DEMYSTIFYING CANNABIS

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BACKGROUND AND HISTORY

Cannabis is one of humanity's oldest economic plants, in use for over 6000 years for food (seeds), fiber (hemp), and medicine. Cannabis originates from Central Asia, where it expanded into different regions. These "landraces" formed what we know as the *C. sativa*, *C. indica*, and even *C. ruderalis* species.

The first recorded use of Cannabis dates back to 2700BCE, indicated by the presence of Cannabis flowers a burial site of a shaman in the Yanghai tombs in China. In Ancient China, both the seeds and flowers were used.

- *Ma Fen* (flowers) used in the Han Dynasty for certain types of pain
- *Ma Ren* (hemp seeds) used as a moistening and laxative digestive remedy

Cannabis was also utilized in Ayurvedic medicine and practices, where its psychoactivity was viewed as a negative side effect.

- Ganga (female flowers)
- Bhang (tender branches containing leaf and seed)
- Hashish (compressed resin)

Most Ayurvedic preparations involve boiling the cannabis in milk (lipids are a suitable solvent for extracting cannabinoids). Cannabis was understood as light, hot, sharp, and penetrating in energy. It increased pitta, decreased kapha, relieved pain, promoted sleep, and increased digestive activity.

Cannabis was not used in Western societies until William O'Shaughnessy, an English physician, brought the herb back to the Royal Society in 1840 as an analgesic and antiemetic. By the 1850's it was in the US Pharmacopoeia, where it remained until the 1930's as a tincture and fluid extract for pain, nausea, and insomnia. Its use was also described in the King's American Dispensatory for nervous depression, genito-urinary irritation, and insomnia.

The Revolution of 1910 brought Mexican immigrants to US border towns. In the subsequent decade, recreational cannabis use increased in immigrant communities and among jazz musicians. Worsening economic conditions amplified this xenophobia, and "marihuana" was vilified as a drug associated with social ills and deviance. The Marihuana Tax Act of 1937 effectively outlawed cannabis and was hotly protested by the American Medical Association. It was finally classified as a Schedule 1 substance in 1970, meaning it cannot have any beneficial properties. This has stunted cannabis research and therapeutics.

BOTANY

Cannabis is an annual, dioecious plant. Both male and female plants bear flowers, but the female flowers comprise *Cannabis inflorescence*. Growth, flower production, and cannabinoid production are regulated by day length, temperature, humidity, and soil nutrients. In the 1970's and 1980's, cannabis production moved indoors, allowing growers to tightly control growing environments and develop novel recreational cultivars.

Indoor growing:

- control over growing conditions (set up expenses)
- higher risk of pest

Outdoor growing:

- more environmental fluctuation, risk of lower cannabinoid production
- predisposition to mold/mildew

Growers have consistently selected for THC in cannabis cultivars, and cannabinoids like CBD have been all but bred out. This is changing with advances in CBD research.

A common distinction is sativa vs. indica, also known as narrow-leaf and broad-leaf varieties. Growers have used morphological characteristics (i.e. leaf shape) to distinguish between the 2 strains. Patients and users also use these 2 designations to select cannabis. Sativa is known as elevating, psychedelic, and sometimes anxiety-inducing due to supposedly high THC, with indica known for its sedating "couch lock" features due to lower THC and higher CBD. In practice, cannabis is frequently cross bred and hybridized, and the constituent profiles do not often align with these designations. It's more helpful to look at lab-verified cannabinoid profiles and constituents levels and use this to help patients select cannabis.

THE ENDOCANNABINOID SYSTEM

The endocannabinoid system (ECS) modulates neurotransmitter release, the pain response, hunger, and cancer development. Its functions are to functions: "relax, eat, sleep, forget, protect". It affects many of the body's homeostatic mechanisms, and is implicated in nearly even human disease and disorder. It consists of-

- Cannabinoid receptors (CBRs) – G-coupled protein receptors found in all organs and tissues
    - CB1 – CNS (affects retrograde signaling)
    - CB2 – Immune cells and tissues (decreases cAMP)
    - CB3 – (presence is rumored but not confirmed)
- Endocannabinoids – bioactive lipids similar to the eicosanoids and prostaglandins, paracrine/autocrine materials
    - Anandamide (AEA)
    - 2-Arachidonoylglycerol (2-AG)

Cannabinoids supplement and stimulate this system and can be classified as-

- endocannabinoids (produced endogenously)

- phytocannabinoids (sourced from Cannabis)
- synthetic cannabinoids (lab derived research materials and pharmaceuticals)

They can treat what Ethan Russo characterizes as *Endocannabiniod Deficiency Syndrome*, and may play a role in migraines, IBS, and fibromyalgia. The exact therapeutic effect depends on the person and their resting "ECS tone". Cannabinoid can have biphasic activity dependent upon the ECS context and CBR resting state.

CANNABIS PHYTOCHEMISTRY

Cannabinoids – a class of C21 phenolic compounds, over 100 of which are found in cannabis. Classified into major and minor cannabinoids

- Delta-9-THC (tetrahydracannabinol)
    - main psychoactive compound, present in some strains up to 30%
    - CB1 agonist
    - Affects dopamine, seratonin, norepinephrine
        - Pain
        - Apetite
        - Nausea and vomiting
    - neuroprotective
    - Strains can contain up to 30%
    - Concentrates up to 95%

- CBD (cannabidiol)
    - nonpsychoactive, THC antidote
    - CB2 ligand
        - Immune function and inflammation
    - Antipsychotic
    - Pediatric seizure disorders
    - low-THC/high CBD strains
        - Harlequin
        - AC/DC

- THCV (tetrahydracannabivarin)
    - Antispasmodic, analgesic, antiinflammatory
- CBN (cannabinol)
    - breakdown product, sedative
- CBG (cannabigerol)
    - Precursor molecule, antiinflammatory, analgesic
- CBC (cannabichromene)
    - antidepressant, antiinflammatory
- Others including Delta-8-THC, CBE, CBT, CBL, CBND, etc.
    - Neuroprotection, analgesia, antispasmodic, antiinflammatory

Cannabinoids exist in the plant as carboxylic acid precursors (as THCA, CBDA, etc.). They must be decarboxylated (losing a –COOH) to be converted into their neutral forms for bioavailability. Decarboxylation occurs naturally with light and oxidation, and even

in vivo to some extent. For reliable cannabinoid bioavailability, heat is deliberately applied for 15 minutes.

Decarboxylation temperatures
- THC - 105° C
- CBD - 120° C

"Entourage effect": terpenes, cannabis therapeutics, and whole plant synergy
1. Multi-target effects
2. Pharmacokinetic effects (improved solubility or bioavailability)
3. Interactions affecting bacterial resistance
4. Modulation of adverse events

Terpenes – volatile terpene compounds, responsible for flavor/aroma
- Limonene (citrus)
    - Antidepressant, anxiolytic, antioxidant
- Pinene (conifers)
    - Antiinflammatory, neuroprotective, bronchodilator
- Myrcene (hops, lemongrass)
    - Antiinflammatory, analgesic, sedatives
- Linalool (lavender, tulsi)
    - Antidepressant, analgesic, anxiolytic, anticonvulsant
- B-caryophyllene (black pepper, cardamom, oregano)
    - Antiinflammatory, CB2 ligand

All have antimicrobial properties. Other botanicals can be incorporated into protocols to reduce THC side effects, including Ginger, Calamus, and others.

FORMS AND PHARMACY

Dried herb
- dried female flowers
- inhalation, starting base for other preparations
- look for mold and microbial contamination (poor drying practices, humid climate) and pesticide residues

Cannabis oil
- evaporated and concentrated tincture
- syringes for dispensing
- vaporization, or ingestion in capsules
- watch for naming confusion: hemp oil, RSO, BHO
- ensure food grade solvents are used, watch for solvent residues

Medibles
- unpredictable onset time and effects
- varying levels in food products

- ensure cannabinoids are decarboxylated

Routes of Administration

Inhalation

- 10-30% bioavailability
- Onset in seconds
- Vaporizing: cleaner alternative
- Dried herb, oil concentrate
- Pain, nausea, appetite
- Ease of dose titration

Ingestion

- 6-10% bioavailability
- Delayed onset
- 11-OH-THC
- Unpredictable effects
- Good for high dose treatment

Mucosal

- Buccal, rectal
- 34-46% bioavailability
- 10 minute absorption
- Oil concentrates
- Used in cancer support settings

Topical

- little known about transdermal absorption of cannabinoids
- Infused oils, salves, liniments
- Local inflammation, pain, dermatitis, psoriasis

Clinical Applications

It's important to note that, while effective medicine, cannabis is not the first choice for these syndromes. Cannabis has significant side effects and

Cancer

- Hyperbole, preclinical evidence
- Palliative effects, antineoplastic effects at higher doses
- Side effects alleviated by CBD, terpene-rich botanicals
- Not the first herb or treatment to think about—other treatment have more substantiation and success

Pediatric seizure disorders

- CBD oil
- medical refugees to CO
- CBD movement and CBD-specific laws

Pain

- Muscle spasticity (Sativex Phase III trial, 1:1 THC:CBD ratio)
- Gynecological pain
- Opiate adjunct (dose reduction)
    - Opioid system: sister system and cross-talk

IBD – Crohn's (CBD-rich oil)

- other nutritional and herbal treatments likely more effective

Glaucoma

And any other conditions characterized by pain, nausea, vomiting, wasting, cramping, seizures, muscle spasticity.

DOSING

- Low vs. high dose treatment
- Low: 2.5-5mg – self titrate for symptom management
- High dose antineoplastic treatment
- Up to 1g/day
- Build up incrementally over 4 weeks
- Side effects and withdrawal

Determining THC content

- Know THC% in herb
- Calculate total THCmg in 1g herb
    - 15% THC, 150mg THC in 1g sample
    - Estimate 25% bioavailability
    - 37.5mg absorbed
- Targeted dose was 3.75mg, .1g needed

SAFETY AND TOXICOLOGY

Cannabis has a very favorable safety profile—no death has ever been attributed to cannabis, and the LD50 of THC is 1,270 mg/kg. Areas of safety concerns include:

Adolescents

- the ECS is already on high alert
- adolescent brains are different than adult brains
- adolescent brains are more sensitive to the negative side effects of THC
    - memory impairment
    - cognitive dysfunction
    - psychosis
- Avoid use

Psychiatric disorders

- correlation between cannabis and psychotic disorders
    - causation not determined
    - chicken and egg problem: do cannabis users become psychotic, or do people with psychosis self medicate?
- genetic predispositions
    - COMT polymorphisms
    - Akt1 variants
- safety concern over near-pure THC concentrates
    - CBD as an antipsychotic is especially indicated
- careful clinical monitoring

Pregnancy

- use in morning sickness
- cannabinoid influence on brain development in the fetus - the research is mixed
    - one ethnographic study of mothers in Jamaica found no effects
    - another study found that more adverse birth outcomes were associated with cannabis
        - low birth weight
        - cognitive problems
- cannabinoids are found in nursing mother's breast milk
- may exert influence on oxytocin
- use extreme caution
    - infrequent and mild use probably OK
    - not long term use

Drug Interactions

- Drug-induced nausea and vomiting – palliative effects
- Opiods - beneficial interactions
- NSAIDs inhibit effects of THC
    - inhibits prostaglandin synthesis
    - avoiding during cannabis therapies should be avoided
- Antidepressants
    - may decrease effects of certain SSRIs - potential is higher in chronic smokers
- CYP system/drug metabolism
    - in vitro effects have been seen in CYP3A4

Problems with products on the market

- chemical residues, microbial contaminants
- solvent residues for concentrates
    - harsh and toxic solvents are used - hexane, methane, etc.
- crude/dried herb
    - many growers have little to no experience
    - Aspergillus/microbial contaminants
    - pesticide use and residues - come through in smoke

QUALITY CONTROL AND TESTING

It's important to view the lab reports for cannabis products. Patients usually respond to a select cannabinoid profile, and this is preferable to use instead of strain names or sativa/indica designations.

A good lab report or Certificate of Analysis will contain:

- cannabinoid profile via HPLC (GCMS methods change cannabinoid profiles)
- (preferably) terpene profile via GCMS
- microbiological contaminants
- pesticide residues (crude herb)
- solvent residues (concentrates)

SUGGESTED READING

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