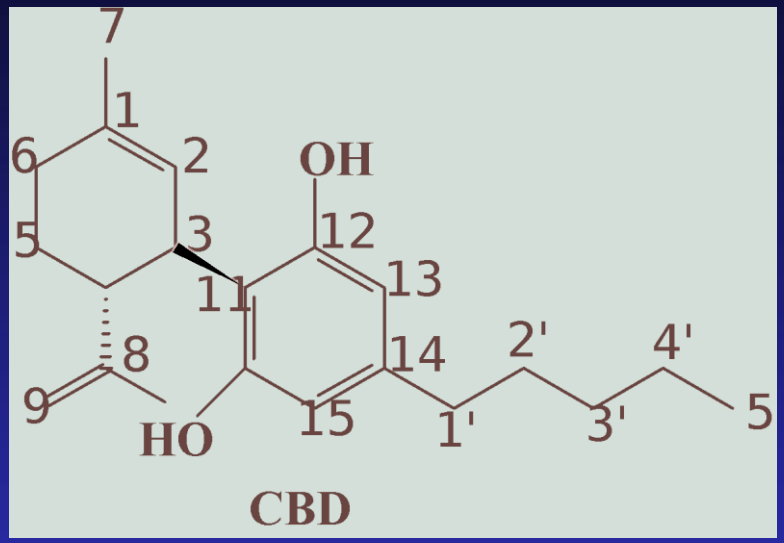
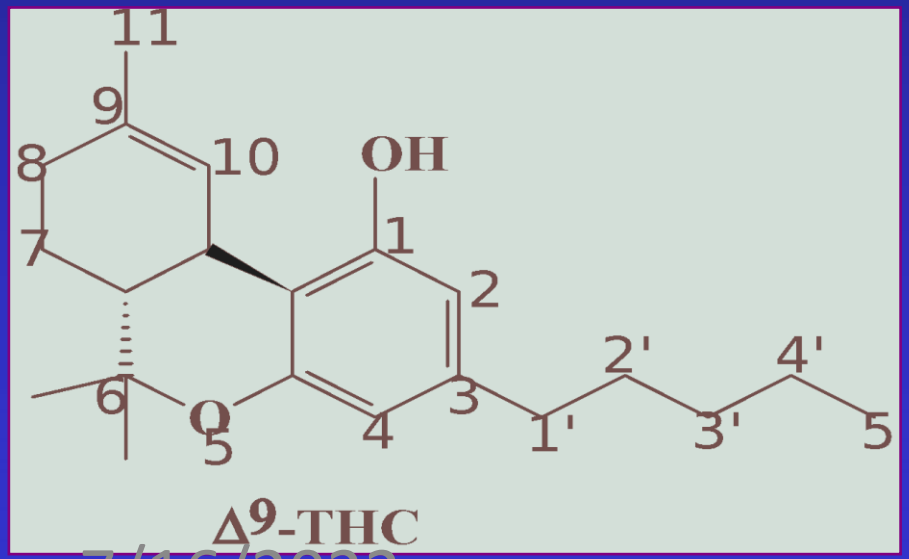
Cannabinoids



CBD



Δ^9-THC

- Cannabis contain ~500 chemicals
- Compounds with a skeleton made of a resorcinol type ring with a terpene moiety derivative attached to it (around 70 identified)
- 80+ cannabinoids(21-carbon molecule)
- Among cannabinoids, THC and Cannabidiol (CBD) are the most abundant.

Some of the more prominent cannabinoids include:

- Delta-9-tetrahydrocannabinol (THC)
- Cannabidiol (CBD)
- Cannabinol (CBN)
- Tetrahydrocannabivarin (THCV)
- Cannabichromene (CBC)
- Cannabicyclol (CBL)
- Cannabidivarin (CBDV)
- Yet still another est. 80-100 other cannabinoids

CLINICAL PHARMACOLOGY OF CANNABIS

- 95-99% plasma protein bound
- Hydroxylation, oxidation, and conjugation for rapidly clearance from plasma
- 1st-pass metabolism with oral admin(11-OH-THC)
- Elimination over several days (adipose)
- Breast milk distribution, Pregnancy Category C

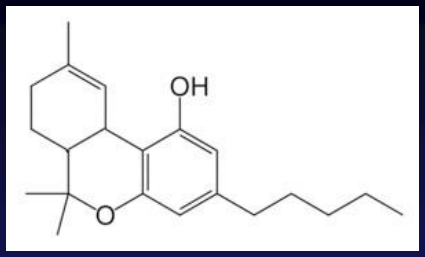
(พบว่ายามีความเสี่ยงต่อการเกิดความผิดปกติของตัวอ่อนในครรภ์ แต่ไม่มีการศึกษาการใช้ยาในหญิงมีครรภ์)

- Excretion: days to wks 20-35% found in urine
- 65-80% found in feces

CLINICAL PHARMACOLOGY OF CANNABIS

- 5% as unchanged drug (when given PO)
- Synthetic THC, called dronabinol, does not contain CBD, CBN, or other cannabinoids, which is one reason why its pharmacological effects may differ significantly from those of natural *Cannabis* preparations (Entourage effect).

THC (Delta-9-Tetrahydrocannabinol)



- 1964 - THC, Main Psychoactive Component of Cannabis, First Identified and Synthesized by Dr. Raphael Mechoulam, Professor of Medicinal Chemistry at the Hebrew University of Jerusalem
- He is the first to identify **delta-9-tetrahydrocannabinol** (THC), as the main psychoactive component of cannabis.
- Delta-9-THC and Delta-8-THC are the only compounds in the marijuana plant that produce all the psychoactive effects of marijuana.

Phamacokinetics

Possible Routes of Administration

- Oral - absorbtion slow, variable
  - bioavailability usually < 15%
  - 1St pass metabolism (But product active) -

- Rectal - suppositories of hemisuccinate
  - good absorption
  - bioavailability 2 X as good
  - avoid 1st pass metabolism

Possible Routes of Administration (cont'd)

IV	- very low water solubility, requires special formulation - rapid onset of action - dosage limitations → short duration of effect
Smoking	- rapid absorption (like IV) - bioavailability ดูด ซึม 18-50% - high variability due to smoking techniques
Topical	- very limited applicability

Methods of Administration

Inhalation

30 sec – 1 min.

Smoking/Vaping

Flower & concentrated oils

Easy titration

Ingestion

20 to 120 min.

Wide variety: Tincture, foods, beverages

Can be difficult to titrate

Topical

5 to 10 min

Can be helpful for neuropathic pain, psoriasis

No psychoactivity

Common Modes of
Administration and Formulations

Metabolic Disposition

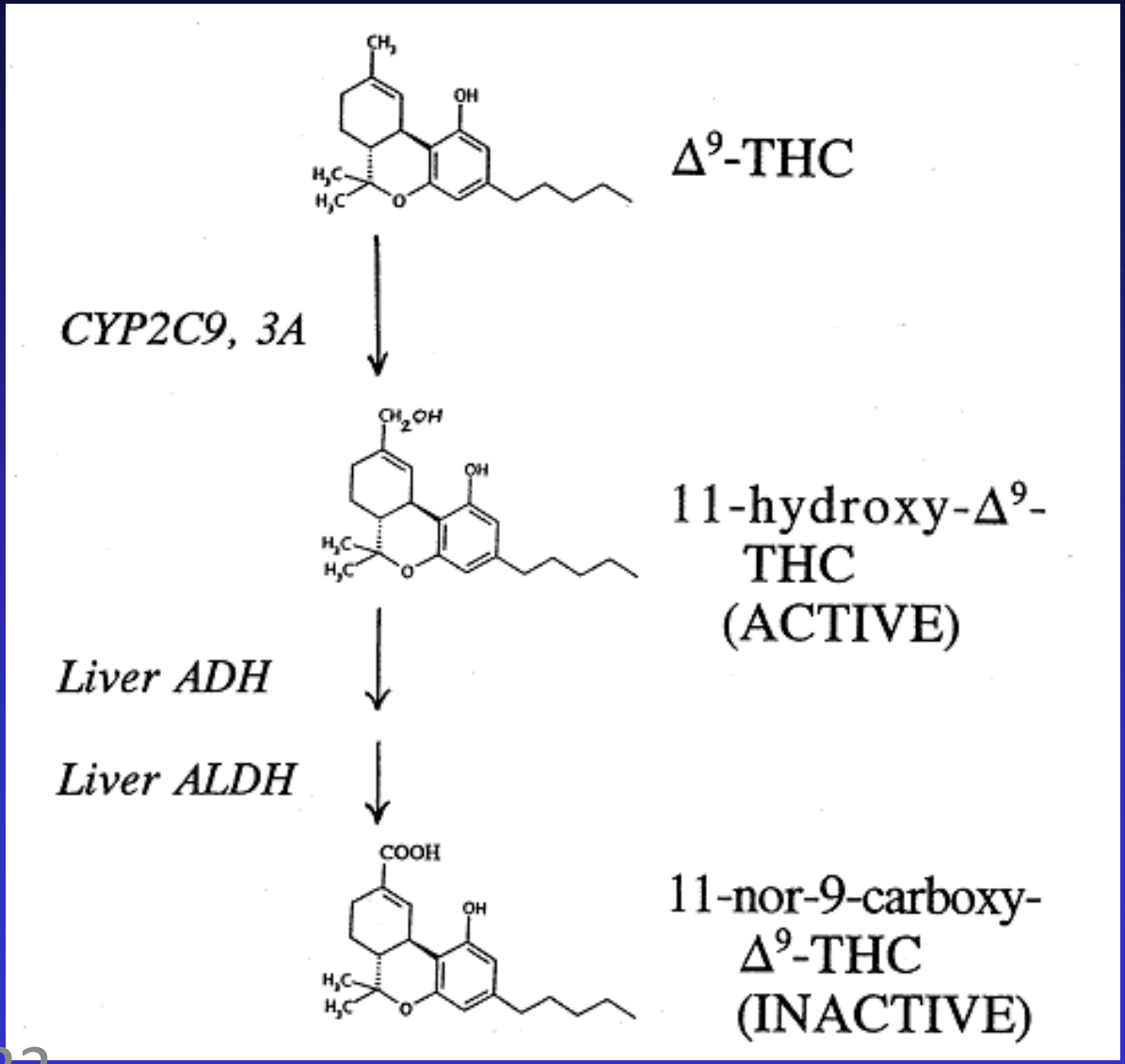
- Highly lipid-soluble, protein bound in plasma
- Enter tissue rapidly
- Plasma concentration curve after smoking is therefore triphasic:
  - 1 absorption phase with T50 = 50 sec
  - 2 distribution phase T50 = 40-50 min
  - 3 elimination phase T50 = 2-3 days

Metabolic Disposition (cont'd)

- No evidence for metabolic tolerance in chronic users
- i.e. little or no increase in rate of elimination
- Risk of cumulative build up of tissue concentration over time

- Many different final metabolites in both urine and feces, 72 hour cumulative excretion in
  - urine - 13-17% of dose
  - Feces - 25-30% after IV
    - 48-53% after oral

Major Metabolic Pathway



Pharmacokinetics

- Cannabinoids are highly lipophilic.
- Rapidly absorbed into the blood from inhaled marijuana smoke, with plasma levels becoming detectable within seconds
- Peak plasma levels noted in fewer than 10 minutes.
- Bioavailability from smoking marijuana varies based on depth of inhalation, puff, and breath-holding duration.

Pharmacokinetics

- Smoking marijuana through a pipe instead of a cigarette can result in higher cannabinoid absorption because this results in less side stream smoke.
- Slow and erratic absorption orally resulting in irregular plasma levels, and reaching peak concentrations in 1-2 hours.
- Cannabinoids are acid-labile and degraded in the stomach thereby significantly reducing absorption.
- They also exhibit extensive first- pass effect.
- Crosses placenta and found in breast milk.

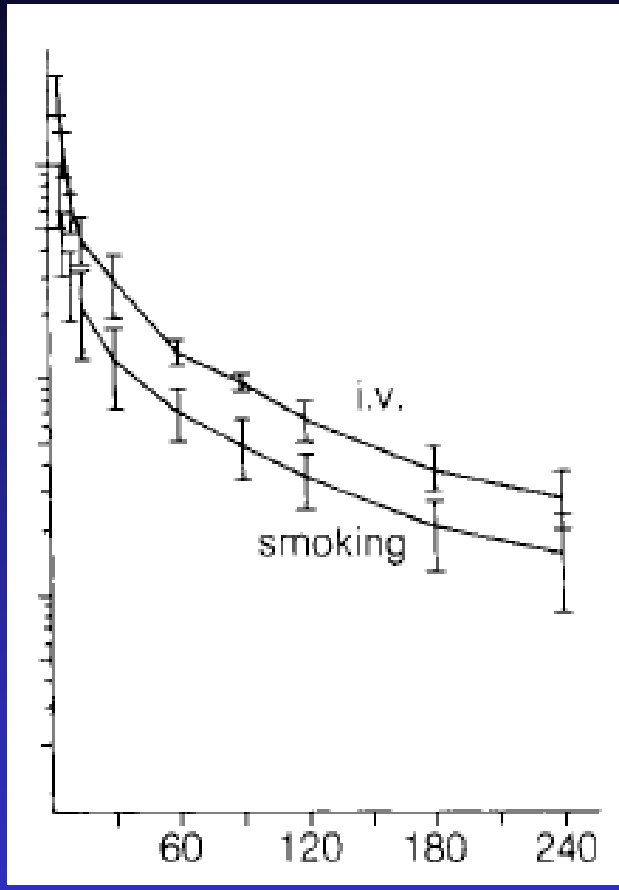
Pharmacokinetic profile of THC

Smoking

1 absorption phase with T50 = 1 minute

2 distribution phase T50 = 30 min

3 elimination phase T50 = 30 hrs



Smoking:

Bioavailability: 10-25%

50% of the THC content is delivered into smoke

50% of smoke is exhaled again

60% of inhaled smoke may be metabolized in the lung

Agurell S, 1986; Strougo A, 2005

Vaporization of medical cannabis

- Cannabinoids vaporize at a temp lower than combustion
- Increasingly popular
- Lower % of noxious chemicals

http://www.volcanovaporizer.com/products-page/complete-sets/ Accessed 08/31/2012

Pharmacokinetic profile of THC

Oral

Peak concentration are low and reach 1-3 hour

1 absorption phase with T50 = 0.8 hour

2 distribution phase T50 = 3.8 hour

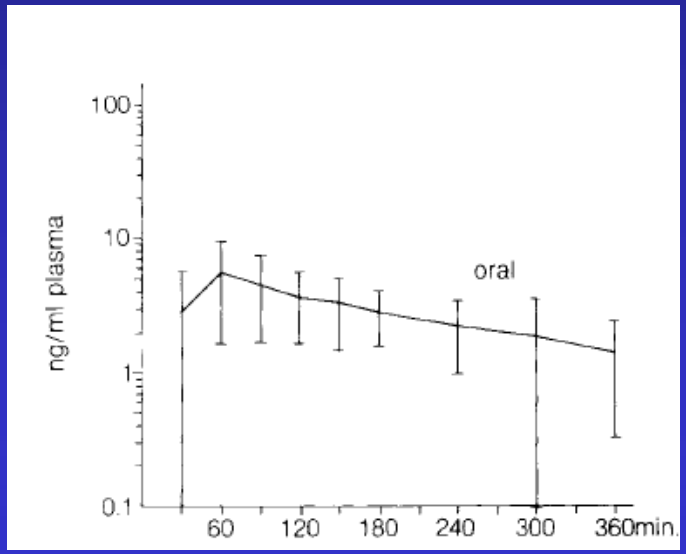
3 elimination phase T50 = 25 hour

High intra-patient variability!

Oral:

Bioavailability: 5-20%

- Often considered 1/3 that of smoked due to gastric degradation and extensive first-pass effects



Agurell S, 1984; Ohlsson A, 1980

THC is the most psychoactive component of cannabis

Typical “effective” dosing of THC

- Low dose < 7 mg
- Medium dose = 7 – 18 mg
- High dose > 18 mg

GPO Standard Extraction	
CBD	100 mg/ml
THC	17 mg/ml
THC + CBD 1:1	THC 27mg + CBD 25 mg/ml

Zuurman L, Brit J Clin Pharm 2009

Labeling of product

A net weight statement;

- THC potency and the potency of such other cannabinoids or other chemicals, including CBD,
- A serving size for edible retail marijuana products that does not contain more than ten milligrams of active THC,
- And limitations on the total amount of active THC in a package that is no more than one hundred milligrams of active THC;

The pharmacodynamics of THC

Evaluated 165 studies to determine consistently found PD effects

- Elevation in heart rate (average >19 bpm)
- Increase in subjective feeling high
- Decrease in subjective alertness
- Increase in motor instability (body sway)

Zuurman L, Brit J Clin Pharm 2009

Population response to medical cannabis

Hormones:

Males: decreased LH, FSH, prolactin, and GH levels

Females: more sensitive to THC effects (pain, behavior, reward) with higher estrogen levels

Tobacco:

greater increases in HR and carbon monoxide, despite lower THC concentrations

MDMA: amphetamine or ecstasy

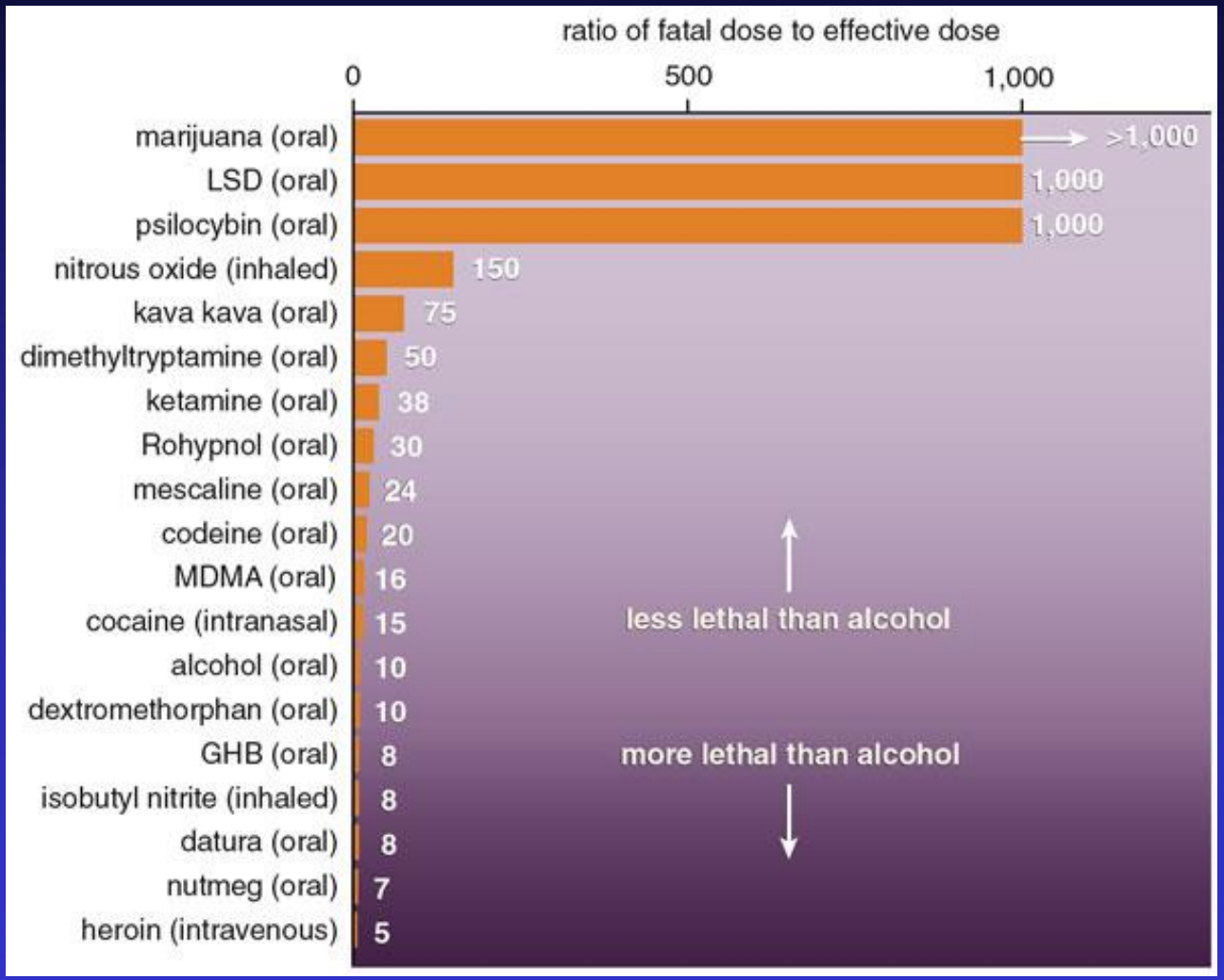
synergistic impairment in working memory

CV patients:

↑HR and ↓HRV with cannabis use

Acute toxicities

- Hallucinations
- Tachycardia
- Hypotension
- Dyspnea
- Drowsiness



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