Dissertation Series

Endocannabinoid Mediation as an Effective Treatment Modality for Mental Illness

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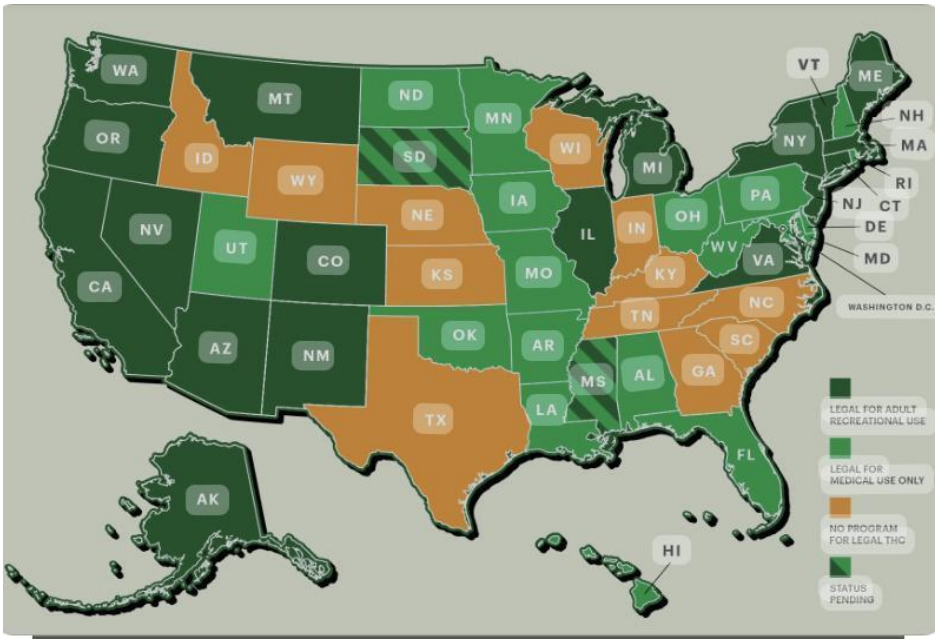
How Does Endocannabinoid Mediation Work as an Effective Treatment Modality for Mental Illness?

The medical use of cannabis continues to flourish across the globe as researchers substantiate the therapeutic use of the ancient medicinal plant, although it has been used for millions of years. Prohibition, unjust drug classifications, and racism constitute the demise of the natural healing plant, giving rise to patented pharmaceutical drugs with detrimental side effects.



The study of anthropology suggests a strong likelihood that the ancient Rawat civilization, who lived in the Himalayan mountains 2 million years ago, grew cannabis as well as the Sonan culture, existing 500,000 years ago.

Agricultural hemp was grown along the banks of great rivers in China, India, Mesopotamia, and the Nile in Egypt for the purpose of producing hemp fibers. The oldest known written record of cannabis use dates back to 2727 BC when the Chinese emperor Shennong investigated botanical compounds for the potential medicinal properties, using it for conditions like pain, rheumatism, and digestive disorders. Shennong is considered to be the father of Chinese medicine and known to have written the Pen-ts'ao; a book consisting of hundreds of drugs derived from vegetable, animal, and mineral sources. The Chinese used a mixture of cannabis resin and wine as an anesthetic to perform painless surgery in the second century. They were also the first people to report the use of recreational cannabis.

India is believed to be the first culture to use cannabis for religious and social purposes, often used in conjunction with weddings and special festivities. In the Vedas, a large body of religious text, the god Shiva takes refuge in the cool shade of a cannabis plant after becoming angry due to a family disagreement. Shiva ate some of the plants and it became his favorite food.

Cannabis has historically and continually been used to control the ego, accelerating the evolution of human consciousness.

The cannabis plant was also consumed as a liquid refreshment made from its leaves early in the twentieth century. Its variety of physical and spiritual medicinal compounds led the Indian Hemp Drug Commission to conclude the cannabis plant to be an integral part of the culture, religion, and confirmed its medicinal virtues.

Some of the earliest uses of medicinal cannabis in the United States were to treat a multitude of chronic problems like insanity, depression, gout, tetanus, uterine hemorrhage, hydrophobia, convulsions, and other epidemic conditions. The US Pharmacopeia, established in 1820, defined hemp extraction for medicinal purposes. The British Indian Hemp Drug Commission Report determined cannabis to be safe in moderation in 1894. By the late 1930’s cannabis was routinely used and prescribed to patients by physicians in the United States.

In addition to the many medicinal therapeutic uses of cannabis, virtually all items used by people across the world can be manufactured from hemp. For this reason, the United States the Virginia Assembly mandated every farmer to grow hemp in the year 1619. The cultivation of the cannabis crop was essential to the agriculturally-based economy. Threads from fibers provided clothing for civilians as well as uniforms for soldiers. Betsy Ross created the first American Flag while in Philadelphia with hemp material in 1776. In fact, presidents George Washington and Jefferson were both hemp farmers. The crop was so widely utilized that peak production from 1840 - 1860 yielded a $5 million dollar crop value.

William Brooke O'Shaughnessy, a surgeon who learned of the medicinal benefits of cannabis while working for the British East India Company, introduced cannabis into Western medicine in 1839. It was promoted for its analgesic, sedative, anti-inflammatory, antispasmodic, and anticonvulsant properties.

The French psychiatrist, Moreau, published a book titled *Hashish and Mental Illness* in 1845. He described psychological phenomena he had observed in experimental participants like happiness, excitement, dissociation, distortion of time and space, sensory enhancement, delusions, emotional fluctuations, illusions, and hallucinations. These types of symptoms are often observed with the consumption of excess amounts of THC, typically orally ingested.

The British Parliament required the colonial government of India to establish a royal commission on opium and an Indian Hemp Drugs Commission in the 19th century. It was concluded that moderate use of cannabis had no appreciable physical effects on the body, no harmful effects on the brain, and no adverse effects on morality. A system of taxation to control and restrict (not prohibit) was implemented.

The use of cannabis as a medicine began to diminish as technology facilitated the study of organic chemistry and pharmacology. Researcher’s efforts to isolate active ingredients from natural products paired with the synthesis of new molecules (like morphine) overshadowed the plant. The hypodermic needle development along with newly created synthetic drugs provided a quick way of administering morphine (the first alkaloid isolated from a plant) for pain relief. Later in the nineteenth century aspirin, barbiturates, and other medications were mainstream drugs. Complexed unrefined

herbal medicines became less used in mainstream medicine and cannabis became medically obsolete.

The early twentieth century started a growing interest in international cooperation in the control of opium. During the second opium conference held in 1925, cannabis and the resin used to produce hashish were also discussed but the medical community did not defend the use of cannabis as a medicine.

In the twentieth century in the United States, marijuana was used for its psychoactive properties mostly by Mexicans and African-American jazz musicians. Its recreational use first became widespread in New Orleans then gradually spread to other cities. The influx of immigrants who entered the southern United States from Mexico brought the plant under suspicion by authorities and eventually led to prohibition. Anti-immigrant and racism endeavors led The Federal Bureau of Narcotics to declare the use of marijuana as promoting violent crimes. In the late 1930s newspaper articles wrote stories about “killer weed” and the US Congress passed the Marijuana Tax Act, effectively banning the use of the plant medicine and outlawed it as a dangerous narcotic in 1937. Renaming cannabis to “Marihuana” denoted its influence from Mexican culture.

The World Health Organization (WHO) reported that cannabis had few medical benefits in 1954, despite evidence of historic medicinal use. In 1961 an international treaty established limits on the production, manufacturing, and extraction of raw materials from narcotic drugs. Psychoactive substances were categorized into one of four schedules. The most restrictive schedule contains drugs deemed dangerous for abuse with little or no therapeutic value, and with a high potential for abuse. Cannabis, its resins, extracts, and tinctures were placed in the most restrictive schedule.

At the 1971 convention on psychotropic substances, THC and its isomers were placed in schedule 1 along with heroin, although no potential threat of overdose exists. Drugs in this category are considered to be the most dangerous drugs of all. This prohibited all use of cannabis except for scientific purposes or limited medical purposes used by authorized persons specifically approved by a government body. Other cannabinoids like cannabidiol (CBD) were not controlled under the 1971 UN Psychotropic Convention. The non-psychoactive cannabinoids are still not controlled by many countries but the United States and Canada have chosen to include them in the same restrictive schedule as THC.

In 1964, investigation of cannabis effects discovered the principal psychoactive ingredient in the plant; delta-9-tetrahydrocannabinol (THC). The psychoactive effects of THC produced on the brain was discovered 20 years later at the Saint Louis University Medical School where the cannabinoid 1 (CB1) receptors were discovered. The brain distribution of these receptors was found to be consistent with the known pharmacological effects of THC, raising questions of the brain's receptors for plant-derived material. It was seemingly apparent to researchers that the brain must produce chemicals similar to THC. Shortly thereafter, scientists discovered the endocannabinoids anandamide and 2 arachidonic glycerol (2-AG). These endogenously synthesized cannabinoids act on the same receptors as THC. The CB2 cannabinoid receptor was later discovered, primarily in the immune system.

The CB1 receptor is widespread in the upper regions of the brain and brain stem primarily in the presynaptic terminals and dopamine cells.

The CB1 receptor is a G protein-coupled receptor (GPCR), a very complicated receptor, that crosses the membrane several times. These receptors are a very important target of modern pharmaceutical drugs. An estimated 50% of pharmaceutical drugs target some type of GPCR. ***The CB1 is the most abundant GPCR of all the G protein-coupled receptors.*** This helps explain cannabis as an effective medicine for a wide array of conditions and diseases. ***Delta-9 tetrahydrocannabinol (THC) is the only molecule known to date that directly works with the CB1 receptor.***

The CB1 receptor drives energy production. The receptors are located inside the cells and neurons but not on the membrane wall. In the lysosomes and endosomes, they aid in the highly regulated removal of cell waste products (misfolded proteins). This can help explain why the CB1 receptor regulates mitochondria and assists in neurodegenerative disease.

The location of the CB1 receptor is in very important brain regions. They are neuroprotective on brain glial cells. ***CB1 receptors regulate glutamate***, a neurotransmitter in the brain that is vitally important and responsible for basic excitatory neurotransmitter function. Blocking glutamate helps the brain to slow down which can improve symptoms of schizophrenia, depression, and anxiety disorders. Additionally,

the CB1 receptor can be useful in the treatment of PTSD as it impairs memory. Implications of mental illness relative to the associative receptor sites include:

Cerebral Cortex

- Schizophrenia

Basal ganglia

- Suicidal ideology, anxiety disorder, addictions, depression, dyskinesia

Hippocampus

- PTSD, major depressive disorder, bipolar disorder

Hypothalamus

- Stress, depression, bipolar disorder

Medulla

- Schizophrenia

The site of action of THC has uncovered a brain chemical system that is intimately involved in all aspects of brain functioning. Researchers have provided considerable scientific knowledge about the metabolism, biochemistry and pharmacology of THC in animal models. The number of such studies in humans has increased exponentially since the discovery of the endocannabinoid system in 1988 by Dr. Machoulam while tracing the metabolic pathway of THC.

The CB2 receptors are most present in the immune cells of the blood and are anti-inflammatory across a wide range of diseases and illnesses. Terpenes and cannabinoids (additional medicinal cannabis compounds) combine for an entourage of maximized therapeutic healing effect.

Beta caryophyllene (a cannabis terpene), binds to CB2 receptors. Cultivars with high levels of this terpene reduce lipopolysaccharide-induced intensification of long term depression and improves chronic stress related behavioral and biochemical changes.

The use of cannabis containing beta caryophyllene can be an effective treatment for depression and stress related mental illnesses.

Cannabidiol (CBD) is considered to be the cousin of marijuana. While the medicinal constituents closely mirror each other, the most significant difference is identified by the cannabinoid profile of delta 9 tetrahydrocannabinol. Strains of cannabis must be 0.3% or less of delta 9 THC to be classified as hemp (CBD).

CBD has roughly 65 biochemical changes it causes at the cellular level.

It indirectly stimulates the activation of the CB2 receptor.

The highest concentration of CB2 receptors are located on the peripheral blood immune cells of nerve cells; the T cells (the immune system's killer cells). They are highly involved in disease and inflammation regulation and found in the entire nervous system, smooth muscle, myocardium, endocrine cells of the pancreas, endothelial cells, and more. Many cannabinoids, terpenes, and flavonoids contribute to CB2 activation making it difficult to segment the way in which cannabis influences the endocannabinoid system. Nonetheless, the mechanism of action is not needed to assess the efficacy of the molecule as an effective treatment modality.

2-Arachidonoylglycerol (2-AG) is a neuroprotective endogenous cannabinoid. It works on the vagus nerve axis and is more present in the central nervous system than anandamide. It is metabolized by Cox-2 enzyme which enables various versions of the molecule to be present and is responsible for apoptosis (programmed cell death as dictated by genetics). The metabolites are thought to have a downstream effect. Reducing 2-AG can provide therapeutic effects which leads pharmaceutical companies to research the hydrolysis of these enzymes.

Fatty acid amide hydrolase (FAAH) is an integral membrane protein located in the endoplasmic reticulum (ER) in the brain that breaks down anandamide to regulate the endocannabinoid system. The ER is an important subcellular organelle for the synthesis, folding, modification, and transport of proteins, a process that is highly developed in neuronal cells. Endoplasmic reticulum stress activates the unfolded protein response and mediates the pathogenesis of psychiatric diseases including depression. FAAH may balance anandamide and 2-AG to maximize the endocannabinoid system. Variations of the molecule may explain the differences in response to symptoms like anxiety among different individuals.

The FAAH molecules are located on the neurons themselves, on the astrocytes inside the brain, and a number of the immune system cells including the lymphocytes and macrophages. An inhibitor of the fatty acid amide hydrolase molecule is suggested for anxiety. FAAH inhibitors increase physiological levels of the endocannabinoid anandamide, which may confer improved efficacy and safety relative to direct cannabinoid receptor (CBR) agonists. Pharmaceutical companies show a significant interest in using this molecule as a tool to harness the ECS. ***Antidepressant drugs like URB 597 affect the endocannabinoid signaling through CB1 receptors.***

The enzyme monoacylglycerol lipase (MAGL) is responsible for the breakdown of 2-AG. Inhibiting MAGL allows for more 2-AG availability for cannabinoid receptor interactions. The genetic ***inhibition of MAGL significantly enhances short-term synaptic depression.***

Pharmaceutical companies have been working hard on inhibitors of the FAAH and MAGL molecules due to their demonstrated ability to lessen the effects of anxiety, inflammation, and other factors influencing mental health.

Considerable preclinical scientific evidence in the field of endocannabinoid research has shown therapeutic potential in almost all diseases affecting human neurodegenerative diseases like psychosis, PTSD, depression, anxiety, and other psychiatric disorders by modulating endocannabinoid activity. Cannabis does not change the body’s chemistry, rather it attaches to the receptors to regulate the body through the existing endocannabinoid system thus creating homeostasis.

Hundreds of phytocannabinoid (plant cannabinoids) have been identified in the cannabis plant. THC is the only compound in marijuana that causes the typical euphoric, or mental high effect. Other compounds including cannabidiol (CBD) can modify the effects of THC.

THC is not evenly distributed throughout the plant. Unpollinated female floral material called sinsemilla (meaning without seeds in Spanish) is a primary source of THC with concentrations as high as 25%. It is absent from the roots and seeds, and is found only at very low concentrations in the stems. The lower leaves contain less THC, typically 2 to 3%.

Varieties of cannabis plants differ in their cannabinoid contents. The presence or absence of glandular or capitate trichomes determine the concentration of cannabinoids. Cannabinoids are synthesized and sequestered in the trichomes. A concentration of THC in industrial hemp (CBD) is less than 0.3%. In the 1960s it was about 5%, whereas marijuana contained 2 to 3%. In the twenty-first century, strains of marijuana have been developed to contain up to 25% or more. As of 2022, the highest THC strain is Godfather OG, reported to be the most potent strain in the world. A report claims that the Indica flower contains a THC concentration of 34%. Academic botanists argue that cannabis is a polymorphic species because all types are able to interbreed.

Cannabis contains hundreds of cannabinoid compounds, delta 9 THC (THC), delta 8 THC, cannabidiol (CBD), cannabichromene (CBC), cannabielsoin (CBE), cannabigerol (CBG), cannabicyclol (CDL), cannabinoid (CBND), cannabinol (CBN), cannabicitran

(CBT) and others. The plant also contains a variety of additional medicinal compounds called terpenes. The different biochemical cannabinoid and terpenoid profiles are responsible for their various effects and give the plant its characteristic smell. The compounds have been demonstrated as having anti-inflammatory, antibacterial, and anti-anxiety effects. Non-psychoactive compounds of delta 9-THC are shown to have medicinal value. The carboxylic acid precursor of THC, delta 9-THC acid (THCa) in the fresh plant is decarboxylated by heating or burning. THCa has shown to inhibit the pro-inflammatory cytokines tumor necrosis factor-alpha (TNF-alpha) which contributes to the pathogenesis of depression by an activation of the hypothalamo-pituitary-adrenocortical (HPA) axis leading to tryptophan depletion. Tetrahydrocannabivarin (THCV), identified in the 1970s, was initially described as sharing with Delta 9-THC's ability to produce catalepsy.

Pharmacokinetics has been studied in humans in a variety of forms namely synthetic purified forms as well as in purified extract. Whole plant forms have been studied via intravenous, oral, sublingual, rectal, and inhalation routes. The science of pharmacokinetics is useful to practitioners and patients by allowing better cultivar consideration, method of ingestion, providing tools for predicting effects of preparations, and helping to reduce potential unwanted side-effects. Pharmacokinetics describes the science of what the body does to a drug, whereas pharmacodynamics is what the drug does to the body.

Specifically, pharmacokinetics addresses the dynamics of a drug's absorption, distribution in the body after absorption from its route of entry into the body, its metabolism by the body (how the body converts it and processes it once it's reached its distribution site) and the elimination or excretion of the drug via respiratory, fecal, and urine excretion

Factors and properties of the human membrane that influence pharmacokinetics include:

- Physicochemical properties of the molecule
- Body chemistry
- Genetic polymorphism
- Acidic or basic
- Environmental factors (stress)
- Lipo-soluble or water soluble
- Ionized or nonionized
- Age
- Gender
- Pregnancy status
- Stomach acidity
- Metabolism (liver enzymes

Understanding pharmacokinetics of THC such as half-life, volume distribution, maximum concentration, C-Max steady-state, T-Max, and T-Max steady state are important when considering the use of medical cannabis and useful for determining bio individualized cultivars.

The half-life of a drug refers to the time it takes for the plasma concentration of the drug to be reduced by half. A compound with a long half-life can take hours or days to reduce itself by half. Conversely, a compound with a short half-life can reduce itself by half within minutes or seconds. A longer half life does not necessarily elicit longer effects.

The volume distribution is the extent to which a drug travels to tissues outside of the bloodstream. The vascular compartment of the body (the blood in the blood vessels) contains an average blood volume of 5.5 liters. If a drug has a small volume of distribution, it tends to stay in the bloodstream and doesn't demonstrate an affinity for the tissues. This does not necessarily mean it doesn't have any effects, it just provides

understanding of the character of the drug. A drug with a large volume of distribution travels to lots of tissues outside of the body.

C_{max} (maximum concentration) refers to the maximum concentration of drug in the bloodstream that is achieved after the very first dose of the drug. This information can help provide clarity concerning bioavailability.

C-Max steady-state (C-MaxSS) is the maximum concentration of the drug in the bloodstream that is achieved after consecutive dosing at a constant rate.

T-Max and T-Max steady state (Tmax, TmaxSS) refers to the amount of time after initial dose or consecutive doses of Cmax and CmaxSS respectively.

Accurate dosing is not necessarily essential to achieving a desired and predictable outcome due to the variability of THC. Literature regarding pharmacokinetics of THC routinely uses the phrase *considerable interest in individual variation*. Clinical trials of bio-identical synthetic THC (Dronabinol) showed a dose of 5 mg given to two patients of the same genetics, gender, and weight will not have the same effects. Thus lending the requirement of THC in cannabis to be bio individually customized.

THC demonstrates linear pharmacokinetics. Linear pharmacokinetics implies direct proportionality between dose and exposure. Administration of a THC dose is measured in blood. The dose is doubled and measured as a requisite increase of the THC in the blood. As the dose increases, the amount of THC in the blood increases. THC dosing shows some predictability. Higher doses result in higher amounts in the bloodstream and greater delivery to the tissues. Greater effects both subjectively and objectively such as measurements of emotionally, psychoactive effects, heart rate, and blood pressure can be recorded.

THC absorption is the rate at which a drug exits its site of administration. Inhaled dried flower is measured for the rate at which THC enters the bloodstream after smoke enters

the lungs. Measuring ingested forms of cannabis (edibles and tinctures) measure the rate at which THC enters the bloodstream after it enters the stomach and liver.

Factors affecting plasma levels of cannabinoids

- Plasma protein binding site
- Cannabis metabolism in the human body
- The role and health of the liver in metabolism
- Genetic factors that can influence cannabis metabolism
- Difference in metabolite profile and clinical effects

Bioavailability is the extent to which an administered dose reaches an area or site of action. Any drug administered intravenously automatically has a bioavailability of 100%, which is impossible with oral administration. Oral doses go through digestion. Anything that goes through the stomach automatically goes through the liver where the first pass effect occurs. The concentration of a drug, specifically when administered orally, is greatly reduced before it reaches the systemic circulation. A large first pass affects the liver and inactivates most of the drug. This lessens the amount of active drug in the bloodstream. A small first pass effect results in more drugs available in the bloodstream to potentially access the sites of therapy.

Inhalation is the most studied method of cannabis administration, although estimating dosage is difficult. This method of ingestion has a short duration of action. Plasma levels of THC peak at 2 to 5 min and steadily drop over the next hour at a 5 - 10% maximum. 90% of THC is diffused from plasma into the organs within 90 minutes making it an effective method for immediate absorption. It is detected in plasma virtually immediately. Bioavailability has been clinically measured from 2% to 56%. Variables such as inter-individuality in inhalation and medicine lost to the air in side-stream smoke that is not inhaled impact bioavailability. An average of 25% bioavailability of an administered dose of a typical joint is common. The World Health Organization (WHO) considers 750 mg of dried cannabis material to be a standard joint. Pulling from a joint pulls resin-rich material throughout the entire thing, making the last ½ of the joint more potent than the 1st half. This gives rise to the consideration of using ½ gram joints instead of a full gram.

The total THC content is calculated by adding THCA (raw cannabis acid) plus delta 9. THCA will convert when heated (decarboxylation). Total cannabinoid content is all cannabis acids plus active cannabinoids added together.

THC content:

- Low potency: < 6%
- Normal potency: 6 to14%
- High potency: 14 to 30%

Estimating inhaled THC content using a flame:

- Product weight x THC% = maximum THC availability + loss for flame + exhalation
- 25-50% THC is lost with flame, 25% exhalation loss
    - Example: ½ gram lit with lighter = 12.5 mg maximum

Vaporized cannabis has a higher bioavailability of 60 to 90%.

- Example ½ gram = 28 mg vaped
- 55% of maximum dose x weight x % of canna

Dabs are concentrated forms of cannabis that come in a variety of textures. The process of dabbing is extremely hot and flash vaporizes in the range of 400 - 600°F using a dab rig (electronic rig or dab pen), whereas combusting or smoking flower happens at around 350°F. Dabs have 55% higher concentration of THC. The average dab is a 10th of a gram with 70% THC (70 mg THC available) and 60 to 90% availability. 25% availability is lost during exhalation, equalling an average dose of 40 mg THC.

Inhalation delivers the drug rapidly to the bloodstream. C-Max achieved (maximum THC concentration in bloodstream) from the administered dose of inhalation is about 10

minutes. As rapidly as it gets into the bloodstream, it rapidly leaves the bloodstream. The blood rapidly distributes THC to tissues including the brain.

Inhalation of dried cannabis flower (activated cannabis concentrate) is an efficient way to introduce cannabis to the bloodstream and gauge its effects. It compares to intravenous administration with peak levels of IV slightly higher with inhalation. IV administration of cannabis has no medical necessity due to the relatively immediate effects of inhalation. No current methods of intravenous administration cannabis exist in medicine to date.

Although inhalation is a quick route of administration, this method comes with negative effects as new compounds are formed when heated. These compounds are carcinogens and toxic byproducts like carbon monoxide, PAH, and tar. The fatty lining in lung tissue can be irritated by long term use. Additionally, toxic pesticides and herbicides from non-organic plants can be inhaled.

Dabs, vape concentrates, and oils contain organic hydrocarbon solvent residues (hexane, butane, propane) from extraction processes that can lead to solvent induced encephalopathy when inhaled. Symptoms include mood disturbances, memory loss, impairment and sensory disorders.

Sublingual preparations of THC are advantageous due to blood vessels in the mouth, especially under the tongue. Some of the drug is absorbed directly into the bloodstream and bypasses the liver like inhalation. Sublingual administration allows the drug to enter the bloodstream directly and much more quickly than oral dosing. Sativex® is a pharmaceutical spray of equal parts CBD and THC which can be beneficial for individuals who can not smoke or vaporize cannabis flower.

Rectal suppositories skip hepatic 1st pass, creating less 11 hydroxy THC thus lowering psychoactivity. It has an average of 15 to 20 minute duration and can last 4 to 6 hours. The mucous lining of the colon can dictate uptake.

THC is bound and made into a salt form making it more dissolvable. Pure THC is not bioavailable by rectal route and only available in the specially prepared salt forms. Rectal suppositories that are made and used by patients in medical cannabis states lack data on bioavailability in the salt form. In studies, monkeys had about 13% availability. Small studies in humans compared oral and rectal routes. The rectal format was twice as available, resulting in lower blood levels and lower C-Max compared to ingested application.

Patient testimonials report positive effects of topical applications of cannabis. The molecular weight of THC is 314. Molecular weight less than 400 is permeable in human skin. Topically applied THC will cross the skin and enter the bloodstream. Anecdotal data exists for both bioavailability, dosing, and effects at this time.

Oral administration involves THC preparations which are ingested through the stomach. The onset of oral THC is longer with a longer duration time than smoking. Delta 9 has higher availability in smoking while 11 hydroxy is higher in ingested products.

Published data from the clinical trials of synthetic THC (Dronabinol or Marinol®), standardized natural THC extract (Namisol® in the Netherlands), and data from THC whole plant extracts put into food (whether administered in pure or encapsulated substance) shows the most erratic kinetic levels in the bloodstream with a low 6% bioavailability. Clinical trials on Dronabinol demonstrate a 10 to 20% bioavailability which is significantly lower than inhalation. The time to C-Max was the longest at 2 to 6 hours, resulting in a delayed effect on the brain. In oral dosing, the psychoactive effects of THC lags between the plasma concentration compared to inhaled THC. Inhaled cannabis results in an instantaneous rise in blood levels and nearly instantaneous effect in the brain.

Sublingual and buccal oral absorption methods include tinctures, sprays, gum, and lozenges that are held in the mouth a minute or more prior to swallowing, allowing cannabinoids to be absorbed through the buccal membrane, bypassing the digestive tract for fast uptake into the blood. It is more discreet than smoking.

Edibles are absorbed into the bloodstream by the small intestine. Duration of action is 4 to 12 hours which can help with sleep. They can be used prophylactically for inflammation reduction by stimulating CB1 receptors in the brain and CB2 receptors in the gut. Poor quality flower is often used in edibles due to the sale of highest grade buds for smoking and concentrates. The majority of flower used for edibles comes from oil extracted from shake or trim which is not separated by strain and comes from different sources. The various sources are mixed together causing large variations from batch to batch and uneven results due to unequal distribution of cannabinoids in the product. One bite of an edible may contain more cannabinoids than another bite. The fat content of the product also influences onset.

Stomach acidity degrades a portion of ingested THC and can impact the oral absorption of cannabis. A highly acidic stomach degrades more THC whereas a less acidic stomach degrades less THC. The longer an orally administered dose remains in

the stomach and intestines, the more potential for the drug to be absorbed into the bloodstream and delivered.

Tinctures are the most widely used oral methods and distributed in tincture bottles with a dropper. Alcohol-based dissolves cannabinoid-rich trichomes and terpenes from the bud. This decarboxylizes the bud and strips the chlorophyll from it giving most alcohol based tinctures a bright green color.

Glycerin-based products infuse a glycerine base with extracted cannabinoids into the form of hash oil. Candies and honeys can be sucked for oral absorption but should be used with caution in diabetics and those with ketogenic diets. This route of administration has a 15 to 30 minute onset time with 3 - 4 hour duration.

Tinctures can be made at home with ethyl alcohol, grain alcohol, or any liquor over 90 proof. Estimated potency of homemade tinctures is nearly impossible due to variations in growing technique resulting in potency variations. Re-titration is required with each batch to determine potency unless plant material is weighed. Lab-tested buds purchased from a dispensary are suggested for consistency in potency.

Tincture protocol:

1. CBD only
2. Add indica
3. Add sativa
    - At least 6 hours apart or alternate days between cultivars

Patients with high anxiety or fear of THC:

1. CBD only
2. Add THCA (non-psychoactive)

Patients can use indica to augment CBD one day and sativa the next to compare which they prefer for their condition. Self-titration can be obtained by keeping a treatment journal of dose method, onset, duration, and effects for 2 to 4 weeks.

The kinetics of drug distribution refers to the movement of the drug from the bloodstream into the tissues (outside or inside the cells). It is influenced by many factors like blood flow to the tissue, the tissue type and volume, and the degree to which the drug binds to tissue

After inhalation, THC rapidly leaves the bloodstream and perfuses first into the lungs, then the kidneys, heart, liver, adipose tissue, brain, muscle tissue, and immune system where it exerts its effects. THC is a highly plasma protein bound drug. Some drugs have a high affinity for these proteins and remain an inactive bound drug. Although THC has a high affinity for fat tissues, a significant amount of it remains in the bloodstream and recirculates on these proteins until eventually it is released and gets excreted.

There are many drugs that are bound to plasma proteins. THC is 97% bound by plasma protein. One of the most popular pharmaceutical medications is aspirin, which is a highly plasma protein bound drug. Plasma bound drugs like aspirin and THC can compete for binding sites. Theoretically, if a person is taking a daily or therapeutic dose of aspirin, administration of THC by any route may deliver higher doses of THC due to the binding sites taken up by the aspirin. This results in more THC leaving the bloodstream and entering the tissues. Other factors that can reduce plasma proteins include anticonvulsant medications, kidney disease, hepatic disease, pregnancy, stress, and trauma. Dosing and routes of administration should be carefully weighed in these conditions.

First pass metabolism refers to the metabolism of a drug by the liver prior to distribution, after administration and with the onset of desired effects. Elimination metabolism happens to the drug after it goes through the liver, before distribution to the tissues. It is the time a drug is eventually eliminated.

Liver metabolism is primarily done by a class of enzymes called cytochrome P450. These enzymes are crucial for metabolizing most drugs, including THC. They can have genetic variability (poor metabolizers versus rapid metabolizers). Genetic defects in P450 causes unresponsiveness to opioids or hyper metabolism of opiates. These people do well using cannabis for pain control.

Poor response to opioids is a marker to indicate cannabis use for pain control.

Poor metabolizers have a higher drug impact than rapid metabolizers with a lower drug impact. Lifestyle habits such as tobacco and alcohol consumption can induce or inhibit

enzymes. Tobacco induces enzymes whereas alcohol ties them up, requiring more liver enzymes to metabolize THC. The same principle applies to all pharmaceuticals. All approved FDA pharmaceuticals have this prescribing information.

In orally ingested cannabis, the liver converts THC into 11-Hydroxy THC which is more potent than THC. It crosses the blood-brain barrier more readily and is not as protein bound as inhaled cannabis. It is more available to interact with tissues and interact with the brain. Edible forms of THC provide longer lasting extensive psychoactive effects compared to inhalation. Instant titration occurs with inhalation whereas oral dosing is more erratic and subject to interpersonal genetic and disease state. The blood brain barrier limits access of THC and 11 hydroxy to the brain accounting for delay between peak plasma levels and psychoactive effect. Ingested capsules show twice as much 11 hydroxy than all other oral absorption methods. CBD attenuates the psychoactive effects of THC. A 1:1 or higher ratio of CBD strain can reduce psychoactive effects. The metabolites from 1st pass, 11 hydroxy and 11-non carboxy THC (non-active/non-psychoactive), are excreted in urine and shown in drug screening.

The majority of THC is eliminated in the feces and about 20% in the urine. After the liver metabolizes it into 11 hydroxy THC, the liver metabolizes it further into 11 nor carboxy-THC (inactive metabolite) and it is excreted in that form.

Typical duration of oral and edible applications last from 6 to 12 hours. Variation depends on metabolism and fat composition. Re-distribution and slow release of cannabinoids from fatty tissue can appear weeks after cessation of edibles and can cause spontaneous re-intoxication. Ectomorphs tend to experience quicker onset, shorter duration, and clear cannabis quickly. Endomorphs and higher triglyceride patients need higher doses. Ingested non-responders do better with inhalation. OTCs, Rx meds, and/or alcohol users tend to hyper respond.

Hyper responders need less than 10 mg to trigger paranoia

Found in hemp seeds and hemp oil, raw cannabis does not decarb to convert to delta 9. The omega 3 (3:1) can assist with fat metabolism. The raw cannabis acids THCA, CBDA, and CBG stimulate the CB2 receptors in gut, organs, and the immune system.

CBDA, found in raw cannabis juice, influences the 5-HT1A serotonin receptors which governs emotion related behavior. Other cannabinoids like CBGA are known for being strong antagonists of GPR55, a pro-inflammatory receptor, mediating anxiolytic-like effects. 1-2 oz of raw cannabis juice can work to improve mental wellness within 2 to 4 weeks.

Cannabis compounds can be obtained through skin absorption. Topicals penetrate epidermis, but do not bind to plasma proteins or pull into blood stream, therefore not detectable by blood or urine samples and non psychoactive. Cannabinoids bind to CB2 receptors and act as localized anti-inflammatories and muscle relaxers. Preparations include creams, salves, balm, and bath salts (epsom salt, magnesium, natural mineral salts and other natural ingredients for soaking in a full tub).

Transdermal gels and lotions last 2 to 4 hours. Transdermal patches last considerably longer from 8 to 12 hours. The adhesive controls the rate of uptake and the surface area of the patch determines the dose. Patches can be cut for lower dose administration. Transdermal patches pull cannabinoids into the bloodstream. Active (THC) or non-psychoactive (CBD) forms are used over venous areas like ankles and wrists but not necessarily the area of pain.

The pharmacokinetics of CBD has also been studied in both oral preparations and intravenously. Doses as high as 40 mg intravenously were administered to healthy participants with no ill effect.

While the mechanism has yet to be fully elucidated, CBD attenuates some of the psychoactive effects of THC, however, it does not antagonize THC or act readily at endocannabinoid receptors.

CBD has a similar absorption profile to THC but it is more extensively metabolized in the liver, tying up CYP P450 enzymes more than THC. Normal doses of CBD typically do not interfere with medication metabolism, however, extremely high oral doses (600 mg and over) may possibly interact with prescription drugs.

The endocannabinoid system is dysregulated in people with depression.

Increased inflammatory markers in individuals with depression are exhibited by microglial cell activation. Because the ECS and the immune system tightly regulate the other's activity, cellular homeostasis can reduce inflammation and activation to microglial cells and calm an overactive nervous system.

Dietary deficiencies abolish retrograde neurotransmitter signaling, making food a major contributor in mood disorders. Endocannabinoids link food and mood disorders together because they are made from lipid precursors like polyunsaturated fats (omega 3).

Polyunsaturated fat imbalances are known to negatively impact depression and bipolar disorder. Dietary polyunsaturated fat deficiency modifies brain lipid composition. Hemp seeds are a rich source of omega 3.

Conclusion

THC is a dynamic individual molecule with predictability of blood level concentrations resulting in effects. Today's use of cannabis continues to grow as more and more states legalize its use. Anxiety and depression are among the top five reasons for individuals to seek the ancient plant's healing powers.

Mental health statistics worldwide

- Anxiety affects 284 million people in the world
- Depression affects 264 million people
- Alcohol use disorder affects 107 million people
- Drug use disorder affects 71 million people
- Bipolar disorder affects 46 million people
- Schizophrenia affects 20 million people

Mental health statistics in the U.S

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- More than a quarter (26.3%) of adults aged 18 to 25 years old had any mental illness in 2018
- Nearly 8% of adults aged 18 to 25 years old had a serious mental illness in 2018.
- Anxiety disorders affect 40 million adults in the U.S. (18.1% of the population) making them the most common mental illness. (Anxiety and Depression Association of America)
- The rate of individuals aged 18 to 25 years old that reported symptoms consistent with major depression increased 63% from 2009 to 2017. (American Psychological Association, 2019)

An estimated 7% of adults in the United States report using marijuana for medical purposes. The most common medical reasons for use are anxiety (49%), insomnia (47%), chronic pain (42%), and depression (39%). The most common forms of use despite medical conditions were smoking and edibles followed by vaping, concentrate, and topical. Women are more likely to use marijuana for posttraumatic stress disorder (PTSD), sleep, and anxiety. Among those using marijuana for medical purposes, 21% did not have a physician. Among those with doctors, 33% did not inform them of cannabis use. Of the 28% that reported cannabis use, their doctor was reported as neutral. 32% reported their doctor was supportive, and 8% reported their doctor was not supportive. Those who lived in states where medical marijuana was illegal were less likely to disclose cannabis use to their physician.

The endocannabinoid system exists in all animals except insects and is critical to overall health by providing cellular homeostasis. The receptor-site system is very similar to the nervous system in how neurotransmitters work. This system regulates brain function, nervous system, immune system, digestive system, inflammation, and other factors implicated in mental illness. Modulating the endocannabinoid system has therapeutic potential in all diseases. Therapeutic use of cannabinoids can effectively treat illness of the nervous system disorder like anxiety, suicidal ideology, and PTSD

While the body synthesizes its own endocannabinoids, ECS Deficiency Syndrome can account for insufficiencies in the CB1 and CB2 receptor sites. A diet consisting of poor nutrition, chronic stress, and other significant factors compromise the ECS. Nutrition care plans that contain cannabinoids can be beneficial for individuals with ECS deficiencies. Supporting the ECS is critical and starts nutritionally with phytocannabinoids (from plants: herbs/spices) and omega 3 (monounsaturated fat).

Adaptogenic herbs + morning vegan protein + hydration + cannabinoids

=

improved anxiety management

The idea of cannabis as an evil drug is a relatively new concept. All ancient cultures and religions revered cannabis. Dozens of actions and indications for the use of cannabis have arisen in the Ayurvedic tradition. More than 50 traditional Ayurvedic formulas include the medicinal plant. Therapeutic use includes analgesic, anticonvulsant (epilepsy), and mood disorders.

Anything that ushers us to the Divine is sacred. Cannabis is an entheogenic plant used to remove fear from the mind, and distractions that inhibit conscious present awareness. Cannabis treats all three realms; the spiritual, psychic, and physical needs of an individual. All three realms must be addressed for true healing to occur.

Important Considerations

Smoked or Vaporized Cannabis

Smoked or vaporized cannabis in its whole herb form is the most commonly used route of administration. Varying levels of THC (most active psychoaffective cannabinoid) along with cannabinoids like CBD and terpenes can have other moderating effects on THC. Inhaling cannabis smoke or vapor leads to an immediate feedback of the psychotropic effects. When cannabis is smoked or vaporized, a person can determine how much is sufficient to treat unwanted ailments, like anxiety, typically right away.

Responsibly-labeled cannabis edibles indicate the milligram dosing of THC in each serving. Bio Individuality dictates the appropriate dosing of edible products among people. Caution is advised when initiating dosing. It is suggested to start with the lowest therapeutic amounts until individualized titration is achieved.

Challenges with Edible Cannabis Preparations

Absorption of cannabinoids is much slower when ingested orally versus smoking or vaporizing. Variables affecting cannabinoid absorption and distribution can make oral dosing crucial to initiate conservatively and to monitor frequently. Oral cannabis consumption provides longer and stronger-acting effects than smoking or vaporizing. This knowledge can help adjust doses for new users, prevent overconsuming, and avoid unwanted side effects.Oral cannabis preparations are available in various forms including capsules, tinctures, oils, chocolates, brownies, ice cream, granolas, gummies, and more. Careful consideration of accidental excess cannabis intake by overeating is a concern with edibles, as they can be highly concentrated and unpredictable.

Stomach Acid Levels Influence THC Blood Levels

During the process of digestion, stomach acid de-activates a portion of THC in ingested cannabis products. Individuals with low stomach acidity (like the elderly or people taking prescription OTC antacids) will metabolize a higher percentage of active THC following consumption which delivers more THC to the bloodstream. People taking prescription and OTC antacids such as proton-pump inhibitors, histamine blockers, or calcium-based antacids (like Tums) must start with a much lower oral dose of cannabis.

Oral Cannabis Dosing Produces More Active Metabolites than Inhaled Cannabis

When cannabis is orally ingested, the liver converts roughly half of the THC into its primary active metabolite; 11-hydroxy-THC (11-OH-THC). This conversion is much higher than with smoking or vaporizing cannabis. 11-OH-THC has a significantly stronger psychoactive effect and crosses the blood-brain barrier more effectively than THC. As a result, *orally dosed cannabis promotes increased psychoactive effects that may last longer than smoked or vaporized cannabis (up to 12 hours or more).*

THC Binds Strongly to Plasma Proteins

THC enters the bloodstream by binding strongly to plasma proteins after digestion by the stomach and processing by the liver. Drugs that are bound to plasma proteins are not free to perfuse into tissues and activate receptors. Only a small percentage of blood THC can be considered to be active.

THC is a lipophilic (a fat-loving compound) with a high affinity to plasma proteins. Its' high affinity for distribution into fatty tissues of the body draws it to the brain. People with low plasma proteins (chronic kidney failure or those taking other highly protein-bound drugs) may experience increased effects from oral dosing.

11-OH-THC (THC's primary active metabolite) has also been shown to have less of an affinity for plasma proteins than THC, contributing to increased brain-perfusion and prolonged psychoactive effects.

Different formats and cultivars of cannabis can be used for an array of conditions. Phytocannabinoids, cannabinoids, terpenes, and other various medicinal compounds glorify the healing potentials of the ancient plant. Raw juice can be consumed to reduce systemic inflammation (the underlying etiological theme of all mental illness), delta 9 THC can be inhaled to provide immediate relief for panic disorder, edibles can be consumed to sustain sleep (mitigating somniphobia due to nightmares and terrors), while full spectrum cannabidiol (CBD) can be used prophylactically to nourish the endocannabinoid system providing neuronal cellular homeostasis and an overall sense of relief.

Phytocannabinoid found in hemp (the non-psychoactive strain of the cannabis plant)

- Interact with the serotonin receptor (5-HT)1A

- CB1 receptor impacts

    - Stress
    - Anxiety
    - Depression
    - Schizophrenia
    - Suicidal ideology
    - Addictions
    - PTSD
    - Major depressive disorder
    - Bipolar disorder I & II

Cannabis is a safe natural medicament that can be used to treat a variety of mental health conditions without causing detrimental side effects often associated with antipsychotic medications. It is nontoxic but not innocuous. One cannot overdose and die from cannabis use.

Regardless of any negative uses that can derive from the use of the cannabis plant, the positive and essential uses of the plant far outweigh them. THC is essential to the entourage effect. The entourage effect of cannabinoids, terpenes, flavonoids, and other molecules create a host of effects, accounting for the multitude of medicinal properties of cannabis. No THC means no entourage effect. Full spectrum CBD contains 0.3% or less THC which does not create a mental high commonly associated with marijuana strains. Hemp with THC percentages over 0.3% are considered marijuana even if the total CBD exceeds the total THC.
Cannabis initiates homeostasis to reduce inflammation and activate the immune system to modulate a response. Biodiversity among individuals' endocannabinoid system and cannabinoid response are essential components of a personalized lifestyle approach to cannabinoid medicine. Biodiversity means titration is individualized to each person and their specific needs. Microdosing can be used to achieve baseline dosing. Sprays, tinctures, and inhalation can be used for quick relief.

Oral dosing is more discreet and convenient, however, effects can be unpredictable and the effects last much longer due to the conversion 11 hydroxy THC. While this can provide extended periods of relief, it can also extend the mental high effets. It is hard to test for dosing accuracy of foodstuff cannabis preparations (candy, granola, brownies, gummies, ice cream, etc.) due to inaccurate labeling from unequal distribution of cannabinoids and poor quality cannabis used. It is recommended to start with low doses of edibles (1 to 5 mg). Tolerance takes about 2 weeks.

Conservatism and caution is warranted when dosing oral cannabis with cannabis naive, elderly, and medically fragile patients. Factors such as age, gastrointestinal acidity, plasma protein status, medication use, comorbidities, genetic metabolic status, and other considerations are essential. THCA can be beneficial for geriatric and pediatric use.

Using general guidelines for choosing a cultivar, form, dose, and administration route can lead to the most predictable and desirable effects while reducing unwanted side effects. The research has shown how THC in the body can provide general guidelines that will help therapeutic dose selection, type of preparation, and what route to take in achieving a desired dynamic effect.

Given the need to eliminate the detrimental side effects of mainstream antipsychotics and their weak efficacy, cannabis have been suggested as a possible alternative treatment for mental illnesses like schizophrenia due to the medicinal properties of phytocannabinoids and cannabinoid constituents of delta 9 tetrahydrocannabinol (THC), cannabidiol (CBD), cannabigerol (CBG), tetrahydrocannabivarin (THCV), and all others. Evidence suggests that CBD can ameliorate positive and negative symptoms of schizophrenia.

" For every drug that benefits a patient, there is a natural substance that can produce the same effect." - Carl C. Pfeiffer, MD, PhD

Behavioral and neurochemical models suggest that CBD has a pharmacological profile similar to that of atypical antipsychotic drugs.

Cannabis Cannabinoids Recap

- Phytocannabinoid are found in hemp strains of cannabis (the non-psychoactive strain of the cannabis plant)
    - Interact with the serotonin receptor (5-HT)1A
- CB1 receptor functionality is crucial in all mental health
- Delta 9 THC works directly with CB1
    - Excessive amounts or unbalanced with other cannabinoids can worsen symptoms
    - No THC = No entourage effect

- Full spectrum CBD contains 0.3% or less THC

    - Percentages over are considered marijuana, even if the total CBD exceeds the total THC

CANNABINOID DOSING

- Adults under 150 lbs: start 2 - 5.5 mg THC
- Adults 150 to 200 lbs: 5 - 10 mg THC
- Adults over 200lb: 10 - 15 mg THC
- Pediatric under 90 lbs: 1 - 2.5 mg CBD
- 1 mg per 20 lbs of body weight: 1:1 ratio (CBD:THC)

- Increase CBD if anxiety occurs
- Start edibles at bedtime

METHOD OF ADMINISTRATION: ONSET and DURATION

● Inhalation:	1 - 3 min	1 - 3 hours
● Sublingual:	15 - 30 min	2 - 4 hours
● Ingestion:	30 - 90 min	6 - 12 hours
● Topicals:	30 - 60 min	2 - 4 hours
● Transdermal:	15 - 30 min	6 - 12 hours
● Rectal:	15 - 30 min	6 - 8 hours
● Raw:	cumulative effect over time	

Peanut Butter Cacao Hemp Seed Bars

Psychiatric conditions are heavily associated with nutritional defciencies and unsuspecting IgG mediated food intolerance. Gluten and casein are among the top offenders for arousing conditions like anxiety, depression, schizophrenia, and bipolar disorder. Removing these food items and incorporating cannabinoids and omega 3s (found in hemp) can improve brain functioning and mood by mediating the endocannabinoid system.

This recipe contains ingredients that are nutritionally supportive to mental wellness. Gluten-free oats stimulate the parasympathetic nervous system while cacao's antioxidant favanols support the neurotransmitter functions of serotonin, endorphins, phenylethylamine, tryptophan, and anandamide *which have all been shown to* ***ease***

***depression*.**

Genesis 1:29

Prep Time:	10 minutes
Cook Time:	0 minutes
Chill	1 hour
Total Time:	1 hour 10 minutes
Servings	16

Organic Ingredients

- 1 cup quick oats certifed gluten free
- ½ cup hemp seeds
- 1 cup peanut butter
- 1/3 cup pure maple syrup
- 1 tsp pure vanilla extract
- ¼ cup cacao powder
- ¼ tsp himalayan pink salt
- ¼ cup vegan dark chocolate chips

Directions

1. In a large mixing bowl, stir together the oats and hemp seeds. Set aside.
2. In a small saucepan over medium low heat, melt together the maple syrup and peanut butter. Once well blended, stir in vanilla, salt, and cacao powder.
3. Add the peanut butter mixture to the oats & hemp seeds. Thoroughly combine.
4. Place the bowl into the refrigerator for fve minutes to cool before adding the vegan chocolate chips.
5. Stir in the chocolate chips and mix well.
6. Scoop a golf ball sized amount of the mixture and form into balls. Wet your hands every now and then to prevent sticking. Place into the freezer for about an hour to frm them.
7. Store in the fridge or freezer.

CANNA BUTTER

Butter is a popular medium for cannabis preparations because THC needs to bind to fat molecules. Milk is a top food allergen and known to trigger conditions like anxiety, depression, schizophrenia, and bipolar disorder. *Vegan* cannabutter is the better option.

Materials

- Baking sheet
- Unbleached parchment paper
- Oven
- Cast iron or stainless steel saucepan, double-broiler, slow cooker, or stock pot
- Mesh strainer or cheesecloth
- Container for cannabutter
- Grinder

Organic Ingredients

- 1 cup of vegan butter (2 sticks worth)
- 1 cup of clean water (no tap water)
- 1 cup of ground cannabis 7-10 grams, decarboxylated

Cannabis Adult Beginner Starting Dose:

- 5-10 mg CBD to 2-5.5 mg THC

Basic Cannabutter Recipe

Cannabinoids and terpenes are temperature-sensitive. For maximum therapeutic effect, preservation of these molecules is essential. To preserve cannabinoids and terpenes during decarboxylation, keep temperatures low!

1. Preheat the oven to 245°F.
2. Cover the baking sheet with unbleached parchment paper.
3. Gently break apart cannabis and place onto baking sheet.
4. Heat cannabis in the oven 30-40 minutes. Gently mix the herb every 10-15 minutes to evenly distribute heat. Older and/or drier cannabis may required less time.
5. Gently grind the cannabis. Do not overgrind. Small pieces will pass through the straining process.

6. Melt the vegan butter in the saucepan, double-broiler, slower cooker, or stock pot.
7. Add 1 cup of clean water to the melted butter (no tap water).
8. Add the decarbed cannabis into the fully melted butter.
9. Simmer on low heat (160-200°F) 2 - 3 hours, stirring occasionally. DO NOT BOIL.
10. Strain the mixture with a fne strainer or cheesecloth over a jar (no plastic or rubber containers). DO NOT AGGRESSIVELY SQUEEZE the cheesecloth.
11. Discard plant material or use in other infusions.
12. Pour the melted cannabutter into glass formed butter containers.
13. Place in refrigerator overnight.
14. Drain any excess water that forms at the bottom of the jar

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