Phytocannabinoid DDIs and their clinical implications

UNIVERSITY OF ALBERTA
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Phytocannabinoid drug-drug interactions and their clinical implications

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Outline

1. Introduction
2. Phytocannabinoids chemistry and indications
3. Phytocannabinoids metabolic route
   A. Reported in the literature
   B. Predicted by ADMET Predictor®
4. Potential DDIs involving phytocannabinoids
5. Conclusion

1. Introduction

Cannabis: Fiber, Food, Medicine or Narcotic?

- What should you know about Cannabis?


October 17
Legal Cannabis in Canada

Canada History

Drug prohibition in Canada began with the Opium Act of 1908, which prohibited the sale, manufacture, and importation of opium for other than medicinal use.

This was followed by the Opium and Drug Act of 1911, which outlawed the sale or possession of morphine, opium, or cocaine.

Cannabis was added under the *Narcotics Drug Act Amendment Bill* in 1923.

The government introduced the *Act to Prohibit the Improper Use of Opium and other Drugs*;

Since than marijuana was listed as narcotic drug.

October 17th 2018 legalized.

USA

- Attorney General John Mitchell of the Nixon administration placed marijuana in Scheldule I category in **1972** as part of the ranking or "scheduling" of all drugs under the 1970 Controlled Substances Act.
- Schedule I drugs are deemed to **have no medical use and a high potential for abuse**.

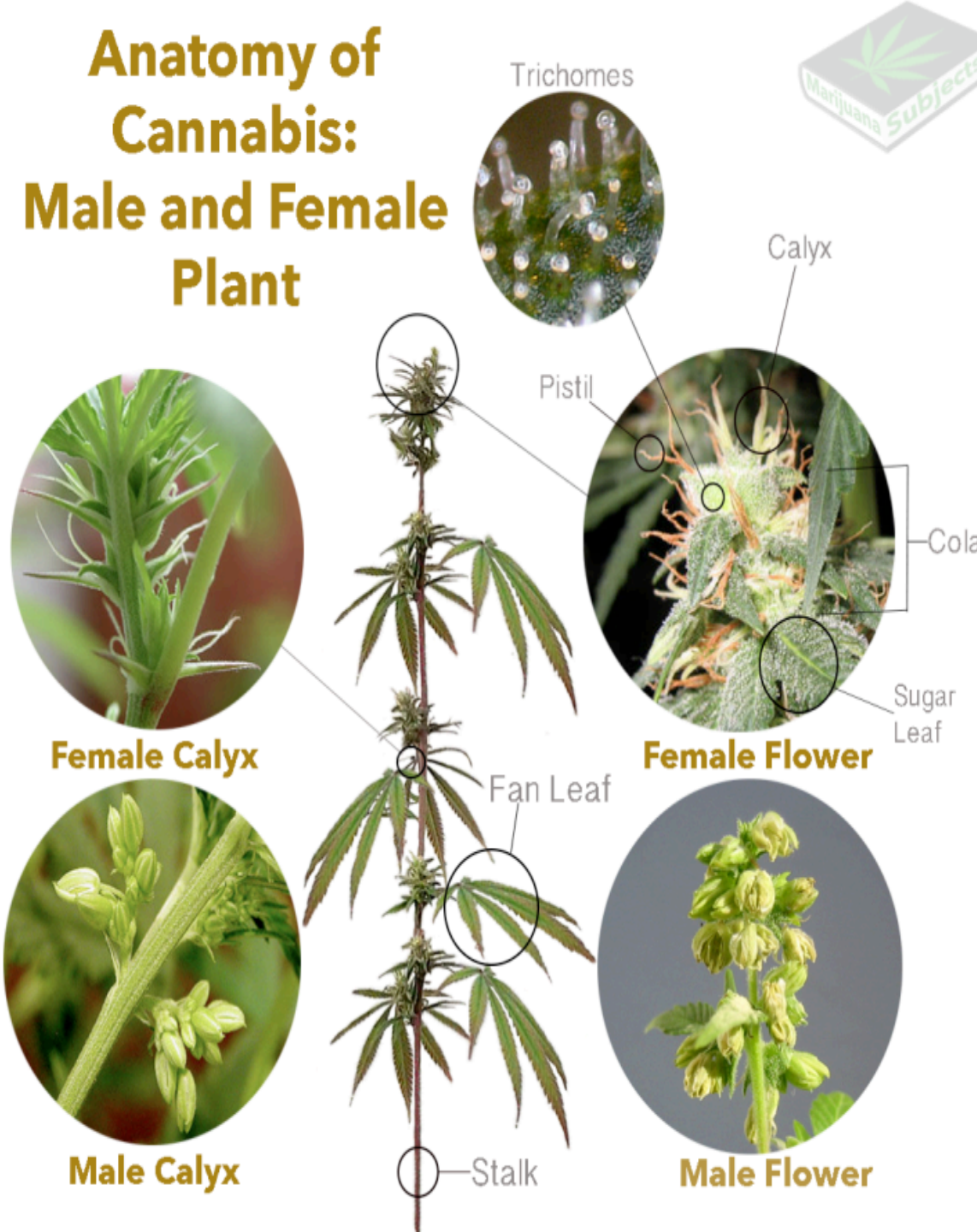
- **"In strict medical terms marijuana is far safer than many foods we commonly consume. For example, eating 10 raw potatoes can result in a toxic response. By comparison, it is physically impossible to eat enough marijuana to induce death. Marijuana in its natural form is one of the safest therapeutically active substances known to man. By any measure of rational analysis marijuana can be safely used within the supervised routine of medical care.**

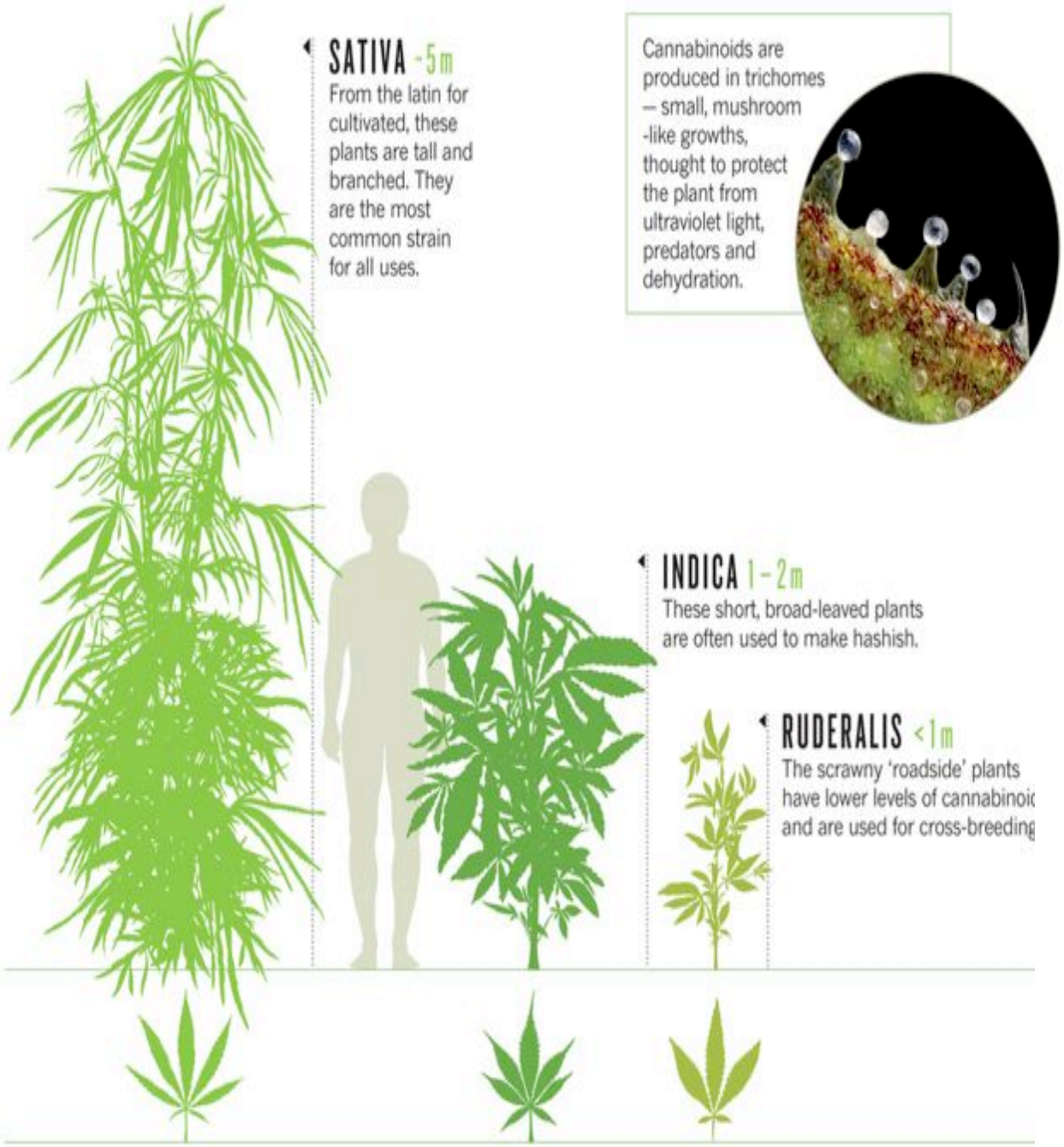
  [DEA Administrative Law Judge - 1988]"

Marijuana is the most trafficked drug in the world

- In Canada alone the illegal trade of marijuana reaps an estimated $7 billion in income annually for organized crime.
- In addition, the administrative burden and social harms associated with the enforcement of marijuana laws, particularly for simple possession, are onerous, and need to be balanced with other safety priorities.

Dioecious male and female plants





In his original 1753 classification, Carl Linnaeus identified just one, *Cannabis sativa*. The first indication of dissent came in 1785 when another eminent biologist, Jean-Baptiste Lamarck, was given some plant specimens collected in India. *C indica*

TAXON 25(4): 405-435. AUGUST 1976

A PRACTICAL AND NATURAL TAXONOMY FOR CANNABIS*

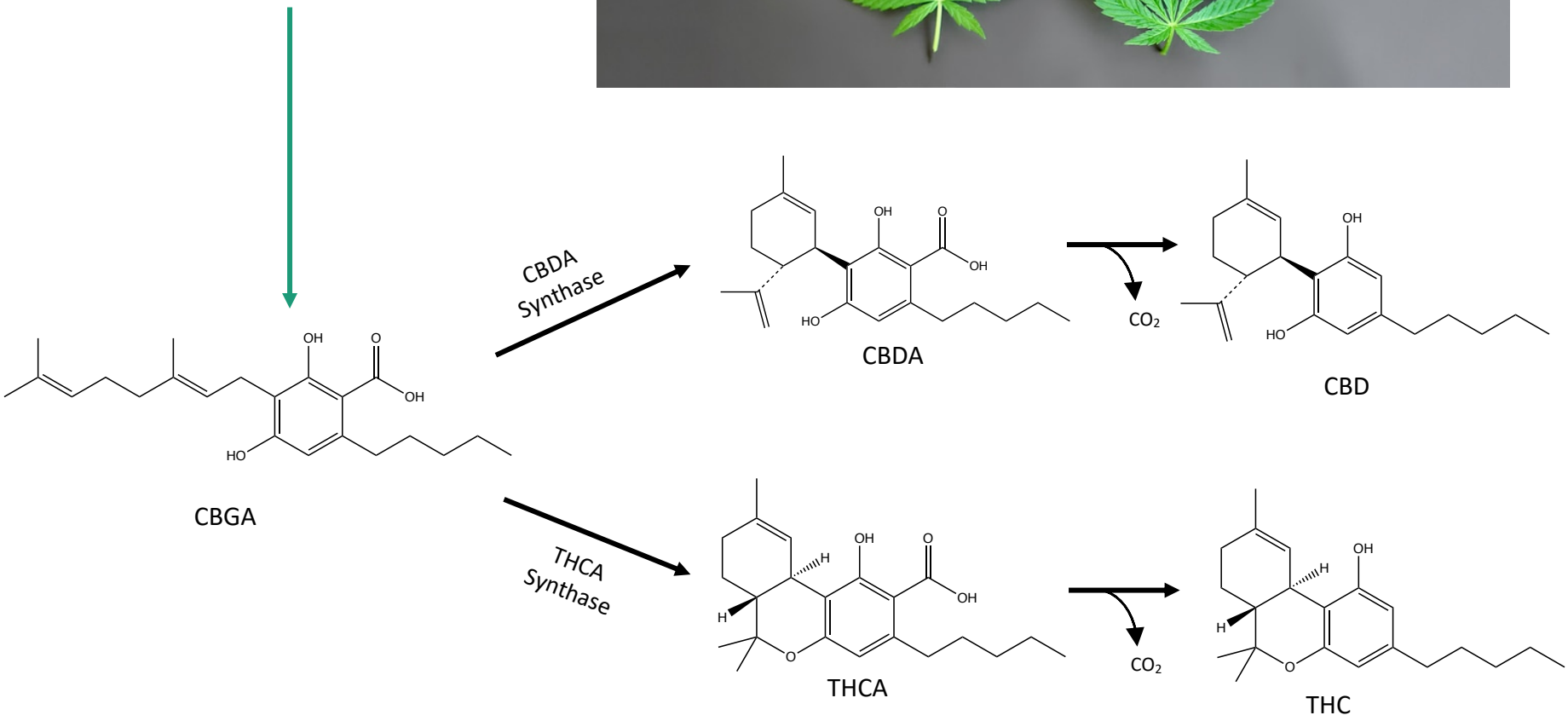
*Ernest Small** and Arthur Cronquist****

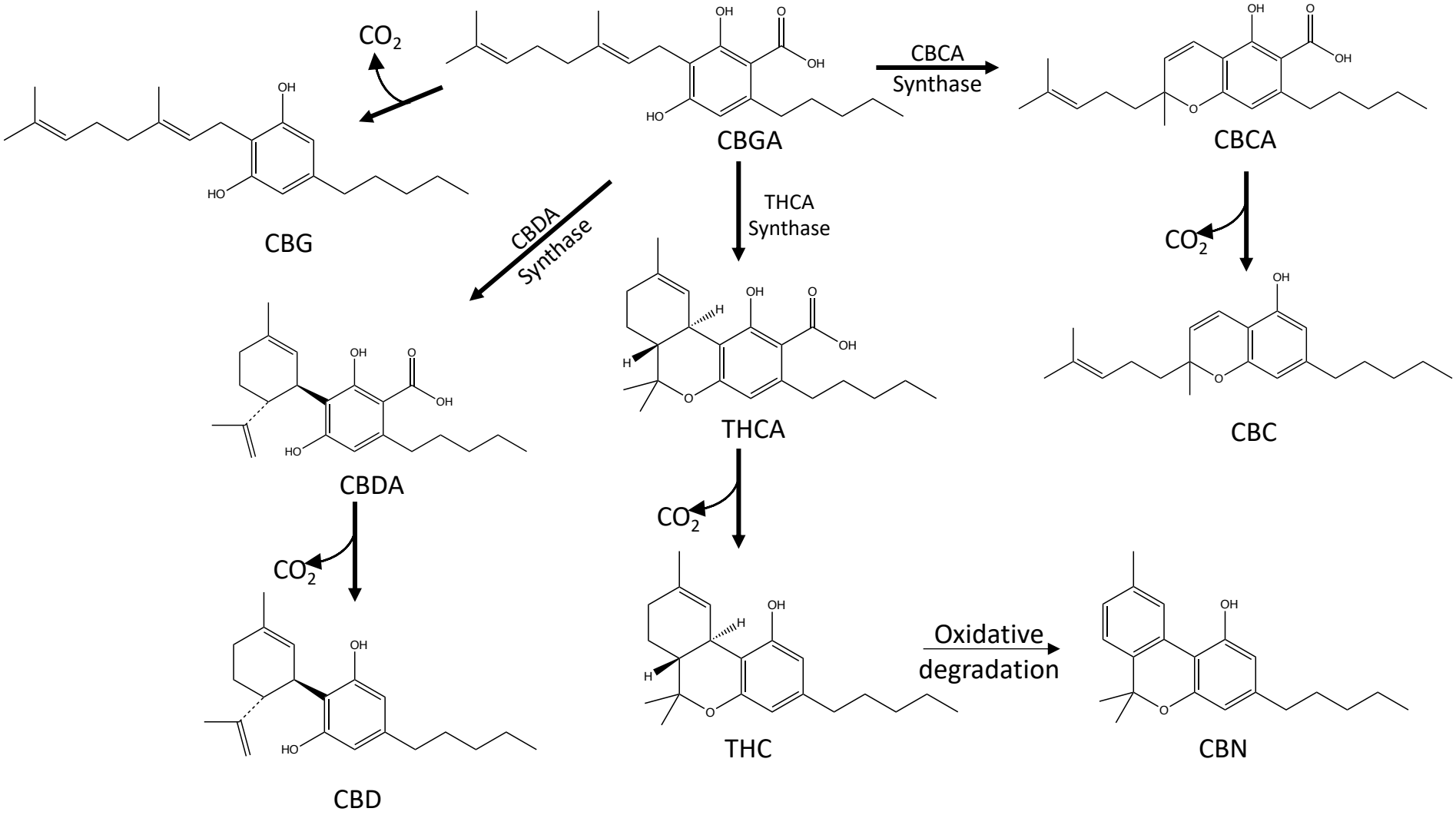
Summary

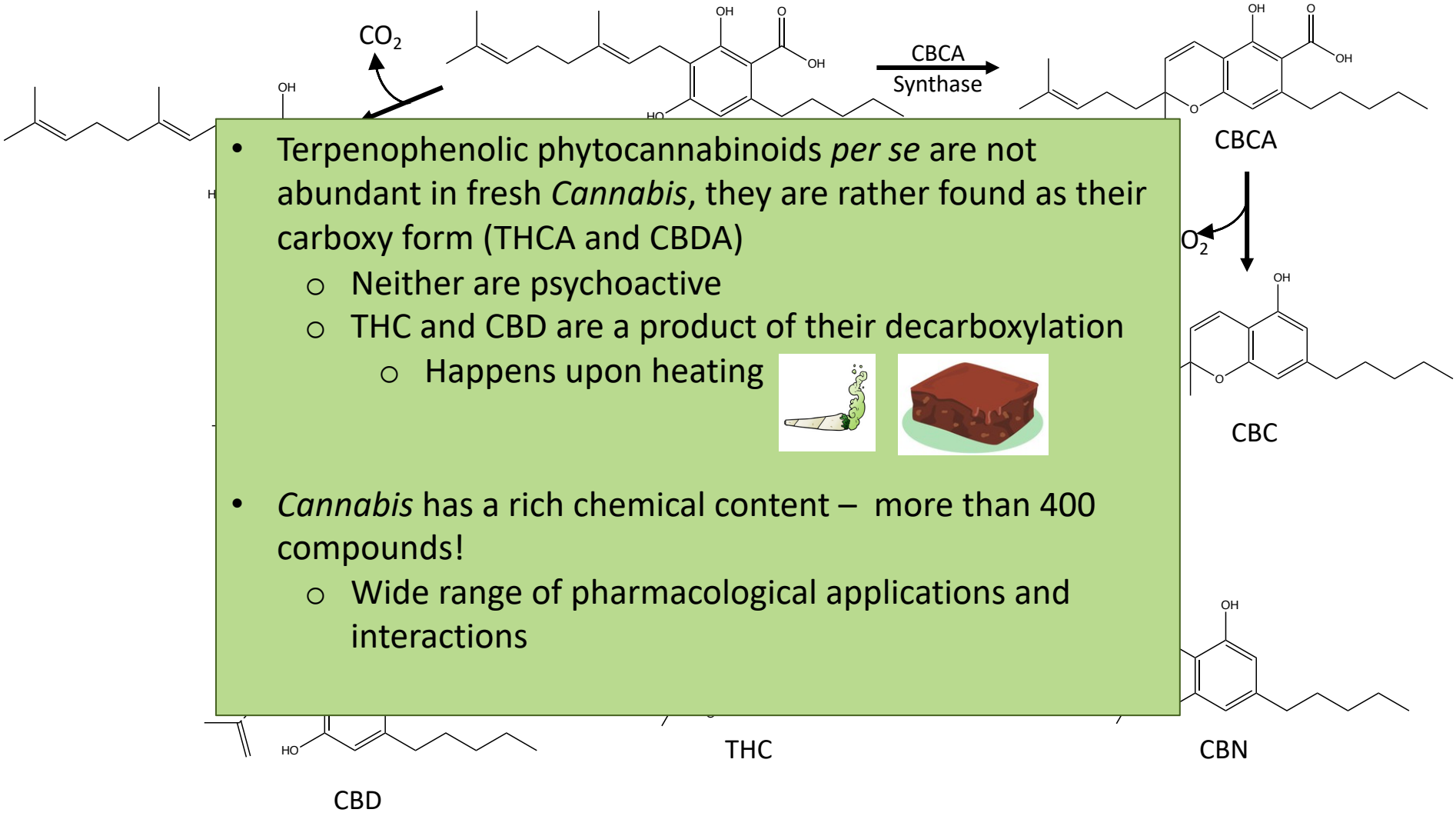
Variation in *Cannabis* is evaluated in the context of the confusing systematic history of this genus. Aside from some experimentally produced polyploids, all *Cannabis* is diploid ($n = 10$), and there appear to be no barriers to successful hybridization within the genus. The present pattern of variation is due in large part to the influence of man. Two widespread classes of plant are discernible: a group of generally northern plants of relatively limited intoxicant potential, influenced particularly by selection for fibre and oil agronomic qualities, and a group of generally southern plants of considerable intoxicant potential, influenced particularly by selection for inebriant qualities. These two groups are treated respectively as subsp. *sativa* and *indica*, of *C. sativa*, the only species of the genus *Cannabis*. Within each subspecies two parallel phases are recognizable. The "wild" (weedy, naturalized or indigenous) phase is more or less distinguishable from the domesticated (cultivated or spontaneous) phase by means of an adaptive syndrome of fruit characteristics. The resulting four discernible groups are recognized as varieties.

2. Phytocannabinoids chemistry and indications

Two major chemical constituents: CBD and THC

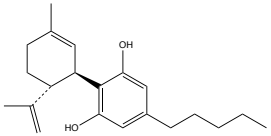



CO2
CBG
CBGA
CBCA Synthase
CBCA
CBDA Synthase
THCA Synthase
CO2
CBDA
THCA
CBC
CO2
CO2
CBD
THC
Oxidative degradation
CBN



- Terpenophenolic phytocannabinoids *per se* are not abundant in fresh *Cannabis*, they are rather found as their carboxy form (THCA and CBDA)
  - Neither are psychoactive
  - THC and CBD are a product of their decarboxylation
    - Happens upon heating

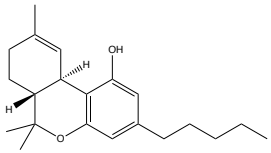
- *Cannabis* has a rich chemical content – more than 400 compounds!
  - Wide range of pharmacological applications and interactions



CBD

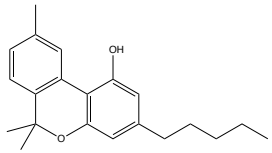
- Non-psychoactive
- Epidolex®
  - Epilepsy

- Sativex® (whole plant extract)
  - Neuropathic pain from MS
  - Cancer pain



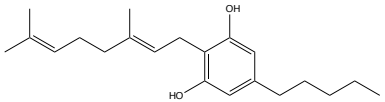
THC

- Psychoactive
- Pain management
- Antiemetic
- Antispasmodic
- Appetite stimulant
- Has been suggested for glaucoma and asthma
- Marinol® (synthetic THC) and Cesamet® (THC analog)
  - Anorexia and nausea



CBN

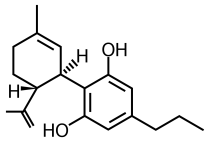
- Sedative
- Antibacterial



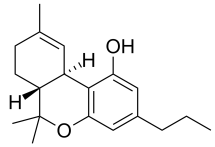
CBG

- Anti-inflammatory
- Antibiotic
- Antifungal

Propyl homologues of CBD and THC



CBDV



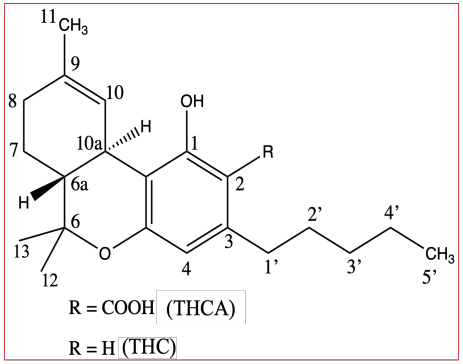
THCV

- Therapeutic potential for reducing nausea

3. Phytocannabinoids metabolic route

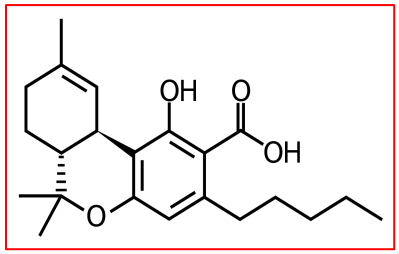
A. Reported in the literature

Dibenzopyran numbering system



THCA

Non-psychoactive and is not converted to THC *in vivo*



Glucuronic acid conjugation

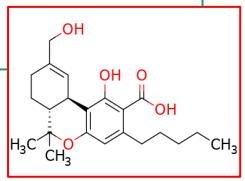
CYP — Hydroxylation at C8

8α-OH-THCA and 8β-OH-THCA

Dehydration

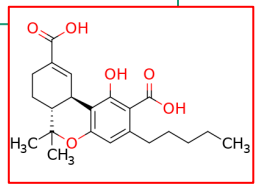
CYP — Hydroxylation at C11

11-hydroxy-Δ9-tetrahydrocannabinolic acid-A (11-OH-THCA)

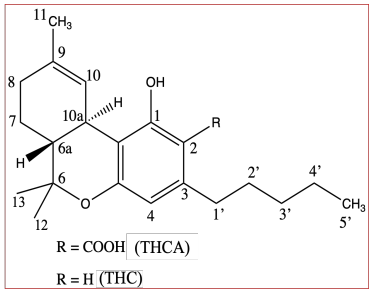


CYP

11-nor-9-carboxy-Δ9-tetrahydrocannabinolic acid-A (THCA-COOH)



Main CYP enzymes involved:
2C9
3A4
2C8
2C19
3A5



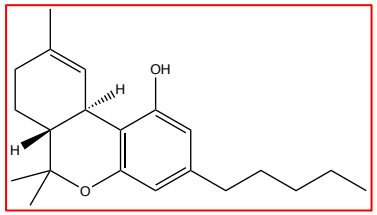
THC

Hydroxylation at C8 followed by dehydration

CYP3A4

CYP3A4

Epoxide at C9–10 followed by hydrolysis or glutathione conjugation.



Hydroxylation at C'1 to C'5 of the side chain

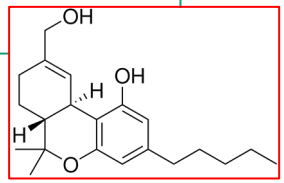
Glucuronic acid conjugation

CYP2C9

Hydroxylation at C11

MAJOR METABOLITE IN FECES

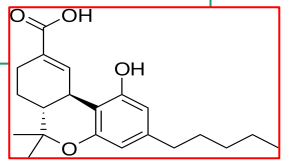
11-hydroxy-Δ^9-tetrahydrocannabinol (11-OH-THC)



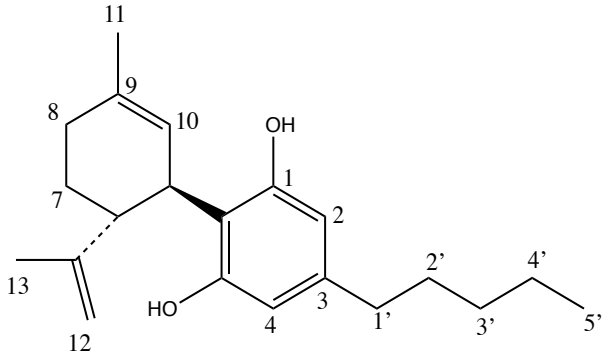
CYP

MAJOR METABOLITE IN URINE (as glucuronide conjugate)

11-nor-9-carboxy-Δ^9-tetrahydrocannabinol (THC-COOH)



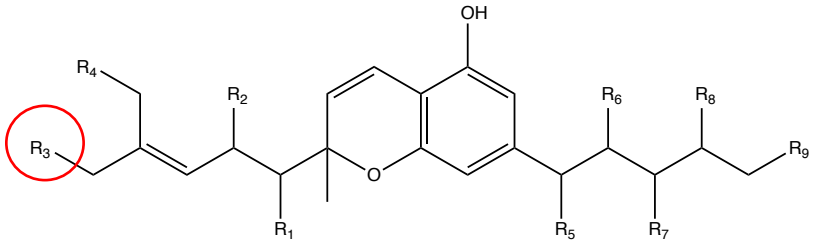
CBD



ENZYME	METABOLITE
CYP1A1	8α/β-OH-, 11-OH-, and 1'-OH-CBD
CYP1A2	8α/β-OH-CBD, 1'-, 2'-, 3'-, and 4'-OH-CBD
CYP2C19	8α-OH-, 11-OH-, and 4'-OH-CBD
CYP2D6	8α/β-OH-CBD, 11-OH-, 4'-OH-, and 5'-OH-CBD
CYP3A4	8α/β-OH-CBD, 11-OH-, 2'-OH-, 4'-OH-, and 5'-OH-CBD
CYP3A5	8α/β-OH-CBD, 11-OH-, 2'-OH-, 3'-OH, and 4'-OH-CBD
CYP2A9 (Minor)	8α/β-OH-, 11-OH-, 4'-OH-, and 5'-OH-CBD

Phase II metabolism involves glucuronidation of CBD at the phenolic oxygen as well as the hydroxylated metabolites. Sulfonation of CBD species may also occur

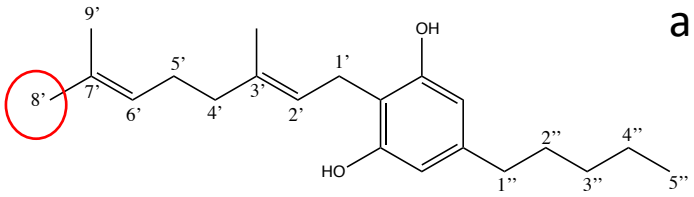
Rank order of *in vitro* CBC metabolites identified in mouse and rabbit microsomes



CBC

METABOLITE	R1	R2	R3	R4	R5	R6	R7	R8	R9	MOUSE	RABBIT
1'-OH	OH	H	H	H	H	H	H	H	H	8	-
2'-OH	H	OH	H	H	H	H	H	H	H	4	-
5'-OH	H	H	OH	H	H	H	H	H	H	1	1
6'-OH	H	H	H	OH	H	H	H	H	H	2	4
1''-OH	H	H	H	H	OH	H	H	H	H	5	6
2''-OH	H	H	H	H	H	OH	H	H	H	7	10
3''-OH	H	H	H	H	H	H	OH	H	H	6	3
4''-OH	H	H	H	H	H	H	H	OH	H	3	2
5''-OH	H	H	H	H	H	H	H	H	OH	5	5
1'',5'-Di-OH	H	H	OH	H	OH	H	H	H	H	-	12
1'',6'-Di-OH	H	H	H	OH	OH	H	H	H	H	-	13
3'',5'-Di-OH	H	H	OH	H	H	H	OH	H	H	-	9
3''-6'-Di-OH	H	H	H	OH	H	H	OH	H	H	-	8
4'',5'-Di-OH	H	H	OH	H	H	H	H	OH	H	-	7
4'',6'-Di-OH	H	H	H	OH	H	H	H	OH	H	-	6
5'',5'-Di-OH	H	H	OH	H	H	H	H	H	OH	-	11
5'',6'-Di-OH	H	H	H	OH	H	H	H	H	OH	-	6

Rank order of *in vitro* CBG metabolites identified in liver microsomes from different animals



CBG

METABOLITE	MOUSE	RAT	GUINEA PIG	RABBIT	CAT
1''-OH	4	7	T	4	7
2''-OH	-	-	6	-	-
3''-OH	7	6	2	5	6
4''-OH	2	4	5	3	3
5''-OH	4	7	T	4	7
4'-OH	3	3	3	5	5
8'-OH	5	1	1	1	1
9'-OH	7	5	6	5	2
6',7'-Epoxide	1	2	4	2	4
6',7'-Di-OH	6	-	6	-	T
6',7'-H2	-	5	-	-	1

3. Phytocannabinoids metabolic route

B. Predicted by ADMET Predictor®

In silico predictions can be useful to suggest the role of CYP isoforms in phytocannabinoid metabolism → guidance for *in vitro* metabolism studies with recombinant human enzymes.

Chemical Structures:
THC, THCA, CBD, CBDA, CBC, CBCA, CBG ,CBGA, THCV and CBDV

CYP Inhibitor

5 CYP isoforms:
1A2, 2C9, 2C19, 2D6 and 3A4

CYP Substrate

9 CYP isoforms:
1A2, 2C9, 2C19, 2D6, 3A4, 2A6, 2B6, 2C8 and 2E1

1 cycle

Metabolites (and their %)

Additional Information:
- Fraction unbound to plasma protein
- OATP and OCT inhibition
- Pgp substrate and inhibition

Predicted phytocannabinoid substrates of CYP isoforms by ADMET Predictor®. The percentages shown within parentheses represent the degree of confidence.

CYP isoform	THCA	THC	CBDA	CBD	CBCA	CBC	CBGA	CBG	THCV	CBDV
CYP1A2	No (97%)	Yes (54%)	No (97%)	**No (89%)**	No (66%)	Yes (73%)	No (89%)	Yes (88%)	Yes (67%)	No (84%)
CYP2A6	No (60%)	Yes (69%)	No (98%)	No (88%)	No (86%)	Yes (61%)	No (98%)	No (98%)	Yes (69%)	No (79%)
CYP2B6	No (98%)	**No (89%)**	No (98%)	No (98%)	No (98%)	No (98%)	No (98%)	No (98%)	Yes (60%)	No (98%)
CYP2C8	Yes (77%)	**No (71%)**	Yes (77%)	No (71%)	Yes (77%)	No (76%)	Yes (64%)	No (83%)	No (67%)	No (71%)
CYP2C9	Yes (73%)	**Yes (73%)**	Yes (73%)	**Yes (73%)**	Yes (73%)	Yes (73%)	Yes (73%)	Yes (55%)	Yes (73%)	Yes (73%)
CYP2C19	No (80%)	**Yes (71%)**	No (82%)	**Yes (71%)**	No (71%)	Yes (71%)	Yes (31%)	Yes (71%)	Yes (71%)	Yes (71%)
CYP2D6	No (82%)	Yes (41%)	No (86%)	**Yes (42%)**	No (86%)	Yes (42%)	No (95%)	Yes (45%)	Yes (48%)	Yes (42%)
CYP2E1	No (89%)	No (97%)	No (81%)	No (81%)	No (85%)	No (97%)	No (70%)	No (59%)	No (97%)	No (79%)
CYP3A4	No (41%)	**Yes (83%)**	No (59%)	**No (43%)**	No (52%)	No (47%)	No (84%)	No (84%)	Yes (85%)	No (43%)

Green indicates prediction in agreement with literature data
Red indicates prediction in disagreement with literature data

Predicted phytocannabinoid inhibitors of CYP isoforms by ADMET Predictor®. The percentages shown within parentheses represent the degree of confidence.

CYP isoform	THCA	THC	CBDA	CBD	CBCA	CBC	CBGA	CBG	THCV	CBDV
CYP1A2	Yes (55%)	**No (59%)**	No (86%)	**No (97%)**	No (51%)	No (73%)	No (90%)	No (97%)	No (73%)	No (97%)
CYP2C9	Yes (63%)	**Yes (34%)**	Yes (43%)	**Yes (64%)**	Yes (57%)	Yes (39%)	Yes (63%)	Yes (43%)	Yes (61%)	No (62%)
CYP2C19	No (99%)	No (82%)	No (58%)	**Yes (18%)**	No (99%)	No (81%)	No (99%)	Yes (78%)	No (86%)	No (82%)
CYP2D6	No (95%)	No (65%)	No (86%)	**Yes (70%)**	No (84%)	Yes (44%)	No (80%)	Yes (45%)	No (72%)	Yes (55%)
CYP3A4	No (71%)	No (90%)	No (66%)	**No (71%)**	No (68%)	No (81%)	No (68%)	No (78%)	No (90%)	No (81%)

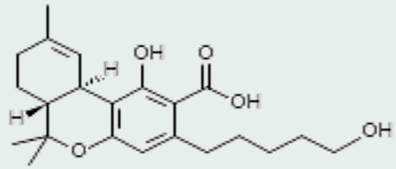
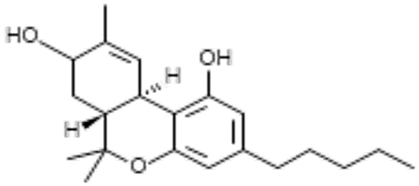
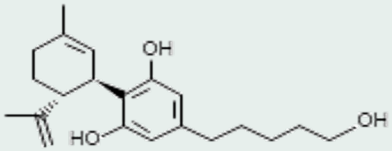
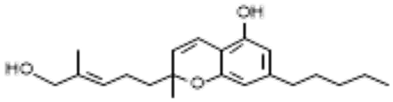
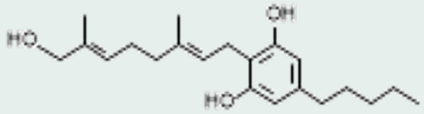
Green indicates prediction in agreement with literature data
Red indicates prediction in disagreement with literature data

BCRP

OCT2

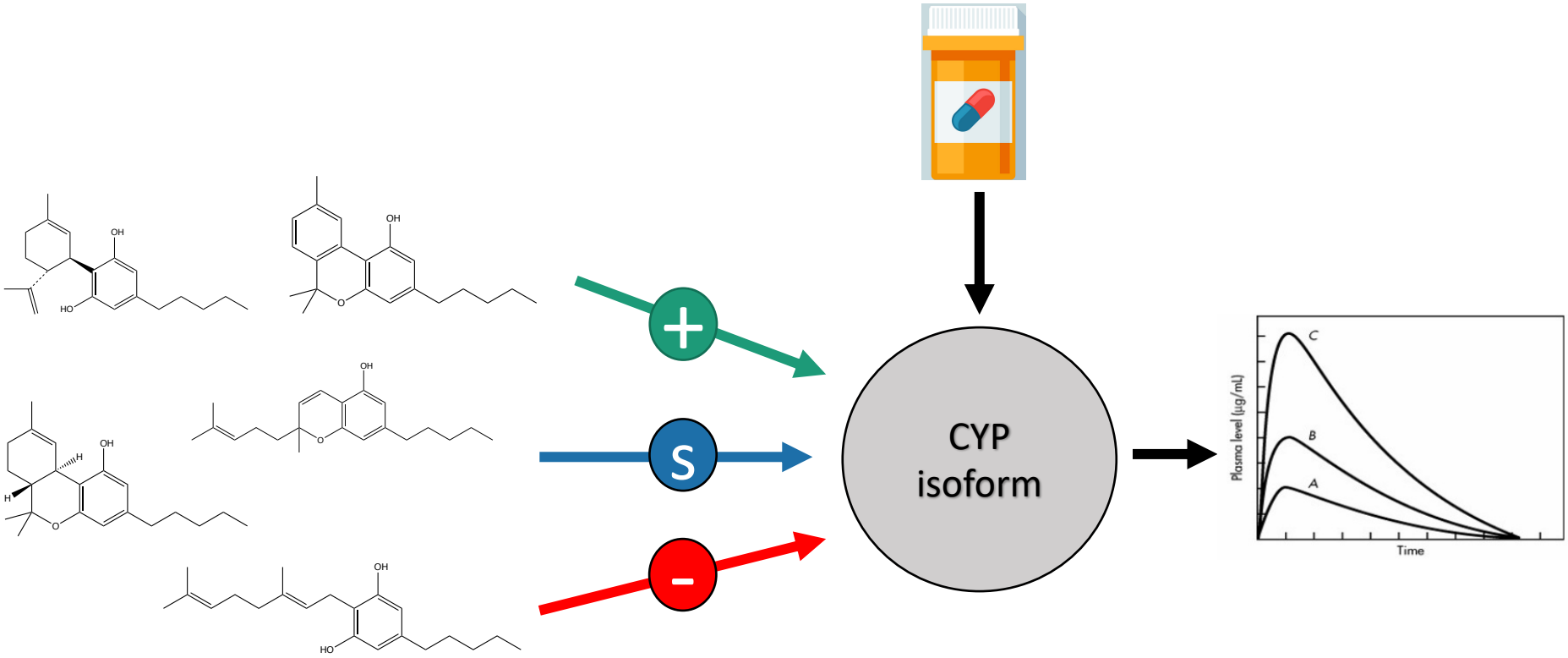
OATP

Pg-P

Cannabinoid	Metabolite structure (highest yield)	Metabolizing enzymes	Observed
THCA	 (38%)	(CYP2C8);CYP2C9	11-OH-THCA vs. Predicted only to be 19%
THC	 (25%)	CYP1A2;(CYP2A6);CYP2C9; CYP2C19;CYP2D6;CYP3A4	11-OH-THC vs. Predicted only to be 9%
CBD	 (23%)	CYP2C9; CYP2D6	NA
CBC	 (37%)	CYP1A2;(CYP2A6); CYP2C9;CYP2C19;CYP2D6	Accurate
CBG	 (24%)	CYP1A2;CYP2C9;CYP2C19;C YP2D6	Accurate

4. Potential DDIs involving phytocannabinoids

Important PK drug-interactions are CYP-based, and can occur when a compound inhibits, induces or competes for a CYP isoform that metabolizes the other concomitantly administered drug.



Probable consequence of CYP inhibition based on *in silico* results

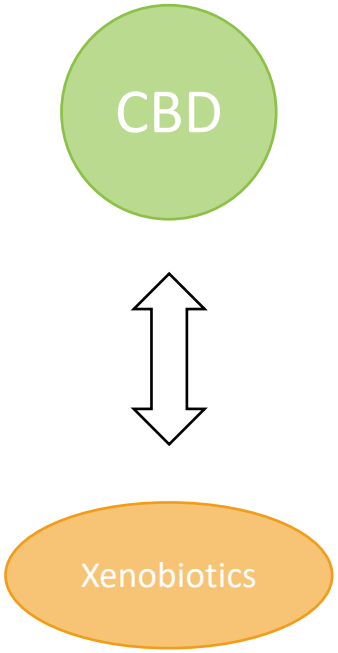
Cytochrome	Prototypical substrates[#]	Inhibited by*	Probable consequence/ Recommendation
CYP1A2	Acetaminophen, haloperidol, theophylline, warfarin	THCA	Increased drug plasma concentration/ Drug dose adjustment (Reduce)
CYP2C9	Amitriptyline, celecoxib, clopidogrel, fluoxetine, losartan, piroxicam, valproate	THCA, THC, CBDA, CBD, CBCA, CBC, CBGA, CBG, THCV	
CYP2C19	Amitriptyline, citalopram, esomeprazole, indomethacin, phenytoin	CBD, CBG	
CYP2D6	Amphetamine, carvedilol, codeine, duloxetine, lidocaine, propranolol	CBD, CBC, CBG, CBDV	
CYP3A4	Alprazolam, fentanyl, omeprazole, ritonavir, simvastatin, tamoxifen, verapamil	-	No interaction/ Maintain dose

* Based on *in silico* predictions; [#]Taken from FlockhartTable.

THC

PHARMACODYNAMIC INTERACTIONS		
Concomitant Drug	**Clinical Effect(s)**	**Recommendation**
Amitriptyline, amoxapine, desipramine, other tricyclic antidepressants	Additive tachycardia, hypertension, drowsiness	Dose adjustment
Amphetamines, cocaine, other sympathomimetic agents	Additive hypertension, tachycardia, possibly cardiotoxicity	Discontinue in cases of serious cardiac events
Atropine, scopolamine, antihistamines, other anticholinergic agents	Additive tachycardia, drowsiness	Dose adjustment
Disulfiram	A reversible hypomanic reaction was reported after smoking marijuana	Avoid smoking; Dose adjustment when taking medicinal cannabis
Fluoxetine	Hypomanic reaction after smoking marijuana.	Avoid smoking; Dose adjustment when taking medicinal cannabis
PHARMACOKINETIC INTERACTIONS		
Antipyrine, barbiturates	Decreased clearance of these agents, presumably via competitive inhibition of metabolism.	Dose adjustment, therapeutic drug monitoring
Theophylline	(CYP1A2) Increased theophylline metabolism reported with smoking of marijuana.	Avoid smoking
Valproate	(CYP2C9) Can theoretically potentiate the psychotropic effects of THC by decreasing plasma clearance.	Dose adjustment
Phenytoin	(CYP2C9) THC increased the in vitro metabolism of phenytoin	Therapeutic drug monitoring
Ethanol	Gut motility THC may delay alcohol absorption	Avoid alcohol consumption when taking medicinal cannabis

CBD is both a substrate and an inhibitor of CYP450 enzymes



- Hexobarbital (increased the bioavailability and elimination half-time) (Dose: 600mg/day).
- Clobazam (increased plasma level by 60%, and the level of its active metabolite (norclobazam) by 500%. (5 mg/kg/day - titrating up until 25 mg/kg/day).
  - ↓ clobazam dose - ↓ consequential side-effects
  - CYP3A4 and CYP2C19
- Warfarin (increased INR values
  - Warfarin dosage adjustment.
  - CYP2C9 and CYP3A4
- CYP3A4 - Macrolides, calcium channel blockers, benzodiazepines, cyclosporine, sildenafil (and other PDE5 inhibitors), antihistamines, haloperidol, anti-retrovirals, and some statins
- CYP2D6 - antidepressants, antipsychotics, beta blockers, opioids.

- Rifampicin (CYP450 inducer) - ↓ peak plasma concentration of CBD
- Ketoconazole (CYP450 inhibitor) - ↑2x peak plasma concentration of CBD

DDI is not only about metabolizing enzymes…
What about:

Pharmacodynamic interactions?

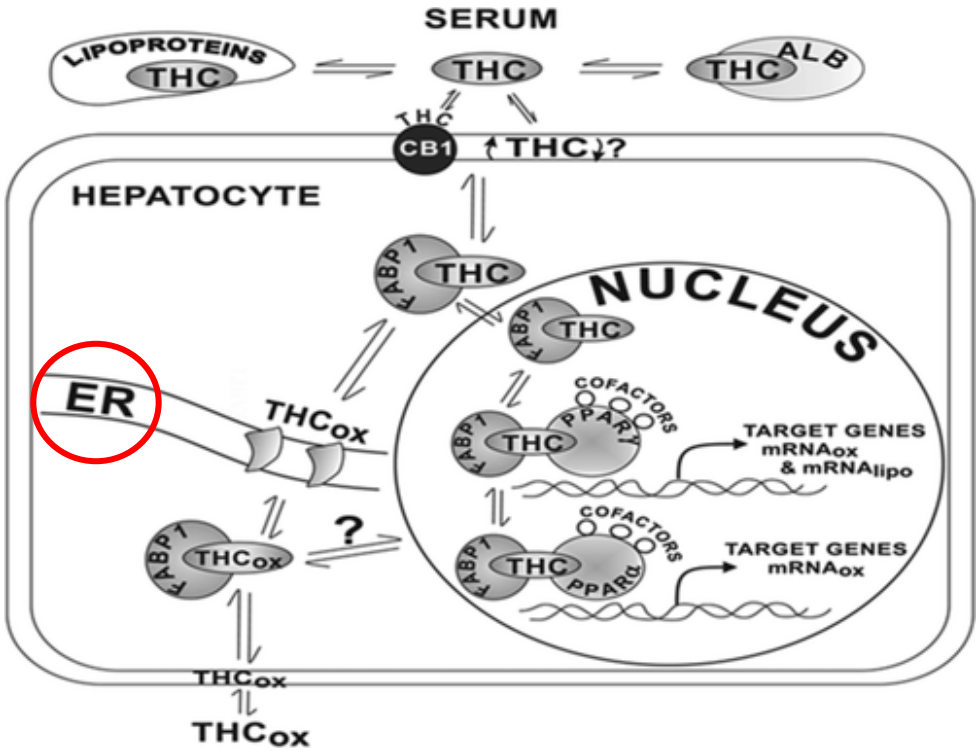
Protein binding/ displacement?

Effects on gastric motility?

Transporters inhibition?

Fatty acid binding protein - FABP

- The most prevalent hepatic binding/chaperone protein with a broad specificity for multiple lipidic ligands and xenobiotics.
- Phytocannabinoids are highly lipophilic molecules - cytoplasmic transport?
- Phase I and Phase II enzymes → Endoplasmic Reticulum of hepatocytes
- FABP1 plays a major role in governing phytocannabinoid metabolism by transporting it to hepatic CYP enzymes



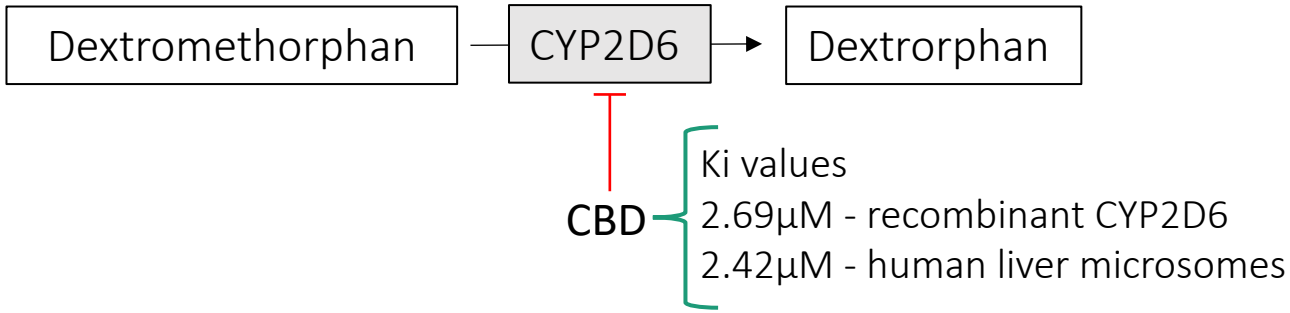
Previously unrecognized site of DDI – competition for cellular uptake/ cytosolic trafficking

- Could lead to unpredictable pharmacological responses

Clinically significant inhibitory effects cannot be ruled out entirely….

- Is there substantial clinical risk?
- More specific human data is needed
- What about the dose at which phytocannabinoids are used in the clinic?

- Is it high enough for the blood plasma concentration to reach Ki and/or IC50 values?



Cmax for CBD after four buccal sprays of Sativex® (10 mg of CBD) → 9.62 nM

Cannabis cigarette (20 mg of CBD) → 0.363 µM

- Low oral doses of CBD are not anticipated to exhibit *in vivo* inhibition of CYP2D6.

Conclusions

- Understanding of phytocannabinoid metabolism is a key factor within the drug development process to reduce the risk of costly late-stage project failure due to adverse ADMET properties.

- With the increased widespread use of legal marijuana (medically and recreationally), DDI knowledge is of essential practical importance to avoid clinical complications.

- Computer modeling methods of metabolic pathways are a powerful tool to predict DDIs but more metabolism data is needed to build robust and reliable *in silico* methods.

- More investigational efforts are required in this field which should motivate more studies along this line in the near future.

Thank you!

Questions?