Quality Control of Cannabis-Derived Prescription Drugs

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Outline

Cannabis as a source of mainstream (prescription) drugs

The origin issue: Natural vs synthetic phytocannabinoids

Coping with the residual phytochemical complexity of Cannabis extracts

Conclusions

Mainstream pharmaceuticals derived from Cannabis

Dronabinol (1986)*

Semi-synthetic Δ^9-THC

- Indications:

HIV/AIDS-induced anorexia

chemotherapy-induced nausea /vomiting

- Formulation:

Suspension in sesame oil encapsulated in soft gel gelatin capsules (2.5-10 mg)

Nabiximols (2010)**

Combo of two carbonic extracts from Δ^9-THC and CBD-rich Cannabis strains

- Indications:

Spasticity associated to MS (overactive bladder, neuropathic pain)

- Formulation:

Oral spray delivering 2.7 mg THC and 2.5 mg CBD per puff

Epidi(y)olex (2018)***

Natural CBD

- Indications:

Adjunctive therapy for seizures associated with LGS and DS and tuberous sclerosis complex

- Formulation:

Oral solution (100 mg/mL) dosed At 2-12.5 mg/Kg BID

* FDA approval (Schedule III drug) ** MHRA approval (Schedule 4 drug) *** FDA approval (Schedule V drug)

Why the focus on the origin and the production method?

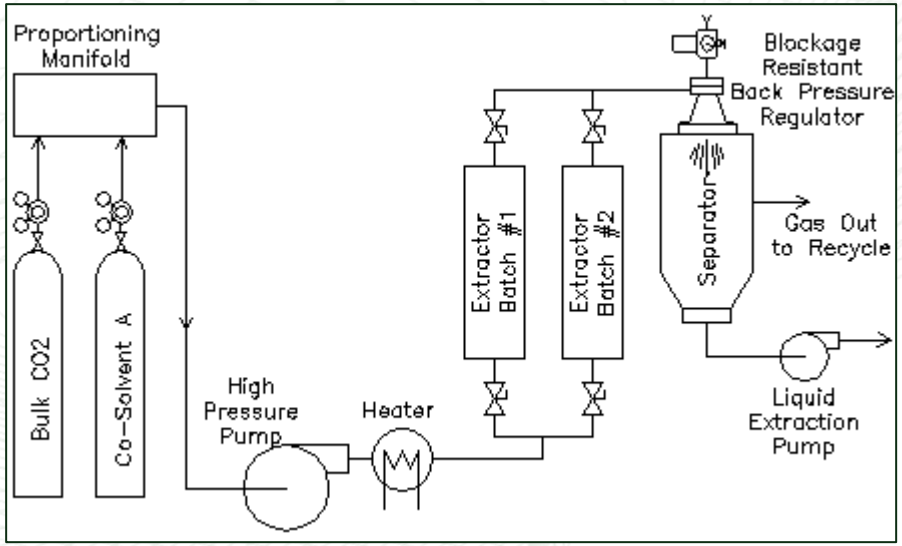
The qualification of the starting material

The qualified starting material depends on the nature of the product:

Cannabidiol (CBD)(from hemp) for the semi-synthesis Δ^9-THC

Non narcotic Cannabis strains for the isolation of CBD as an API (Epidiolex)

Specific Cannabis strains (*Cannabis sativa folium cum flore*, *Botanical Drug Substances*) for the preparation of the carbonic extracts of Nabiximols



A rose is a rose is a rose… Or not? Synthetic *vs* natural phytocannabinoids

Isolation

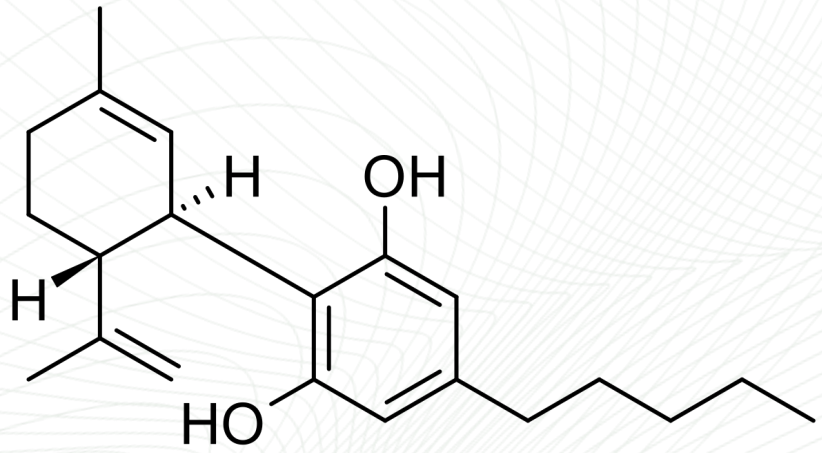
a) from *marijuana* (*Cannabis* > 0.3% THC)

b) from hemp (*Cannabis* <0.3% THC)

b) from non-*Cannabis* plant sources*

c) from transgenic organisms (plants, yeasts)

Semi-synthesis



* Claim from flax is unconfirmed and the one from hops have been shown to be fraudolent

CBDs of different origin have different regulatory status

USA:

CBD from marijuana: schedule I controlled substance

CBD from hemp: API, also a cosmetics ingredient but not a dietary ingredient (federal law, allowed by regional law in some States (CA, NY)

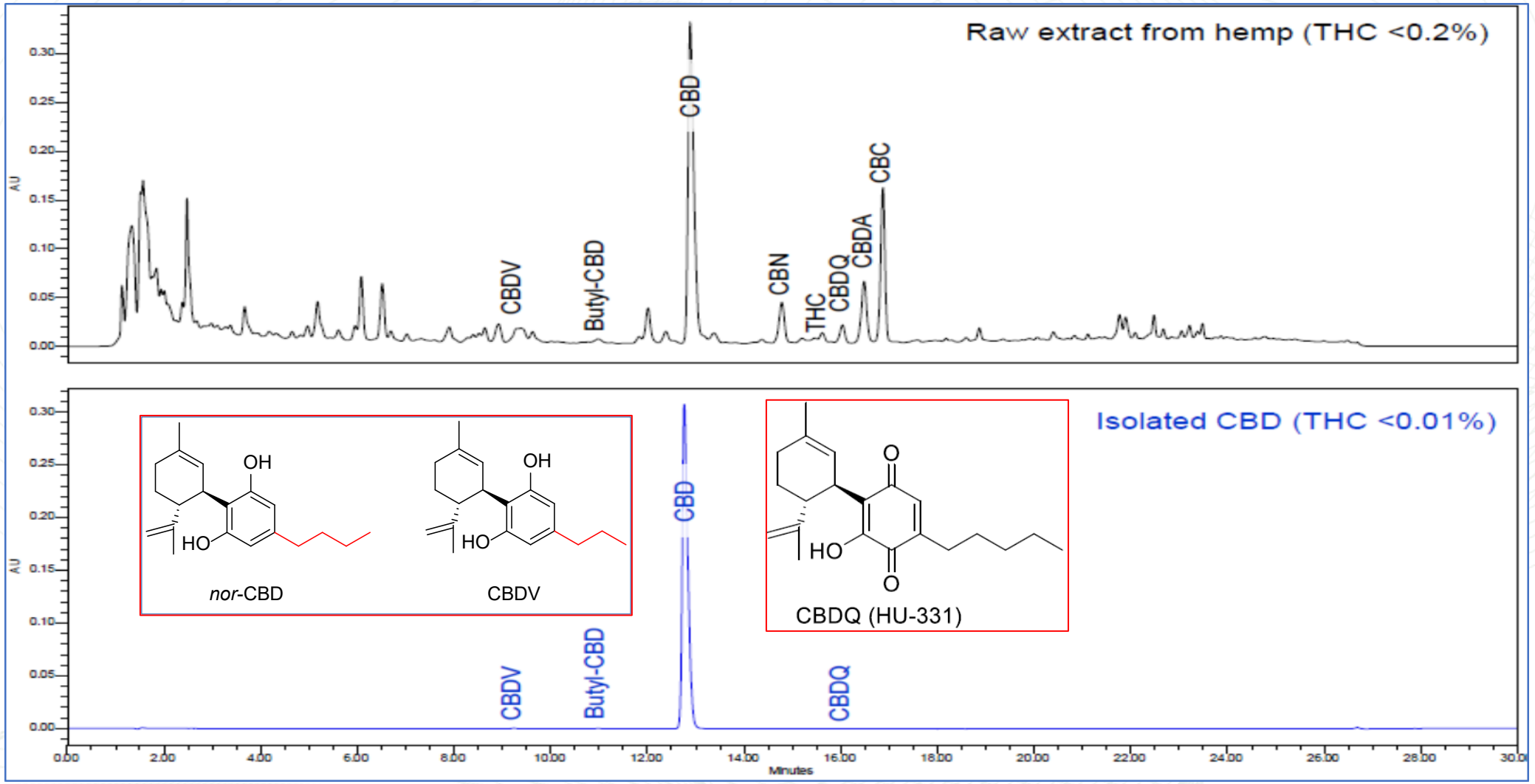
Semi-synthetic CBD: schedule I controlled substance

EU:

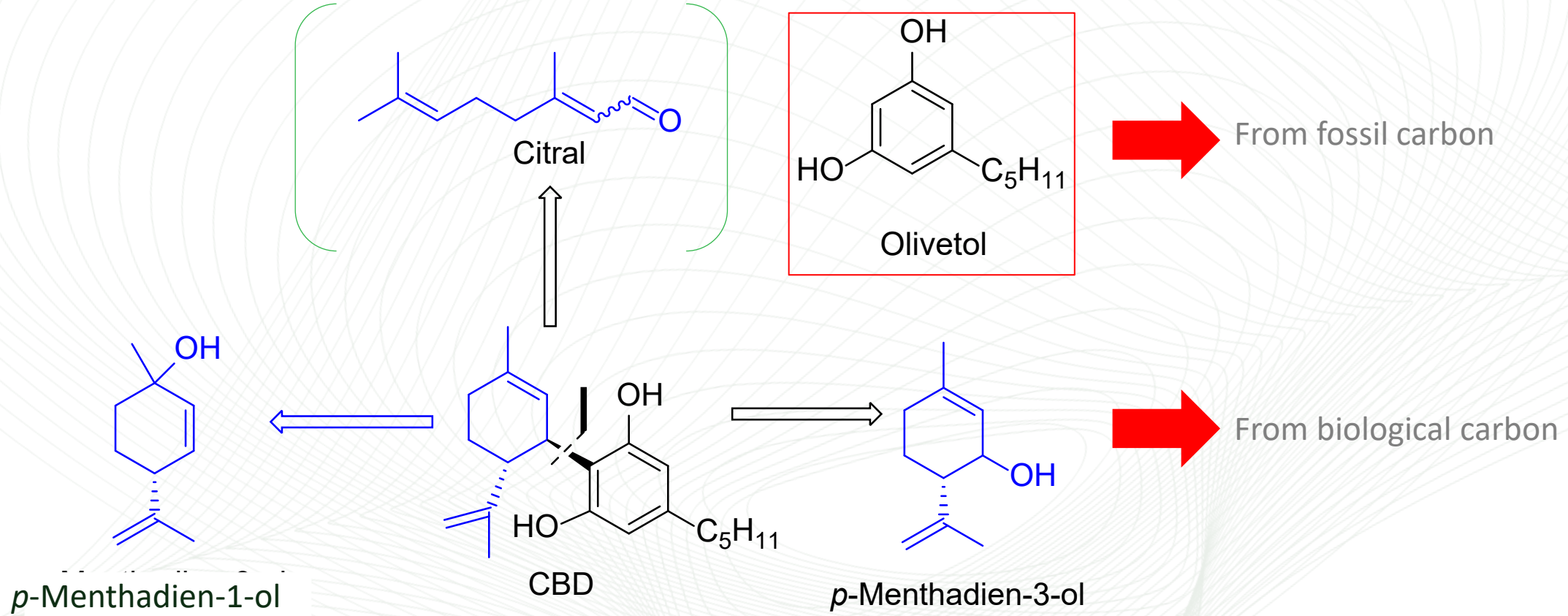
CBD from isolation : API and cosmetic ingredient

CBD from semi-synthesis: API and cosmetic ingredient

Natural *vs* synthetic phytocannabinoids: Chromatographic differentiation based on residual phytochemical complexity

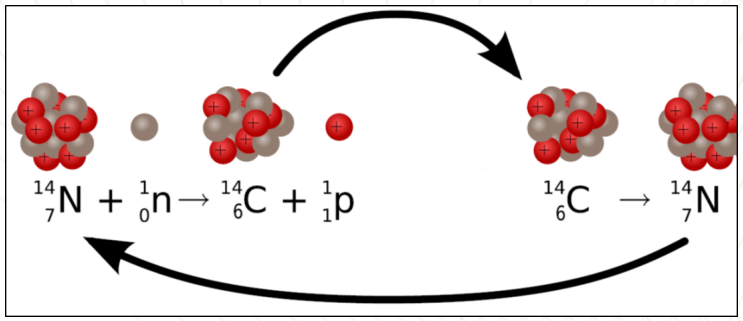


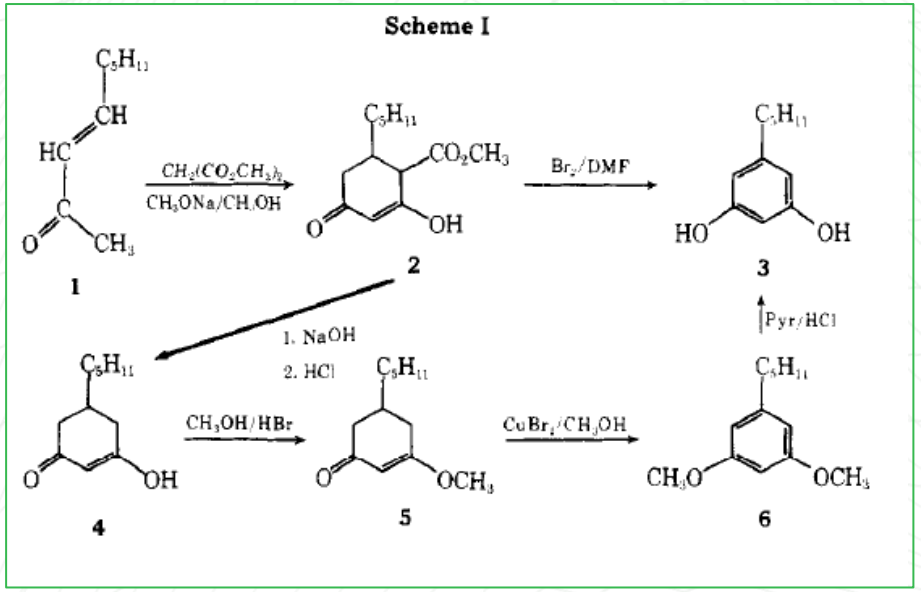
The synthesis of phytocannabinoids



Natural vs synthetic phytocannabinoids: Differentiation based on isotopical analysis and residual synthetic complexity

Isotopic analysis:
Olivetol is synthesized from ^{14}C-depleted carbon sources (methylheptenylketone and dimethylmalonate)





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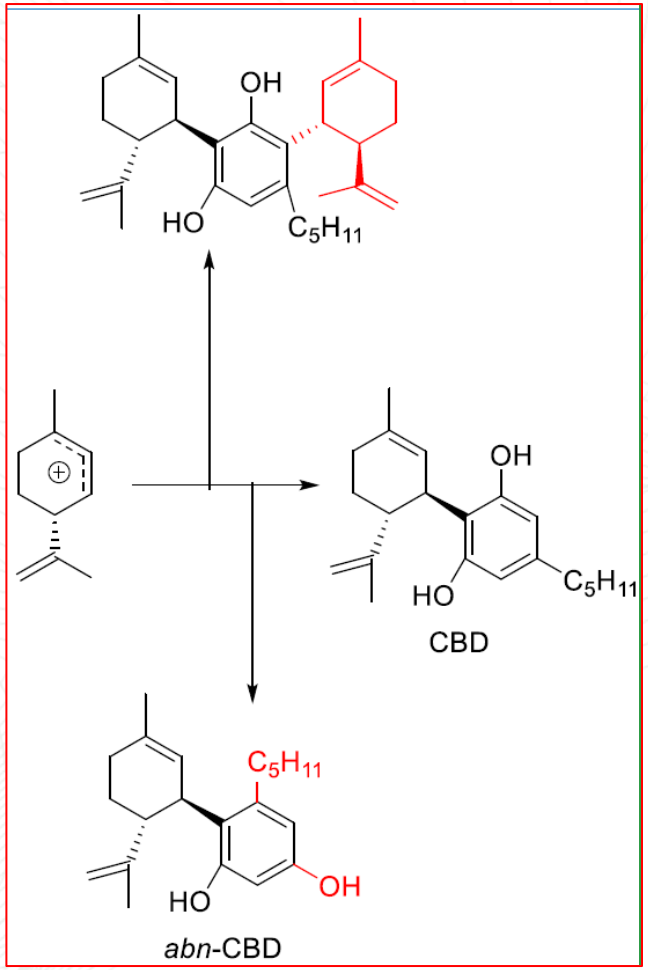
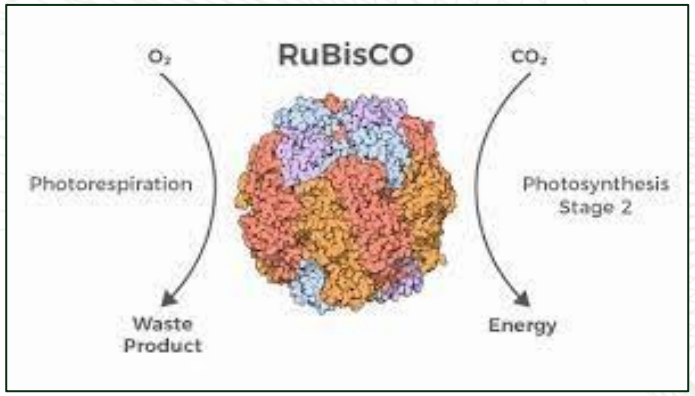


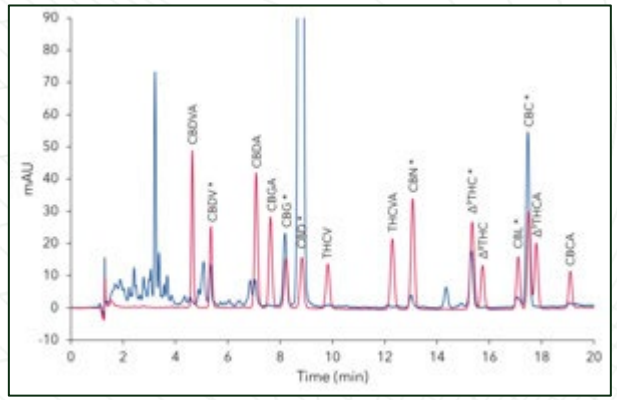
Natural carbon is lighter than geological carbon due to a lower contents of the ^{13}C isotope



The residual synthetic complexity is different from the residual phytochemical complexity

Coping with the exuberance of Cannabis phytochemistry

To qualify an extract as a Botanical Drug Substance:



- The starting plant material (herbal substance) need to be grown under GAP practices and its batches proved to comply with the proposed specs
- The preparation of the extract need to be adequately described, and appropriate in-process controls implemented
- COA (certificates of analysis) are needed for all starting material (herbal substance and solvents), along with specific identification tests
- Appropriate characterization of the extract need to have been undertaken and appropriate specs provided
- All potential toxic impurities present in the extract need to be identified and characterized
- Appropriate data of stability need to be provided to support a proper retest period
- Analytical methods need to be appropriately validated and be satisfactory for ensuring compliance with the extract specifications

Conclusions

- ✓ For Cannabis-based pharmaceutical products, origin and not only identity is important
- ✓ The regulatory status of CBD needs harmonization between EU and USA in terms of origin (natural/semi-synthetic) and realms of use
- ✓ Natural and synthetic phytocannabinoids can be distingued based on residual chemical complexity (phytochemical vs synthetic) and isotopic contents
- ✓ The qualification of an extract as a Botanical Drug Substance requires interfacing GAP and GMP rules

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