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Predicted Pharmacokinetic Properties of Botanical Constituents

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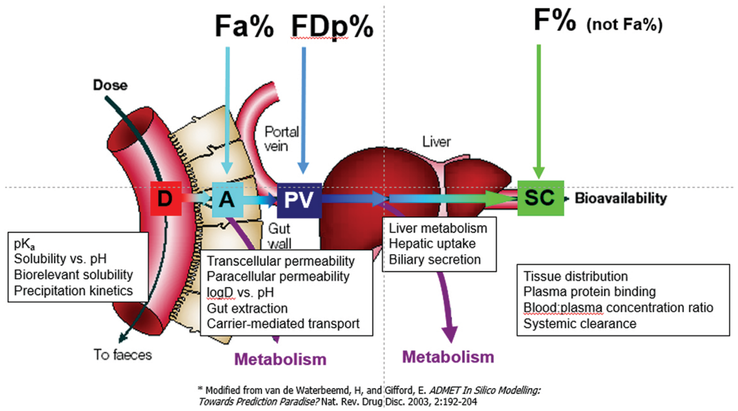
BOTANICAL SAFETY CONSORTIUM

INTRODUCTION

Botanicals are used as traditional medicines, natural health products, and dietary supplements globally. Due to the complexity and variability in chemical constituents, safety testing for botanicals is challenging. Pharmacokinetic (PK) simulations predict the internal concentration, e.g., plasma concentration, of a specific dose of a botanical constituent. The estimated internal concentration can then be used to assess safety. Thirteen (13) botanicals were obtained, and analytical methods were used to identify the chemical constituents. Ninety-five (95) constituents were identified, their daily dose was estimated, and used in physiologically based pharmacokinetic (PBPK) simulations. Input parameters, e.g., solubility, pKa, etc. were estimated by machine learning models.

METHODOLOGY

- LC-MS/MS identified the amount of each constituent in one (1) gram of botanical extract
- The dose of each botanical constituent is based on doses from labels of botanical products and measured fraction of the constituents
- Input parameters, e.g., pKa, solubility, logP, for the PBPK simulations were predicted with ADMET Predictor® 10.4[1]
- Each constituent was assigned a Biopharmaceutical Classification System[2] (BCS) category using the dose and predicted intrinsic solubility and human jejunal permeability
- Fraction absorbed (%Fa) and oral bioavailability (%Fb) were predicted using the HTPK Simulation module in ADMET Predictor
- PBPK simulations were performed for each botanical constituent using GastroPlus® 9.8.2[3]



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

RESULTS

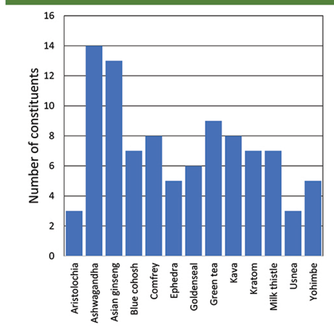


Figure 1 - Number of constituents identified for each botanical.

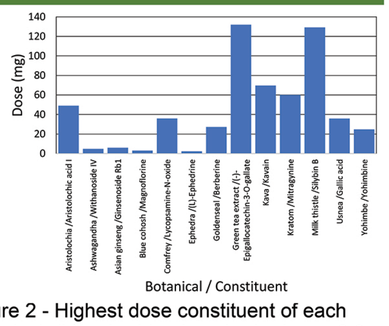


Figure 2 - Highest dose constituent of each botanical. (L)-ephedrine in ephedra has a 2.3 mg dose and (-)-epigallocatechin-3-O-gallate in Green tea extract has a dose of 132 mg.

RESULTS

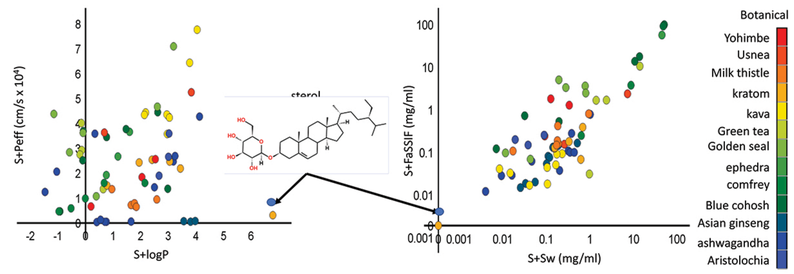


Figure 3 - Predicted properties of constituents; S+Peff (human jejunal permeability), S+logP (logP), S+FaSSIF (simulated fasted intestinal fluid solubility), and S+Sw (aqueous solubility). Properties that are outside of the applicability domain of the model are not displayed. The low S+Peff compounds, like daucosterol, contain sugar rings that lead to low passive permeability. Daucosterol is unique because it has a high predicted logP but low predicted passive human jejunal permeability.

RESULTS

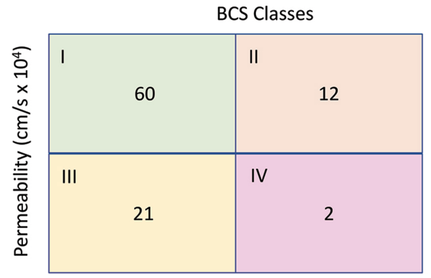


Figure 4 – Number of constituents in each BCS class. 20 compounds in classes III and IV are glycosides and are expected to have low fraction absorbed.

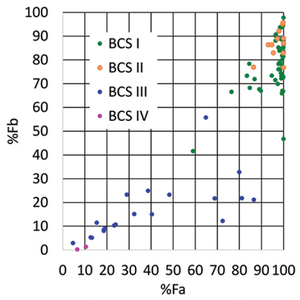


Figure 5 – Plot of oral bioavailability (%Fb) versus percent absorbed (%Fa). Points are colored by BCS class. BCS classes III and IV have the lowest fraction absorbed.

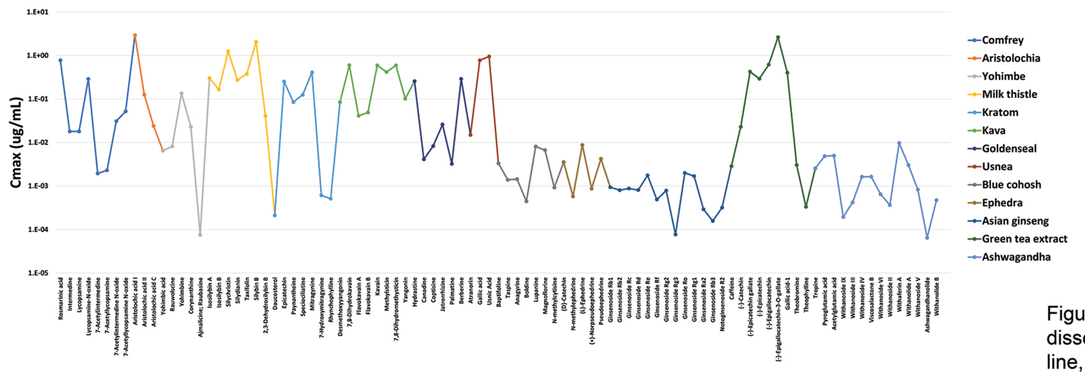


Figure 6 - Cmax (ug/ml) for the 95 botanical constituents. Points are colored by botanical. The average and median Cmax values were 0.2 and 6.7 x 10^{-3} ug/ml, respectively. The highest Cmax (2.9 ug/ml) is aristolochic acid I in Aristolochia and the lowest Cmax (6.6 x 10^{-5} ug/ml) is ashwagandhanolide in ashwagandha.

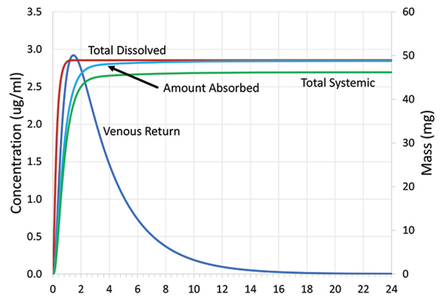
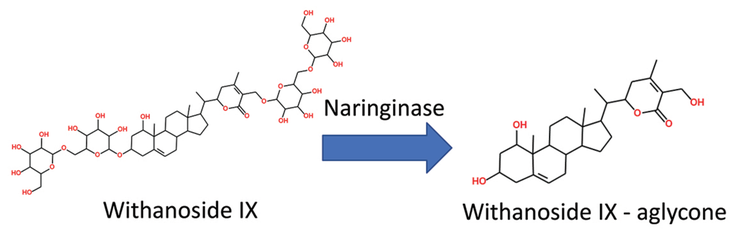


Figure 7 – Simulated Cp time curve (blue line), total amount dissolved (red line, right axis), total amount absorbed (cyan line, right axis), and total amount entering systemic circulation (green line, right axis) for a 49 mg dose of aristolochic acid I.



Compound	S+Peff (cm/s x 10^4)	S+Sw	BCS Class	%Fa
Withanoside IX	0.017	1.014	III	5
Withanoside IX-aglycone	2.3	0.02389	I	98

Figure 8 -Glycosides on withanoside IX can be metabolized by enterobacterial β-glucosidases like naringinase[4] to create the aglycone molecule. This decreases the solubility but increases permeability and results in a much higher predicted fraction absorbed.

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SUMMARY

- Compounds in BCS classes III and IV are mostly glycosides and predicted %Fa were typically low for these compounds
- Enzymatic cleavage of glycosides decrease solubility but increase permeability and result in higher predicted %Fa for the aglycone
- The five compounds with the highest predicted Cmax values (>1 ug/ml) are aristolochic acid I (aristolochia), (-)-epigallocatechin-3-O-gallate (green tea extract), silybin B (milk thistle), silychristin (milk thistle), and usnic acid (asnea)
- These PBPK simulations can guide future experiments to evaluate toxicity, e.g., gut metabolism, *in vitro* toxicity, *in vitro* to *in vivo* extrapolation, etc.

REFERENCES

[1] ADMET Predictor, Simulations Plus, Inc. Lancaster CA 95354.
[2] Amidon GL et al. *Pharm Res.* **1995**, Mar;12(3):413-20.
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[4] Kuboyama T et al. *Euro J Neuroscience*, **2006**, 23, 1417-1426.

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