4056/P755

Physiologically based pharmacokinetic (PBPK) simulations and modeling of botanical constituents

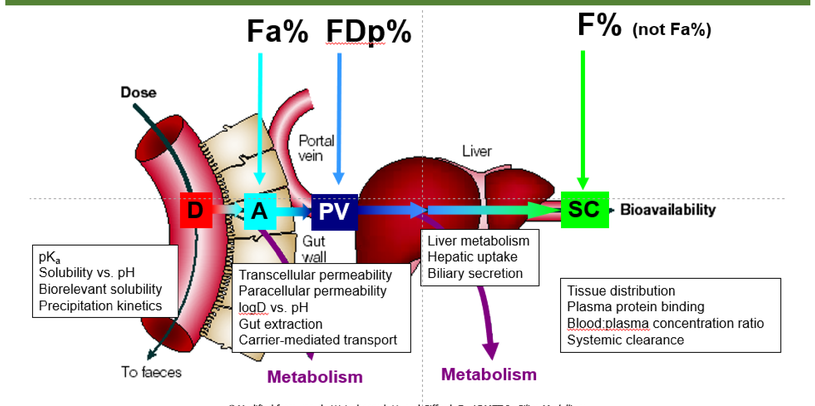
Michael Lawless[1], Annie Lumen[2,5], Miao Li[2], Michelle Embry[3], Connie Mitchell[3], and Yitong Liu[4]

[1]Simulations Plus, Lancaster, CA; [2]US FDA, Jefferson, AR; [3]HESI, Washington, DC; [4]US FDA, Laurel, MD; and [5]Amgen, Thousand Oaks, CA

INTRODUCTION

Botanicals have broad use as traditional medicines, natural health products, and dietary supplements around the world. Due to the complexity and variability in chemical constituents, safety testing for botanicals is challenging. The Botanical Safety Consortium, created to address this challenge, is a partnership among industry, academia, and government experts to promote new approach methodologies, such as *in silico* modeling, to enhance the botanical safety toolkit. Here, high-throughput pharmacokinetic (HTPK) simulations were used to predict pharmacokinetic (PK) properties of 211 constituents in 13 botanicals. Additionally, PBPK models were created to mimic *in vivo* PK profiles of constituents in Ashwagandha, Goldenseal, and Yohimbe.

METHODOLOGY



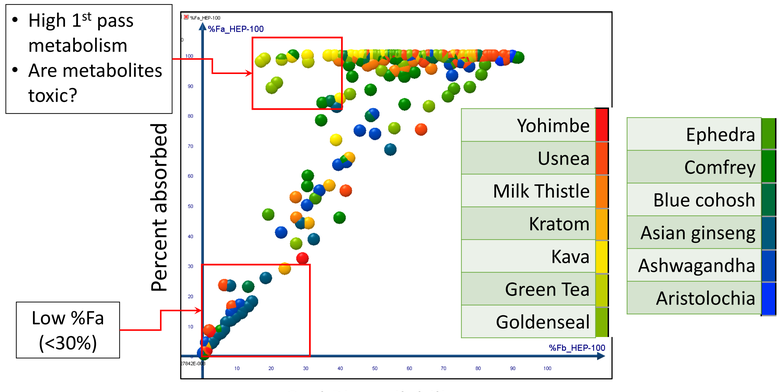
* Modified from van de Waterbeemd, H, and Gifford, E. *ADMET In Silico Modelling: Towards Prediction Paradise?* Nat. Rev. Drug Disc. 2003, 2:192-204

HTPK simulations were performed using ADMET Predictor® (Simulations Plus) for a 100 mg dose of each constituent to a 70 kg human subject using an immediate release tablet dosage form. PBPK models were created using GastroPlus® (Simulations Plus). Input parameters, e.g., solubility, logP, permeability, and liver metabolism, were either predicted using artificial neural network models in ADMET Predictor or obtained from *in vitro* studies. Parameters were adjusted to improve the match between predicted and observed *in vivo* profiles.

RESULTS

Below is a plot of the predicted percent absorbed (%Fa) versus oral bioavailability (%Fb) for the 211 constituents. Compounds in the lower left-hand corner will have low plasma concentrations because a small percent reaches systemic circulation. The compounds in the upper left-hand corner have low oral bioavailability due to high first pass metabolism.

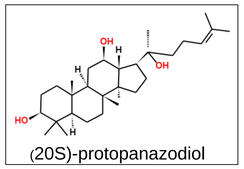
- High 1st pass metabolism
- Are metabolites toxic?

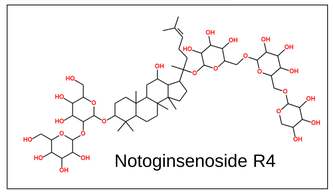


RESULTS

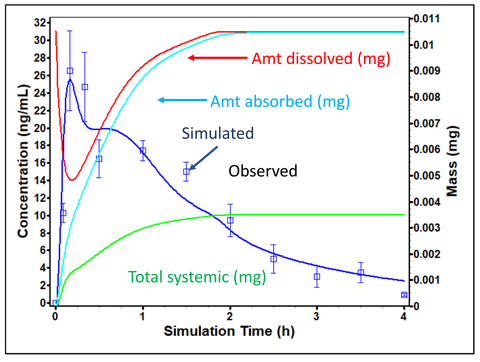
Asian ginseng constituents have low predicted %Fa, for example (20S)-protopanazodiol and notoginsenoside R4 have predicted %Fa below 5%. (20S)-protopanazoldiol has a low predicted aqueous solubility (S+Sw) that severely restricts its dissolution in the gastrointestinal (GI) tract. Notoginsenoside R4 contains five sugar rings that makes it very hydrophilic and capable of forming many hydrogen bonding pairs. This combination results in a low predicted human jejunal permeability. (S+Peff).

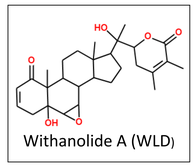
Constituent	%Fa	S+Sw (mg/ml)	S+Peff (10^{-4} cm/s)
20S protopanaxadiol	4.1	$2.6x10^{-4}$	3.8
Notoginsenoside R4	4.4	$1.7x\ 10^{-1}$	0.016





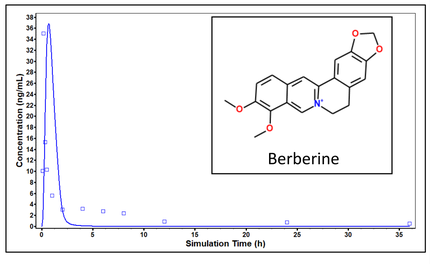
A PBPK model was created to mimic an oral dose of 0.48 mg/kg (0.01 mg) of withanolide A (WLD), a major phytochemical in Ashwagandha, to Swiss albino female mice[1]. The plasma concentration versus time (Cp-time) curve contains a shoulder that could be modeled by optimizing the solubility and mean precipitation time. Liver intrinsic clearance (CLint) was also optimized. The red line in the graph below indicates that WLD initially precipitates in the GI tract and then dissolves slowly to produce the shoulder.





Parameter	Observed	Simulated
%Fa		99.4
%Fb		33.2
Cmax (ng/ml)	26.6	25.6
Tmax (h)	0.17	0.17
$AUC_{0\text{-}inf}$ (ng*h/ml)	41.0	45.4

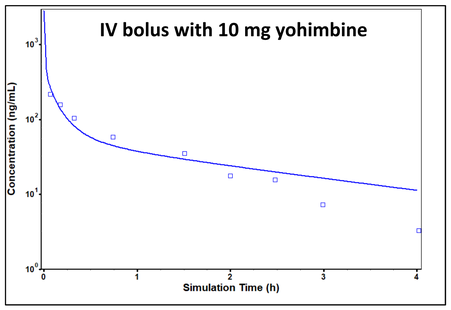
Another PBPK model was established to model an oral dose of 100 mg/kg of berberine, a major constituent in Goldenseal, in Sprague Dawley rats.[2] Km and Vmax values of CYP2d1 and P-glycoprotein from *in vitro* studies were input into the model. After incorporating enzyme and transporter kinetics in both liver and intestine, Cmax and AUC of berberine were predicted within 2-fold of experimental data.

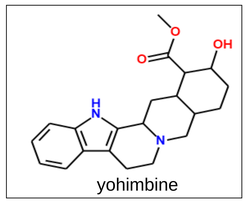


	Observed	Simulated
%Fa		52.4
%FDp		33.7
%Fb		0.2
Cmax (ng/ml)	35.1	36.9
Tmax (h)	0.2	0.7
$AUC_{0\text{-}inf}$ (ng-h/ml)	73.2	41.6
$AUC_{0\text{-}t}$ (ng-h/ml)	57.8	39.8

RESULTS

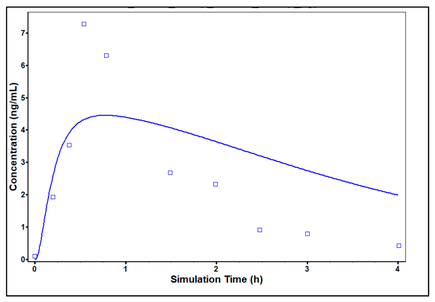
A PBPK model was developed to simulate PK data from healthy volunteers[3] for both IV bolus and oral administration of 10 mg of yohimbine (a constituent of Yohimbe). Lower or upper bounds from ADMET Predictor's regression uncertainty of intestinal effective permeability, fraction unbound in plasma, CLint, and blood to plasma ratio were used to produce the best fit to *in vivo* data. The model simulations compared with representative observed PK data are shown below. Yohimbine's PK values vary greatly from subject to subject. A population model will be carried out, in the future, to simulation PK data with intra-individual variabilities.





	Observed	Simulated
$AUC_{0\text{-}inf}$ (ng-h/ml)	162	210
$AUC_{0\text{-}t}$ (ng-h/ml)	158	180

Oral administration with 10 mg yohimbine



	Observed	Simulated
%Fa		22.1
%FDp#		21.9
%Fb		9.2
Cmax (ng/ml)	7.3	4.5
Tmax (h)	0.5	0.8
$AUC_{0\text{-}inf}$ (ng-h/ml)	162	210
$AUC_{0\text{-}t}$ (ng-h/ml)	158	180

%FDp: Percent dose to portal vein

CONCLUSIONS

- HTPK simulations using *in silico* parameters can be used to estimate various PK parameters including %Fa and %Fb
  - Compounds with low predicted %Fa will have lower safety concerns
  - The metabolites of compounds with high %Fa and low %Fb should be examined for safety
- *In silico* and *in vitro* data were used to create PBPK models that mimic *in vivo* PK profiles of botanical constituents
- *In vivo* PK properties, such as Cmax and AUC, will be used to prioritize and guide further *in vitro* testing of botanical safety

REFERENCES

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[2] Liu, et. al, *Drug metabolism and Disposition* **2010**, 38, 1779.
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