Evaluating pharmacokinetics and toxicity of botanical constituents by *in silico* methods

Yitong Liu, PhD, DABT

Division of Toxicology, Office of Chemistry and Toxicology,
Office of Laboratory Operations and Applied Science,
Human Foods Program, Food and Drug Administration

Abstract

Botanicals have been extensively used throughout history, especially as natural medicines and dietary supplements. Botanicals contain complex mixtures of chemicals, many of which lack pharmacokinetic and toxicity data in humans. *In silico* modeling, such as quantitative structure–activity relationships (QSAR) and physiologically based pharmacokinetic (PBPK) modeling and simulation, are becoming important tools to evaluate botanical constituents. These *in silico* methods have emerged as rapid means for screening, prioritizing subsequent studies, and filling data gaps for botanical safety assessment.

Here, several applications of QSAR and PBPK modeling and simulation to evaluate botanicals are presented. First, physicochemical and pharmacokinetic properties of botanical constituents were predicted by QSAR models. These properties were then used to classify the botanical constituents into the biopharmaceutical dassification system (BCS) and the extended clearance classification system (ECCS), to predict the absorption and clearance routes, respectively. Additionally, plasma and tissue concentrations of the botanical constituents in humans were predicted by PBPK modeling and simulation. Finally, botanical constituents were screened using QSAR models to predict potential organ toxicities, including hepatotoxicity, cardiotoxicity, reproductive and developmental toxicity in humans and animals.

Together, *in silico* predictions for physicochemical properties, pharmacokinetics, and organ toxicity provide a comprehensive view of potential effects of botanical constituents on the human body. As the research and regulatory framework move forward to adopt alternative methods for chemical safety assessment, computational modeling and simulation may help identify hazards and facilitate decision-making to support the safe use of botanical products.

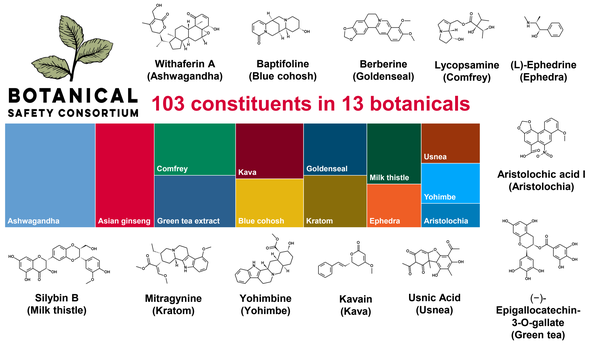
Introduction

Human consumption of botanicals can lead to complex and dynamic internal exposure profiles (i.e., phytochemical constituent plasma concentration and time profiles) that in aggregate determine the degree and range of human biological responses (e.g., toxicity). Therefore, a clear understanding of the ADME (absorption, distribution, metabolism, and excretion) properties of phytochemical constituents is pivotal for botanical safety evaluation.

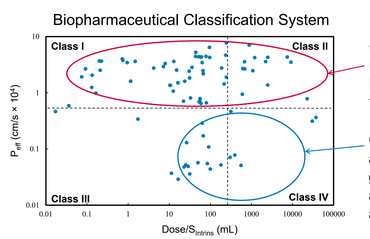
Botanicals contain complex mixtures of numerous phytochemical constituents. There are limited *in vitro* and *in vivo* studies on these phytochemical constituents. Since structural information is often the only data available, *in silico* modeling could serve as an initial screening tool for botanical safety evaluation.

Case studies

QSAR predicts absorption and clearance

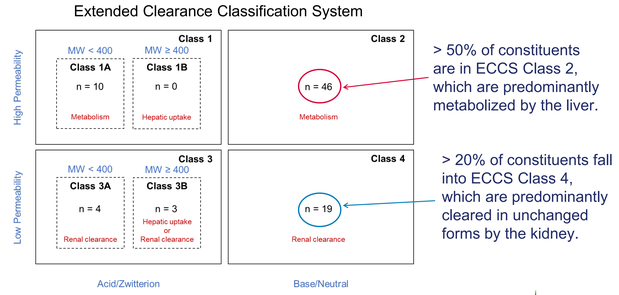


QSAR-predicted physicochemical properties (e.g., solubility, permeability) were used to predict absorption and clearance of botanical phytochemical constituents.



Over half of constituents are in BCS classes I and II and have good absorption in GI track.

Glycosides in ashwagandha and Asian ginseng are in Classes II and IV and have poor absorption.

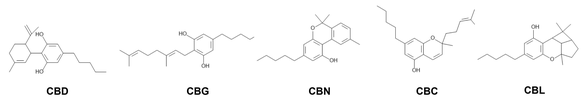


> 50% of constituents are in ECCS Class 2, which are predominantly metabolized by the liver.

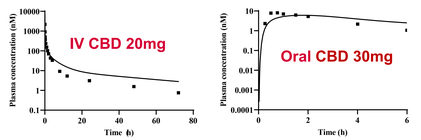
> 20% of constituents fall into ECCS Class 4, which are predominantly cleared in unchanged forms by the kidney.

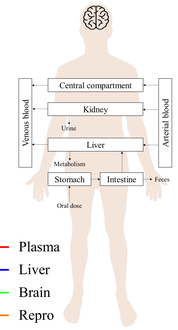
PBPK predicts plasma and tissue concentrations

Cannabis sativa L.

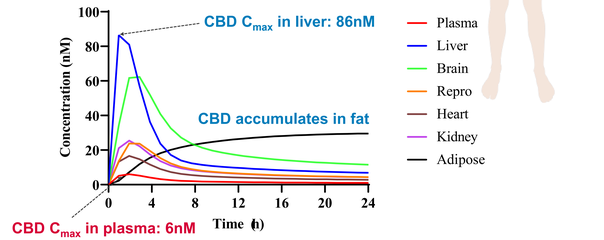


Predicted CBD plasma profiles agree well with clinical data.

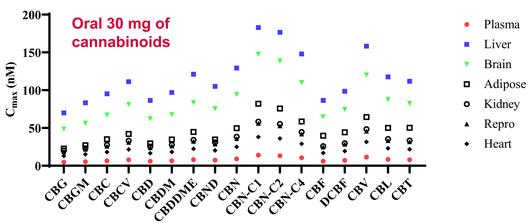




Predicted CBD tissue concentrations are higher than plasma.

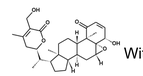


Predicted concentrations of 17 cannabinoids in plasma and tissues

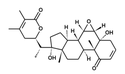


QSAR predicts organ toxicity

- Ashwagandha is a medicinal plant used in traditional Asian medicines as an adaptogen to promote both physical and mental health.
- Reports of hepatotoxicity, cardiotoxicity, and reproductive toxicity in humans and animals have been associated with its use.
- Withanolides are the major bioactive phytochemicals in Ashwagandha.



Withaferin A



Withanone

- For 14 selected withanolides, QSAR predicted liver toxicity in humans, as well as reproductive and developmental toxicities in animals.
- Withanolides were out of the applicability domain for heart and kidney QSAR models.

Conclusion

- *In silico* modeling fill data gaps in evaluating botanicokinetics and safety of data-poor phytochemical constituents.
- Future effort is needed to expand QSAR applicability domain for phytochemical constituents.
- More *in silico*, *in vitro*, and *in vivo* concordance studies are needed to evaluate and improve performance of new approach methodologies (NAMs) in predicting human effects.

Related publications

Liu Y, et al. Prediction of physicochemical and pharmacokinetic properties of botanical constituents by computational models. Journal of Applied Toxicology. 2024, 44, 1236-1245.

Liu Y and Sprando RL. Physiologically based pharmacokinetic modeling and simulation of cannabinoids in human plasma and tissues. Journal of Applied Toxicology. 2023, 43, 589-598.

Liu Y. *In silico* evaluation of pharmacokinetics and acute toxicity of withanolides in Ashwagandha. Phytochemistry Letters. 2022, 47, 130-135.

In silico programs used in present studies