The Cannabinoids:
Looking Back and Ahead

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"….modulating endocannabinoid activity may have therapeutic potential in almost all diseases affecting humans,

including obesity/metabolic syndrome, diabetes and diabetic complications, neurodegenerative, inflammatory, cardiovascular, liver, gastrointestinal, skin diseases, pain, psychiatric disorders, cachexia, cancer, chemotherapy-induced nausea and vomiting, among many others."

Pacher and Kunos review, FEBS, 2013
Gan-zi-gun-nu – the drug that takes away the mind
Azallu – hand of ghost, poison of all limbs (neurological diseases?)
Qunnabu – used in religious rites
Phases of cannabinoid research

1. Phytocannabinoid research

2. Endocannabinoid research (anandamide and 2-AG)

3. Endogenous, anandamide-like compounds
Representative natural cannabinoids

cannabigerol (CBG) (Gaoni and Mechoulam, 1964)
cannabidiol (CBD) (Mechoulam and Shvo, 1963)
Δ⁹-tetrahydrocannabinol (Δ⁹-THC) (Gaoni and Mechoulam, 1964)
cannabinol (CBN) (Adams et al., 1940)
cannabichromene (CBC) (Claussen et al., 1966; Mechoulam and Gaoni, 1966)
cannabicyclol (CBL) (Crombie et al., 1968)
Mechoulam and Shvo: Tetrahedron 19, 2073 (1963)

Gaoni and Mechoulam: J.Amer.Chem.Soc. 86, 1646 (1964)
Entourage effect – enhancement of cannabinoid effects by non-cannabinoid compounds.

Thus, Cannabis indica differs from Cannabis sativa although their cannabinoid content may be the same.
THC medical actions:

Pain

Elimination of side effects of cancer chemotherapy

Post trauma
CBD actions
Epilepsy

Double blind.
Drug: CBD in capsules
Patients: 15 epileptic patients, who did not benefit from known antiepileptic drugs.
Dose: 200-300 mg/day for 4.5 months.
Results: 4 patients (out of 8) remained almost completely free of seizures.
  3 patients had partial improvement
  1 patient showed no improvement
Placebo patients: only one showed improvement

Cunha, Carlini, Mechoulam, 1980
Graft-versus-host disease

Graft-versus-host disease (GVHD) is a complication that can occur after a bone marrow transplant in which the newly transplanted donor cells attack the transplant recipient’s body.

M. Yeshurun et al., (2014) administered CBD (300mg/day) to 46 patients with hematological malignancies for 30 days and followed them for 8 months.
Chronic GVHD (after 100 days)

<table>
<thead>
<tr>
<th>Grade</th>
<th>101 patients control</th>
<th>46 patients (with CBD)</th>
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<tbody>
<tr>
<td>2-4 grade</td>
<td>46%</td>
<td>12%</td>
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<tr>
<td>3-4 grade</td>
<td>10%</td>
<td>5%</td>
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Schizophrenia
In a double-blind, anti-schizophrenia clinical trial of CBD vs amisulpride (a potent antipsychotic) both treatments led to significant clinical improvement, but CBD displayed a superior side effect profile. Moreover, CBD treatment was accompanied by a significant increase in serum anandamide levels (Leweke et al., 2012)
Diabetes type 1
Histological analysis of pancreas tissue from mice treated with CBD and untreated.

Untreated: 5% intact cells
CBD: 77% intact cells
<table>
<thead>
<tr>
<th>Brain regions in which cannabinoid receptors are abundant</th>
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<tbody>
<tr>
<td><strong>Basal ganglia</strong></td>
</tr>
<tr>
<td>Substantia nigra pars reticulata</td>
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<tr>
<td>Enteropeduncular nucleus</td>
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<tr>
<td>Globus pallidus</td>
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<tr>
<td>Putamen</td>
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<tr>
<td><strong>Cerebellum</strong></td>
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<tr>
<td>Body-movement coordination</td>
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<tr>
<td><strong>Hippocampus</strong></td>
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<tr>
<td>Learning and memory, stress</td>
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<tr>
<td><strong>Cerebral cortex</strong>, especially cingulate, frontal, and parietal regions</td>
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<tr>
<td>Higher cognitive function</td>
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<tr>
<td><strong>Intrabulbar anterior commissure</strong></td>
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<tr>
<td>Link between cerebral hemispheres</td>
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<tr>
<td><strong>Nucleus accumbens</strong></td>
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<tr>
<td>Reward pathway</td>
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Δ⁹-tetrahydrocannabinol (Δ⁹-THC)

anandamide

2-arachidonoyl glycerol (2-AG)

Physiological systems and conditions affected by cannabinoids (a partial list)

Anxiety
Appetite/feeding
Blood pressure
Bone formation
Cerebral blood flow
Digestive system
Emesis and nausea
Immune system

Inflammation
Memory
Mood
Movement
Neuroprotection
Pain
Reproduction
Stress
Neuroprotection
Levels of 2-AG in mouse brain after CHI

Anova with Tukey post-test: P<0.0001, F=36.01

- ★★★ P<0.001 vs. control
- ★★ P<0.01 vs. control
- ★ P<0.05 vs. control

Nature 413, 527 (2001)
2-AG Reduces Infarct Volume 24 h After CHI

2-AG

control

unpaired t-test, P=0.03
Role of CB2 receptor signaling in disease

Myocardial infarction

Atherosclerosis

Stroke

Liver fibrosis

Rheumatoid arthritis

Neurodegenerative diseases

Pain
Brain injury

- Glutamate, cytokines, ROS
- Neuronal & glial cell death
- Cerebral ischemia
- Vasoconstrictors (e.g., ET-1, Thromboxane)

2-AG

Cerebroprotection
Regulation of vasodilation
anandamide

2-arachidonoyl glycerol (2-AG)

arachidonoyl serine
Bone Remodeling
arachidonyl ethanolamide (anandamide)

oleoyl serine (HU-639)

PNAS, 2010
Oleoyl Serine Rescues Ovariectomy-induced Bone Loss

- **Day 0**: OVX
- **Day 42**: OS treatment (5 mg/Kg/day)
- **Day 84**: Analysis

Bar graph showing BV/TV (%) with the following comparisons:
- Sham OVX vs OVX/VEH: p = 0.065
- Sham OVX vs OVX/OS: p = 0.017

Legend:
- Sham OVX
- OVX/VEH
- OVX/OS
Oleoyl glycine blocks nicotine addiction in mice and (possibly) in addicted humans.
SUMMARY

1. Endocannabinoids are involved in a large number physiological processes. THC – a plant cannabinoid – mimics their actions.

2. CBD derivatives – may lead to a wide spectrum of novel drugs.

3. Endocannabinoid-like compounds may lead to better understanding of biological processes as well as to novel drugs.

4. CB₂ specific agonists – may lead to a wide spectrum of novel drugs. May be part of a general protective system.
Collaboration in Israel

Jerusalem

Prof. L. Hanuš
Prof. E. Fride
Dr. W. A. Devane
Dr. A. Breuer
Dr. S. Ben-Shabat
Dr. D. Panikashvili
Dr. G. Milman
Dr. N. Kogan

Jerusalem

Prof. I. Bab
Prof. E. Shohami
Prof. R. Gallily
Prof. E. Berry
Dr. R. Durst

Haifa

Prof. A. Mandelbaum

Rehovot

Prof. Z. Vogel

Tel Hashomer

Dr. S. Almog
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<th>Collaboration abroad</th>
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<td><strong>Aberdeen</strong></td>
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<tr>
<td>R. Pertwee</td>
</tr>
<tr>
<td><strong>Bonn</strong></td>
</tr>
<tr>
<td>M. Karsak</td>
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<tr>
<td>A. Zimmer</td>
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<tr>
<td><strong>Brno</strong></td>
</tr>
<tr>
<td>A. Šulcová</td>
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<tr>
<td><strong>Greece</strong></td>
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<tr>
<td>C. Simeonidou</td>
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