

Medical Cannabis: Pharmacology and Mechanism of Action

Assoc.Prof.Dr. Narisa Kamkaen
College of Pharmacy, Rangsit University

Outline

- ▶ Timeline of medical cannabis
- ▶ Definition of medical marijuana
- ▶ Phenotype and chemotype of *Cannabis sativa* L.
- ▶ Chemistry of marijuana
- ▶ Pharmacokinetics of cannabis
- ▶ Pharmacodynamics of cannabis
- ▶ Route of administration
- ▶ Mechanism of action
- ▶ Pharmacological actions of cannabis
- ▶ Information for health care professionals

Timeline of medical cannabis

- ▶ **Cannabis**, or **marijuana**, was first used for medicinal purposes in 2737 B.C.
- ▶ **The United States Pharmacopeia** initially classified marijuana as a legitimate medical compound in 1851.
- ▶ Although criminalized in the United States in 1937 against the advice of the American Medical Association, cannabis was not removed from the United States Pharmacopoeia until 1942.
- ▶ Given the **schedule I** status of this drug, patients have continued to obtain cannabis for medical purposes through statewide programs and cannabis dispensaries, which are facilities or locations where medical cannabis is made available to qualified patients.

Timeline of medical cannabis

- ▶ **Dronabinol** and **nabilone** were approved in 1985 for the treatment of nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic therapy.
- ▶ In 1992, **dronabinol** was also approved for the treatment of anorexia associated with weight loss in patients with acquired immune deficiency syndrome.

Timeline of medical cannabis

- ▶ **Nabiximols** is a cannabis-derived liquid extract formulated from two strains of *Cannabis sativa* into an oromucosal spray.
- ▶ It is approved in Canada, New Zealand, and eight European countries for three indications:
- ▶ (1) symptomatic relief of spasticity in adults with multiple sclerosis who have not responded adequately to other therapy and who demonstrate meaningful improvement during an initial trial of therapy,
- ▶ (2) symptomatic relief of neuropathic pain in patients with multiple sclerosis, and
- ▶ (3) intractable cancer pain.

Timeline of medical cannabis

- ▶ Marijuana is classified as a schedule I substance by the FDA, so it is difficult for contemporary researchers to study marijuana even though its therapeutic properties have been known for more than 5000 years.
- ▶ Cannabis contains many compounds, of which at least 60 are known to be cannabinoids (active components of cannabis).
- ▶ In the 1960s, when marijuana was increasingly used as a recreational drug, the cannabinoid D9-tetrahydrocannabinol (D9-THC) was isolated and determined to be the principal cause of marijuana's psychoactive effects.
- ▶ Other cannabinoids have been isolated and found to be present in cannabis, but they are not nearly as psychoactive.

Medical Cannabis



Definition of medical marijuana

- ▶ **“Marijuana”** is dried material from the *Cannabis sativa* plant, from leaves, stems and flower buds, and consists Tetrahydrocannabinol (**THC**), Cannabidiol (**CBD**) and other cannabinoids.
- ▶ **“Medical marijuana”** as defined by state laws is available in herbal form utilizing dried parts of the cannabis plant (only in some states), and essentially the same form that is sold illicitly.
- ▶ **THC** is the active ingredient sought after for its psychoactive effects.

Definition of medical marijuana

- ▶ **Marijuana** is highly lipophilic which leads to its storage in adipose tissue, liver, muscle and spleen and redistributed into the users blood stream long after ingestion.
- ▶ Because of the persistence in the body, **marijuana** can cause highly potent mental, physical and toxic effects in the users that are hard to control or predict.
- ▶ In addition, **Marijuana** causes dependence, tolerance and addiction.
- ▶ The attempt to discontinue its use causes withdrawal symptoms consisting of: anxiety, depression, decreased appetite, headaches, insomnia, irritability, muscle tension, nausea, nightmares and unpleasant vivid dreams.

Phenotype of *Cannabis sativa* L.



SATIVA

Cannabis Sativa Sativa is characterized by leaflets that are more narrow, branches that are farther apart, and coloration that tends more toward spring green. Sativa Sativa plants tend to be taller and produce fewer flowers.



INDICA

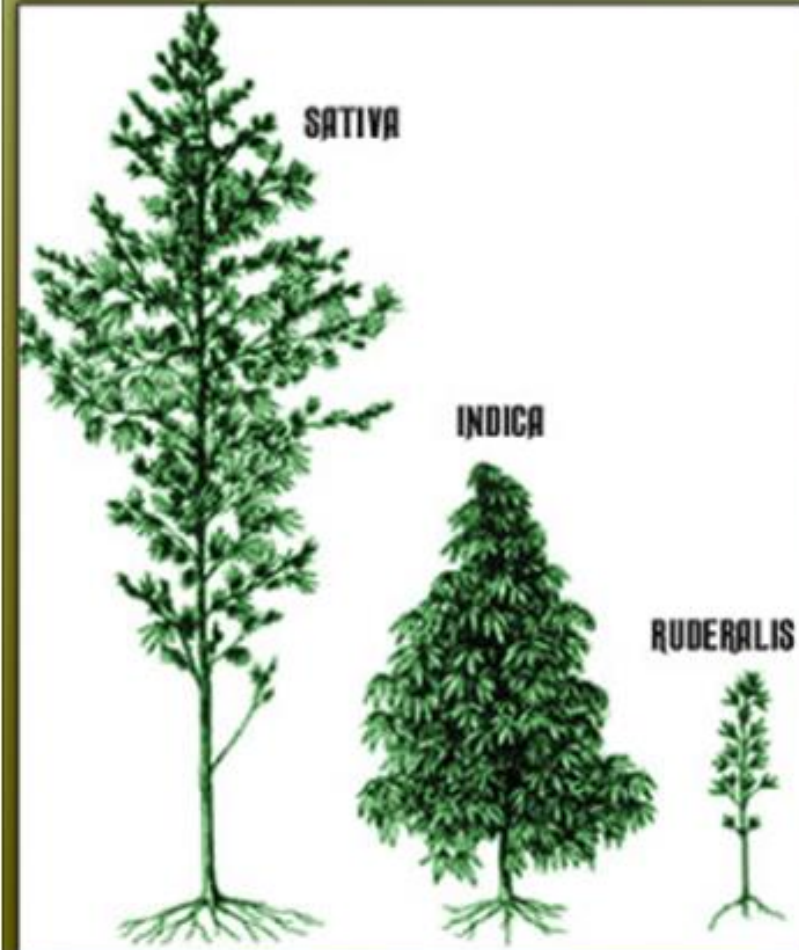
Cannabis Sativa Indica is characterized by broad leaflets that offer overlap, branches that are closer together, and coloration that tends more toward deep olive green. Sativa Indica plants tend to be shorter and bushier, producing fuller, denser flower buds.



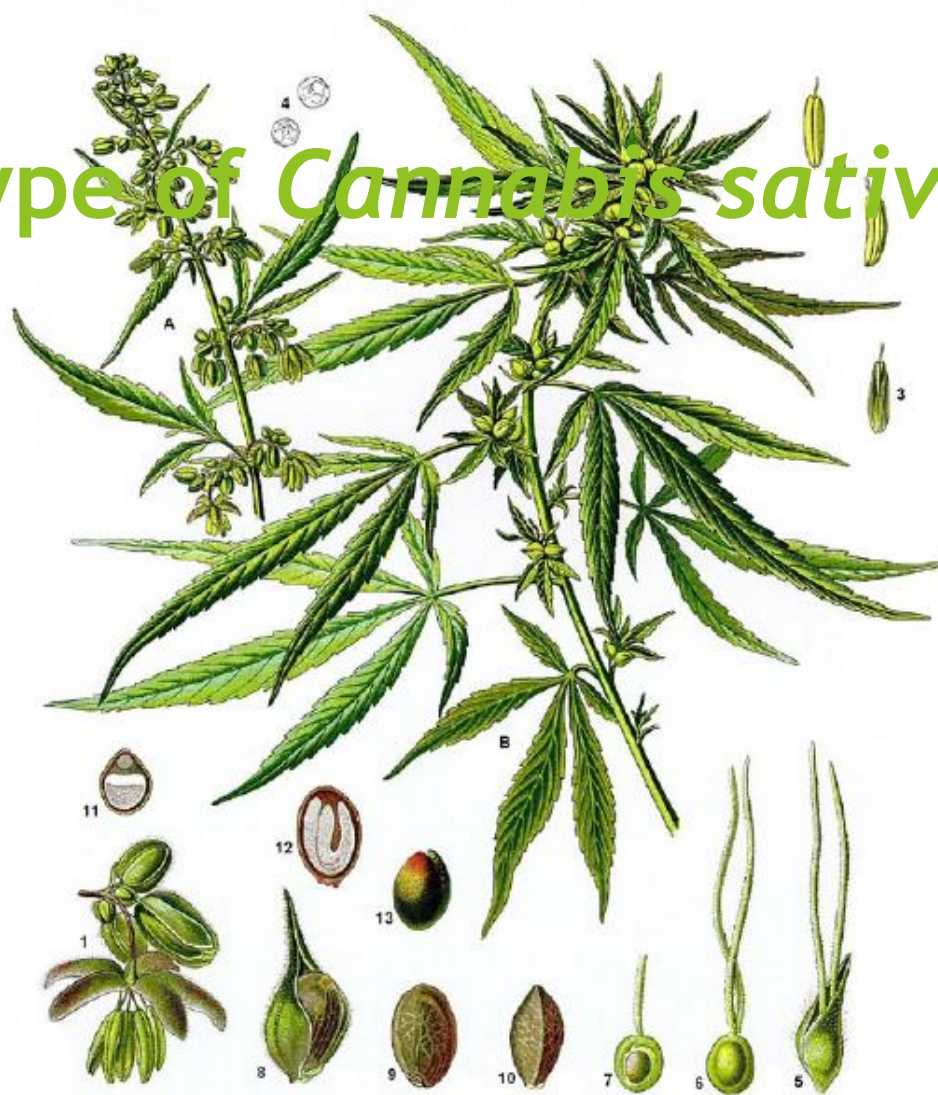
RUDERALIS

Cannabis Ruderalis is characterized by varied leaflets in the mature leaves, a shorter stature and generally small size. This subspecies is used to create S. Sativa or S. Indica hybrids with select desired traits.

The Cannabis Family



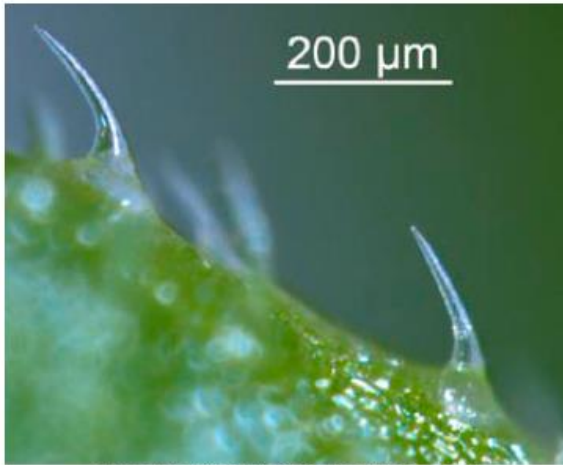
Phenotype of *Cannabis sativa* L.



- | | | | |
|---|---|----|--|
| A | Inflorescence of male (staminate) plant | 7 | Pistillate flower showing ovary (longitudinal section) |
| B | Fruiting female (pistillate) plant | 8 | Seed (achene*) with bract |
| 1 | Staminate flower | 9 | Seed without bract |
| 2 | Stamen (anther and short filament) | 10 | Seed (side view) |
| 3 | Stamen | 11 | Seed (cross section) |
| 4 | Pollen grains | 12 | Seed (longitudinal section) |
| 5 | Pistillate flower with bract | 13 | Seed without pericarp (peeled) |
| 6 | Pistillate flower without bract | | |

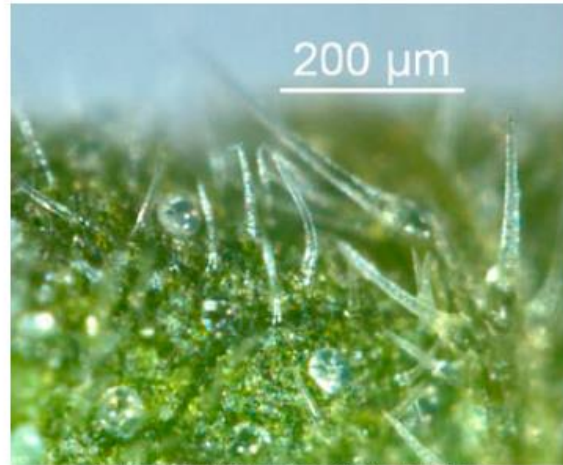
Reference : United Nations Office on Drugs and Crime, 2009.

Phenotype of *Cannabis sativa* L.



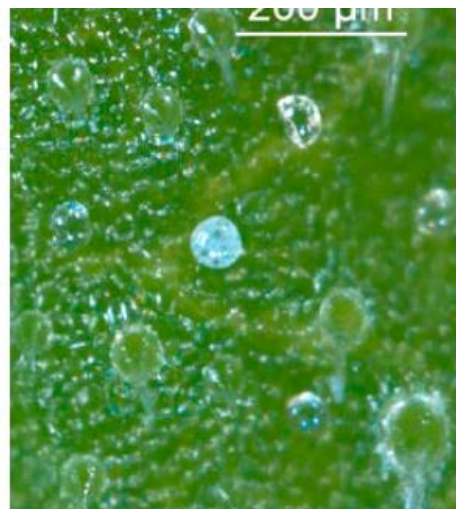
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Cystolithic trichomes



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Non-cystolithic trichomes



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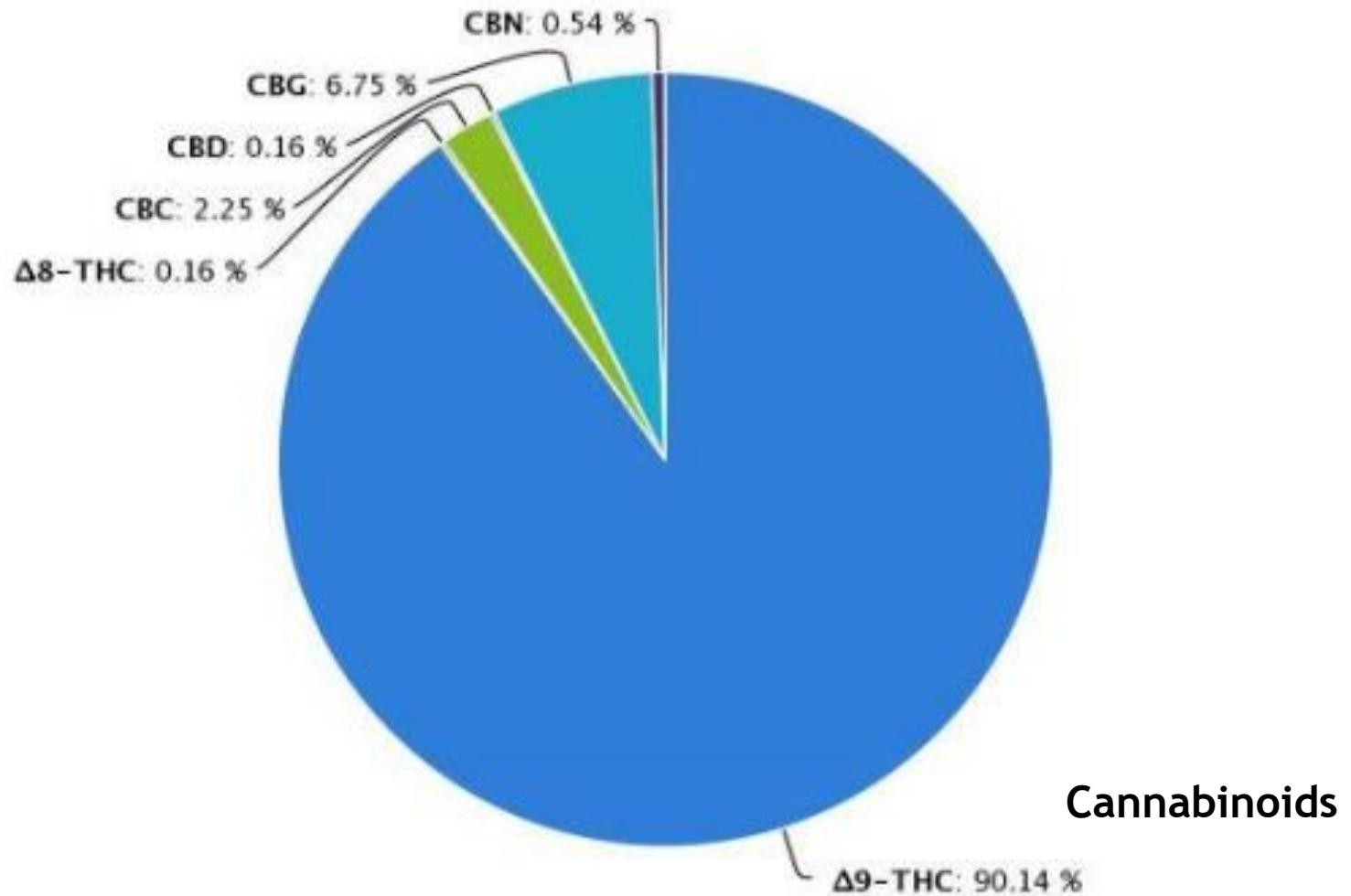
Sessile glands



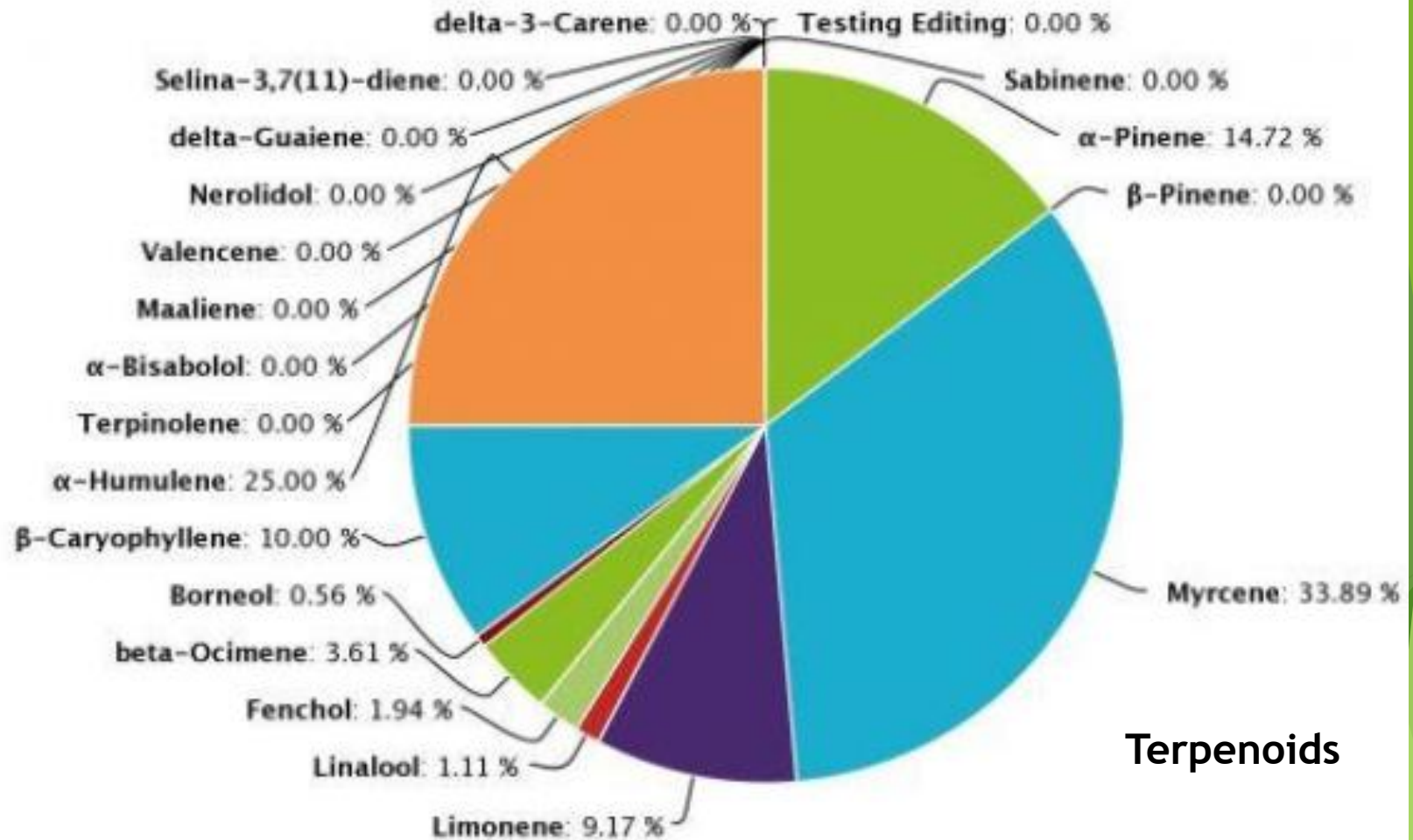
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Stalked glandular trichomes

Chemotype of *Cannabis sativa* L.

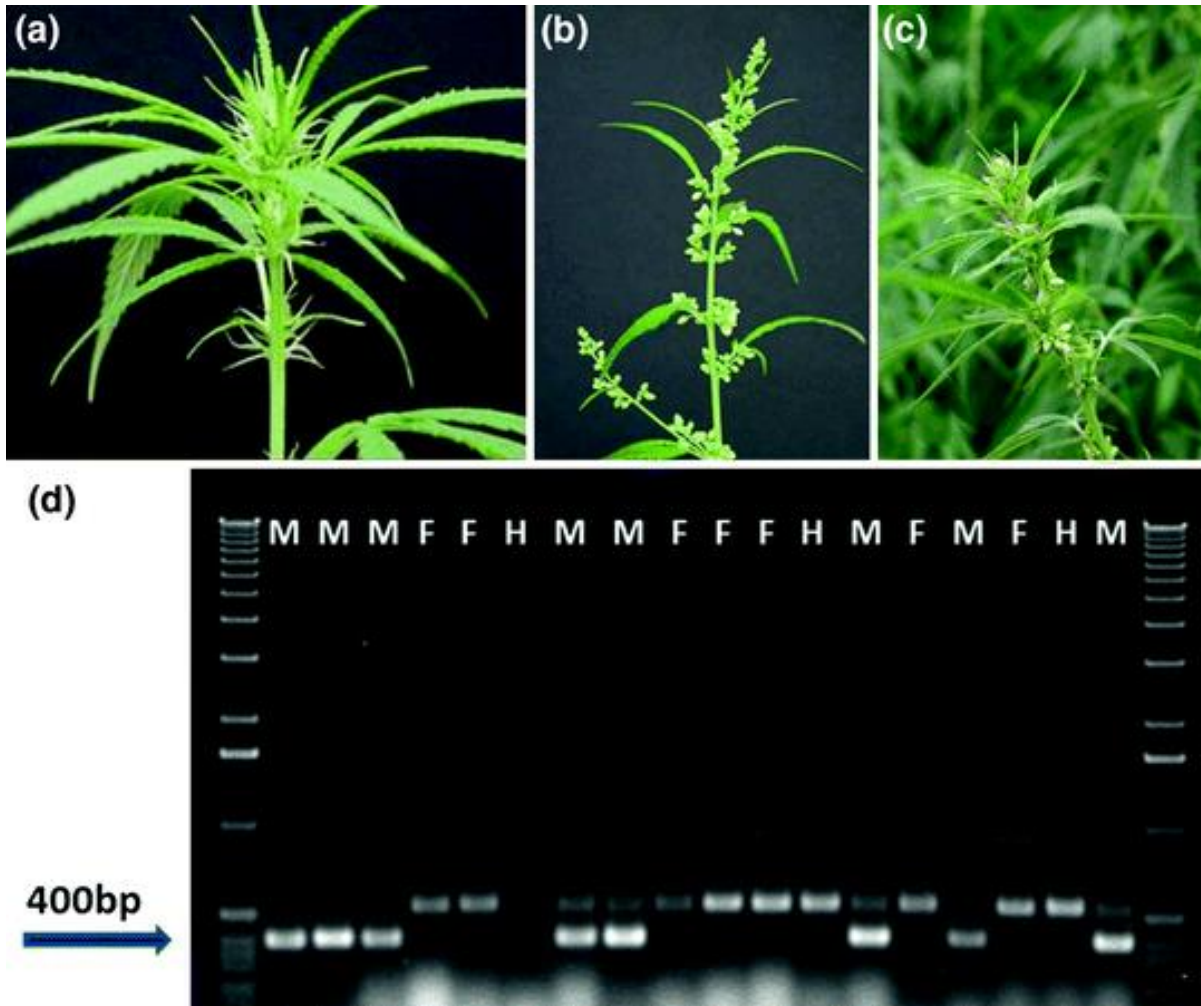


Chemotype of *Cannabis sativa* L.

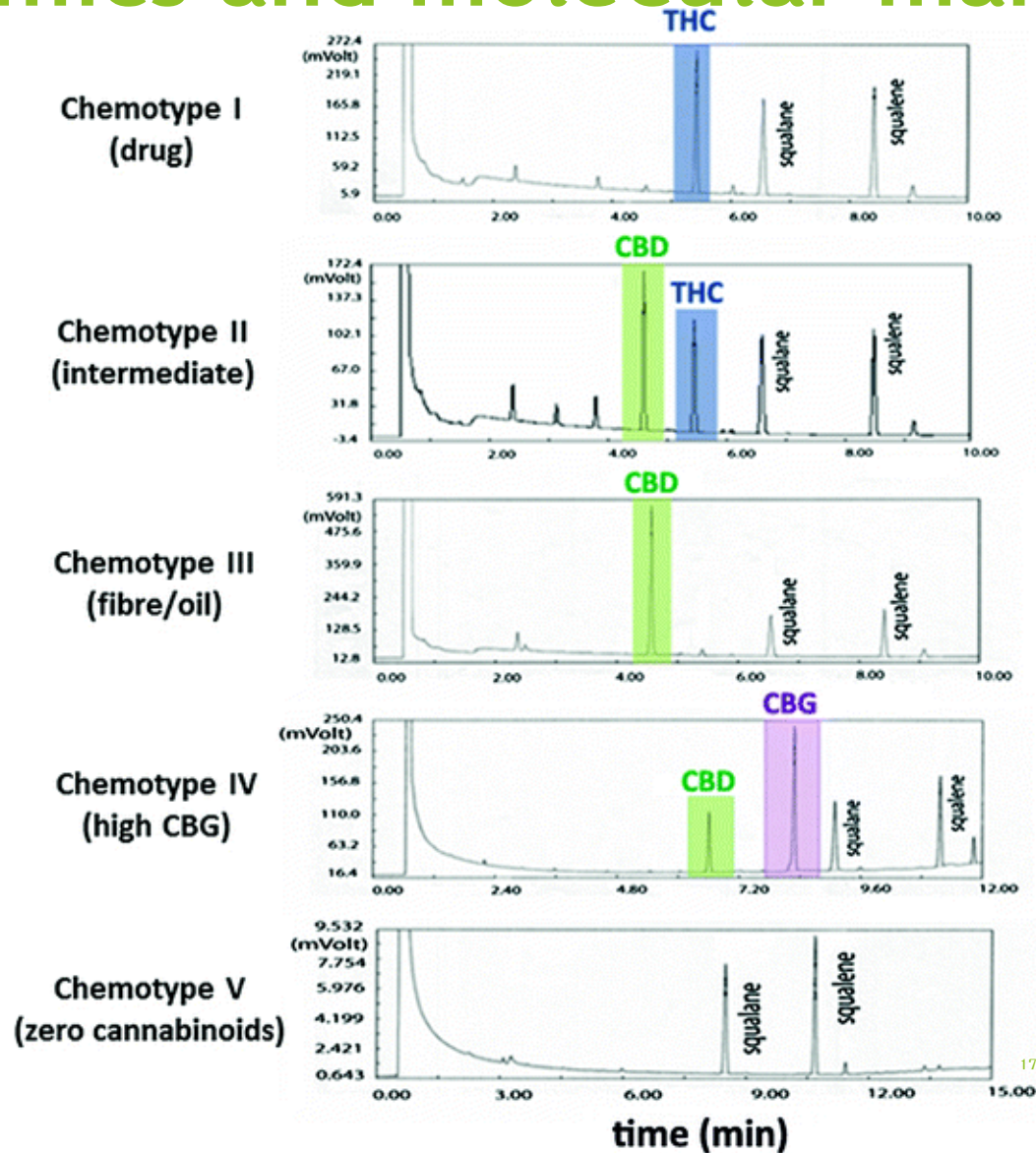


Terpenoids

Genomics and molecular markers



Genomics and molecular markers



Chemistry of Marijuana

- ▶ Marijuana, as used in the general population for smoked consumption, is an extract of the plant *Cannabis sativa* (Indian hemp).
- ▶ It consists of more than 421 components and more than 60 pharmacologically active **cannabinoids**.
- ▶ The two most well described cannabinoids in marijuana are delta9-tetrahydrocannabinol (**THC**) and cannabidiol (**CBD**).
- ▶ **CBD** does not produce any of the psychoactive responses and appears to block some of the effects of THC by acting as an antagonist at the cannabinoid receptors.

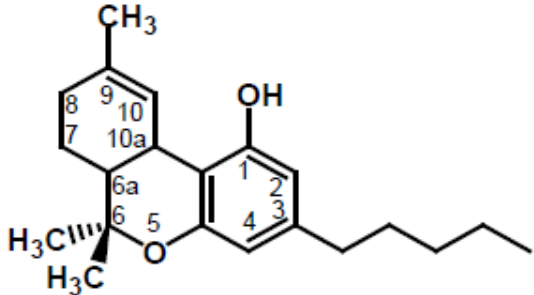
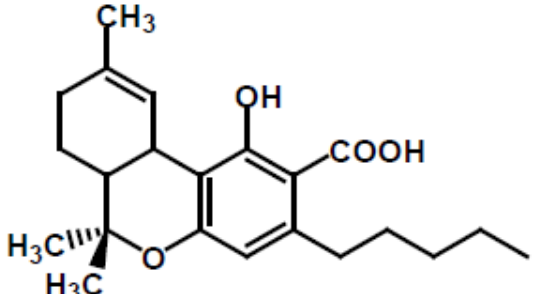
Chemistry of Marijuana

- ▶ **THC** has a tri-cyclic 21-carbon structure without nitrogen and with 2 chiral centers in transfiguration.
- ▶ THC is volatile viscous oil with high lipid solubility and low water solubility and a pKa of 10.6.
- ▶ The primary active metabolite of THC is 11-hydroxy-delta-tetrahydrocannabinol (11-OH-THC) and the primary inactive metabolite is 11-nor-9- carboxy-delta-9-tetrahydrocannabinol (THC-COOH).

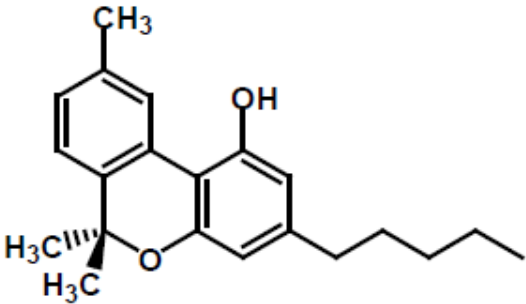
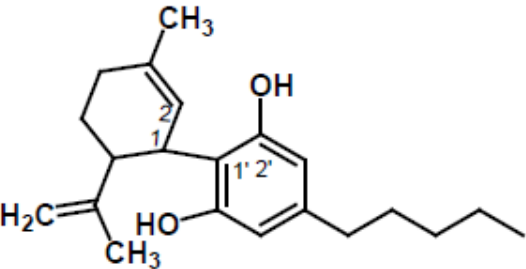
Chemistry of Marijuana

- **THC** and **CBD** are just two compounds from a family of around **113 bi- and tri-cyclic compounds** cannabinoid compounds found naturally in cannabis.
- Both **CBD** and **THC** share the exact same molecular formula, $C_{21}H_{30}O_2$, containing twenty-one atoms of carbon, thirty of hydrogen and two of oxygen.
- Their molecular mass is practically identical with **THC** and **CBD** having masses of 314.469 g/mol 314.464 g/mol, respectively.

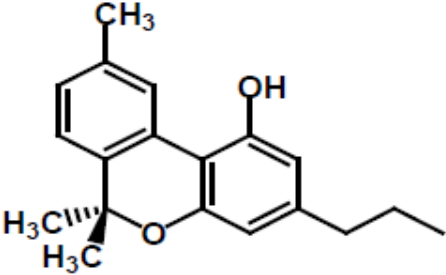
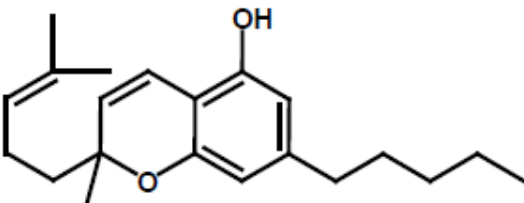
Chemical constituents

<p>(-)-Δ^9-trans-Tetrahydrocannabinol Tetrahydrocannabinol, THC</p>  <p>Main pharmacological characteristics:</p> <ul style="list-style-type: none"> - Euphoriant - Anti-inflammatory - Analgesic - Anti-emetic 	<p>CAS: 1972-08-3</p> <p>Empirical formula: $C_{21}H_{30}O_2$</p> <p>Molecular weight: 314.46 g/mol</p> <p>Melting point: viscous oil</p> <p>pKa: 10.6</p> <p>log P: 6.99 (octanol/water)</p> <p>Solubilities:</p> <p>Water: insoluble (2.8 mg/L 23°C)</p> <p>Ethanol: soluble</p> <p>Chloroform: soluble</p> <p>Hexane: soluble</p>
<p>(-)-Δ^9-trans-Tetrahydrocannabinolic Acid THCA</p>  <p>Main pharmacological characteristics:</p> <ul style="list-style-type: none"> - Antibacterial - Antibiotic 	<p>CAS: 23978-85-0</p> <p>Empirical formula: $C_{22}H_{30}O_4$</p> <p>Molecular weight: 358 g/mol</p> <p>Melting point: n/a (decomposition/ decarboxylation of THCA to THC at about 125-150°C)</p> <p>Solubilities:</p> <p>Water: insoluble</p> <p>Ethanol: soluble</p> <p>Chloroform: soluble</p> <p>Hexane: soluble</p>

Chemical constituents

<p>Cannabinol CBN</p>  <p>Main pharmacological characteristics:</p> <ul style="list-style-type: none"> - Sedative - Anticonvulsant - Antibiotic - Anti-inflammatory 	<p>CAS: 521-35-7 Empirical Formula: $C_{21}H_{26}O_2$ Molecular Weight: 310.43 g/mol Melting Point: 76–77 °C log P: 6.23 (octanol/water)</p> <p>Solubilities:</p> <table border="0"> <tr> <td>Water</td> <td>insoluble</td> </tr> <tr> <td>Ethanol</td> <td>soluble</td> </tr> <tr> <td>Chloroform</td> <td>soluble</td> </tr> <tr> <td>Hexane</td> <td>soluble</td> </tr> </table>	Water	insoluble	Ethanol	soluble	Chloroform	soluble	Hexane	soluble
Water	insoluble								
Ethanol	soluble								
Chloroform	soluble								
Hexane	soluble								
<p>Cannabidiol CBD</p>  <p>Main pharmacological characteristics:</p> <ul style="list-style-type: none"> - Anxiolytic - Anti-inflammatory - Antipsychotic - Antispasmodic - Analgesic 	<p>CAS: 13956-29-1 Empirical formula: $C_{21}H_{30}O_2$ Molecular weight: 314.46 g/mol Melting point: 66–67 °C log P: 5.79 (octanol/water)</p> <p>Solubilities:</p> <table border="0"> <tr> <td>Water</td> <td>insoluble</td> </tr> <tr> <td>Ethanol</td> <td>soluble</td> </tr> <tr> <td>Chloroform</td> <td>soluble</td> </tr> <tr> <td>Hexane</td> <td>soluble</td> </tr> </table>	Water	insoluble	Ethanol	soluble	Chloroform	soluble	Hexane	soluble
Water	insoluble								
Ethanol	soluble								
Chloroform	soluble								
Hexane	soluble								

Chemical constituents

<p>Cannabivarin CBV</p>  <p><chem>CC1=CC=C2C(=C1)OC(C)(C)C2=CC(O)=CC=C3CCCC3</chem></p>	<p>CAS: 33745-21-0 Empirical formula: $C_{19}H_{22}O_2$ Molecular weight: 282.38 g/mol</p>
<p>Cannabichromene CBC</p>  <p><chem>CC1=CC=C2C(=C1)OC(C)(C)C2=CC(O)=CC=C3CCCCCCC3</chem></p> <p>Main pharmacological characteristics:</p> <ul style="list-style-type: none">- Anti-inflammatory- Antifungal- Antibiotic- Analgesic	<p>CAS: 20675-51-8 Empirical formula: $C_{21}H_{30}O_2$ Molecular weight: 314.46 g/mol</p>

Presumptive tests by TLC

Plate: HPTLC 10 x 10 cm Silica gel		
System A:	Petroleum ether 60/90 Diethyl ether	80% v/v 20% v/v
System B:	Cyclohexane Di-isopropyl ether Diethylamine	52% v/v 40% v/v 8% v/v
System C: (for cannabinoid acids)	n-Hexane Dioxane Methanol	70% v/v 20% v/v 10% v/v
Tank conditioning: 30 min. with filter paper on one side.		

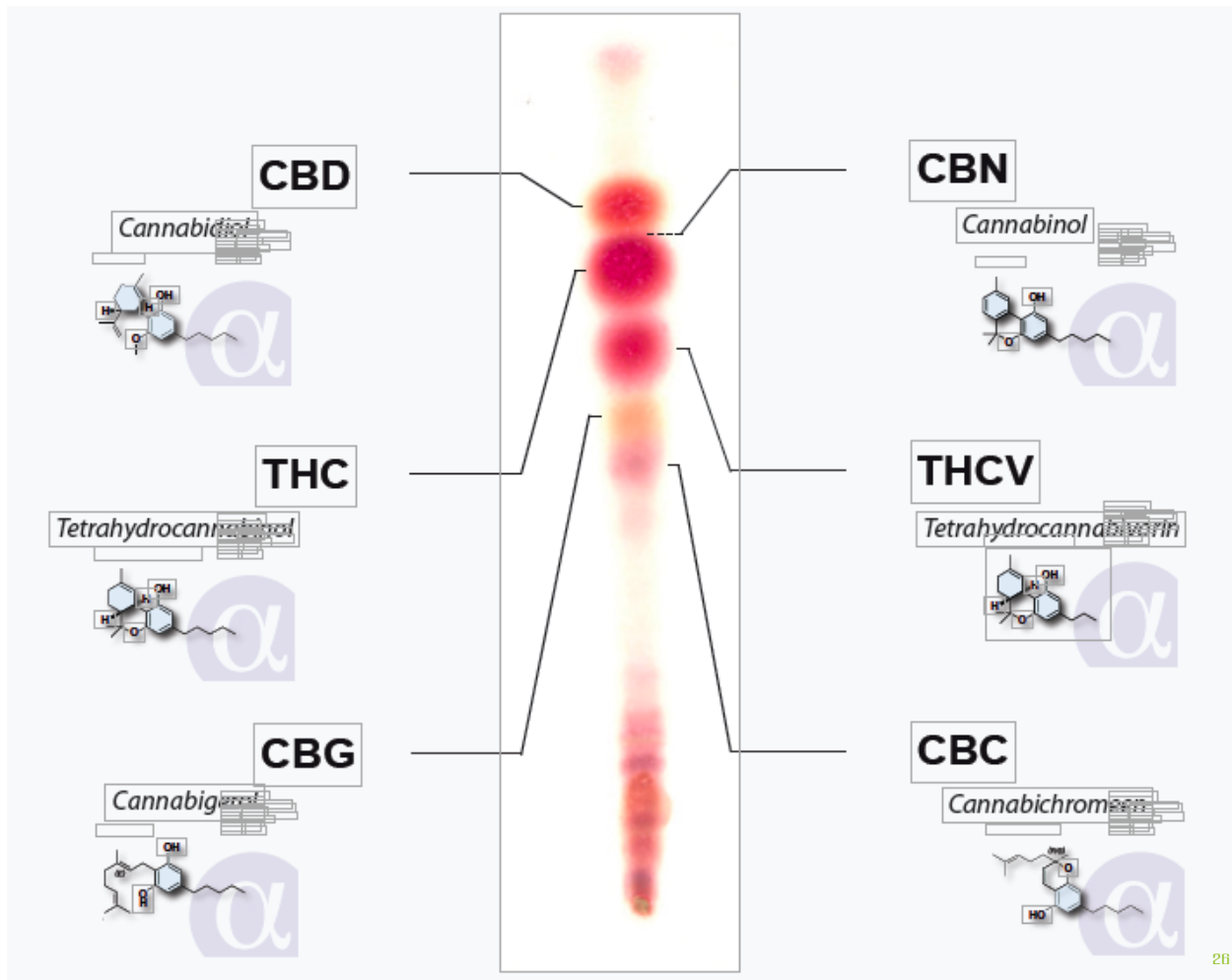
Presumptive tests by TLC

Compound	Developing system, Rf x 100 values*		
	A	B	C**
CBN	33	26	47
THC	37	38	49
CBD	42	42	47
THCA	6	–	36

*Results refer to employment of method using HPTLC plates, as described in this section. Traditional 20x20 plates with a 0.25 mm thick layer of silica gel provide comparable separations, but the corresponding Rf values will have to be determined.

**System C is only recommended for the separation and identification of cannabinoid acids. It does not provide adequate separation of CBN, THC and CBD.

Cannabinoid Analysis Tool (CAT)



CHEMOTYPES AND CANNABINOID PROFILE

Type 1	Type 2	Type 3	Type 4	Type 5	Type 6	Type 7	Type 8
Mexican Haze type	CBC - Haze type	Indian type	Kenyan type	Thai type	CBC - Thai type	Skunk type	Haze type

Type 9	Type 10	Type 11	Type 12	Type 13	Type 14	Specimen
						<ul style="list-style-type: none"> - CRYPTIC 1 - CBGM - CBD - CBN - THCV - CBG - CBC <p>CRYPTICS {</p> <p>} ACIDS</p>
Hashplant African type	Hash type	Skunk Hashish type	Ruderalis type	Hemp CBD type	Hemp CBG type	Full cannabinoid fingerprint

Pharmacokinetics of Cannabis

- ▶ **Inhalation/Smoking** marijuana has the highest addictive potential due to rapid and efficient drug delivery from the lungs to the brain.
- ▶ A major fraction of THC is destroyed by pyrolysis, which causes the variance in systemic bioavailability between heavy and occasional users.
- ▶ More than 2000 compounds mostly unknown in their exact clinical structure and physical and mental effects are produced by pyrolysis during smoking of marijuana.
- ▶ These chemicals include different classes of chemicals including nitrogenous compounds, amino acids, hydrocarbons, sugar, terpenes and simple fatty acids.

Pharmacokinetics of Cannabis

- ▶ Compared to inhalation, the onset of effects is delayed in **oral** use, peak concentrations are lower but the duration of pharmacokinetic effects are extended with a delayed return to baseline.
- ▶ First pass metabolism means that only a fraction of the marijuana ingested actually becomes available in the blood stream.
- ▶ The **suppository** form of natural marijuana as well as synthetic THC is available as an ovular capsule that can be inserted vaginally or rectally.
- ▶ The capsules are typically about an inch long and are made from a mixture of coconut oil infused with marijuana or FECO (Full Extract Cannabis Oil)-infused cocoa butter.
- ▶ Once inserted, the capsule dissolves and is absorbed into the bloodstream through the thin lining of the intestinal wall .

Pharmacokinetics of Cannabis

- ▶ In **transcutaneous** absorption, the transport across the skin layers is limited by the hydrophobic qualities of cannabis, making it the rate limiting step.
- ▶ A transcutaneous carrier selected from the group consisting of water, short carbon chain alcohols, dimethylsulfoxide, polyethylene glycol, polypropylene glycol, glycerin, mineral oil and mixtures thereof.
- ▶ The delivery to the brain when administered transcutaneously is much slower compared to smoking.
- ▶ Steady state plasma concentrations were found to be maintained for at least 48 h.

Metabolism of Cannabis

- ▶ **THC** is metabolized in the liver by microsomal hydroxylation and oxidation via **CP450** enzymes.
- ▶ The hydroxylation of **THC** through **CP450** enzymes leads to the production of the equipotent active metabolite **11-OH-THC**.
- ▶ Cytochromes involved in the oxidation of **THC** are **CYP 450 2C9**, **2C19** and **3A4**.
- ▶ More than 100 **THC** metabolites including di- and trihydroxy compounds, ketones, aldehydes, and carboxylic acids, have been identified.
- ▶ The oxidation of the psychoactive **11-OH-THC** produces the inactive metabolite **THC-COOH**, which is with its conjugates the major end product of biotransformation.
- ▶ Extra-hepatic sites in the brain, intestine and lung might contribute to the metabolism of cannabis.

Metabolism of Cannabis

- ▶ **Marijuana** has been shown to affect the pharmacokinetics of other drugs in several ways through inhibition of the CP450 enzyme.
- ▶ It mediates the absorption of other drugs and may also slow down the absorption of others and to enhance or delay the penetration of drugs into the brain.
- ▶ Marijuana interacts through CP 450 with medications levels for example **warfarin** and **theophylline** and is linked to toxic levels or supra-therapeutic INR values.
- ▶ Also **antidepressants** for example SSRIs inhibit the hepatic CP450 enzymes.
- ▶ **Prozac** and **Paxil** extend the availability of marijuana in the serum due to competition with the enzyme.

Distribution of Cannabis

- ▶ Central to Marijuana's toxicity is that it is a highly lipophilic substance that is taken up by tissues that are highly perfused in the blood circulation, such as **heart, lung, brain, muscle and liver** as well as **adipose tissues**.
- ▶ With prolonged marijuana exposure, fatty acid conjugates of **THC** and **11-OH-THC** are formed, increasing the stability of these compounds and allowing even its extended storage in the tissues.
- ▶ Studies with radioactive tracers for THC have shown a large volume distribution of the active form of THC and its slow elimination from body stores long after use for continued pharmacological effects.
- ▶ The half-life of infrequent users is 1.3 days and for frequent user it is 5 to 13 days.

Distribution of Cannabis

- ▶ Therefore the pharmacological effects of marijuana and also its toxic effects can persist for a prolonged period of time after the last ingestion or exposure, which makes it highly unpredictable.
- ▶ Also the effects of marijuana increase in potency in frequent and long term users since cannabis release from storage in the tissues to be added to the newly ingested amount of marijuana.
- ▶ The pharmacokinetics of **marijuana** is distinct from other addictive substances, for example **alcohol** and **opioids**, which have a much shorter half-life and do not have the quality to be stored and recirculate into the blood system.
- ▶ Marijuana's toxic effects persist and are much more unpredictable.

Excretion of Cannabis

Overall Clearance rate	Route of excretion	Conjugation	Primary metabolites
Woman 11.8+-3 L/h	Feces 65%	Hepatic: water-soluble metabolite after conjugation with glucuronic acid	Feces: 11-OH-THC
Men 14.9 +-3.7 L/h	Urine 20%	Renal: Tubular reabsorption and low renal excretion of the unchanged drug	Urine: THC-COOH

Pharmacodynamics of Cannabis

- ▶ In the 1990s, the mechanism of action for many of the cannabinoids was determined with the discovery of the cannabinoid **CB1** and **CB2** receptors.
- ▶ The **CB1** receptors are found in high densities in the neuron terminals of the basal ganglia (affecting motor activity), cerebellum (motor coordination), hippocampus (short-term memory), neocortex (thinking), and hypothalamus and limbic cortex (appetite and sedation).
- ▶ To a lesser extent, the CB1 receptors are found in periaqueductal gray dorsal horn (pain) and immune cells.

Pharmacodynamics of Cannabis

- ▶ **CB2 receptors** are primarily found on immune cells and tissues and, when activated, can affect inflammatory and immunosuppressive activity.
- ▶ For example, CB2 receptors on leukocytes may modulate cell migration, although these effects are difficult to elicit from standard dosing.
- ▶ CB2 receptors are also found in the brain.

Pharmacodynamics of Cannabis

- ▶ **The full agonist** is the compound HU-210, which is a synthetic cannabinoid.
- ▶ **The partial agonists** are D9-tetrahydrocannabinol (THC), which is a cannabinoid found in cannabis, and anandamide, which is an endocannabinoid found in humans.
- ▶ **The antagonist** is rimonabant, a synthetic cannabinoid studied for weight control.
- ▶ **The inverse agonist** is cannabidiol (CBD), which has no direct CB1 activity but is postulated to be an example of an inverse agonist.

Route of Administration of Cannabis

Formulation	Absorption	Peak concentration	Factors impacting absorption	Bioavailability
Inhalation/ Smoking	Quick Fast, rapid drug delivery to the brain	22 min	Depth of inhalation, frequency of puffs, breath hold	Varies 2-56 percent; Heavy users 23-27 percent; Occasional users 10-14 percent
Oral mucosal/ sublingual	Fast	30 min	High first pass metabolism	Similar to oral route
Rectal	Fast	15 min	Low first pass metabolism	Twice of oral route

Route of Administration of Cannabis

Formulation	Absorption	Peak concentration	Factors impacting absorption	Bioavailability
Oral	Slow	1-2 h, can be delayed to up to 8 h	Degradation of the drug in the stomach and First-pass	Ranges from 10-20 percent
Transcutaneous	Slow	2 h Steady state plasma concentrations were found to be maintained for at least 48 h	Transport across the skin layers No first-pass metabolism	10 percent

Mechanism of Action

- ▶ Marijuana's main sites of action are in the brain and the spinal cord. It binds to two types of G-protein-coupled receptors, **CB1** and **CB2**.
- ▶ **CB1** receptors are predominantly expressed in the brain and located in the basal ganglia, cerebellum, hippocampus, association cortices, spinal cord and peripheral nerves.
- ▶ Through antagonistic effects on the **CB1** receptor, marijuana induces its mental and behavioral effects.
- ▶ By acting on **CB1** receptor, marijuana alters the user's perceptions and mood and disturbs memory function and learning and leads to impaired judgment.

Mechanism of Action

- ▶ Additional central effects of marijuana are a disruption of psychomotor behavior, psychosis and loss of time perception as well as impairment in movement coordination.
- ▶ Because of these perceptual aberrations, marijuana was originally classified as an hallucinogen.
- ▶ The **CB2** receptors are mainly found in the peripheral tissues on cells in the immune system, the hematopoietic systems and in the spleen.
- ▶ These receptors may play a role in the immune-suppressive activity of cannabis.

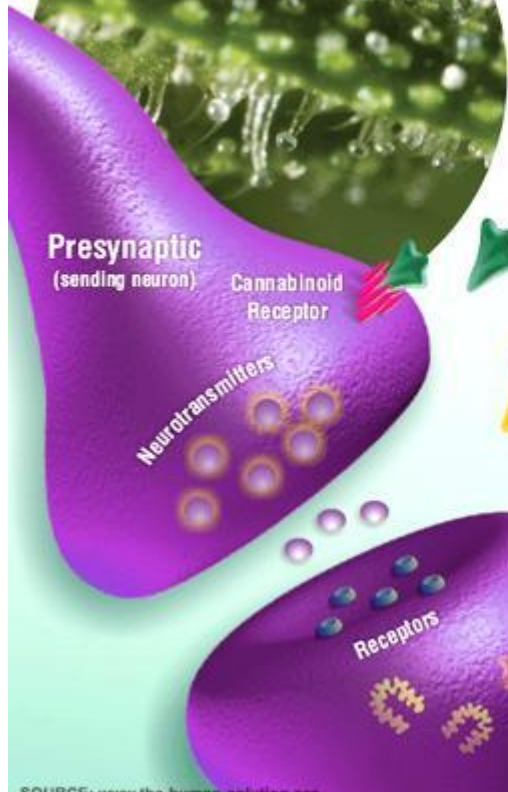
Mechanism of Action

- ▶ Both cannabinoid receptors, **CB1** and **CB2**, are G-protein coupled and become activated through inhibition of the adenylate-cyclase.
- ▶ The activation of these receptors cause an inhibition of the release of the neurotransmitters acetylcholine and glutamate while indirectly affecting γ -aminobutyric acid, N-methyl-D-aspartate, opioid and serotonin receptors.
- ▶ The cannabinoid receptors are predominantly located presynaptic rather than postsynaptic which means that cannabinoids modulate the neurotransmitter releases.

Mechanism of Action

- ▶ Recent studies have shown that **marijuana** decreases the sensitivity to **dopamine** in the reward center in the brain, mainly the region in the mesolimbic dopamine system.
- ▶ **Dopamine neurons** are located in the midbrain and dopamine is the neurotransmitter responsible for the brain's pleasure and reward center.
- ▶ The limbic system consists of the amygdala, the nucleus accumbens, the prefrontal cortex and the hippocampus.
- ▶ In addition to the pleasure and reward, the mesolimbic dopamine system is associated with the functions of movement, preservation, and compulsion.

Mechanism of Action



Tetrahydrocannabinol



Cannabidiol

CBD does not directly "fit" CB1 or CB2 receptors but has powerful indirect effects still being studied.

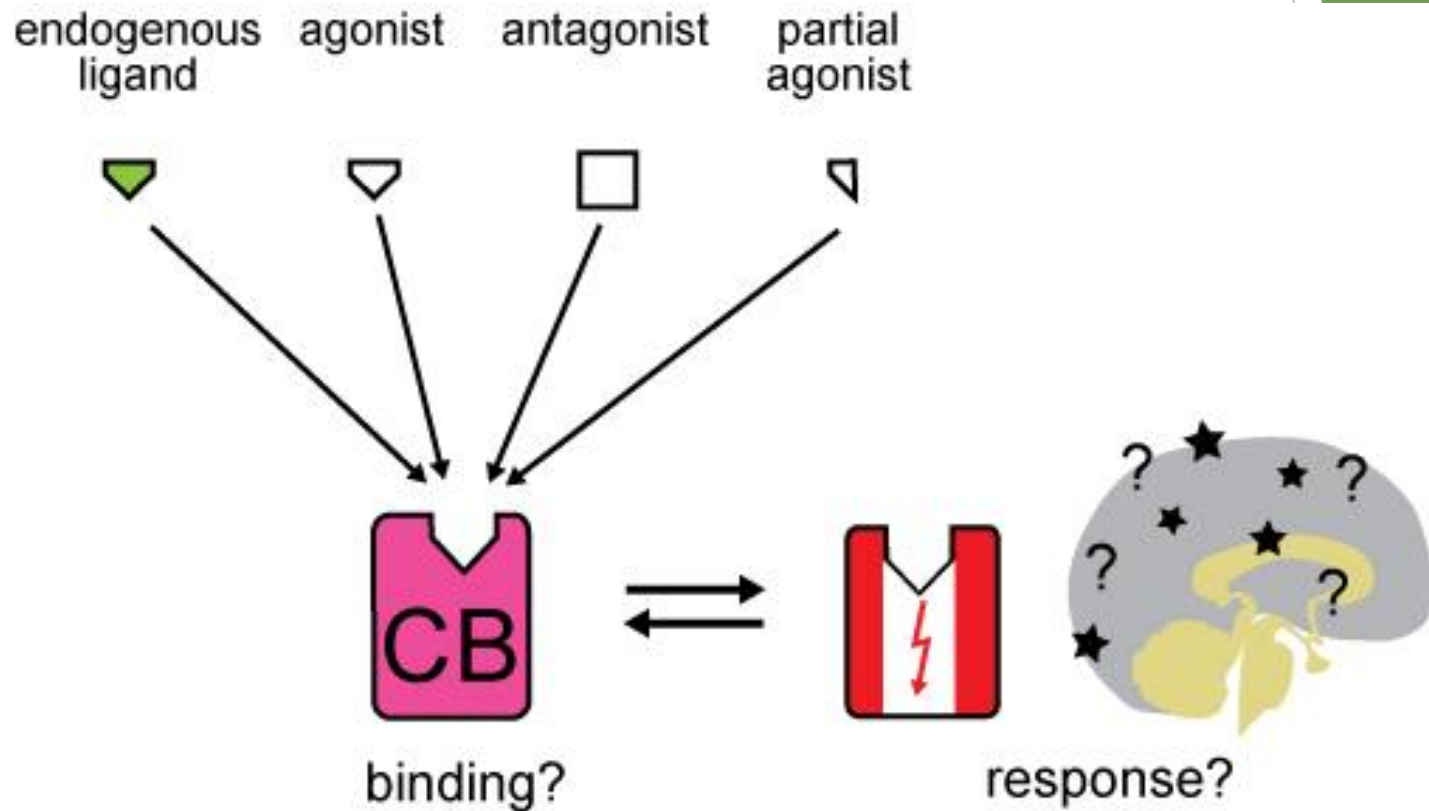


Cannabinol

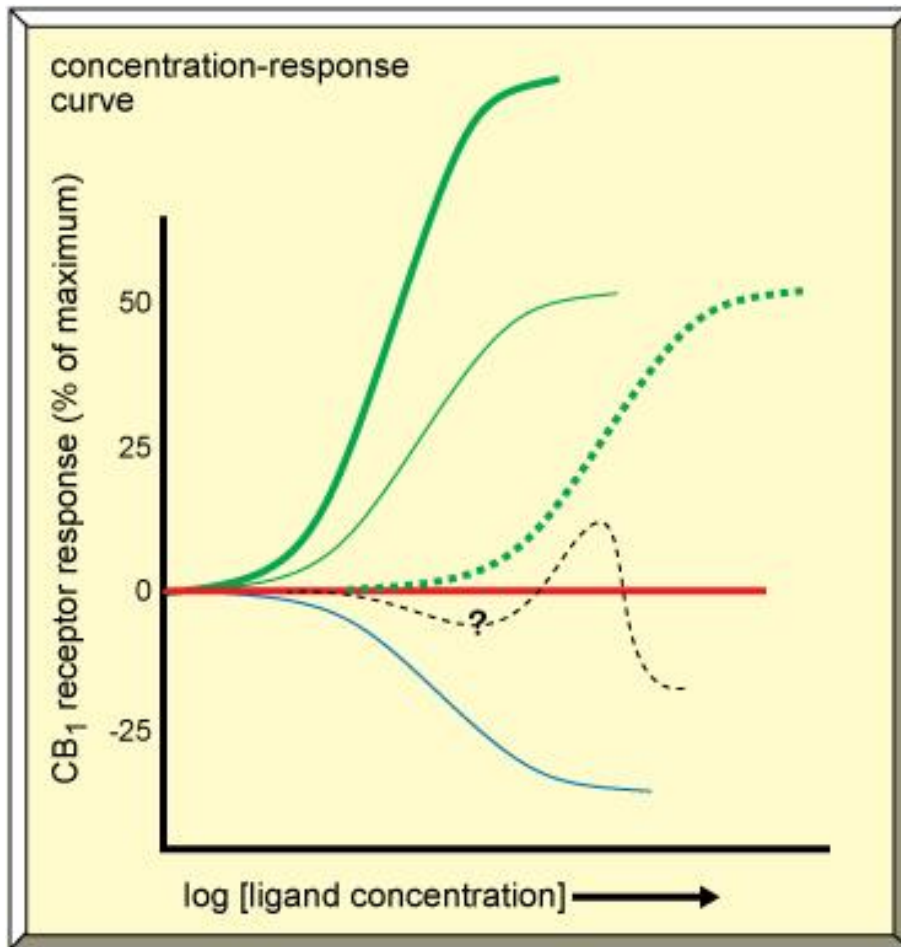


CB2 receptors are mostly in the peripheral organs especially cells associated with the immune system.

Cannabinoid/CB receptor interactions

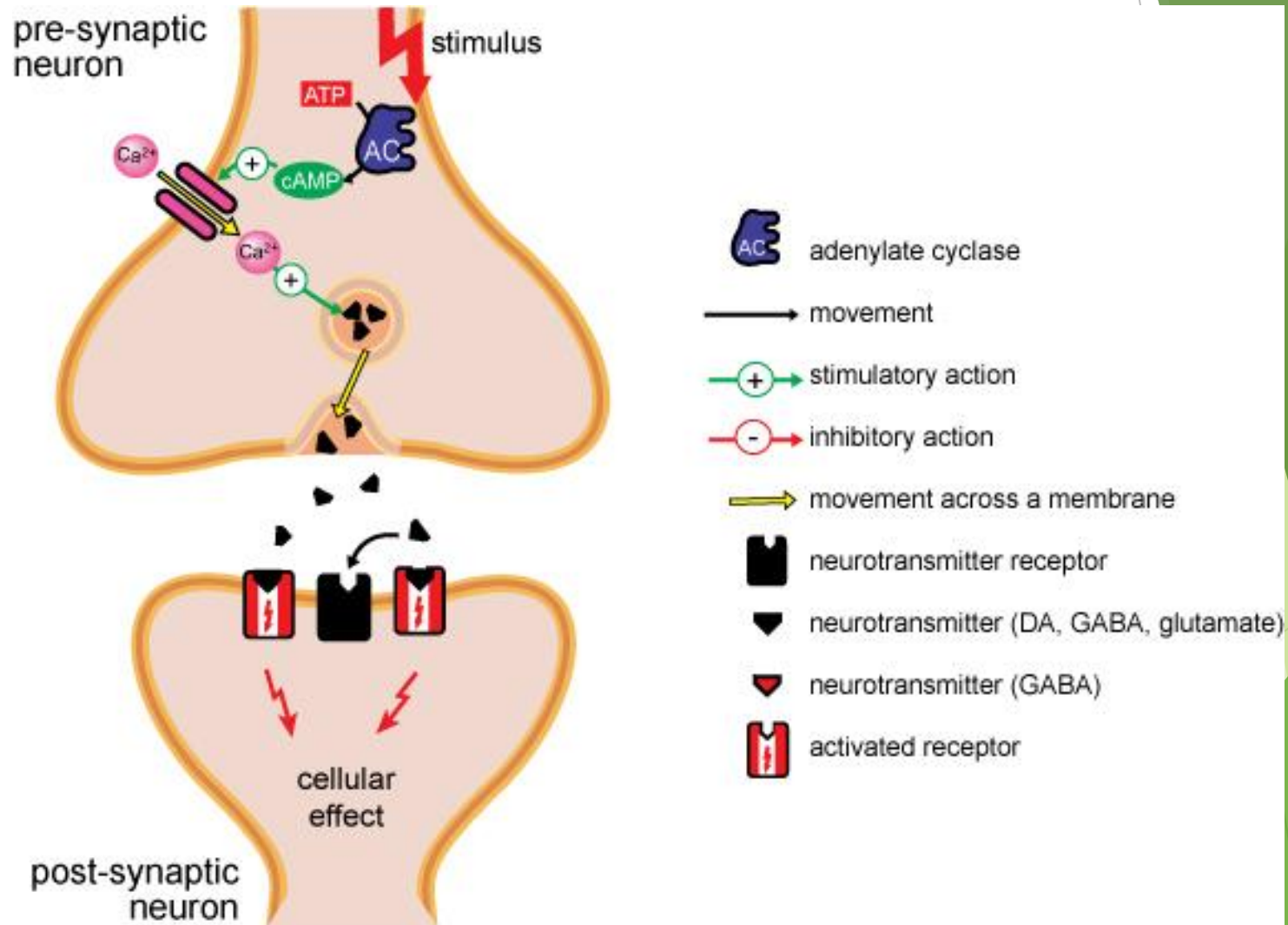


Cannabinoid receptor active ligands

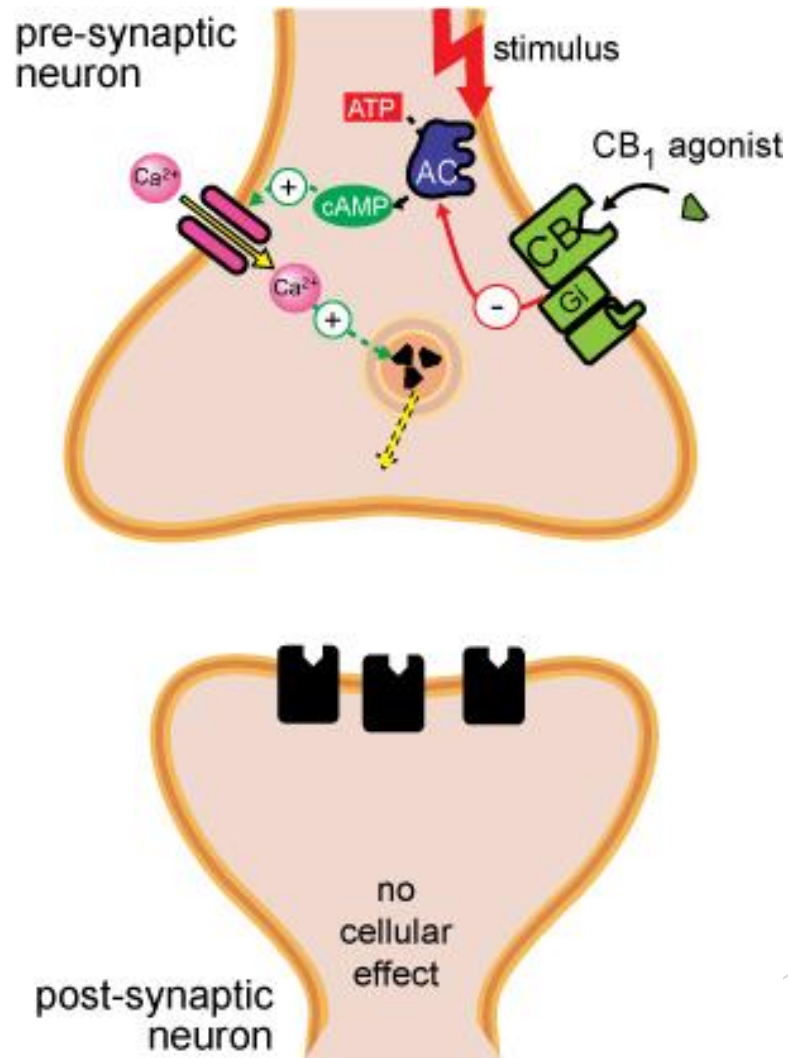


- full agonist (HU-210)
- partial agonist (THC & anandamide)
- antagonist (surinabant)
- partial inverse agonist (CBD)
- agonist + antagonist (THC + surinabant)
- ?- agonist + inverse agonist (THC + CBD)

Normal neurotransmission in network

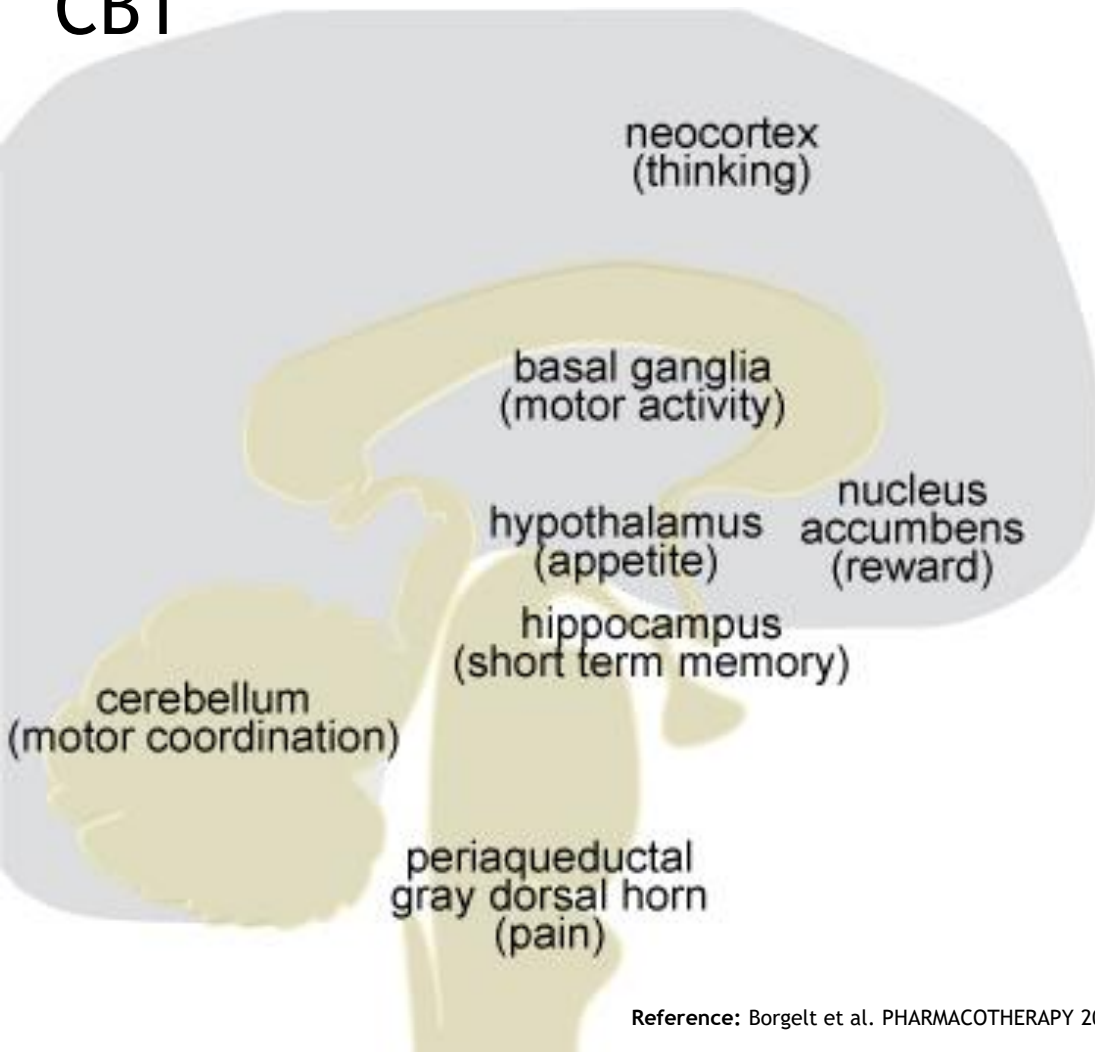


Regulatory effects of cannabinoids



Distribution of CB1 & CB2 receptors

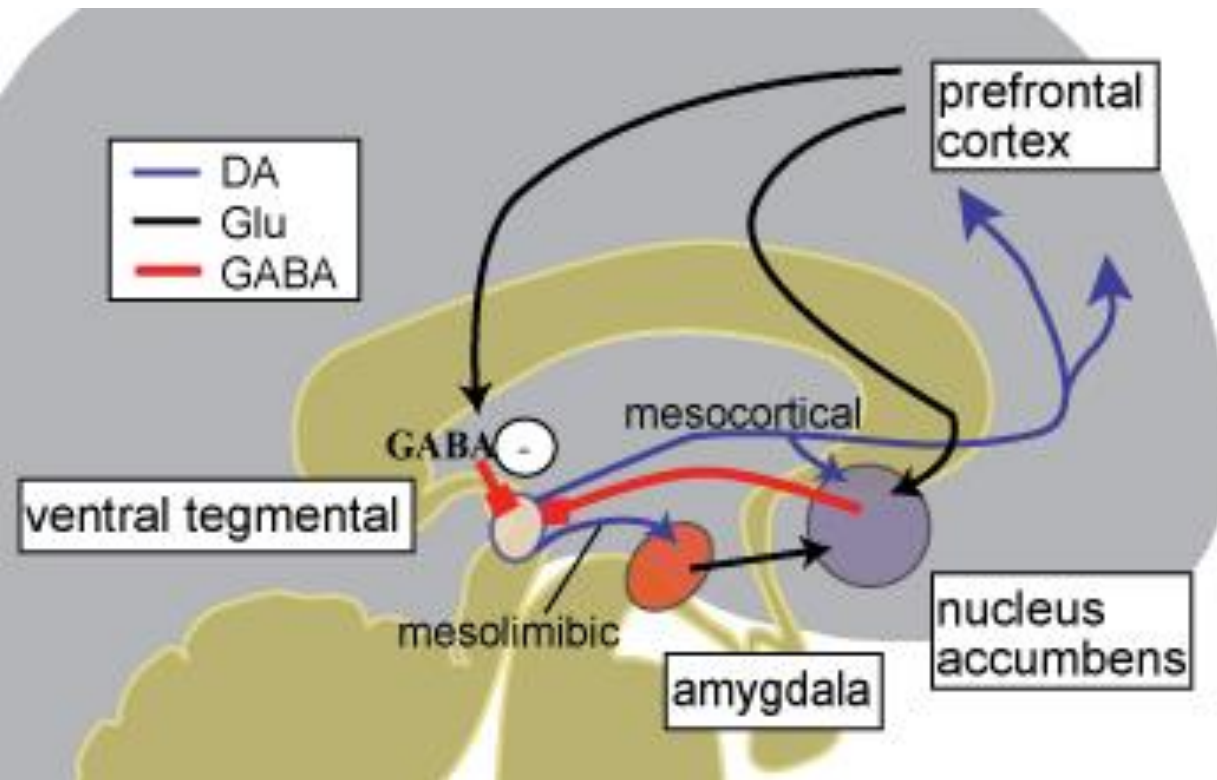
CB1



CB2

- ▶ immunologic cells (modulation cell migration)
- ▶ microglia (possible role in Alzheimer's?)

Cannabis effect on reward pathway



DA: reward and motivation

Glu: learning and memory

GABA: inhibition of neuronal activity

Pharmacological actions of cannabis

Central Nervous System (CNS)

Psychological	Euphoria (“high”), dysphoria, anxiety, depersonalization, precipitation or aggravation of psychosis, schizophrenia or bipolar disorder (esp. in vulnerable individuals) and suicidal ideation/attempts (esp. among men), limited and mixed evidence in PTSD, mixed evidence for amotivational syndrome
Perception	Heightened sensory perception, distortion of space and time sense, hallucinations, misperceptions
Sedative	Generalized CNS depression, drowsiness, somnolence (dose-dependent effect on sleep); additive with other CNS depressants (opioids/alcohol)
Cognition, psychomotor performance	Fragmentation of thoughts, mental clouding (attention and concentration), memory impairment/amnesia, global impairment of performance especially in complex and demanding tasks and additive effect with other CNS depressants (e.g. alcohol)

Pharmacological actions of cannabis

Central Nervous System (CNS)

Motor function	Incoordination, ataxia, falls, dysarthria, weakness. Limited and mixed evidence in dystonia, Huntington's disease, Tourette's syndrome and Parkinson's disease.
Epilepsy	Anti-epileptiform and anti-convulsive properties with CBD (and possibly also with CBDV and THCV). Mixed pro- and anti-epileptiform and pro- and anti-convulsive effects with THC.
Analgesic	Limited evidence of mixed effects for acute pain. Modest effect for chronic noncancer pain (mainly neuropathic). Modest/mixed effect for cancer pain. Mixed "opioid-sparing" effect. Very limited evidence for mixed effects for headache and migraine.
Anti-nausea/anti-emetic; hyper-emetic	Observed with acute doses. Tolerance may occur with chronic use. Conversely, nausea and/or vomiting may also be observed with use for medical purposes. Hyperemesis has also been observed with larger doses or chronic use in non-medical contexts.

Pharmacological actions of cannabis

Central Nervous System (CNS)

Appetite	Increased in normal, healthy subjects, but also in patients suffering from HIV/AIDS-associated anorexia/cachexia. Evidence mixed and modest for loss of appetite in cancer. Evidence weak for anorexia nervosa.
Tolerance	To most behavioural and somatic effects, including the “high” (with chronic use).
Dependence, withdrawal syndrome	Dependence has been produced experimentally, and observed clinically, following prolonged intoxication. Abstinence leads to withdrawal symptoms which can include anger, anxiety, restlessness, irritability, depressed mood, disturbed sleep, strange dreams, decreased appetite, and weight loss.

Pharmacological actions of cannabis

Cardiovascular and Cerebrovascular System

Heart rate/rhythm	Tachycardia with acute dosing; tolerance developing with chronic exposure. Premature ventricular contractions, palpitations, atrial fibrillation, ventricular arrhythmia also seen with acute doses.
Peripheral circulation	Vasodilatation, conjunctival redness, supine hypertension, postural hypotension.
Cardiac output	Increased cardiac output and myocardial oxygen demand.
Cerebral blood flow	Increased with acute dose, decreased with chronic use, region-dependent variations.
Myocardial infarction	Increased risk of acute myocardial infarction within one hour after smoking cannabis especially in individuals with existing cardiovascular disease.
Stroke	Increased risk of experiencing stroke after an acute episode of smoking cannabis.

Pharmacological actions of cannabis

Respiratory System	
Histopathological changes/ inflammation	Chronic cannabis smoking associated with histopathological changes in the lung (basal cell hyperplasia, stratification, goblet cell hyperplasia, cell disorganization, inflammation, basement membrane thickening, and squamous cell metaplasia). Long-term smoking associated with cough, increased production of phlegm, and wheeze.
Bronchodilatation	Acute THC exposure causes dilatation; possibly reversed with chronic exposure (by smoking) 364. Smoked/vapourized cannabis may worsen asthmatic symptoms.
Pulmonary function (FEV1; FVC)	Acute, low-level exposure possibly stimulatory; long-term, heavy smoking possibly associated with decreased lung function.

Pharmacological actions of cannabis

Gastrointestinal System

GI tract	Decreased gastrointestinal motility, decreased secretion, decreased gastric/colonic emptying, anti-inflammatory actions, limited and mixed evidence of benefit in irritable bowel syndrome and inflammatory bowel disease. Abdominal pain, nausea, vomiting, diarrhea.
Liver	Increased risk of hepatic steatosis/fibrosis, especially in patients with Hepatitis C. Increased Hepatitis C treatment adherence resulting in a potential sustained absence of detectable levels of Hepatitis C virus.
Pancreas	Risk of acute pancreatitis with chronic, daily, heavy use.

Pharmacological actions of cannabis

Reproductive System

Males

Follicle stimulating hormone (FSH), luteinizing hormone (LH) and testosterone levels either unaffected or decreased with chronic cannabis smoking (but some report increased testosterone levels). Decreased sperm concentration and sperm count and altered morphology with chronic cannabis smoking in men. Decreased sperm motility, capacitation and acrosome reaction with *in vitro* THC exposure.

Dosedependent

stimulatory (low-dose) or inhibitory (high-dose) effects on sexual behaviour in men (but some report which suggests increased coital frequency with increased frequency of use in men and women).

Pharmacological actions of cannabis

Reproductive System

Females

- Acute administration of THC suppresses release of gonadotropin-releasing hormone (GnRH) and thyrotropin-releasing hormone (TRH) with decreased release of prolactin and gonadotropins (FSH and LH) in animal and human studies. Association between cannabis use and menstrual cycle disruptions in women including: slightly elevated rate of menstrual cycles lacking ovulation (i.e. anovulatory cycles), higher risk of decreased fertility, prolonged follicular phase/delayed ovulation, though evidence is mixed.
- Chronic/sub-chronic administration of THC in animals: altered hypothalamic-pituitary-ovarian (HPO) axis function, disruption of follicular development, decreased estrogen and progesterone production, blocking of LH surge, anovulation. Cannabis can alter HPO axis functionality and ovarian hormones produced by the HPO axis. Dose-dependent stimulatory (low-dose) or inhibitory (high-dose) effects on sexual behaviour in women (but some report suggests increased coital frequency with increased frequency of use in men and women).

Information for Health Care Professionals

- ▶ **Cannabis (marihuana, marijuana) and the cannabinoids**
- ▶ Dried or fresh plant and oil administration by ingestion or other means Psychoactive agent
- ▶ Cannabis is not an approved therapeutic product, unless a specific cannabis product has been issued a drug identification number (DIN) and a notice of compliance (NOC).
- ▶ The provision of this information should not be interpreted as an endorsement of the use of this product, or cannabis and cannabinoids generally, by Health Canada.