365] Of these alleles, the CYP2C9*2 and CYP2C9*3 variants have been most well-studied because of their effect on warfarin metabolism (warfarin is a medication that is commonly prescribed as a blood thinner to treat blood clots and to help prevent stroke in people who have cardiovascular disease).
In one clinical study, subjects were administered a 15mg oral dose of Δ9-THC. Subjects who had two copies of the CYP2C9*3 variant had Δ9-THC plasma levels

that were 3 times higher than subjects who had two copies of the most common variant CYP2C9*1. Subjects with one copy of CYP2C9*3 and one copy of CYP2C9*1 had Δ9-THC plasma levels that were 2 times as high as subjects with two copies of CYP2C9*1.[366] The decreased enzyme activity of subjects with the CYP2C9*3 variant will likely be more sensitive to the effects of Δ9-THC.

Research suggests that Δ9-THC, CBD, and CBN are all potent inhibitors of CYP2C9 activity.[367] [368]

CYP2C19

CYP2C19 is the primary enzyme responsible for the metabolism of approximately 10% of prescription medications, including medications prescribed to treat ulcers, seizures, malaria, and anxiety. The CYP2C19 enzyme metabolizes both Δ9-THC and CBD.

Approximately 40 variant alleles have been identified for CYP2C19.[369] For example, the CYP2C19*2 and *3 variants are associated with diminished enzyme activity and the CYP2C19*17 is associated with increased activity. The CYP2C19*2 and *3 variants are significantly higher in Chinese populations than in European or African populations.[370]

Research suggests that CBD is a potent inhibitor of CYP2C19 activity.[371] [372]

CPY1A2

CYP1A2 is partly responsible for the metabolism of cholesterol, steroids, and lipids.[373] Approximately 13 variant alleles have been identified for CYP1A2.[374] This enzyme does not metabolize CBD or Δ9-THC but remains relevant in ECS activity. For example, research suggests that CBD is a potent inhibitor of CPY1A2 activity.[375] And, while research suggests that Δ9-THC might also inhibit CYP1A2 activity,[376] combusting and inhaling cannabis flower (or any organic material) likely *induces* CYP1A2 activity. For example, clinicians monitoring subjects who are attempting to quit tobacco smoking have identified rapid downregulation of CYP1A enzymes in these subjects.[377] [378]

Keywords: *polymorphism* refers to two or more possibilities of a trait (the trait is sometimes referred to as an *allele*) on a gene and accounts for genetic variation. For example, blood type in humans can vary depending on which allele occurs at a specific position in the genome.

Drug Transporters

The human body has evolved to promote mechanisms that prevent foreign substances from breaching cell membranes and also from reaching the brain, and this mechanism is facilitated via drug transporters. Drug transporters are proteins that help move drugs from the inside of a cell membrane to the outside of a cell membrane. They influence the amount of a drug that is absorbed from the gastrointestinal tract and distributed into tissues, and they can limit the amount of a drug that crosses the blood-brain barrier. The blood-brain barrier (BBB) protects neurons and limits access of drugs to the brain. Drug transporters in the BBB pump drugs and toxins back into the blood.[379]

P-glycoprotein (PGP) is one of the most important drug transporters and can control the penetration and the duration of effects of a drug. PGP is a transmembrane protein that is called an efflux transporter—efflux transporters push molecules out of cells. Efflux transporters were discovered in the 20th century during the development of chemotherapy and anti-tumor agents. Because PGP was discovered during chemotherapy research and development, PGP is also referred to MDR1 (multidrug resistance protein 1).[380]

PGP is concentrated in the gut lumen. When a drug diffuses into the cells lining the gut lumen, PGP can bounce the drug back into the lumen so that the body can subsequently eliminate the substance. PGP proteins are also concentrated in the liver, kidneys, and at the blood brain barrier, where the PGP attempts to keep foreign substances away from the brain and the central nervous system.[381]

PGP proteins recognize a wide range of molecules, but there are some substances that PGP proteins do not recognize. PGP proteins recognize hydrophobic molecules more efficiently than hydrophilic molecules. Molecules can be defined as a substrate of PGP, meaning that the molecule has a high affinity for PGP and will likely bind to PGP and be transported out of cells (if this molecule were a drug, for example, high affinity with PGP would make the drug less effective); molecules can also be modulators of PGP binding, meaning that they might allosterically inhibit or induce function; or a molecule can be defined as an inhibitor, interfering with PGP bind. Often, drugs that modulate the cytochrome P450 enzyme CYP3A4 will also have the same effect on PGG—for example, inhibitors at CYP3A4 will also inhibit PGP.[382]

Research in animal models suggest that some drug transporters are inhibited by multiple cannabinoids. This research[383] [384]suggests that CBD is the most potent inhibitor, followed by CBN and Δ9-THC.[385] One review[386] suggested that

concentrations of cannabinoids used in several animal studies are much higher than the concentrations measured in most cannabis smokers and the results might not be applicable.

A study[387] in mice is a good example of how PGP can limit the concentrations of Δ9-THC in the brain and impact the duration of the effects of Δ9-THC. In this study, mice were genetically modified so that they did not have any PGP proteins. These mice were administered Δ9-THC and researchers compared the concentration of Δ9-THC in the brain compared to normal mice. In the normal mice, the concentrations of Δ9-THC in the brain began to decline 1 hour after administration and were close to normal at 3 hours. The concentrations of Δ9-THC in the brain of the genetically modified mice continued to climb up to two hours after administration and were more than twice as high at 3 hours compared to the normal mice.

In humans, genetic variants of PGP and other drug transporters can determine how sensitive a person will be to cannabis, how long they feel the effects of cannabis, and whether they are at greater risk of cannabis dependence.[388] Interestingly, people who have greater expression of PGP proteins (meaning that the concentration of Δ9-THC would be lower in the brain and the effects would be shorter) are associated with higher rates of dependence.[389]

Cannabinoid Metabolism

When ingested, cannabinoids are mostly metabolized in the liver by the cytochrome P450 enzymes:

- Δ9-THC is mostly metabolized by CYP2C9 and CYP3A4. CYP2CP is the enzyme primarily responsible for converting Δ9-THC into 11-hydroxy-THC (11-OH-THC) and then into 11-carboxy-THC (11-COOH-THC). [390] 11-OH-THC is a metabolite that is more potent and longer lasting than Δ9-THC. Outside of the liver, Δ9-THC metabolism occurs in tissues that also express CYP enzymes, including the small intestine and the brain. [391] Some long-term storage of Δ9-THC occurs in body fat.
- CBD is metabolized in the liver by the CYP enzymes, mostly by CYP2C19 and CYP3A4, and is converted to 7-hydroxy-cannabidiol (7-OH-CBD). [392]
- CBN undergoes a metabolism that is similar to that of Δ9-THC (CBN is metabolized by CYP2C9 and CYP3A4).[393] CBN, however, contains one additional aromatic ring and is metabolized less extensively and more slowly than Δ9-THC. Liver metabolism converts CBN into 11-OH-CBN and

this metabolite has greater binding affinity at CB_1, which suggests that CBN might contribute to the pharmacological effects of cannabis.[394]

- Δ8-THC is likely metabolized by the same enzymes that are most involved in Δ9-THC metabolism: CYP2C9 and CYP3A4.[395] Δ8-THC has two known metabolites: 11-OH-delta 8-THC and 11-oxo-delta 8-THC.

Fatty Acid Amide Hydrolase

Fatty Acid Amide Hydrolase (FAAH) is an enzyme that metabolizes the endogenous cannabinoid anandamide, which makes FAAH an interesting target for novel therapeutic drugs. Inhibiting FAAH can potentiate anandamide signaling and produce the positive effects of CB_1 and CB_2 activation. In fact, there exists a case report about a Scottish woman with a genetic mutation in a FAAH gene which contributed to unusually high levels anandamide in her system. She reportedly has been immune to anxiety and fear and insensitive to pain for her entire life.[396]

In studies evaluating the combined effects of CBD and Δ9-THC, some of the positive effects of CBD were reversed by CB_1 receptor inverse agonists or were absent in CB_1 receptor knockout mice. This data suggests that CBD is an indirect agonist at CB_1 receptors and can somehow augment CB_1 activity.[397] Research from animal models suggested that CBD can inhibit FAAH and might subsequently potentiate anandamide, indicating that CBD inhibition of FAAH might be the source of the CB_1 indirect agonism. Additional research suggested, however, that while CBD is effective for inhibiting FAAH in rodents, it does not inhibit FAAH in humans).[398]

Fatty acid binding proteins (FABPs) facilitate the removal of endocannabinoids by moving them from the cell membrane to the enzymes that metabolize them. Researchers suggested that at least three human FABPs bind to Δ9-THC and CBD and that Δ9-THC and CBD can inhibit the metabolism of endocannabinoids by competitively binding at FABPs. This mechanism might describe why phytocannabinoids raise endocannabinoid levels.[399] [400]

Elimination

Complete elimination of cannabinoid metabolites occurs over several days through a slow re-diffusion of cannabinoids from body fat and other tissues, with approximately 20% to 35% eliminated in urine and 65% to 80% eliminated in feces,[401] [402] [403] [404] with nearly 90% excreted within five days.

However, residual levels of cannabinoids remain in the body for some time in long-term users. For example, the half-life of Δ9-THC for infrequent user is 1.3 days and 5-13 days for frequent users. After inhalation, the metabolite 11-carboxy-THC (11-COOH-THC) can be detectable in plasma for as long as one week.[405]

In a perinatal setting, Δ9-THC is able to cross the placenta [406] and is excreted in human breast milk.[407] While synthetic and phytocannabinoids distribute into the breast milk of lactating mothers, it should also be noted that significant amounts of endocannabinoids are naturally produced in breast milk.[408]

CBD also has a long half-life. The average half-life following intravenous dosing is approximately 24 hours. The half-life following inhalation is approximately 31 hours. The half-life of CBD following repeated daily oral administration can range from 2 to 5 days. [409]

Cannabinoid Pharmacodynamics

Pharmacodynamics is the study of what a drug does to the body. The response of an organism to a drug depends on the drug binding to its target and the concentration of the drug at the receptor site. Of course, additional factors can also influence the effects of a drug on an organism. For example, some diseases can change receptor binding, alter the number of binding ligands and decrease receptor sensitivity. Furthermore, aging can affect pharmacodynamic responses through alterations in receptor binding or in postreceptor response sensitivity. Finally, combinations of other drugs and subsequent interactions result in competition for receptor binding sites or alter postreceptor response.

Cannabinoid-Influenced Cell Receptors

The effect of a cannabinoid can depend on the receptor to which it binds, or by whether the cannabinoid is inhibiting an excitatory neurotransmitter like glutamate or whether the cannabinoid is inhibiting an inhibitory neurotransmitter, like GABA. For example, when Δ9-THC binds to CB_1 receptors in the brain it can produce a pharmacodynamic effect that is different than the effect it has when it binds to the CB_2 receptor. Moreover, the concentration of the cannabinoid can also influence the pharmacodynamic effect. Researchers conducting a study intending the measure the effects of Δ9-THC on stress suggested that a low dose of Δ9-THC can be anxiolytic, but higher doses might exacerbate negative feelings.[410] This biphasic effect at the CB_1 receptor is likely

due to the influence of Δ9-THC on other inhibitory and excitatory neurotransmitters.

This section discusses receptor families that are assumed to be critical to the endocannabinoid system, and it discusses how cannabinoids interact with these receptor families. The list of receptors is certainly not exhaustive—new receptors and ligands continue to be discovered and these relationships remain an exciting area of research.

CB_1 Receptors

CB_1 receptors are G protein-coupled receptors located mostly in the central and peripheral nervous system,[411] [412] but also in the immune system (in the bone marrow, thymus, spleen, tonsils) and in the heart, lungs, adrenals, kidneys, liver, colon, prostate, pancreas, testes, ovaries, and placenta.[413] In the brain, CB_1 receptors are concentrated in regions associated with the behaviors that the receptors influence. For example, CB_1 receptors help regulate appetite (through receptors in the hypothalamus), influence memory and emotional processing (through receptors in the amygdala), and mediate sensation to pain (through receptors in nerve endings).

CB_1 receptors can be activated by endocannabinoids (for example, by anandamide and 2-AG), by phytocannabinoids, and by synthetic cannabinoids, and are responsible for the psychoactive effects of Δ9-THC and for many therapeutic effects of cannabis. The Δ9-THC metabolite, 11-hydroxy-THC, interacts more efficiently than Δ9-THC at CB_1 receptors.[414] There are very few CB_1 receptors in the brainstem or in the cardiorespiratory centers, which accounts for the absence of a lethal dose with cannabis. [415] Δ8-THC is a partial agonist at CB_1.[416] Studies suggest that CB_1 receptor *activation* helps mediate:

- Anxiety and stress[417]
- Pain and inflammation[418]
- Symptoms related to multiple sclerosis [419] [420]
- Neurodegenerative disorders[421]
- Post-traumatic stress[422]
- Depression[423]
- Intestinal inflammation[424]
- Blood pressure[425]

In human skin, CB_1 receptors are expressed in keratinocytes in epidermal layers, hair follicle cells, sebaceous glands, sensory neurons, and immune cells.[426]

Because CB_1 activation reduces the expression of keratins, CB_1 activation might help address:

- Psoriasis, a condition where keratin expression is upregulated[427]
- Pain, through modulation of sensory neurons[428]
- And inflammation, by modulating keratinocyte cytokine production and by modulating immune cells[429]

CB_1 receptor *antagonists* and *inverse agonists* have been studied for the treatment of obesity as an adjunct to diet and exercise,[430] for liver fibrosis,[431] and nicotine addiction.[432] Research suggests that a hyperactive endocannabinoid system (levels of endocannabinoids chronically raised above healthy levels) contributes to obesity, a significant and widespread global disease. As CB_1 receptor activation can stimulate appetite, blocking these receptors might produce a decreased appetite. Driven largely by the search for an effective treatment for metabolic syndrome and obesity, most CB_1 research has focused on decreased consumption and satiety research. CB_1 receptor antagonists or inverse agonists might help bring raised endocannabinoid levels back into a healthy range.

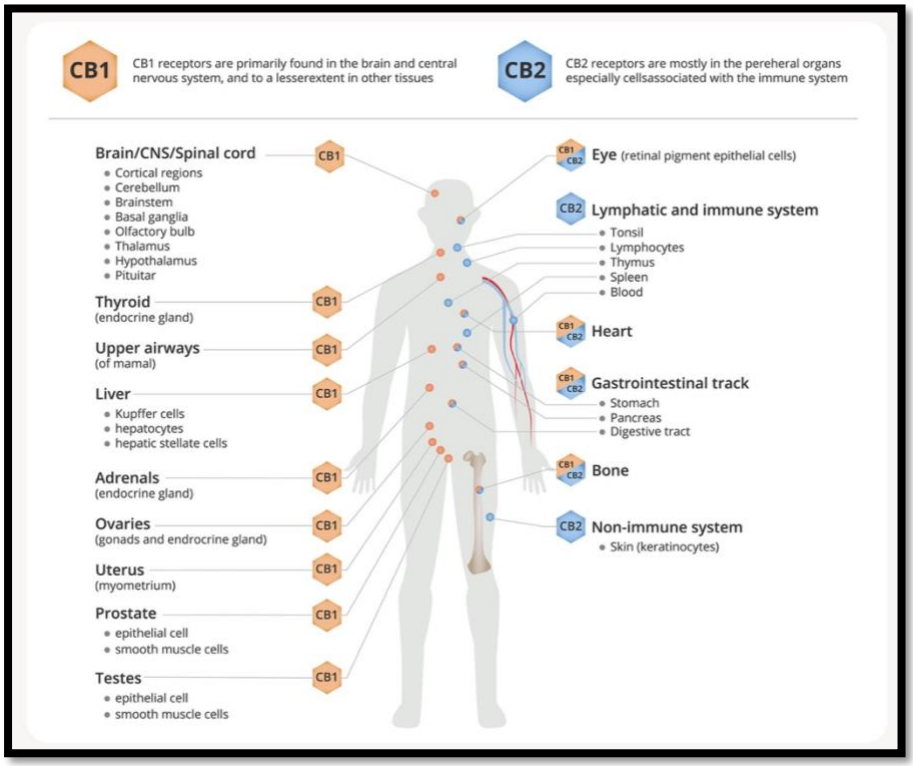
Rimonabant was one of the first CB_1 inverse agonists developed to treat obesity. Rimonabant was first approved in Europe in 2006 but was withdrawn in 2008 due to serious psychiatric side effects. Rimonabant and other similar ligands were never approved in the United States due to concerns about increased anxiety, depression, and suicidal ideation [433] (further highlighting these concerns, mice bred without CB_1 receptors demonstrated increased morbidity, premature mortality, age-related neuron loss, higher probability of epilepsy, and exhibited aggressive, anxious, and depressive behaviors).[434]

In 2018, one inverse agonist (Drinabant) was licensed by Opiant Pharmaceuticals, which intends to develop it for the treatment of acute cannabinoid overdose as an injectable for administration in an emergency department setting.[435]

CB_1 receptors exist on glutamatergic neurons and GABAergic neurons. Consequently, the activation of CB_1 receptors on these neurons can inhibit the release of the neurotransmitters glutamate and GABA. Glutamate is an excitatory neurotransmitter and can produce anxiety, and GABA is an inhibitory neurotransmitter than can quell anxiety.

Some research[436] suggests that CB_1 receptors might be more susceptible to activation on glutamatergic neurons than on GABAergic neurons. At low

concentrations, CB_1 agonists might only activate the CB_1 receptors on glutamatergic neurons, which can subsequently reduce glutamate and anxiety. At high concentrations, CB_1 agonists might activate CB_1 receptors on GABAergic neurons, which reduces GABA release, subsequently increases glutamate levels, and might increase anxiety.[437] This research might help explain some of the biphasic dosing effects of Δ9-THC, especially as related to anxiety.



CB_2 Receptors

CB_2 receptors are G protein-coupled receptors located in the brain and in the peripheral nervous system,[438] but concentrated in the peripheral immune cells[439] (for example, in the bone marrow, thymus, spleen, and tonsils).[440] CB_2 receptors are also located in the uterus, lungs, microglia, and brainstem neurons.[441] The number of available CB_2 receptors increases significantly during inflammation, and CB_2 receptor activation does not produce the psychoactivity

associated with CB_1 receptor activation.[442] Studies suggest that CB_2 receptor activation helps mediate:

- Inflammation[443] [444]
- Neuroprotection, especially in Alzheimer's disease,[445] Parkinson's disease,[446] [447] Huntington's disease,[448] [449] and multiple sclerosis[450]
- Addiction and drug-seeking behaviors[451]
- Depression[452]
- Bipolar disorder[453]
- Schizophrenia[454] [455]
- Alcoholism[456]
- And eating disorders[457]

In the human skin, CB_2 receptors are expressed in keratinocytes, sebaceous glands, sensory neurons, and in immune cells. [458]

GPR18 and GPR55 Receptors

In biochemistry, orphan receptors refer to receptors for which no endogenous ligand has been identified (in other words, researchers discovered a receptor before understanding what molecules bind to the receptor). When orphan receptors are detected, they are typically named with *GPR* (*G P*rotein *R*eceptor) followed by a number. In the G protein-coupled receptor family, there are approximately 100 orphan receptors. When endogenous ligands are discovered, the orphan receptors are considered *adopted*. [459] Two important adopted GPR receptors that are modulated by the endocannabinoid system are GPR18 and GPR55. In fact, some researchers have proposed that GPR18 and GPR55 are, in fact, novel cannabinoid receptors.[460]

GPR18 Receptors

GPR18 receptors (these receptors are sometimes referred to as N-arachidonyl glycine receptors, or *NAGly receptors*) are located in the testis, gastrointestinal tract, brain, white blood cells, and lymph nodes. This receptor is activated by N-arachidonoylglycine, which is created during anandamide metabolization.[461]

The expression of GPR18 receptors in white blood cells suggests that these receptors influence immune system activity and activation of these receptors likely helps reduce inflammation. [462] There is also evidence that activation of GPR18 lowers intraocular pressure (IOP). For example, in one rodent

study, researchers noted that Δ9-THC lowers IOP by activating both CB_1 and GPR18 receptors (interestingly, this effect was much more pronounced in the male mice).[463] Finally, GPR18 might also reduce the transmission of pain signals and might help alleviate pain.[464]

Keywords: *White blood cells* help protect against infectious disease and foreign invaders. All white blood cells are produced in the bone marrow.

The expression of GPR18 receptors in the brain, especially in microglial cells, suggests that activation of GPR18 receptors might help treat neurodegenerative disorders. [465] Microglia cells are the brain's immune cells that protect the brain against injury and disease by removing toxic agents and dead cells. In neurodegenerative disorders such as Alzheimer's disease, however, microglia cells can become hyperactivated and can promote neuroinflammation. This inflammation promotes the toxic protein deposits of amyloid plaques. The modulation of GPR18 might contribute to the management of neuroinflammation.[466]

GPR55 Receptor

GPR55 receptors are located in the brain, gastrointestinal tract, pancreas, and adipose tissue (body fat).[467] L-α-lysophosphatidylinositol (LPI) is the endogenous ligand that binds to GPR55.[468] GPR55 receptor activation has been associated with cancer cell proliferation and disease progression,[469] [470] inflammation, and certain types of pain.[471] For example, mice genetically bred without GPR55 receptors demonstrated lower levels of inflammation, inflammation-induced pain, and neuropathic pain after nerve constriction.[472]

Although the study of GPR55 seems uniquely difficult, some data suggest that CBD is an antagonist of GPR55.[473] If CBD does inhibit GPR55 signaling, it might provide a non-cannabinoid receptor mechanism to explain specific therapeutic effects of CBD. For example, CBD might reduce seizures by blocking the activity of GPR55 in the hippocampus.[474] And, inhibition of GPR might also explain CBD's anti-tumor effects in colorectal cancer, [475] breast cancer,[476] pancreatic cancer,[477] and brain cancer.[478] Finally, GPR modulation might also help explain how CBD can reduce gastrointestinal inflammation in conditions such as inflammatory bowel disease, Crohn's disease, and ulcerative colitis.[479] [480]

5-HT Receptors

Most receptors in the 5-HT receptor family are G protein-coupled receptors that are typically activated by the neurotransmitter serotonin (*5-HT* is an abbreviation for 5-hydroxy-tryptamine) and are collectively referred to as the serotonin receptors. 5-HT receptors can influence aggression, anxiety, appetite, cognition, learning, memory, mood, nausea, sleep, and internal body temperature (also referred to as *thermoregulation*).[481]

Serotonin receptors are pharmaceutical targets of multiple neuropsychiatric disorders and gut-related disease. In fact, 5-HT receptors are largely concentrated in gastrointestinal tract, where they help regulate intestinal motility. [482] Also, these receptors are targets of hallucinogens and many prescription medications, such as antidepressants, antipsychotics, anti-migraines, and anti-emetics. There are seven distinct families of 5-HT receptors, and most of the 5-HT families have subtypes.

5-HT_{1A} Receptors

5-HT_{1A} receptors are one of five subtypes of the 5-HT_1 family and are the most widespread of all 5-HT receptors. These receptors are located in high densities in the central nervous system. 5-HT_{1A} receptor activation can decrease blood pressure, heart rate, and body temperature.[483] Additionally, 5-HT_{1A} receptor agonists can help relieve anxiety, depression, nausea, and pain.[484] [485] [486]

Mice bred without 5-HT_{1A} receptors demonstrated an increase in anxiety behaviors and clinical studies suggest that patients with panic disorders have impaired 5-HT_{1A} receptor function. [487] [488] [489] 5-HT_{1A} receptor activation might also improve symptoms of schizophrenia and Parkinson's disease.[490] [491] [492] [493]

Research in animal models suggests that CBD activation of the 5-HT_{1A} receptors can help mitigate liver damage, anxiety, depression, pain, and nausea.[494] CBDA is a potent 5-HT_{1A} receptor agonist and has demonstrated efficacy for the treatment of nausea and vomiting, especially anticipatory nausea, for which there exists no current treatment. Anticipatory nausea is a condition of psychological nausea and vomiting and is believed to be a learned response to chemotherapy. This condition appears to link psychological, neurological, and physiological systems.[495] [496]

5-HT_{2A} Receptors

5-HT_{2A} receptors are one of three subtypes of the 5-HT_2 family, are distributed throughout the central nervous system, and are concentrated in the

learning and cognition centers of the brain. [497] Extensive preclinical and clinical data demonstrates that 5-HT_{2A} activation produces hallucinatory experiences.[498] For example, LSD and psilocybin are both 5-HT_{2A} receptor agonists (in fact, any substance that binds to 5-HT_{2A} receptors as an agonist or partial agonist is considered a psychedelic).[499]

Preclinical studies suggest that 5-HT_{2A} receptor *antagonists* can produce antipsychotic, antidepressant, and anxiolytic effects. [500] Conversely, more recent studies suggest that 5-HT_{2A} receptor *agonists* might provide novel therapeutic approaches to treating depression, anxiety, and post-traumatic stress. [501] Despite the recent stigma associated with hallucinogens, these substances are now being studied for the effective treatment of emotional and mental disorders.[502]

Impaired function of 5-HT_{2A} receptors is associated with schizophrenia, Alzheimer's disease, depression, anxiety, and drug addiction.[503] [504] For example, suicidal and depressed patients have more 5-HT_{2A} receptors than normal patients[505] and selective serotonin reuptake inhibitors (SSRIs) and classical antipsychotics attempt to block these receptors.

CBD seems to have some affinity for 5-HT_{2A} as a weak partial agonist, and the effect of CBD on this receptor is not fully understood. Additionally, the manner in which Δ9-THC interacts with 5-HT_{2A} receptors remains unclear. One current hypothesis is that CB_1 receptors can combine with 5-HT_{2A} receptors to form heterodimers,[506] which suggests that chronic exposure to cannabinoid receptor agonists might increase the expression of 5-HT_{2A} receptors in the brain and produce higher than normal levels of signaling. Researchers suggest that this cannabinoid-induced upregulation of 5-HT_{2A} receptors might be the reason why chronic use of cannabis might promote earlier onset of some mental disorders in persons predisposed to those disorders.[507]

Keywords: *Heterodimers* and *homodimers* are created when two proteins—such as cell receptors—combine to form a single entity (heterodimers are made up of two different types of proteins, and homodimers are made up of the same kind of proteins). G-protein coupled receptors can form heterodimers and homodimers. For example, CB_1 receptors can sometimes become entangled and combine to form a single unit.[508] While the effects of dimerization are not yet fully understood, research does suggest that when two different types of receptors combine to form a single unit, they can produce unique effects that neither can do alone. [509]

5-HT_3 Receptors

5-HT_3 receptors are ionotropic receptors and are therefore structurally distinct from all other 5-HT family receptors. Activation of these receptors is associated with nausea, vomiting, seizures, pain, and mood disorders.[510] Δ9-THC, CBD, and anandamide are all potent negative allosteric modulators of 5-HT_{3A} receptors, and 5-HT_{3A} antagonists can help treat chemotherapy-induced nausea and vomiting.[511] Interestingly, alcohol is a positive allosteric modulator of 5-HT_{3A} receptors, which might help explain why, in large concentrations, alcohol can promote nausea and vomiting. [512]

> **Keywords:** When neurotransmitters attach to *ionotropic* receptors, a channel opens in the receptor and allows ions to flow into the cell. These ions increase or decrease the probability that an action potential will fire in the cell and carry and signal to the next cell.

Dopamine Receptors

Dopamine receptors are G protein-coupled receptors that are concentrated in the central nervous system. The neurotransmitter dopamine is an endogenous ligand for dopamine receptors. The dopamine neurotransmitter is integral to the brain's reward system and is released in response to pleasurable stimuli. For example, the brain produces dopamine when we eat, sleep, procreate, and exercise. Activation of dopamine receptors can affect motivation, pleasure, cognition, memory, and learning. [513] Disfunction of dopamine receptor signaling can contribute to neuropsychiatric and neurodegenerative disorders, including Parkinson's disease, drug addiction, compulsive behavior, attention-deficit and hyperactivity disorder, and schizophrenia.[514] Consequently, dopamine receptors are common prescription drug targets.[515]

The relationship between cannabinoids and dopamine release is complex. Cannabinoids do not directly bind to dopamine receptors, but some cannabinoids do seem to influence dopamine release. In fact, the endocannabinoid system seems to modulate the release of dopamine, and cannabinoid receptor modulation appears to impact dopamine function. Consequently, cannabinoid receptor agonists—such as Δ9-THC —influence dopamine differently than cannabinoids with little affinity for CB_1 and CB_2—such as CBD.[516]

The effects of Δ9-THC on dopamine suggest a biphasic effect. Short-term, acute use of Δ9-THC produces increases in dopamine release, while long-term, chronic use inhibits dopamine release. [517]

The dopamine receptor D_2 is a subtype of one the two main families of dopamine receptors (D_1–like and D_2–like) and is also referred to as D2R. These are G protein-coupled receptors and act as the primary target for most antipsychotic drugs.

Drugs acting at D2R are commonly used to alleviate symptoms produced by Parkinson's disease, schizophrenia, and depression.[518] Antipsychotics are often prescribed for these diseases because they are potent partial agonists of D2R and can increase dopamine signaling.

CBD is also a potent partial agonist of D2R. D2R agonists can produce adverse effects that include GI distress (abdominal pain, diarrhea), dizziness, headache, and fatigue.[519]

Adenosine Receptors

Adenosine receptors are G protein-coupled receptors that are concentrated in the central nervous system and throughout a variety of different types of tissue, including tissue in the cardiovascular system (where adenosine modulates vasoconstriction and vasodilation of veins and arteries).[520] The neurotransmitter adenosine is an endogenous ligand for adenosine receptors.

There are four families of adenosine receptors: A_1, A_{2A}, A_{2B} and A_3. Adenosine receptor activation causes drowsiness and memory impairment.[521] Caffeine is the most common adenosine receptor antagonist—caffeine inhibits adenosine signaling and produces stimulating effects.

Δ9-THC and CBD do not bind directly to adenosine receptors, but they can influence adenosine receptor signaling. Δ9-THC and high doses of CBD can potently inhibit adenosine uptake, which enables adenosine to remain active longer and to activate more receptors.[522] Cannabinoids inhibit the reabsorption of adenosine by competitively binding to a glycoprotein drug transporter that carries the adenosine back into the cell.[523]

Adenosine agonists have anti-inflammatory effects, and adenosine uptake is the primary mechanism that terminates adenosine signaling. It's well established that cannabinoids also have anti-inflammatory effects,[524] [525] [526] [527] and some of these effects are mediated by the CB_2 receptor. CBD, however, binds weakly (if at all) to CB_2. By inhibiting adenosine uptake, CBD enhances

endogenous adenosine signaling and suggests a non-cannabinoid receptor mechanism by which CBD can decrease inflammation.

Some research suggests that adenosine receptor A_{2A} antagonists might help mitigate the memory deficit adverse effects of chronic CB_1 activation. For example, researchers disrupted recognition memory with a synthetic cannabinoid CB_1 agonist but were able to reverse the effect by concurrently administering an A_{2A} receptor antagonists.[528] While older research contradicts this conclusion (for example, one study in rats suggested that using caffeine—a potent adenosine receptor antagonist—together with Δ9-THC would impair memory more than Δ9-THC alone[529]), more recent research seems to support the hypothesis that A_{2A} receptor antagonists should mitigate the adverse effects of CB_1 agonists. For example, the National Institute on Drug Abuse (NIDA) Intramural Research Program (IRP) used a computational model to determine that adenosine A_{2A} receptor antagonists should counteract some of the adverse effects of cannabinoids.[530]

Glycine Receptors

Glycine receptors are ionotropic receptors that are concentrated in the brain, brainstem, and spinal cord and help regulate motor control and pain perception. [531] These receptors appear early in brain development and possibly influence the development of the brain and central nervous system.[532] The neurotransmitter glycine is an endogenous ligand for glycine receptors, though the receptor can also be activated by several simple amino acids. Strychnine has high-binding affinity for glycine receptors and is a potent antagonist. Ethanol is a positive allosteric modulator at glycine receptors.[533] Caffeine is also and antagonist.

Glycine receptors are among the most widely distributed inhibitory receptors in the central nervous system and mediate inhibitory neurotransmission in the spinal cord and brainstem. [534] Glycine receptor dysfunction is associated with neuromotor deficiencies (for example, hyperekplexia and epilepsy) and chronic inflammatory pain. Glycine receptor activation promotes pain relief, but there exist few drugs that specifically activate glycine receptors.[535]

Research suggests that some of the analgesic properties of cannabinoids might be mediated through glycine receptors. Anandamide, Δ9-THC, and CBD are all positive allosteric modulators of glycine receptors.[536] [537] Studies in mice[538] [539] suggest that both Δ9-THC and CBD can potentiate glycine receptors (which helps

to inhibit transmission of pain signals) and help treat chronic pain and inflammation.[540]

GABA Receptors

GABA receptors are a class of receptors that respond to the neurotransmitter gamma-aminobutyric acid, also known as GABA. GABA is the main inhibitory neurotransmitter in the nervous system—it inhibits neurons from firing and initiating an action potential. There are two families of GABA receptors, $GABA_A$ and $GABA_B$.

GABAa receptors are ionotropic receptors and are the target for multiple types of prescription drugs, including barbiturates, benzodiazepines, and anticonvulsants. GABAa receptors also mediate the effects of alcohol. Drugs that target GABAa are usually agonists or positive allosteric modulators. Agonists and positive allosteric modulators increase the effects of GABA activation, producing anxiolytic, anticonvulsant, amnesic, sedative, hypnotic, euphoric, and muscle relaxing effects.[541] Antagonists and negative allosteric modulators produce the opposite effect and are not widely used as prescription medications. Flumazenil is an example of a negative allosteric modulator at GABAa, and it is used only to reverse an overdose of benzodiazepines.[542]

Endocannabinoids can modulate GABA activity. During excessive release of GABA, neurons synthesize 2-AG and anandamide and, via retrograde signaling, send these endocannabinoids across the synapse to the presynaptic neuron, where they bind to CB_1 and CB_2 receptors. This binding initiates a cascade of reactions that reduces GABA release.[543]

CBD is a positive allosteric modulator of $GABA_A$ and this mechanism might help explain CBD's anti-epileptic and anxiolytic properties.[544] Δ9-THC can also influence GABA signaling by inhibiting the uptake of GABA.[545] [546] Research from the mid-1970s suggests that CBG inhibits GABA uptake more efficiently than either Δ9-THC or CBD.[547]

TRP Receptors

Transient receptor potential (TRP, and pronounced as *trip*) channels are ion channels that mediate temperature, pressure, and pain sensation. TRP channel receptors are highly sensitive to chemical and physical stimuli, and they act as biological sensors critical to the functioning of our senses, including sight, touch, taste, hearing.[548] Human bodies can detect very subtle changes in ambient temperature (this sensation is referred to as *thermoreception*). TRP receptors

help to mediate the awareness of these changes. The range of temperatures that these channels can detect is broad, from painfully hot to excruciatingly cold.

Additionally, studies suggest that these channels might be potential targets for modulating immune response and for treating inflammatory disorders and some cancers (interactions among immune cells and cancer cells can largely influence tumor progression and disease outcomes).[549]

There are approximately 28 TRP channel families and subtypes, which are grouped into the following categories: TRPC (*canonical*), TRPV (*vanilloid*), TRPM (*melastatin*), TRPN (*no mechanoreceptor potential C*), TRPA (*ankyrin*), TRPP (*polycystic*), and TRPML (*mucolipin*).

TRPA1 Receptors

TRPA1 receptors detect pain, cold, and itch and are sensors for a large number of noxious chemicals found in plants, food, cosmetics and pollutants (TRPA1 is colloquially known as the Wasabi Receptor).[550] Additionally, these receptors can be triggered by internal pain signals from tissue damage and inflammation. When activated, TRPA1 receptors serve as protective mechanisms that trigger warning impulses in response to stimuli that can potentially cause injury.

TRPA1 antagonists are effective in blocking pain behaviors induced by inflammation. In animal models, CBG, CBC, CBD, CBN, and THCV are all potent TRPA1 *agonists* (THCV being the most potent; Δ9-THC is a weak agonist at TRPA1).[551] When activated, however, TRP channels can become rapidly desensitized and subsequently fail to respond any additional stimulation (in fact, receptor desensitization—which refers to decreased receptor responsiveness after repeated exposure to an agonist—is common among many membrane receptors). Consequently, some TRPA1 *antagonists* can also be effective in blocking pain behaviors induced by inflammation. Some research suggests that some of the analgesic, anti-inflammatory, and anti-cancer effects of cannabinoids are produced by TRPA1 activation and desensitization. [552]

TRPM8 Receptors

TRPM8 receptors are responsible for producing cold and cold pain sensations.[553] TRPM8 (TRP melastatin 8) is also sometimes referred to as the *cold and menthol receptor 1* (CMR1). This receptor is activated by chemical cooling agents (such as menthol) or when ambient temperatures drop below approximately 80 °F. Our bodies can perceive the cooling of temperatures even

when ambient temperatures drop as little as 2°F below normal body temperature. Ambient temperatures that drop below 60°F can elicit cold-related pain, which can feel like burning, aching, and prickling.[554]

TRPM8 antagonists might provide relief from pain hypersensitivity. CBG, THCv, Δ9-THC, and CBD are all potent antagonists of TRPM8.[555] [556] In addition to signaling associated with thermoreception, TRPM8 receptor expression in multiple tissues suggests additional biological roles. For example, TRPM8 is concentrated in the bladder and male genital tract, and receptor expression increases dramatically in prostate, breast, colon, lung, and skin cancers. [557] Research[558] suggests that CBG not only potently blocks TRPM8, but it also activates TRPA1, TRPV1, and TRPV2 receptors, and inhibits the reuptake of endocannabinoids. This study demonstrated that CBG inhibited colon cancer progression in vitro and in animal models and selectively inhibits the growth of colorectal cancer cells in a manner similar to other TRPM8 antagonists. Researchers stated that CBG should be considered for colorectal cancer prevention and cure.

TRPV1 Receptors

TRPV1 receptors are expressed in sensory neurons and in the brain, and they mediate pain and temperature sensation.[559] This receptor is commonly referred to as the capsaicin receptor (the molecule that makes chilies taste spicy) and helps detect noxious stimuli. In fact, TRPV1 receptors are activated by temperatures greater than 109 °F, by acidic conditions, by capsaicin, and by allyl isothiocyanate, which is a pungent compound in mustard and wasabi. The activation of TRPV1 produces a painful and burning sensation.

TRPV1 antagonists seem to help mitigate acute pain but are less effective at treating chronic pain. [560] TRPV1 agonists seem more effective at managing chronic pain through prolonged exposure and receptor desensitization. CBD, CBN, CBG, CBGv, and THCV are all TRPV1 agonists.[561]

TRPV1 receptors can also be activated proinflammatory cytokines, which are associated with pain and inflammation. Activation of TRPV1 by capsaicin, however, has been associated with anti-cancer effects.[562]

TRPV2 Receptors

TRPV2 receptors are similar to TRPV1 receptors in that the activation and desensitization of TRPV2 can help mediate inflammation and chronic pain and these receptors might be potential targets in the treatment of cancer,

inflammatory disease, and cardiovascular disease.[563] For example, TRPV2 activation might enhance the uptake and efficacy of chemotherapy in triple negative breast cancer (TNBC) patients. Triple negative breast cancer is an aggressive disease with limited therapeutic options. While chemotherapy remains the first line of treatment, TNBC is often resistant or unresponsive to chemotherapy.

All non-acid cannabinoids (except CBC and CBN) are potent agonists and can desensitize TRPV2.[564] [565] Additionally, CBD—by enhancing TRPV2 expression and activation—potentiates standard chemotherapeutic agents and might help mediate the progression of human glioblastoma cells.[566]

PPAR Receptors

PPARs (peroxisome proliferator activated receptors and pronounced as *pea pars*) are nuclear receptors that regulate the expression of genes that control sugar and fat metabolism, inflammation, and cancer. [567]PPARs are categorized in three subtypes: PPARα (alpha), PPARγ (gamma), and PPARδ (delta). PPAR receptor activation might have clinical relevance when treating:

- *Inflammation*: PPARα activation and PPARγ activation both inhibit inflammation.[568]
- *Cancer*: PPARγ activation is anti-proliferative and has induced tumor regression in human lung cancer cell lines. Conversely, some PPAR agonists can increase risk of cancer.[569]
- *Diabetes and obesity*: Two FDA-approved PPAR-activating classes of drugs—fibric acid derivatives and thiazolidinediones—are currently available for the treatment of obesity and type II diabetes. [570]
- *Neurodegenerative disorders:* PPARγ agonists have demonstrated efficacy when treating Parkinson's disease, Alzheimer's disease, brain injury, and ALS,[571] possibly because PPARγ activation degrades amyloid beta plaque in the brain.[572]
- *Schizophrenia*: some research demonstrates that increasing PPARα activation might help treat schizophrenia.[573] [574] PPARα activation is anti-inflammatory, decreases dopamine release, and might help minimize schizophrenic symptoms.

Several mechanisms to describe cannabinoid influence on PPARs have been proposed. For example, cannabinoids might directly bind to and activate PPAR receptors, or cannabinoid metabolites might activate PPARs. Some research

suggests that cannabinoids can be carried into the interior of a cell by fatty acid binding proteins and this mechanism might result in PPAR activation.[575] Regardless of the binding mechanism, cannabinoids can activate some types of PPARs and this influence might contribute to the neuroprotective, antinociceptive, antiproliferative, anti-inflammatory, and metabolic properties of cannabinoids. For example, Δ9-THC (in vitro and in animal models) activates PPARγ and this pathway might contribute to the antitumor effect of cannabinoids.[576] Also, CBD is a PPARγ agonist and might prove useful when treating Alzheimer's patients. Furthermore, some PPAR receptor agonists are metabolized by fatty acid amide hydrolase. CBD might promote PPARα signaling by inhibiting FAAH and subsequently increasing receptor agonist levels. This may help to explain how and why CBD has anti-psychotic effects. Cannabinoid modulation of PPAR might be a novel approach for treating cardiovascular and neurodegenerative disorders, cancer, diabetes, and obesity. [577]

Glutamate Receptors

The neurotransmitter glutamate is the most abundant excitatory neurotransmitter in the brain. When released, glutamate binds to glutamate receptors and potentiates neurons to initiate an action potential. Glutamate receptors can be ligand gated ion channels (ionotropic receptors) and G-protein coupled receptors (metabotropic receptors).[578]

Glutamate receptor activation (and neuronal excitation) is associated with learning and memory. Synaptic signaling among neurons and neuron plasticity is fundamental to learning and memory function. One type of ionotropic glutamate receptor called NMDA is one of the most important involved in learning and memory because of its role in information encoding. G-protein coupled glutamate receptors are also fundamental to memory, as they seem to be involved in retrieving and storing information.[579] While the production and release of glutamate is essential for healthy functioning, excessive levels of glutamate can produce toxic effects. Glutamate toxicity occurs when too much glutamate is released. This toxicity can destroy neurons and is associated with neurodegenerative disorders such as dementia and Alzheimer's disease, as well as mood and anxiety disorders.

Keywords: *Neuroplasticity* (or neuron plasticity) refers to the ability of neural networks in the brain to make new connections and to reorganize.

Plasticity enables us to learn from and adapt to different experiences and environments.

The impact of cannabinoids on glutamate is complex and not well elucidated. Recall that CB_1 receptors exist on glutamatergic neurons and on GABAergic neurons and that the activation of CB_1 receptors on these neurons can inhibit the release of the corresponding neurotransmitter. Glutamate is an excitatory neurotransmitter and can produce toxic effects when too much glutamate is released. Some research[580] suggests that CB_1 receptors might be more susceptible to activation on glutamatergic neurons than on GABAergic neurons. At low concentrations, CB_1 agonists (such as Δ9-THC) might only activate the CB_1 receptors on glutamatergic neurons, which can subsequently reduce glutamate release. At high concentrations, CB_1 agonists might activate CB_1 receptors on GABAergic neurons, which reduces GABA release, subsequently increases glutamate levels, and can promote glutamate toxicity.[581]

Low levels of glutamate can also contribute to disease and disorders. For example, NMDA receptor antagonists can induce psychotic symptoms, suggesting that dysfunctional glutamate release might be involved in the development of schizophrenia.[582] The results of a recent clinical trial support the use of CBD in the treatment of psychosis. In this study, participants were given a single dose of CBD (600mg), after which they were administered an MRI brain scan. Patients with psychosis and treated with CBD demonstrated an activation of specific brain areas that was similar to the activation observed in participants without psychosis.[583]

In fact, CBD can bind with multiple receptors that are involved in the regulation of glutamate, resulting in the both the suppression and potentiation of glutamate. For example, CBD potentiates glutamate release by binding to TRPV1 receptors. Conversely, CBD can inhibit glutamate release via 5-HT1A receptor agonism and via GPR55.[584]

Ligand and Receptor Binding Tables

The following tables provide information about how endocannabinoid and phytocannabinoid ligands bind with receptors modulated by the endocannabinoid system. Information missing from these tables represent gaps in the medical literature.

Table Key

	Shaded areas represent combinations with no verifiable data.
2-AG	2-Arachidonoylglycerol
AEA	N-arachidonoylethanolamine (Anandamide)
2-LG	2-Linoleoylglycerol
PEA	Palmitoylethanolamide
NADA	*N*-oleoyl dopamine
NAM	Negative Allosteric Modulator
PAM	Positive Allosteric Modulator

Endocannabinoids

Receptor	2-AG	AEA	2-LG	NADA	PEA
CB_1	Full Agonist[585]	Partial Agonist[586]	Partial Agonist[587]	Agonist[588]	
CB_2	Full Agonist[589]	Partial Agonist[590]		Agonist[591]	
GPR18	Partial Agonist[592]	Full Agonist[593] [594]			
GPR55	Partial Agonist[595]	Partial Agonist[596]		Agonist[597]	Agonist[598]
TRPV1	Agonist[599]	Agonist[600]		Agonist[601]	Agonist[602]
TRPV2	Agonist[603]	Agonist[604]			
TRPA1		Agonist[605]			
TRPM8	Antagonist [606]			Antagonist [607]	
$5\text{-}HT_{3A}$		NAM[608]			
Glycine	PAM[609]	PAM[610]			
PPARγ				Agonist[611]	
$GABA_A$	PAM[612]				

Phytocannabinoids

Receptor	Δ9-THC	CBD	CBN	THCv
CB_1	Partial Agonist[613]	NAM[614 615]	Weak Partial Agonist[616]	Antagonist[617] Agonist[618]
CB_2	Partial Agonist[619]	Weak Antagonist[620]	Weak Partial Agonist[621]	Partial Agonist[622]
GPR18	Full Agonist[623]	Antagonist[624]		
GPR55	Agonist[625]	Antagonist[626]		Weak agonist[627]
TRPV1	No effect[628]	Agonist[629]	Agonist[630]	Agonist[631]
TRPV2	Agonist[632]	Agonist[633]		Agonist[634]
TRPA1	Agonist[635]	Agonist[636]	Agonist[637]	Agonist[638]
TRPM8	Antagonist[639]	Antagonist[640]	Antagonist[641]	Antagonist[642]
$5\text{-}HT_{1A}$	No Effect	Full Agonist[643]		Agonist[644]
$5\text{-}HT_{2A}$		Partial Agonist[645]		
$5\text{-}HT_{3A}$	NAM[646]	NAM[647]		
Dopamine D2		Potent Partial Agonist[648]		
Adenosine	Inhibits Uptake[649]	Inhibits Uptake[650]		
Glycine	PAM[651]	PAM[652]		
PPARγ	Agonist[653]	Agonist[654]		
$GABA_A$		PAM[655]		
μ-opioid	Antagonist NAM[656]	NAM[657]		
δ-opioid	Antagonist NAM[658]	NAM[659]		

Receptor	CBG	THCA	CBC	Δ8-THC
CB_1	NAM[660]	No Effect[661]	Weak Partial Agonist[662]	Partial Agonist[663]
CB_2	Weak Partial Agonist[664]	No Effect[665]	Weak Partial Agonist[666]	Partial Agonist[667]
GPR18				
GPR55	Weak Antagonist[668]			
TRPV1	Agonist[669]			
TRPV2	Agonist[670]	Agonist[671]	Agonist[672]	
TRPA1	Agonist[673]	Agonist[674]	Agonist[675]	
TRPM8	Antagonist[676]	Antagonist[677]	Antagonist[678]	
$5\text{-}HT_{1A}$	Antagonist[679]			
Adenosine	Agonist[680]			

Downregulation and Upregulation

The cell's ability to respond to a specific signal is dependent on the number of receptors that can receive that specific signal—more receptors able to receive that message will facilitate the cell to respond to a specific signal. Receptors are created, or expressed, from instructions in the DNA of the cell, and receptors can be increased (or upregulated) when the signal is weak, or decreased (or downregulated) when the signal is too strong.

Downregulation of receptors can also occur when receptors have been chronically exposed to an excessive amount of a ligand, either from endogenous mediators or from exogenous drugs. This results in ligand-induced desensitization or internalization of that receptor.

For example, when exposed to high, chronic doses of cannabinoids, cannabinoid receptors can downregulate and become desensitized, producing a tolerance to cannabinoids. [681] This downregulation process occurs when a cell decreases the quantity of a receptor type in response to an external stimulus—the overstimulation of CB_1 receptors by Δ9-THC causes the CB_1 receptor to leave

the cell membrane and retreat back inside the cell. These internalized receptors are unavailable for binding, meaning that there are fewer receptors available.

G-protein couple receptor desensitization is facilitated by an uncoupling of the receptor from the associated G protein. Following desensitization, receptors are endocytosed into an intracellular compartment from which they can be recycled to the membrane (resensitization) or targeted for degradation leading to receptor downregulation. These processes can contribute directly to tolerance by decreasing the number of functional cell surface receptors. [682]

This tolerance can manifest differently in different areas of the brain. For example, downregulation and desensitization can occur more quickly in receptors concentrated in the hippocampus than in those concentrated in the basal ganglia. The hippocampus regulates memory and the basal ganglia regulates the euphoric effect of Δ9-THC—the difference might be the reason why memory loss decreases among frequent cannabis users, but euphoric effects remain consistent.[683]

Upregulation of receptors, on the other hand, can result in super-sensitized cells especially after repeated exposure to an antagonistic drug or prolonged absence of the ligand. Just as receptor *agonists* (especially full agonists) can cause downregulation of their respective receptors, receptor *antagonists* can temporarily upregulate their associated receptors. The disequilibrium caused by these changes can be responsible for tolerance and withdrawal when during the long-term use and discontinuation of any substance.

Chapter 6: Cannabis Testing

There are a number of diverse analytical methods and instruments available for testing cannabis samples, and these methods facilitate the identification, quantification, and purification of cannabinoids and other important compounds in a cannabis mixture. Cannabis testing includes the identification of cannabinoids, terpenes, toxins, and other compounds, and labs must rely on methods of detection *and* identification to ensure that products are safe to consume and that labels are accurate. Not only is identification important, but chemists must also measure the amounts of compounds in cannabis samples, especially the active ingredients, such Δ9-THC or CBD. Finally, some samples might require further testing of an isolated compound. Or, some products might require purification (during the manufacturing process) to remove specific compounds—for example, CBD-only products that initially contain small amounts of Δ9-THC would require purification by removing Δ9-THC. Identification, quantification, and purification are all essential facets of cannabis testing and manufacturing. Usually, combinations of multiple tools and processes are required to achieve all three.

Chromatography is a process that enables the physical separation of compounds by using a stationary phase and a mobile phase. Cannabis laboratories employ different types of chromatography to analyze compounds in cannabis samples, such as cannabinoids, terpenes, and toxins. Importantly, chemists can also use chromatography to isolate and purify cannabis compounds during manufacturing.

Thin layer chromatography (TLC) is a very common technique and is mostly used to quickly detect cannabinoids. TLC methods are less costly and easier to perform than other processes described below. TLC produces specific color indicators for different cannabinoids. While the intensity of the colors can provide data about quantification, this process is typically used for identification only.[684]

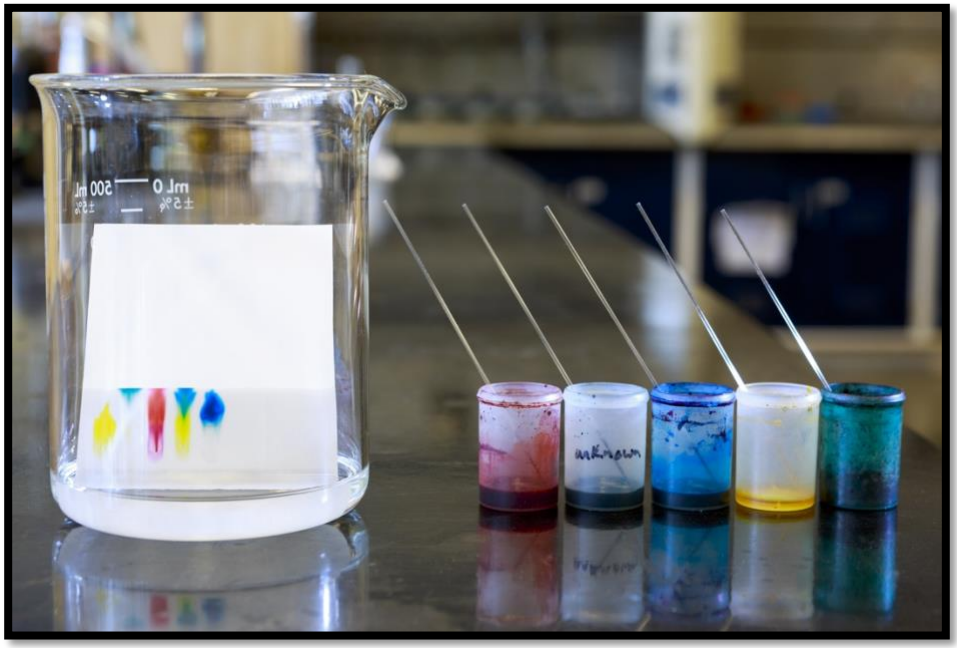


Figure 3 Thin Layer Chromatography

Gas chromatography (GC) coupled with mass spectrometry (*spectroscopy* is the study of the interaction of light and matter) has been the most widely used technique for detecting and separating cannabinoids, but this process has been largely replaced by other techniques because GC applies heat and causes decarboxylation of acidic cannabinoids.[685]

Chemists frequently use preparative liquid chromatography to purify single cannabinoids from raw extracts because this process enables the separation of each targeted compound based on the rate of elution of each compound. Then, using mass spectrometry, chemists can measure the molecular mass of the compounds to help identify them. The use of analytical high-performance liquid chromatography (HPLC) coupled with mass spectrometry (HPLC-MS) can enable chemists to establish cannabinoid profiles, potency (quantification of Δ9-THC and other cannabinoids), and to identify contaminants, such as molds, bacteria, or pesticides.

The expanding cannabis and hemp markets have necessitated the development of faster, more automated testing processes, such as nuclear

magnetic resonance spectroscopy (NMR).[686] Chemists can use NMR to determine the content, purity, and molecular structure of a cannabis sample.

Chromatography

Chromatography was developed in 1900 and was first used to separate diverse plant pigments, such as chlorophylls (green pigments), carotenes (orange pigments), and xanthophylls (yellow pigments). The term *chromatography* was later applied to this technique and is derived from two Greek words that translate as *writing in color*.[687]

Chromatography is now a technique used to separate compounds from a mixture. The mixture of compounds is dissolved into a substance—water, a solvent, a gas, and so forth—and is called the mobile phase because this mixture is passed through or over a second material that is fixed into position. This fixed material, referred to as the stationary phase, might be packed into a column or tube, applied to a glass plate, or applied to a piece of paper.

The compounds in the mixture can have unique affinities for the solvent used in the mobile phase or for the material fixed in the stationary phase. Some compounds might interact more closely with the molecules in the stationary phase, causing these compounds to stay attached to the stationary phase for longer periods. Other compounds might interact less with the molecules in the stationary phase, and these compounds would travel more quickly through the stationary phase. The difference among the compounds and the affinities for the material in the stationary phase cause the target compounds to separate over time. The rate at which the compounds travel through the stationary phase is called the *rate of elution*. Because different compounds will have different rates of elution, it's possible to distinguish and isolate compounds from a mixture.

For example, in a mobile phase comprised of an organic solvent (such as hexane), cannabinoids—which are highly lipophilic—would elute very quickly through a stationary phase made with silica gel (a hydrophilic substance). The lipophilic cannabinoids would closely interact with hexane and would not interact very much (if at all) with the silica. Some cannabinoids are more lipophilic than others, however. For example, CBD has 2 hydroxy groups and Δ9-THC includes only a single hydroxy group, suggesting that CBD is more water soluble than Δ9-THC and is therefore less lipophilic than Δ9-THC.[688] In this example with a lipophilic mobile phase, we can expect CBD to interact more with the stationary phase and elute more slowly than Δ9-THC. Applying chromatography to a

substance with both Δ9-THC and CBD can enable the separation and capture of these two similar compounds from a single mixture.

The purpose of separating the compounds can be *preparative* or *analytical*. In analytical chromatography, the purpose is simply to establish the presence of or to measure the amount of various substances in a mixture. This type of chromatography can be achieved with smaller amounts of raw material and is generally the type of chromatography used for performing the cannabinoid potency tests that produce the data compiled for a certificate of analysis.

In preparative chromatography, the target compounds are separated for use in a subsequent experiment or measurement that requires an isolated or purified target compound. Of course, both types chromatography can be applied to a single sample (assuming there is sufficient quantities of the sample).

In the cannabis space, many testing labs use high-performance liquid chromatography (HLPC) when performing analytical chromatography to test for the presence and the potencies of cannabinoids. Because there is no heat applied to a sample during HLPC testing, an analysis can include a more accurate account of the terpene and cannabinoid profiles, especially considering that acidic cannabinoids can degrade when heat is applied.[689]

Preparative HPLC chromatography enables the separation and isolation of compounds from a crude extract, an outcome similar to that of fractional distillation. In fractional distillation, an extract is heated to evaporate, condense, and then recapture specific compounds in the extract. Preparative HPLC chromatography can be a heatless alternative to fractional distillation. Cannabis companies might employ preparative chromatography, for example, if they intend to remove Δ9-THC from an extract to produce a broad-spectrum product—one that includes an array of cannabinoids and terpenes but that excludes (typically) Δ9-THC. The stationary phase can include a material that binds to different cannabinoids with a range of binding affinities, facilitating a range of elution rates such that each cannabinoid can be individually captured and then either recombined with or excluded from the final concentration.[690] And, in addition to isolating and separating plant compounds, preparative chromatography can also remove residual solvents.[691]

Because cannabinoids are lipophilic, reverse-phase chromatography can be used effectively to separate and purify cannabinoids, especially when separating Δ9-THC from CBD. In reverse-phase chromatography, the stationary phase is lipophilic and the mobile phase is hydrophilic. In this process, compounds

that are more hydrophilic elute more quickly. And, of course, multiple solvents can be used at various concentrations to refine the process.

Mass Spectrometry

Chemists can use mass spectrometry to measure the molecular mass of compounds, which enables the chemists to help identify them. *Atomic* mass is a measurement of the mass of a single atom of an element and is comprised of the combined mass of protons, neutrons, and electrons. *Molecular* mass is the sum of the atomic mass of all atoms in a molecule—the protons, neutrons, and electrons. Because the mass of electrons is negligible, we can assume that the molecular weight is equal to only the sum of all protons and neutrons of all atoms in a molecule. Typically, the unit of measure that describes atomic mass is atomic mass units (amu) and the unit of measure that describes molecular mass is Daltons (Da).[692]

For example, to determine the molecular mass of Δ9-THC, CBD, and anandamide, we must first obtain the molecular formula of each:

- Δ9-THC[693] = $C_{21}H_{30}O_2$
- CBD[694] = $C_{21}H_{30}O_2$
- Anandamide[695] = $C_{22}H_{37}NO_2$

Based on the molecular formulas, we can immediately see that CBD and Δ9-THC are isomers—they have the same molecular formula but with different bonding or organization of atoms. The subscripts noted in the formulas of each molecule represent the number of each element present in the molecule. For example, in anandamide, there are 22 carbons elements, 37 hydrogen elements, 2 oxygen elements, and a single nitrogen element.

Before calculating the molecular mass, we also need the atomic mass of each element. We can refer to the periodic table of elements to obtain the atomic mass of all elements (the periodic table of elements will also provide the atomic number, which is the number of protons in the nucleus of the element). The atomic mass of an element might be displayed with multiple fractional digits, but for the calculations below, the atomic mass number was rounded to the hundredths.

To calculate the molecular mass (m) of anandamide, we will multiple the number of each element in the molecule by its own atomic mass and calculate the sum:

m = (number of carbon atoms)(C atomic mass) + (number of H atoms)(H atomic mass) + (number of oxygen atoms)(O atomic mass) + (number of nitrogen atoms)(N atomic mass)
or
m=(22)(12.01) + (37)(1.01) + (2)(16) + (1)(14.01)
or
m= 264.22 + 37.37 + 32 + 14.01 = ***347.6 Da***

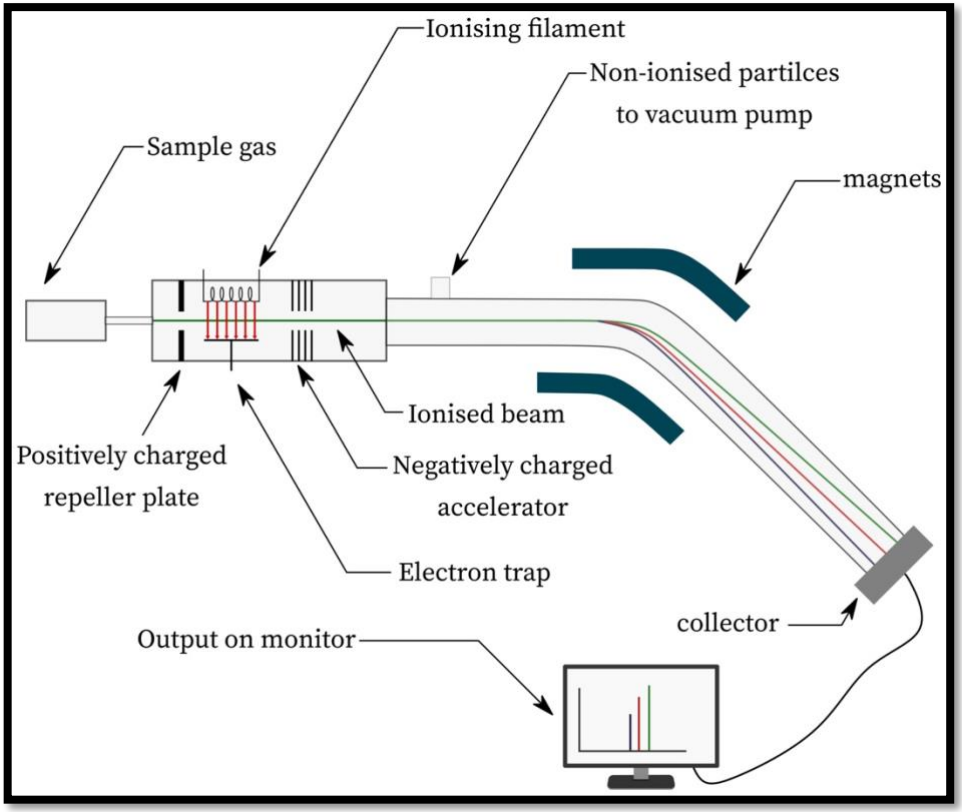
We can use the same process to calculate the molecular mass of both Δ9-THC and CBD:

m = (number of carbon atoms)(C atomic mass) + (number of H atoms)(H atomic mass) + (number of oxygen atoms)(O atomic mass)
or
m = (21)(12.01) + (30)(1.01) + (2)(16)
or
m = 252.21 + 30.3 + 32 = ***314.51 Da***

Why is mass spectrometry important in cannabis testing? To identify the presence of and the amounts of cannabinoids, terpenes, and other compounds in a sample, chemists require multiple tools and processes. If a lab were using only chromatography, for example, they would be able to separate different compounds in a sample based on the rate of elution of each substance. However, chromatography alone cannot *identify* the substance. Using mass spectrometry alone is insufficient, as well, as some substances (such as Δ9-THC and CBD) are isomers with the same molecular mass. Mass spectrometry cannot distinguish between these isomers. Using chromatography with mass spectrometry enables chemists to *separate* compounds in a sample based on their rate of elution and to *identify* them based on their molecular mass.

The molecular mass measured by a spectrometer can sometimes vary, depending on the process used to ionize the sample and whether the sample was fragmented during ionization. There are two common processes to ionize the molecule and give it a charge: electron impact (EI) and chemical ionization (CI). If ionization of the molecule was achieved through EI, the molecule typically loses an electron and becomes positively charged. Electrons, however, do not contribute to atomic mass. So, in this scenario, the mass to charge ratio (m/z) is equal to mass divided by charge, or *m/1*. If the charge is 1, then the mass

spectrometer can capture the exact mass of the parent ion. During chemical ionization, however, the molecule can pick up or can lose a *proton*, affecting the charge but also impacting the molecular mass measured by the spectrometer. If the charge is not equal to one, then the instrument will record a different molecular mass.



Schematic of Mass Spectrometry

Nuclear Magnetic Resonance

Nuclear Magnetic Resonance (NMR) is a non-separation technique. This process leverages the energy transfer of nuclear spin when an external magnetic field is applied. The energy transfer generates a wavelength in the radio frequency spectrum that can be measured. The frequency that is emitted is affected by the chemical environment of the molecule, and the information

collected can convey specific information about how the molecule is comprised (that is, how the atoms are bonded and arranged in space).[696]

Chemists can use NMR to determine the content, purity, and molecular structure of a cannabis sample. For example, NMR can determine the amounts of known compounds in a cannabis sample—such as Δ9-THC, CBD, or other known cannabinoids, as well as terpenes and flavonoids. Also, chemists can use NMR to identify unknown compounds in a mixture by matching data to established libraries or by inferring compounds based on the molecular structure. After identifying the basic structure, chemists can use NMR to determine spatial arrangement of the atoms in the molecules included in the mixture. [697]

Using NMR to analyze cannabis samples has advantages over other methods used for detecting and measuring analytes. NMR can reveal the chemical composition of compounds in a sample quickly and can determine the concentrations of those analytes accurately, without evaporating or separating the compounds (which can impact the final measurement of total Δ9-THC and total CBD).[698]

NMR provides a vast amount of information about a cannabis sample, even enabling chemists to differentiate among different chemovars. Because there now exist data libraries, the NRM process is fast, stable, and economical.[699] NMR requires a simpler sample preparation, shorter measurement times, and less solvent than other detection and purification processes.

NMR has other advantages, too. For example, NRM can quickly detect the presence of and the amounts of compounds in complex samples (such as topicals and edible), including lipids, sugars, residual solvents, water, or synthetic cannabinoids.[700]

Even when using NMR, chemists might still require other techniques. For example, because NMR is a non-separation technique, this process does not facilitate the purification of mixtures. For example, a hemp product might be below the .3% Δ9-THC threshold, but the manufacturer might require a pure CBD product or a broad-spectrum CBD product that excludes Δ9-THC. In this case, we might employ preparative chromatography to isolate and remove Δ9-THC from the extract, leaving the CBD, minor cannabinoids, terpenes, and flavonoids in the extract.[701]

Combining processes and techniques enables chemists to identify, quantify, and purify cannabis mixtures and to provide the data that companies and consumers require to safely use cannabis products.

USP Reference Standards

The United States Pharmacopeia (USP) refers to the compendium of drug information that is published annually, and to the organization that publishes that information (the organization is more formally named the U.S. Pharmacopeial Convention). The USP is the single non-profit, independent, and nongovernmental pharmacopeia in the world and the organization develops quality, purity, strength, and identity standards for medicines, food ingredients, and dietary supplements.[702]

The annual publication describes documentary standards (called monographs) and the organization develops USP Reference Standards, which are physical products against which manufacturers can compare their own products to ensure that manufactured products meet required specifications.[703] Multiple independent commercial and regulatory laboratories test and evaluate USP reference standards to ensure their integrity and accuracy. The USP does not enforce the standards it promotes—that responsibility is under the purview (primarily) of the U.S. Food and Drug Administration (FDA).[704]

Despite evidence of medical efficacy and the legal status of cannabis in most U.S. states, cannabis remains a Schedule I drug in the Controlled Substances Act. With the exception of three cannabis-derived or synthetic drugs approved by the FDA, the federal government does not recognize cannabis as a legal drug product. In the United States, the USP standards are enforced by FDA, so the USP has determined that it is currently unable to create formal standards for cannabinoids. The USP, has, however, published a white paper in lieu of an official USP monograph, authored by a panel of experts who recommended that USP develop reference standards for the quantitative measurements of cannabinoids.[705]

Currently, cannabis regulations consist of a patchwork of state-specific regulatory structures. Some states enforce rigorous regulations, and other states have very few regulations (especially states where the medical or adult use markets are immature). Moreover, given that the cannabis industry is moving from an illegal industry to a regulated industry, there exist very few policy makers and elected officials who have expertise in this field. These inexperienced agents are required to draft legislation and regulations. Because this inexperience and inconsistency puts consumers at risk, national standards are desperately needed in the cannabis industry.

A national set of adopted standards would help ensure that the identity, purity, and potency of cannabis products are consistent across states and help

customers trust that the products they buy have not been adulterated with synthetic cannabinoids or contaminated with heavy metals, solvents, or pathogens. And, USP standards can provide consistent, high-quality material for use in cannabis clinical trials. [706] [707]

To date, the USP has developed multiple cannabis reference standards in two separate mixtures (one mixture that includes neutral cannabinoids and a second that includes acidic cannabinoids). [708] These mixtures enable the quantitative measurement of the following cannabinoids:

- The *Cannabinoids Mixture* includes Δ9-THC, Δ8-THC, CBD, CBG, CBC, CBDV, THCV, and CBN (CBN is used as a marker to measure the degradation of a sample).[709]
- The *Cannabinoids Acid Mixture* includes THCA, CBDA, CBGA, CBDVA, and THCVA. This reference standard must be neutralized with formic acid before performing HPLC analysis because it includes triethylamine and ascorbic acid as a stabilizer.[710]

In addition to these mixtures, an *Exo- Δ9-THC* USP reference standard exists for applications in urine drug testing, clinical toxicology, and forensic analysis.[711] And, solutions of isolated CBD and Δ9-THC reference standards are also commercially available. These reference standards can be used in quantitative analytical procedures to identify analytes in cannabis product samples, to help determine potency of samples, and to conduct stability testing (to test how the stability of cannabinoids—especially acidic cannabinoids—are impacted by storage and working conditions). [712]

Currently, there remain gaps in the cannabis-related USP reference standards. Of course, as less-known cannabinoids undergo further study, the USP might add those cannabinoids to the panel included in the standards. And, importantly, there exist no standards for terpenes. The pharmacological uniqueness of cannabis chemovars might be related to the diversity of terpenes and their interactions with cannabinoids. At minimum, the USP should consider developing reference standards for five terpenes that are commonly abundant in cannabis chemovars: β-caryophyllene, D-limonene, β-myrcene, α-pinene, and γ-terpinolene.[713] More clinical research is required to determine what role individual terpenes and combinations of terpenes play in the pharmacology of cannabis and how terpenes might influence the efficacy of cannabis products for specific conditions or disease. USP standards would help facilitate terpene

labeling requirements and would help researchers determine the clinical relevance of terpenes in cannabis.[714]

Toxins

All cannabis plants—even those grown indoors—can be susceptible to pests. While pesticide limits are defined by the Environmental Protection Agency for food crops, there still exist no federal standards for pesticide limits for cannabis crops. And, even if cannabis farmers voluntarily follow the limits established for food crops, the pesticides identified and the limits imposed at the federal level for food crops might be insufficient for cannabis flowers, given that many consumers burn and inhale cannabis flowers.

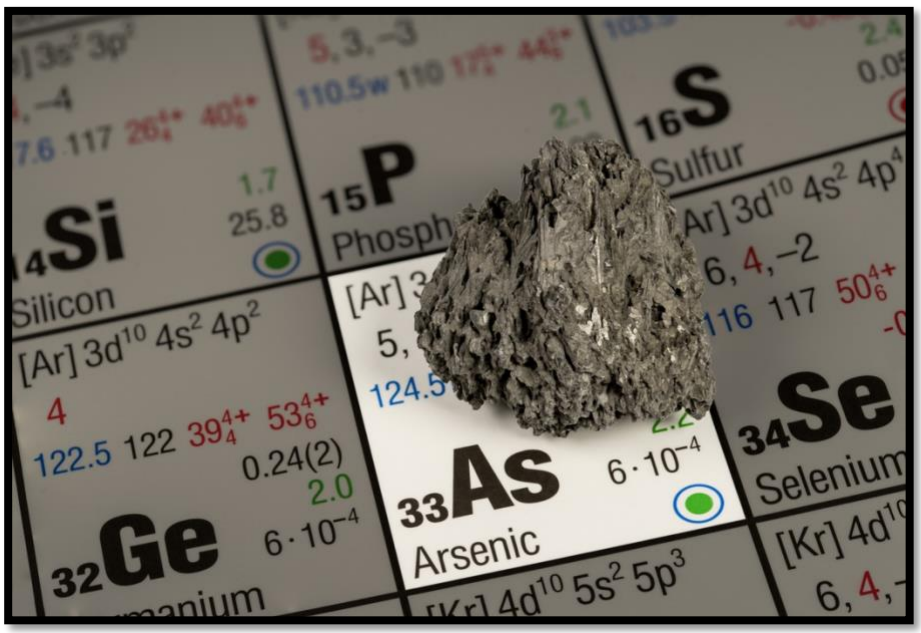
The onus, then, falls to each state to determine the list of toxins and the acceptable limits. While U.S. states can reference the guidelines established for orally ingested drugs (which are published by the United States Pharmacopeia) and guidelines established by the EPA for food crops, these states must establish lists and limits of pesticides that are *specific* to the cannabis industry. For example, cannabis farmers often use azadirachtin (the active ingredient in neem oil) to control infestations of multiple pest species, including Lepidoptera, Diptera, Hemiptera, Coleoptera, and Thysanoptera.[715] Azadirachtin is not included in the USP general chapter <561> *Articles of Botanical Origin*.[716] States have taken different approaches to controlling the use of pesticides in the cannabis industry, and the lack of federal standards has precipitated a patchwork of solutions, meaning that consumers have different levels of protection, depending on the state in which they live. For example, California tests for 66 pesticides which are organized into a two-tier system—a top tier of pesticides that must not be present and a lower tier of pesticides with allowable limits. Colorado tests for only 13 pesticides.[717] Between 2014 and 2019, the state of Washington required no pesticide testing at all.[718]

The risks of pesticide exposure in humans are severe. Many pesticides are neurotoxic and carcinogenic, and some are endocrine disruptors, meaning that they might cause cancerous tumors, birth defects, and developmental disorders.[719] [720] These dangers exist not only for consumers of exposed products but also for employees who work with these chemicals. Moreover, the effects of these toxins are cumulative, especially the potential carcinogens.[721]

Even small amounts of pesticides in raw products can be toxic, especially in concentrated cannabis products, as processes that concentrate cannabinoids also concentrate the toxins.[722] And, the risks of burning and inhaling pesticides

are not well-defined. It can be assumed, however, that out of all the cannabis routes of administration, inhalation of pesticides carries the most risk, given that most of the residue in the product will reach the bloodstream (compared to, for example, oral ingestion, where toxins can be filtered out by the gastrointestinal tract and the liver). And, while one might assume that the cannabis industry can simply reference data gleaned from pesticide exposure in tobacco, that data (shockingly) does not exist[723] (a strong and well-funded tobacco lobby has obfuscated product danger and stymied appropriate legislative responses).

In addition to pesticide toxins, cannabis employees and consumers can also be exposed to heavy metal exposure. Cannabis plants are bio-accumulators—they readily absorb nutrients, metals, and toxins from the soil. In fact, they can be used effectively as soil remediators. For example, for almost two decades, industrial hemp has been planted near the abandoned Chernobyl nuclear power plant in the Ukraine to help reduce soil toxicity.[724] When hemp plants are sourced from unregulated markets, they can be riddled with heavy metals, mold, bacteria, pesticides, and other contaminants.[725]



Arsenic can damage multiple organs, even at low levels of exposure

In cannabis consumers, heavy metals harm cellular components, including cell membranes, mitochondria, lysosomes, the endoplasmic reticulum, and cell nuclei.[726] And, heavy metals can also harm enzymes required for metabolism of toxins. Mercury, lead, cadmium, and arsenic can all cause damage to multiple organs, even at low levels of exposure. The Environmental Protection Agency has classified these metals as known or probable carcinogens based on data that demonstrates an association between exposure and cancer incidence in humans and animals.[727]

During the absence of federal guidelines or standards, states must enforce cannabis manufacturers to employ quality controls that keep all toxins below acceptable limit levels. And, cannabis testing labs should use instruments that are calibrated to detect levels of toxins well below the level of acceptable limits. Finally, consumers should understand that toxins above the action limit are not necessarily harmful, and levels below the action limit are not necessarily safe to consume. Consumers should always ask to see certificates of analysis to help them make informed choices.

Chapter 7: Cannabis Drug and Product Formulation

Drug formulation defines the process in which an active drug is combined with other chemical substances to produce a medicinal product.[728] Formulation enables the facilitation of the safe delivery of the correct quantity of a drug, at the correct rate and to desired target of action. Formulation can improve the absorption and bioavailability of an active substance, improve the stability, and improve the taste, odor, and other characteristics important to patients. Furthermore, formulation guarantees a stable and safe product up to an established expiry date.[729]

The formulation of the design of any cannabinoid and terpene drug product must include considerations for good growing and testing practices, solubility and bioavailability issues, odor, color, and size of the final product, among other considerations. Cannabinoids are botanical medicines, so good formulation begins with properly controlled growing, drying, curing, packaging, and storage practices. Raw cannabis and extracted cannabinoids should be processed, manufactured, packaged, and stored in a manner that adheres to the World Health Organization's guidelines on good manufacturing practices for herbal medicines and other applicable regulations and best practices.[730]

Testing raw cannabis material is also a critical prerequisite to any cannabinoid drug formulation if the final product will rely on extractions or mixtures of extracted compounds. All cannabis extractions should be tested for potency of cannabinoids, for terpene content, molds, pesticides, bacteria, residual solvents, moisture and water content, and heavy metals.

Solubility is one of the most important considerations for formulating medicines that include cannabinoids and terpenes. Cannabinoids are classified in the Biopharmaceutics Classification System as a class 2 substance, meaning that they have low solubility (in aqueous solutions) and high permeability (the ability to pass from the gastrointestinal tract through the gut wall and into the rest of the body).[731]

Cannabinoids are highly lipophilic and hydrophobic (their lipid attributes can be predicted based on the prevalence of hydrocarbons in these compounds). Terpenes, generally, are even more lipophilic than cannabinoids (myrcene, limonene, and beta caryophyllene, for example, are all comprised entirely of hydrocarbons. Linalool is also comprised of nearly all hydrocarbons, save for a single hydroxyl group). When substances have poor solubility, they have low bioavailability in the body. Drugs can reach intended targets only if they reach systemic circulation, and poor bioavailability limits a drug's ability to reach the bloodstream. During early phase testing, the active substance is usually the most expensive ingredient in the medicine. If bioavailability is low, more of the active substance is required to achieve efficacy, thereby further increasing costs.[732]

Oral bioavailability, specifically, is a major consideration in drug formulation. Generally, patients prefer to administer medicines orally and in the form of tablets.[733] [734] Cannabinoids, however, have low oral bioavailability, in the range of 4−20%.[735] Also, orally administered cannabinoid medicines have highly variable onset and undergo significant first-pass metabolism. Moreover, Δ9-THC initially converts to a highly potent metabolite, 11-OH-THC.

In the early stages of a drug formulation process—for example, during toxicology and safety phases—chemists can improve cannabinoid solubility (and subsequently, improve bioavailability). For example, some companies are using existing nanoemulsion technology to produce products that are water-compatible and that can be mixed into beverages in varied concentrations. Manufacturers claim that these products have very fast onset (in some cases, similar to inhalation) and very high bioavailability (some industry advocates suggest a bioavailability of up to 75%).[736] However, these steps can be costly and time consuming, and substances with low solubility often fail to advance beyond these early drug development stages.[737]

Another consideration during drug formulation is the stability of the active substance. Cannabinoids are susceptible to degradation from both heat and light. For example, in one study, extracted cannabinoids that were stored at room temperature and exposed to light degraded significantly faster than the degradation rate of raw flowers stored in the same manner (35 days half-life and 330 days half-life, respectively).[738]

Cannabis contains over 500 unique compounds.[739] And, generally, chemicals are reactive. When these compounds react with or degrade into other compounds (through environmental factors or within the body), byproducts are created. These byproducts can also react and degrade, and they can cause

additional byproducts and impurities. All of these reactants must be tested prior to approving a drug for human consumption, increasing the complexity and cost of formulation and testing. [740]

The boiling points of cannabinoids and terpenes must also be considered during formulation. Cannabinoids and terpenes include a range of boiling points—many falling into the range of 220 °F to 400 °F. Manufacturing processes must maintain temperatures below this range to ensure that the key ingredients don't degrade before the product reaches the market.

Additional formulation considerations for a medicine containing cannabinoids and terpenes include the odor, color, and size of the final products. Cannabinoid medicines often have a vegetal, unpleasant taste and many terpenes are highly aromatic. These strong flavor and odor profiles can prove challenging, especially in pediatric and geriatric patient populations.

Some companies use emulsifying agents to reduce the viscosity of inhalable cannabis products. However, many of the additives and cutting agents that have been widely used in cannabis products have not been tested at high heat or for inhalation and should be considered unsafe for inhalation. For example, vitamin E acetate—which, until recently, was used in cheap and illicit market vape pens—is commonly used in topical products and dietary supplements. There is no data, however, to study its effects when inhaled. Moreover, fats or oils that enter into the lungs can be highly toxic and can lead to lipoid pneumonia.[741]

Other additives that were (and to some extent, remain) common to cannabis vape cartridges are propylene glycol and glycerol, both of which degrade into formaldehyde when vaporized at high heat. Formaldehyde, of course, is a carcinogen.[742] Again, cannabis products should be made with the fewest possible ingredients. However, some excipients might be required to facilitate inhalation, especially in a delivery system that does not rely on heat. For example, products such as dry powder inhalers might include a combination of plant-derived and pharmaceutical grade excipients that have been tested in clinical trials. These ingredients are used to encapsulate the cannabinoids and to improve flow.[743] [744]

Transmucosal Delivery Systems

Transmucosal delivery refers to the delivery of a drug through the mucosal barrier and into systemic circulation. While transmucosal routes include nasal, rectal, vaginal, and ocular routes, the oral cavity route offers the best accessibility and patient acceptability. Ideally, drugs formulated for this route

produce higher bioavailability than ingested medications, with fewer adverse effects.[745]

Transmucosal delivery offers several advantages. First**,** this route can be desirable for patients who have difficulty swallowing or who suffer from nausea and vomiting. Also, transmucosally-delivered drugs can absorb directly into the blood vessels in the mucosa, bypassing first-pass metabolism (when formulating cannabinoid medicines, bioavailability via oral ingestion is quite low and metabolism in the liver creates unwanted and potent metabolites).

When combined with a permeation enhancer (for example, polyethylene glycol or propylene glycol), cannabinoids become more soluble and can more effectively penetrate the mucosa. Better absorption enables patients to use smaller dosages of Δ9-THC. And, this delivery method facilitates relatively constant blood concentration levels over longer periods (unlike inhalation, for example, where Δ9-THC is rapidly metabolized and concentration levels in the bloodstream decrease rapidly). Of course, smaller doses of any drug can reduce the potential for abuse.[746] And finally, some drugs formulated for transmucosal delivery (for example, thin films) rapidly disintegrate when exposed to saliva. Faster dissolution times enables more of the drug to disintegrate and absorb into the oral cavity and less of the drug is swallowed and lost to the gastrointestinal tract. [747]

There are some challenges to overcome. For example, although transmucosal drugs are intended to bypass first-pass metabolism, often there exists a *mixed absorption spectrum*,[748] where some of the drug is absorbed through the mucosa directly, but where much of the drug is ingested (in this case, the pharmacokinetics appear similar to oral ingestion). Solid dosage forms—such as hard lozenges—can produce higher variations in absorption and bioavailability because sucking produces saliva and encourages swallowing, meaning that the drug is moved into the gastrointestinal tract. Finally, alcohol-based tinctures can include high alcohol toxicity and can cause irritation, especially when administered under the tongue.

When developing transmucosal cannabinoid medications, formulators must consider how the excipients can improve absorption, bioavailability, and patient compliance. Typically, formulators must consider:

- A mucoadhesive to sustain contact between the cannabinoids and the mucosa, thereby improving therapeutic efficacy. Adhesive agents

maintain prolonged contact with site of absorption and can reduce the amount of the drug washed away by saliva.[749]

- A penetration enhancer to promote the absorption of cannabinoids. There are multiple mechanisms by which enhancers can help increase absorption. For example, mucus and saliva can form layers that have both viscous and elastic properties, creating varying layers of thickness that can thwart drug absorption. Some permeation enhancers can reduce this viscosity. [750] Or, some enhancers can compromise the lipids that exist between the epithelial cells to allow intercellular permeation. Permeation enhancers should be safe and non-toxic, inert, non-irritant, and non-allergenic. [751] Common penetration enhancers include bile salts, surfactants, and terpenes, among a host of other enhancers.[752]
- Enzyme inhibitors and preservatives, both of which can protect the cannabinoids from degradation.
- Sweeteners, flavorings, or coloring agents, all of which can be added to improve patient experience and compliance.
- The manufacturing process, especially when heat is involved. Heating can cause cannabinoids to degrade, so formulators must keep heat to a minimum during the processing. Also, formulators must confirm that there exist no adverse or unexpected interactions among the active drugs and various excipients. For applications that are processed using hot-melt extrusion, hot-melt molding, admixing processes, or solvent cast techniques, formulators must ensure that the drug solution is mixed properly to achieve homogeneity, that it has the proper viscosity for application, that the product has the proper drying time and moisture content, and can be peeled, cut, and packaged without compromising the final product.

One example of a transmucosally-formulated cannabinoid drug is Sativex, produced by GW Pharmaceuticals. Sativex (which is not yet currently FDA approved for use in the U.S.) is an oral-mucosal spray that contains Δ9-THC and CBD, but also contains anhydrous ethanol (ethyl alcohol with a purity of at least ninety-nine percent and no added denaturants), peppermint oil, and propylene glycol. Consequently, Sativex can be effectively administered buccally because it includes a surfactant, an oil that improves the smell and taste, and a permeation enhancer (Sativex is comprised of 50% by volume of ethanol—enough to help

solubilize the cannabinoids but at a low enough concentration to avoid toxicity).[753]

However, despite that Sativex is a product specifically formulated for buccal administration, one small study demonstrates the challenges of administering cannabinoids transmucosally—this study found no statistically significant differences in maximum concentrations or time to maximum concentration between orally administered Δ9-THC and buccally administered Sativex. These results suggest that much of the active drug in Sativex is swallowed and the pharmacokinetics follow the pattern of ingestion.

Other examples of oral transmucosal delivery exist—thin films that are between 50-150 nanometers in thickness and that dissolve rapidly after contact with saliva, lozenges similar to hard candy, soft chews, and so forth. Many existing cannabis products that are marketed as sublinguals, however, fail to include excipients that facilitate mucoadhesion or solubility. These oil-based tinctures do often contain long-chain medium-chain triglycerides (olive oil or MCT oil, for example), but likely produce effects via ingestion.

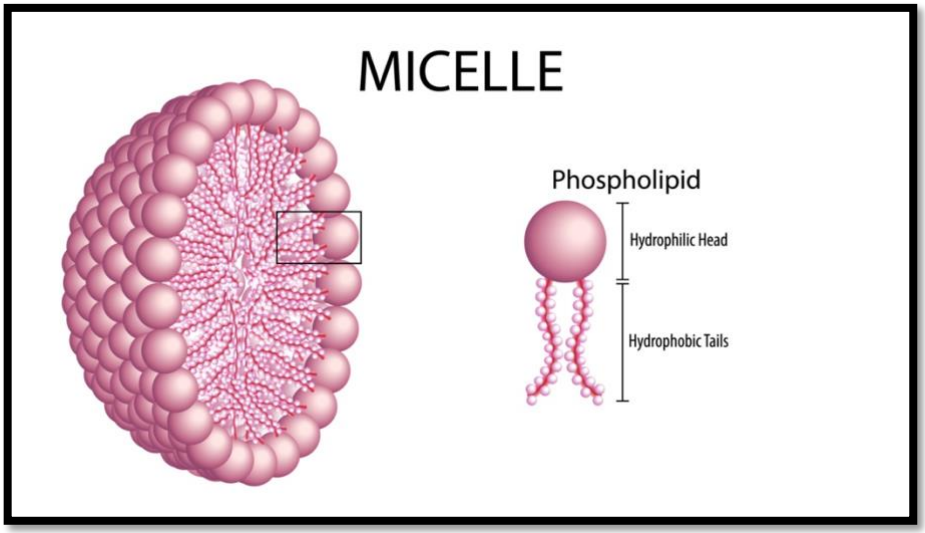
Product Formulation Example: Nanoemulsions

When formulating any cannabis medicine, there exist many inherent challenges—cannabinoids are highly lipophilic, they degrade rapidly during oxidation, they have poor aqueous solubility, and poor bioavailability. Oral administration forms can facilitate the use of pharmaceutical-grade ingredients with standardized dosing protocols. However, ingested cannabinoids degrade in the stomach, undergo excessive first pass metabolism in the liver, and produce psychoactive metabolites. Also, consumers often fail to understand the delayed onset of ingested cannabinoids and might consume more than the intended amount before the product takes effect, resulting in adverse effects.[754]

The goal of cannabis drug formation is to improve efficacy and stability, and to reduce variabilities (for example, variable onset during oral ingestion). A micro- or nanoemulsion (technologies that are used in other industries to improve clarity, weight, and flavor of beverages, for example) can address many of these challenges. [755] [756]

This section discusses the considerations of formulating an oral cannabis solution with a nanoemulsion, a process which encases the cannabinoid payload into micelles, creating a soluble effect. Formulating a nanoemulsion for a cannabinoid medicine requires cannabinoids, a carrier oil, a surfactant, and a

homogenization process. The remaining steps assume that the cannabis oil has been extracted using CO_2 and has been winterized and decarboxylated.



Nanoemulsions encase the cannabinoid payload into micelles.

Microemulsions and nanoemulsions are very similar processes. Microemulsions, however, require a much greater amounts of surfactants. Nanoemulsions can use less surfactant because formulators can use mechanical energy to break the droplets apart.[757]

To create a nanoemulsion, the cannabis oil must be encapsulated in a carrier oil. For oral ingestion, the carrier oil must be food grade and must not compromise the appearance, taste, texture, or stability of the end product. Long-chain triglycerides form a hydrophobic core large enough to accommodate the cannabinoid payload (cannabinoids are long molecules). Medium chain triglycerides can be 100 times more soluble in water than long chain triglycerides, but they have cores that are too small to accommodate cannabinoids.[758] Medium-long-chain triglycerides make a logical compromise, but consumers often prefer label-friendly products with natural-sounding ingredients.[759]

Co-administration of cannabinoids and fats (either dietary or pharmaceutical) can substantially increase the absorption of cannabinoids, as the presence of lipids facilitates intestinal transport.[760] Using a long-chain triglyceride carrier oil that is high in saturated fat might produce better absorption than one that is low in saturated fats. Coconut oil or palm oil are both extremely high in

saturated fat, but both are semi-solid at room temperature. Olive oil seems to be a good choice here, as it contains only a small amount of polyunsaturated fat (highly unstable and easily oxidized),[761] is not as allergenic as soybean oil, and has a large amount of healthy monounsaturated fat.

A separate mixture of water surfactant is prepared. Food-grade Polysorbate 80 is a surfactant that is commonly used in medical and food products. It works well as a stabilizer and emulsifier.[762] Polysorbate 80 has been studied in drug delivery and appears to be both safe and effective.[763] In one study, mixed-surfactant-based nanoemulsions demonstrated efficacy for incorporating vitamin D into food and beverages. In this study, Polysorbate 80 was mixed with soya lecithin.[764]

Industrial Sonomechanics creates a product called NanoStabilizer. They state[765] that formulators can create:

- Stable milky nanoemulsion using 100 mg/ml of cannabinoids, 200 mg/ml of carrier oil (300 mg/ml total oil) and 30 - 50 mg/ml of surfactants
- Translucent nanoemulsions using 50 mg/ml of cannabinoids, 100 mg/ml of carrier oil (150 mg/ml total oil) and 100 - 120 mg/ml of surfactants

The cannabis/carrier oil mixture should be combined with the water/surfactant mixture. These combined mixtures must then be homogenized. During homogenization, the emulsion droplets are broken down into smaller sizes. For nanoemulsions, this process is typically mechanical, often using high intensity and low frequency ultrasonic waves.[766] To produce transparent emulsions, formulators must reduce the droplet size to approximately 50nm (a nanometer is one billionth of a meter), although 100nm can facilitate the inclusion of the emulsion in a water-based solution.

The final step of formulation is to sterile-filter the nanoemulsion and transfer it to a light-protected container. Formulators can use a hydrophilic filter membrane with 220 nm pores to remove all contaminates, including microorganisms, dust, plant matter, and other contaminates formed during the homogenization process. Because the emulsion is comprised of droplet sizes smaller than 100 nm, the droplets can pass through the filter membrane. Using a hydrophilic membrane ensures that the droplets will not stick to it.[767]

Prior to capping, some companies recommend adding a layer of liquid nitrogen to dispel any oxygen and to pressurize the content.[768] Expelling atmospheric gases by using heavy, inert gases is a practice widely used in the wine industry (argon, for example, is another inert gas heavier than oxygen that is

commonly used). When added to the container, liquid nitrogen rapidly expands as it changes from a liquid to a gas inside the bottle, pushing oxygen out of the container.[769]

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