Suche nach neuen Wirkstoffen: Wo liegt die Zukunft?

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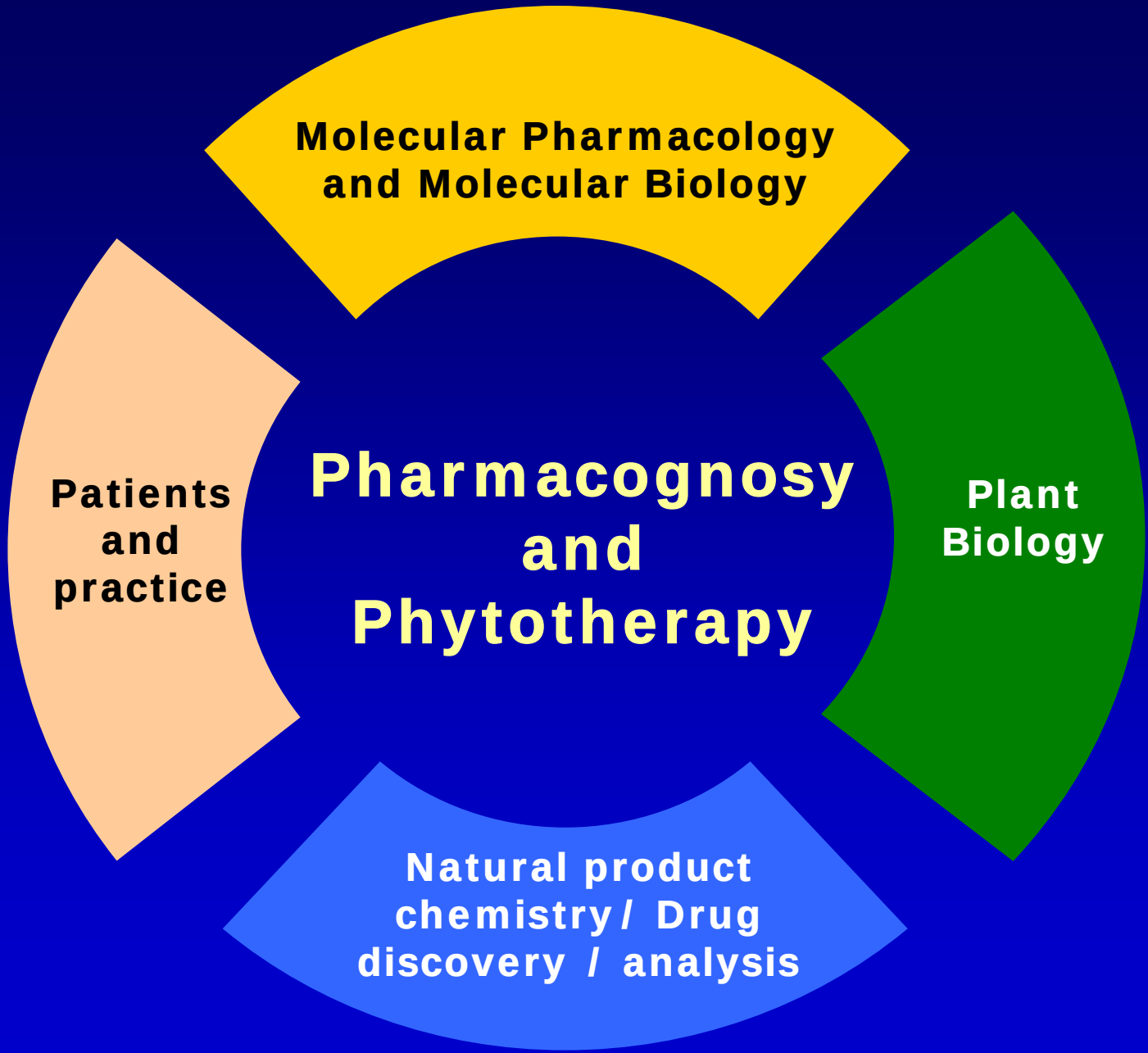

Molecular Pharmacology and Molecular Biology
Plant Biology
Natural product chemistry / Drug discovery / analysis
Patients and practice
Pharmacognosy and Phytotherapy

New drugs from old medicines – Some examples from the 19th century

- *1804 - Morphine* from opium poppy (*Papaver somniferum*, Papaveraceae) first identified by F.W. Sertürner (Germany), It took until 1817 to chemically characterise it as an alkaloid. The structure was established in 1923, by J.M. Gulland & R. Robinson,
- 1817 - *Emetine* from ipecacuanha (*Cephaelis ipecacuanha*, Rubiaceae) was fully characterised as late as 1948 and used as an emetic as well as in cough medications
- 1817 - *Strychnine* from *Strychnos* spp., Loganiaceae, used as a tonic and stimulant
- 1820 – *Quinine*, first isolated by Pierre Joseph Pelletier & Joseph Bienaime Caventou of France. The structure elucidated in the 1880's by various laboratories

Established medicines derived from local and traditional knowledge

- *Digitalis purpurea* → *Digitoxin*
- *Papaver somniferum* → *codeine, morphine, papaverine*
- Vinca alkaloids (vincristine, vinblastine) from *Catharanthus roseus* used in the treatment of various cancers (esp. leukaemia)
- *Taxol from the American yew tree (Taxus brevifolia)* used in the treatment of various cancers
- Derivatives of tubocuraine from South American arrow poisons (e.g. *Chondrodendron* spp) used as a muscle relaxant
- Galanthamin from snowdrop (*Leucojum* spp.) and related plants used against Alzheimer's disease
- Aspirin derived from *Salix* and *Filipendula* species…….

The Shield of the School of Pharmacy, University of London

New Medicines

- "Artemisinin, triptolide, celastrol, capsaicin, and curcumin are "poster children" for the power and promise of turning traditional medicines into modern drugs. However, their stories highlight the ongoing interdisciplinary research efforts that continue to be necessary to realize the pharmaceutical potential of traditional therapeutics" (Corson and Crews 2007).

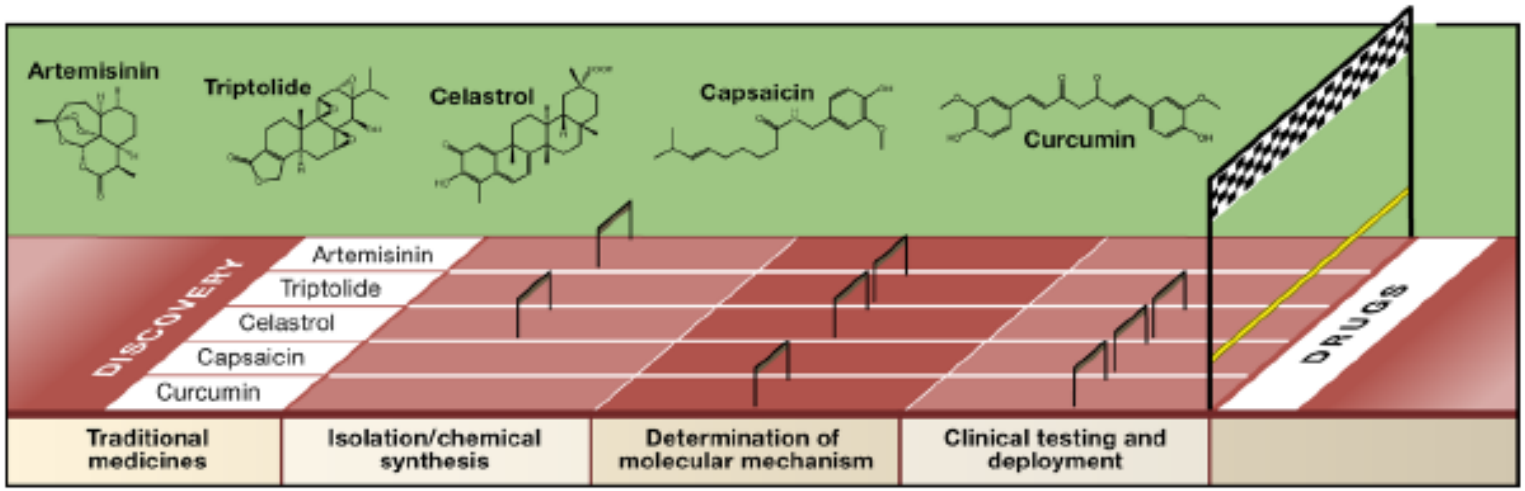
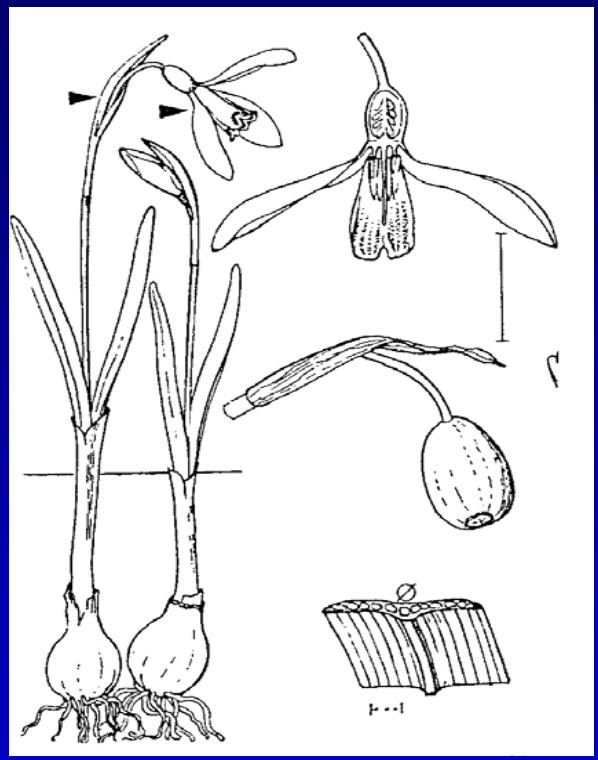
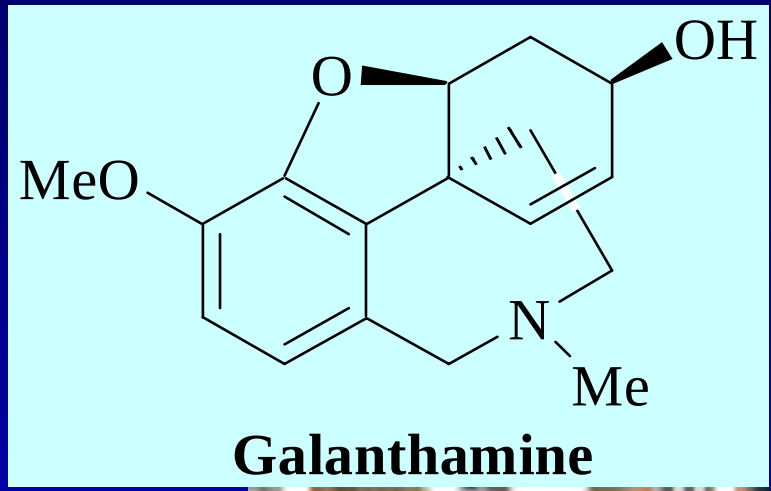


Figure 1. The Route from Traditional Medicine to Modern Drug
Shown are five traditional medicines—artemisinin, triptolide, celastrol, capsaicin, and curcumin—and the points in the pathway from ancient remedy to modern drug where they face the biggest hurdles.

Corson, T. W. and C. M. Crews (2007) Molecular Understanding and Modern Application of Traditional Medicines: Triumphs and Trials. *Cell* 130: 769-774

Pure natural Products as Pharmaceuticals: Galanthamine - a drug for Alzheimer's disease





Galanthamine

Heinrich, M. and H.L. Teoh (*2004) Galanthamine from snowdrop – the development of a modern drug against Alzheimer's disease from local Caucasian knowledge. Journal of Ethnopharmacology 92: 147 – 162. (doi:10.1016/j.jep.2004.02.012)

Heinrich, M. (2005) Galantamin – Vom Schneeglöckchen zum Alzheimer Medikament. Pharmazeutische Zeitung 150: 20 – 25.

The drug's history 1

Early 1950s: According to unconfirmed reports. a Russian pharmacologist discovers that local villagers living at the foot of Ural mountain use wild Caucasian snowdrop to treat (what he considers to be) poliomyelitis in children.

1951:Maskovsky and Kruglikova-Lvova demonstrate GAL's (galanthamine's) AChE inhibiting properties and its antagonising efects on curare's action

1952 GAL first described from *Galanthus woronowii*.

1956/7: Suggestions for alternative sources of GAL incl. the leaves of *Narcissus* spp. and *Galanthus nivalis* as well as *Leucojum aestivum* (the main source of GAL in the Eastern European countries until its introduction onto the Western pharmaceutical market)

The drug's history 2

Late 1950s: Various pre-clinical studies on the pharmacology of GAL were carried out. GAL registered under the trade name "Nivalin" and commercially available in Bulgaria for treating poliomyelitus

1960s: The first data on anticholinesterase activity of GAL was reported from an *in vivo* study (anaesthetised cat.

1980s: Preclinical development: Researchers searching for novel treatments of Alzheimer's disease started investigating the therapeutic effects of galanthamine.

The drug's history 3

1990s: Clinical development of GAL into a medication for Alzheimer's disease

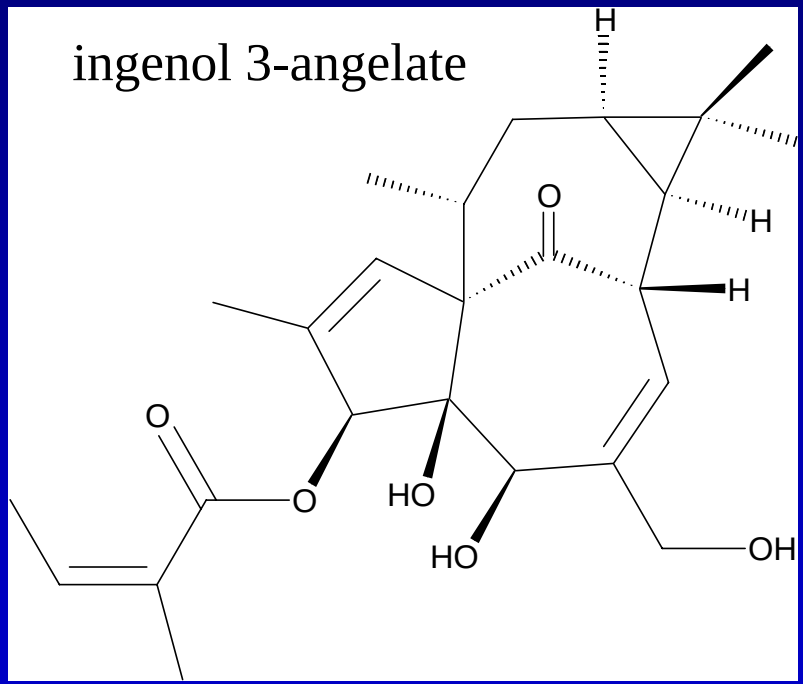
1996: Sanochemia Pharmazeutika obtained the first patent on the synthetic process of galanthamine.

1997: Sanochemia began collaboration with a Belgium based company (Janssen Pharmaceutica) and an emerging British Company (Shire Pharmaceuticals Group plc).

2000: GAL licensed in the first countries (Iceland, Ireland, Sweden, UK) for the treatment of Alzheimer's Disease

Currently (2003 - …..): GAL has been approved for use in the United States, many European countries and some Asian countries, but the UK's NICE does not consider it cost effective since it is a symptomatic treatment

Peplin from *Euphorbia peplus:*
'Indigenous' Knowledge and Drug Discovery



http://flora.nhm-wien.ac.at/Seiten-Arten/Euphorbia-peplus.htm

Heinrich, M. (2008) Ethnopharmacology and drug development. Invited MS for Comprehensive Natural Products Chemistry II (EDITORS-IN-CHIEF: Lewis N. Mander, Australia and Hung-Wen (Ben) Liu, USA Volume 6: Discovery, Development and Modification of Bioactivity. Volume Editor: Robert Verpoorte

Peplin from *Euphorbia peplus*

- Peplin Ltd, currently develops ingenol 3-angelate (or PEP005), an unusual diterpene ester isolated from *Euphorbia peplus* or petty spurge (Euphorbiaceae), a weedy plant originally from temperate Europe
- *E. peplus* is common in disturbed habitats and a garden weed. In Europe and, for example, Morocco
- Most advanced are studies on the topical use for treating actinic keratoses and non-melanoma skin cancer. IN addition it is develop for intravesicular treatment of bladder cancer and, lastly, systemically agains leukaemia.
- It was very widely used especially in the treatment of warts and other skin conditions. The species was introduced into Australia and in many other temperate countries.
- During the 1970'ies and 80'ies a significant numbers of the Australian public used the sap from *E. peplus* to treat skin cancers and solar keratoses

Peplin from *Euphorbia peplus*

- Ingenol 3-angelate (PEP005) had an initial LD90 of 180 – 220 against a range of human and mouse cell lines. *In vivo* experiments using various tumours transplanted into mice indicated that a topical application for three days of 42 nmol formulated as an isopropanol-based gel was the most effective. The compound induced an acute erythrema.
- Mechanistic studies indicated a rapid disruption of the plasma membrane, swelling of mitochondria and cell death via primary necrosis. Experimental evidence exists that at a second stage a neutreophil-mediated antibody –dependent cellular toxicity plays an important role.
- *In vitro* it has potent antileukemic effects in a large number of cell lines, inducing apoptosis in myeloid leukemia cell lines and primary acute myeloid leukemia cells at nanomolar concentrations[v].
- It was then established that this activity is correlated with expression of PKC-δ Interestingly it induced a translocation pattern of PKC-δ different from the one of the well known tumour co-promotot PMA (Phorbol 12-myristate-13-acetate (also known as PTA). At low concentrations (10 nmol/ml) ingenol 3-angelate induces a rapid translocation of PKC-δ simultaneously to the internal membranes and the nuclear membranes.
- Phase III clinical trials of topical use are planned. This example offers some amazing insights into the

Extractor for herbal medical products, W. Ransom, Hitchin, UK, picture MH

Extracts as medicines

We know it, but how do we deal with it?

Aspirin tablets contain:

- Aspirin
- (excipients)

Tablets containing extract of St John's wort herb, contain:

- Hyperforin, adhyperforin, hypericin, pseudohypericin, isohypericin, protohypericin, protopseudohypericin, kaempferol, quercetin, luteolin, hyperoside, isoquercitrin, quercitrin, rutin, bi-apigenin, amentoflavone, catechins, tannins, other phenols etc.
- (excipients)

Medicinal *Cannabis* :

Developers

	Bedrocan The Netherlands	**GW Pharma** UK	**Cannabis CRAFT** European Consortium
Source	Germ Prop. Chemvars Indoor Production	Germ Prop. Chemvars Indoor Production	Seed Prop.Chemvars Outdoor production
Chemical profile	Δ^9-THC/CBD fixed ratios	Δ^9-THC /CBD ratios THCV /CBDV ratios	low content of Δ^9-THC Metabolomic approach
Therapeutical Application/s	Neuropathic Pain Cancer (Relief)	Neuropathic Pain Post-trauma Pain Anticonvulsant Arthritis Bowel Infl. Dis. Psicotic disorders	Arthritis Migraine
Final Product	Crude Drug (smoked/ingested)	Oromucosal Spray	Oral and rectal formulations

What is needed for drug development in case of phytomedicines

• Clearly defined activity / activities	(mostly **yes**)
• Reproducible phytochemical profile of the *extract* or at least lead compounds for use as 'activity markers' for the final products / quality dossiers	Generally **no,** incomplete characterisation of many 'leads
• Reliable supply of material with the above profiles	**No** (often no legal supply)
• Demonstrated safety	Controversial
• Acceptance by consumer	**Possibly**
• For full licensing: Demonstration of efficacy	**Partially**

In vitro evaluation for anti-inflammatory effects – lead extracts based on effects on cell viability, TNF-alpha, IL6, NF-kappaB and other targets

Summary of In Vitro Assays

	ASSAY	UNITS	CONCENTRATION	CELL LINE	CBG 1-xH	CBG 2-xH	CBG 3-xH	CBD 1-xH
1	TNF induced NF-kB	% Inhibition	(25 µg/ml)	5.1	78.97	60.42	63.32	78.59
2	TNF induced NF-kB	% Inhibition	(10 µg/ml)	SW982-KBF-Luc	18.54	5.13	15.6	25.18
3	TNF induced NF-kB	% Inhibition	(100 µg/ml)	SW982-KBF-Luc	78.3	83.98	83.89	60.62
4	Cell viability	%Cell viability	(25 µg/ml)	5.1	78.2	83.2	80.1	84.6
5	Dox induced Luciferase	% Inhibition	(25 µg/ml)	Hela TET-ON-Luc	-5.01	-28.1	-49.15	*ND*
6	Cell viability	% Cell viability	(25 µg/ml)	AGS	78.45	85.47	51.33	34.43
7	TNF induced p65 phosphorylation	% Inhibition	(100 µg/ml)	SW982	85	34	53	92
8	TNF induced p38 phosphorylation	% Inhibition	(100 µg/ml)	SW982	58	55	-36	60
9	TNF induced IkB phosphorylation	% Inhibition	(100 µg/ml)	SW982	94	-220	-224	88
10	TNF induced IkB degradation	Fold recovery	(100 µg/ml)	SW982	1.88	3.14	2.62	0.78
11	TNF induced ERK phosphorylation	% Inhibition	(100 µg/ml)	SW982	-52	-209	-187	-110
12	TNF induced c-JUN phosphorylation	% Inhibition	(100 µg/ml)	SW982	-0.1	12	-60	0
13	LPS induced IL1 release	% Inhibition	(10 µg/ml)	Human Monocytes	76.00	76.00	70.00	87.00
14	LPS induced IL1 release	% Inhibition	(100 µg/ml)	Human Monocytes	97.04	97.98	97.47	97.80
15	LPS induced TNF release	% Inhibition	(10 µg/ml)	Human Monocytes	39.00	33.00	36.00	19.00
16	LPS induced TNF release	% Inhibition	(100 µg/ml)	Human Monocytes	98.28	99.55	95.35	99.10
17	LPS induced IL6 release	% Inhibition	(10 µg/ml)	Human Monocytes	70.00	70.00	63.00	77.00
18	LPS induced IL6 release	% Inhibition	(100 µg/ml)	Human Monocytes	98.12	92.63	95.54	98.20
19	LPS induced IL8 release	% Inhibition	(10 µg/ml)	Human Monocytes	58.00	49.00	49.00	44.00
20	LPS induced IL8 release	% Inhibition	(100 µg/ml)	Human Monocytes	93.37	94.05	97.98	95.90
21	LPS induced PGE2 release	% Inhibition	(10 µg/ml)	Human Monocytes	73.00	72.00	81.00	42.00
22	LPS induced PGE2 release	% Inhibition	(100 µg/ml)	Human Monocytes	86.42	81.46	87.67	29.40

Summary	16	14	12	12
Extra Points (see explanation below)	18	18	14	15
Ranking (biolgical)	1	3	4	2
Ranking (extract production)	4	2	1	5

Calzado, M; Schmitz, ML,(Giessen); Fiebich B (Freiburg), Prieto, J; Heinrich, M. et al

In vitro evaluation for anti-inflammatory effects – lead extracts based on effects on cell viability, TNF-alpha, IL6, NF-kappaB and other targets

Summary of In Vitro Assays

The project identified a series of lead extracts with reproducible in vitro anti-inflammatory activity

Summary				16	14	12	12
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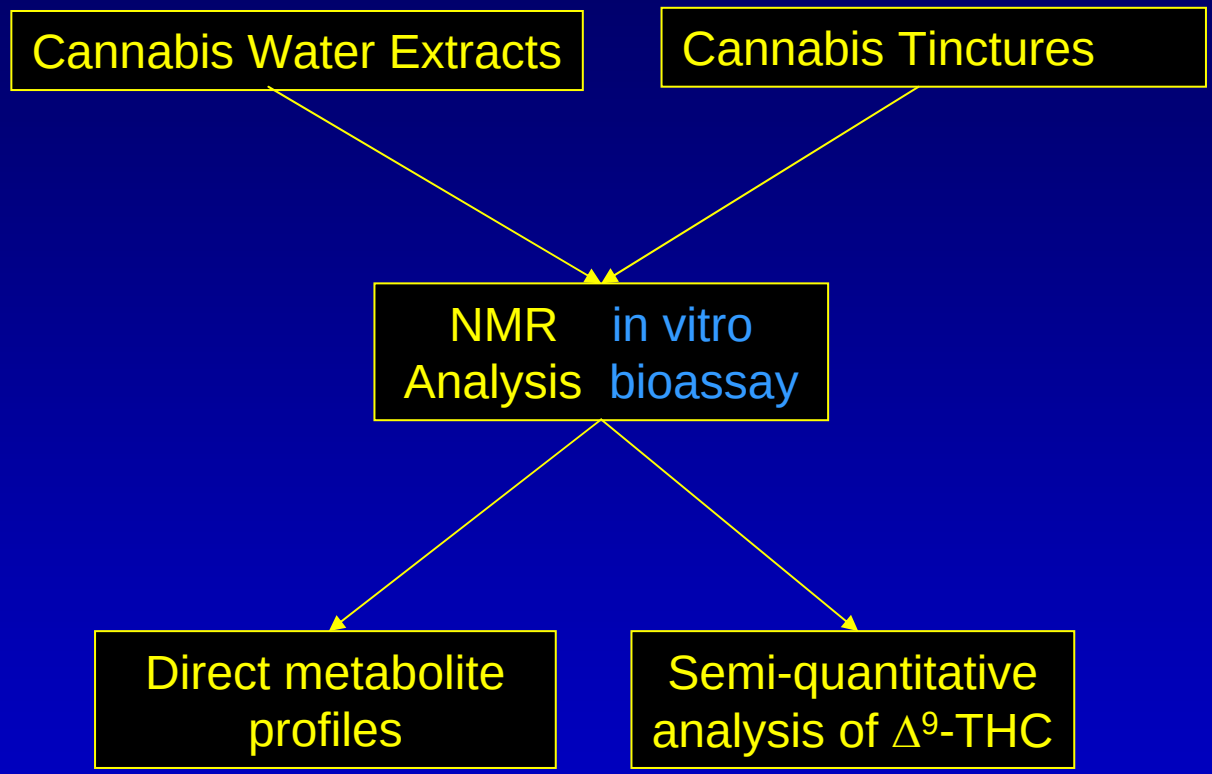
Calzado, M; Schmitz, ML,(Giessen); Fiebich B (Freiburg) et al unpublished

Assessing Extracts – A Metabolomic strategy

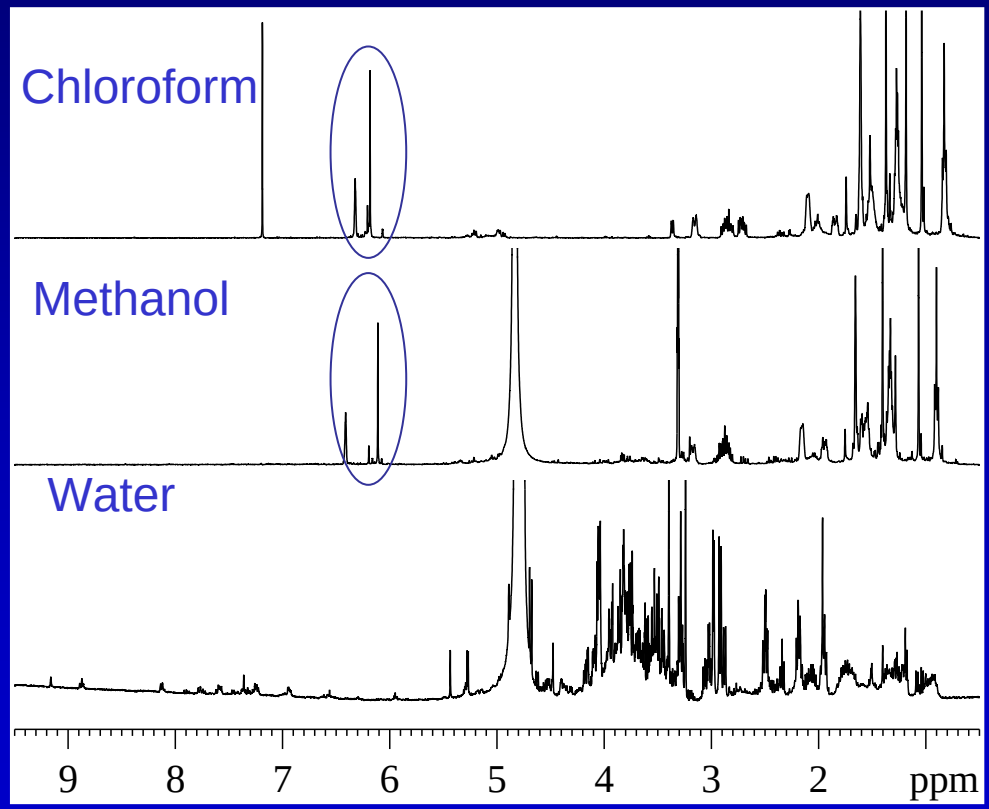


Hot and cold water extracts as well as ethanol/water mixtures (tinctures) of cannabis were compared in order to better understand how these extracts differ in their overall composition using NMR analysis and *in vitro* cell assays

Politti et al. 2008. Phytochemistry 69: 562–570

NMR analysis of Cannabis extracts

- 1H NMR spectra of three extracts obtained from three aliquots of THC-rich cannabis material after maceration in deuterated chloroform, methanol and water.
- The typical cannabinoid proton signals of the extracts in chloroform and methanol emerge in particular in the NMR region between 6-6.5 ppm mostly due to Δ9-THC (**1**) and Δ9-THC-acid (**2**)



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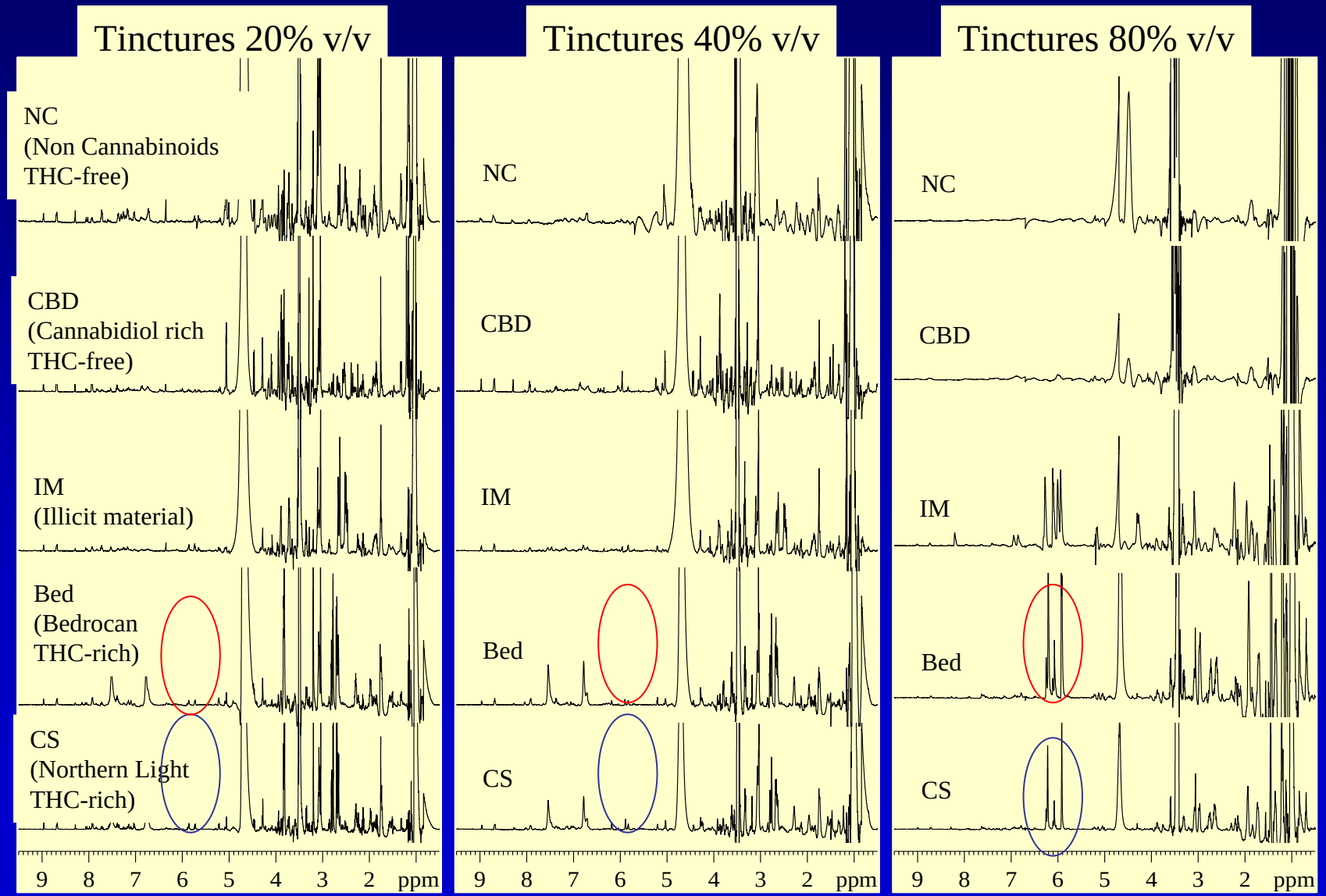
Comparison of three tinctures (20%, 40% and 80% v/v) from five different cannabis cultivars



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Comparison of three tinctures (20%, 40% and 80% v/v) from five different cannabis cultivars

Metabolomic techniques offer unique and state of the art tools for assessing complex extracts (and their effects on the human body), but industrial applications still need to be developed