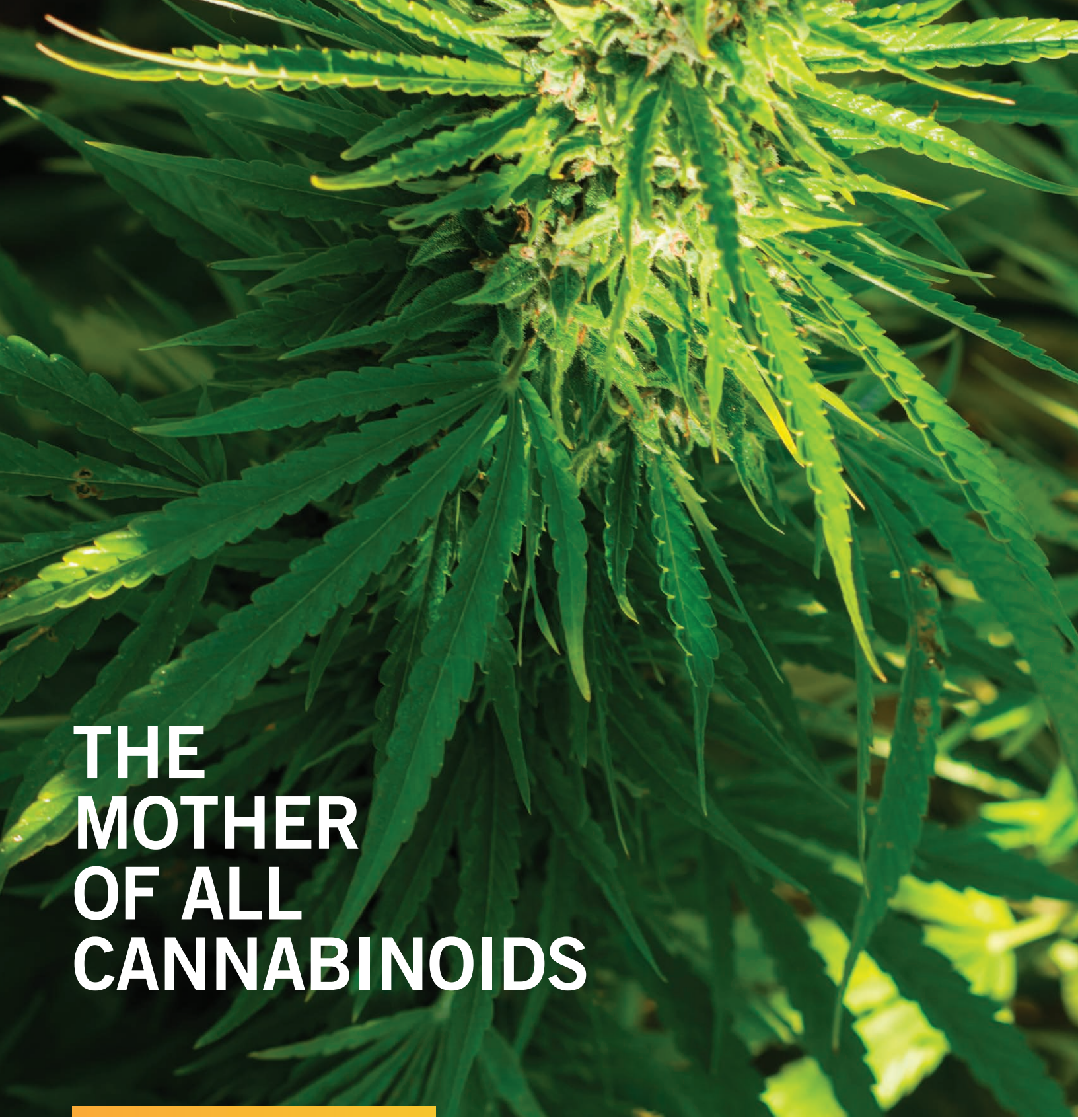

THE MOTHER OF ALL CANNABINOIDS

HEMPTOWN USA

CANNABIGEROL (CBG) WHITE PAPER

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PART 1
OVERVIEW / STATEMENT OF PURPOSE

The plant species ***cannabis sativa*** has been employed by humans and wellness practitioners for literally thousands of years—as illustrated by recent carbon-dated archeological discoveries cited within this white paper. Several traditional medicinal schools of thought have employed this unique herb (which also qualifies as a vegetable) throughout ancient and modern history. These have included Ayurvedic, Tibetan, traditional Chinese, and 19 th century Western medicine.

Modern medicine has largely forgotten the healing powers of the cannabis plant, due mostly to the cultural and economic ramifications of more than a century of legal prohibition.

According to one **study**, only 13 percent of medical schools in the United States offer any training regarding the medicinal benefits of cannabis for humans.

American pharmaceutical companies as recently as the 1930s produced a variety of cannabis-infused products (typically in the form of alcohol-based tinctures) intended for medical use (not recreational euphoria).

It was not until U.S. federal prohibition of cannabis began in the late 1930s that major drug vendors — including Eli Lily and Company, Squibb & Sons (Bristol-Myers-Squib today), and Parke Davis and Company (Pfizer in modern form)—ceased marketing such products. The inclusion of cannabis tinctures and related products in the U.S. Pharmacopoeia (a compendium of drug information that served as a national standard), which began in 1851, ended in 1942.

WHY **CANNABIGEROL?**

Cannabigerol or CBG, is one of a family of more than 100 molecules called cannabinoids that are produced by cannabis. CBG is unique among its peers due to the pivotal role that it plays in the synthesis of other cannabinoids and the overall chemical composition of the plant. This fact would be trivial if not for the considerable potential of this family of molecules for humans (and all mammals) that has been revealed by thousands of peer-reviewed research studies (citations appear throughout this white paper).

Before investigating the health and wellness merits of CBG, it is important for readers and students to understand the botanical and physiological framework and underlying mechanisms by which this molecule functions.

PART 2
EXECUTIVE SUMMARY

Homo sapiens for thousands of years have been utilizing the plant that is today commonly known as hemp, cannabis, marijuana, and pot (the most objective and scientific moniker is cannabis). The prohibition of this herb by government bodies is a fairly modern phenomenon within the scope of human history.

Ironically, the illegality of the cultivation, possession, and consumption of cannabis began in **California** in 1913 as part of an update to the 1907 Poison Act. The legislation outlawed "extracts, tinctures, or other narcotic preparations of hemp, or loco-weed, their preparations, and compounds."

This trend quickly spread to Wyoming (1915), Texas (1919), Iowa (1923), and other U.S. states as part of narcotics legislation that was sweeping the nation during the period. In 1923, Canada embraced cannabis prohibition at the federal level (propelled by the influence of the Emily Murphy book The Black Candle). This social and political momentum eventually culminated in federal-level prohibition of cannabis in the United States in August of 1937—a highly contested and controversial situation that has pervaded until present day.

A **2016 research study** entitled "Ancient Cannabis Burial Shroud in a Central Eurasian Cemetery" documented cannabis remains believed to be part of a religious ritual that are approximately 2,800 years old. "An extraordinary cache of ancient, well-preserved cannabis plant remains was recently discovered in a tomb in the Jiayi cemetery of Turpan, China. Both morphological and anatomical features support the identification of the plant remains as cannabis," reported the study's authors.

Despite what appears to be an understanding of the overall efficacy of the plant, ancient societies obviously did not possess the technology to observe and interpret the underlying chemistry of this unique herb and its evolutionary path with humans.

CANNABIGEROL (CBG)

Modern science and technology-driven research methodologies have allowed insight into the composition and dynamics of the cannabis plant. Of the more than 450 chemicals identified in the herb, one of the most compelling — from the perspective of human health and economic development—is cannabigerol, or CBG.

This molecule is of great significance to all vertebrates because it rivals the potential of its peer cannabinoids and terpenes (the molecules that give cannabis its aroma and also possess medicinal qualities). Of the hundreds of unique chemicals produced by the herbal species cannabis sativa, none plays a more pivotal role than cannabigerol.

There have been multiple studies conducted over the course of the past three decades, particularly in the primary areas of analgesia (pain relief), reductions in systemic inflammation, decreased anxiety and nausea, and anti-cancer research.

Of the hundreds of unique chemicals produced by the herbal species cannabis sativa, none plays a more pivotal role than cannabigerol.

TWO CATEGORIES OF CANNABINOIDS

The best research to date indicates that cannabis phytocannabinoids evolved to adapt to the mammalian ECS, not the opposite.

Cannabinoids from cannabis are called phytocannabinoids to differentiate them from similar molecules produced by the human body called endocannabinoids . Both sets of chemicals are part of a relatively newly discovered network of specialized cellular receptors called the endocannabinoid system, or ECS. Interestingly, some form of an ECS is present in all mammals (including canines, felines, and horses) —and all vertebrates.

The best research to date indicates that cannabis phytocannabinoids evolved to adapt to the mammalian ECS, not the opposite. In fact, the major phytocannabinoids have been labeled by researchers “mimetic molecules” because they mirror the behavior of major endocannabinoids in what is arguably an elaborate game of crashing the ECS party.

CBG: **UNIQUE CANNABINOID**

CBG is a subject worthy of investigation by both medical professionals, businesses, and consumers due to the unique role that it plays within the metabolic lifespan of the plant. Of the hundreds of different molecules produced by the resin glands (called ***trichomes***) within the flowers of mature female cannabis plants, none is more compelling or important than CBG.

THE UNIQUENESS OF CBG IS DUE TO TWO PRIMARY CHARACTERISTICS OF THIS MOLECULE. CBG IS THE:

1 **Origin of all most other cannabinoids produced by hemp and cannabis.**

2 **Dominant cannabinoid of a fourth cannabis chemotype that research has revealed sometimes yields up to 94% CBG and as little as 0.001% THC.**

PART 3 **ENDOCANNABINOID SYSTEM**

To understand the efficacy of cannabinoids such as CBG and cannabidiol (CBD), it is important for readers and students to first gain insight into how and why the human body responds to these molecules.

The endocannabinoid system, or ECS (sometimes denoted as eCS), is an integral network of microscopic cellular receptors that is spread throughout the body. ECS receptors can appear in multiple numbers on the surface of individual cells. This network is scattered throughout nearly every organ and tissue of the human body.

GOVERNS **BODILY FUNCTIONS**

First discovered as recently as the early 1990s, research has revealed that this collection of neurotransmitters acts as a command center for a variety of physiological functions and critical bodily systems. These systems include immune response, sleep, appetite, cardiovascular function, mood, pain, respiration, metabolism and energy level, cognition, and libido.

The role of the ECS is potentially significant enough that some scientists believe that deficiencies in this system may result in common diseases and health conditions, including migraine headaches, fibromyalgia, arthritis, and even cancer (see *Part 4: Clinical Endocannabinoid Deficiency*). Any influence over immune function and its important role in human health obviously makes the ECS a biological system worthy of further investigation by scientists, researchers, and product developers.

> **As the chemical source of all other plant-based cannabinoids, CBG is commonly known as the "Mother of Cannabinoids".**

The ECS is characterized by a family of cellular receptor sites, each of which acts as a neurotransmitter, partnering with specialized chemicals produced by both the human body and the plant cannabis that are called ***cannabinoids***. (Merriam-Webster defines neurotransmitter as a "substance [such as a chemical or molecule] that transmits nerve impulses across a synapse.")

A **2015 study** defined the ECS as "comprised of cannabinoid receptors, endogenous cannabinoids (endocannabinoids), and the enzymes responsible for the synthesis and degradation of the endocannabinoids." Examples of cannabinoids produced by the body include anandamide and 2-arachidonoylglycerol (2-AG). Cannabinoids produced by cannabis include CBD, CBG, THC, THCA, and CBDV (explained in more detail below). As the chemical source of all other plant-based cannabinoids, CBG is commonly known as the **"Mother of Cannabinoids"**.

ECS COMMONALITY

Humans are among thousands of species of creatures that feature an ECS of varying levels of complexity. In fact, this intricate network of cellular transmitters is a characteristic of all vertebrates . "[The ECS] is present in all ***vertebrates***—mammals, birds, reptiles, amphibians, fish, etc. all produce endocannabinoids," reported ***UCLA Health***.

Dr. Dustin Sulak is a physician based in the United States who specializes in natural remedies and employs cannabinoids in his clinical practice. "Sea squirts, tiny nematodes, and all vertebrate species share the endocannabinoid system as an essential part of life and adaptation to environmental changes. By comparing the genetics of cannabinoid receptors in different species, scientists estimate that the endocannabinoid system evolved in primitive animals over 600 million years ago," said Sulak during an interview.

The discovery of the ECS is strikingly recent in human history, especially in comparison to other bodily systems. The endorphin system, for example, was discovered in 1801, 191 years prior to the ECS. Despite this, some basic characteristics of the ECS have been identified.

ENDO VS. PHYTO CANNABINOIDS

The specialized receptors embedded within the cell membranes of the ECS feature an ability to attach to and interact with molecules from cannabis. Such molecules are called ***phytocannabinoids*** or ***exocannabinoids*** (and sometimes referred to as ***exogenous cannabinoids***).

Research has revealed that phytocannabinoids are mimetic molecules, meaning that they are basically impersonating similar chemicals produced within the body. Called ***endocannabinoids***, these internally produced molecules were first discovered in 1992 by Czech chemist Lumír Hanuš and American pharmacologist William Devane while working with Raphael Mechoulam's famous research team at Hebrew University in Jerusalem, Israel.

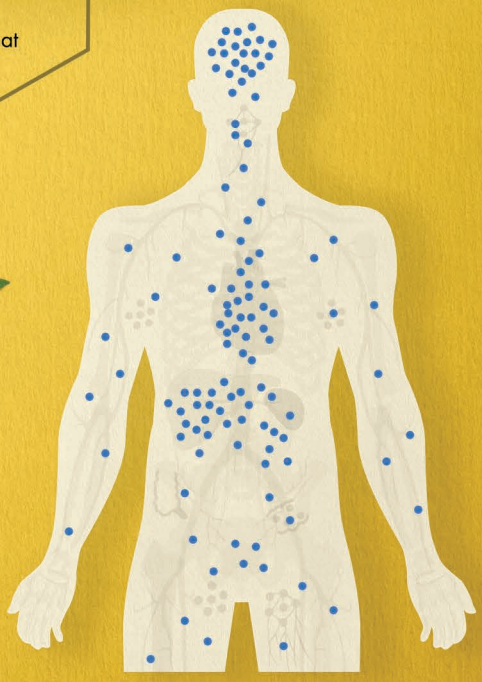
TWO CATEGORIES OF
CANNABINOIDS

What's a cannabinoid?

Simply speaking, cannabinoids are molecules that exist naturally in both the human body and cannabis plants.

CBG & CBD Supplements

The human ECS requires supplementation to maintain homeostasis and health. The best way to achieve this is with phytocannabinoids like CBG and CBD.



MEANING PLANTS

PHTYO CANNABINOIDS

Phytocannabiniods are cannabinoids found in the cannabis plant. Phyto, meaning from plants, is used to differentiate them from similar molecules produced by the human body.

ENDO CANNABINOIDS

MEANING INSIDE US

Endocannabinoids are similar molecules, but they're created naturally by the human body and are part of the endocannabinoid system – which helps regulate most of our other body systems.

HEMPTOWN USA

Did you know?

All mammals have an endocannabinoid system. In fact, an ECS is present in *all* vertebrates.

Hanuš and Devane isolated the first endocannabinoid (from the human brain), naming it ***anandamide***, the Sanskrit word for "joy" and "bliss" (sometimes cited in research studies as ***AEA*** or ***arachidonylethanolamide***). Three years later, in 1995, a second endocannabinoid, 2-AG, was discovered by Mechoulam's team at Hebrew University. This discovery provided additional characteristics and detail of the ECS and its nuanced interaction with both endocannabinoids and phytocannabinoids.

"Anandamide and 2-AG are the two main endocannabinoids, being synthesized from membrane lipids," reported a **2018 research study**. Confirming the molecular source of cannabinoids as terpenes, the study's authors reported, "Phytocannabinoids are phenolic terpenes biosynthesized in nature nearly exclusively in the cannabis...plant."

Because the phytocannabinoids from herbs such as cannabis are mimetic in nature, an understanding of exactly how plant-based cannabinoids mirror human endocannabinoids is of obvious value to scientists and medical professionals. Research to date demonstrates that tetrahydrocannabinol (THC), the infamous cannabinoid responsible for the psychoactive effects of the plant, mimics endocannabinoid anandamide, while its cannabinoidal cousin, cannabidiol (CBD), a non-psychoactive phytocannabinoid, may mirror the mechanisms and efficacy of 2-AG.

ECS **EVOLUTIONARY PATH**

Insight is gained from a comparison of the relative evolutionary paths of mammals and the cannabis sativa plant. Upon further examination, the fact that phytocannabinoid molecules from cannabis bind perfectly, in a virtual lock-and-key mechanism, with receptors within the human ECS yields many questions. For example, which appeared first, the human ECS or cannabis phytocannabinoids? Which system mirrored the other—and why?

> **In a cellular game of impersonating a party guest, phytocannabinoids mimic endocannabinoids to gain entry into the ECS.**

Scientists now believe that the endocannabinoid system in mammals evolved prior to the phytocannabinoids produced by cannabis. This means that this plant species evolved to adapt to humans and other vertebrates, not the inverse. In a cellular game of impersonating a party guest, phytocannabinoids mimic endocannabinoids to gain entry into the ECS.

A **2008 review article** entitled "The Endocannabinoid System: An Osteopathic Perspective" reported that cannabinoid receptors in the ECS evolved long before the phytocannabinoids in cannabis. This is logical because the ECS emerged to feed itself "medicine" in the form of endocannabinoids such as 2-AG and anandamide.

"Humans likely did not evolve receptors for a cannabis compound. Indeed, the cannabinoid receptor evolved long before cannabis," reported the study.

The **2006 study** "Evolutionary Origins of the Endocannabinoid System" examined 12 different animal species to determine that vertebrates and mammals developed an ECS prior to the appearance of cannabis-based phytocannabinoids. Reported the researchers, "Within this limited number of twelve organisms, the endocannabinoid genes exhibited [themselves in] mammals, vertebrates, [and] chordates."

Reported the researchers, "Within this limited number of twelve organisms, the endocannabinoid genes exhibited [themselves in] mammals, vertebrates, [and] chordates."

ECS **RECEPTOR TYPES & DISTRIBUTION**

A variety of ECS receptor types have been discovered by research studies conducted during the past few decades. While ECS science remains in its relative infancy, two major receptor variants have emerged: CB1 and CB2. In medical research parlance, both of these receptors are members of the G protein-coupled receptor (GPCR) family.

CB1 receptors are located most abundantly in the brain and central nervous system (CNS). CB2 receptors are found in their greatest numbers (a measure called ***receptor density***) in the glands, tissues, and organs of the immune system that are distributed throughout the body. Researchers have learned that CB1 receptors appear outside of the brain and CNS, populating most regions of the body (but are vastly outnumbered by their CB2 peers in these "peripheral" regions). Likewise, CB2 receptors have been found in the brain and CNS, but in relatively small numbers.

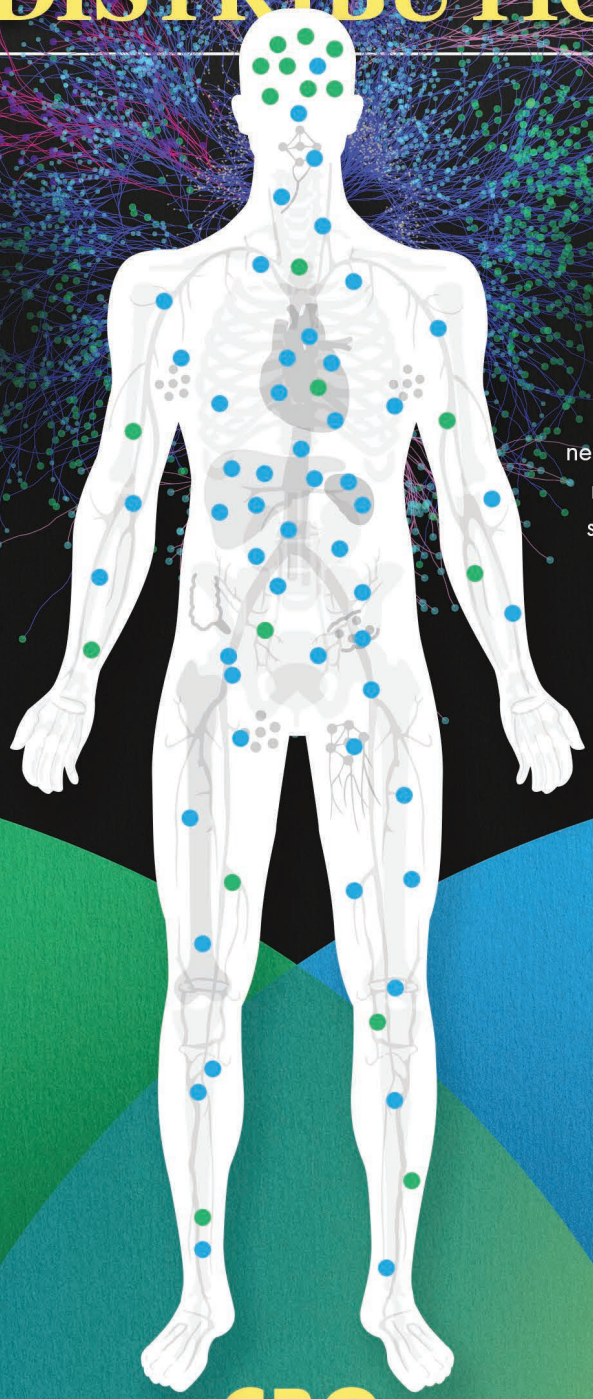
Research (cited below) has identified CB1 receptors in the cardiovascular system, GI tract, liver, reproductive system, and skeletal muscles. A **2018 study** revealed the distribution of CB1 receptors in the brain. "CB1 receptors are distributed throughout the brain, with the highest levels in the cerebellum, cerebral cortex, and hippocampus and much lower levels in the brainstem." The low levels of CB1 receptors in the brainstem is one of the reasons that no overdose deaths from cannabis have been recorded.

Reported a **2014 study**, "The widespread distribution of cannabinoid receptors [CB1 and CB2] regulate a variety of central and peripheral physiological functions, including neuronal development, neuromodulatory processes, [and] energy metabolism." The research also found that CB1 and CB2 receptors are involved in "cardiovascular, respiratory, [and] reproductive functions."

ECS RECEPTOR TYPES & DISTRIBUTION

The endocannabinoid system is populated by millions of specialized cellular receptors that bind perfectly with both endocannabinoids (such as anandamide and 2-AG) and the phytocannabinoids from cannabis, such as CBG and CBD. Two primary variants of ECS receptors have been discovered, CB1 and CB2.

The widespread distribution of cannabinoid receptors [CB1 and CB2] regulate a variety of central and peripheral physiological functions, including neuronal development, neuromodulatory processes, [and] energy metabolism," reported a 2014 research study. The research also found that CB1 and CB2 receptors are involved in "cardiovascular, respiratory, [and] reproductive functions."



CB1

CB1 is found in greatest density in the brain and central nervous system (CNS), but present throughout the body in lower numbers.

CB2

CB2 receptors are found mostly in the tissues, glands, and organs of the immune system. CB2 receptors have been found in the brain and CNS, but are vastly outnumbered by their CB1 peers.

CBG

According to a 2018 research study, CBG binds with both CB1 and CB2 receptors. This gives CBG greater potential efficacy than cannabinoids that bind with only a single type of receptor, such as CB2. Reported the study's authors, "The results indicate that CBG is indeed effective as regulator of endocannabinoid signaling."

AGONISTS & ANTAGONIST MOLECULES

Medical cannabis studies involving organic chemistry and other specialized research-based disciplines must inevitably employ technical terminology that may be unfamiliar to readers outside those disciplines. Two such terms are agonist and antagonist.

An ***agonist*** is a substance, typically in the form of a chemical or molecule, that initiates a physiological response in an organism when combined with a cellular receptor (a process called ***binding***). It is important to note that an agonist may partially or fully activate the receptor with which it binds and that this status varies based on receptor type. Thus, a particular phytocannabinoid may fully bind with one receptor type, partially bind with another, and possibly feature no binding ability with other receptor types. The level of binding is known as the ***binding affinity***.

An ***antagonist*** is a chemical or molecule that binds to an ECS receptor, but does not activate it. This mechanism results in the ability of antagonists to block the activity of agonists (thus the naming convention), further complicating the interactions of such molecules — and adding credible supporting evidence to the theory of the entourage effect (see ***The Entourage Effect***).

According to a **2015 research study**, CB1 is the most common cannabinoid receptor in the ECS. This research also revealed that cannabinoids bind with receptors and mechanisms outside of the ECS. "The most abundant cannabinoid receptor is the CB1; however, CB2 cannabinoid receptors, Transient Receptor Potential (TRP) channels, and Peroxisome Proliferator Activated Receptors (PPARs) are also engaged by some cannabinoids," reported the study.

Other receptor types being researched may, in the future and after additional research, qualify as members of the ECS receptor family. These include GPR18 and GRP55. A **2012 study** found that GRP18 binds with both the phytocannabinoid THC and the endocannabinoid anandamide.

Reported the study's authors, "[Anandamide] and THC…act as full agonists at GPR18. The [endocannabinoid] 2-AG acts as a full agonist, whereas anandamide is a partial agonist at both CB1 and CB2 receptors."

It should be noted that each receptor type has the ability to bind with multiple types of cannabinoids—sometimes simultaneously, due to the fact that a single cell may feature multiple receptors. Likewise, each cannabinoid can bind with numerous types of receptors. As reported by the above study, "In 1995, Mechoulam and Fride isolated 2-AG from canine intestines and demonstrated binding to both CB1 and CB2 receptors."

ECS **RESEARCH STUDIES**

A variety of both in vitro and in vivo research studies regarding the endocannabinoid system have been conducted since its discovery more than 25 years ago.

A considerable amount of research has been invested into the ECS and how it interacts with internally produced cannabinoids such as anandamide and 2-AG, as well as phytocannabinoids like CBG and CBD.

RECEPTOR DISTRIBUTION

A **2018 study** entitled "Cannabinoid Receptors and the Endocannabinoid System: Signaling and Function in the Central Nervous System" that was published in the ***International Journal of Molecular Sciences*** explored "several potential roles of cannabinoid receptors in the modulation of signaling pathways and in association with several pathophysiological conditions."

Noted the researchers, "The initial discovery and subsequent intensive research of the endocannabinoid system in the last three decades have revealed probably the most well-known retrograde neurotransmission system."

> **It is critical to keep in mind that the study of the endocannabinoid system should be region- and condition-specific, along with the consideration of other neurotransmission systems.**

Scientists now believe that the endocannabinoid system in mammals evolved prior to the phytocannabinoids produced by cannabis. This means that this plant species evolved to adapt to humans and other vertebrates, not the inverse. In a cellular game of impersonating a party guest, phytocannabinoids mimic endocannabinoids to gain entry into the ECS.

This study also demonstrated—despite misperceptions that CB1 receptors are located only in the brain and CNS—the presence of this cellular receptor throughout the body, including in the liver, reproductive system, cardiovascular system, skeletal muscles, and GI tract. This research further hinted at why and how problems with the ECS can lead to conditions such as arthritis, osteoporosis, and Crohn's disease.

Wrote the researchers, "CB1 is also abundantly expressed in the peripheral nervous system, as well as in the peripheral tissues." The researchers concluded, "It is critical to keep in mind that the study of the endocannabinoid system should be region- and condition-specific, along with the consideration of other neurotransmission systems."

DIRECT & INDIRECT MECHANISMS

A **2018 study** entitled "Review of the Neurological Benefits of Phytocannabinoids" that was published in the journal ***Surgical Neurology*** Review investigated the history and use of cannabinoids such as CBG and CBD.

Reported the researchers, "Numerous physical, psychological, and emotional benefits have been attributed to [cannabis] since its first reported use in 2,600 BC in a Chinese pharmacopoeia."

The researchers described how endocannabinoids and phytocannabinoids exert their efficacies via both direct and indirect mechanisms (more support for the entourage effect) and that the ECS governs many bodily physiological systems.

Concluded the study's authors, "Through direct and indirect actions, intrinsic endocannabinoids and plant-based phytocannabinoids modulate and influence a variety of physiological systems [controlled] by the ECS."

SAFETY PROFILE INVESTIGATED

A **2013 study** entitled "The Endocannabinoid System, Cannabinoids, and Pain" that was published in the ***Rambam Maimonides Medical Journal*** investigated the role of the ECS in "a host of homeostatic and physiologic functions, including modulation of pain and inflammation."

The researchers reported that phytocannabinoids and terpenes "have been found to exert significant analgesic effects" for a variety of chronic pain conditions. In unofficial support of endocannabinoid deficiency theory, the research reported that cannabinoids and terpenes are "promising candidates" for the treatment of pain.

The study's authors also noted the safety profile of phytocannabinoids. "Other phytocannabinoids in combination, especially cannabidiol and *β*-caryophyllene, delivered by the oral route appear to be promising candidates for the treatment of chronic pain due to their high safety and low adverse effects profiles," they wrote.

A **2012 research study** entitled "The Evolution and Comparative Neurobiology of Endocannabinoid Signalling" that was published in the journal ***Philosophical Transactions B*** identified CB1 and CB2 receptors as "the focal points for a phylogenetic survey of endocannabinoid signalling."

The study's authors concluded that CB1 and CB2 receptors share more genetic sequence similarity than "any other mammalian GPCRs." The study also found that the two receptors are paralogs, meaning that they originated by duplication of a common ancestral gene in the DNA of the human genome.

GPR18 & GPR55 RECEPTORS

A **2012 research study** defined cannabinoid receptors as featuring "a complex molecular architecture." The study, entitled "Cannabinoid Receptors: Nomenclature and Pharmacological Principles," was published in the journal ***Progress in Neuro-Psychopharmacology and Biological Psychiatry***.

This study identified several aspects of ECS receptors. Among these was the fact that a single ECS receptor can recognize multiple classes of compounds and "produce an array of distinct downstream effects."

The study's authors noted newly discovered receptors that have not been officially categorized as part of the ECS, including GPR18 and GPR55. Regardless of the classification of GPR18, this research noted that this receptor binds with both the phytocannabinoid THC and the endocannabinoid anandamide. This is further evidence that GPR18 may be a valid member of the ECS receptor family.

The study's authors reported that the endocannabinoid anandamide THC "act as full agonists at GPR18," adding, "It is now generally accepted that [the endocannabinoid] 2-AG acts as a full agonist, whereas anandamide is a partial agonist, at both CB1 and CB2 receptors."

Readers wishing to further investigate the GPR18 and GPR55 receptor types should review the **2007 study** entitled "The Orphan Receptor GPR55 is a Novel Cannabinoid Receptor" and the **2014 study** "Activation of GPR18 by Cannabinoid Compounds: A Tale of Biased Agonism," both of which were published in the British Journal of Pharmacology .

NATURAL **POLYMORPHISMS**

This research also reported more nuanced aspects of ECS receptors, including the fact that they can feature natural polymorphisms (availability in several different forms) and "alternative splice variants" (when a single DNA gene produces several different proteins).

A **2008 research study** entitled "The Endocannabinoid System as an Emerging Target of Pharmacotherapy" that was published in the journal Pharmacological Reviews investigated the "current thoughts about the role of endocannabinoids in a given physiological or pathological process" and then surveyed "attempts to explain this role for therapeutic gain."

This detailed study revealed the role of the ECS in the function and health of the reproductive system, musculoskeletal disorders, gastrointestinal and liver conditions, issues of the eye (specifically glaucoma and retinopathy), and cardiovascular and respiratory conditions.

It also examined the existing research literature for the role of the ECS in a variety of conditions, including pain and inflammation, neurological conditions, epilepsy, mental diseases, and asthma—among others.

Reported the researchers, "Cannabis has been used to treat epilepsy for centuries. Hashish was reported to cure the sick son of the chamberlain of the Caliphate Council in Baghdad by the medieval Arab writer Ibn al-Badri."

The study noted how, almost four centuries later, William O'Shaughnessy, an Irish physician and scientist working at the Medical College of Calcutta, confirmed the benefit of cannabis for patients (in the form of hash, a traditional concentrate of the plant in India at the time). O'Shaughnessy found the plant to be effective for treating convulsions, muscle spasms, and pain. "The benefit of cannabis in epilepsy was also reported by a British neurologist (**Reynolds, 1890**), but the medicinal use of cannabis was prohibited in the early 20 th century in most countries."

A **2008 research study** entitled "The Endocannabinoid System: An Osteopath Perspective" that was published in the ***The Journal of the American Osteopathic Association*** considered the origins of the ECS, including a review of the existing research literature. The study's authors found that, in 1992—the year that the ECS was discovered—only two citations for ECS research were listed. Fifteen years later, in 2007, the term "endocannabinoid" yielded 480 study citations.

MORE RECEPTOR **DISTRIBUTION DATA**

A **1997 human trials study** involved 11 subjects—including one fetal, two neonatal, and eight adult subjects—found that cannabinoid receptors "were distributed in a heterogeneous fashion throughout the adult human brain and spinal cord."

The study revealed that the greatest density of ECS receptors in the brain was located in the frontal and limbic lobes, with the lowest densities in the primary sensory and motor cortical regions.

Concluded the study's authors, "Cannabinoid receptor binding sites in the human brain are localized mainly in: Forebrain areas associated with higher cognitive functions; forebrain, midbrain, and hindbrain areas associated with the control of movement; and in hindbrain areas associated with the control of motor and sensory functions of the autonomic nervous system."

More information is provided by the **2010 study** entitled "Endocannabinoid Binding to the Cannabinoid Receptors: What Is Known and What Remains Unknown" that was published in the journal Current Medical Chemistry , as well as the **2008 study** "Cannabinoid Receptors: Where They Are and What They Do" that was published in the ***Journal of Neuroendocrinology.***

PART 4
CLINICAL ENDOCANNABINOID DEFICIENCY

Dr. Ethan Russo, an American neurologist and author who is director of research and development for the International Cannabis and Cannabinoids Institute, in 2004 observed a characteristic of the ECS that he labeled ***Clinical Endocannabinoid Deficiency Syndrome***, or CED. CED is also sometimes referred to as ***Endocannabinoid Deficiency Theory.***

> **It's not that you're balancing the endocannabinoid system. It's the endocannabinoid system's job to balance the body.**

The celebrated cannabinoid researcher suggested that deficiencies in the ECS—in terms of available cannabinoids such as anandamide, CBG, and CBD—could result in a wide range of common diseases and conditions, including fibromyalgia, migraine headaches, and even cancer.

Russo published his observations in a **groundbreaking research study** entitled "Clinical Endocannabinoid Deficiency (CED): Can this Concept Explain Therapeutic Benefits of Cannabis in Migraine, Fibromyalgia, Irritable Bowel Syndrome, and Other Treatment-resistant Conditions?" in the journal ***Neuro Endocrinology Letters***. In the study, Russo investigated the role of ECS health in a small range of common conditions.

Northern California-based cannabis researcher **Mara Gordon** believes that the best mental framework for properly understanding the position of the ECS in human health involves the system not necessarily being itself balanced, but rather a model in which the ECS balances other critical bodily systems and functions. This includes immune response, metabolism, and mood.

"It's not that you're balancing the endocannabinoid system. It's the endocannabinoid system's job to balance the body," said Gordon during a **2019 podcast** interview.

CED RESEARCH STUDIES

A variety of research studies have been conducted during the past three decades by Russo, Mechoulam, and others that have provided insight into the possible mechanisms behind an endocannabinoid deficiency and its potential relationship to human health.

The **2016 study** conducted by Russo entitled "Clinical Endocannabinoid Deficiency Reconsidered: Current Research Supports the Theory in Migraine, Fibromyalgia, Irritable Bowel, and Other Treatment-Resistant Syndromes" reported that an ECS deficiency could lead to conditions such as Alzheimer's disease, depression, and a variety of gastrointestinal conditions (among others).

"When first proposed, this theory was based on genetic overlap and comorbidity, patterns of symptomatology that could be mediated by the endocannabinoid system, and the fact that exogenous cannabinoid treatment frequently provided symptomatic benefit," wrote Russo.

The study explained how an ECS deficiency could lead to a variety of brain disorders with their origins in neurodegeneration, including Alzheimer's disease and Parkinson's disease. "The theory of CED was based on the concept that many brain disorders are associated with neurotransmitter deficiencies, affecting acetylcholine in Alzheimer's disease, dopamine in parkinsonian syndromes, and serotonin and norepinephrine in depression—and that a comparable deficiency in endocannabinoid levels might manifest similarly in certain disorders that display predictable clinical features as sequelae of this deficiency."

Concluded the report, "Additional studies have provided a firmer foundation for the theory, while clinical data have also produced evidence for decreased pain, improved sleep, and other benefits to cannabinoid treatment and adjunctive lifestyle approaches affecting the ECS."

THE ECS & DEPRESSION

A **2005 study** entitled "Is There a Role for the Endocannabinoid System in the Etiology and Treatment of Melancholic Depression?" that was published in the journal ***Behavioral Pharmacology*** investigated the neurobiology of depression and how the state of the ECS, including a deficiency, might influence the onset of this common psychological condition.

The study's authors reported, "The endocannabinoid system may play a role in the etiology of melancholic depression." The study identified a mechanism in which depression may result from a blockade of CB1 receptors in the brain—a situation in which these receptors are basically turned off and no longer active. In such subjects, the study noted that their depression manifested as "reduced food intake, heightened anxiety, increased arousal and wakefulness, deficits in extinction of aversive memories, and supersensitivity to stress."The study concluded that a deficiency in the ECS may be a root cause of depression.

PART 5
THE ENTOURAGE EFFECT

With hundreds of types of cannabinoids and terpenes, any potential influences that these molecules play on one another is of considerable importance in terms of the medicinal efficacy of cannabis products.

ANOTHER MECHOULAM DISCOVERY

In 1998, Israeli researchers Raphael Mechoulam (the scientist who first isolated THC in 1964) and S. Ben-Shabat published a **research paper** entitled "An Entourage Effect: Inactive Endogenous Fatty Acid Glycerol Esters Enhance 2-arachidonoyl-glycerol Cannabinoid Activity." In the study, the scientists first identified and described a potential synergy between cannabinoids that they dubbed the ***entourage effect***.

> **...cannabis efficacy is an issue of the whole being greater than the mere sum of its parts.**

In basic terms, this theory observed that cannabinoids and terpenes engage in intricate mechanisms in which they boost and buffer one another, sometimes increasing or decreasing the efficacy of a particular molecule—and the overall effect of a cannabis sample or formulation. In essence, the combined efficacy of a group of cannabinoids is greater than the sum of the individual effects of the molecules. In other words, cannabis efficacy is an issue of the whole being greater than the mere sum of its parts.

The theory of the entourage effect is important due to the reality of the ways in which modern cannabis products are formulated and consumed. Although isolates of individual molecules, such as CBG and CBD, are available, they are rare. Typically, patients and consumers utilize broad-spectrum or full-spectrum products containing a wide variety of cannabinoids and possibly terpenes.

31 https://www.ncbi.nlm.nih.gov/pubmed/9721036

CANNABINOID **RATIOS**

It should be noted that the overall potency of a particular hemp or cannabis formulation depends on not only the specific cannabinoids and terpenes present, but also their ratios. Full-spectrum products, in which no cannabinoids or terpenes have been added or removed, obviously reflect the inherent profile of the particular plant(s) used to create them (in legal markets, this is documented by a Certificate of Analysis, or CoA, from an independent and certified testing laboratory).

Some products are formulated with particular cannabinoid ratios. Examples include both topicals and tinctures featuring ratios such as 20:1, 3:1, and 1:1 of cannabinoids such as CBD and THC.

RESEARCH OF **DR. ETHAN RUSSO**

In 2011, thirteen years following publication of the Mechoulam/Ben-Shabat research, Dr. Ethan Russo expanded on the theory of the entourage effect with his pinnacle **research paper** entitled "Taming THC: Potential Cannabis Synergy and Phytocannabinoid-terpenoid Entourage Effects."

In the study, Russo emphasized the analgesic qualities of a mix of different cannabinoids and the role of CBD in this mechanism. "The synergistic contributions of cannabidiol to cannabis pharmacology and analgesia have been scientifically demonstrated," he wrote. The study identified other cannabinoids that have been found to contribute to an entourage effect, including CBG. "Other phytocannabinoids, including tetrahydrocannabivarin [THCV], cannabigerol, and cannabichromene [CBC] exert additional effects of therapeutic interest," reported the study.

CBG **ANTIFUNGAL QUALITIES**

The research also identified the antifungal properties of multiple cannabinoids, including CBG and CBD. "It has been known for some time that CBG and CBC are mildly antifungal, as are THC and CBD against a cannabis pathogen."

> **Normally, CBG appears as a relatively low concentration in the plant, but recent breeding work has yielded cannabis chemotypes lacking in downstream enzymes that express 100% of their phytocannabinoid content as CBG.**

The researchers also found that new cultivars of cannabis are being bred that yield significantly greater amounts of CBG. "Normally, CBG appears as a relatively low concentration in the plant, but recent breeding work has yielded cannabis chemotypes lacking in downstream enzymes that express 100% of their phytocannabinoid content as CBG."

32 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3165946/

PART 6
CANNABINOIDS

Unlike terpenes—which are produced by cannabis, as well as tens of thousands of other plant species in nature—cannabinoids (as their name suggests) are unique to cannabis. More than 100 cannabinoids have been identified, but most of these are variants, or ***analogs***, of a considerably smaller set of core molecules.

It should be noted that no individual cultivar or plant produces the entire set of cannabinoids that are possible in the species. The same is true for terpenes. The genome provides merely a "capability set" for the production of particular cannabinoid and terpene profiles. The exact manifestation of the genome's blueprint is determined by environmental factors.

For example, CBG manifests as several analogs of itself other than its ***neutral form*** (CBG). These include CBGA, CBGV, and CBGVA (see ***Cannabinoid*** Analogs below for more information).

Major cannabinoids are defined as those found in the greatest quantities (percentages) in cannabis. CBG is defined as a minor cannabinoid because it is available in relatively low quantities in mature cannabis plants produced by common cultivars (strains).

ISOLATE VS. **BROAD-SPECTRUM** VS. **FULL-SPECTRUM**

Three primary categories of cannabis extract (concentrate) products exist: Isolate, broad-spectrum, and full-spectrum. These three types are significantly different from one another. Medical professionals and consumers who do not understand the pros and cons of each suffer a distinct disadvantage in terms of selecting optimal cannabis products.

An isolate, typically in the form of a crystal or powder (but also available as a liquid or pre-infused into a beverage) is a concentration involving a single molecule. Thus, a CBD isolate features none of the other cannabinoids or terpenes produced by the cannabis plant. In terms of what it includes, an isolate is the most limited and restricted of all extraction types. This can be either good or bad, depending on the specific use case scenario and desired outcome.

Broad-spectrum extracts feature most, but not all, of the constituent elements of the original plant. The molecule that is typically removed is THC, in an effort to gain a federally legal product or avoid an overtly psychoactive effect.

Full-spectrum extracts contain the complete complement of original cannabinoids and terpenes from the cannabis plant. Sometimes called "whole plant," products featuring full-spectrum cannabis are perceived by some wellness practitioners and patients to be healthier due to a potential synergistic effect.

The dynamic observed is that the interaction of these molecules results in a result that is greater than the sum of its parts (the individual cannabinoids and terpenes). *(**See Part 5: The Entourage Effect**)*

Note: Some modern extraction and manufacturing processes employed in the production of cannabis concentrates and extracts may strip away, or degrade, relatively delicate cannabinoid and terpene molecules. Thus, even products that claim to be full-spectrum are not necessarily capturing and delivering the complete cannabinoid profile and terpene profile of the original plant.

CANNABINOID **ANALOGS**

Readers are aware of the two major categories of cannabinoids, the phyto (plant-based) and endo (produced by the body) varieties. Other important differences should be addressed, however. Some of these discrepancies pertain to where a molecule exists within its lifecycle or, in some cases, the environmental conditions to which it has been exposed (including UV light, oxygen, and temperature).

There are three primary categories of cannabinoids: Neutral ("active") versions, acidic precursors, and varin versions (explained in detail below). It should be noted that varin versions feature varin-specific acidic precursors, such as CBGVA. Each variant of a single neutral cannabinoid, such as CBG, is labeled an analog. Thus, CBG, CBGA, CBGV, and CBGVA are all analogs of one another.

According to research published in the 2016 book Neutraceuticals , most cannabinoids are categorized as analogs of the following core set of eight individual variants:

1. Cannabichromene (CBC)
2. Cannabicyclol (CBL)
3. Cannabidiol (CBD)
4. Cannabielsoin (CBE)
5. Cannabigerol (CBG)
6. Cannabinol (CBN)
7. Cannabitriol (CBT)
8. Tetrahydrocannabinol (THC)

For example, these researchers identified seven different analogs of CBD, including CBD (the neutral version), CBDA, CBDV, CBDVA, CBD-C1 (cannabidiorcol), CBD-C4 (cannabidiol-C4 or nor-cannabidiol), and CBDM (cannabidiol monomethyl ether).

According to a **2017 study**, this accounts for the wide disparity in the number of cannabinoids produced by the plant that are cited in research studies and the popular press.

CANNABINOID ANALOGS

Cannabinoids exist not in a single state, but rather multiple versions of a source molecule called an *acidic precursor*. These variants are called *analogs*. This is significant to health and wellness due to the fact that different analogs of a single cannabinoid deliver significantly different efficacies. For example, THC, the neutral analog of this cannabinoid, increases appetite. However, THCV, its varin analog, has been found to decrease appetite.

ACIDIC PRECURSORS ARE LIKE THE LARVAL STAGE OF ALL CANNABINOIDS – INCLUDING VARINS AND NEUTRAL VARIANTS.

THEY ALLOW SCIENTISTS AND CULTIVATORS TO FINE-TUNE PRODUCTS TO CREATE PARTICULAR CANNABINOID PROFILES.

OTHER

OTHER ANALOGS DERIVED FROM ACIDIC PRECURSORS:

CBNA
CBVNA
CBGA
CBGNA

CBG ANALOGS

The cannabinoid CBG is produced as seven different analogs, or versions. Different effects are gained from CBG, CBGA, CBGV, and the other variants of this family of sibling phytocannabinoids. CBGV appears to increase the bioavailability of CBD, while research has suggested CBG decreases ocular pressure along with a long list of other potential applications.

Like CBD, CBG also features seven cannabinoid analogs. These include CBG (the neutral version), CBGA (the acidic precursor to CBG), CBGV (the varin version), cannabinerolic acid (CBNA), cannabigerovarinic acid (CBNVA), and two "cousin molecules" (technically dubbed ***monomethyl esters***) of CBG and CBGA called, respectively, CBGM and CBGAM.

ACIDIC PRECURSORS

Acidic precursors, indicated by an "A" following the cannabinoid name (and sometimes denoted as CBD-A or CBDa), are best considered the "larval stage" of a cannabinoid. Each analog of an acidic precursor delivers its own distinct set of medicinal qualities. Thus, a consumer might gain greater value from consuming both CBGA and CBG (depending on dosing and their specific condition) than either of these cannabinoids individually.

"In clinical practice, we often see cannabis products that contain large amounts of CBGA providing impressive value for patients who struggle with bowel diseases, such as irritable bowel syndrome, Crohn's disease, ulcerative colitis, and recurrent nausea," said Dr. Ben Caplan, a Boston-based family physician and Founder of the CED Foundation, in an exclusive interview for this white paper.

A **2018 research study** entitled "Cannabigerol Action at Cannabinoid CB1 and CB2 Receptors and at CB1–CB2 Heteroreceptor Complexes" that was published in the journal ***Frontiers in Pharmacology*** confirmed the role of acidic precursors as the genesis of all cannabinoids.

"In the cannabis plant, all cannabinoids are biosynthesized in the acid form, mainly THCA, CBDA, etc. CBGA is the first molecule formed in the ***biosynthetic pathway*** and the substrate of Δ9-tetrahydrocannabinol-synthase and CBD-synthase," reported the study's authors.

VARIN ANALOGS

Varin, analogs of cannabinoids, indicated by a "V" following the cannabinoid name (and sometimes denoted as CBD-V or CBDv), are slightly different versions of their neutral siblings.

Chemically, varin versions feature fewer carbon atoms, which changes the half-life of the molecule (the time it takes for the concentration in blood plasma or the total amount in the body to be reduced by 50 percent). Doug's Varin is an example of a cultivar that produces unusually large volumes of the varin cannabinoid THCV.

Some users claim that varin cannabinoids feature a shorter duration of effect than other cannabinoids. While the efficacy of varins is often quite similar to that of their non-varin analogs, there are sometimes significant—and even polar opposite—differences. For example, while THC delivers psychoactive effects at nearly all dosage levels, THCV is psychoactive only at relatively large doses.

CBG is a common cannabinoid found in relatively low quantities in cannabis. It exemplifies the progression of chemical morphology that occurs in the life of a cannabinoid molecule. The acidic precursor to CBG, CBGA, produces the acidic precursors to both CBD (CBDA) and THC (THCA). CBDA and THCA, in turn, morph into CBD and THC, respectively, under certain environmental conditions (such as the application of heat, a process called ***decarboxylation***).

Adding complexity to the issue is the fact that varins feature their own acidic precursors. Thus, CBGV is produced by CBGVA. CBGVA transmogrifies into THCVA, CBDVA, and CBCVA (similar to how the acidic precursors CBDA and THCA result in CBD and THC, respectively). Varins exemplify the central role played by CBG and its acidic precursor CBGA.

CONSUMPTION AVENUES & BIOAVAILABILITY

For consumers who are serious about health and wellness, the smoking of cannabis is typically not a consideration. Despite Hollywood stereotypes, many avenues of consumption are available to accommodate a wide variety of lifestyles, preferences, and desired outcomes.

An important term for consumers of cannabis products is ***bioavailability***. Technically, this is the percentage of a drug that is present and active in the bloodstream.

For the average consumer of cannabinoids and terpenes, there are three aspects of bioavailability of importance: Onset, peak, and duration. Onset is when the effects of a cannabis or CBG product begin to take effect. Peak is when the effects are the greatest and typically occurs roughly midway through the lifecycle of the molecule in one's body. Duration is the total time over which a chemical such as CBG or CBD delivers effects, regardless of potency.

Ingestion is when one eats a cannabis product. Because it is metabolized by the stomach and liver, this route results in modified molecules that deliver different efficacy. For example, when the cannabinoid THC is metabolized by the liver, it becomes 11-hydroxy THC (sometimes denoted as delta-11). In this form, the molecule more easily crosses the highly selective blood-brain barrier to bind with CB1 receptors and is more potent than when inhaled.

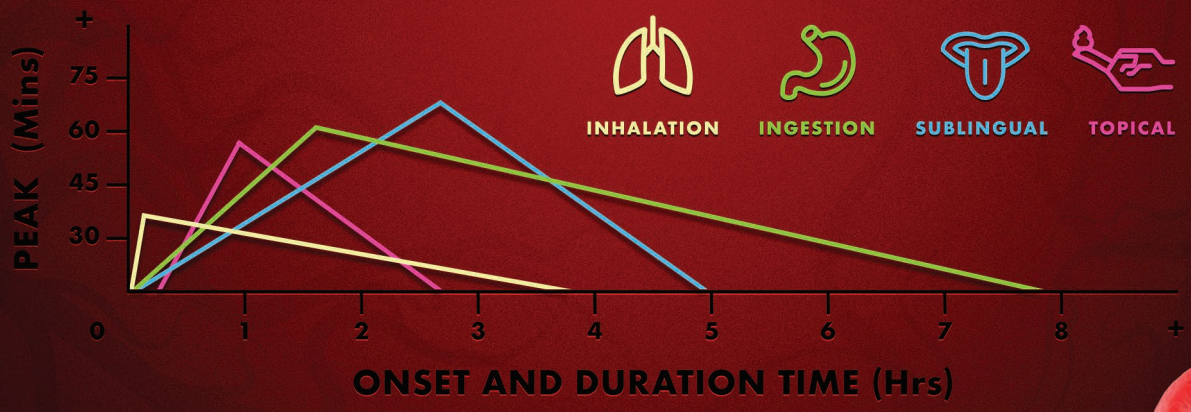
Inhalation of cannabinoids and terpenes involves an onset of approximately 2-2.5 minutes as the molecules travel from the lungs to the heart, where they are pumped directly to all areas of the body. Inhalation peaks in potency typically under an hour and has an overall duration of three to five hours.

Topical products involve creams, salves, balms, and spray-ons that can address localized problems, such as inflammation and swelling from exercise or injury. Cannabinoids such as CBG can also be applied via transdermal patches. Topicals feature a relatively fast onset, but the overall bioavailability of such products varies significantly and is largely dependent on the localized issue being treated.

UNDERSTANDING BIOAVAILABILITY

Technically speaking, bioavailability is the amount of a molecule or chemical that is readily available in the bloodstream. In terms of the consumption of CBG and CBD products, bioavailability features three stages: **Onset**, **peak**, and **duration**. Onset is the length of time required for the molecule to begin having an effect on the consumer. Peak is when the effects of a molecule or chemical are greatest, often in the middle of its overall duration. Duration is the total length of effect of a molecule. Different paths of consumption result in vastly different bioavailability.

BIOAVAILABILITY DEPENDS ON DELIVERY



CBG VERSATILITY

CBG and other cannabinoids are among the most versatile produced by the plant kingdom. CBG and CBD lend themselves especially well to topicals due to their ability to permeate the epidermal layer. However, a longer bioavailability can be achieved when these molecules are delivered via ingestion.

Sublingual consumption involves use of a liquid tincture that is absorbed in the mucosa (soft tissue below the tongue). Unlike ingestion, which involves metabolism of molecules in the stomach and liver, sublingual absorption transports chemicals directly to the bloodstream. The bioavailability of sublingual consumption depends on whether a tincture is based in oil or alcohol, with the latter providing faster, more complete absorption. Onset of sublingual remedies results in 10 to 20 minutes, placing it between inhalation and ingestion in terms of onset.

RELATIONSHIP TO TERPENES

Terpenes are a family of 200 molecules produced by the cannabis genome that display characteristics that are strikingly similar to those of cannabinoids. Once thought to merely convey intense aroma (as an evolutionary defense mechanism against pests and predators within the plant), research during the past several decades has revealed that terpenes deliver medicinal efficacy that approximates that of their chemical cousins the cannabinoids.

Scientists theorize that plants other than cannabis may produce cannabinoids. However, this has yet to be proven. Terpenes, however, appear throughout nature. Pinene, one of the major terpenes produced by cannabis that conveys an aroma of pine needles and rosemary, is also manufactured by a large number of other plants (including pine trees and rosemary).

Terpenes are important not only because of their medicinal value, but also because they are the molecular ancestors to cannabinoids. In their **2015 book** entitled ***Cannabinoids in Neurologic and Mental Disease***, authors Fabriana Piscitelli and Vincenzo Di Marzo explored the metabolic lifespan of cannabinoids.

“The name ‘cannabinoid’ indicates any secondary metabolite from various strains of cannabis with biogenetic origin from a terpene , normally geranyl pyrophosphate , and a phenol , i.e., olivetol or olivetolic acid,” wrote the authors.

The relationship between terpenes and cannabinoids is illustrated by the terpene beta-caryophyllene (BCP). Discovered in 1964 by Raphael Mechoulam and his research team in Israel, this chemical was first categorized as a terpene. In 2008, however, a **German study** found BCP to exhibit traits indicating that it is a cannabinoid.

The study demonstrated that BCP displays a strong binding affinity for the ECS receptor CB2, which is uncommon for terpenes and a characteristic of cannabinoids like CBD and THC. Reported the study’s authors, “None of the other major cannabis terpenes showed a significant displacement...in either CB2 or CB1 receptor...binding.”

PART 7
CANNABIGEROL

Of the more than 100 special medicinal molecules produced by the cannabis plant called cannabinoids, few are as unique or important as ***cannabigerol***, or CBG. Unlike its infamous sibling THC, CBG produces no overt psychoactive effect. It does, however, deliver a broad spectrum of health and wellness value.

CBG was discovered in 1964 by Raphael Mechoulam and his team at Hebrew University in Israel, the researchers that first isolated and synthesized THC in the same year. The importance of CBG is rooted in the fact that it is the source of several other cannabinoids—including the most common variants, CBD and THC.

Some researchers believe that CBG may partially counteract the psychoactive effect of THC (similar to CBD), especially when the latter is consumed in potent doses or by novice consumers.

MINOR BUT **COMMON**

Technically, CBG is categorized as a minor cannabinoid and available in relatively low quantities from most cultivars (strains) of cannabis. As measured in weight by volume, CBG typically composes below 1 percent, although cultivars and individuals may reach 6-8 percent. Commonly available cultivars of cannabis rarely exceed 10 percent CBG.

While it is found in relatively low volumes, CBG offers the benefit of being produced by ***all*** cultivars of cannabis. According to noted endocannabinoid system researcher Dr. Ethan Russo, CBG can best be thought of as "pre-THC" or "pre-CBD." Wrote Russo, "[CBG] is more or less a way station on the path to these other cannabinoids." The fact that most of the CBG produced by cannabis is converted to other cannabinoids explains why it is extremely common in all cultivars, but present in relatively low quantities.

In fact, cannabis cultivars that feature relatively high volumes of CBD or THC tend to contain less CBG. It is theorized that the root of this dynamic is the fact that such plants are more efficient at converting the acidic precursor analog of CBG, CBGA, to other cannabinoids (***this mechanism is explained in detail below***).

Hemp cultivars (defined as cannabis cultivars that contain less than 0.3 percent THC in the U.S. and Canada and under 0.2 percent in the European Union), because they are bred to contain under the legal limit for hemp, frequently contain significantly more CBG. In fact, some industrial hemp cultivars have tested with in excess of 90 percent CBG.

Hemp cultivars, because they are bred to contain under the legal limit for hemp, frequently contain significantly more CBG.

MOTHER OF CANNABINOIDS

Molecules transmogrify from one form to another based on exposure to environmental elements such as UV (Ultraviolet) light, heat, and oxygen. All cannabinoids evolve (in something called the ***biosynthetic pathway***) from something called an acidic precursor. Acidic precursors can be considered the "larval form" of the neutral cannabinoid that results. From a molecular perspective, acidic precursors are extremely similar to their neutral and varin versions.

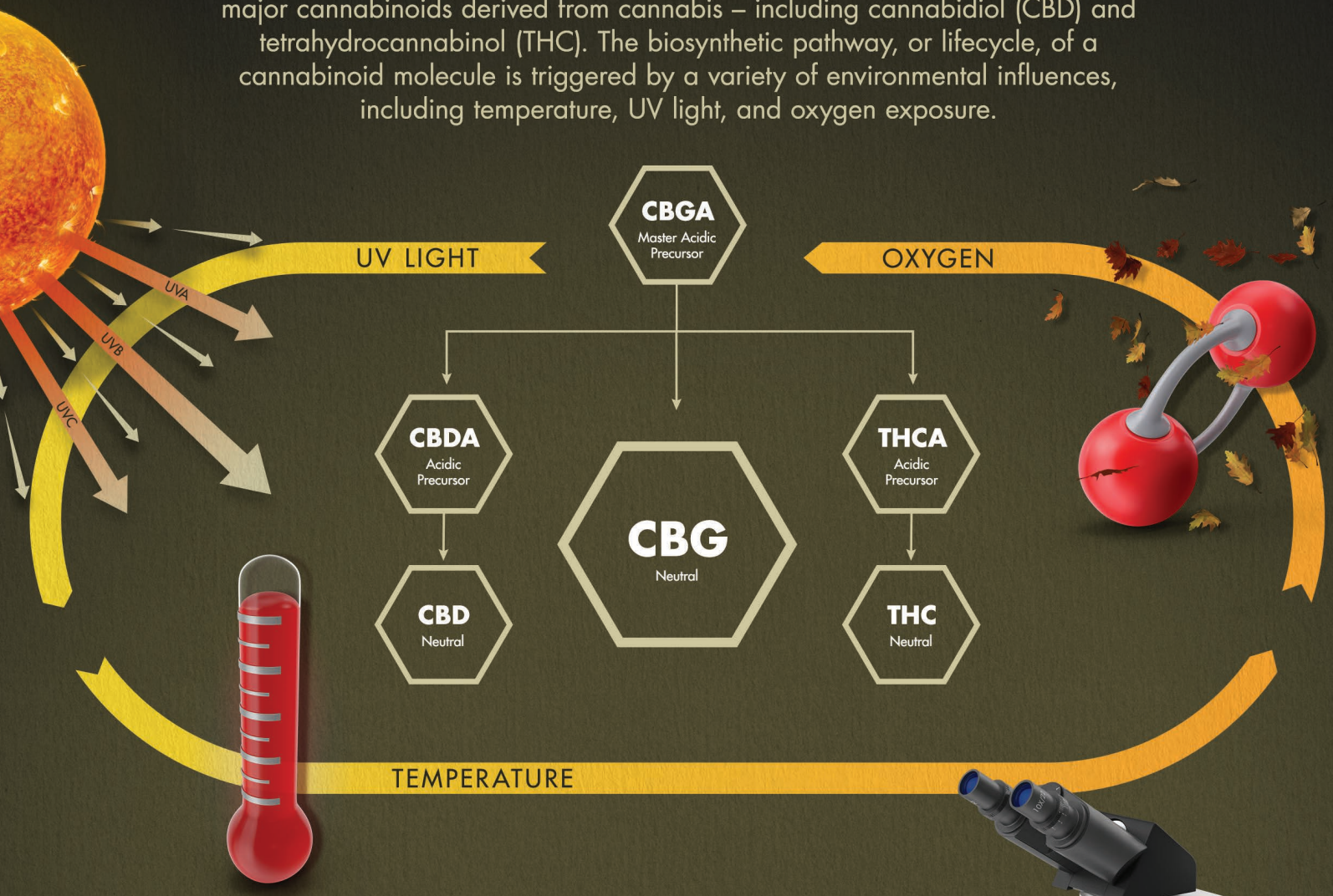
A **research 2005 study** identified CBG as the metabolic source of the most dominant phytocannabinoids, including CBC, CBD, and THC. Reported the study's authors, "CBG is the direct precursor of the cannabinoids CBD, THC, and CBC. Plants strongly predominant in CBG have been found in different fibre hemp accessions."

Reported a **2018 research study**, "In the cannabis plant, all cannabinoids are biosynthesized in the acid form, mainly THCA, CBDA, etc. CBGA is the first molecule formed in the biosynthetic pathway."

The acidic precursor to CBG, CBGA (often denoted as CBG-A or CBGa in research studies and literature reviews), plays an even more central and important role than CBG. This is because it is the source of the acidic precursors of other critical cannabinoids, including those for CBD (CBDA), THC (THCA), and cannabichromene (CBC; CBCA).

CBG MOTHER OF CANNABINOIDS

CBGA, the acidic precursor to cannabigerol (CBG), is the genesis of many major cannabinoids derived from cannabis – including cannabidiol (CBD) and tetrahydrocannabinol (THC). The biosynthetic pathway, or lifecycle, of a cannabinoid molecule is triggered by a variety of environmental influences, including temperature, UV light, and oxygen exposure.



SEVEN CANNABINOIDS IN ONE

CBGA results in not only seven analogs of itself, but produces the acidic precursors for all other major cannabinoids. By understanding the lifecycle of this molecule, scientists can craft special cultivars of cannabis and create products with unique and specialized cannabinoid profiles.

If not for CBGA, molecules such as CBD and THC would not exist.

In this biosynthetic pathway, CBGA converts to CBCA, which in turn yields CBC after exposure to UV light or heat (via the decarboxylation process). If not for CBGA, molecules such as CBD and THC would not exist.

It should be noted that claims that CBG, the neutral version of the cannabinoid, produces the neutral version of all other cannabinoids (including CBC, CBD, and THC) are, technically, incorrect. The mechanism is indirect, with CBGA acting as a "master" acidic precursor, producing other acidic precursors—but never directly producing the neutral version of other cannabinoids.

POTENTIAL **FOURTH** CHEMOTYPE

Beyond its central role as the genesis of all other cannabinoids produced by cannabis, CBG has been shown to dominate an entire slice of the cannabis sativa genome. This phytocannabinoid was identified by a **2002 research study** and confirmed by multiple follow-on studies as a potential ***fourth cannabis chemotype*** —in addition to the universally recognized sativa, indica, and ruderalis. In simple terms, a chemotype can be thought of as a sub-species.

Reported the study, "A rare, additional chemotype, characterized by a very low content of both THC and CBD and with CBG as the predominant constituent, was later identified."

The topic of CBG categorization and the observance that it is not merely a random cannabinoid was further examined in a **2005 follow-on study** by the same group of researchers entitled "The Inheritance of Chemical Phenotype in Cannabis Sativa: Cannabigerol Predominant Plants." This study cited the fact that CBG typically (in sativa, indica, and ruderalis chemotypes) is present in percentages (in weight by volume) significantly under 10 percent.

CBG-rich chemotypes, however, have been observed to contain as much as 94 percent CBG. These same cultivars feature as little as 0.001 percent THC, the dominant cannabinoid in most modern cultivars that typically constitutes 8-25 percent of the flowers of the plant. These cultivars are believed to have evolved and still grow naturally in areas of high altitude that favor particular hemp strains that are acclimated to this type of microclimate.

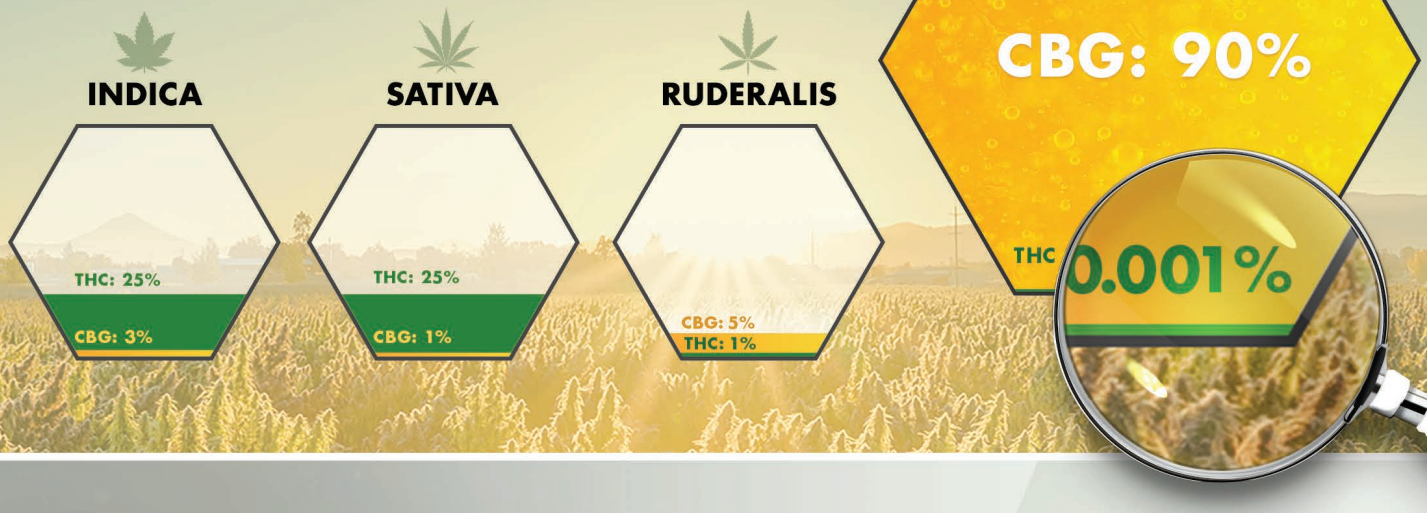
CBG-rich chemotypes, however, have been observed to contain as much as 94 percent CBG. These same cultivars feature as little as 0.001 percent THC, the dominant cannabinoid in most modern cultivars that typically constitutes 8-25 percent of the flowers of the plant. These cultivars are believed to have evolved and still grow naturally in areas of high altitude that favor particular hemp strains that are acclimated to this type of microclimate.

The 4TH Chemotype?

What's a chemotype?

In simple terms, think of a chemotype as a sub-species. For example, a timber wolf and toy poodle are both canines, but they're quite different.

You've probably heard of popular chemotypes like Sativa and Indica, or the lesser-known Ruderalis, but did you know scientists have discovered a possible 4th chemotype? Research goes back as far as 1987, but more recently, studies in 2002 and 2005 have documented a fourth chemotype that features extremely large volumes of CBG and very low levels of THC.

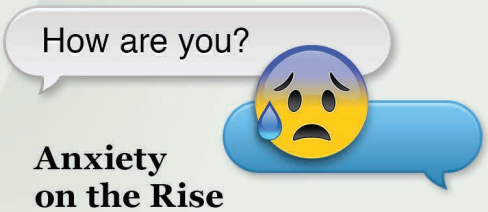


CBG's Powerful Sidekick

Research found that CBG-dominant chemotypes consistently offer significantly larger volumes of the "companion molecule" CBD. Those molecules join forces to provide additional effectiveness for systemic inflammation, anxiety, and pain.

50 MILLION AMERICANS

Chronic pain is experienced by 50 million Americans. Studies have shown that CBD can play a valuable role in the treatment of pain and the inflammation that is often associated with it.



Anxiety on the Rise

40 million Americans suffer from social anxiety, half of whom also experience depression. Studies reveal that CBD and CBG reduce anxiety.

Low THC, Big Potential

With such little THC content, CBG products open up previously untapped consumers.

- Children & Seniors
- Armed Forces
- Aviation
- Emergency Services
- Teachers

Future research may reveal that such regions have served as the genesis for CBG-heavy ***landrace cultivars*** (those that have evolved naturally, void of human intervention in the form of controlled breeding). Whether these varieties constitute a fourth chemotype of cannabis remains to be confirmed by further research studies. Still unnamed, this hypothetical chemotype would chemically compliment CBD. Like CBD, CBG delivers no overt psychoactivity, making it safe for children, seniors, and those in sensitive job positions.

CBD: **COMPANION MOLECULE**

Other cases of CBG-rich chemotypes were reported by the study's authors. Of special significance, the study revealed that cannabis cultivars rich in CBG also feature a companion, or "complementary cannabinoid." This molecule is typically CBD. The researchers found that CBG-dominant genotypes feature up to 15 percent CBD (an amount far greater than exhibited in common sativa and indica chemotypes).

Thus, it is believed that product formulations rich in both of these phytocannabinoids may provide enhanced value due to the synergy of their combined effects (see ***Part 5: The Entourage Effect***).

"Grassi found an individual with a CBG proportion of 80–85% in the cannabinoid fraction in a Southern Italian hemp accession*. Recently, we observed CBG predominance (85%) in an individual from the Ukrainian fibre cultivar USO-31. In each of these CBG-predominant plants, CBD was the single significant complementary cannabinoid," wrote the researchers in the above cited research study.

CANNABIGERIVARIN (CBGV)

One of the most beneficial medicinal cannabinoids offered by the cannabis herb is cannabigerivarin (CBGV), an analog of CBG.

Like most cannabinoids, CBGV produces no psychoactive effects when ingested or inhaled. Researchers theorize that it may boost the ability of the cellular receptors in the ECS to more readily bind with THC molecules. Some studies suggest that CBGV also boosts CBD metabolism within the body, making CBD more potent when paired with this cannabinoid.

* (According to The Ohio State University, an **accession** is a "group of related plant material from a single species which is collected at one time from a specific location. Each accession is an attempt to capture the diversity present in a given population of plants.")

PART 8
CBG RESEARCH

The following are major peer-reviewed research studies have revealed the value of CBG:

A **2018 study** entitled "Cannabigerol Action at Cannabinoid CB1 and CB2 Receptors" that was published in the journal ***Frontiers in Pharmacology*** investigated the binding affinity of CBG with the CB1 and CB2 receptors of the ECS. The study reported, "The results indicate that CBG is indeed effective as [a] regulator of endocannabinoid signaling."

A **2017 research study** involving mice entitled "Beneficial Effect of the Non-psychotropic Plant Cannabinoid Cannabigerol on Experimental Inflammatory Bowel Disease" that was published in the journal ***Biochemical Pharmacology*** explored how CBG might help those suffering from inflammatory bowel disease (IBD). "We investigated the effect of CBG, a non-psychotropic cannabis-derived cannabinoid, in a murine model of colitis," reported the study.

Stated the researchers, "CBG attenuated murine colitis, reduced nitric oxide production in macrophages (effect being modulated by the CB2 receptor)," concluding that "CBG could be considered for clinical experimentation in IBD patients."

A **2016 research study** entitled "Cannabigerol is a Novel, Well-tolerated Appetite Stimulant" that was published in the journal ***Psychopharmacology*** investigated the ability of CBG to stimulate appetite (hyperphagia) and was the first to prove that this molecule increases appetite. The study also identified the safety profile of CBG, reporting that it conveyed "no adverse effects on any parameter in the neuromotor tolerability test battery."

Regarding the toxicity and safety of CBG, the study's authors reported, "CBG produced no adverse effects on any parameter in the neuromotor tolerability test battery." They concluded, "We demonstrate for the first time that CBG elicits hyperphagia by reducing latency to feed and increasing meal frequency, without producing negative neuromotor side effects." The study recommended "investigation of the therapeutic potential of CBG for conditions such as cachexia and other disorders of eating and body weight regulation."

A **2015 research** study entitled "Neuroprotective Properties of Cannabigerol in Huntington's Disease" published in the journal ***Neurotherapeutics*** found that CBG may help in the fight against Huntington's disease (HD). This in vivo study employed mice as test subjects.

HD is a condition involving "a fatal genetic disorder that causes the progressive breakdown of nerve cells in the brain. It deteriorates a person's physical and mental abilities during their prime working years and has no cure," according to the **Huntington's Disease Society of America**.

The study observed that cannabinoids such as CBG deliver medical benefits through a variety of channels and mechanisms. "Different plant-derived and synthetic cannabinoids have shown to be neuroprotective in experimental models of Huntington's disease through cannabinoid receptor-dependent and/or independent mechanisms," reported the study.

The researchers emphasized the neuroprotective qualities delivered by CBG. "CBG was extremely active as a neuroprotectant in mice, improving motor deficits and preserving striatal neurons against toxicity." The study also noted the antioxidant properties of CBG, stating that it "improved the levels of antioxidant defenses."

The study's authors concluded, "Our results open new research avenues for the use of CBG, alone or in combination with other phytocannabinoids or therapies, for the treatment of neurodegenerative diseases such as HD."

A **2015 study** entitled "Effect of Non-psychotropic Plant-derived Cannabinoids on Bladder Contractility: Focus on Cannabigerol" that was published in the journal ***Natural Product Communications*** investigated the characteristics of multiple cannabinoids, including CBG, CBD, CBDV, THCV, and CBC . The study found CBG to offer the greatest efficacy among the cannabinoids, followed by THCV, CBD, and CBDV, in this order.

The researchers concluded the effectiveness of CBG and other cannabinoids for the treatment of bladder disorders. "CBG...reduced acetylcholine-induced contractions in the human bladder."

A **2014 study** entitled "Cannabinoids as Therapeutic Agents in Cancer: Current Status and Future Implications" that was published in the journal ***Oncotarget*** explored the ability of a variety of cannabinoids, including CBG and its varin analog, CBGV, to treat a range of different types of cancer. These cancers included breast cancer (which accounts for 30 percent of new cancer diagnoses in the United States), oral cancer, bone cancer, pancreatic cancer, lung cancer, lymphoma, and thyroid carcinoma.

The study investigated the expression, or presence, of CB1 and CB2 receptors in cancer patients. "It is important to understand which of the cannabinoid receptors are expressed and activated in different tumors, as each receptor follows a different signaling mechanism," reported the study.

The researchers found CB1 expression in 14 percent of breast cancer tumor tissues and 28 percent of human breast carcinoma. CB2 receptors, on the contrary, expressed in significantly greater numbers, with CB2 immunoreactivity (effectiveness) detected in 72 percent of human breast tumor tissue and 91 percent of "ErbB2-positive tumor tissue."

The study also found that cannabinoids "modulate the growth of hormone-sensitive breast cancer cells." In addition to exploring the effectiveness of CBG and CBGV in the role of treating cancer and reducing tumor size and growth, this research identified the role of endocannabinoids such as anandamide in this anti-cancer mechanism. "Endocannabinoids such as anandamide (AEA) are important lipid ligands regulating cell proliferation, differentiation, and apoptosis [pre-programmed cellular suicide]."

Concluded the study's authors, "Cannabinoids exert a direct anti-proliferative effect on tumors of different origin [and] modulate other major processes in our body like energy metabolism, inflammation, etc." *[OUTQUOTE CANDIDATE]*

A **2014 study** entitled "Colon Carcinogenesis is Inhibited by the TRPM8 Antagonist Cannabigerol, a Cannabis-derived Non-psychotropic Cannabinoid" that was published in the journal ***Carcinogenesis*** investigated CBG's ability to treat colon tumourigenesis (the formation of cancerous tumors) and decrease cancerous cell growth in colorectal cancer.

Like other research, the study's authors found that CBG was effective in treating cancer via multiple underlying mechanisms, including cell apoptosis. "CBG promoted apoptosis...and reduced cell growth in CRC [colorectal cancer] cells." *[OUTQUOTE CANDIDATE]*

"CBG inhibited the growth of xenograft tumours, as well as chemically induced colon carcinogenesis," reported the study. It found that CBG delivers an efficacy that "hampers colon cancer progression in vivo and selectively inhibits the growth of CRC cells," concluding that "CBG should be considered...in [colorectal cancer] prevention and cure."

A **2014 study** entitled "A Cannabigerol Derivative Suppresses Immune Responses and Protects Mice from Experimental Autoimmune Encephalomyelitis" that was published in the journal ***PLOS ONE*** investigated the ability of CBG to help treat autoimmune conditions and, specifically, multiple sclerosis.

Reported the study, "A cannabigerol quinone has been shown to alleviate symptoms in a viral model of multiple sclerosis (MS). Hence, we studied T cells and macrophages as targets for [CBG] and its efficacy in an autoimmune model of MS."

The research noted that, although it found evidence of decreases in systemic inflammation and improved immune function, "The mechanisms underlying the improvement in EAE induced by [CBG] treatment are not clear, although the suppression of immune and inflammatory cell activity seems to be involved."

The study's authors did, however, note the ECS receptor types with which CBG interacts to deliver its efficacy for MS sufferers. "The primary findings of this study show that [CBG] is an immunosuppressive compound targeting PPARγ and CB2 receptors," they wrote. The study, like others, also noted the safety profile of CBG, reporting, "At the concentration tested, [CBG] does not show cytotoxicity in primary T cells and represents a potential therapeutic agent for the treatment of human diseases with both inflammatory and autoimmune components."

A **2013 research study** entitled "Non-hallucinogenic Cannabinoids are Effective Anti-cancer Drugs" that was published in the journal ***Anticancer Research*** investigated the cancer-fighting properties of six cannabinoids: Two analogs each of cannabidiol (CBD), CBG, and CBGV. The specific form of cancer investigated was leukemia.

Reported the study's researchers, "These agents are able to interfere with the development of cancerous cells, stopping them in their tracks and preventing them from growing. In some cases, by using specific dosage patterns, they can destroy cancer cells on their own. Significantly, these compounds are inexpensive to produce and could result in much more cost effective anti-cancer drugs in the future."

The study concluded that CBG and other phytocannabinoids could be effective and affordable in the treatment of cancer. "Used in combination with existing treatment, we could discover some highly effective strategies for tackling cancer."

A 2013 in **vivo study** conducted using mice as subjects and entitled "Beneficial Effect of the Non-psychotropic Plant Cannabinoid Cannabigerol on Experimental Inflammatory Bowel Disease" that was published in the journal Biochemical Pharmacology investigated the ability of CBG to treat inflammatory bowel disease, forms of which include irritable bowel syndrome, colitis, and Crohn's disease. This study specifically explored the efficacy of CBG for colitis.

Reported the authors, "Anecdotal and scientific evidence suggests that cannabis use may have a positive impact in IBD patients." The study's authors concluded, "CBG attenuated murine colitis…[and]…could be considered for clinical experimentation in IBD patients."

A **2013 study** entitled "Enhancing the Activity of Cannabidiol and Other Cannabinoids in Vitro through Modifications to Drug Combinations and Treatment Schedules" that was published in the journal ***Anticancer Research*** explored the ability of six different cannabinoids, including CBG and its varin analog, CBGV, to damage or kill leukemia cancer cells. "We explored the activity of six cannabinoids, used both alone and in combination, in leukaemic cells," reported the study.

The authors concluded that CBG and other cannabinoids exhibit strong anti-cancer characteristics. "Cannabinoids were cytostatic [inhibiting cell growth and division] and caused a simultaneous arrest at all phases of the [cancer] cell cycle." *[OUTQUOTE CANDIDATE]*

A **2012 study** entitled "A Cannabigerol Quinone Alleviates Neuroinflammation in a Chronic Model of Multiple Sclerosis" that was published in the journal of ***Neuroimmune Pharmacology*** investigated the ability of CBG to treat the symptoms of multiple sclerosis (MS) by "identifying cannabigerol...as a potent anti-inflammatory agent."

The researchers identified CBG as an effective agent in the treatment of several aspects and symptoms of MS and that its value may extend to other diseases involving nerve damage and inflammation. "We found that [CBG] ameliorated the symptoms associated to [MS] infection, decreased microglia reactivity, and modulated the expression of genes involved in MS pathophysiology." The study's authors concluded that CBG demonstrates a "high potential for drug development against MS and perhaps other neuroinflammatory diseases."

A **2009 study** entitled "A Comparison of the Ocular and Central Effects of Δ9-Tetrahydrocannabinol and Cannabigerol" that was published in the ***Journal of Ocular Pharmacology and Therapeutics*** explored the ability of CBG and THC to treat glaucoma *(involving cats as subjects).*

The researchers noted that "a considerable fall in ocular tension occurred" with the administration of topical preparations of these cannabinoids. "Both cannabinoids produced a two- to three-fold increase in aqueous outflow facility," reported the researchers, who concluded that "cannabigerol and related cannabinoids may have therapeutic potential for the treatment of glaucoma."

A **2008 study** entitled "Antibacterial Cannabinoids from Cannabis Sativa: A Structure-activity Study" that was published in the ***Journal of Natural Products*** researched the antibacterial role of several cannabinoids, including CBG, CBC, THC, and CBN. The study tested these cannabinoids against "a variety of methicillin-resistant Staphylococcus aureus (MRSA) [virus] strains."

While the researchers found clear and potent antibacterial benefits derived from these cannabinoids, it also failed to determine the exact mechanism by which this activity occurs. Concluded the study's authors, "[the cannabinoids'] high potency definitely suggests a specific, but yet elusive, mechanism of activity."

A **2007 study** entitled "Recent Advances in Cannabis Sativa Research: Biosynthetic Studies and [Their] Potential in Biotechnology" that was published in the journal ***Current Pharmaceutical Biotechnology*** noted that much research exists regarding the neutral analogs of major cannabinoids, such as CBC, CBD, and THC, but that more research is needed in the area of the potential benefits of the acidic precursor analogs to these molecules, including CBGA and CBDA.

APPENDIX: **GLOSSARY**

Acid Precursor: An analog (see Analog) of a cannabinoid (see ***Cannabinoid***) that is denoted by an "A," such as CBGA. Acidic precursors are responsible for creating the neutral analog form of a cannabinoid. CBG (see ***Cannabigerol***) acts as a master acidic precursor, producing the acidic precursors for all other cannabinoids, including CBD (see ***Cannabidiol***).

Agonist: A substance, typically in the form of a chemical or molecule, that initiates a physiological response in an organism when combined with a cellular receptor (a process called ***binding***). It is important to note that an agonist may partially or fully activate the receptor with which it binds and that this status varies based on receptor type.

Analog: A particular variant form of a single cannabinoid molecule. Different types of cannabinoid analogs exist, including the neutral version (i.e. CBG), the varin version (CBGV), the acidic precursor (CBGA), and the varin-specific acidic precursor (CBGVA), among others. Other cannabinoids, such as CBD and CBN, feature the same sets of analog.

Anandamide: The first human endocannabinoid to be discovered in 1992 by Czech chemist Lumír Hanuš and American pharmacologist William Devane while working with Raphael Mechoulam's famous research team at Hebrew University in Jerusalem, Israel. This term is the Sanskrit word for "joy" and "bliss." Anandamide is sometimes cited in research studies as arachidonylethanolamide or AEA.

Antagonist: A substance, typically in the form of a chemical or molecule, that binds to a receptor but does not activate it. This mechanisms results in the ability of antagonists to block the activity of agonists (see ***Agonist***), further complicating the interactions of such molecules.

Apoptosis: A form of pre-programmed genetic "suicide" in which cancer cells kill themselves. Some cannabinoids, such as CBG, CBD, and THC have been shown to cause apoptosis in certain forms of cancer.

Arachidonoylglycerol (2-AG): The second endocannabinoid to be discovered by the research team of Dr. Raphael Mechoulam (see ***Dr. Raphael Mechoulam***) in 1995. 2-AG revealed more about the dynamics and mechanisms of the endocannabinoid system (see ***Endocannabinoid System***) and the first endocannabinoid to be discovered, anandamide (see ***Anandamide***).

Bioavailability: The amount of a drug or chemical that is actively available in the bloodstream and creating efficacy of some form. Bioavailability is characterized by three elements: Onset (see ***Onset***), peak (see ***Peak***), and duration (see ***Duration***).

Biosynthetic Pathway: The enzyme-catalyzed lifecycle of a molecule in which the chemical becomes more complex or changes function. This pathway results in different versions of molecules called analogs (see ***Analog***). The biosynthetic pathway is influenced by environmental conditions, such as temperature, UV light, and exposure to oxygen.

Biphasic Response Curve: The tendency of some molecules or drugs to elicit a particular response at a low dosage, but a different (and sometimes polar opposite) efficacy at a stronger dose. An example is THC (see ***Tetrahydrocannabinol***). At low doses, this cannabinoid reduces anxiety and can help treat conditions such as PTSD and social anxiety. At stronger doses, however, THC can cause disorientation, confusion, and even panic attacks.

Binding Affinity: The level at which a cannabinoid connects with an ECS (see ***Endocannabinoid System***) receptor. A cannabinoid may fully bind with one receptor type, partially bind with another type, and possibly feature no binding affinity for other receptor varieties.

Broad-spectrum: A full-spectrum (see ***Full-spectrum***) product from which one or more molecules or elements has been removed, or filtered. Broad-spectrum products typically eliminate most or all of the THC (see ***Tetrahydrocannabinol***) in an effort to avoid overt psychoactivity in the user.

Cannabidiol (CBD): One of the major phytocannabinoids (see ***Phytocannabinoid***) produced by cannabis. CBD has been shown to deliver a variety of health benefits, including reductions in systemic inflammation, decreased anxiety and depression, reductions in seizure activity for epileptics, and anti-cancer efficacy.

Cannabigerol (CBG): One of the 113 cannabinoids discovered to date that are produced by the cannabis plant. CBG is a minor cannabinoid, meaning it is typically found in relatively low quantities (about 1 percent). A theorized fourth chemotype has been discovered and investigated in multiple research studies that has demonstrated up to 94 percent CBG (see ***Cannabigerol***) and as little as 0.001 percent THC (see ***Tetrahydrocannabinol***).

Cannabinoid: Any of a family of 113 chemicals produced by the plant species cannabis sativa. Major cannabinoids include CBD and THC, while minor examples are CBG, THCV, and CBN.

Cannabinoid Profile: An analysis of the exact cannabinoids, and their respective percentages as measured in weight by volume, in a particular sample of cannabis. Cannabinoid profiles are typically documented in a Certificate of Analysis (CoA) from an independent, certified testing laboratory.

CB1: One of the two primary receptor types that populate the endocannabinoid system (see ***Endocannabinoid System***). CB1 receptors are most common in the brain and central nervous system, but are found throughout the body.

CB2: One of the two primary receptor types that populate the endocannabinoid system (see ***Endocannabinoid System***). CB2 receptors are most common in tissues and organs of the immune system found throughout the body. CB2 receptors do appear in the brain and central nervous system, but are vastly outnumbered by CB1 (see ***CB1***) receptors in those regions.

Certificate of Analysis (CoA): An official document provided by an authorized testing laboratory that states the chemical contents of a sample of cannabis or a derivative product. CoAs are available in both simple and complex formats; many provide both the cannabinoid profile and terpene profile.

Clinical Endocannabinoid Deficiency: A theory proposed in 2004 by American researcher Dr. Ethan Russo (see ***Dr. Ethan Russo***) in a research study entitled "Clinical Endocannabinoid Deficiency (CED): Can this Concept Explain Therapeutic Benefits of Cannabis in Migraine, Fibromyalgia, Irritable Bowel Syndrome, and Other Treatment-resistant Conditions?" Russo's study reported that major diseases and conditions, especially those based in systemic inflammation, may be treatable by improving the state of the endocannabinoid system (see ***Endocannabinoid System***) to achieve a state called homeostasis (which means balance).

Cultivar: What is commonly referred to as a "strain" of hemp or cannabis. A cultivar falls within a particular chemotype, such as indica or sativa. Individual cultivars feature common characteristics in terms of cannabinoid profile and terpene profile. Variance occurs in cultivars in the form of phenotypes, which is the combination of the genetic tendencies (genotype), or "potential" of the cultivar under particular environmental characteristics. In essence, phenotype = DNA + environmental conditions.

Dr. Benjamin Caplan: Founder and Chief Medical Officer of CED Foundation and solo* sciences, inc., Caplan board-certified Doctor of Family Medicine. Caplan has served as the Chief Medical Officer of Canna Care Docs, overseeing the medical cannabis care of more than 250,000 patients. He has served as Principal Investigator for multiple pharmaceutical research studies and has published in a variety of medical journals, including the ***New England Journal of Medicine***.

Dr. Ethan Russo: An American neurologist and widely published author who is currently director of research and development for the International Cannabis and Cannabinoids Institute. Russo in 2004 proposed the theory of endocannabinoid deficiency (see ***Clinical Endocannabinoid Deficiency***). In 2011, Russo published his pinnacle research study entitled "A Taming THC: Potential Cannabis Synergy and Phytocannabinoid-terpenoid Entourage Effect" in which he investigated the entourage effect (see ***Entourage Effect***) that was discovered in 1998 by the research team of Dr. Raphael Mechoulam (see ***Dr. Raphael Mechoulam***).

Dr. Peter Grinspoon: A Harvard-based medical doctor who has lectured and written extensively about the benefits of cannabinoids and terpenes for human health and wellness. Grinspoon is author of the 2016 book ***Free Refills***.

Dr. Raphael Mechoulam: The Israeli researcher who discovered tetrahydrocannabinol (THC) in 1964 and the first endocannabinoid, anandamide, in 1992. Mechoulam's team went on to discover a second endocannabinoid, 2-AG, in 1995.

Duration: The total time during which a molecule, chemical or drug is active in a subject's bloodstream and causing efficacy (see ***Bioavailability***).

Endocannabinoid: A cannabinoid produced by a human, mammal, or vertebrate. Examples include anandamide and 2-AG. Endocannabinoids are mimicked by the phytocannabinoids from cannabis, which bind with the same receptor sites within the endocannabinoid system (see ***Endocannabinoid System***).

Endocannabinoid Deficiency: A theory proposed in 2004 by Dr. Ethan Russo (see ***Dr. Ethan Russo***) that suggests that deficiencies in the endocannabinoid system (see ***Endocannabinoid System***) and endocannabinoids (see ***Endocannabinoid***) may result inspecific diseases and conditions, including arthritis, fibromyalgia, migraine headaches, diseases involving inflammation, and Alzheimer's disease.

Endocannabinoid System (ECS): The network of cellular receptors that bind with special chemicals produced by humans called endocannabinoids (see ***Endocannabinoid***). The receptors of the ECS also bind with phytocannabinoids from cannabis and hemp.

Entourage Effect: The theory that different cannabinoids (see ***Cannabinoids***) act synergistically and that, in essence, the whole is greater than the sum of its parts. The entourage effect theory was first proposed in 1998 by the research team of Dr. Raphael Mechoulam (see ***Dr. Raphael Mechoulam***). This theory was further investigated by Dr. Ethan Russo (see ***Dr. Ethan Russo***) in 2011 in his pinnacle research paper "Taming THC: Potential Cannabis Synergy and Phytocannabinoid-terpenoid Entourage Effect."

Full-spectrum: A cannabis product featuring the full cannabinoid and terpene spectrum of the plant and sometimes called "whole plant." Many wellness practitioners and consumers prefer full-spectrum products due to an assumption that the entourage effect, and associated health benefits, are greatest when all of the original cannabinoids and terpenes are present. (See ***Isolate and Broad-spectrum***).

GPR18: A theorized endocannabinoid receptor type that has been shown to interact with endocannabinoids (see ***Endocannabinoids***) produced by the body and phytocannabinoids (see ***Phytocannabinoids***) produced by cannabis.

GPR55: A theorized endocannabinoid receptor type that has been shown to interact with endocannabinoids (see ***Endocannabinoids***) produced by the body and phytocannabinoids (see ***Phytocannabinoids***) produced by cannabis.

In vitro: Research studies conducted on non-living creatures, instead using cells and tissue cultures. While solid data can be collected via this method, in vivo research on living creatures typically yields more reliable results.

In vivo: Research studies conducted on living subjects. These may be rodents, household pets, or humans.

Isolate: A cannabis product that feature a single cannabinoid or terpene in the form of a crystal or powder. Isolates, when created properly, can feature 99.9 percent of a single molecule. (See ***Broad-spectrum and Full-spectrum***).

Mara Gordon: A California-based medical cannabis researcher who has contributed to research and education projects of value to consumers and medical professionals.

Mimetic Molecule: A molecule from a plant that imitates, or mimicks, the behavior and characteristics of a molecule produced by the human body. An example is the phytocannabinoid tetrahydrocannabinol (THC), which mimics the endocannabinoid anandamide.

Neurotransmitter: A substance, such as a chemical or molecule, that transmits nerve impulses across a synapse.

Peak: The brief period during which a molecule, chemical, or drug is at maximum potency in a subject. Peak follows onset and varies according to consumption avenue. (See ***Bioavailability***).

Phytocannabinoid: A cannabinoid produced by a plant. Currently, cannabis is the only plant known to produce cannabinoids (see ***Cannabinoid***).

Receptor: Neurotransmitters that appear on the surface of cell membranes within the endocannabinoid system (see ***Endocannabinoid System***). Receptors bind (see ***Binding Affinity***) with endocannabinoids (see ***endocannabinoid***) and phytocannabinoids to affect changes in the endocannabinoid system and overall health and wellness. Major types of receptors include CB1 (see ***CB1***), which appears in the greatest numbers in the brain and central nervous system, and CB2 (see ***CB2***), which appears most in the tissues and organs of the immune system that are found throughout the body.

Terpene: Any of the 200 aromatic molecules produced by the cannabis plant. Terpenes are also produced by more than 20,000 other plants in nature. Believed to serve as an evolutionary defense mechanism against pests and predators, terpenes have been found to deliver medical benefits on par with those of cannabinoids. Major terpenes include pinene, humulene, myrcene (the most common), and limonene.

Terpene Profile: An analysis of the exact terpenes, and their respective percentages as measured in weight by volume, in a particular sample of cannabis. Terpene profiles are typically documented in a Certificate of Analysis (CoA) from an independent, certified testing laboratory.

Tetrahydrocannabinol (THC): The dominant cannabinoid in most chemotypes and cultivars of the cannabis plant. THC is infamous for the psychoactivity it delivers. This molecule also provides a wide range of health benefits, including reduced anxiety, appetite stimulation, and the improvement or alleviation of anxiety and depression.

Varin: A cannabinoid (see ***Cannabinoid***) analog (see ***Analog***). Some varin versions of cannabinoids produce markedly different efficacy than their neutral siblings. For example, THC (see ***Tetrahydrocannabinol***) is known to stimulate appetite. However, its varin version, THCV, reduces or eliminates appetite (and may be an effective treatment for those suffering Type 2 diabetes, diabetes, and some eating disorders).

Whole plant: Another way of expressing "full-spectrum" (see ***Full-spectrum***) cannabis and hemp products that contain the complete complement of cannabinoids and terpenes of the original plant.

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