Extraction, Isolation and Analysis of Cannabis Extract and Preparation

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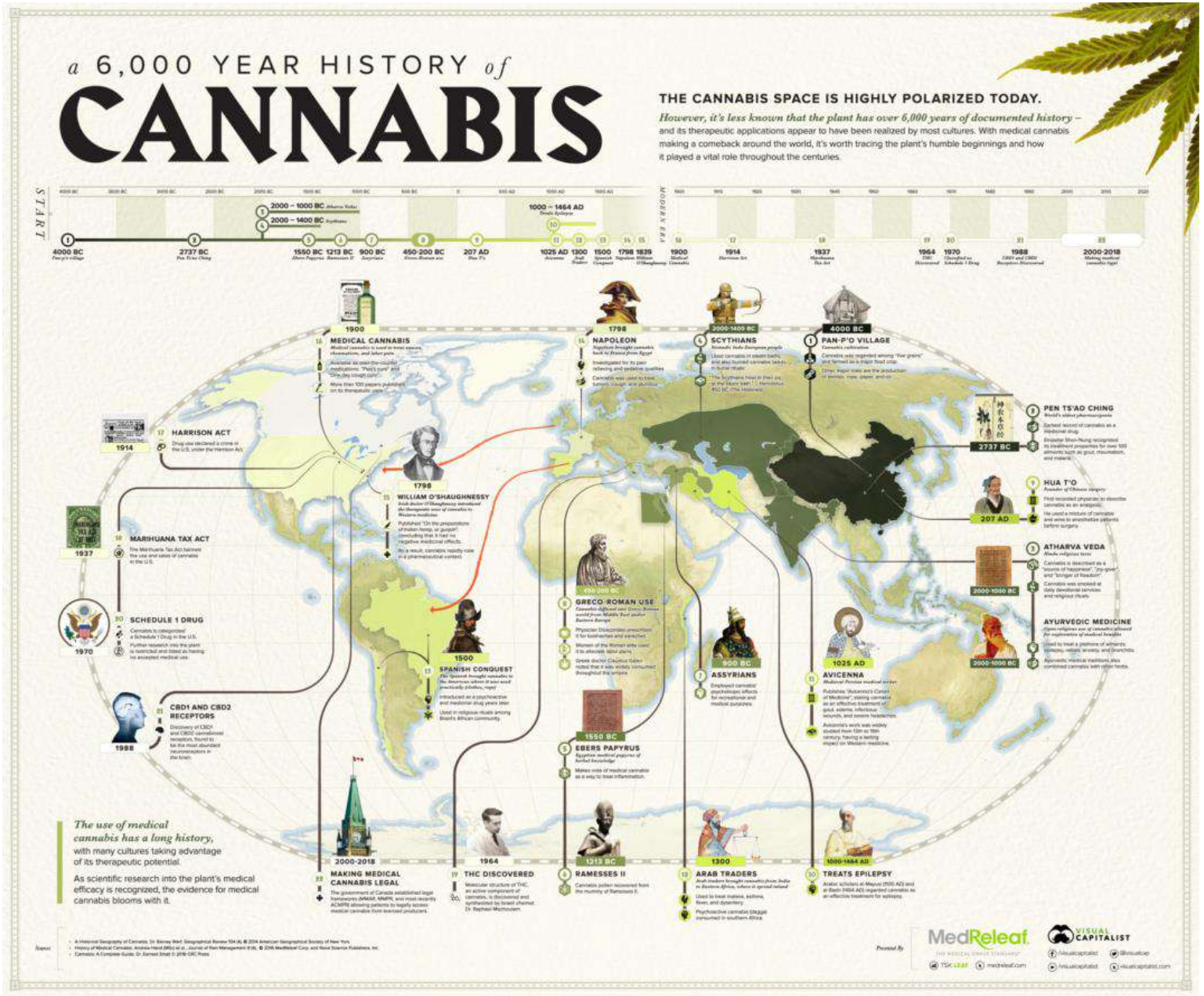
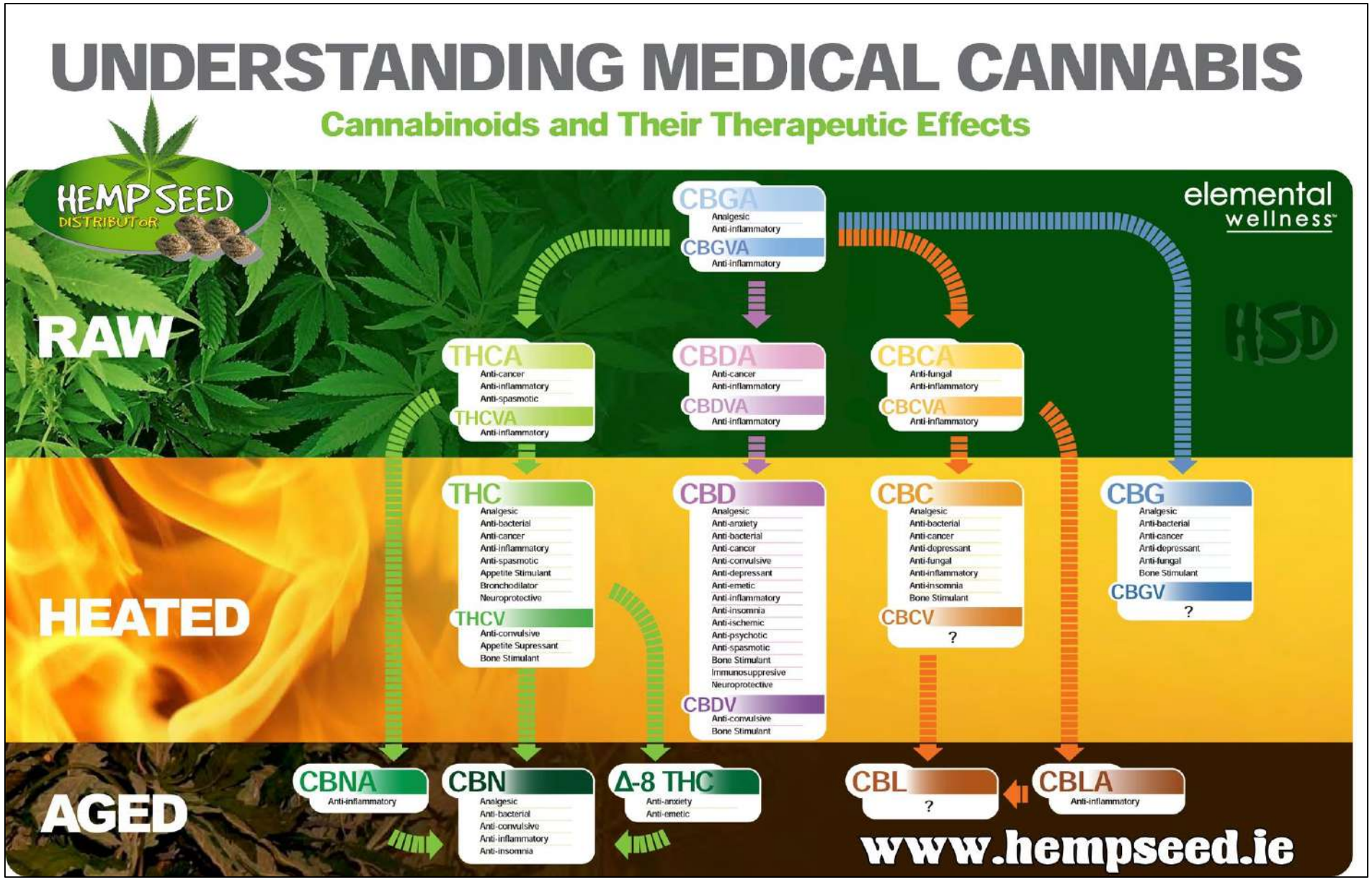
COLLEGE OF PHARMACY, RANGSIT UNIVERSITY

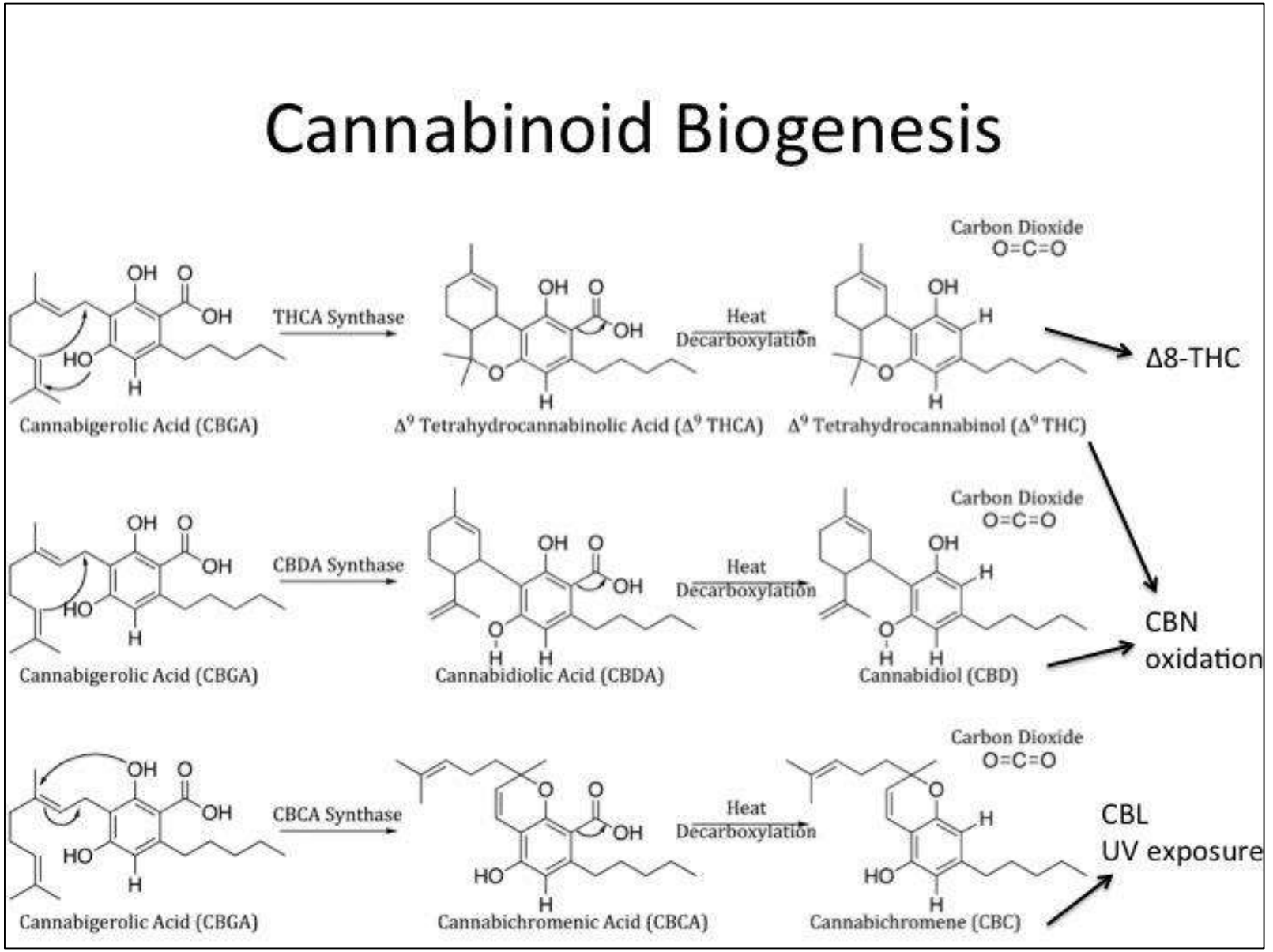
Outline

- Cannabinoids as chemical markers
- Conventional and Modified extraction
- Separation and Isolation of Cannabinoids
- Identification of Cannabinoids
- Formulation of Oromucosal Spray
- Evaluation of Oromucosal Spray

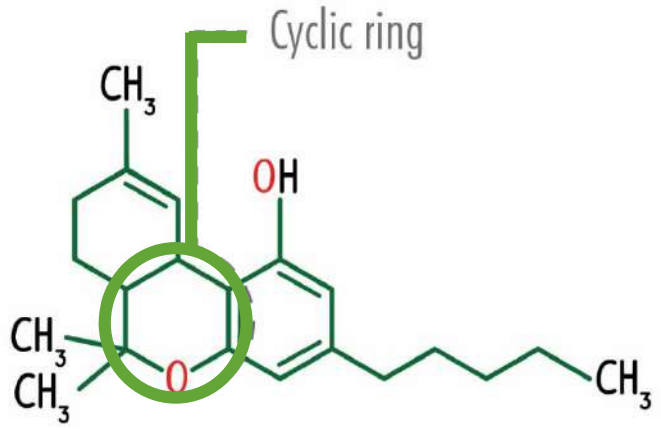

a 6,000 YEAR HISTORY of
CANNABIS
THE CANNABIS SPACE IS HIGHLY POLARIZED TODAY.
However, it's less known that the plant has over 6,000 years of documented history – and its therapeutic applications appear to have been realized by most cultures. With medical cannabis making a comeback around the world, it's worth tracing the plant's humble beginnings and how it played a vital role throughout the centuries.
START
MODERN ERA
4000 BC
2737 BC
2000 – 1000 BC
2000 – 1400 BC
1550 BC
1213 BC
900 BC
450-200 BC
207 AD
1000 – 1464 AD
1025 AD
1300
1500
1798
1839
1900
1914
1937
1964
1970
1988
2000-2018
PAN-P'O VILLAGE
PEN TS'AO CHING
HUA T'O
ATHARVA VEDA
AYURVEDIC MEDICINE
SCYTHIANS
NAPOLEON
MEDICAL CANNABIS
HARRISON ACT
WILLIAM O'SHAUGHNESSY
MARIHUANA TAX ACT
SCHEDULE 1 DRUG
CBD1 AND CBD2 RECEPTORS
GRECO-ROMAN USE
SPANISH CONQUEST
ASSYRIANS
AVICENNA
EBERS PAPYRUS
RAMESSES II
ARAB TRADERS
TREATS EPILEPSY
THC DISCOVERED
MAKING MEDICAL CANNABIS LEGAL
The use of medical cannabis has a long history, with many cultures taking advantage of its therapeutic potential.
As scientific research into the plant's medical efficacy is recognized, the evidence for medical cannabis blooms with it.
MedReleaf
VISUAL CAPITALIST


UNDERSTANDING MEDICAL CANNABIS
Cannabinoids and Their Therapeutic Effects
HEMP SEED DISTRIBUTOR
elemental wellness
RAW
HEATED
AGED
CBGA
Analgesic
Anti-inflammatory
CBGVA
Anti-inflammatory
THCA
Anti-cancer
Anti-inflammatory
Anti-spasmotic
THCVA
Anti-inflammatory
CBDA
Anti-cancer
Anti-inflammatory
CBDVA
Anti-inflammatory
CBCA
Anti-fungal
Anti-inflammatory
CBCVA
Anti-inflammatory
HSD
THC
Analgesic
Anti-bacterial
Anti-cancer
Anti-inflammatory
Anti-spasmotic
Appetite Stimulant
Bronchodilator
Neuroprotective
THCV
Anti-convulsive
Appetite Supressant
Bone Stimulant
CBD
Analgesic
Anti-anxiety
Anti-bacterial
Anti-cancer
Anti-convulsive
Anti-depressant
Anti-emetic
Anti-inflammatory
Anti-insomnia
Anti-ischemic
Anti-psychotic
Anti-spasmotic
Bone Stimulant
Immunosuppresive
Neuroprotective
CBDV
Anti-convulsive
Bone Stimulant
CBC
Analgesic
Anti-bacterial
Anti-cancer
Anti-depressant
Anti-fungal
Anti-inflammatory
Anti-insomnia
Bone Stimulant
CBCV
?
CBG
Analgesic
Anti-bacterial
Anti-cancer
Anti-depressant
Anti-fungal
Bone Stimulant
CBGV
?
CBNA
Anti-inflammatory
CBN
Analgesic
Anti-bacterial
Anti-convulsive
Anti-inflammatory
Anti-insomnia
Δ-8 THC
Anti-anxiety
Anti-emetic
CBL
?
CBLA
Anti-inflammatory
www.hempseed.ie

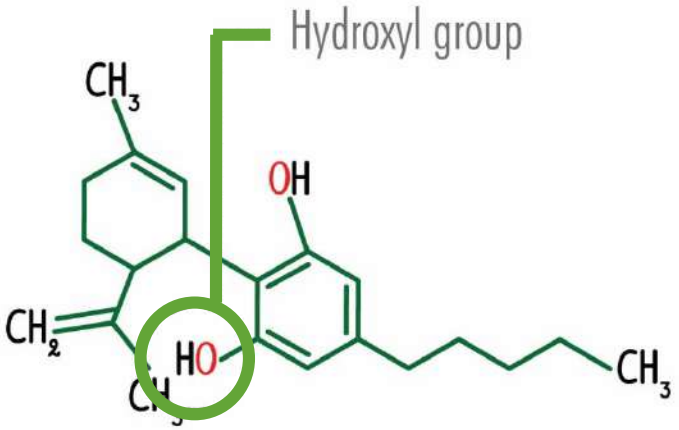
Cannabinoid Biogenesis



https://cannabisindustryjournal.com/tag/cbdv/

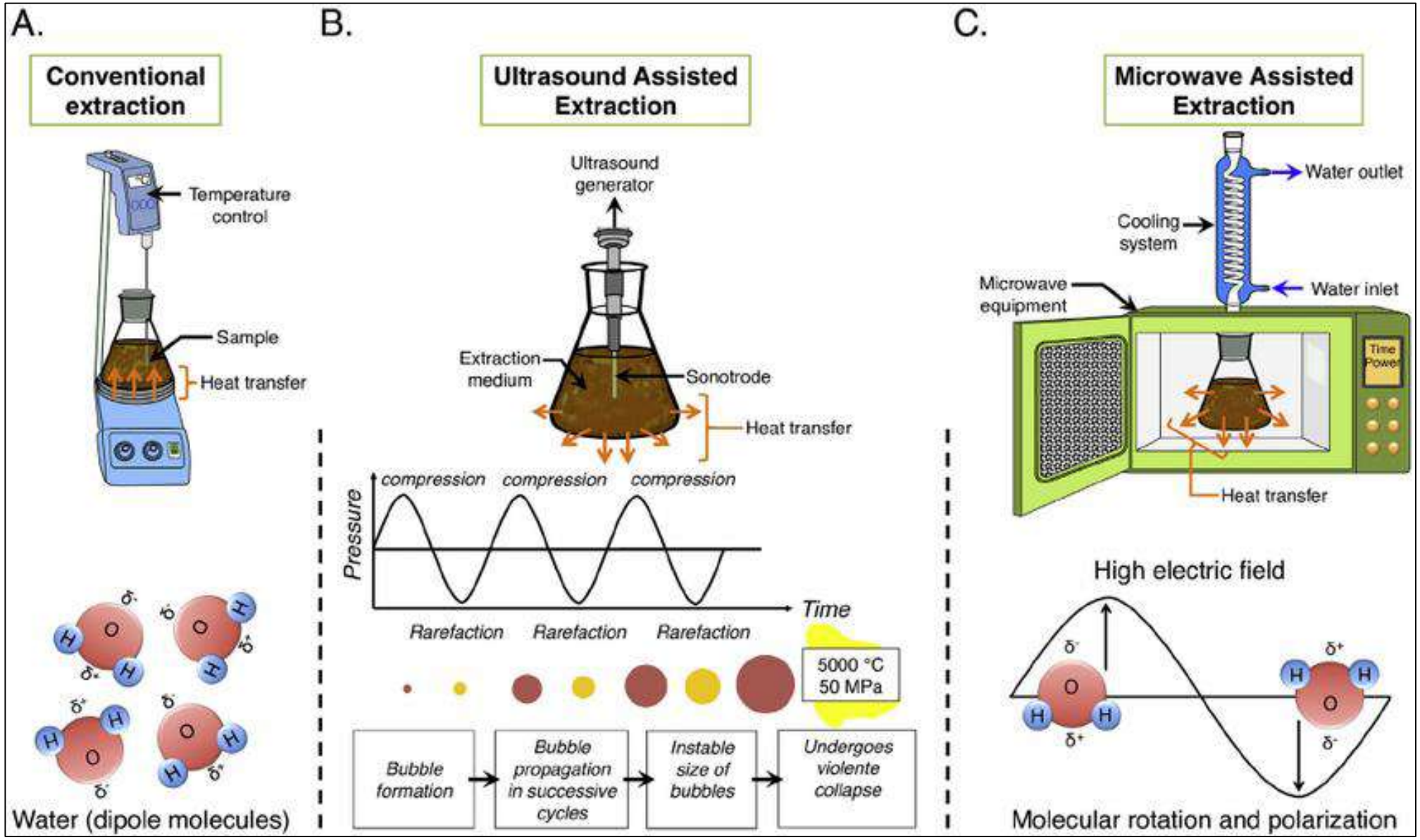


Tetrahydrocannabinol (THC)

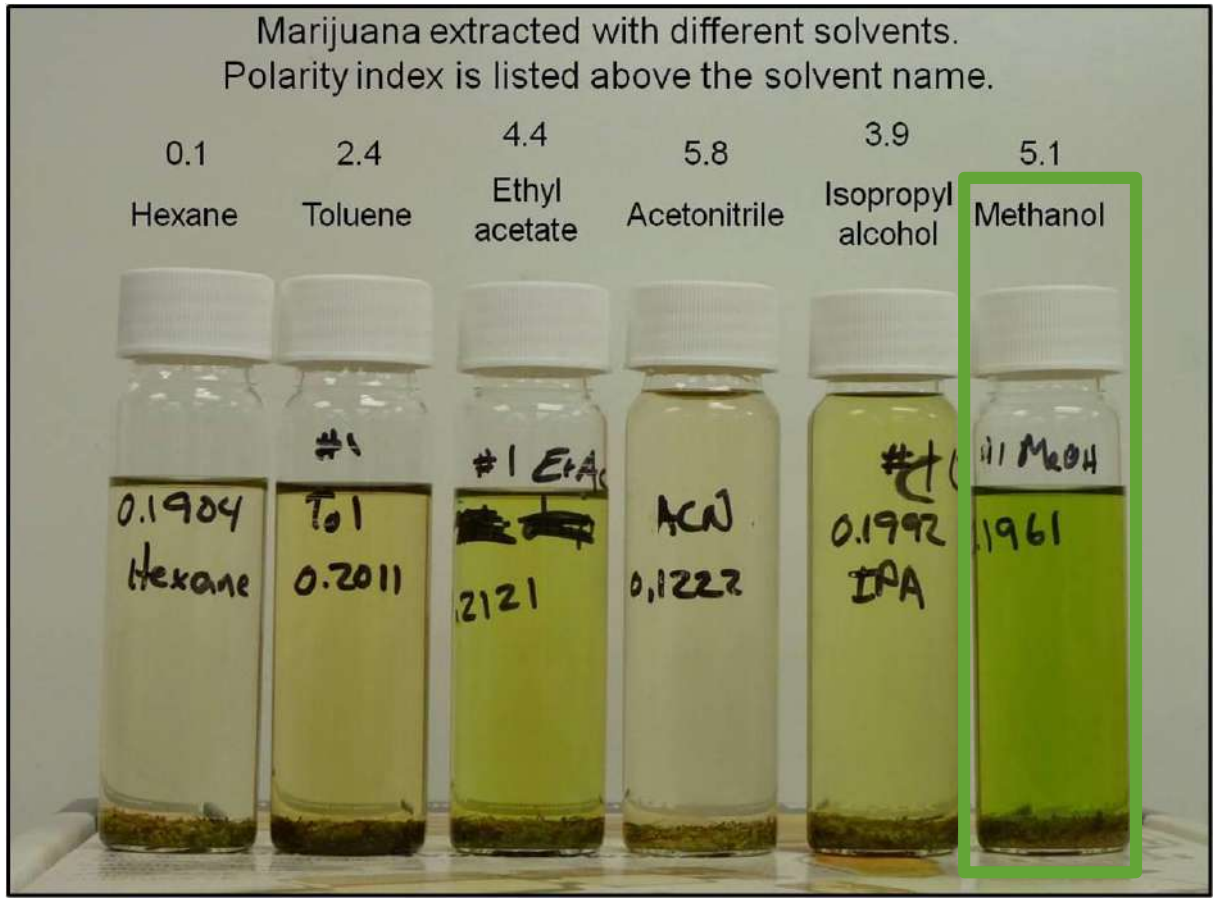


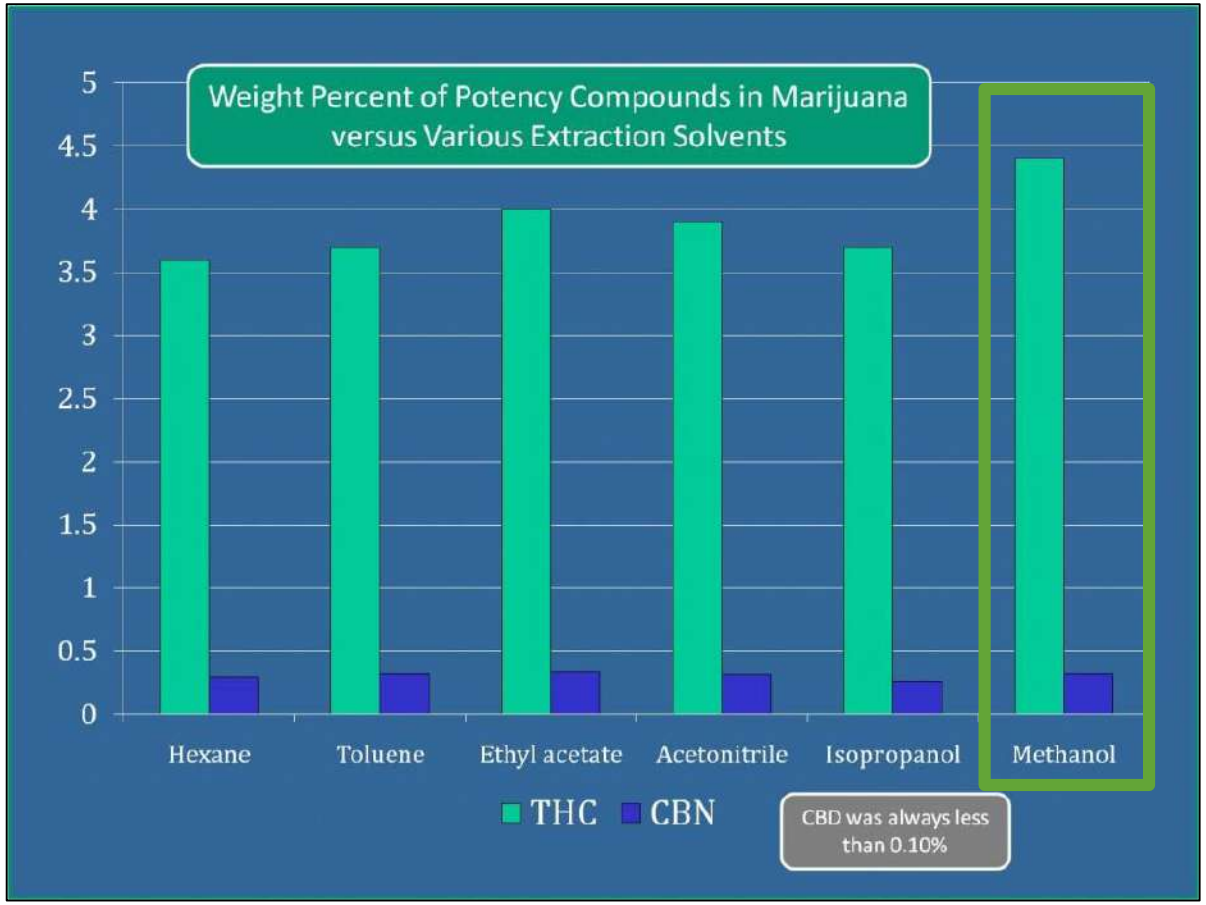
Cannabidiol (CBD)

- Cannabidiol (CBD) and tetrahydrocannabinol (THC) are just two compounds from a family of around 113 bi- and tri-cyclic compounds cannabinoid compounds found naturally in cannabis.
- Both CBD and THC share the exact same molecular formula, $C_{21}H_{30}O_2$, containing twenty-one atoms of carbon, thirty of hydrogen and two of oxygen.
- Their molecular mass is practically identical with THC and CBD having masses of 314.469 g/mol 314.464 g/mol, respectively.
- **https://www.analyticalcannabis.com/articles/cbd-vs-thc-what-are-the-main-differences-297486**

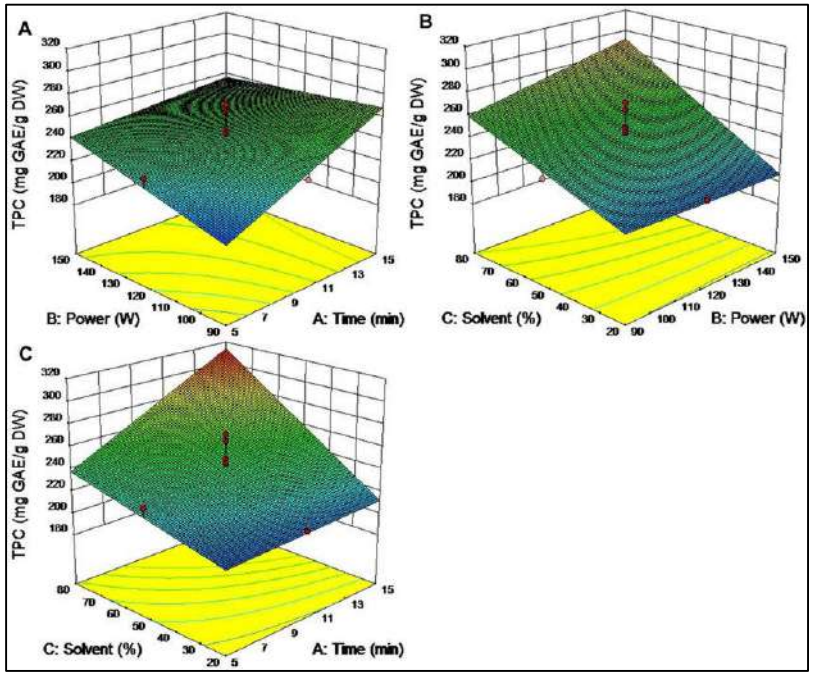


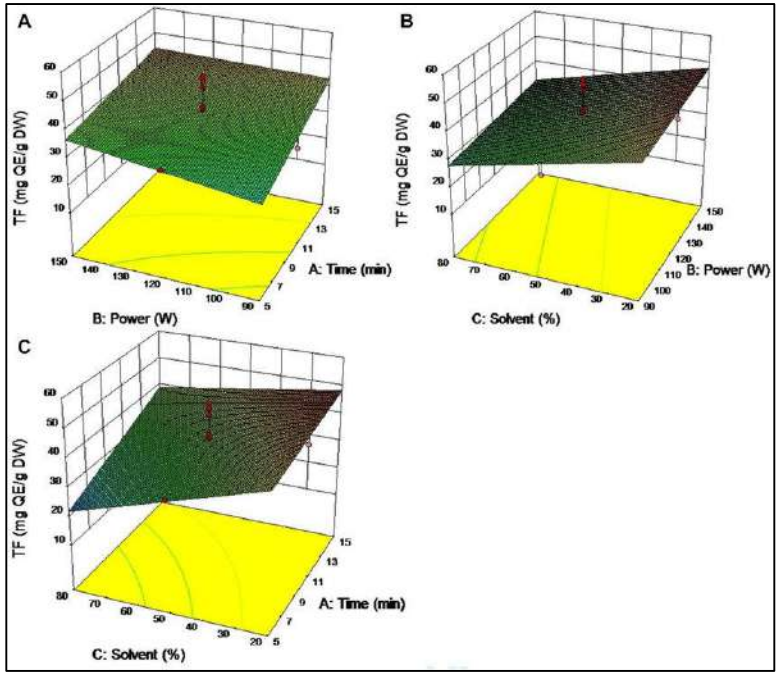
https://extractionmagazine.com/2017/11/28/ultrasound-assisted-extraction-food-natural-products-mechanisms-techniques-combinations-protocols-applications/

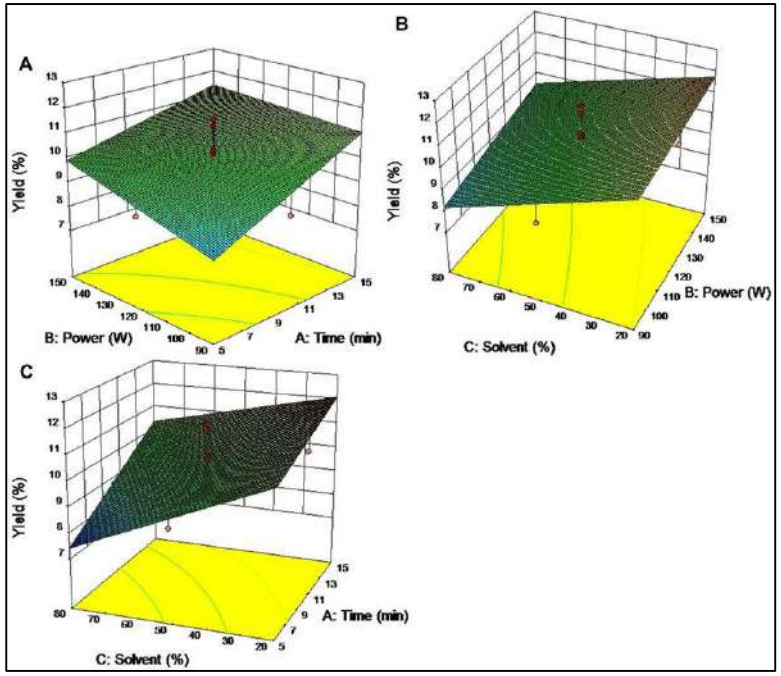




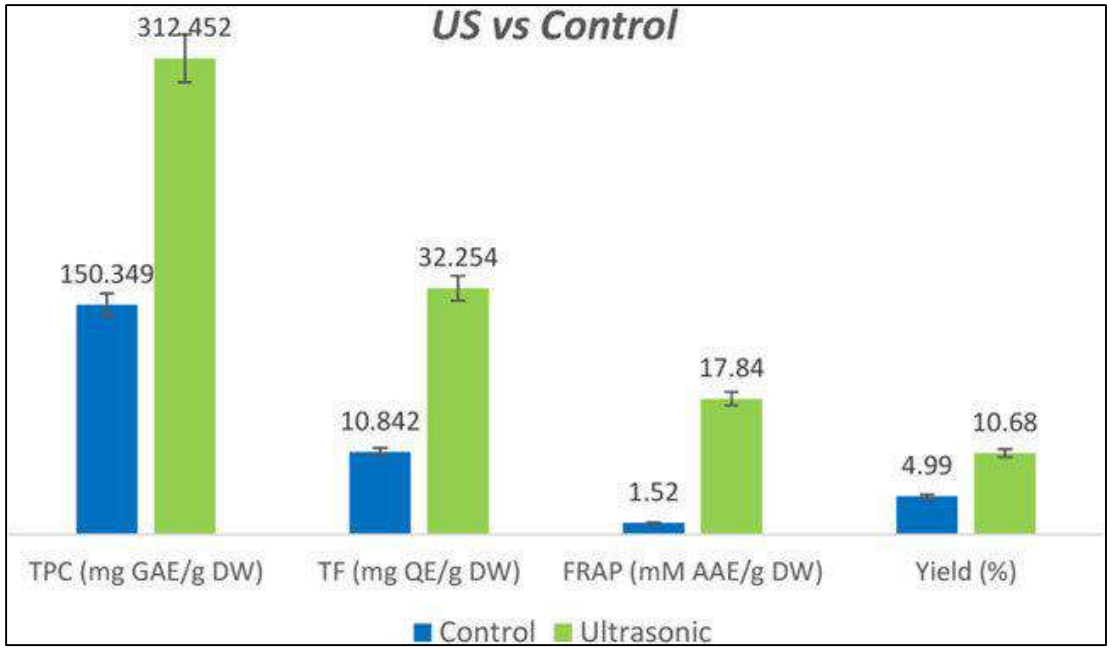
- Methanol was the most efficient extraction solvent for delta-9-THCA (analyzed as THC).
- Generally, the delta-9-THCA extraction efficiency correlated with solvent polarity.
- **Chromablography 2011; https://blog.restek.com/?p=3018**

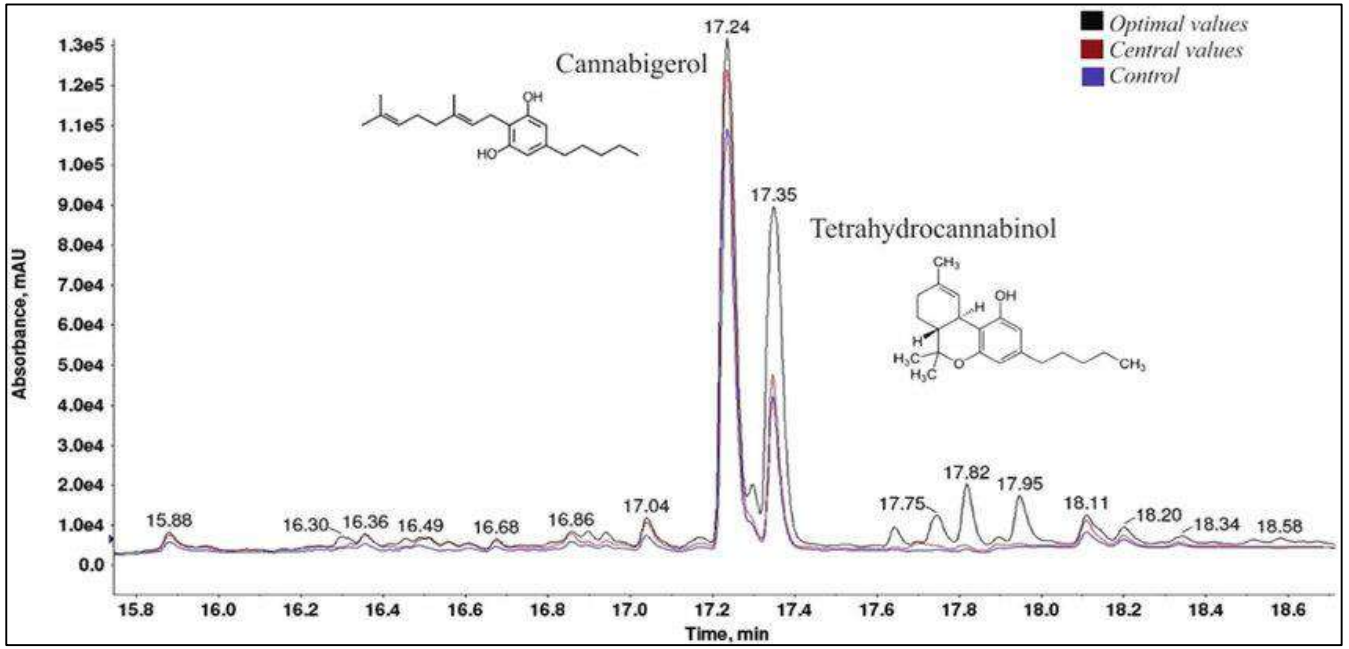






- Ultrasonication was used to extract bioactive compounds from *Cannabis sativa* L. such as polyphenols, flavonoids, and cannabinoids.
- The influence of 3 independent factors (time, input power, and methanol concentration) was evaluated on the extraction of total phenols (TPC), flavonoids (TF), ferric reducing ability of plasma (FRAP) and the overall yield.
- The response predictions obtained at optimum extraction conditions of 15 min time, 130 W power, and 80% methanol were 314.822 mg GAE/g DW of TPC, 28.173 mg QE/g DW of TF, 18.79 mM AAE/g DW of FRAP, and 10.86% of yield.
- **Journal of Food Science 2018 Mar;83(3):700-710. doi: 10.1111/1750-3841.14075. Epub 2018 Feb 13.**





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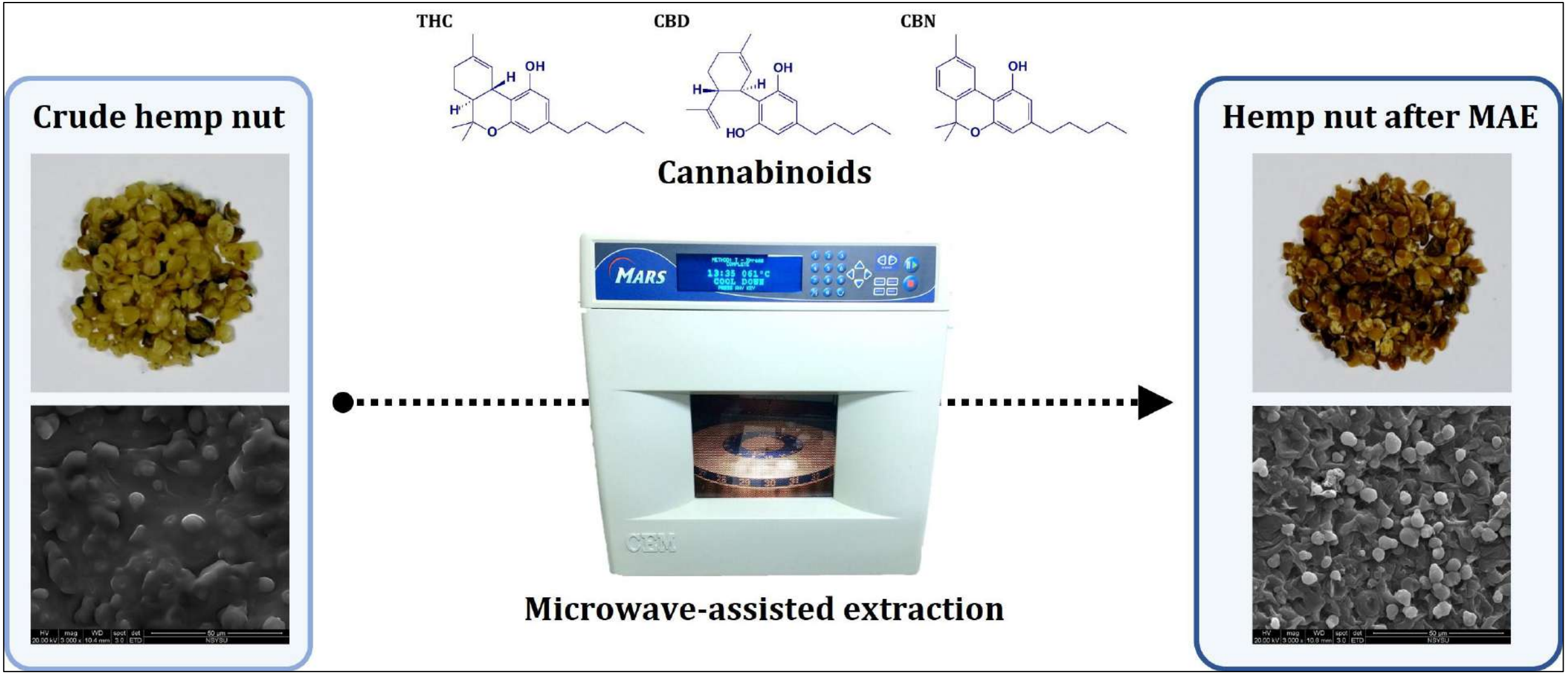
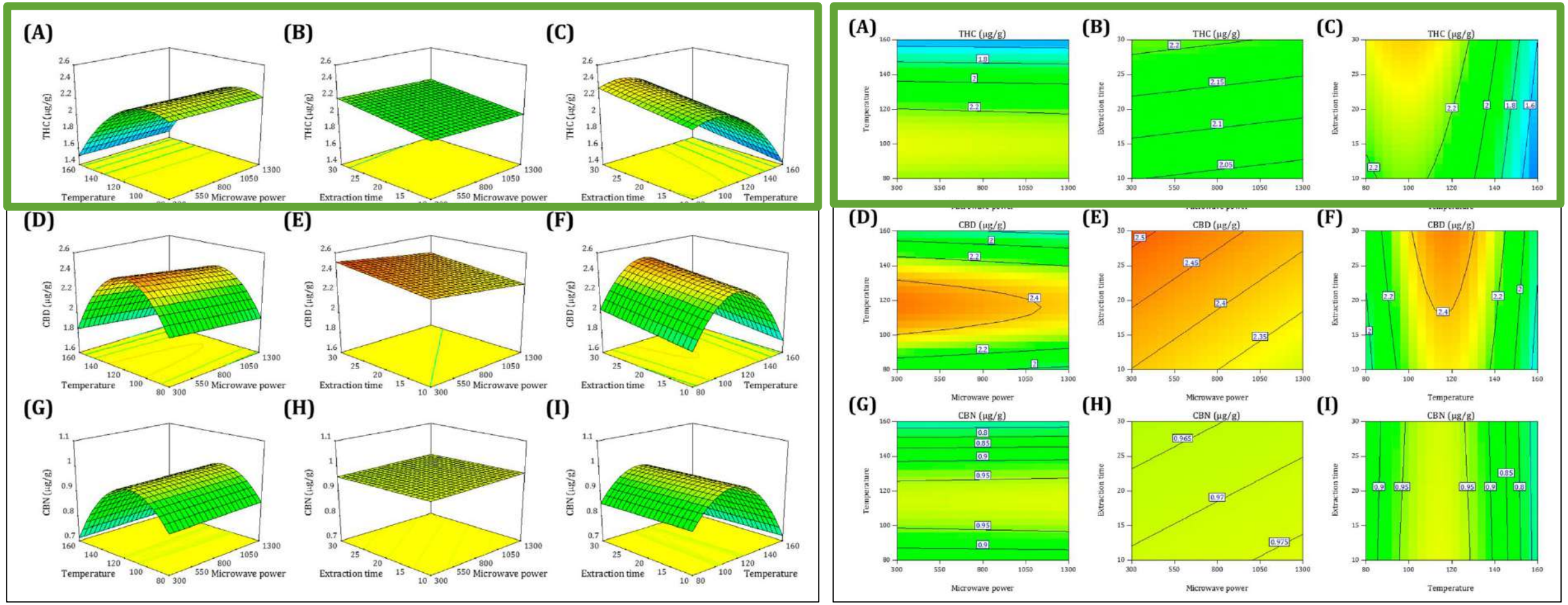
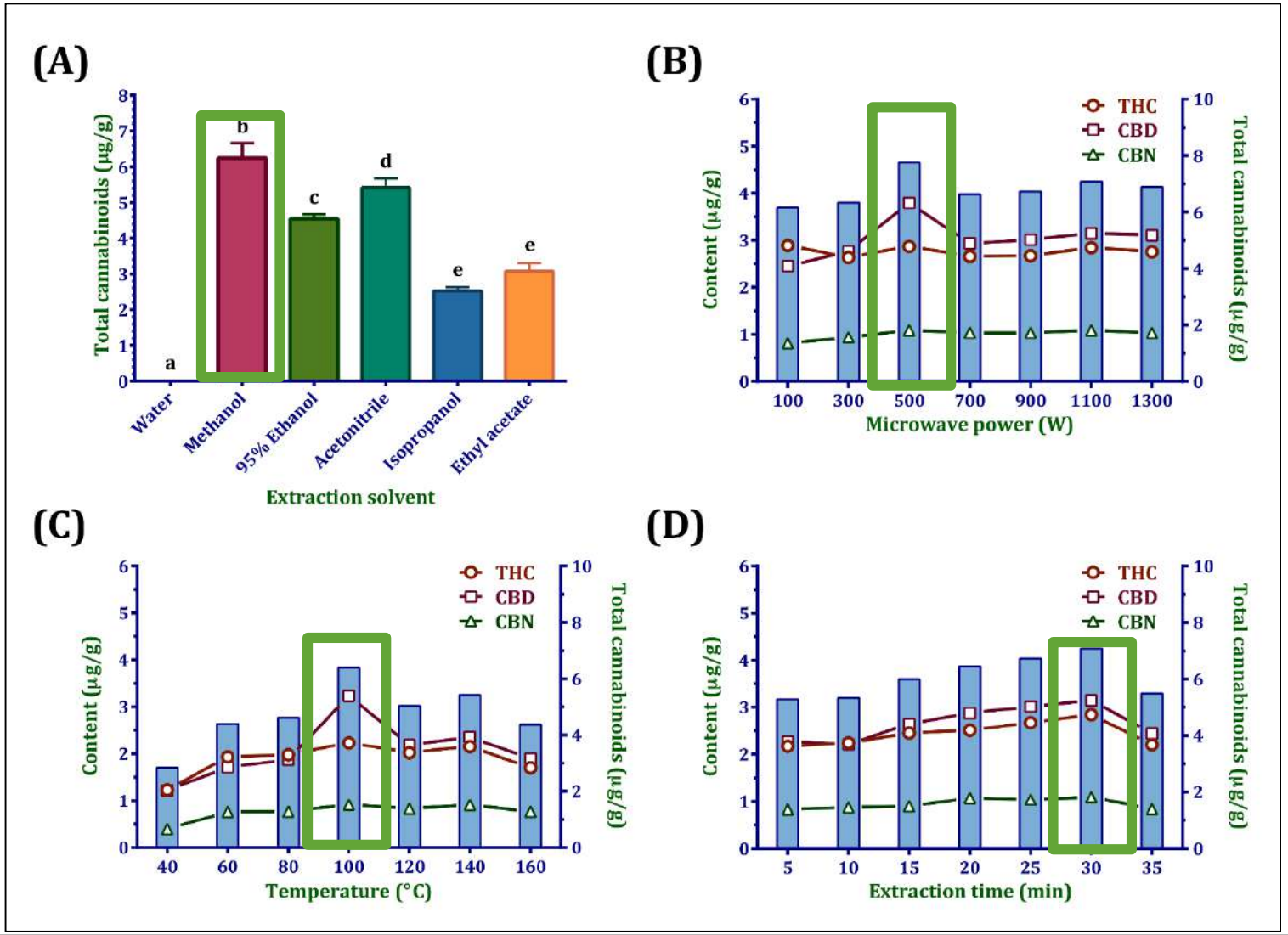


- Effect of (**A**) extraction solvent, (**B**) microwave power, (**C**) temperature, and (**D**) extraction time on the yields of cannabinoids.
- The optimal conditions of MAE were extraction solvent of methanol, microwave power of 375 W, temperature of 109 °C, and extraction time of 30 min.
- **Molecules 2017, 22(11), 1894; doi:10.3390/molecules22111894**



- **Left.** Response surface plots showing the interaction effects of microwave power, temperature, and extraction time on the yields of THC (**A**–**C**), CBD (**D**–**F**), and CBN (**G**–**I**).
- **Right.** Contour plots showing the interaction effects of microwave power, temperature, and extraction time on the yields of THC (**A**–**C**), CBD (**D**–**F**), and CBN (**G**–**I**).
- **Molecules 2017, 22(11), 1894; doi:10.3390/molecules22111894**



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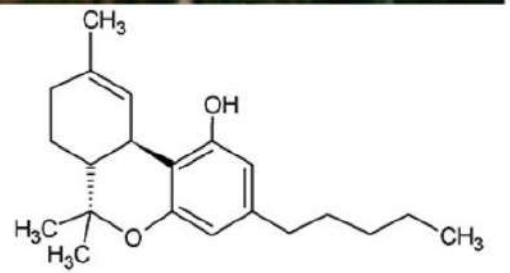
Cannabis Sativa L.



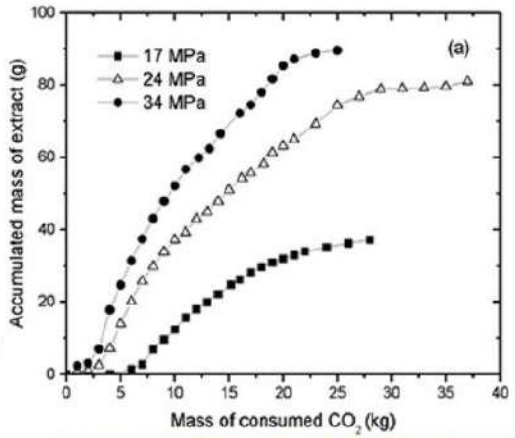
Δ^9 - Tetrahydrocannabinol (THC)

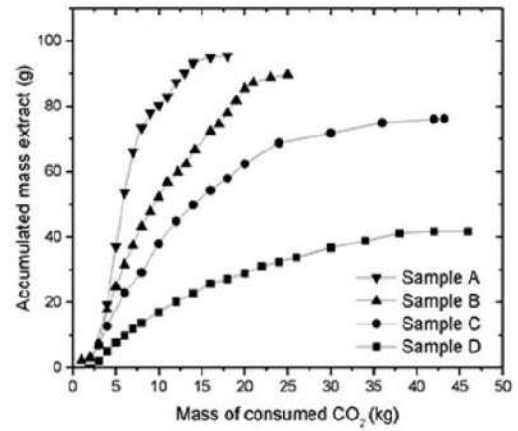
SFE

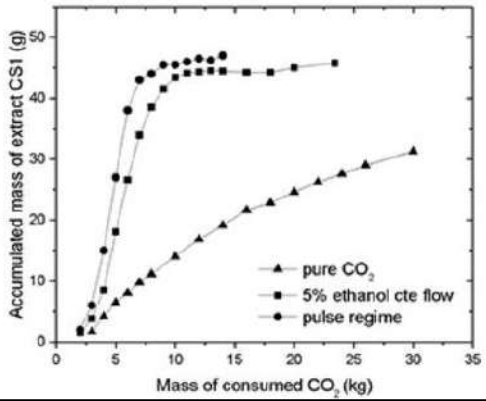
CO_2

+ *Ethanol*

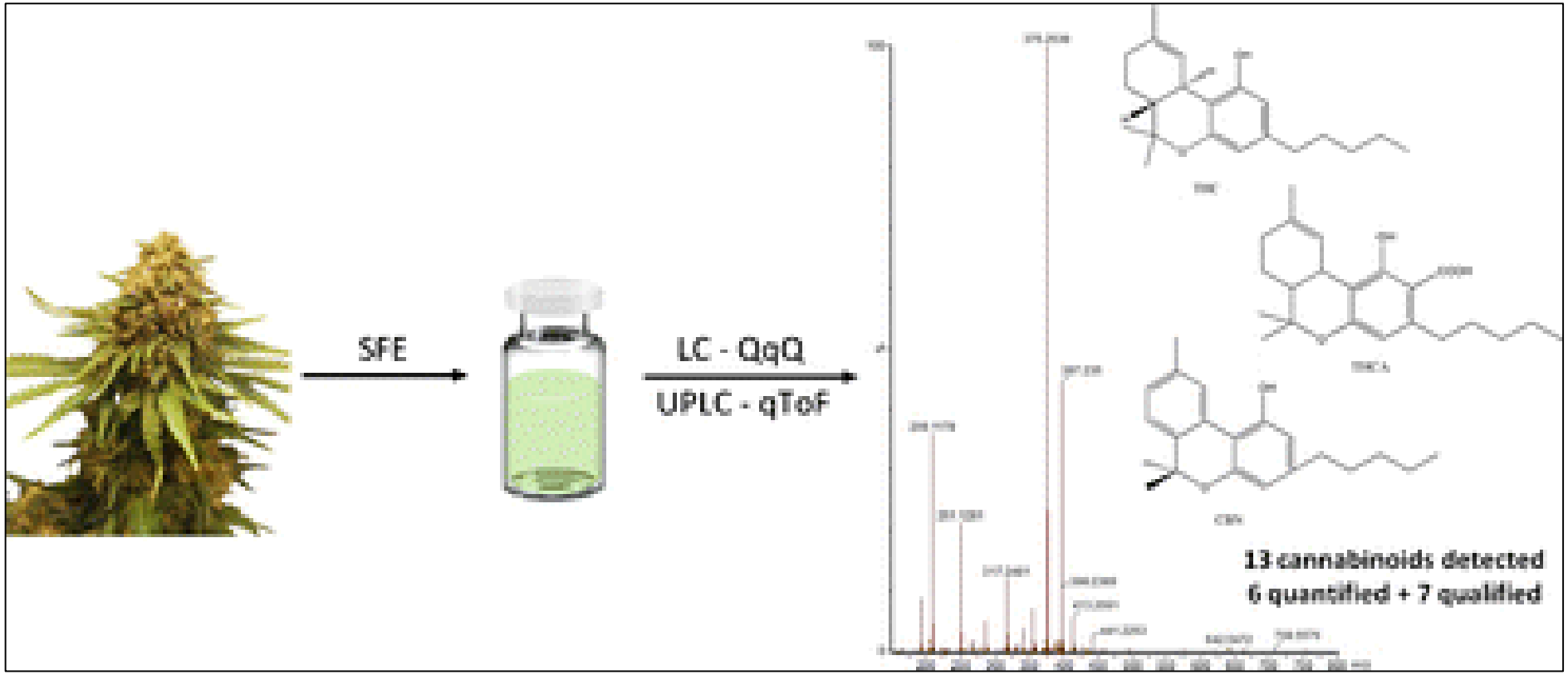
Cannabinoids extracts



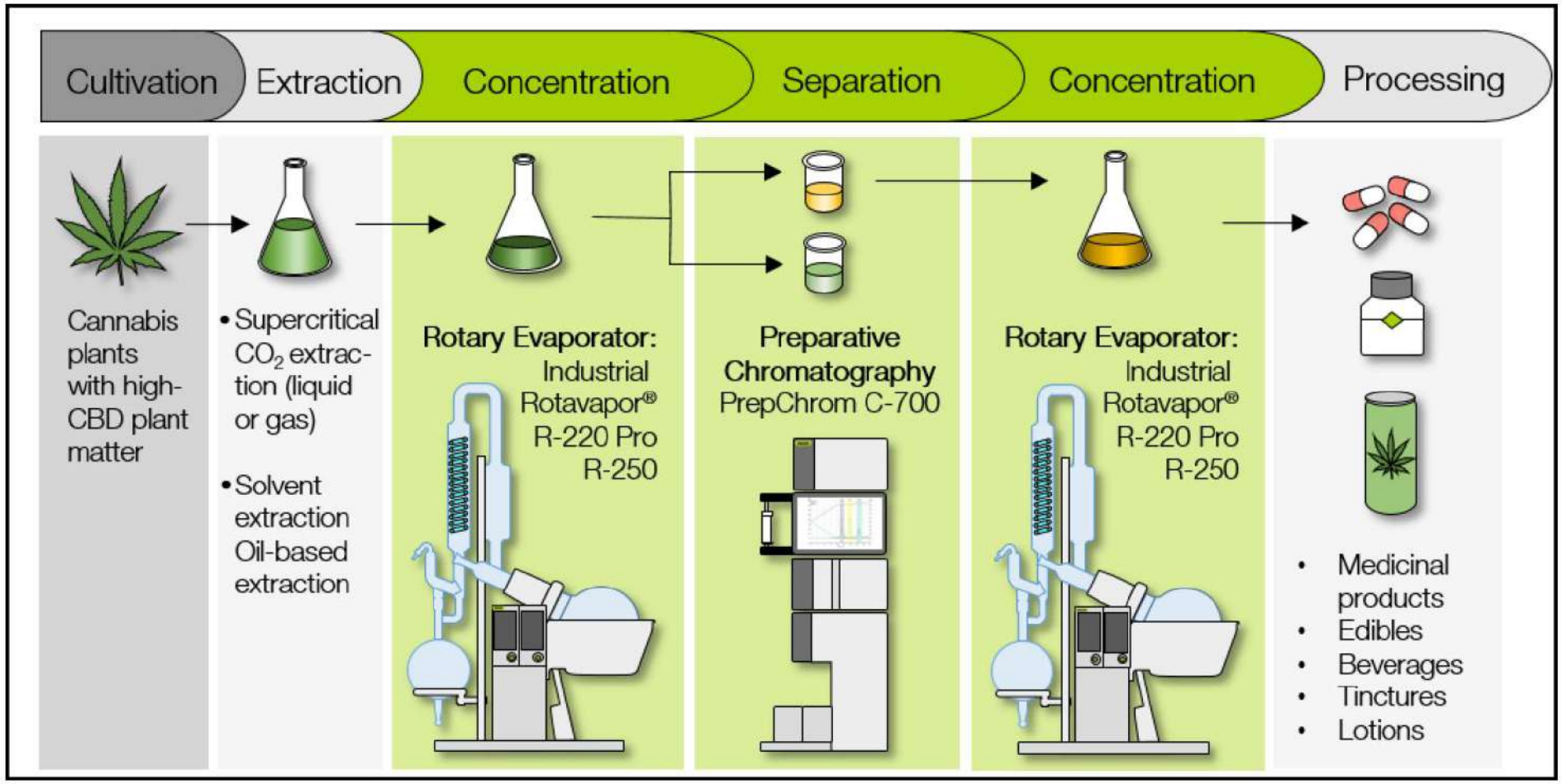




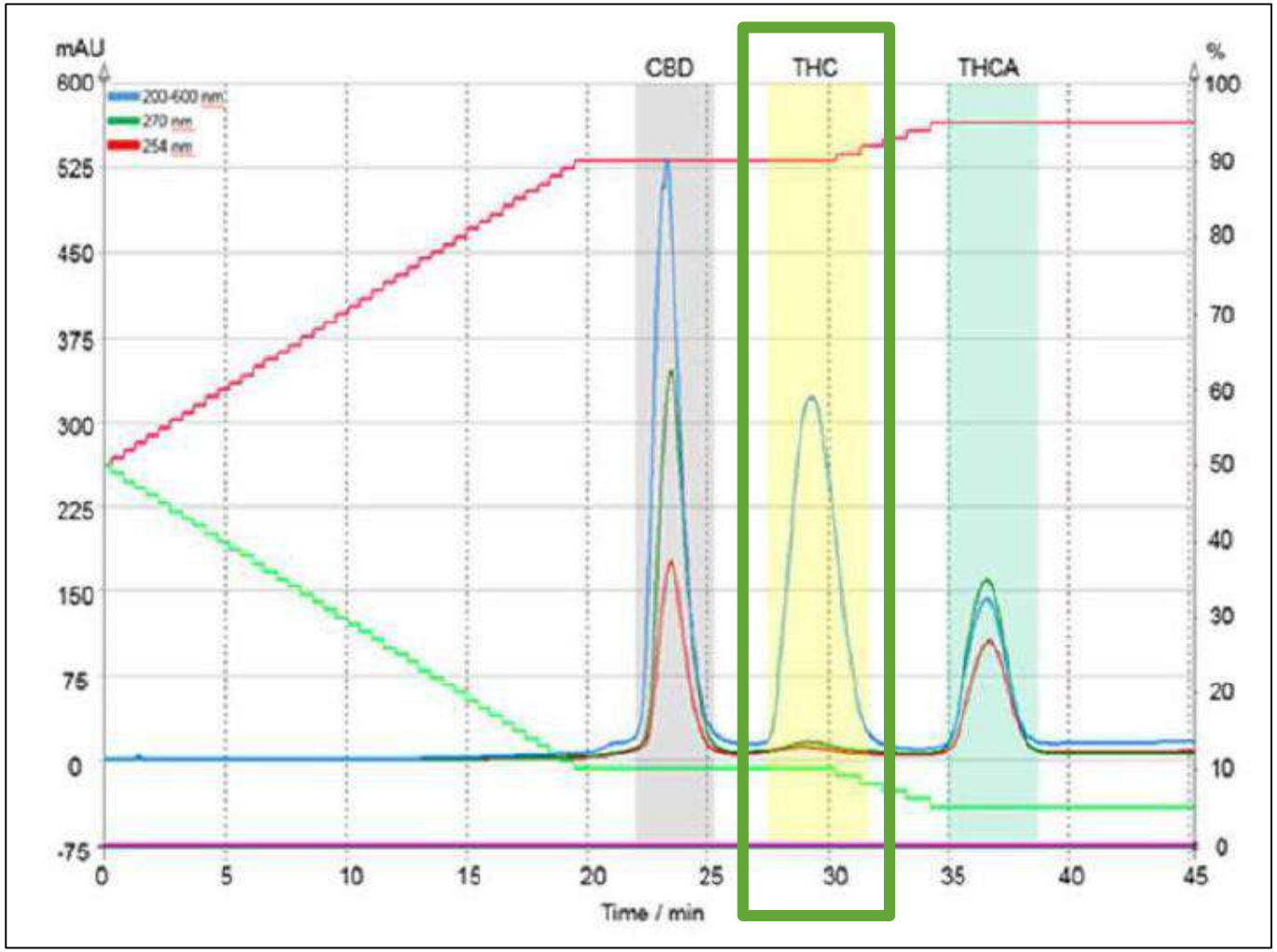
- Supercritical CO_2 was applied to obtain extracts with high cannabinoids concentration. Different operating conditions and regimes were evaluated. Cannabinoids composition was analyzed with time at different extraction conditions.
- Co-solvent pulse regime is the most recommendable extraction strategy.
- **The Journal of Supercritical Fluids, 2017, 129: 16-27**



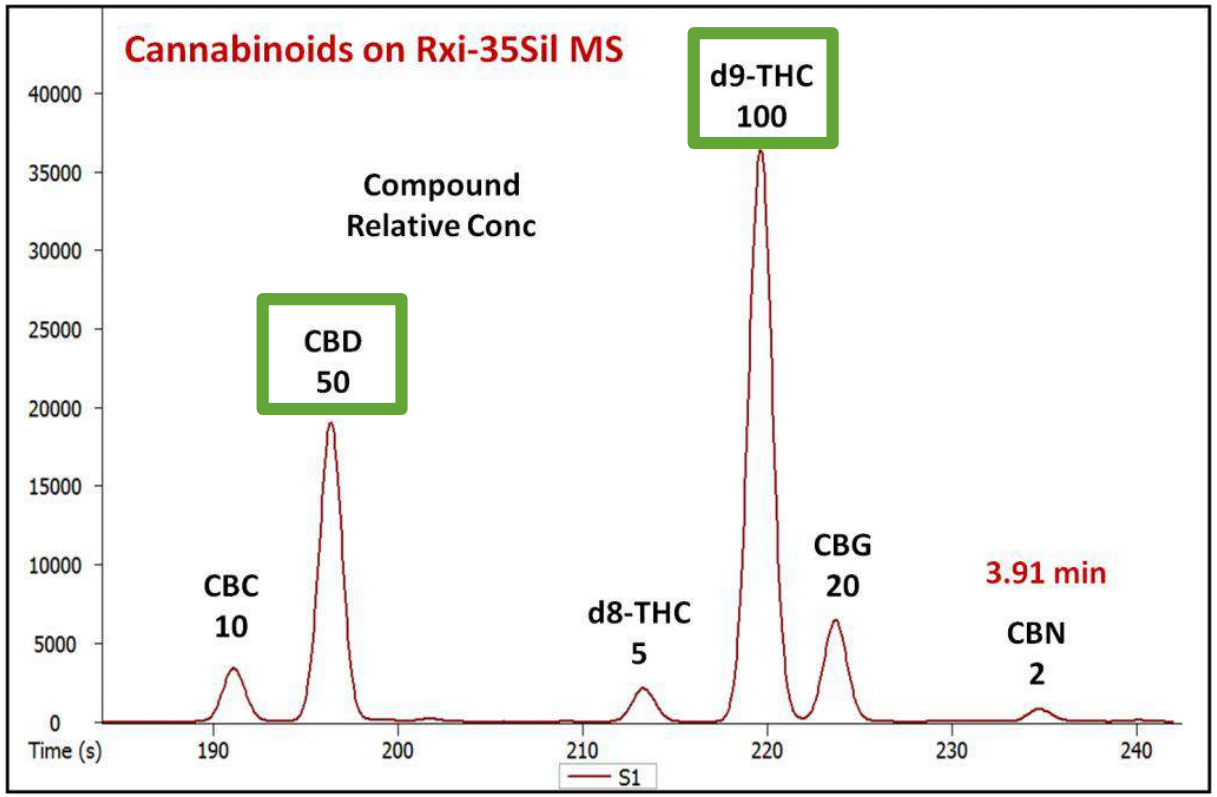
- Six major cannabinoids [tetrahydrocannabinolic acid (THCA), tetrahydrocannabinol (THC), cannabidiol (CBD), tetrahydrocannabivarin (THCV), cannabigerol (CBG), and cannabinol (CBN)] were quantified (RSD < 10%), and seven more cannabinoids were identified and verified by high performance liquid chromatography tandem mass spectrometry **(HPLC-MS/MS).**
- **Analytical and Bioanalytical Chemistry,2014, 406 (29): 7549–7560**



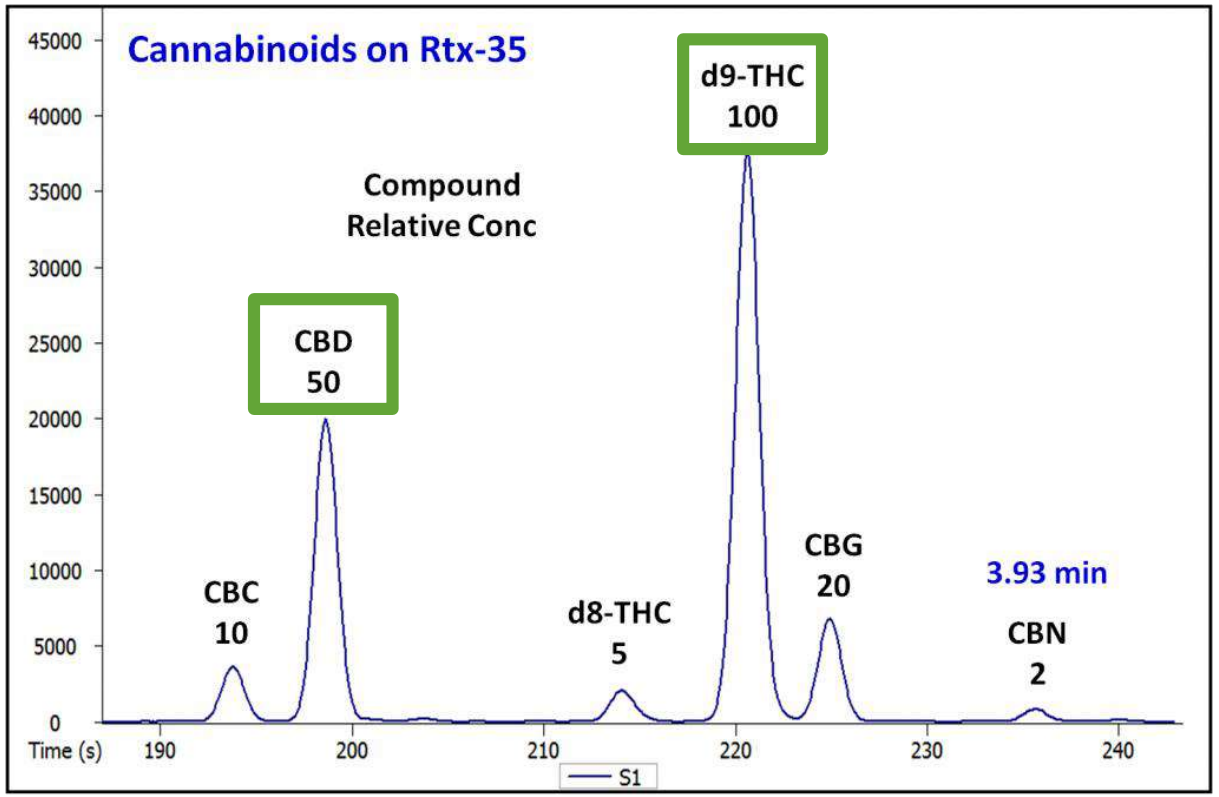
- The industrial scale rotary evaporators R-220 Pro and R-250 are the ideal solutions for efficient concentration of cannabinoid extracts after initial extraction as well as subsequent cannabinoid separation. High purity separation of various cannabinoids (e.g. THC and CBD) is achieved by preparative chromatography using BUCHI's compact PrepChrom C-700 which combines both flash and prep-HPLC purifications.
- **https://www.analyticalcannabis.com/white-papers/industrial-evaporation-chromatography-ideal-combination-for-cannabis-processing-288137**



- Separation by preparative chromatography uses the principle that different cannabinoids travel through a specific stationary phase at different speeds. The substances to separate and purify are eluted and collected successively, as illustrated in the Figure for a cannabis extract containing the three cannabinoids, THC, CBD and THCA (tetrahydrocannabinolic acid).
- **https://www.analyticalcannabis.com/white-papers/industrial-evaporation-chromatography-ideal-combination-for-cannabis-processing-288137**

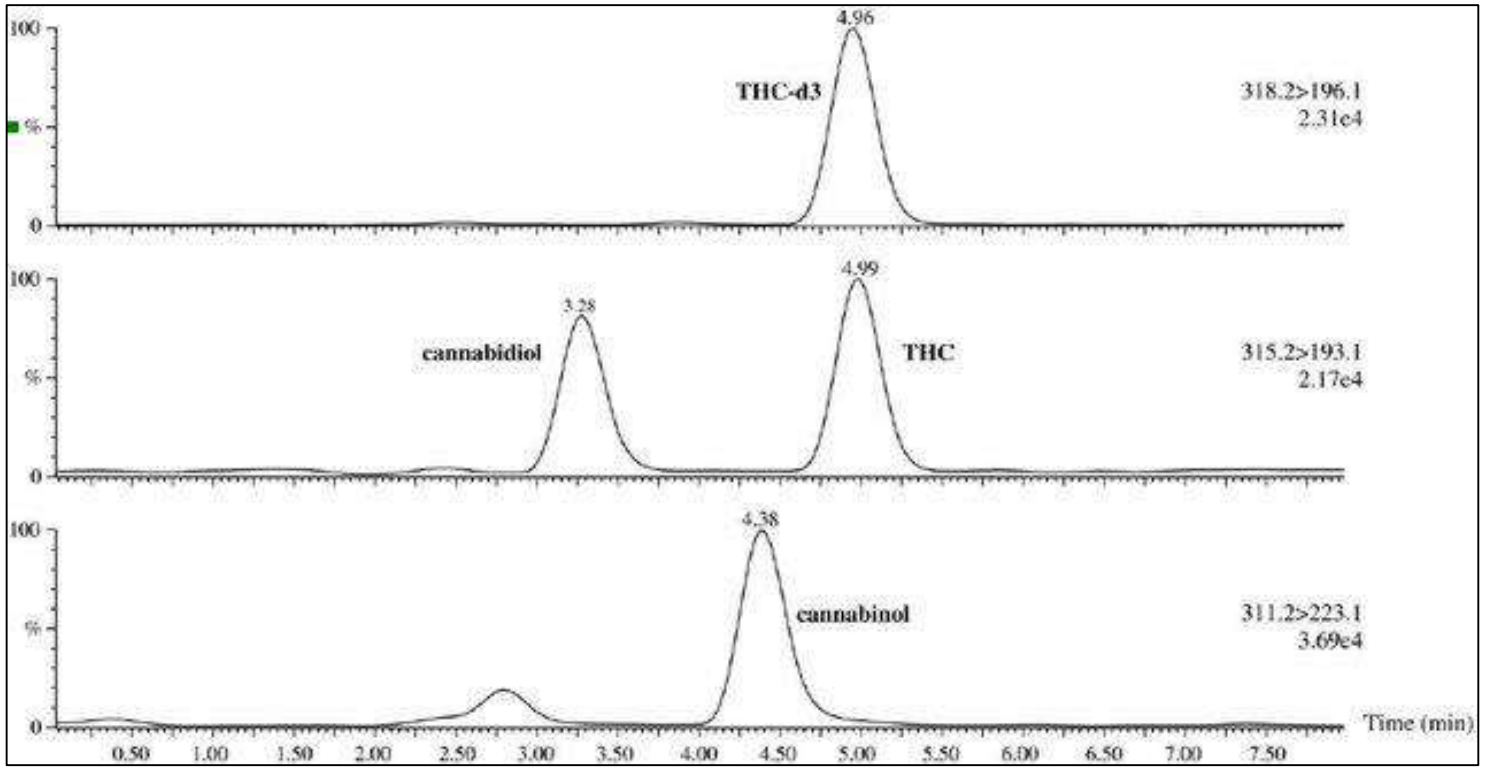


15m x 0.53mm x 0.50µm Rxi-35Sil MS, constant flow H_2 4.2 mL/min; Sky Precision split liner, 250°C, split 10:1
GC oven: 225°C (0.1 min), 19.4°C/min to 330°C (1.5 min), Flame Ionization Detector 350°C



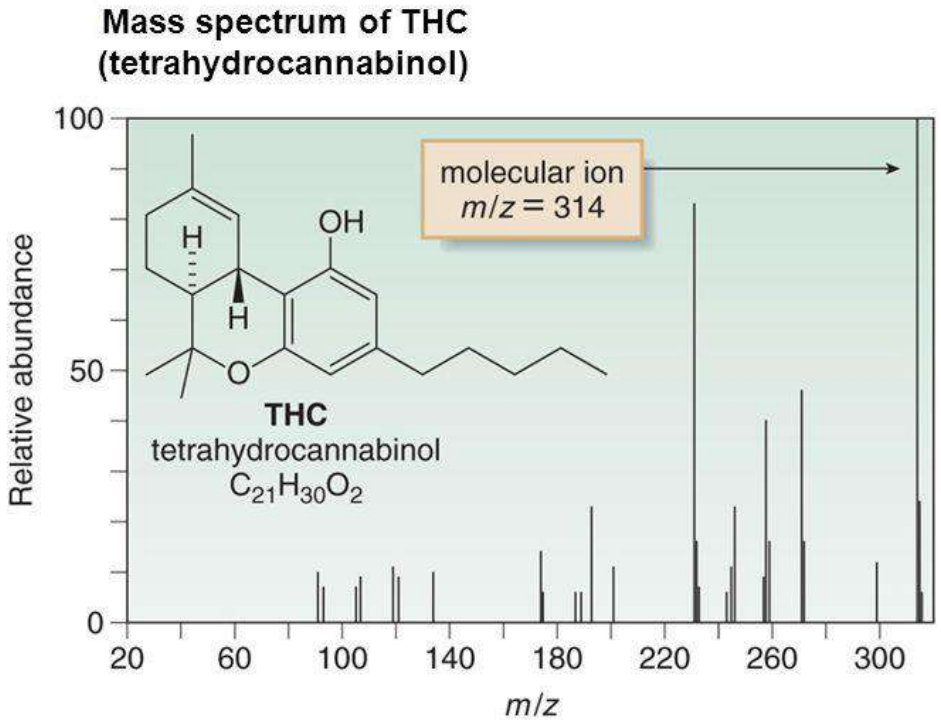
15m x 0.53mm x 0.50µm Rtx-35, constant flow H_2 4.2 mL/min; Sky Precision split liner, 250°C, split 10:1
GC oven: 225°C (0.1 min), 19.4°C/min to 300°C (3.0 min), Flame Ionization Detector 320°C

- Medical Marijuana Cannabinoids Analyzed by Gas Chromatography with Flame-Ionization Detection **(GC-FID)** on Rxi-35Sil MS and Rtx-35.
- **Chromablography 2011; https://blog.restek.com/?p=12038**



- LC–MS-MS analysis of an extracted 100µL blank oral fluid sample enriched with 5 ng/mL THC-d 3 (top trace), THC and cannabidiol (middle trace) and cannabinol (bottom trace). Peak intensity is shown in the top right-hand corner of each trace.
- **Journal of Chromatography A, 2005, 1082(1):15-24.**

Gas Chromatography-Mass Spectrometry (GC-MS):



- Gas Chromatography-Mass Spectrometry (GC-MS) of Tetrahydrocannabinol (THC). THC appears as a GC peak, and gives a molecular ion at 314, its molecular weight.
- **Organic Chemistry, Second EditionJanice Gorzynski SmithUniversity of Hawai'i**

TABLE 1

Absorption of Oral vs Inhaled Medical Marijuana[5,17,18]

Pharmacologic Parameter	Oral	Inhaled
Bioavailability	6-20%*	10-40%†
Time to peak concentrations	1-6 hr	2-10 min
Maximal duration	2-3 hr	Dose-dependent; maximal psychotropic effects: 20 min; with rapid decline lasting 45-60 min
Distribution	90% plasma; protein-bound 10% red blood cells 1% in brain Crosses placenta and found in breast milk	

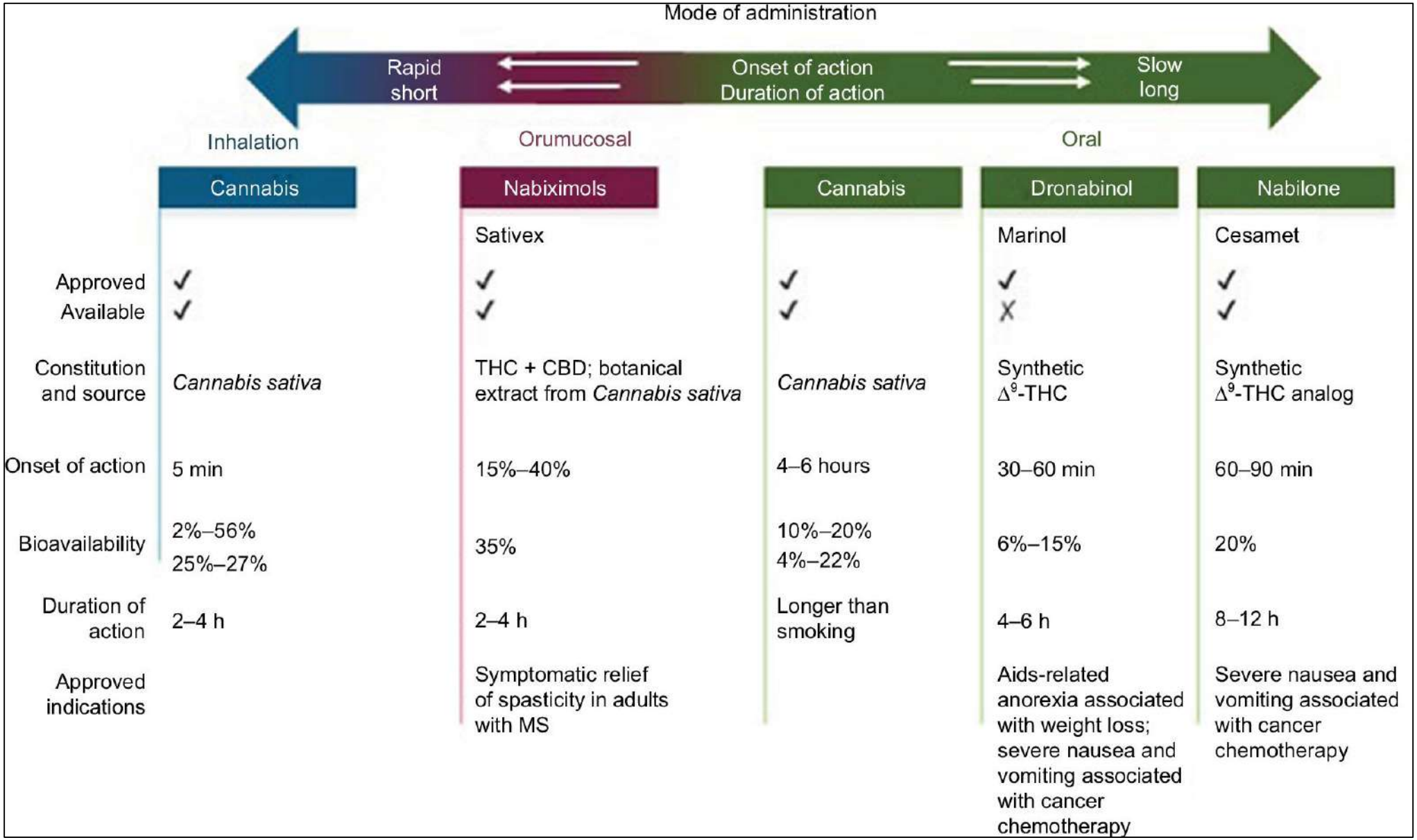
* Liver metabolism converts THC to 11-hydroxy-delta-9-THC, which is believed to be more psychoactive than delta-9-THC.
† Vaporization increases the percentage of cannabinoids inhaled vs combustion by smoking.

- Oral and inhaled medical marijuana products have different absorption rates and bioavailability.
- **Oral** medical marijuana products can take hours to reach peak blood concentrations, versus minutes for inhaled medical marijuana products.
- **Inhaled** medical marijuana products are available in varying percentages of cannabinoids, depending on the strain, and can either be smoked or vaporized.
- **Vaporization** is a much healthier option for the lungs, because it contains fewer carcinogens than smoked marijuana.
- Vaporization also increases the percentage of delta-9-THC and CBD extracted from the marijuana.
- **Sublingual** and **oromucosal** products are another option that bypass first-pass metabolism similar to inhalation routes.
- These routes have shown high bioavailability, eliminate the need to inhale smoke or vapor, and have a faster onset than oral medications, such as edibles or capsules.

Pharmacy Purchasing & Products November 2016, 13 (11): 10.

Product	Australian Medicines Schedule/Registration	South Australia[1]	Commonwealth [2]
Dronabinol (Marinol®, Syndros®, US FDA approved medicine) Nabilone (Cesamet®, US FDA approved medicine) Tablet/capsule form.	Schedule 8. Unregistered synthetic/analogue cannabinoid products.	An authority issued under section 18A of the *Controlled Substances Act 1984* may be required.[1]	TGA Special Access Scheme or Authorised Prescriber Scheme or Clinical Trials Schemes.
Nabiximols (Sativex®) Oral spray form.	Schedule 8. The only registered cannabinoid product in Australia - for symptom improvement in multiple sclerosis.	An authority issued under section 18A of the *Controlled Substances Act 1984* may be required.[1]	Registered on the ARTG – approved product.
Cannabidiol in preparations for therapeutic use where cannabidiol comprises 98 per cent or more of the total cannabinoid content of the preparation.	Schedule 4. Unregistered cannabidiol products. Refer to the Poisons Standard for detail on Schedule 4 listing.	A section 18A authority is not required for Schedule 4 medicines.	TGA Special Access Scheme or Authorised Prescriber or clinical trials schemes.

www.sahealth.sa.gov.au/medicinalcannabis



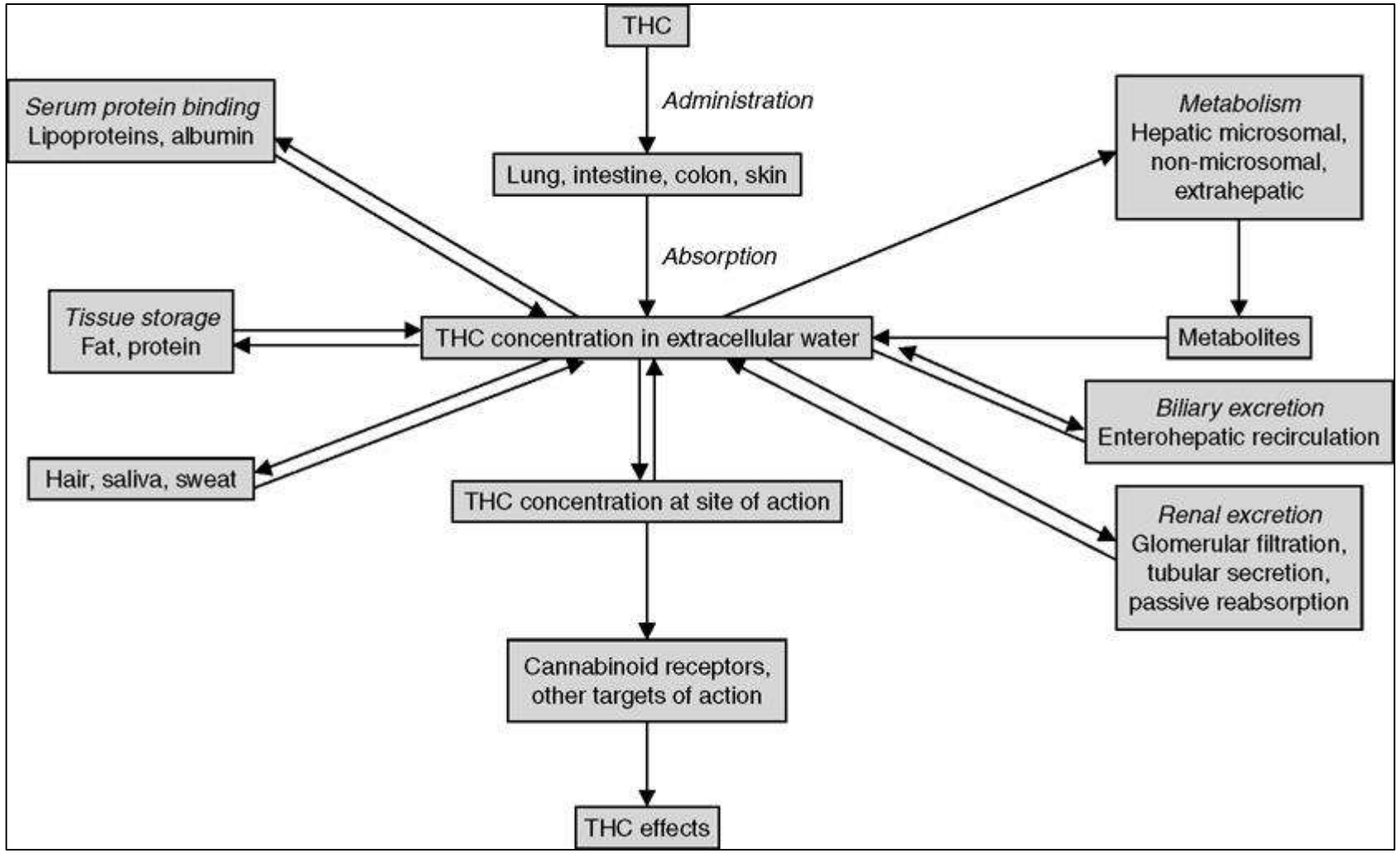
- Common Modes of Administration and Formulations. (1)Inhalation ((2)Oromucosal 3)Oral
- **https://www.dovepress.com/therapeutic-potential-of-medicinal-marijuana-an-educational-primer-for-peer-reviewed-fulltext-article-DHPS**

Image courtesy of GW Pharmaceuticals

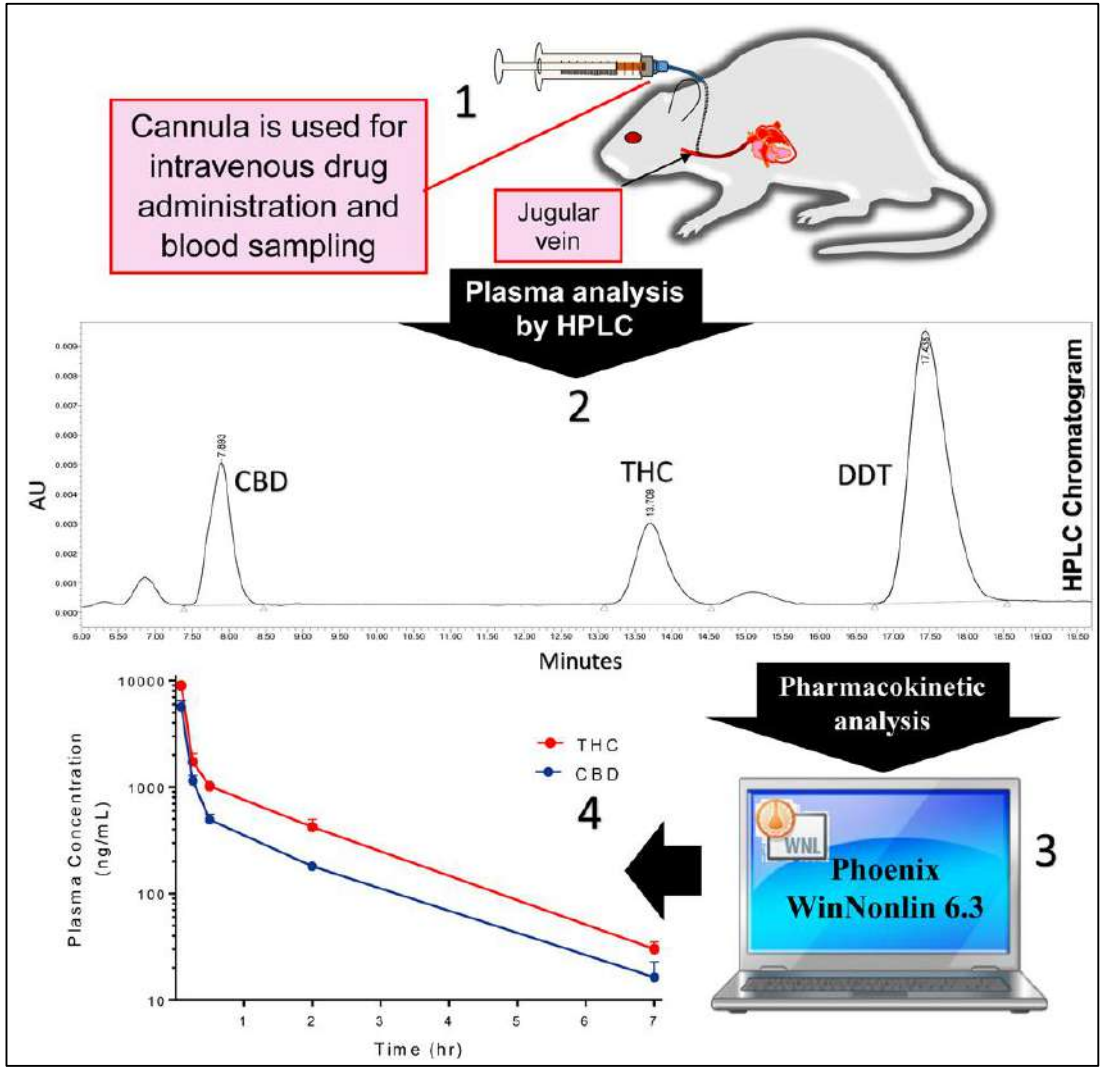
Nabiximols (Sativex™)

- Patented cannabinoid oromucosal spray for MS patients to relieve spasticity, neuropathic pain, overactive bladder and other symptoms
- Contain equal amounts CBD and $^{9}\Delta$THC
- Relieve spasticity and pain more than $^{9}\Delta$THC alone
  - CBD's effects allow patients to tolerate higher amounts of $^{9}\Delta$THC
  - CBD supplements antispastic effects of $^{9}\Delta$THC (local potentiation of glycine signaling, inhibition of endocannabinoid degradation, retardation of demyelination through antioxidant/anti-inflammatory mechanisms

- Sativex® is an oral spray developed by UK-based pharmaceutical company GW Pharmaceuticals, derived from the cannabinoids THC and CBD (cannabidiol). Sativex ® is now fully licensed in the UK, Spain, Canada and New Zealand for the treatment of muscle spasticity in MS patients. It is also approved in Canada for the reduction of cancer pain and neuropathic pain, and is in various stages of the approval process in the European Union and the US.
- **https://www.pharmaceutical-technology.com/features/feature105046/**



- The pharmacokinetics of THC vary as a function of its route of administration. Pulmonary assimilation of inhaled THC causes a maximum plasma concentration within minutes, psychotropic effects start within seconds to a few minutes, reach a maximum after 15–30 minutes, and taper off within 2–3 hours. Following oral ingestion, psychotropic effects set in with a delay of 30–90 minutes, reach their maximum after 2–3 hours and last for about 4–12 hours, depending on dose and specific effect.
- **Clinical Pharmacokinetics, 2003, 42(4), 327–360.**



- Schematic representation of the preliminary pharmacokinetic study following IV bolus administration of 5 mg/kg cannabidiol (CBD) and Δ9-tetrahydrocannabinol (THC) to rats (n=2). (1) Blood sampling from the fitted cannula. (2) Chromatogram shows CBD, THC, and the internal standard DDT following plasma analysis by HPLC. (3) Data analysis by the pharmacokinetic software. (4) Plasma concentration-time profiles of CBD and THC in rats. **https://atlasofscience.org/simple-method-for-measuring/**

US006630507B1

(12) **United States Patent**
Hampson et al.

(10) **Patent No.: US 6,630,507 B1**
(45) **Date of Patent: Oct. 7, 2003**

The U.S.A. Has A Patent On Cannabinoids

(54) **CANNABINOIDS AS ANTIOXIDANTS AND NEUROPROTECTANTS**

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(73) Assignee: **The United States of America as represented by the Department of Health and Human Services**, Washington, DC (US)

(*) Notice: Subject to any disclaimer, the term of this

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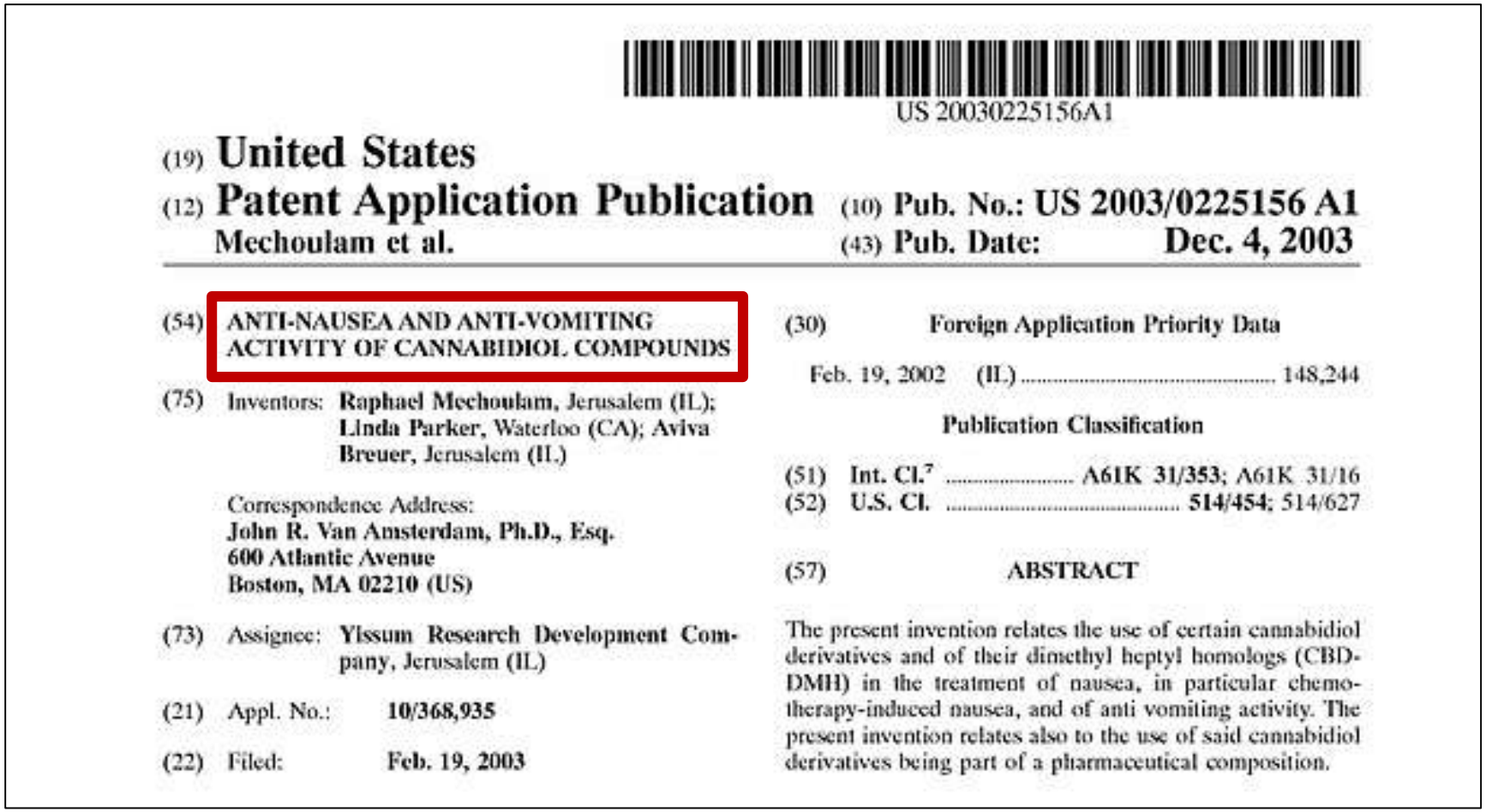
Cunha et al., "Chronic Administration of Cannabidiol to Healthy Volunteers and Epileptic Patients[1]," *Pharmacology,*

- **United States Patent: Cannabinoids as antioxidants and neuroprotectants**



US 20030225156A1

(19) **United States**

(12) **Patent Application Publication** (10) **Pub. No.: US 2003/0225156 A1**

Mechoulam et al. (43) **Pub. Date: Dec. 4, 2003**

(54) **ANTI-NAUSEA AND ANTI-VOMITING ACTIVITY OF CANNABIDIOL COMPOUNDS**

(75) Inventors: **Raphael Mechoulam**, Jerusalem (IL); **Linda Parker**, Waterloo (CA); **Aviva Breuer**, Jerusalem (IL)

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(21) Appl. No.: **10/368,935**

(22) Filed: **Feb. 19, 2003**

(30) **Foreign Application Priority Data**

Feb. 19, 2002 (IL) 148,244

Publication Classification

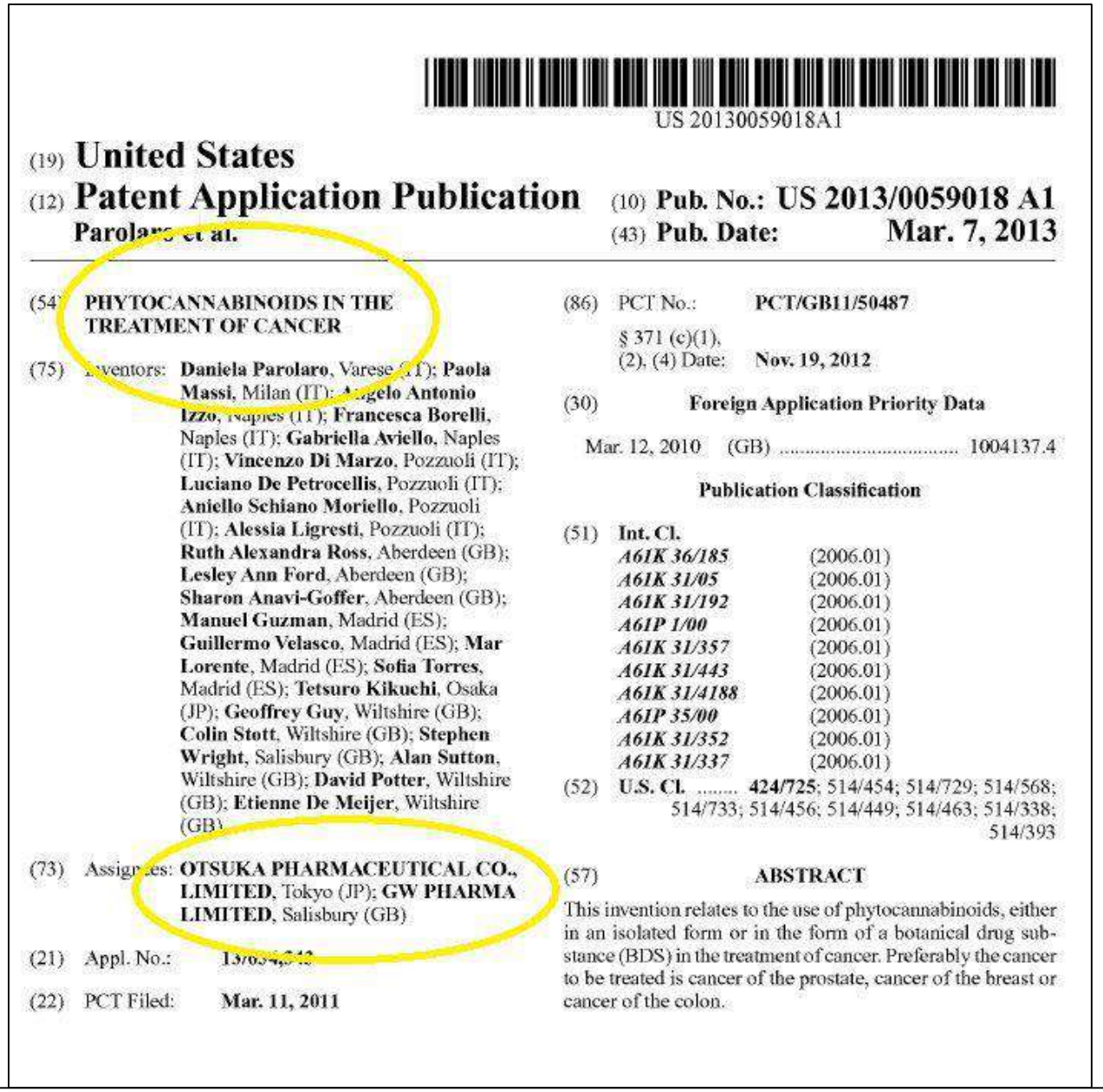
(51) **Int. Cl.**[7] **A61K 31/353**; A61K 31/16

(52) **U.S. Cl.** **514/454**; 514/627

(57) **ABSTRACT**

The present invention relates the use of certain cannabidiol derivatives and of their dimethyl heptyl homologs (CBD-DMH) in the treatment of nausea, in particular chemotherapy-induced nausea, and of anti vomiting activity. The present invention relates also to the use of said cannabidiol derivatives being part of a pharmaceutical composition.

- **United States Patent: Anti-nausea and anti-vomiting activity of cannabidiol compounds**



US 20130059018A1

(19) **United States**

(12) **Patent Application Publication**

Parolaro et al.

(10) **Pub. No.: US 2013/0059018 A1**

(43) **Pub. Date: Mar. 7, 2013**

(54) **PHYTOCANNABINOIDS IN THE TREATMENT OF CANCER**

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(73) Assignees: **OTSUKA PHARMACEUTICAL CO., LIMITED**, Tokyo (JP); **GW PHARMA LIMITED**, Salisbury (GB)

(21) Appl. No.: 13/634,242

(22) PCT Filed: **Mar. 11, 2011**

(86) PCT No.: **PCT/GB11/50487**

§ 371 (c)(1),
(2), (4) Date: **Nov. 19, 2012**

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Publication Classification

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A61K 31/05	(2006.01)
A61K 31/192	(2006.01)
A61P 1/00	(2006.01)
A61K 31/357	(2006.01)
A61K 31/443	(2006.01)
A61K 31/4188	(2006.01)
A61P 35/00	(2006.01)
A61K 31/352	(2006.01)
A61K 31/337	(2006.01)

(52) **U.S. Cl.** **424/725**; 514/454; 514/729; 514/568; 514/733; 514/456; 514/449; 514/463; 514/338; 514/393

(57) **ABSTRACT**

This invention relates to the use of phytocannabinoids, either in an isolated form or in the form of a botanical drug substance (BDS) in the treatment of cancer. Preferably the cancer to be treated is cancer of the prostate, cancer of the breast or cancer of the colon.

- **United States Patent: Phytocannabinoids in the Treatment of Cancer**

US009730911B2

(12) **United States Patent**
Verzura et al.

(10) **Patent No.: US 9,730,911 B2**
(45) **Date of Patent: Aug. 15, 2017**

(54) ***CANNABIS* EXTRACTS AND METHODS OF PREPARING AND USING SAME**

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(73) Assignee: **United Cannabis Corp.**, Denver, CO (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **14/919,245**

(22) Filed: **Oct. 21, 2015**

(65) **Prior Publication Data**

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Related U.S. Application Data

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(51) **Int. Cl.**

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A61K 31/353	(2006.01)
A61K 31/192	(2006.01)
A61K 31/352	(2006.01)
A61K 31/05	(2006.01)
A61K 36/185	(2006.01)

(52) **U.S. Cl.**

CPC ***A61K 31/353*** (2013.01); ***A61K 31/05*** (2013.01); ***A61K 31/192*** (2013.01); ***A61K 31/352*** (2013.01); ***A61K 36/185*** (2013.01)

(58) **Field of Classification Search**

USPC 514/454, 729, 568

See application file for complete search history.

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Primary Examiner — Rei-Tsang Shiao

(74) *Attorney, Agent, or Firm* — Cooley LLP; Ivor Elrifi; Cynthia Kozakiewicz

(57) **ABSTRACT**

The invention relates to the extraction of pharmaceutically active components from plant materials, and more particularly to the preparation of a botanical drug substance (BDS) for incorporation in to a medicament. It also relates to a BDS, for use in pharmaceutical formulations. In particular it relates to BDS comprising cannabinoids obtained by extraction from *cannabis*.

36 Claims, No Drawings