Evaluation of Cannabidiol-Drug Interactions Using Static and Dynamic Models

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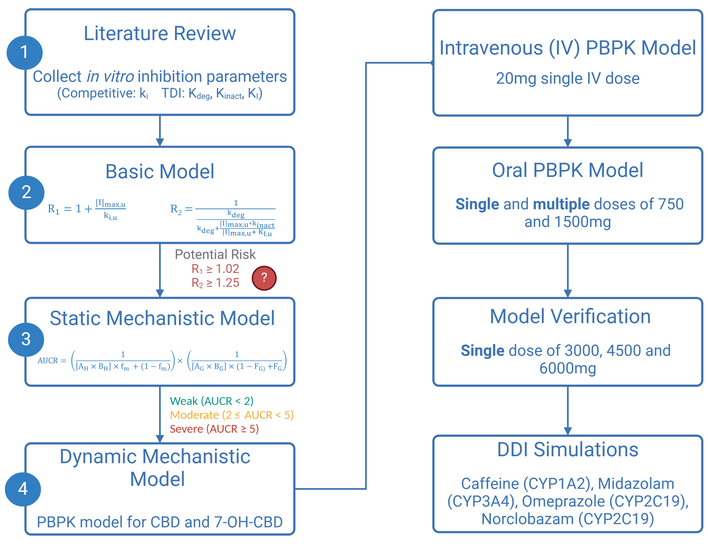
Background

- Cannabidiol (CBD) has been found to exhibit inhibition against many CYP450 enzymes *in vitro* via competitive inhibition on CYP 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4 and time-dependent inhibition (TDI) on CYP 1A2, 2C19, and 3A4.
- Since CBD is a major constituent in medical marijuana, patients concurrently taking other medications may have a higher risk of drug-drug interactions (DDIs).
- Clinical studies on DDIs involving major cannabinoids are scarce due to few FDA-approved products, high costs of confirmatory trials, and legal and ethical issues with medical cannabis.
- We aim to translate the available *in vitro* and clinical data by applying a forward stepwise model-based approach using basic, static mechanistic and dynamic mechanistic (physiologically-based pharmacokinetic (PBPK)) models to evaluate the magnitude of metabolic DDIs involving CBD.

Methods



Results

- Using the basic model, CBD had a potential to precipitate DDIs by inhibiting all major CYP enzymes.
- The static mechanistic model showed that CBD could lead to severe DDIs with drugs metabolized by CYPs 2C19 and 3A, and moderate DDIs with drugs metabolized by CYPs 2C9 and 1A2 (Table 1).

Table 1. Summary of the basic and static mechanistic model results for CBD

Enzyme	Type of inhibition	Potential risk per the basic model	AUCR classification from the static mechanistic model
CYP1A2	Reversible and TDI	Yes	Moderate
CYP2B6	Reversible	Yes	Weak
CYP2C8	Reversible	Yes	Weak
CYP2C9	Reversible	Yes	Moderate
CYP2C19	Reversible and TDI	Yes	Severe
CYP2D6	Reversible	Yes	Weak
CYP3A	Reversible and TDI	Yes	Severe

- The PBPK model successfully predicted CBD and 7-OH-CBD systemic exposure in healthy adults following single dose intravenous and oral administration (Figure 1) and multiple dose oral administration (Figure 2).

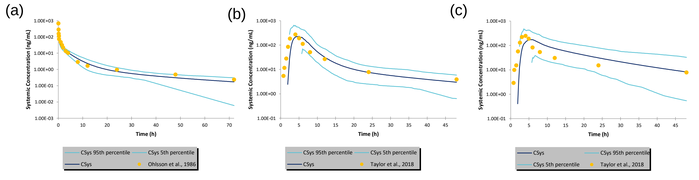


Figure 1. Simulated and observed plasma profile following a) CBD single 20 mg intravenous administration b) CBD single 1500 mg oral administration c) 7-OH-CBD following single 1500 mg oral administration under fasted conditions.

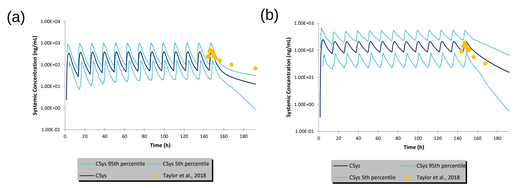


Figure 2. Simulated and observed plasma profile of a) CBD and b) 7-OH-CBD following multiple 750 mg CBD oral administration under fasted conditions.

- The PBPK model was validated using multiple datasets. All predicted exposure parameters (AUC and C_{max}) were within two-fold of the observed clinical values (Figure 3).

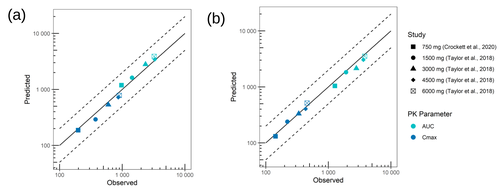


Figure 3. Predicted versus observed exposure parameters of a) CBD and b) 7-OH-CBD following oral administration of ascending doses of CBD.

- The PBPK model successfully predicted the drug interactions of multiple dose administration of CBD with caffeine, midazolam, and clobazam and single dose administration with omeprazole after optimization of some of the *in vitro* inhibition parameters (Figure 4).

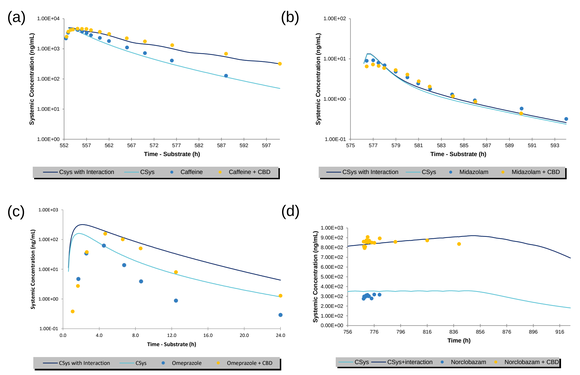


Figure 4. Simulated and observed plasma profile following CBD concomitant administration with of a) Caffeine and b) Midazolam c) Omeprazole d) Norclobazam.

- CBD increased omeprazole AUCR by 211% following a single dose and increased norclobazam AUCR by 206% with repeated doses. CBD did not significantly inhibit any of the other tested enzymes (Table 2).

Table 2. PBPK model predicted magnitude (AUCR) of CYP-mediated CBD-drug interactions after single and multiple oral dose administration.

Enzyme	Substrate	CBD dose	Observed AUCR	Predicted AUCR	Pred/Obs AUCR
CYP1A2	Caffeine	Multiple oral dose of 750 BID for 27 days	1.95	1.92	0.98
CYP3A4	Midazolam	Multiple oral dose of 750 BID for 25 days	0.92	1.04	1.13
CYP2C19	Omeprazole	Single oral dose of 640 mg	3.07	3.11	1.01
CYP2C19	Norclobazam	Multiple oral dose of 750 BID for 14 days	3.4	3.06	0.9

AUCR: area-under the plasma concentration-time curve ratio in the presence and absence of the inhibitor.

Conclusion & Future Directions

- Although CBD showed inhibitory effect on major CYP enzymes *in vitro*, it was not evident clinically; except for CYP2C19, all tested CYP enzymes were not significantly (AUCR <2) affected after CBD administration.
- The PBPK model for CBD and its active metabolite will be extended further to simulate real-world scenarios including the impact of age, food consumption, and liver and kidney function on the magnitude of DDIs.

References

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