In silico Prediction of Botanical Constituents' Metabolites

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Introduction

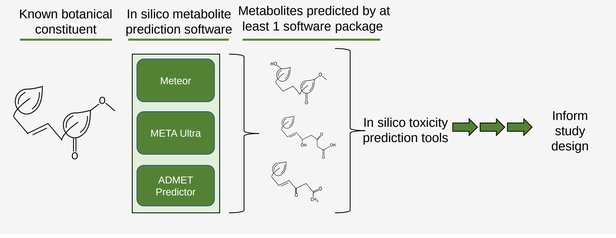
Natural products, such as botanical dietary supplements, are used globally and are growing in popularity, but safety data are sparse. Traditional *in vivo* animal toxicity testing on these complex and variable substances is not always practical and is resource intensive. The Botanical Safety Consortium (BSC) is a public-private partnership, formed by the US FDA, NIEHS, and HESI. The BSC works to improve botanical safety by evaluating the suitability of new approach methodologies (NAMs) for botanicals as complex mixtures.

Many existing *in silico* tools that have been utilized for drug and chemical safety evaluation have potential application in the botanical space. However, these need to be further evaluated to determine their applicability and utility. In some cases, the metabolites of parent botanical constituents may be responsible for toxicity. By utilizing existing *in silico* prediction tools, toxicologically important metabolites can be identified.

These *in silico* tools have the ability not only to identify potentially toxic constituents and metabolites but can inform study design of higher-tier *in vitro* assays.

Objectives

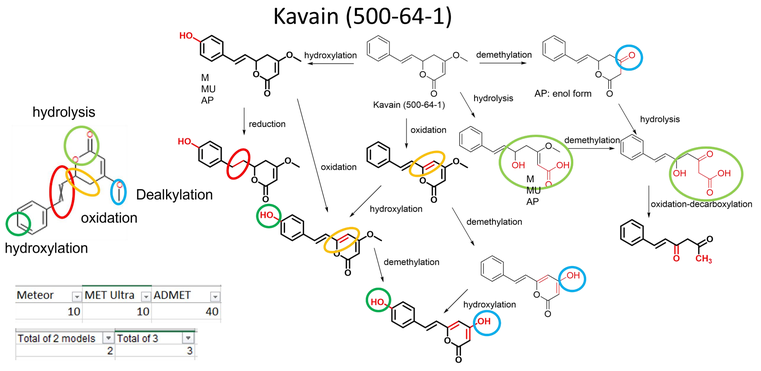
This pilot evaluation of known botanical constituents aims to determine the utility of *in silico* metabolite prediction tools to inform safety evaluation and study design of botanicals.



Methodology

- Three commercially available xenobiotic metabolism prediction software packages (ADMET Predictor®, Simulations Plus; Meteor Nexus v.3.1.0, Lhasa Limited; META Ultra v1.2, MultiCase) were utilized to predict phase I and phase II metabolites of 20 constituents.
- Constituents evaluated are known active or toxic constituents from well-studied botanicas, including green tea extract and blue cohosh.

Example Metabolic Pathway



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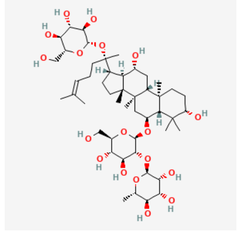
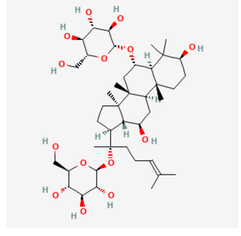
Meteor: M
MetaUltra: MU
ADME Predictor: AP

Bolded structures are detected major phase I metabolites in humans, other metabolites are intermediates. Phase II metabolism are not shown in the figure

Other Absorption Distribution Metabolism & Excretion Considerations



Ginsenoside Re



Ginsenoside Rg1

- Models predicted +180 metabolites for each ginseng constituent, but both likely undergo rapid metabolism to respective aglycones in the gastrointestinal tract prior to absorption.
- This means other aspects such as absorption need to be considered when evaluating when interpreting the data.

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Initial Results

Table 1: Number of predicted metabolites from metabolite prediction models. Total in 2 or 3 models means the same metabolite was predicted by multiple software packages

Constituent Name (CASRN)	Meteor	META Ultra	ADMET Predictor	Number of metabolites	Total in 2 models	Total in 3 models
Aristolochic Acid I (313-67-7)	13	13	14	40	6	1
Withaferin A (5119-48-2)	8	11	41	60	4	0
Withanoside IV (362472-81-9)	4	11	97	112	2	0
Ginsenoside Rg1 (22427-39-0)	3	33	152	188	2	0
Ginsenoside Re (52286-59-6)	2	33	173	208	3	1
Anagyrine (486-89-5)	8	22	56	86	6	3
Intermedine (10285-06-0)	27	6	3	36	1	0
Lycopsamine (10285-07-1)	27	6	3	36	9	4
Ephedrine (299-42-3)	7	42	17	66	5	0
Hydrastine (118-08-1)	27	49	22	98	14	1
Berberine (2086-83-1)	29	23	34	86	11	0
Epigallocatechin-3-gallate (EGCG) (989-51-5)	14	41	6	61	8	3
Methysticin (495-85-2)	2	16	26	44	2	1
Kavain (500-64-1)	10	10	40	60	5	2
Flavokavin B (1775-97-9)	21	41	38	100	13	6
7,8-Dihydrokavain (3384-26-7)	4	13	26	43	3	0
Mitragynine (4098-40-2)	11	30	19	60	7	1
Silybin A (22888-70-6)	18	19	25	62	9	2
(+) Usnic Acid (125-46-2)	8	39	13	60	1	0
Yohimbine (146-48-5)	18	48	33	99	15	10

Conclusions & Next Steps

- Models predicted varying levels of metabolites that did not always agree, but typically major metabolites were predicted in 2/3 models. However, when molecules are more complex, the predictions aligned less.
- Predicted metabolites based on tool concordance will be evaluated using available toxicity prediction tools.
- Knowledge of potential metabolites and metabolic pathways will help inform NAM study design and data interpretation.
- There are ongoing efforts to explore application of these tools across a broader botanical constituent space.
- Future work will focus on data sharing to improve *in silico* metabolism prediction models for botanical constituents.