

Phytocannabinoids in Medicine – An Option ?



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FORO INTERNACIONAL:
Actualización sobre los usos médicos y terapéuticos del Cannabis
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From Galenics to Receptors

Pharmaceutics



Pharmacokinetics



Pharmacodynamics



Formulations
Application forms
Dosage



Absorption
Distribution
Metabolism
Elimination

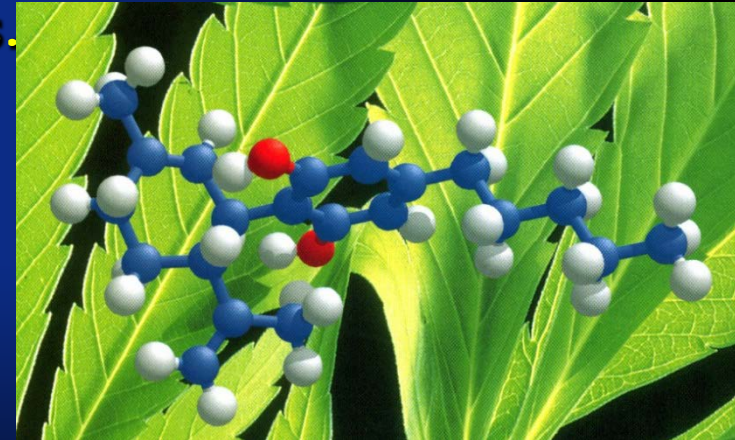


Effects
Indications



Plant of Superlatives

- With approx. 500 mio regular users Cannabis is World's most popular illicit narcotic.
- One of the oldest medicinal plants, >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 Scientific Literature

Papers in "PubMed" -2014

„Cannabis“	➔	12'731
„Cannabinoids“	➔	11'681
„Phytocannabinoids“	➔	87
„Endocannabinoids“	➔	4'537
„THC“	➔	7'491
„Cannabinoids + Medicine“	➔	1'980
„Cannabis + Medicine“	➔	1'803
„Tobacco“	➔	87'998
„Alcohol“	➔	767'493

Reinventing the Wheel ?



Chinese Emperor Shen Nung
Father of TCM ➡ „Pen Ts'ao“ („The Herbal“), 2700 b.c.

➡ First Cannabis Pharmacopoeia Monograph.

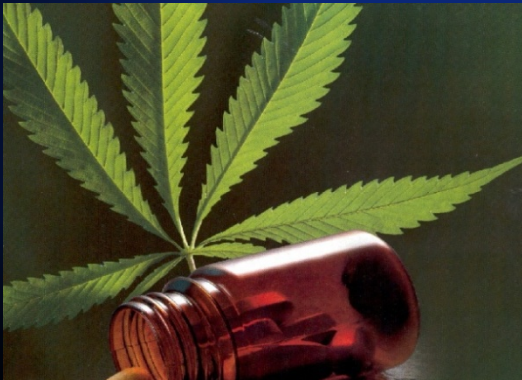
Reinventing the Wheel ?



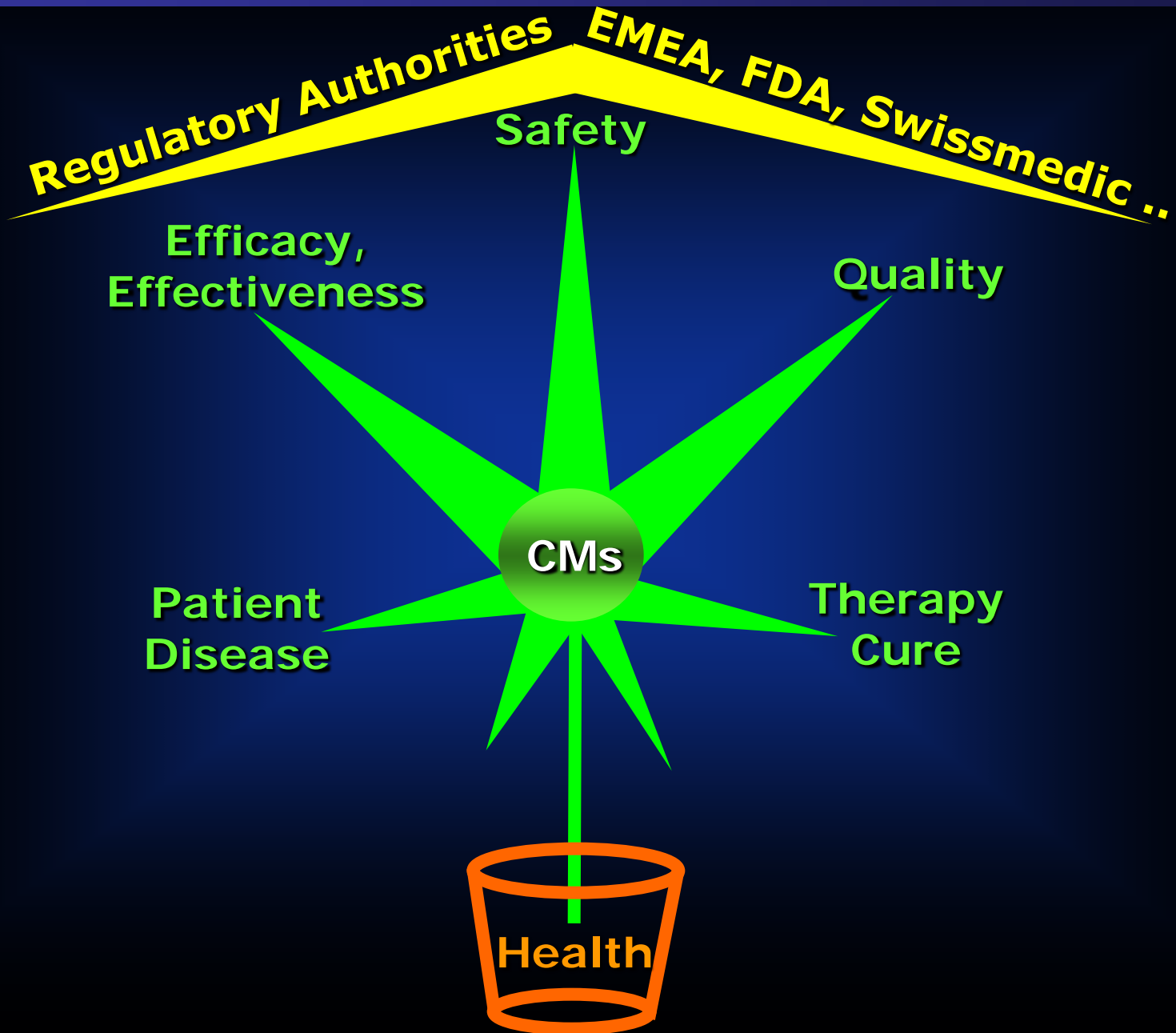
Has Cannabis facilitated the discovery of America?

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

Pharmaceuticals



Safety on the Top



Regulatory Imperatives

Safety assessment / Production phase



**Breeding
(cloning, chemovars etc.)**

Extraction, Formulation



GAP

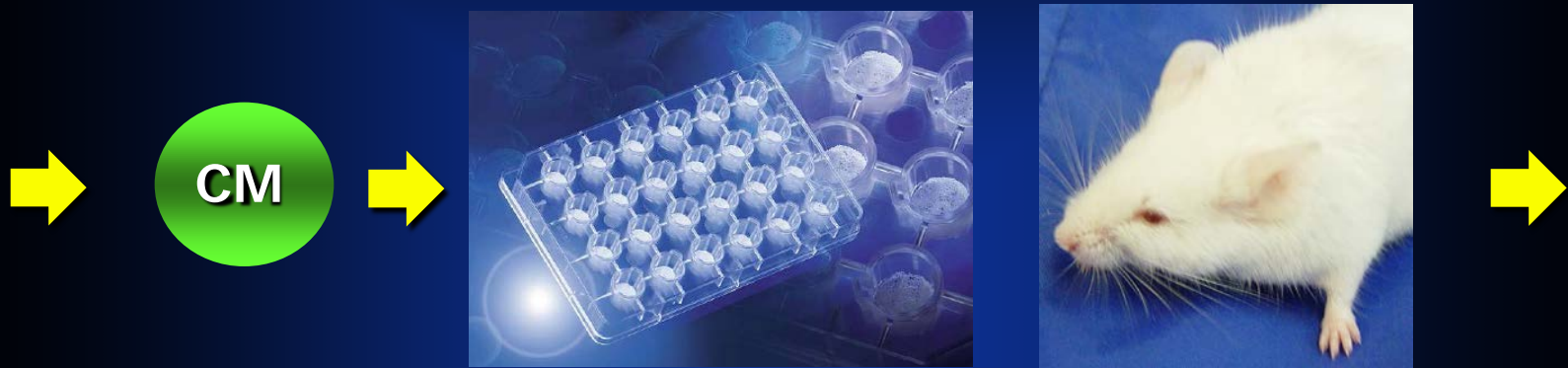
GMP

GLP

GPP

Regulatory Imperatives

Safety assessment / Pre-clinical phase

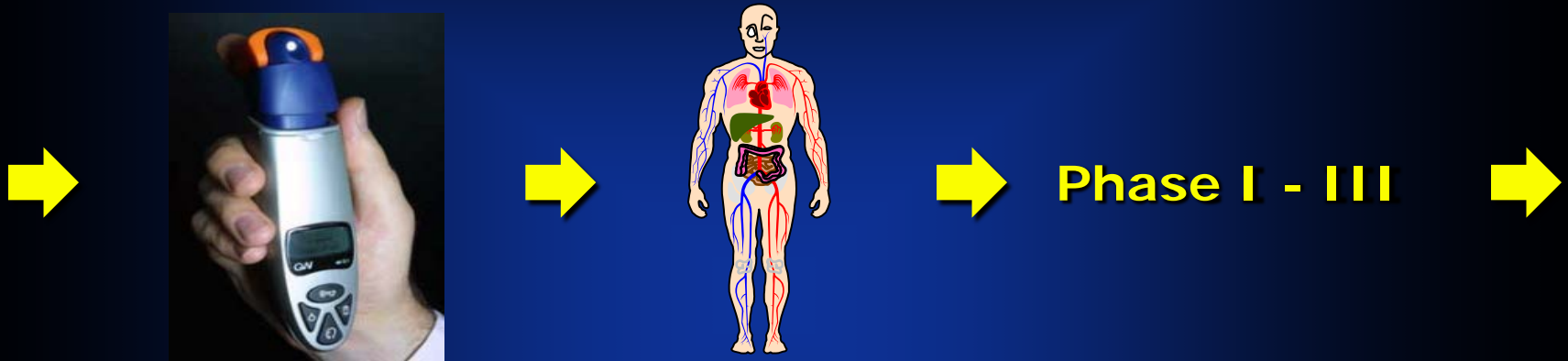


In vitro & in vivo testing
Cell biology, animal pharmacology & toxicology
(general, teratogenicity, mutagenicity, carcinogenicity)

GLP

Regulatory Imperatives

Safety assessment / Clinical phase



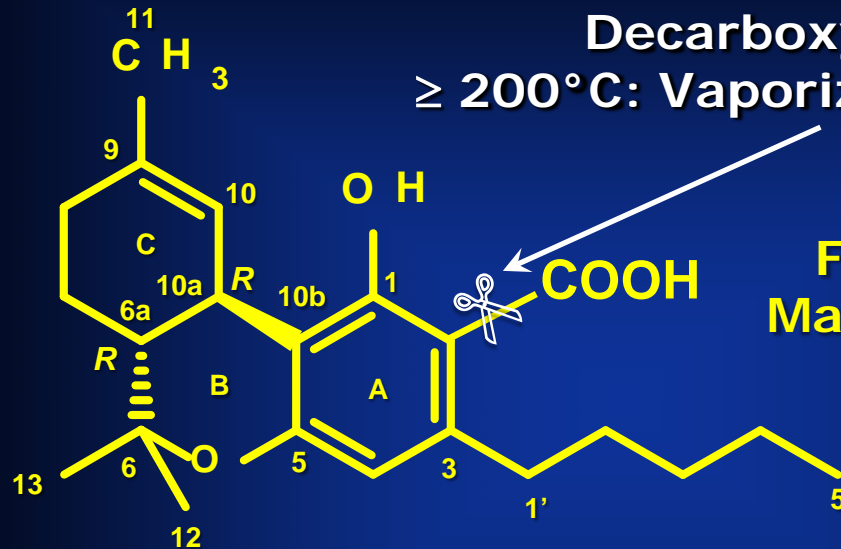
Delivery
technology

GMP GTP

Clinical pharmacology, RCT

GCP

Phytocannabinoids – THC the Star



Decarboxylation
≥ 200°C: Vaporizer, Joint, GC

THC acid A
Fresh THC-type Cannabis
Main biogenic THC 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

CB₁-, CB₂-R

Psychoactive, multiple therapeutic effects

Isolated 1942, structure 1964 [Mechoulam et al.]



Phytocannabinoids – The Wallflowers

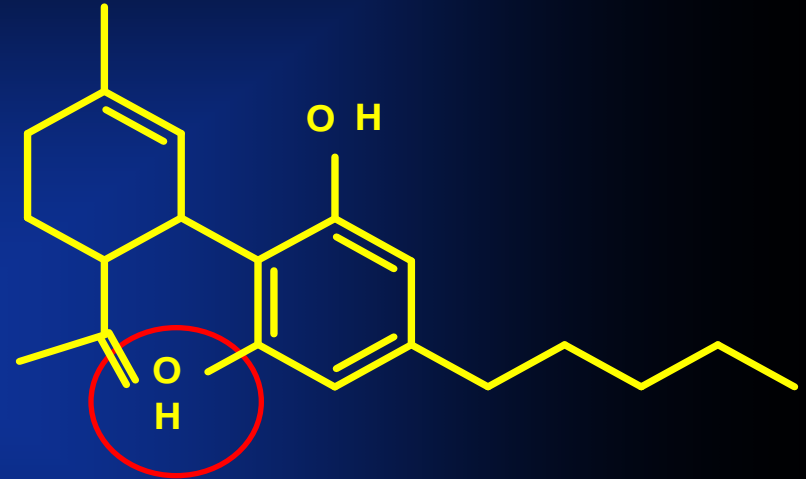
66 identified, exclusively found in Cannabis



Δ^9 -Tetrahydrocannabivarin, THCV, THC-C3

CB₁-R antagonist

Anorectic, antiepileptic, bone-stimulant



Cannabidiol, CBD

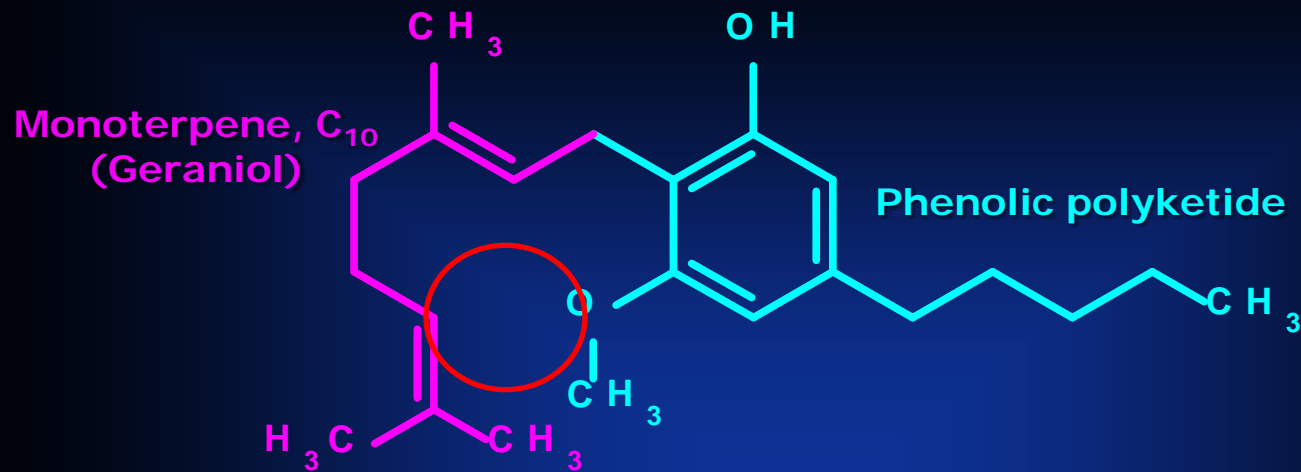
CBD-type (fiber, industrial) Cannabis

CB_x-R ?

Antipsychotic, neuroprotective,
anticarcinogenic, antiepileptic, ...

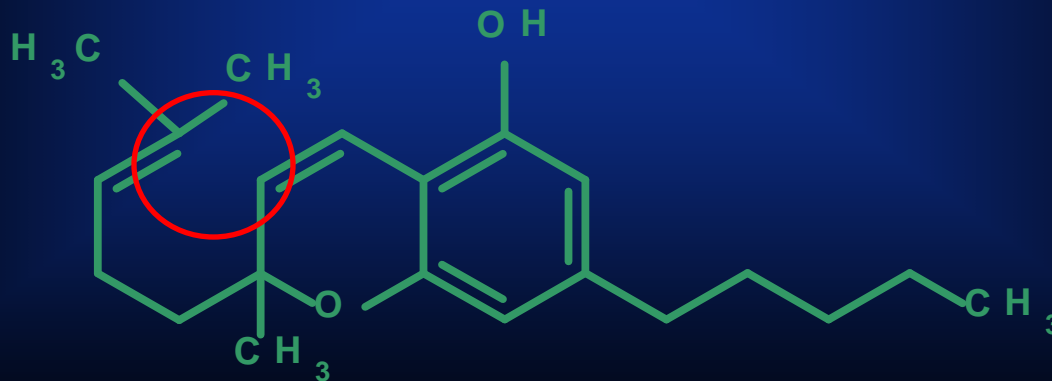


Phytocannabinoids – The Wallflowers



Cannabigerol, CBG

Antimicrobial, antiinflammatory, analgesic, bone-stimulant



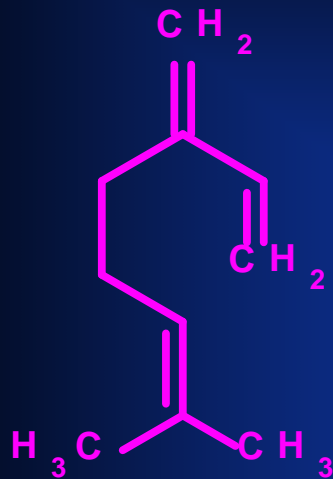
Cannabichromene, CBC

Antimicrobial, antiinflammatory, analgesic



Non-Cannabinoids

140 Mono- and Sesquiterpenoids identified



Myrcene

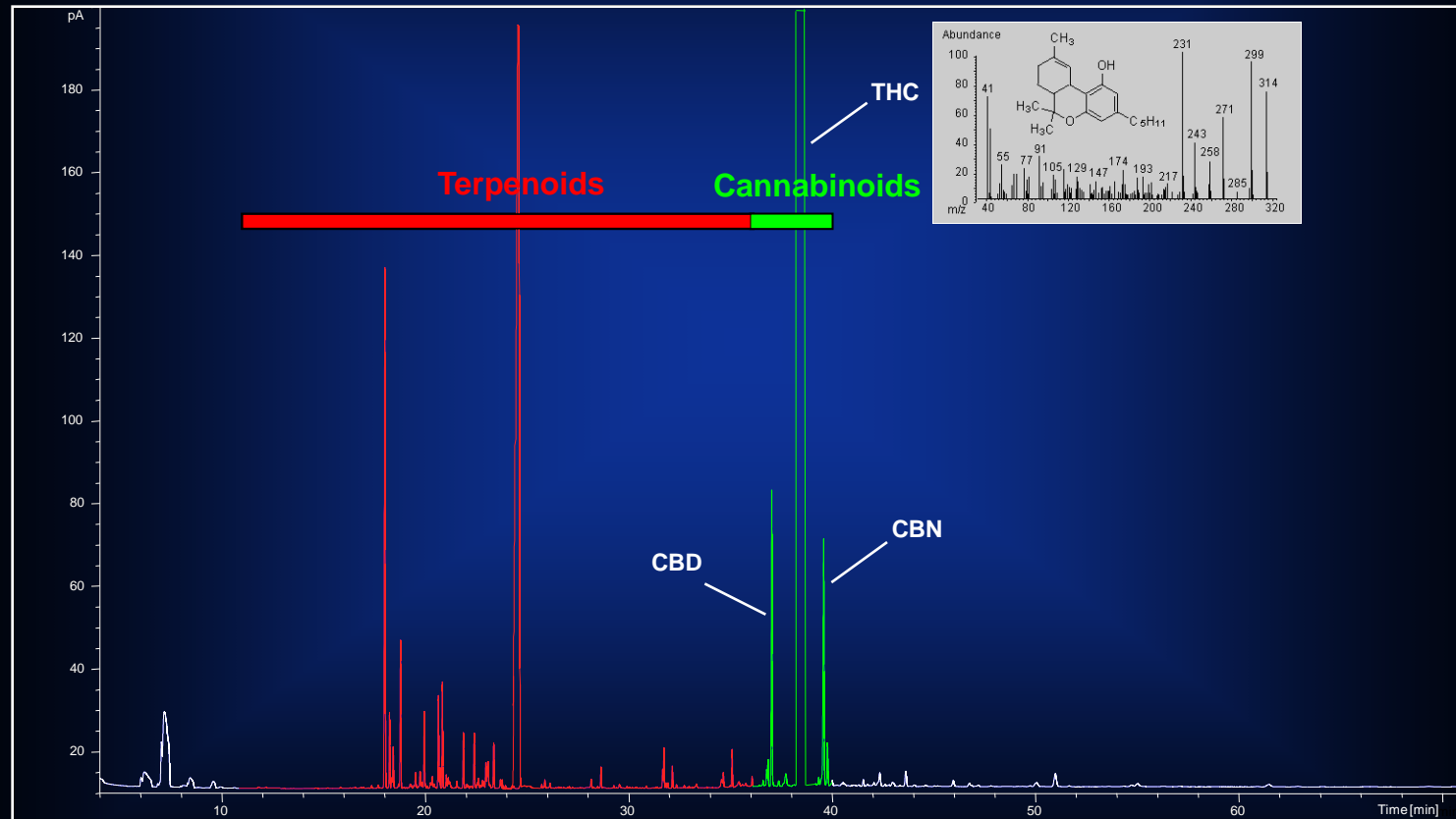


β -Caryophyllene
CB₂-R agonist
Antiinflammatory

[Gertsch 2008]

Cannabis QC

GC/GC-MS profiling, analytical fingerprints

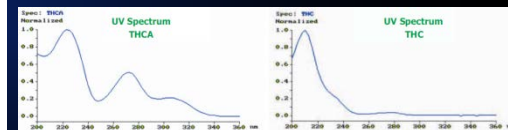
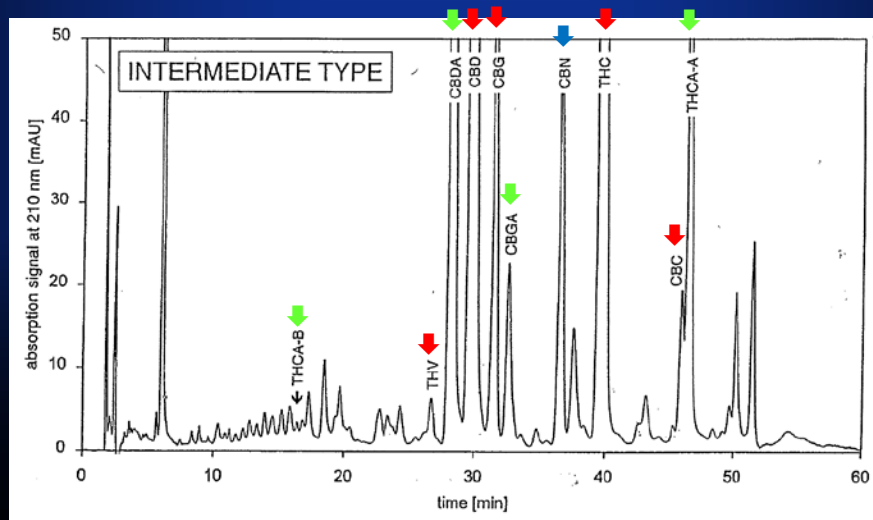
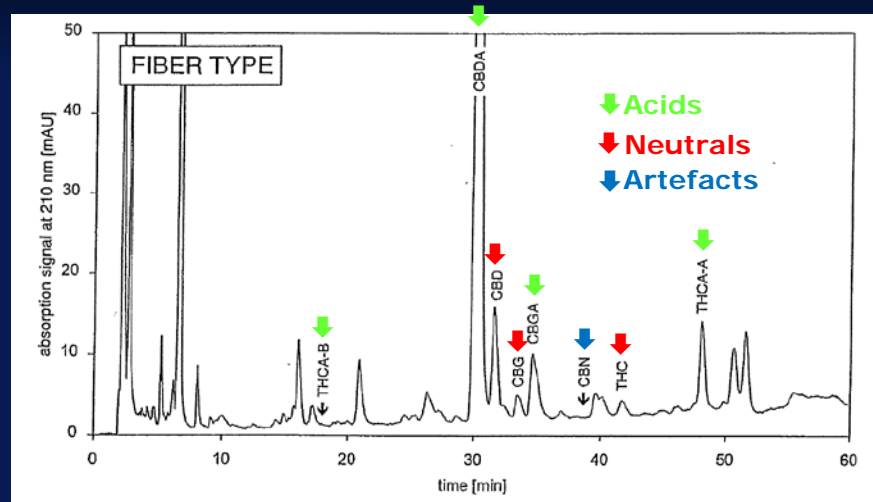


[Brenneisen et al, DEA Project 1987; FOPH Final Report 2005]



Cannabis QC

HPLC-PDA profiling



[Lehmann & Brenneisen 1995]



Cannabis QC

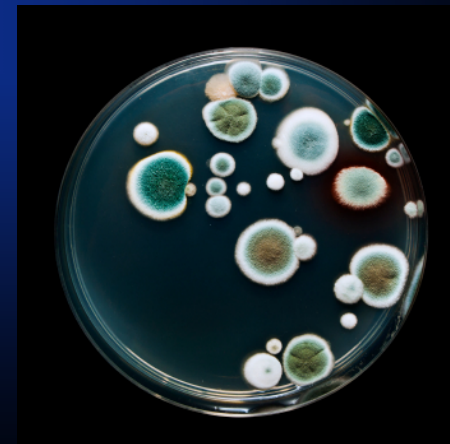
Not to forget testing for:

➔ **Absence of**

- pesticides
- herbicides
- fungicides
- solvents (in case of extracts).



➔ **Microbiological purity.**



Nature and/or Lab ?

Phytocannabinoids

➡ THC, CBD, THCV, CBG, ...

Cannabis, CMs

➡ Stand. Extracts



Multi-component preparations
„Shotguns“

Synthetic Cannabinoids/Deriv.

➡ Dronabinol, Nabilone



Mono-component preparations
„Silver Bullets“

Synthetic Modulators of Endocannabinoids and EC receptors

➡ Non-Cannabinoid Agonists, Antagonists, Inhibitors



Cannabinoid-/Cannabis-Based Drugs

Folk medicine, self-treatment:

➔ Cannabis and home-made preparations

- Joint, tea, „Simpson Oil“, cookies etc.
- Street Cannabis
- Quality and dosage not controlled
- Harmful or inefficient application modes.



Academic, evidence-based medicine:

➔ Cannabinoid-based medicines

- THC (dronabinol, Marinol®)
- Nabilone (Cesamet®)
- Cannabidiol, CBD.



➔ Cannabis-based medicines (CMs)

- Standardized extracts (Sativex®, Epidiolex®)
- Cannabis buds (Bedrobinol®, Bediol® etc.)
- Established galenic formulations, e.g. „formula magistralis“ preparations (tincture, drops etc.)
- Quality and dosage controlled
- Less harmful and more efficient application forms.



Application Routes

**IACM Survey
(2009-2010, N=953, >31 countries)**



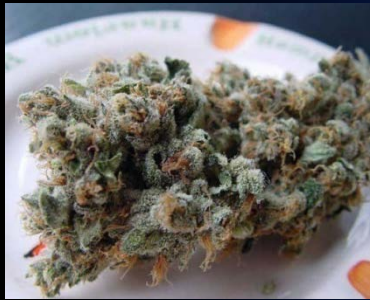
1. Inhalation	95 %	➡	Pyrolytic inhalation (Joint)	92 %
			Non-pyrolytic inhalation (Vaporizer)	50
2. Oral or sublingual	69	➡	Food or Tincture	87
			Tea	33
			Dronabinol/Marinol®	11
			Nabilone/Cesamet®	2
			Sativex®	1
3. Topic	5	➡	Ointment, Oil	

[Hazekamp et al, IACM, unpublished]



Sativa Oil

Validated home-made Cannabis preparation for ALS patients



7.8 mg THC/mL \approx 90% yield

[Goldman and Brenneisen, Project Swiss ALS Assoc.]



Simpson Oil

Concentrated extract

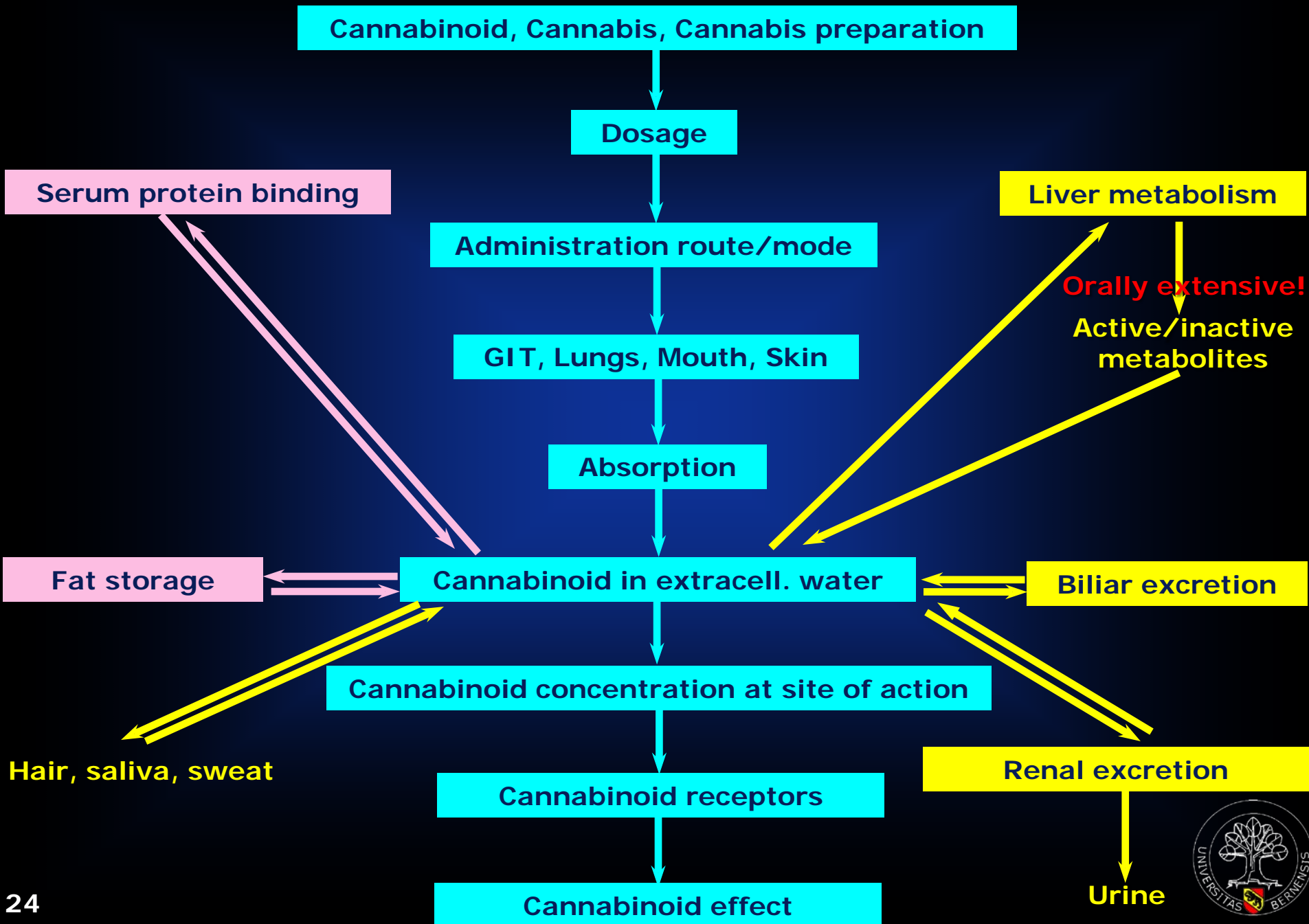
Naptha as solvent ➡ toxic residues
➡ olive oil to be preferred [Hazekamp 2013]

Not validated and clinically not tested cannabis preparation

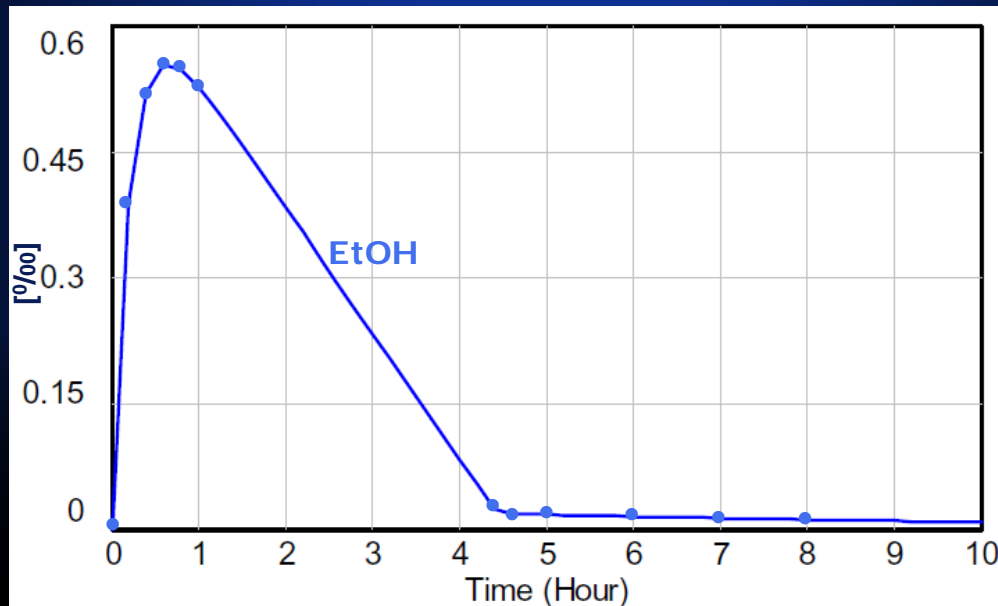
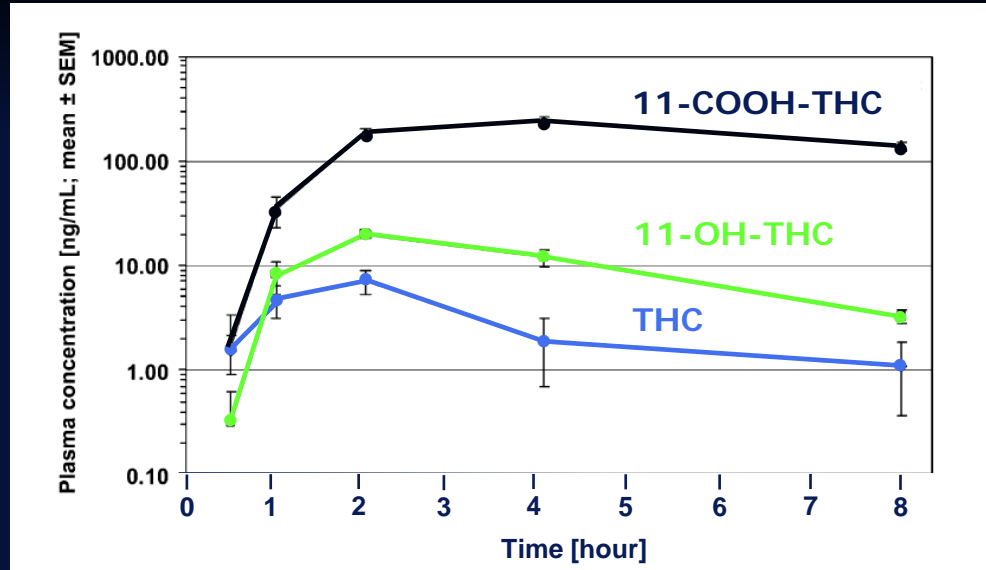
Good for treating cancer?



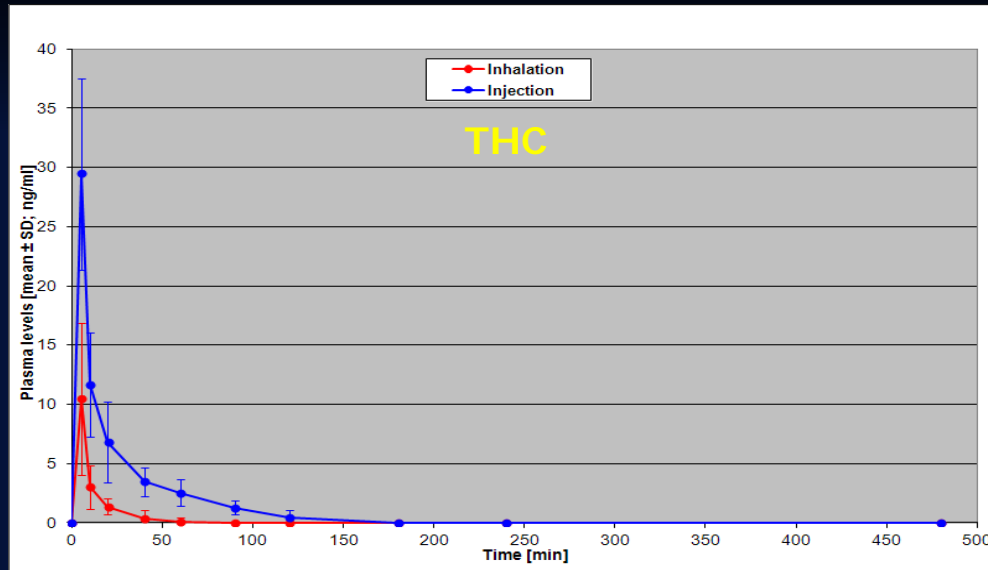
Pharmacokinetics



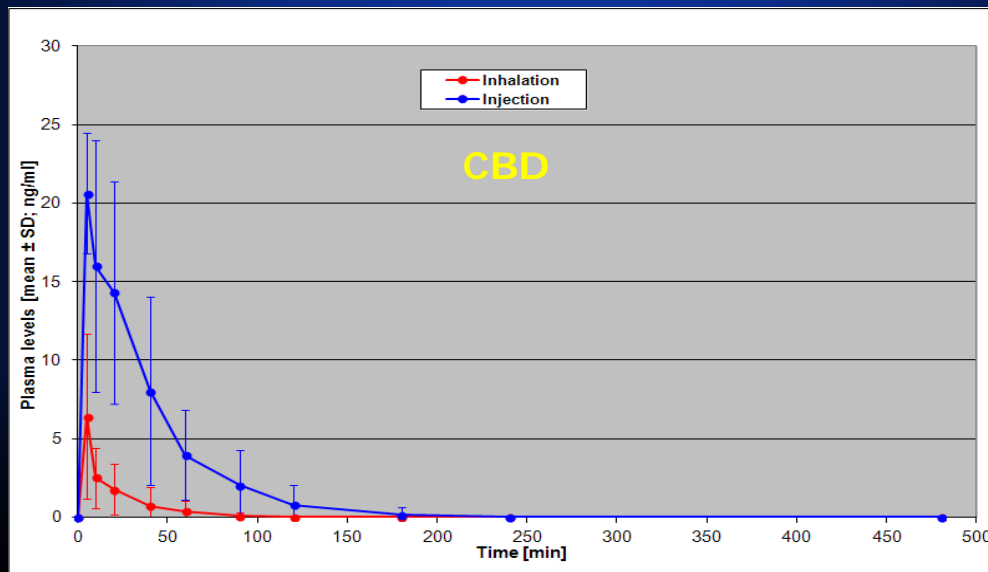
Plasma Levels - THC vs Alcohol



Plasma Levels - THC vs CBD



1.6 mg THC, inh/iv,
males, N=12

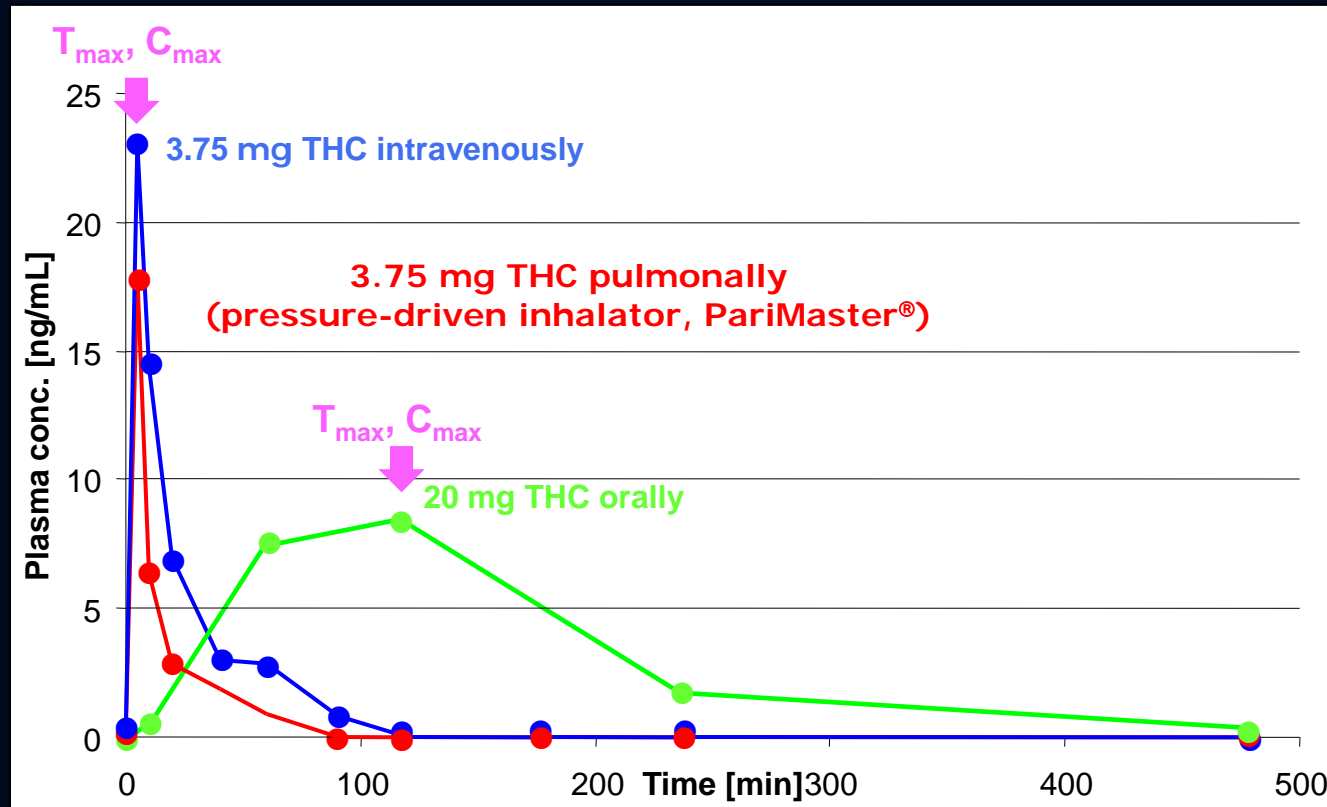


1.6 mg CBD, inh/iv,
males, N=12

[Meyer et al 2010]



Plasma Levels - THC oral vs inhal vs iv

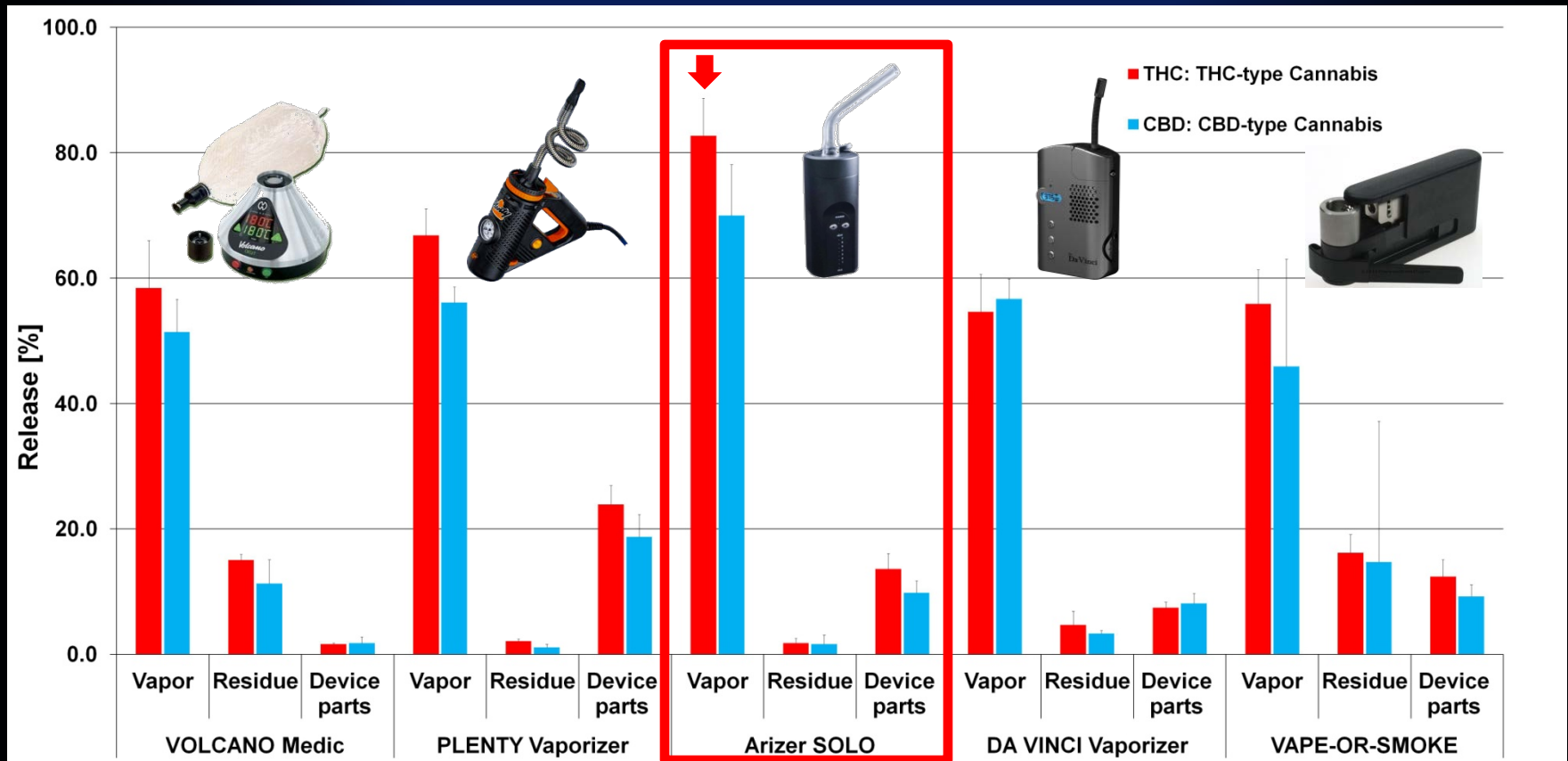


Inhalation with vaporizer \approx injection:

- ☺ **Bioavailability 70-90%, rapid onset of action**
- ☹ **Psychotropic side-effects**

Vaporization

Non-pyrolytic inhalation *In vitro* validation of commercial vaporizer devices



[Lanz et al 2014, submitted]

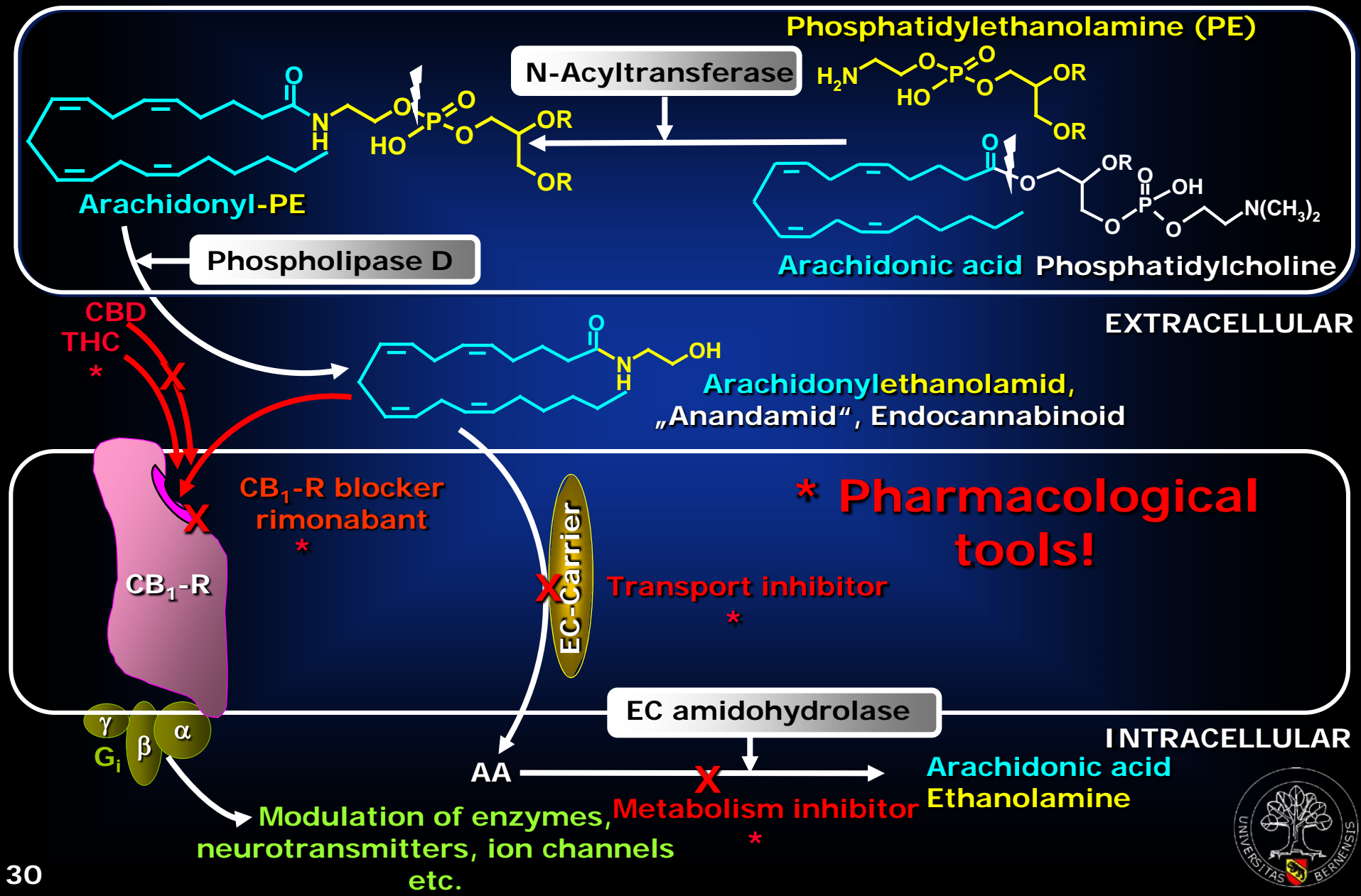


Application Forms

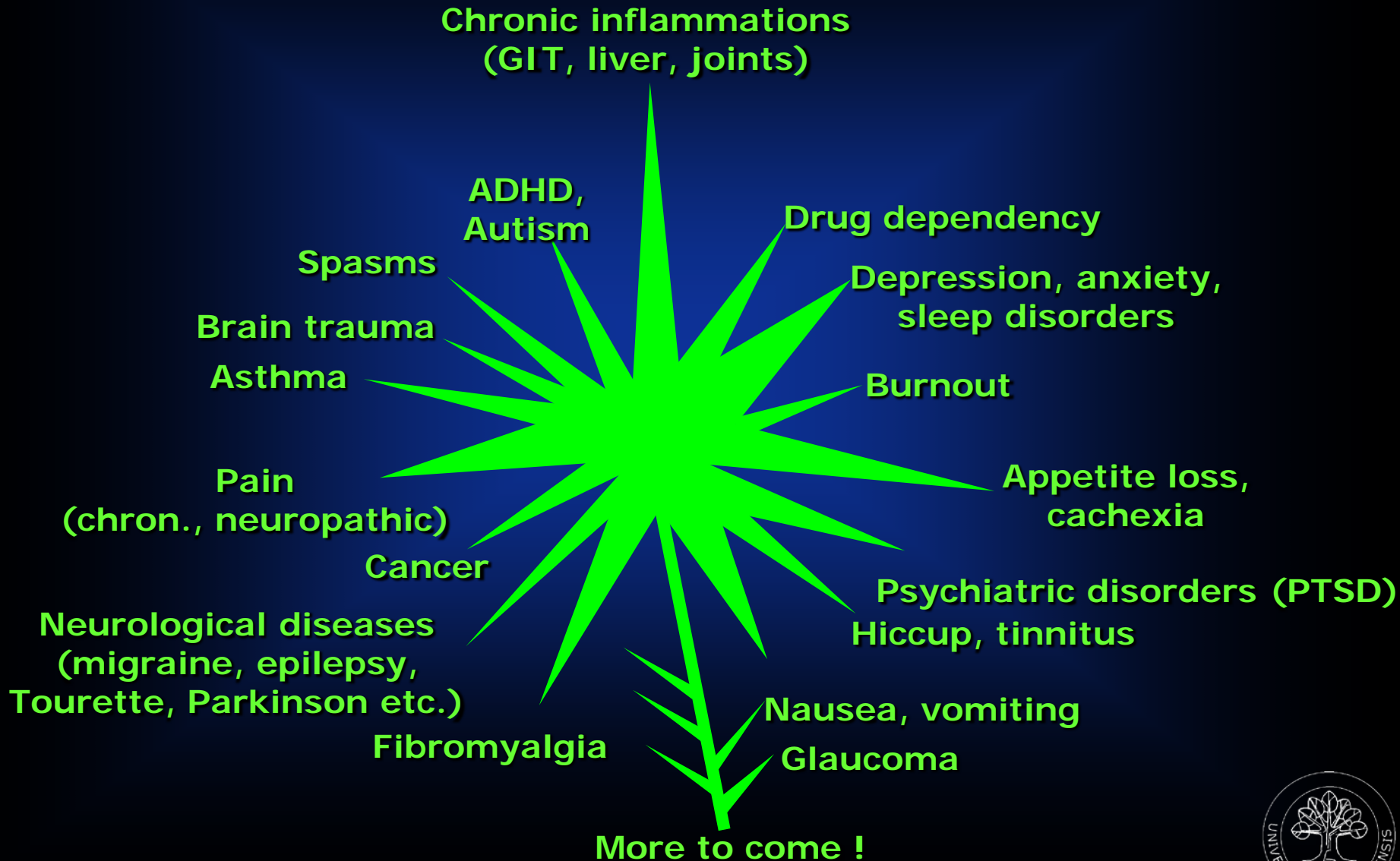
Galenic formulation	Bioavailability	Onset of action
Cannabis cigarette (smoke)	15-25 %	Rapid
Cannabis inhalation aerosol (vapor)	50-90	Rapid
Cannabis sublingual spray	>90	Slow
Cannabis capsule	?	Slow
Cannabis tea	low	Slow
Cannabis oil	?	Slow
THC capsule	5-20	Slow
THC drops	5-20	Slow
THC suppository	20-40	Rel. rapid
THC patch	?	?
THC injection solution	100	Very rapid



Pharmacodynamics - ECS Site of Action



Indication Lyrics ?



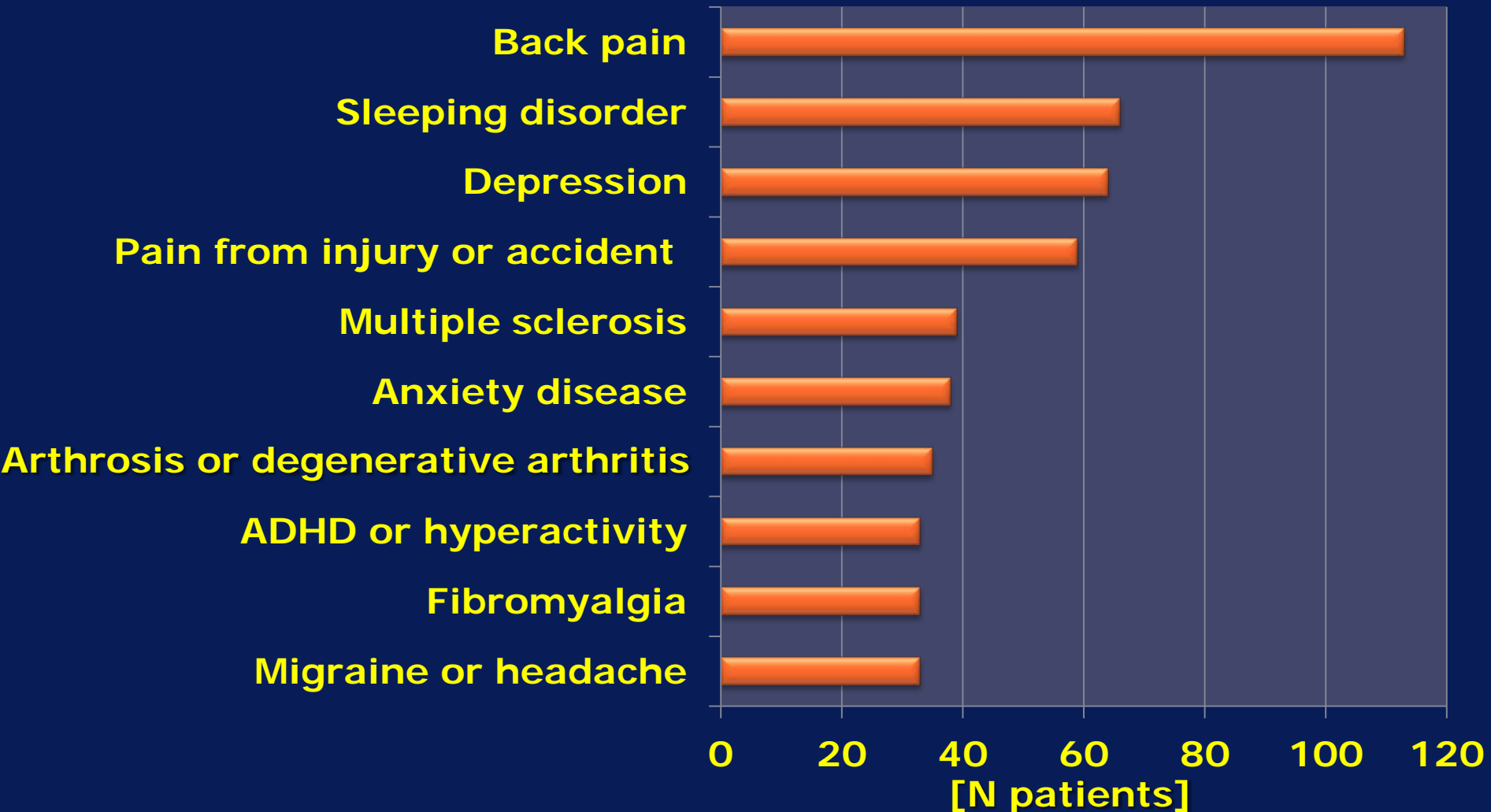
IACM Survey

2009-2010, N=953, >31 countries

[Hazekamp et al, unpublished]



Top 10 of 47



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, polyarthrititis, Tourette Syndrom, ...

Application:

- ➔ Joint, vaporizer, tea, Simpson oil, ...

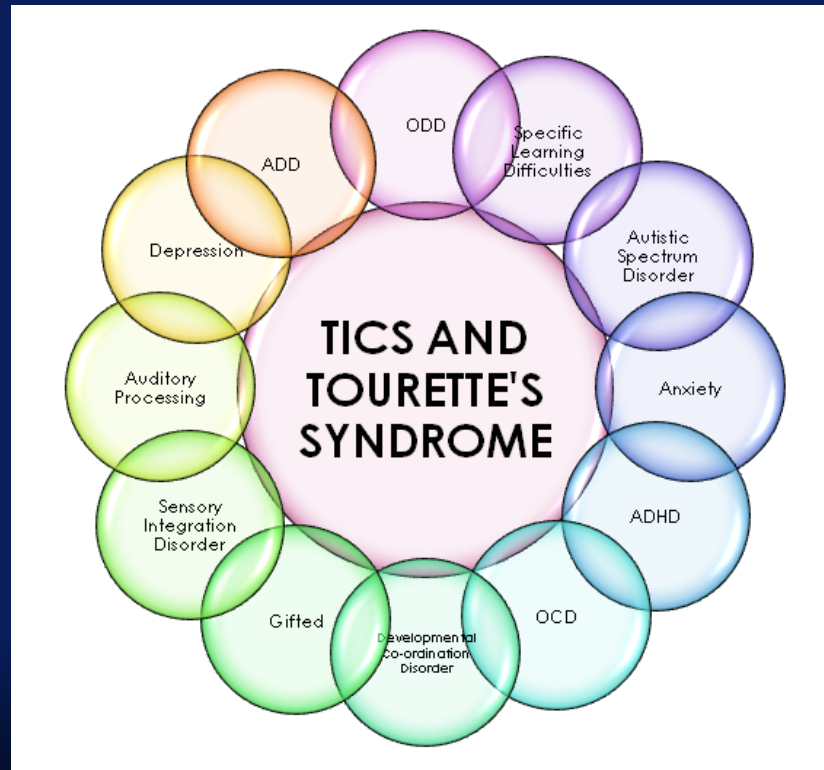
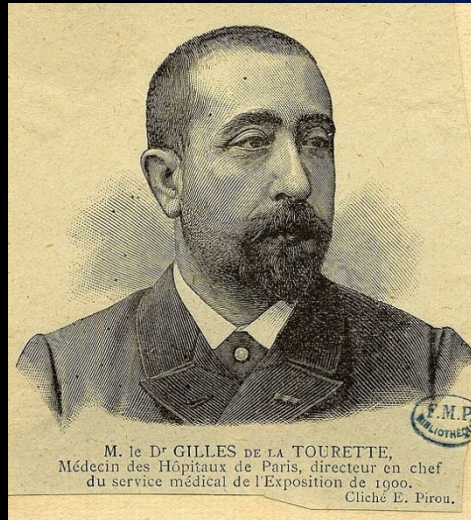
Why medication:

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



Rare Neurological Diseases

Tourette Syndrome (Tics)



Treatment with THC [Müller-Vahl 1999, 2002]
or
Medical Cannabis [Anecdotal patient reports]

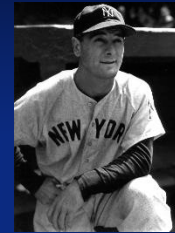


Rare Neurological Diseases

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

- **Preclinical tests:**
 - ➔ **ALS mouse model**
 - ➔ **CB₁-R knockout mouse**
 - ➔ **Spinal marrow culture**
- **Clinical trials with THC:**

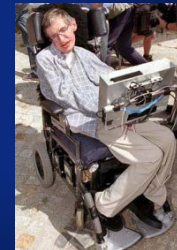
Spasticity ↓, cell damage ↓, neuroprotection
- **Self-treatment with Cannabis:**
 - ➔ **Home-made CM, „Sativa-Oil“**



Lou Gehrig
(1903-41)



Mao Zedong
(1893-1976)



Stephen Hawking
(1942-)



David Niven
(1910-1983)

[Raman 2004; Joerger et al 2012;
Goldman and Brenneisen, Project Swiss ALS Assoc.]



Metabolic Syndrome, Obesity

Appetite ↑ after Joint ➡ THC as CB₁-R agonist

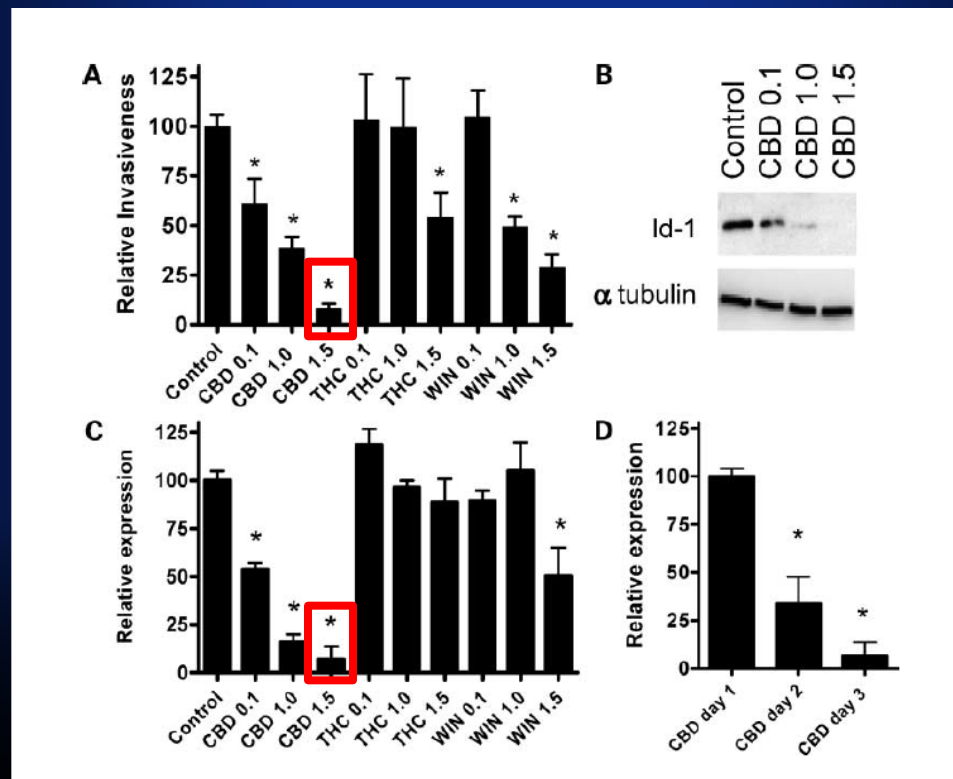


Appetite ↓ after rimonabant ➡ CB₁-R blocker



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 aggressivity ↓; low toxicity, not psychoactive ➔ ideal candidate for chronic application.



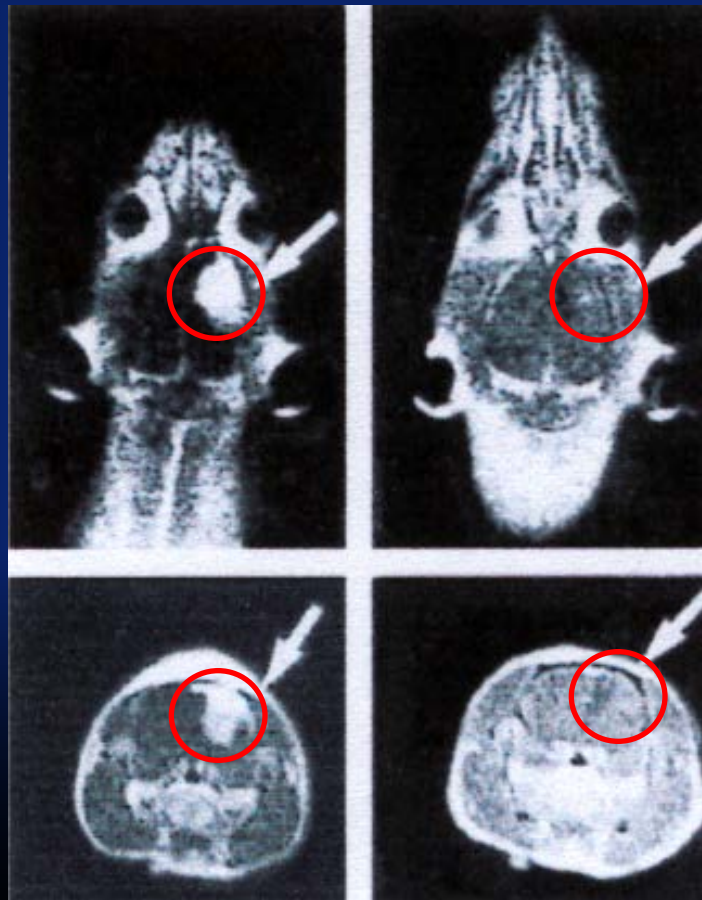
[McAllister 2007]



Cancer

Glial cell brain tumor (glioblastoma), rat, MRI

500 mg THC
Before After



[Galve-Roperh 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“ („Rick Simpson's Oil“?).
- ➔ Complete tumor remission after 2 years.



Pain

Canadian study on neuropathic pain patients (N = 23), post-traumatic or post-operative.

3 x 25 mg/day Cannabis („State Medical Cannabis“) with 9.4% THC, for 5 days, smoked.

- ➡ **Pain intensity ↓, sleep quality ↑**
- ➡ **Few side-effects (headache, cough, dizziness).**



[Ware et al 2010]



PONV

Post-operative nausea and vomiting
Gynecology patients
10 mg i.v. THC just after last suture

THC →



Side-effects of narcosis ↓ , sleep duration ↑

[Theiler et al 2009, unpublished]



PTSD

Pilot study on Israeli war veterans (N = 30).

**Cannabis cigarettes (23% THC, <1% CBD),
max. 100 g/month.**

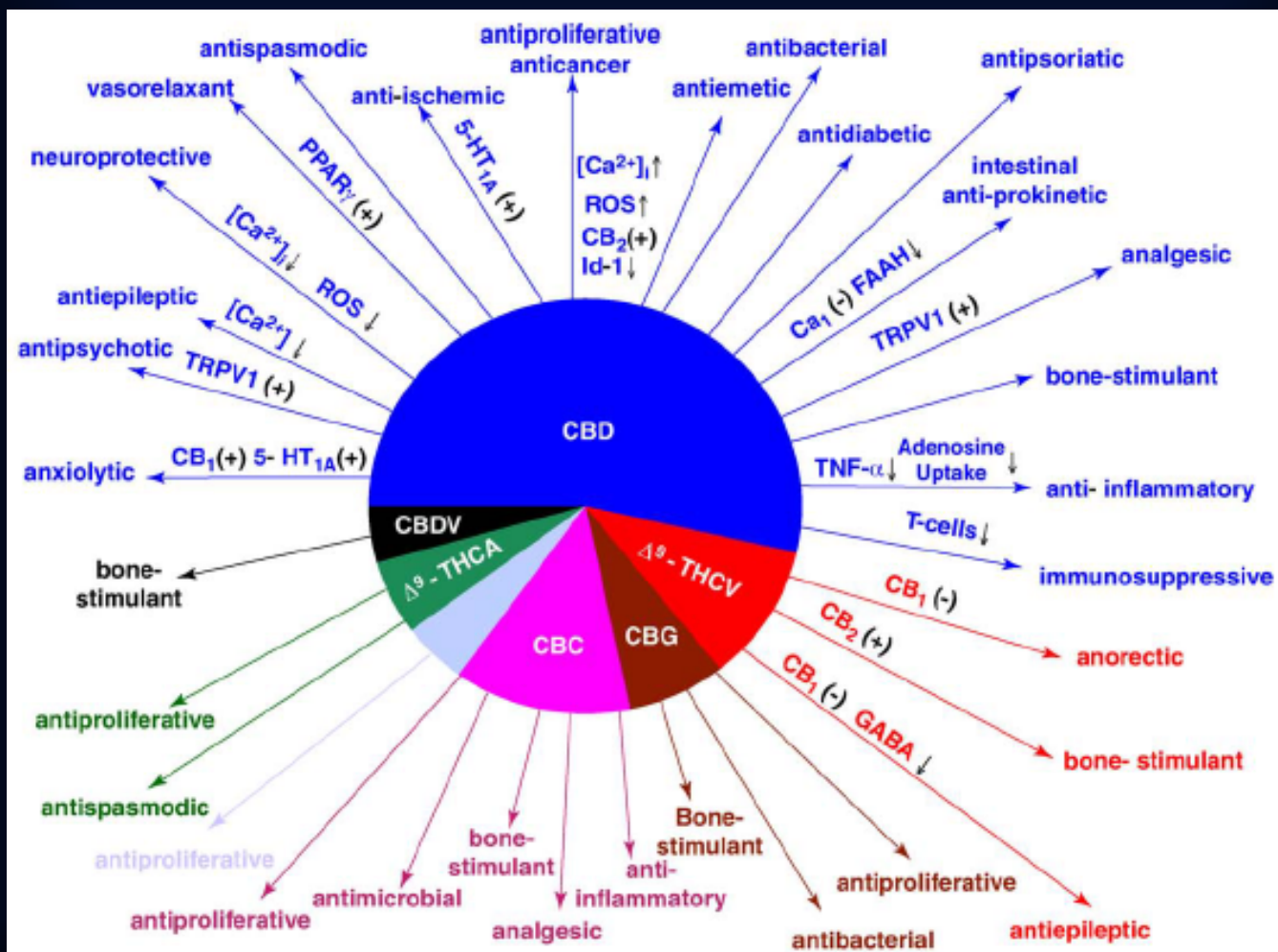
- ➔ **8 Dropouts, e.g. panic attack**
- ➔ **„Intrusive Symptoms“: 51% improvement after 2 months**
- ➔ **„Avoident Symptoms“: 38%**
- ➔ **„Increased Arousal“: 43%.**



[Mashiah, 7th National Conf Cannabis Ther, Tucson 2012]



Non-Psychoactive Cannabinoids



[Izzo et al 2009]



Conclusions, Take-Home Messages (1)

- ➔ **The amazingly complex 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 3 options are: natural or synthetic cannabinoids (THC, CBD, CBG, ...), standardized Cannabis-based medicines (CMs) and synthetic non-cannabinoids.**
- ➔ **A challenge are the particular pharmacokinetic properties requiring optimized application forms and devices.**



Conclusions, Take-Home Messages (2)

Folk medicine, self-treatment without prescription:

- ➡ Access to Medical Cannabis with quality certificate
- ➡ Preferably using validated home recipes and harmless application forms, e.g. vaporizer.

Academic medicine, controlled treatment with prescription:

- ➡ Approved drugs (CMs)
- ➡ Medical Cannabis from licensed producers and suppliers, i.e. public pharmacies
- ➡ Pharmacopoeia monographs, such as „American Herbal Pharmacopoeia 2013“
- ➡ Optimized, patient-individualized formulations, such as „formula magistralis“, respecting GMP.



Conclusions, Take-Home messages (3)

- ➔ **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 re-medicinalization.**
- ➔ **Uncritical, non-controlled self-treatment with „Street Cannabis“ (no QC!) might be harmful, also risking patient's criminalization.**



Conclusions, Take-Home messages (4)

- ➡ **Despite its** very broad indication spectrum, **Cannabis is not an all-round and** miracle drug.
- ➡ **Preparations based on** THC and THC-type Cannabis **are** narcotics, **therefore should not 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.
- ➡ Today Cannabis is still a niche player, tomorrow hopefully a key player!



Vision and Postulate of IACM

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.**



Phytocannabinoids in Medicine: An Option !

