The challenging Cannabis health benefits from a clinical pharmacology perspective: an evidence-based vision

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Satija versus Indica?

**Sativa**
- Tall in stature
- Narrow leaves
- Longer flowering cycles
- Better suited for warm climates with a long season

**Indica**
- Short in stature
- Broad leaves
- Shorter flowering cycles
- Suitable for colder climates with shorter seasons

Uplifting CNS effects, pair well with physical activity  
Physically sedating, possible adverse effects?
Average THC Content in THC-Dominant Strains

Indica 17.3%  Sativa 17.7%  Hybrid 18.2%

Powered by COINCIDENCE ANALYTICS
CANNABIS CERTIFIED
"The clinical effects of the cannabis chemovar have nothing to do with the plant or its leaflets shape." (Dr Russo: Neurologist; Cannabis psychopharmacology)

"not all sativas will energize you, and not all indicas will sedate you" - Placebo?

If Sativa vs. Indica Isn’t Predictive of Effects, What Is?

- **Cannabinoids** versus **Terpenes**
- **Pharmacological** properties:
  - chemical profile of each cannabis,
  - individual (human) biology and pathophysiology,
  - tolerance, dependence, tachyphylaxis, resistance, and
  - dose, frequency, co-administration and route of administration
Cannabinoids

The cannabis is comprised of hundreds of chemical compounds that create a unique harmony of effects

- **Cannabinoids:**
  - **THC** ($\Delta 9$-tetrahydrocannabinol) = feel hungry and high, and relieves symptoms like pain and nausea
  - **CBD** (cannabidiol) = is a less-intoxicating, used to alleviate anxiety, pain, inflammation, and other 'promising' medical uses?
  - **Others?**

- **Terpenes:**
  - aromatic compounds, responsible for distinctive cannabis smell
  - Gelato = **kief**: sedating and energizing effects
  - Linalool (**cinnamon**) = relaxing effects
  - Pinene (sideritis: ironwort) = alerting effect
delta-9-tetrahydrocannabinol (THC)
Cannabidiols (CBD)

↓
Cannabigerols (CBG)
Cannabichromenes (CBC)
Cannabinol (CBN)
cannabinodiol (CBDL)
cannabicyclol (CBL)
cannabielsoin (CBE)
cannabitriol (CBT)
more!!.
THC versus CBD

**THC-dominant** strains:
- primarily chosen by individuals seeking a potent euphoric experience (to control pain, depression, anxiety, insomnia, and CNS-related symptoms). High risk for **adverse effects**

**CBD-dominant** strains:
- limited concentrations of THC, and widely used by individuals seeking pain and neurological symptoms control, who are highly sensitive to THC **(or suffered from THC adverse-effects)**, while enjoying 'clear-headed' symptom relief

**Balanced THC/CBD** strains:
- contain balanced levels of THC, offering mild euphoria alongside symptom relief.
"The Fugitive" grass
What does the 'Lab' say?

Cannabinoid Levels in CBD-rich Strains: All Labs

[Graph showing cannabinoid levels across different labs]
ACDC
THC 5.9%
CBD 8.7%

ACDC
THC 1.0%
CBD 18.6%

genetics
growth
assay
The 'Cannabis' Road Ahead

(1000 km) Evidence-based vision
Identify the main ingredient

CBD/THC balanced strains
- natural
- hybrid
- synthetic

Measured units not percentage/ratio
- mcg, mg, g

Well-tolerated, preferred route of administration
- oral: tablet, capsule, powder (Kief), gum
- liquid: syrup, drops, oil (RSO)
List the major 'therapeutics'

- Psychomotor retardation:
  - mood disorders (depression), anxiety (PTSD), insomnia

- Neurodegenerative disorders:
  - Parkinson's, MS/MND, Alzheimer's, Huntington's

- Anti-inflammatory and analgesic:
  - acute (trauma), chronic (RA, OA), cancer

- Seizure disorder:
  - Epilepsy
PTSD

5-HT1A agonist

Hippocampal neurogenesis
Understand the Endo-cannabinoid system

THC

CBD

CB1

STOP
Partial agonist at (CB1)

CB1 receptor: **Ananadamide**
retrograde endocannabinoid neurotransmitter

Rat: synthetic THC = DA release?

**Withdrawal**: activation of CRF in basal ganglia = generally mild

short t1/2, and low Vd
Clinical trials

Better understanding

Generalisability

Placebo-effect

Efficacy and safety

Healthcare system trust
Learn from others

St. John's Wort:
- introduced as healthy (dietary) supplement
- Identifiable ingredient:
  - *Hypericum perforatum*

Therapeutic efficacy confirmed by RCTs and systematic reviews

**Verdict:** more effective than placebo and similar in effectiveness to low-dose TCAs in the short-term treatment of mild to moderately severe depression
Invest on current evidence

Clinical research

Evidence for cannabis and cannabinoids for epilepsy: a systematic review of controlled and observational evidence

Emily Stockings, Dino Zagic, Gabrielle Campbell, Megan Weier, Wayne D Hall, Suzanne Nielsen, Geoffrey K Herkes, Michael Farrell, Louisa Degenhardt

Evidence for the use of cannabinoids in Parkinson’s disease

Carsten Buhmann, Tina Mainka, Georg Ebersbach, Florin Gandor

- There are a growing number of uncontrolled trials and case reports that suggest beneficial effects of cannabinoids in patients with ....
- Due to large variety of substances investigated, the varying routes of intake, differing doses and time courses make it difficult to compare data.
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Requirements

- Investors
- Healthcare system
- Clinical research experts
- Dispensing system
- Adverse reactions reporting system (pharmacovigilance)
- Legal team
- Community leaders
- Media (pre-filtered, unbiased)
- Awareness campaigns
- Database
Gateway Drug

The use of a psychoactive drug can be coupled to an increased probability of the use of further drugs = Gateway-IN

Cannabis as Gateway-OUT?

Opioid dependence:
• Methadone (agonist)
• Naltrexone (antagonist)
• Buprenorphine (agonist/antagonist)
Challenge what you see!
disbelief, fear and uncertainty