Investigating Cannabidiol-Mediated Drug-Drug Interactions Using Physiologically Based Pharmacokinetics Modeling

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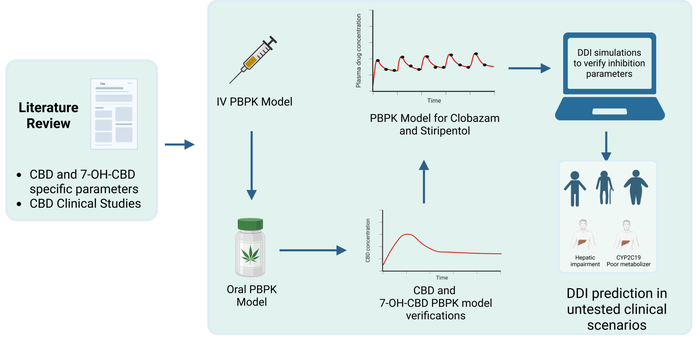
Background

- Cannabidiol (CBD) has seen widespread use driven by legalization in many states in the Unites States prompting concerns about potential drug-drug interactions (DDIs), especially in individuals managing multiple health conditions with various medications.
- CBD inhibits several CYP450 enzymes *in vitro* competitively (CYP 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4) and through time-dependent inhibition (CYP 1A2, 2C19, 3A4) which may interfere with the metabolism of co-administered drugs.
- Despite growing use, clinical DDI studies involving cannabinoids are limited due to the lack of FDA-approved products, high costs of trials, and the additional difficulty of conducting such studies in special populations.
- We aim to utilize physiologically based pharmacokinetic (PBPK) modeling to predict CBD exposure and the extent of CBD-induced metabolic DDIs across diverse populations, including those where clinical studies are limited or unfeasible.

Methods

- A PBPK model for CBD and 7-OH-CBD was developed using Simcyp™ version 22 in healthy adults.
- The PBPK model was validated using different clinical studies available in the literature under fasted and fed conditions.
- The model was used to predict CBD exposure in different population.
- Independent PBPK models for clobazam and stiripentol were also developed in Simcyp™.
- The CBD PBPK model was used to predict the extend of DDI with different victim drugs. The *in vitro* inhibition parameters were revisited to recapitulate the observed DDIs.
- The CBD PBPK model was used to predict the extend of DDI with Norclobazam in different population.

PBPK Model Workflow



Results

- The PBPK model successfully predicted CBD and 7-OH-CBD exposure in healthy adults following single intravenous dose (Figure 1) and oral dose administration under fasted and fed conditions (Figure 2 and 3).

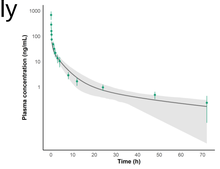


Figure 1. Plasma profile following single 20 mg CBD IV administration.

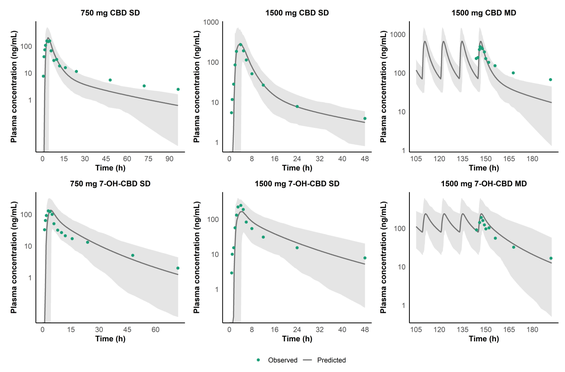


Figure 2. Simulated and observed plasma profile of CBD and 7-OH-CBD following oral CBD administration at single and multiple doses.

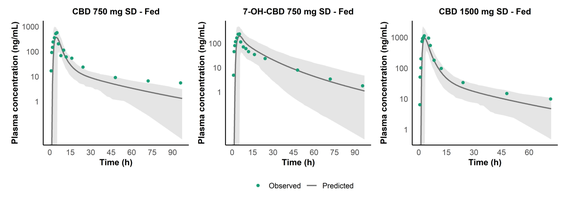


Figure 3. Simulated and observed plasma profile of CBD and 7-OH-CBD following oral CBD single dose administration under fed conditions.

- 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 4).

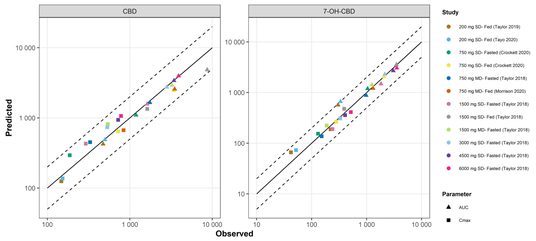


Figure 4. Goodness of fit plots of CBD and 7-OH-CBD for additional datasets across various dosing regimen under fasted and fed conditions for model validation.

- The PBPK model was successfully validated in pediatric and hepatically impaired populations (Figure 5).

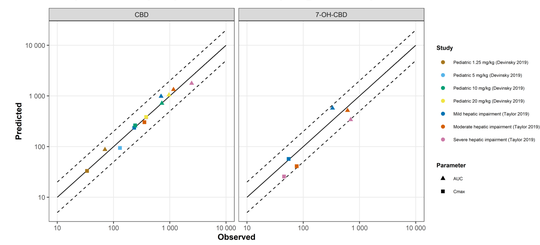


Figure 5. Goodness of fit plots of CBD and 7-OH-CBD following oral administration of CBD for pediatric and hepatic impairment patient for model validation in special population.

- The PBPK model predicted the exposure of CBD and its metabolite 7-OH-CBD in populations where clinical studies are difficult to perform (Figure 6).

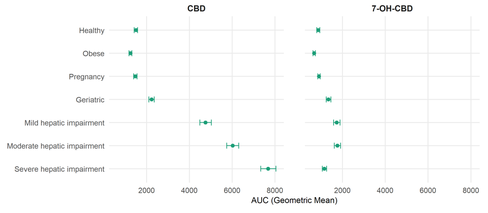


Figure 6. PBPK model predictions of CBD and 7-OH-CBD exposure following oral 750mg CBD multiple doses administration across special populations

- The PBPK model successfully predicted the drug interactions of multiple dose administration of CBD with caffeine, midazolam, stiripentol and clobazam after optimization of some of the *in vitro* inhibition parameters (Table 2).

Table 2. PBPK model predicted magnitude (AUCR) of CYP-mediated CBD-drug interactions after 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	2.02	1.04
CYP3A4	Midazolam	Multiple oral dose of 750 BID for 25 days	0.92	1.04	1.13
CYP3A4 CYP1A2 CYP2C19	Stiripentol	Multiple oral dose of 750 BID for 23 days	1.55	1.28	0.83
CYP3A4 CYP2C19	Clobazam	Multiple oral dose of 750 BID for 14 days	1.21	1.2	0.99
CYP2C19	Norclobazam	Multiple oral dose of 750 BID for 14 days	3.38	3.02	0.89

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

- The validated PBPK model predicted the DDI risk in clinically untested scenarios of CBD co-administration with clobazam (Figure 7). In hepatic impairment and CYP2C19 poor metabolizers, diminished enzyme activity led to a smaller relative impact of CBD's inhibition.

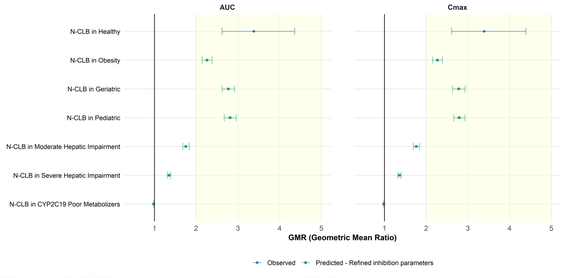


Figure 7. PBPK model predictions of CBD and Norclobazam interaction across special populations. The yellow-highlighted area indicates moderate DDI risk.

Conclusions

- The PBPK model predicted the exposure of CBD and its active metabolite 7-OH-CBD, as well as their drug interaction with clobazam, in populations where clinical evaluation is not feasible.
- Although CBD inhibited multiple CYP enzymes *in vitro*, this effect was not clinically evident except for a moderate CYP2C19 interaction , that was consistent across healthy, pediatric, geriatric, and obese populations.
- *In vitro* inhibition parameters may not reliably predict clinical DDI risk, emphasizing the need for caution when extrapolating *in vitro* data to clinical scenarios.

References

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Acknowledgment

Dr. Cristofoletti received funding from 2022 Research Grants Program of the Consortium for Medical Marijuana Clinical Outcomes Research which is funded through State of Florida appropriations. Any published findings and conclusions are those of the authors and do not necessarily represent the official position of the Consortium for Medical Marijuana Clinical Outcomes Research.

Consortium for Medical Marijuana Clinical Outcomes Research