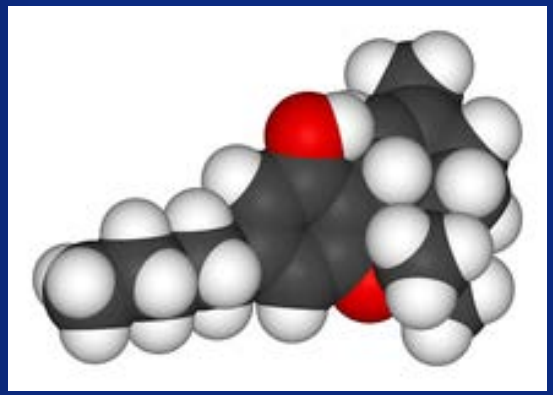
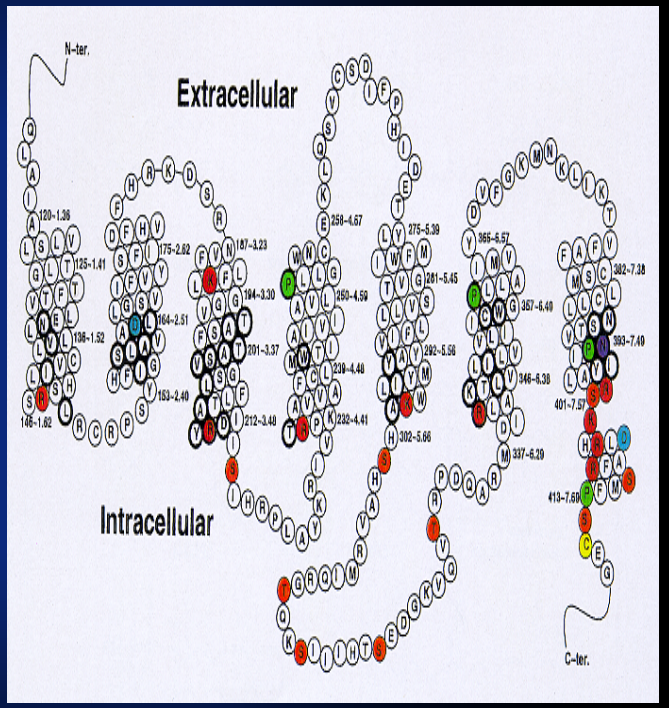
Phytocannabinoids in Medicine – An Option ?

UFS Bloemfontein December 11 2012





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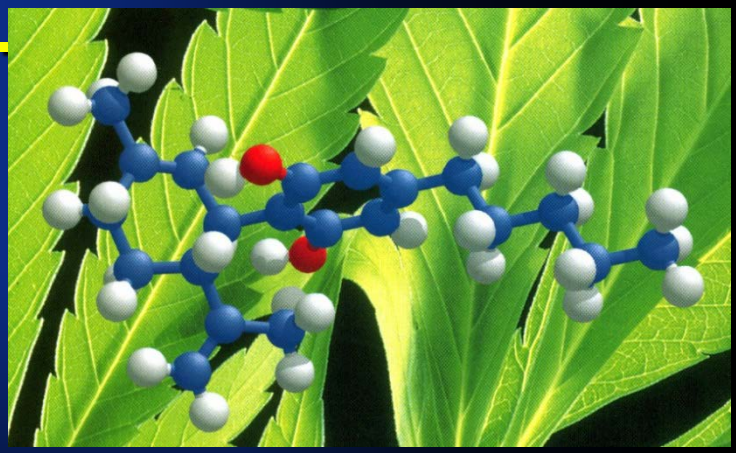
Plant of superlatives

- With approx. 500 mio regular users Cannabis is World‘s most popular illicit narcotic.
- One of the oldest medicinal plant, >5000 years.
- Cultivable even under climatic stress conditions.
- One of the most fiber-rich plants.
- >25‘000 publications.
- >480 constituents identified.
- Psychotropic principle (THC) is not an alkaloid.
- Own receptor system (ECS).
- Enormous therapeutic potential and very broad indication spectrum.



Cannabis in literature

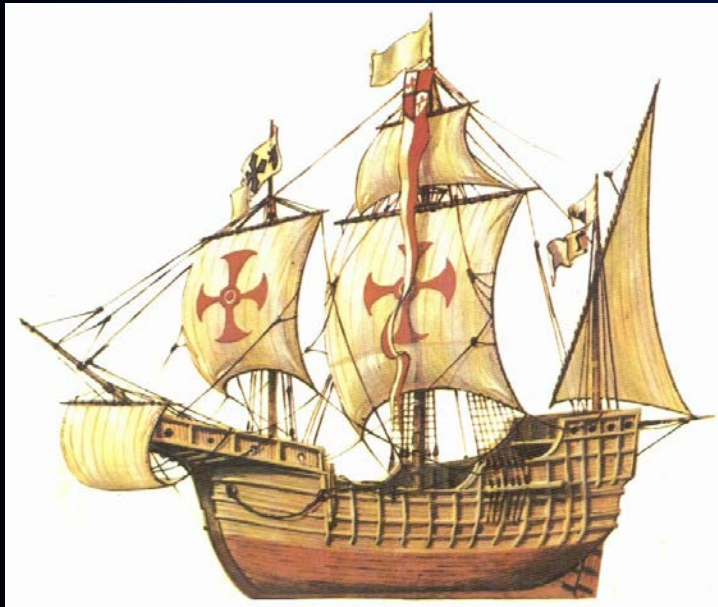
Papers in “PubMed” -2012

„Cannabinoids“	➡	10‘826
„Phytocannabinoids“	➡	69
„THC“	➡	7‘616
„Cannabinoids + Medicine“	➡	1‘734
„Cannabis“	➡	11‘590
„Cannabis + Medicine“	➡	1‘524
„Tobacco“	➡	79‘712
„Alcohol“	➡	721‘403

Reinventing the wheel ?

Chinese Emperor Shen Nung
Father of TCM ➡ „Pen Ts‘ao“ („The Herbal“), 2700 b.c.
1. Cannabis Pharmacopeia Monography

Reinventing the wheel ?



La Santa María
Nave Capitana

Has Cannabis facilitated the discovery of America?

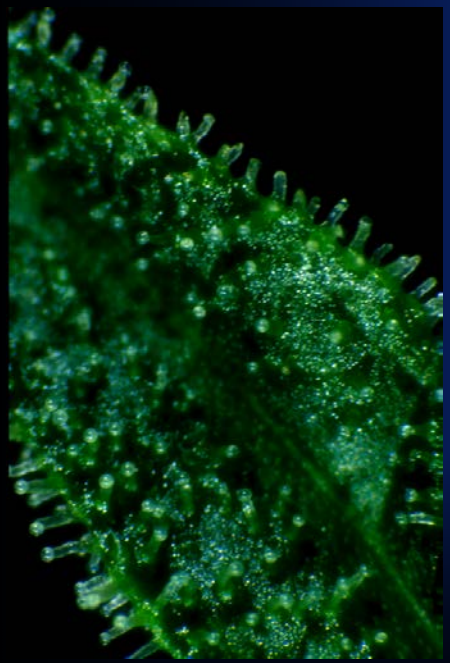
Board pharmacy of „Santa Maria“, 1492-93 a.c.

From the plant to the molecules

Cannabis sativa L.

↓

Female
flowers (buds) / leaves



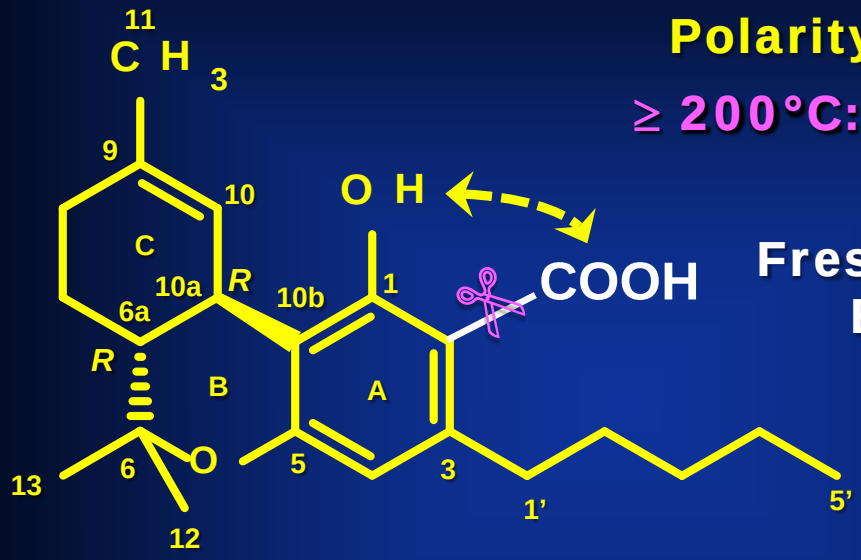
↓

Glandular hairs / Resin glands

↓

Delta-9-tetrahydrocannabinol
(THC)

Phytocannabinoids - The star



Polarity ↓

≥ 200°C: Vaporizer, Joint, GC

THC acid B
Fresh drug-type Cannabis
Biogenic precursor
Not psychoactive

Delta-9-tetrahydrocannabinol (THC)

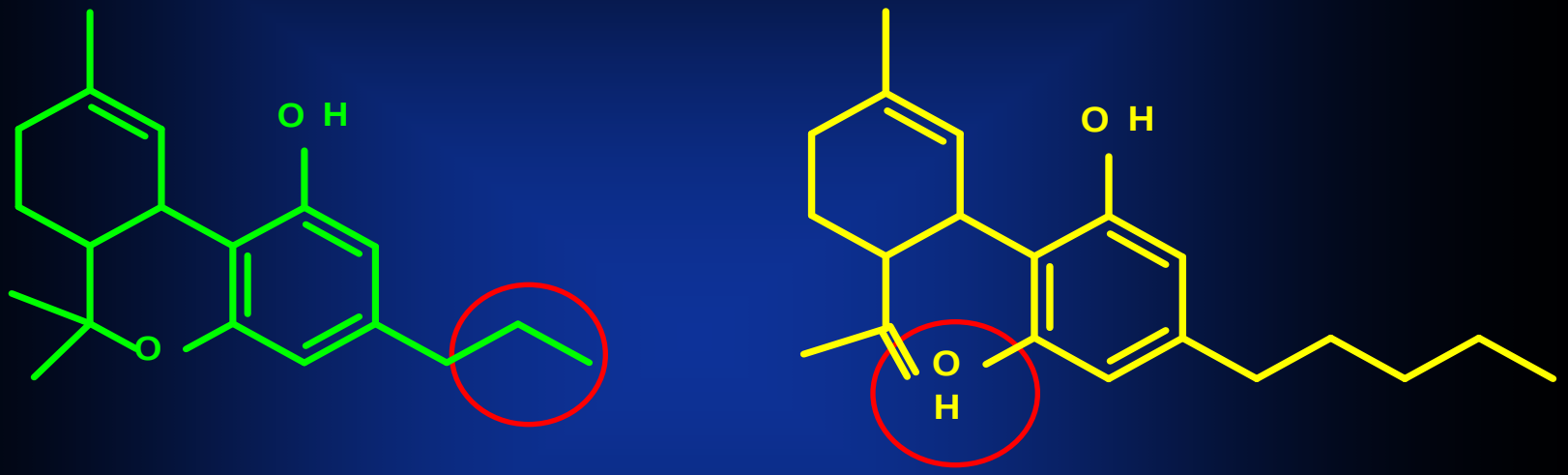
6a,10a-trans-6a,7,8,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol

CB_1-, CB_2-R
Psychoactive, multipe therapeutic effects

Isolated 1942, structure 1964 (Mechoulam et al.)

Phytocannabinoids – The wallflowers

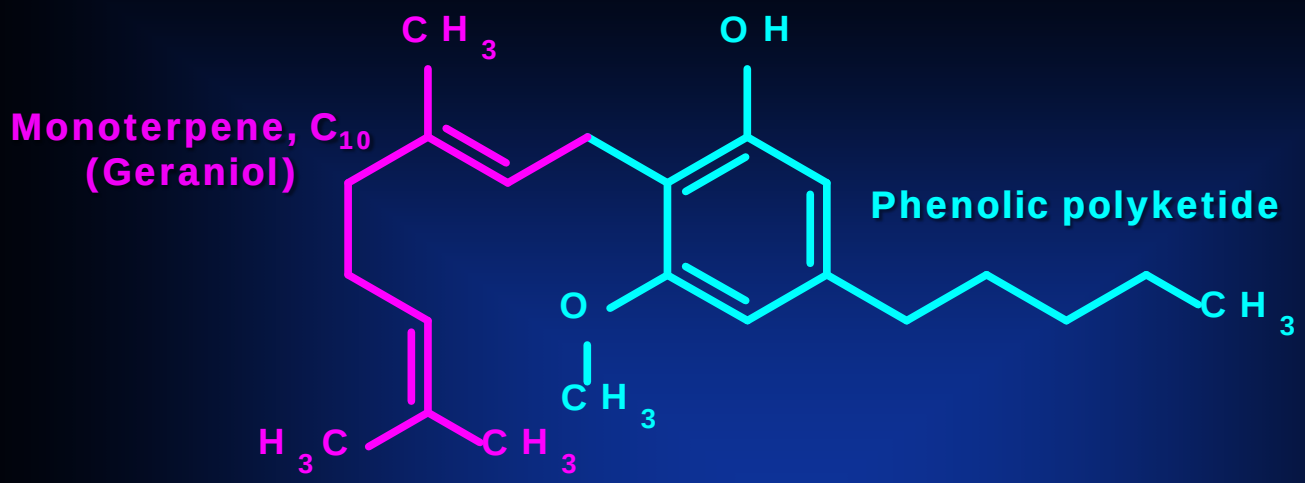
66 identified, exclusively found in Cannabis



Δ^9-Tetrahydrocannabivarin, THCV, THC-C3
CB_1-R antagonist
Anorectic, antiepileptic, bone-stimulant

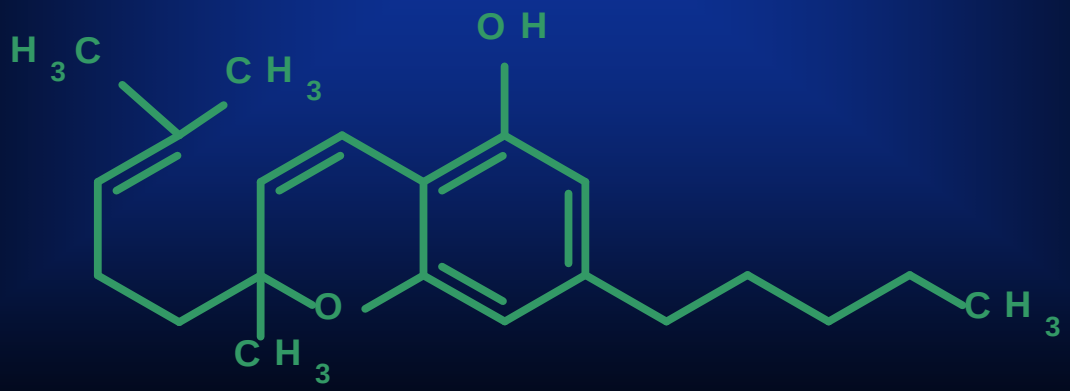
Cannabidiol, CBD
Fiber-type (industrial) Cannabis
CB_1-R + CB_X-R ?
Antipsychotic, neuroprotective, anticarcinogenic, ...

Phytocannabinoids – The wallflowers



Cannabigerol, CBG

Antimicrobial, antiinflammatory, analgesic, bone-stimulant

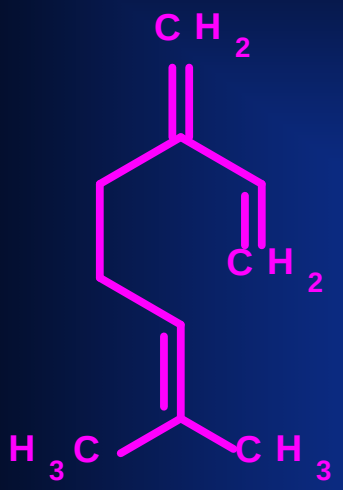


Cannabichromene, CBC

Antimicrobial, antiinflammatory, analgesic

Non-cannabinoids

140 Mono- and Sesquiterpenoids identified



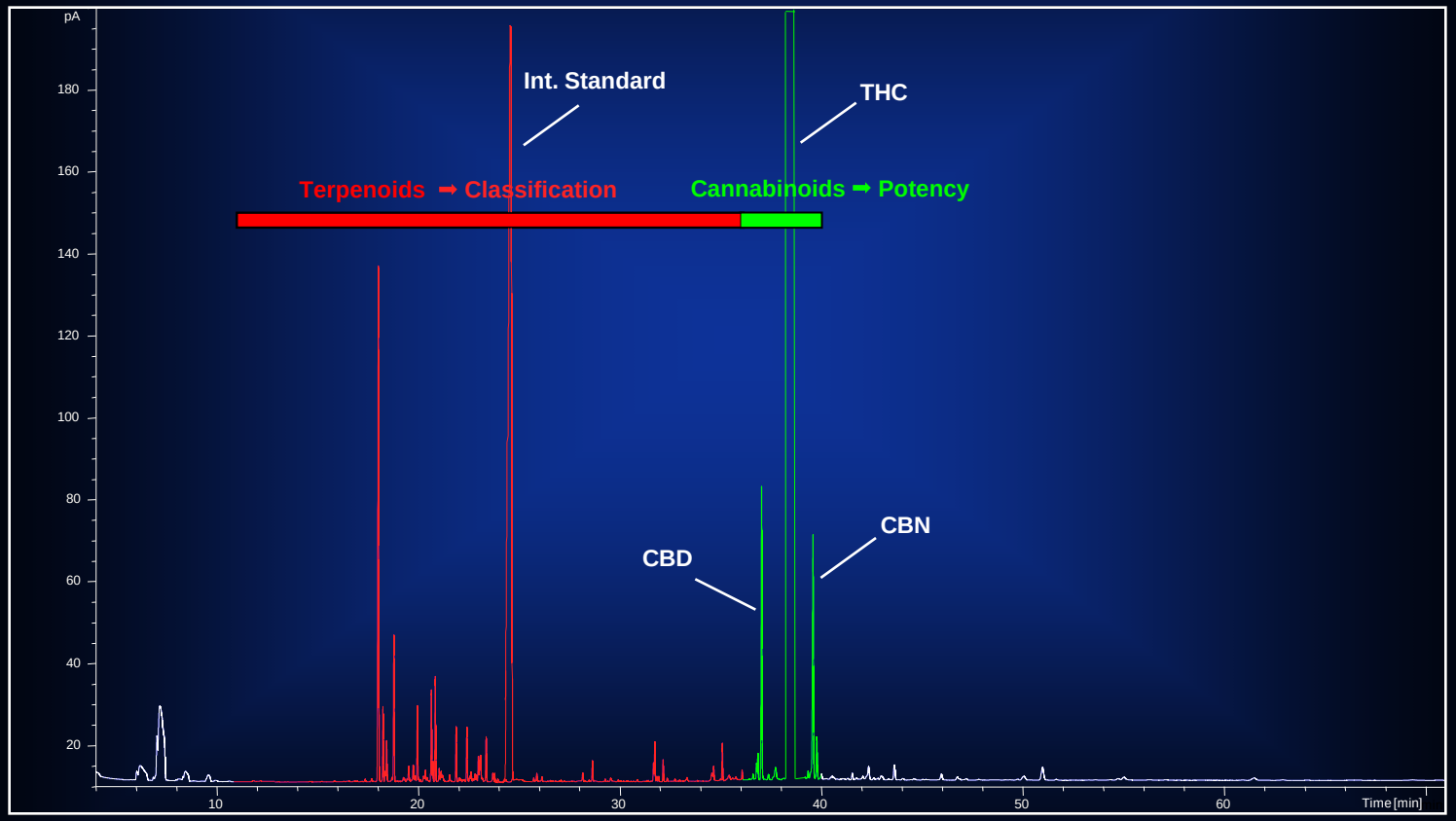
Myrcene

beta-Caryophyllene
CB_2-R agonist
Antiinflammatory

[Gertsch 2008]

Cannabis profiling

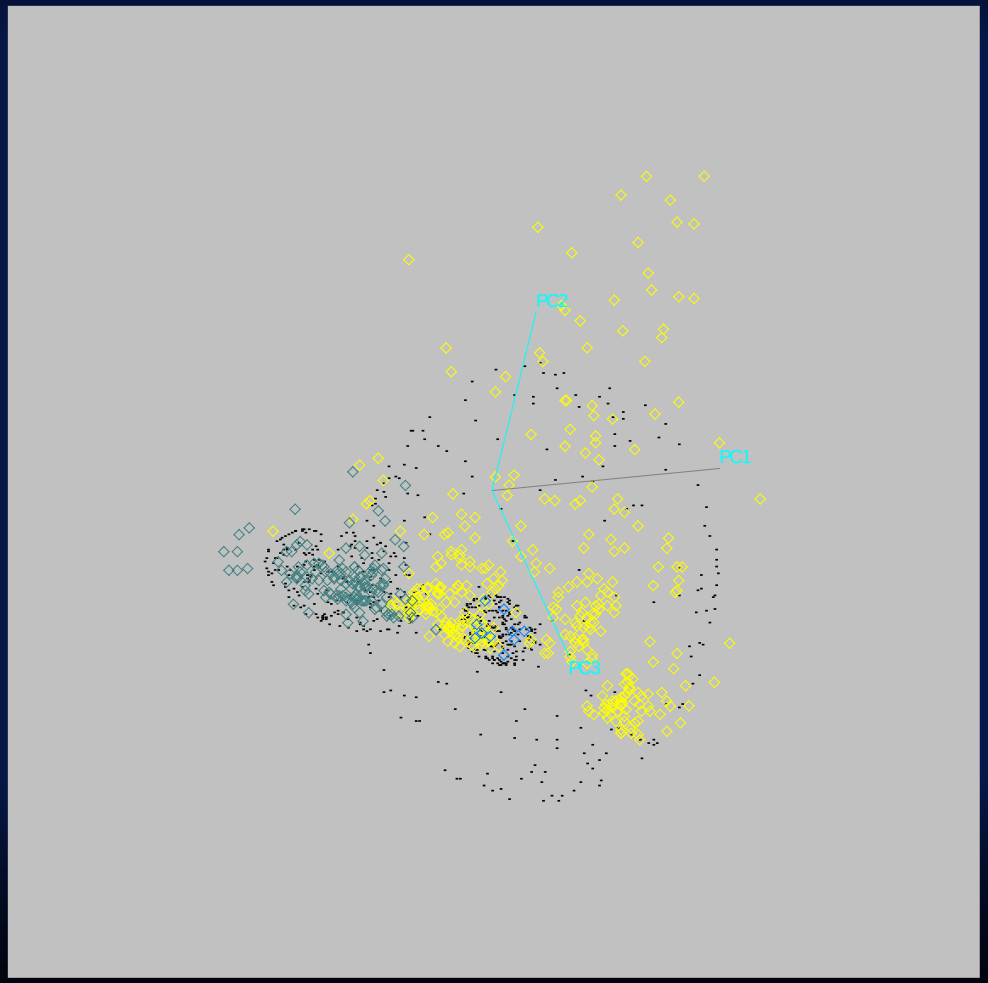
Gaschromatographic fingerprints
➡ QC, Forensics



[Brenneisen, FOPH Final Report 2005]

Cannabis profiling

Chemometric clusters



Domestic Foreign Dutch coffee shops

Nature and/or lab ?

Phytocannabinoids, pCMs
Cannabis, CMs

Multi-component preparations
„Shotguns“

Synthetic Cannabinoids, sCMs
and Non-Cannabinoids

Mono-component preparations
„Silver Bullets“

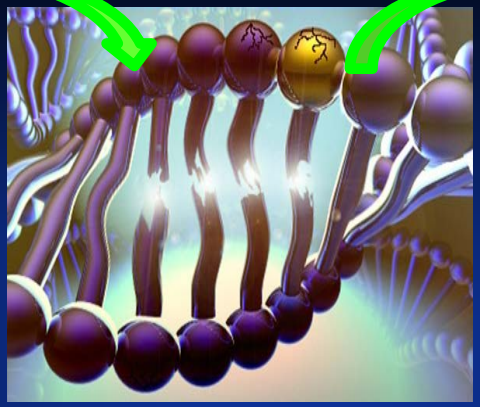
Modulation of Endocannabinoids and EC receptors

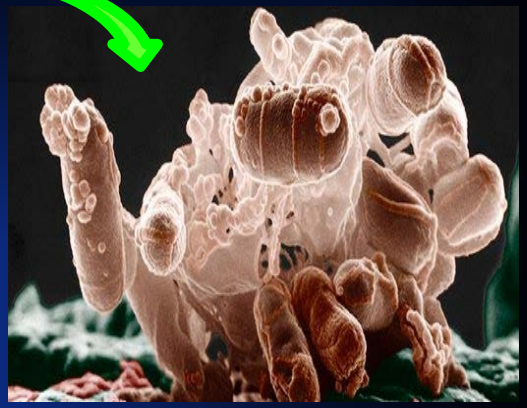
Pharmacological effects

Cannabis from the State ?

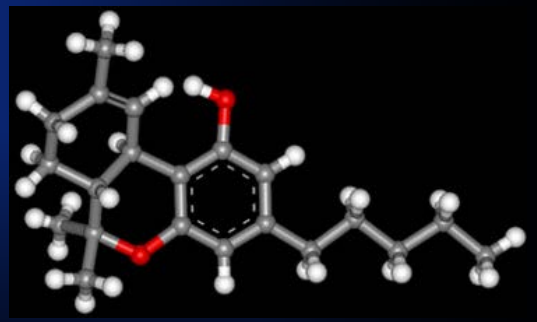
Dutch Medicinal Cannabis

Logistic shortage - THC from E. coli ?





THC

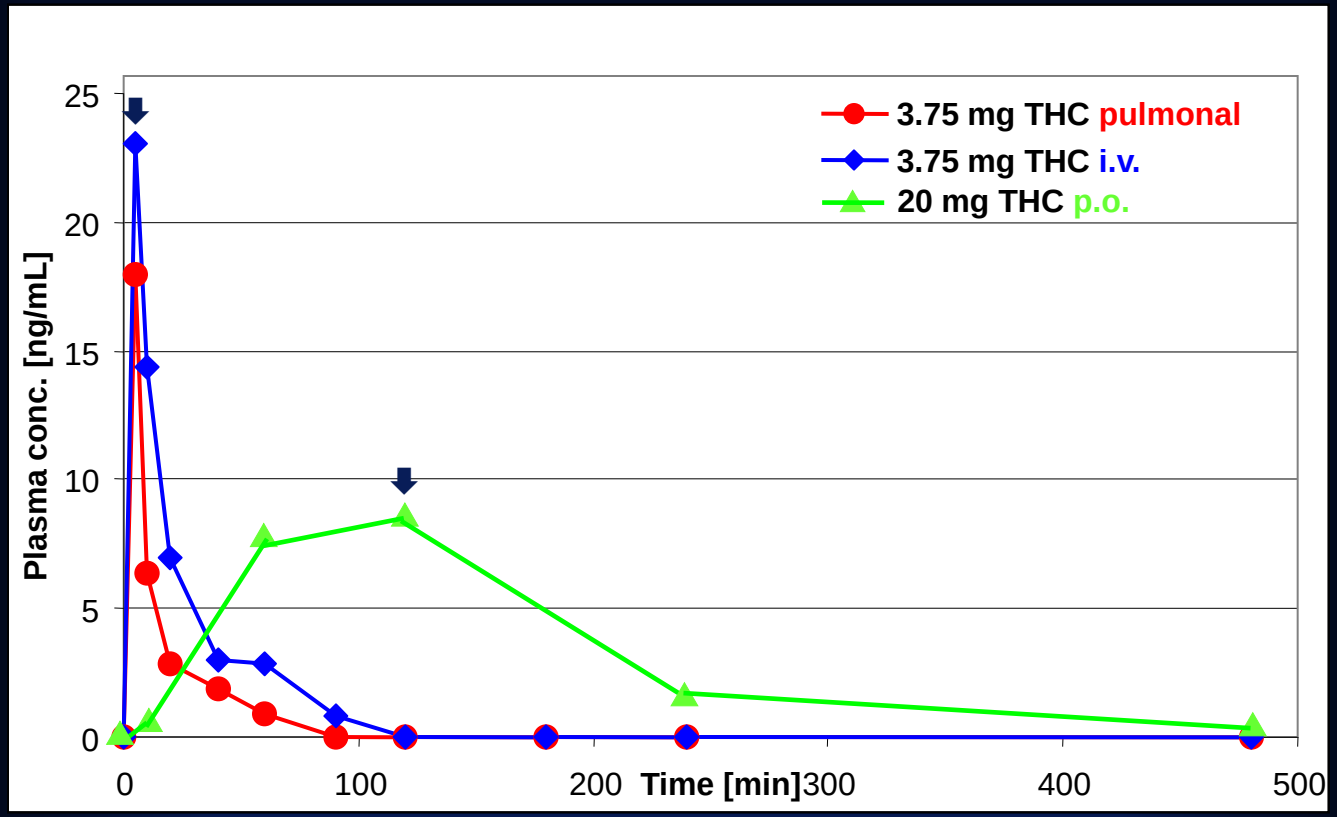


Need Germany: **1 t THC / y.**

- **Partial synthesis from CBD (industrial hemp):** **50‘000 € / kg**
- **Full synthesis:** **>>50‘000 € / kg**
- **Biotechnol. prod.:** **2‘500 € / kg.**

[TU Dortmund 2010]

Smoking, eating or injecting ?



Non-pyrolytic inhalation with Vaporizer:

☺ **Bioavailability 70-90%, rapid onset of action**

☹ **Psychotropic side-effects**

[Naef , J Pharm Sci 2004]

Cannabis in self-medication

Indications:

- Depression, multiple sclerosis, aids, migraine, asthma.
- Backache, hepatitis C, sleep disturbance, epilepsy, muscle spasm, headache, alcoholism, opiate addiction, glaucoma, nausea, appetite loss, polyarthritis, Tourette Syndrom, ...

Application:

- Joint, vaporizer, tea, Simpson oil.

Why medication:

- Alleviation of symptoms, relaxation, triggering euphoria and happiness, decrease of depression and anxiety, boostering energy, ...

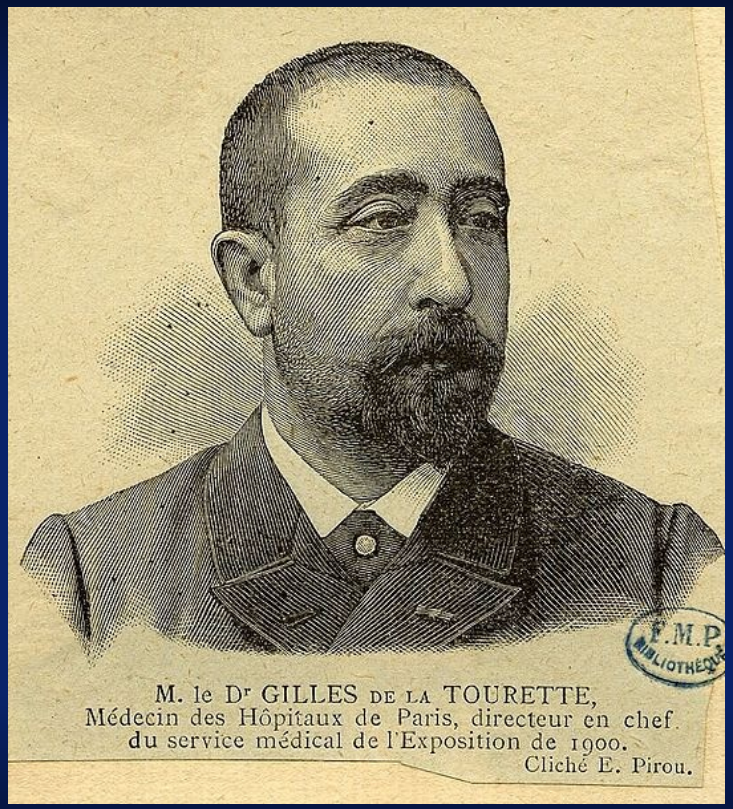
Cannabis in today‘s school medicine

cannabinoid medicines International Association for Cannabinoid Medicines

IACM Data Base

Rare neurological diseases

Tourette Syndrome



Tic Desease - Self medication

Is the criminalization of this patient medically and ethically justified ?

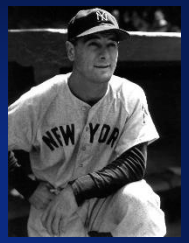
Rare neurological diseases

Amyotrophic Lateral Sclerosis (ALS, „Lou Gehrig Disease“)

- **Preclinical tests:**
  - ➡ **ALS mouse model**
  - ➡ **CB_1-R knockout mouse**
  - ➡ **Spinal marrow culture**
- **Clinical trials with THC:**

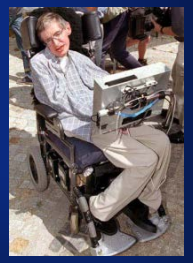
  Spasticity ↓, cell damage ↓, neuroprotection

- **Self-treatment with Cannabis:**
  - ➡ **Home.made CBM, „Sativa-Oil“**



Lou Gehrig (1903-41)

Mao Zedong (1893-1976)



Stephen Hawkin (1942-)

Divid Niven (1910-1983)

[Raman, Amyotroph Lateral Scler Other Motor Neuron Disord 2004]
[Weber, Univ.hospital St. Gallen & Univ. of Bern, 2012]

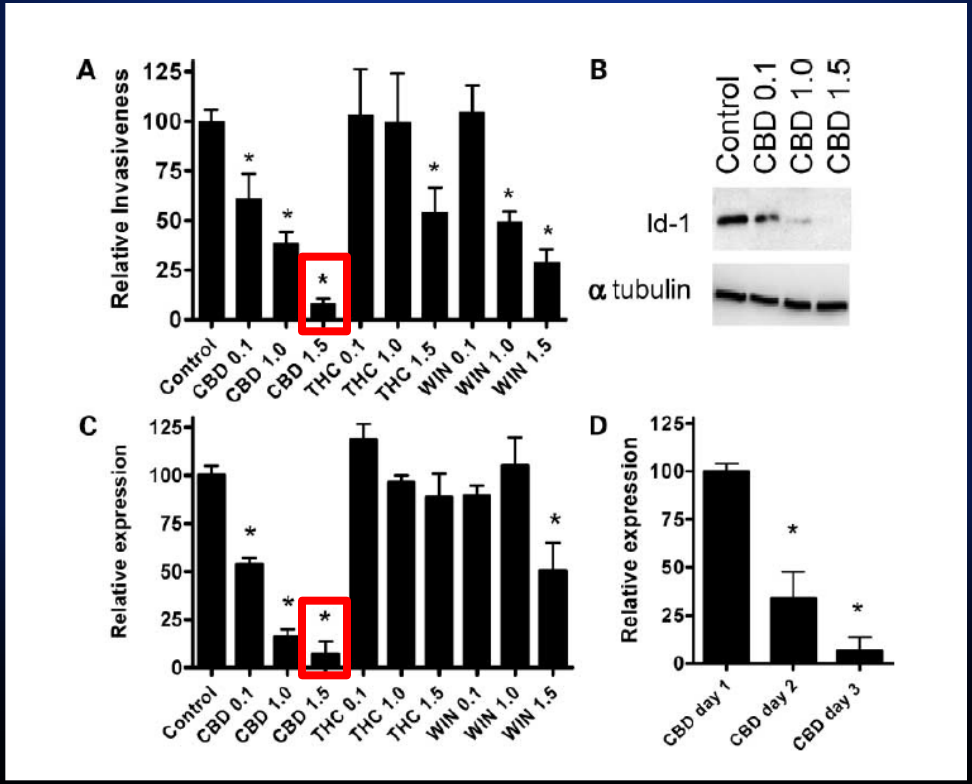
Modern civilization diseases

Appetite ⮭ after Joint ➡ THC as CB_1-R agonist

Obesity, Metabolic Syndrome
Appetite ⮯ after rimonabant (Acomplia®)
➡ CB_1-R blocker

Cancer

- „Id-1“ protein: keyplayer in the development of breast cancer metastases, also upregulated in many other tumors.
- Cannabidiol (CBD) ➡ Id-1 gene expression ⤵ ➡ tumor agressivity ⤵; low toxicity, not psychoactive ➡ ideal candidate for chronic application.

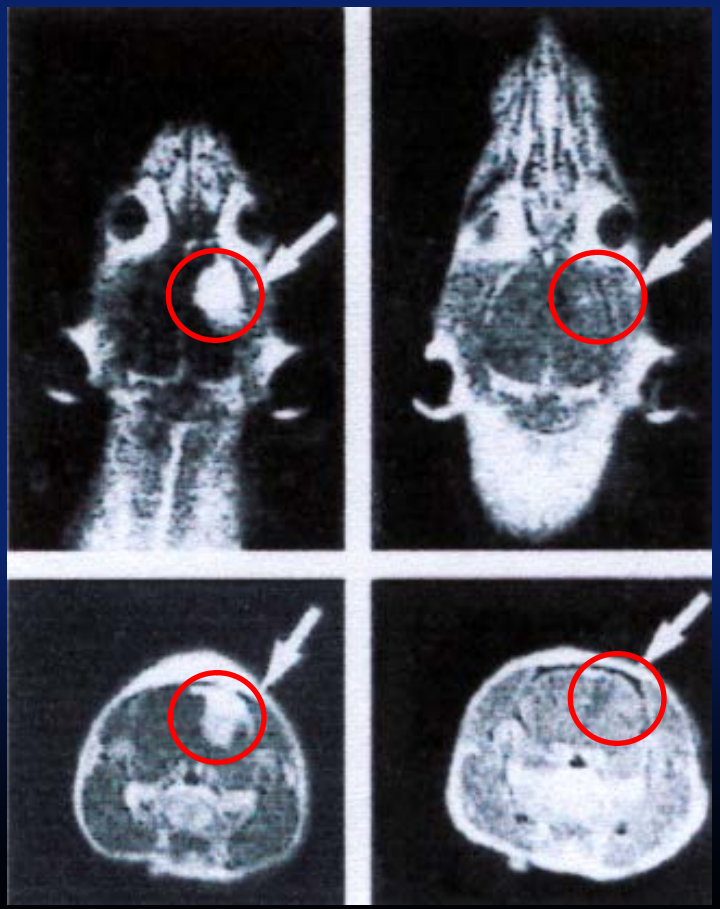


[McAllister, Mol Cancer Ther 2007]

Cancer

Glial cell brain tumor (glioblastoma), rat, MRI

before **after 500 mg THC**



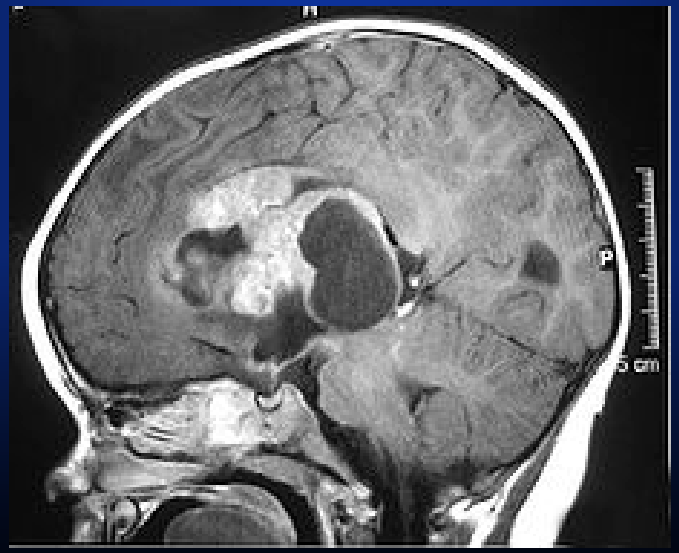
[Galve-Roperh, Nature Med 2000]

Cancer

Pediatric brain stem tumor

- **Infant, 2 y., Oakland Children‘s Hospital; multiple surgeries, radiation therapies, and bone marrow transplantation not successful.**
- **Doctor recommends 200 g/d „Cannabis juice“.**

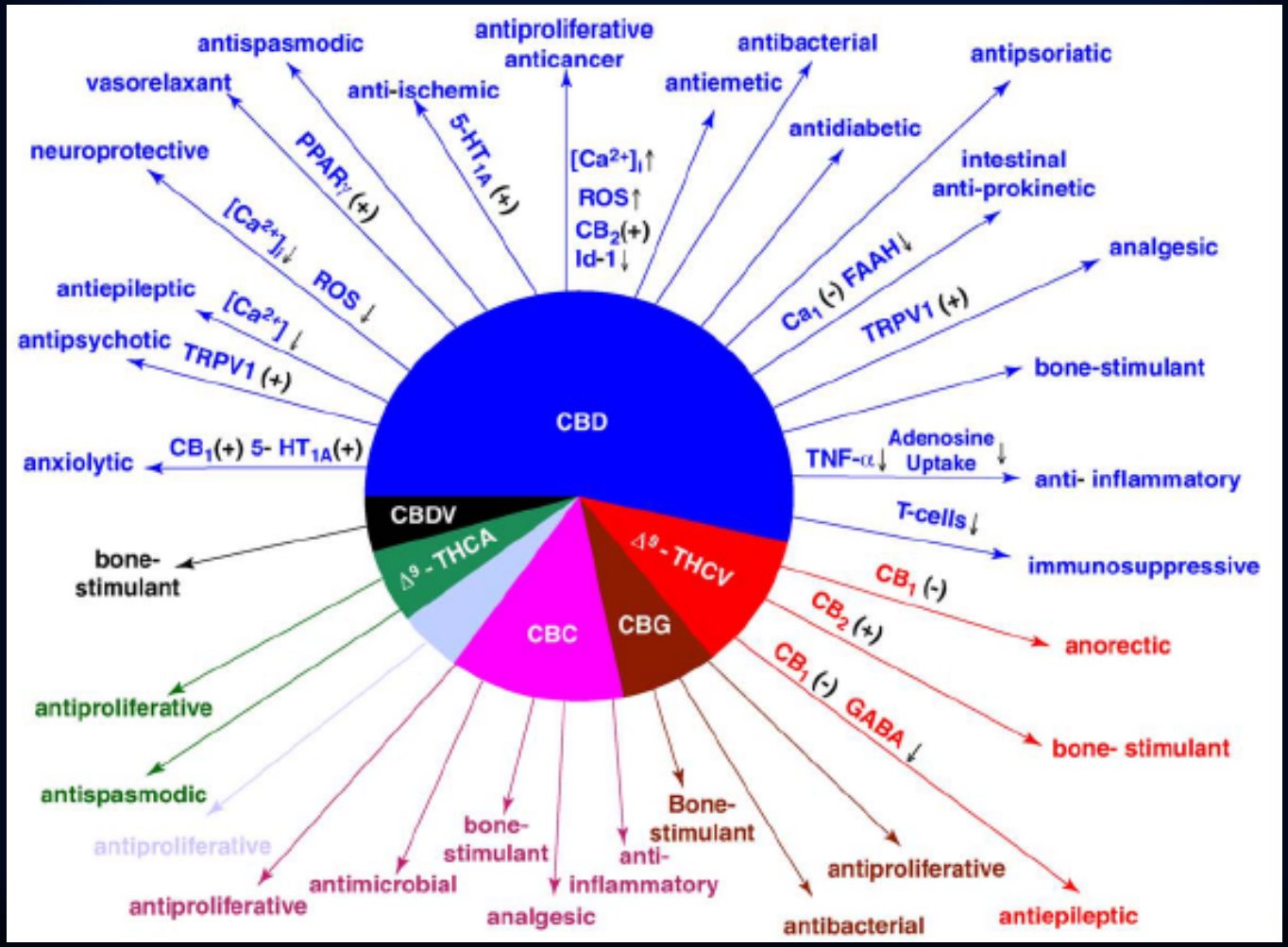
➡ **Complete tumor remission after 2 years.**



Rick Simpson's Hemp Oil

Indications, mechanisms of action

Non-psychoactive phytocannabinoids



[Izzo et al, TIPS 2009]

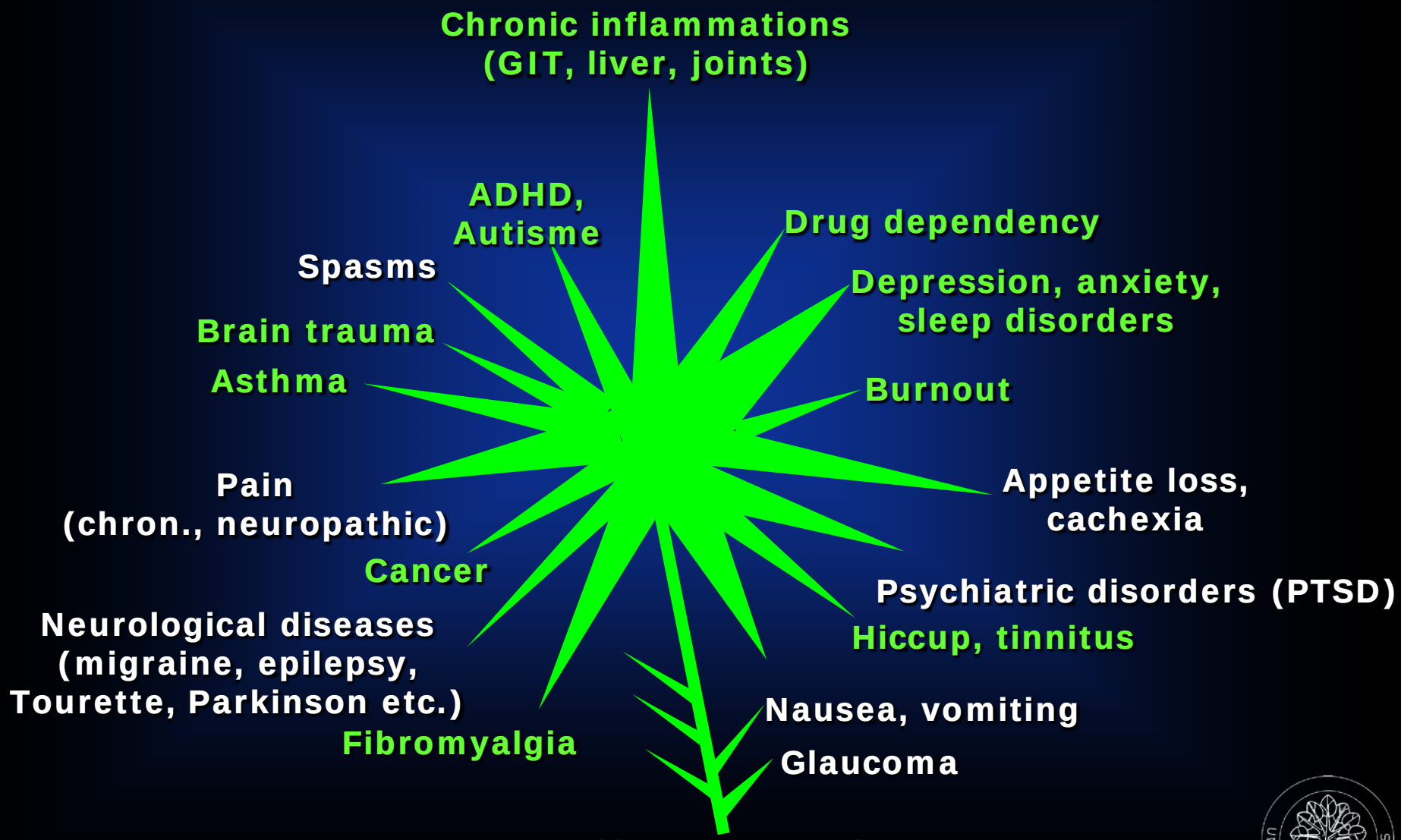
Approved indications for Cannabis in USA

Table 1. Diseases and Conditions for Which Medical Marijuana Use Is Permitted According to State Laws.*

Qualifying Diseases and Debilitating Conditions	Alaska	California	Colorado	Hawaii	Maine	Michigan	Montana	Nevada	New Jersey	New Mexico†	Oregon	Rhode Island	Vermont	Washington
Cancer	X	X	X	X	X	X	X	X	X (if terminal)	X	X	X	X‡§	X
Glaucoma	X	X	X	X	X	X	X	X	X‡	X	X	X		X‡
HIV–AIDS	X	X	X	X	X	X	X	X	X	X	X	X	X‡§	X
Hepatitis C						X						X		X‡
Alzheimer's disease						X					X	X		
Nail–patella syndrome						X								
Amyotropic lateral sclerosis						X			X					
Cachexia, or wasting syndrome§	X	X	X	X	X¶	X	X	X	X¶		X	X	X	X‡
Severe or chronic pain§	X	X	X	X		X	X	X	X¶		X	X	X	X‡
Severe nausea§	X	X	X	X	X¶	X	X	X	X¶		X	X	X	X‡
Seizures§	X	X	X	X	X	X	X	X	X‡	X (epilepsy)	X	X	X	X
Intractable spasticity									X‡					X‡
Anorexia		X												X‡
Severe muscle spasms	X	X	X	X	X	X	X	X			X	X		X‡
Multiple sclerosis									X	X			X	X
Spinal cord damage, with neurologic indication of muscular spasticity										X				
Appetite loss					X¶									X‡
Cramping														X‡
Arthritis		X												
Migraine		X												
Muscular dystrophy									X					
Inflammatory bowel or Crohn's disease						X			X					X‡
Admission to hospice care or terminal illness									X‖	X				
Any other chronic or persistent medical condition		X**												
Any other medical condition approved by state agency	X		X	X	X	X	X	X	X	X	X	X		X

[Hoffmann & Weber, N Engl J Med 2010]

Indication lyrics ?



Conclusions, Take-home messages

- The amazing chemistry of Cannabis is almost completely elucidated.
- The main active principles are cannabinoids.
- Phytocannabinoids are safe but highly potent drugs without risk of dependency if used under strict medical control.
- Their acute physical toxicity is marginal.
- So far, the 2 options are biogenic/synthetic cannabinoid- (THC and/or CBD; pCMs, sCMs) or standardized Cannabis-based medicines (CMs).
- An obstacle are the particular pharmacokinetic properties requiring optimized application forms and devices.

Conclusions, Take-home messages

- The gap between traditional and evidence-based data must be bridged by intensified molecular biological (ECS!), pharmacological, pharmaceutical and clinical research.
- The ethnopharmacological bonus is not valid in school medicine.
- Negative image and stigmatization as „illicit drug“ and not yet fully available clinical evidence still inhibit justified remedicinalization.
- Uncritical, non-controlled self-treatment with „Street Cannabis“ might be harmful, also risking patient‘s criminalization.

Conclusions, Take-home messages

- Despite its very broad indication spectrum, Cannabis is not an all-round and miracle drug.
- Preparations based on pCM, sCM and CM are narcotics, therefore cannot be sold as OTC drugs.
- If (i) only prescribed within approved indications, (ii) not applied by smoking, (iii) dosage carefully „titrated“, then the dependency potential is insignificantly small (see Mô).
- Today still niche player, tomorrow hopefully key player.

Vision

According to the UN Universal Declaration of Human Rights 1948:

- “Everyone has the right to life, liberty and security of person" (Art. 3).

- “Everyone has the right to a standard of living adequate for the health and well-being of himself and of his family, including food, clothing, housing and medical care and necessary social services, and the right to security in the event of unemployment, sickness, disability, widowhood, old age or other lack of livelihood in circumstances beyond his control” (Art. 25, § 1).

Whereas this Declaration applies to everyone and all people, whereas many doctors are banned by legal requirements from treating their patients with cannabis-based medicines and whereas many people cannot afford access to cannabis-based medicines the IACM thus declares that:

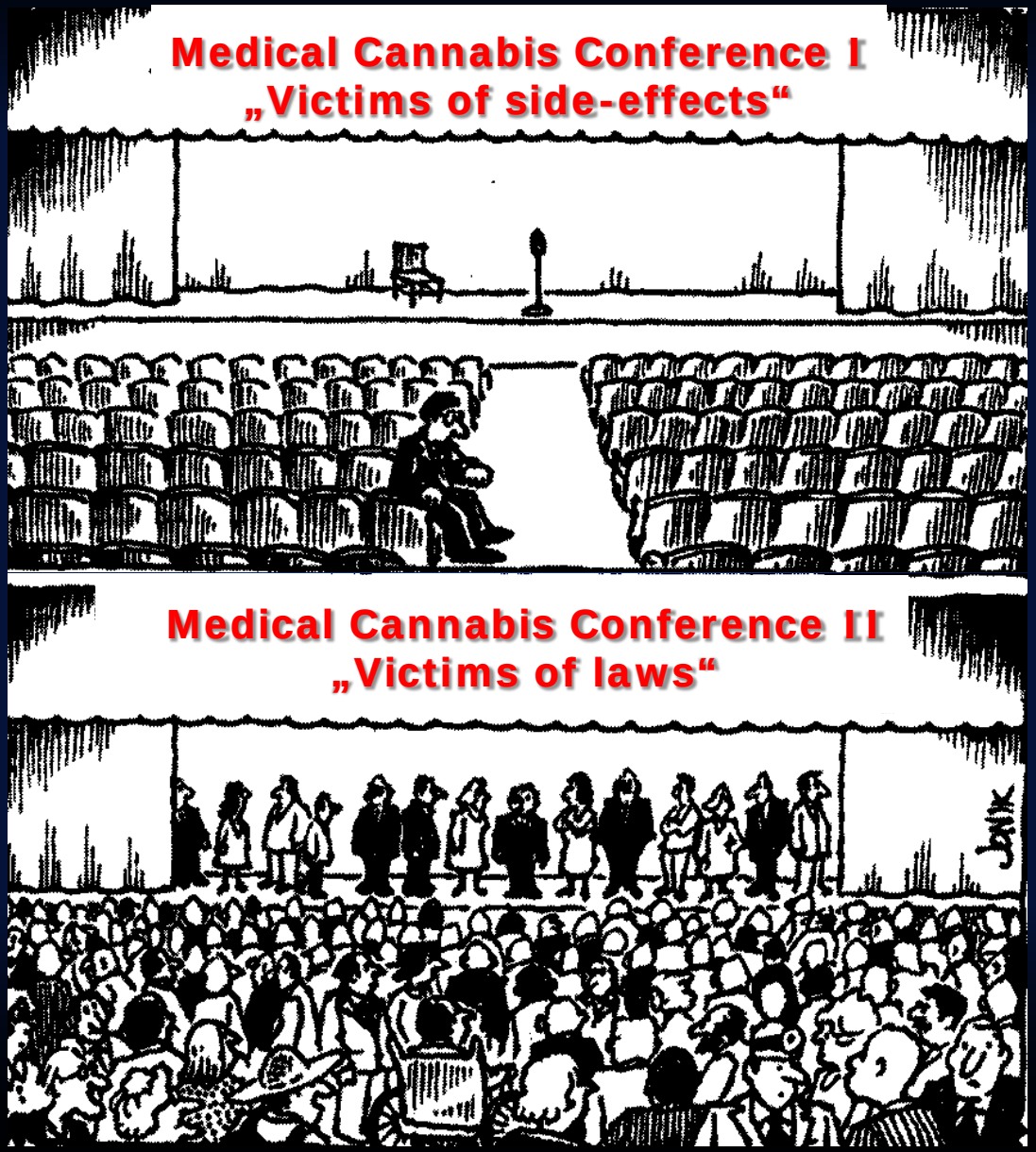
1. Every medical doctor has the right to treat his or her patients with cannabinoids and cannabis products according to the rules of good medical care.
2. Every patient has the right to access cannabis products for medical treatment supervised by a medical doctor, regardless of social status, standard of living or financial means.

UN Declaration of Human Rights 1948

Vision

Phytocannabinoids and Cannabis in Medicine: An option !

Thank you !


Medical Cannabis Conference I
„Victims of side-effects“
Medical Cannabis Conference II
„Victims of laws“

...and to digest slides

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