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BOLOGNA 25-26-27 Ottobre 2021

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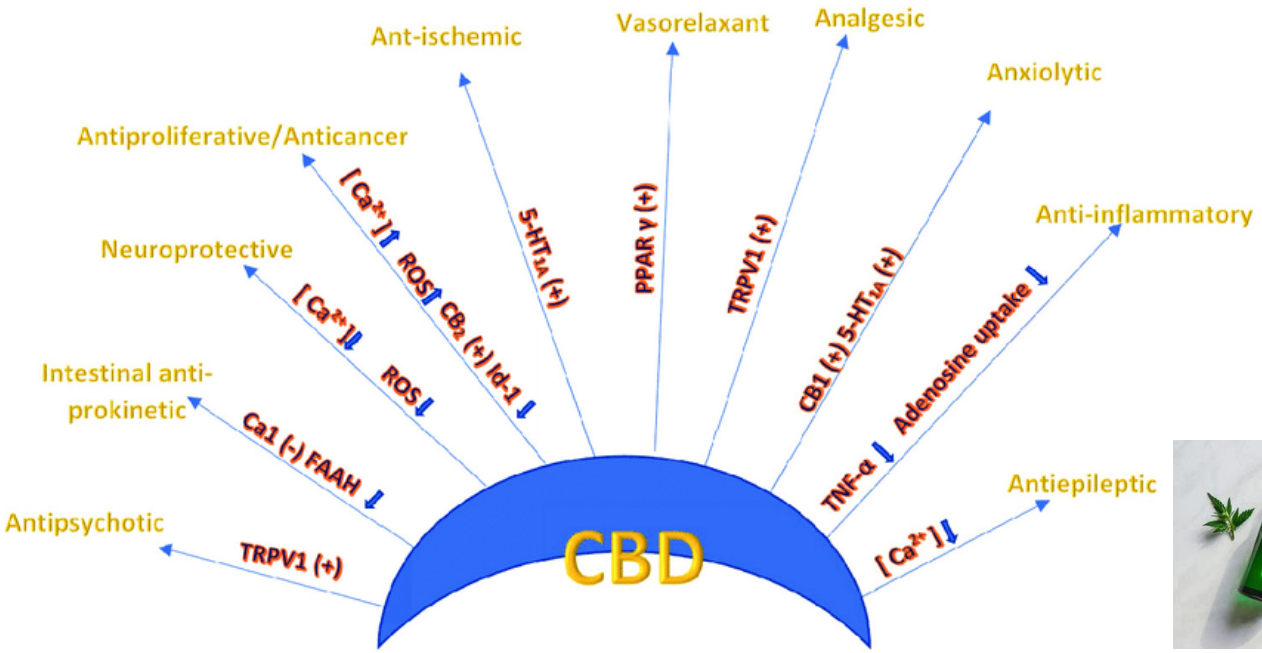
Cannabidiolo (CBD): sostanza realmente sotto controllo? L'origine fa la differenza

Cinzia Citti
cinzia.citti@nanotec.cnr.it
Istituto di Nanotecnologia del Consiglio Nazionale delle Ricerche – CNR NANOTEC Lecce

CNR NANOTEC ISTITUTO DI NANOTECNOLOGIA

UNIMORE UNIVERSITÀ DEGLI STUDI DI MODENA E REGGIO EMILIA

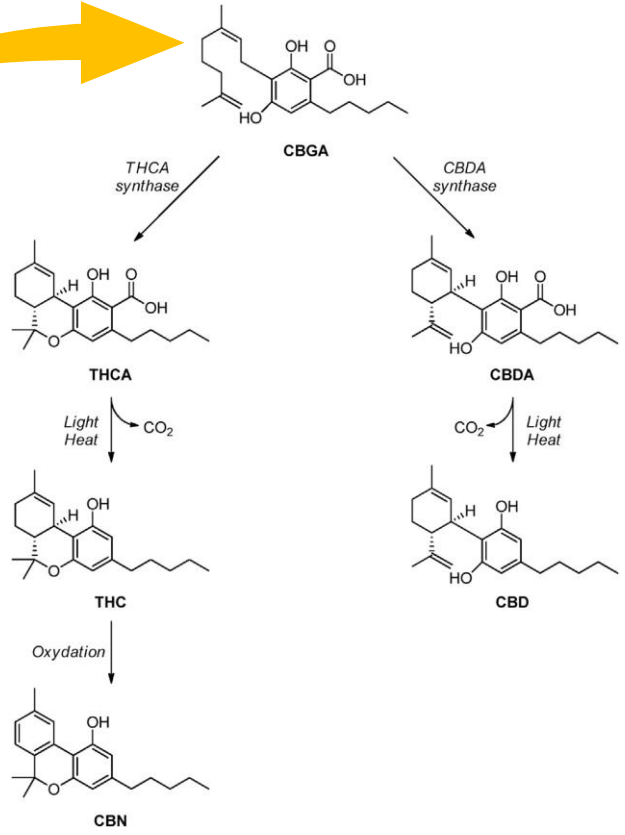
CBD pharmacologocal properties



CBD in nutraceutica

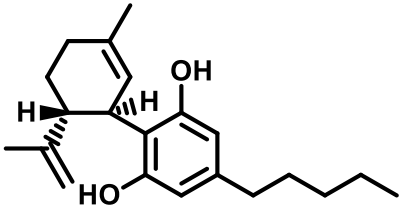
N. Noreen et al. *Crit. Rev. Eukaryot. Gene Expr.* 28 (2018) 73-86

Biosynthesis of phytocannabinoids in *Cannabis sativa* L.

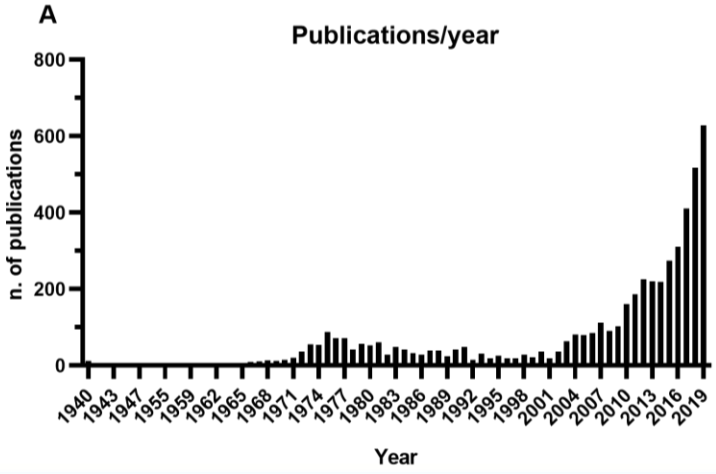


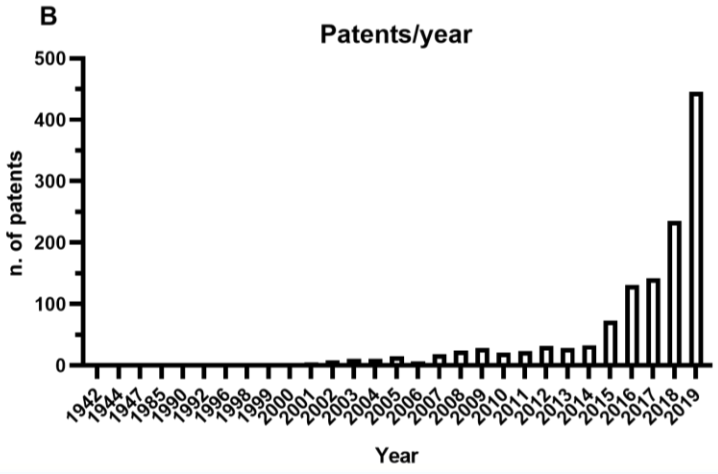
- ✓ The plant **ONLY** biosynthesizes the **carboxylated** forms of **cannabinoids** in the glandular trichomes of female inflorescences (CBGA, THCA, CBDA, etc.)
- ✓ **ONLY a chemical reaction** triggered by heat and/or light converts the acidic precursors into the corresponding decarboxylated counterparts (CBG, THC, CBD, etc.)

Scientific and industrial interest for CBD



EPIDIOLEX® (CBD 100 mg/mL)
Dravet syndrome, Lennox-Gastaut syndrome, Tuberous Sclerosis Complex, and Infantile Spasms



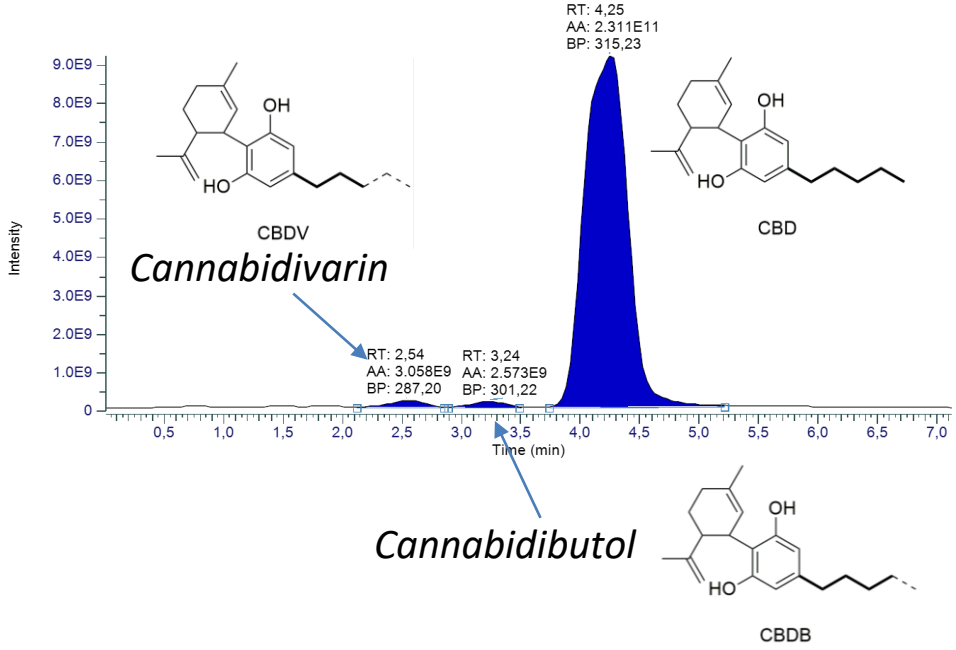


Extracted and synthetic CBD: where is the difference?

Synthetic CBD

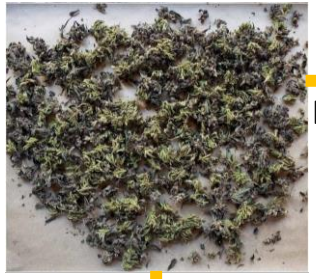
No trace of impurities

Extracted CBD



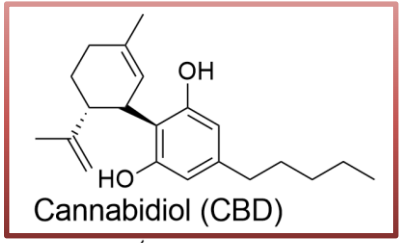
Extracted CBD: where do the impurities come from?

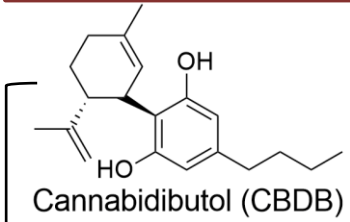
Decarboxylated inflorescence

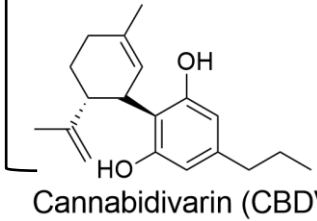


Extraction

Main product





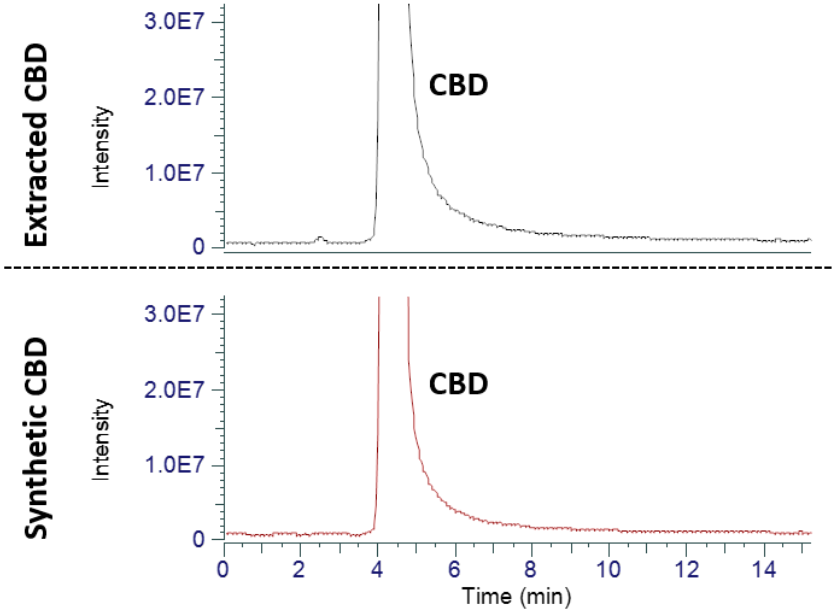


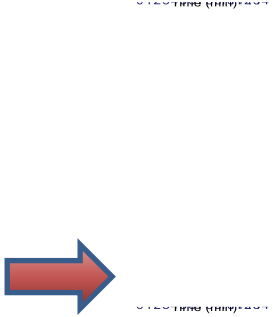
Major impurities

Fresh inflorescence

Extracted CBD: where do the impurities come from?

What about potential THC traces in CBD?





CBD

Δ^8-THC

Δ^9-THC

CBD

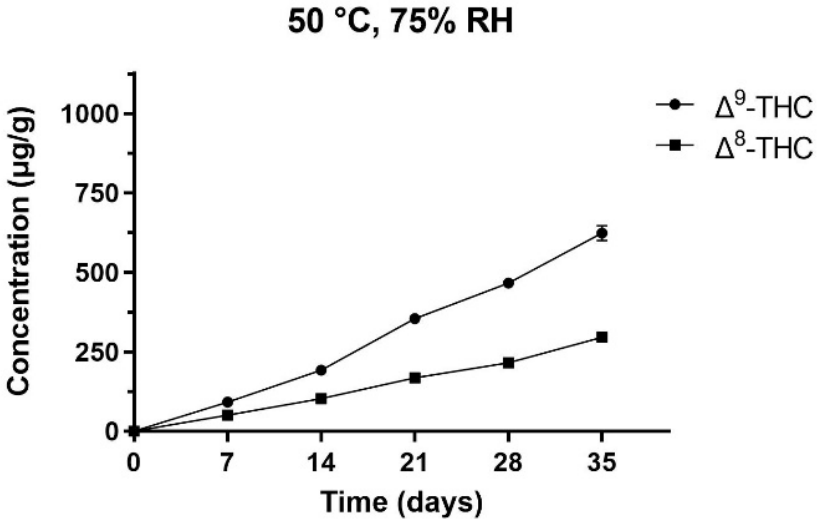
<0.1%

Δ^8-THC

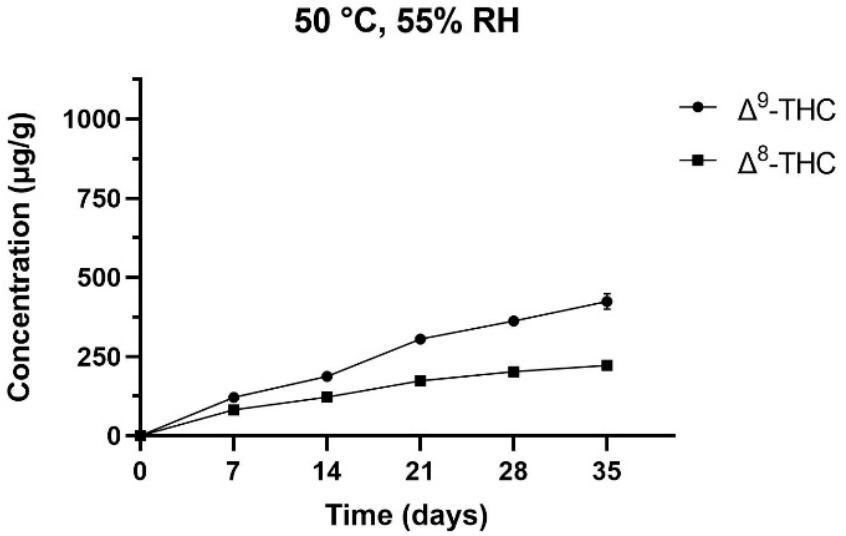
Δ^9-THC

3 months at room temperature in the dark

What causes CBD conversion into THC?

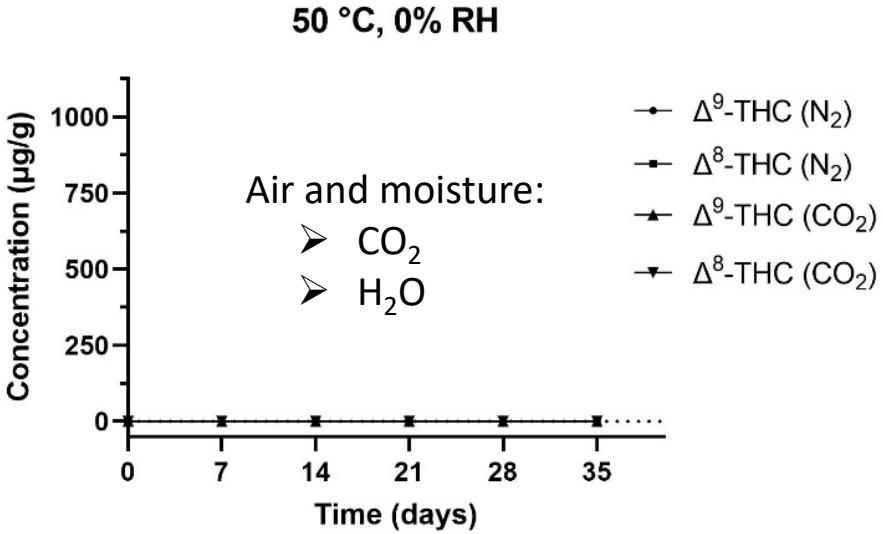


0.09%



0.06%

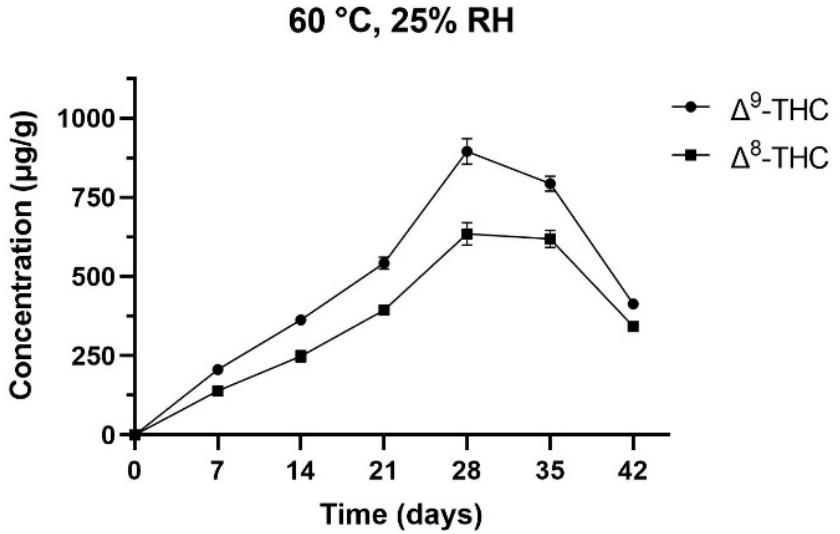
What causes CBD conversion into THC?



Air and moisture:

- CO_2
- H_2O

0%



0.15%

High temperatures accelerate the process

CBD conversion into THC *in vivo*

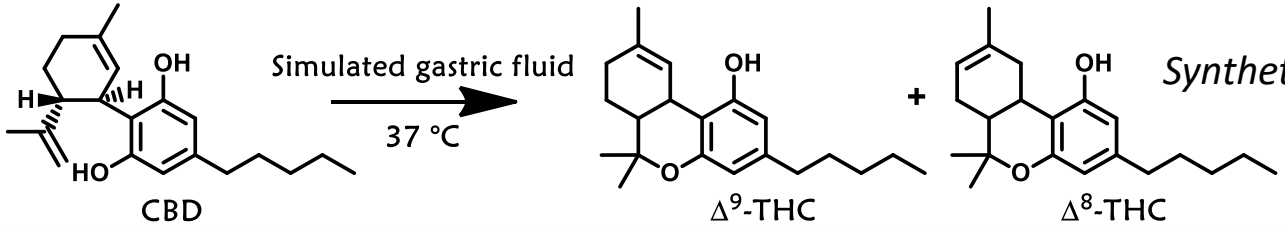
Cannabis and Cannabinoid Research
Volume 1.1, 2016
DOI: 10.1089/can.2015.0004

Cannabis and Cannabinoid Research
Mary Ann Liebert, Inc. publishers

ORIGINAL RESEARCH Open Access

Identification of Psychoactive Degradants of Cannabidiol in Simulated Gastric and Physiological Fluid

John Merrick,[1] Brian Lane,[1] Terri Sebree,[2,*] Tony Yaksh,[3] Carol O'Neill,[2] and Stan L. Banks[2]



CBD Δ^9-THC Δ^8-THC

Synthetic CBD was used

CBD conversion into THC *in vivo*

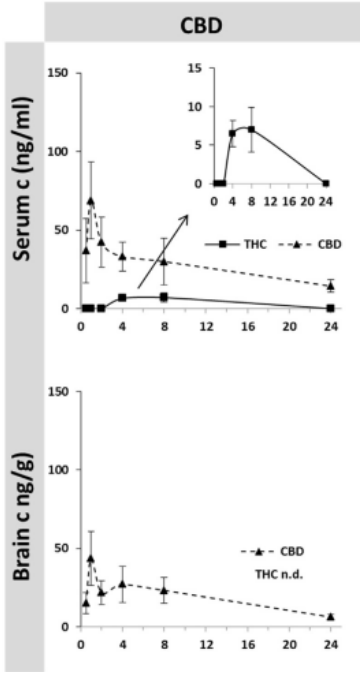
European Neuropsychopharmacology (2017) **27**, 1223-1237

ELSEVIER

www.elsevier.com/locate/euroneuro

Pharmacokinetic and behavioural profile of THC, CBD, and THC+CBD combination after pulmonary, oral, and subcutaneous administration in rats and confirmation of conversion *in vivo* of CBD to THC

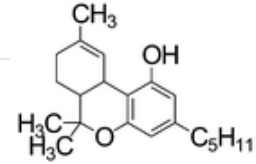
Tomáš Hložek[a,b], Libor Uttl[c,d], Lukáš Kadeřábek[c], Marie Balíková[a], Eva Lhotková[c], Rachel R. Horsley[c], Pavlína Nováková[c], Klára Šíchová[c], Kristýna Štefková[c], Filip Tylš[c], Martin Kuchař[c,e], Tomáš Páleníček[c,f,*]

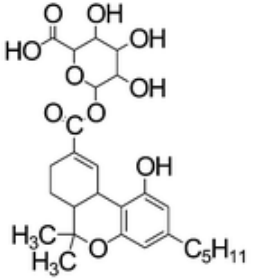


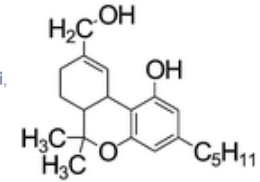
Synthetic CBD was used

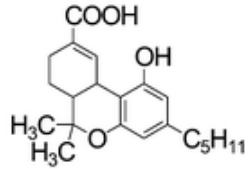
CBD conversion into THC *in vivo*

ELSEVIER
Journal of Pharmaceutical and Biomedical Analysis
Available online 28 November 2017
In Press, Accepted Manuscript — Note to users







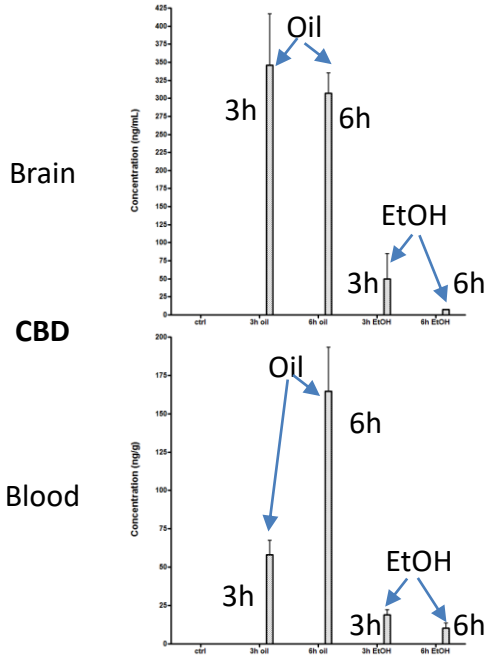


Development of a simple and sensitive liquid chromatography triple quadrupole mass spectrometry (LC-MS/MS) method for the determination of cannabidiol (CBD), Δ^9-tetrahydrocannabinol (THC) and its metabolites in rat whole blood after oral administration of a single high dose of CBD

Federica Palazzoli[a], Cinzia Citti[b, c], Manuela Licata[a], Antonietta Vilella[d], Letizia Manca[d], Michele Zoli[d], Maria Angela Vandelli[e], Flavio Forni[e], Giuseppe Cannazza[c, e]
[a] Dipartimento di Medicina Diagnostica, Clinica e di Sanità Pubblica, Università di Modena e Reggio Emilia, Largo del pozzo 71, 41125 Modena, Italy
[b] Dipartimento di Scienze e Tecnologie Biologiche ed Ambientali, Università del Salento, Via per Monteroni, 73100 Lecce, Italy
[c] CNR NANOTEC, Campus Ecoteckne dell'Università del Salento, Via per Monteroni, 73100 Lecce, Italy
[d] Dipartimento di Scienze Biomediche, Metaboliche e Neuroscienze, Università di Modena e Reggio Emilia, Via Campi 287, 41125 Modena, Italy
[e] Dipartimento di Scienze della Vita, Università di Modena e Reggio Emilia, Via Campi 103, 41125 Modena, Italy

Extracted CBD was used

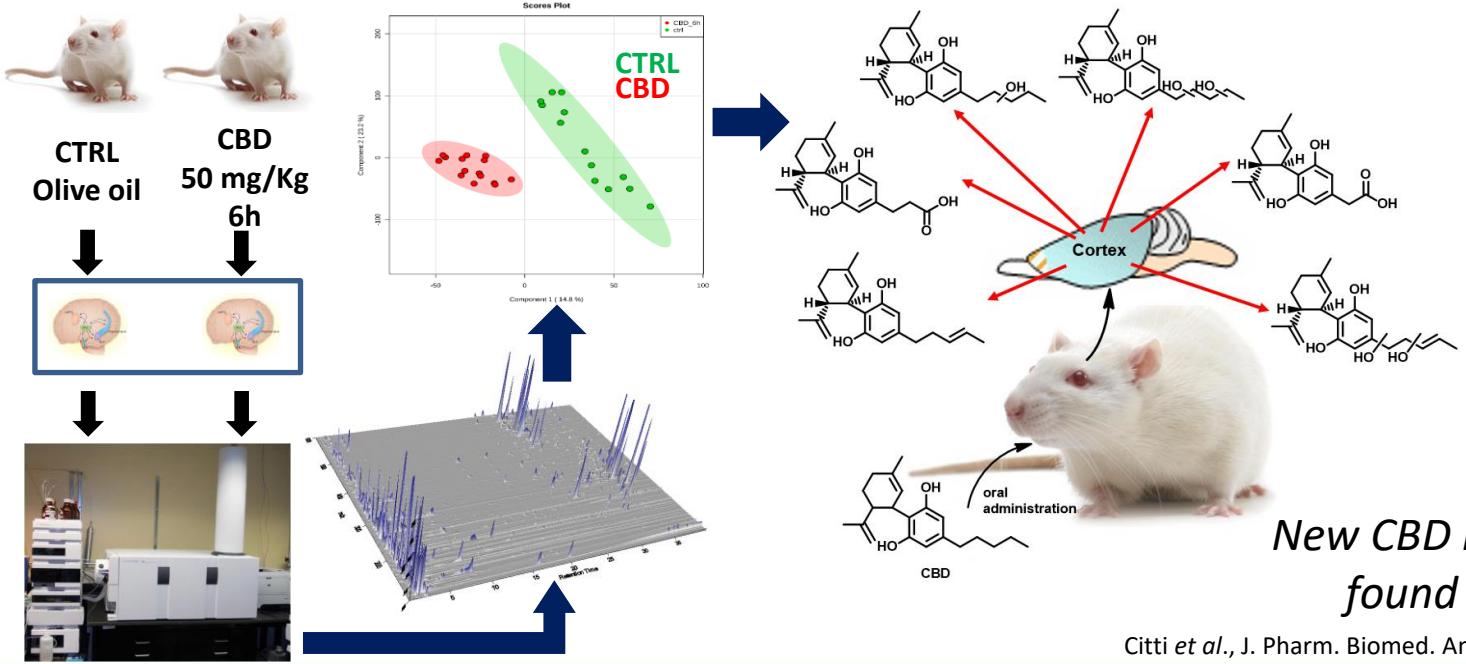
No conversion of CBD into THC *in vivo*



- Neither THC nor its metabolites were observed in blood or brain
- CBD blood and brain levels were higher when administered in olive oil than in EtOH
- Oral administration of CBD in EtOH may cause precipitation of the drug and poor bioavailability
- Olive oil may act as a shield from gastric fluids

Citti *et al.*, J. Pharm. Biomed. Anal. **2018**, *161*, 1-11

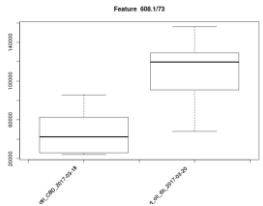
Beyond plant variability: *in vivo pharmacometabolomics*



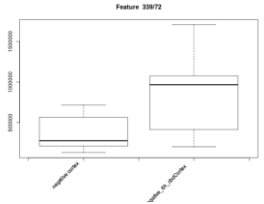
New CBD metabolites are found in the brain

Citti *et al.*, J. Pharm. Biomed. Anal. **2018**, *161*, 1-11

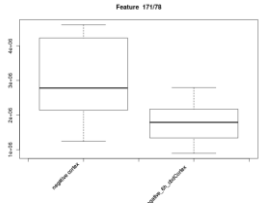
Dys-regulated endogenous substances after oral administration of a single high dose of CBD (50 mg/kg)



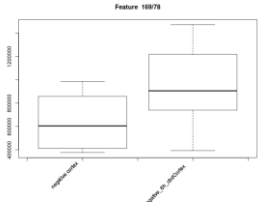
Uridine diphosphate-N-acetylglucosamine



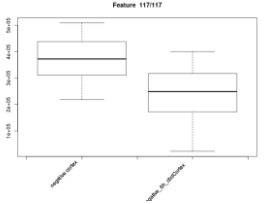
Fructose 1,6-diphosphate



Glycerol 3-phosphate



Dihydroxyacetone phosphate



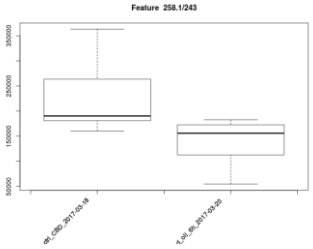
Succinic acid

GLUCOSE consumption

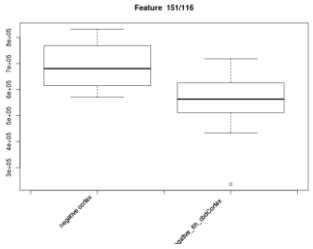
Hypoglycemic activity

Citti *et al.*, J. Pharm. Biomed. Anal. **2018**, *161*, 1-11

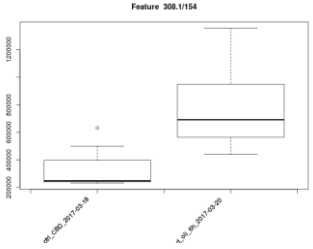
Dys-regulated endogenous substances after oral administration of a single high dose of CBD (50 mg/kg)



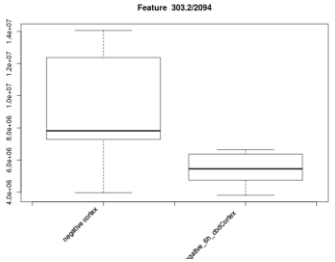
5-methylcytidine



Xanthine



Glutathione



Arachidonic acid

Antioxidant activity

Anti-inflammatory activity

Citti *et al.*, J. Pharm. Biomed. Anal. **2018**, *161*, 1-11

Available resources on CBD conversion into THC

1. J. Merrick et al. **Identification of Psychoactive Degradants of Cannabidiol in Simulated Gastric and Physiological Fluid**, *Cannabis and Cannabinoid Research* 1 (2016) 102-112.
2. T. Hložeket al. **Pharmacokinetic and behavioural profile of THC, CBD, and THC+CBD combination after pulmonary, oral, and subcutaneous administration in rats and confirmation of conversion *in vivo* of CBD to THC**, *Eur. Neuropsychopharmacol.* 27 (2017) 102-112.
3. G. Nahler et al. **A Conversion of Oral Cannabidiol to Delta9-Tetrahydrocannabinol Seems Not to Occur in Humans**, *Cannabis and Cannabinoid Research 2* (2017) 81-86.
4. L. Wray et al. **Cannabidiol Does Not Convert to Δ9-Tetrahydrocannabinol in an In Vivo Animal Model**, *Cannabis and Cannabinoid Research 2* (2017) 282-287.
5. F. Palazzoli et al. **Development of a simple and sensitive liquid chromatography triple quadrupole mass spectrometry (LC–MS/MS) method for the determination of cannabidiol (CBD), Δ9-tetrahydrocannabinol (THC) and its metabolites in rat whole blood after oral administration of a single high dose of CBD**, *J. Pharm. Biomed. Anal.* 161 (2018) 1-11.
6. J. A. S. Crippa et al. **Oral Cannabidiol Does Not Convert to Δ8-THC or Δ9-THC in Humans: A Pharmacokinetic Study in Healthy Subjects**, *Cannabis and Cannabinoid Research* 5 (2020) 89-98.
7. P. Golombek et al. **Conversion of Cannabidiol (CBD) into Psychotropic Cannabinoids Including Tetrahydrocannabinol (THC): A Controversy in the Scientific Literature**, *Toxics* 8 (2020) 41, https://doi.org/10.3390/toxics8020041.

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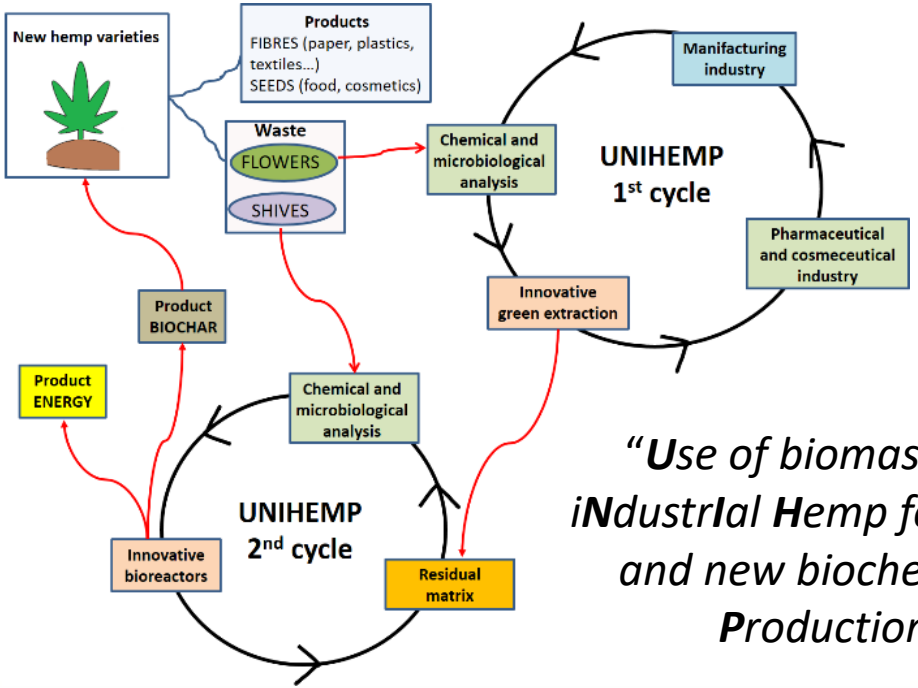

UNIHEMP Project

2019-2022

*"**U**se of biomass from i**N**dustr**I**al **H**emp for **E**nergy and new bioche**M**icals **P**roduction"*

Partners

Dhitech Scarl, CNR NANOTEC
Avantech Group Srl
Ekuberg Pharma Srl
CREA (Council for Agricultural Research and Economics)
Manifatture Sigaro Toscano
University of Modena e Reggio Emilia

Aknowledgements

Giuseppe Cannazza (Project leader, UNIMORE)

Fabiana Russo (Synthesis of new phytocannabinoids, UNIMORE)

Francesco Tolomeo (HPLC-HRMS analysis, CNR NANOTEC)

Pasquale Linciano (Synthesis of new phytocannabinoids, University of Pavia)

Livio Luongo (*In vivo* pharmacological activity of cannabinoids, University of Campania)

Aldo Laganà (Cannabinoids database, University of Rome)

Roberta Paris (Hemp biomass, CREA-CI – Research Centre of Cereals and Industrial Crops)

Thank you for the attention