Assessing Pharmacokinetic Natural Product-Drug Interactions: Challenges and Opportunities

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College of Pharmacy, Washington State University
June 14, 2018
Natural Products umbrella

- Food
- Herbal products
- Other botanicals
- Vitamins
- Minerals
- Amino acids

All but food and non-tobacco botanicals are considered dietary supplements.
Dietary Supplement Health and Education Act (DSHEA)

- Passed by the United States Congress and signed into law by President Bill Clinton in 1994.
- Dietary supplements can be marketed with general functional claims but must be labeled appropriately.

“This claim has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure or prevent any disease.”

- Dietary supplements must be proven unsafe before the Food and Drug Administration can limit marketing.
Herbal product sales in the United States (1994-2016)

Billions of Dollars

Year


Adapted from Smith et al. (2017) HerbalGram
Clinical concerns with rising sales of herbal products

• Patients often seek herbal and other botanical natural products (NPs) as a “natural” (therefore “safe”) means to alleviate illnesses or supplement prescribed therapeutic regimens.

• Co-consuming NPs with conventional medications (prescription and over-the-counter) can lead to adverse NP-drug interactions.
Mechanisms underlying NP-drug interactions

• Pharmacodynamic
  ◦ NP precipitates alteration(s) in the pharmacologic effect(s) of the object drug.
  ◦ Can be additive, synergistic, antagonistic, or a combination of these

• Pharmacokinetic
  ◦ NP precipitates alterations in the absorption, distribution, metabolism, or excretion of the object drug.
  ◦ Inhibition or induction of drug metabolizing enzymes and/or transporters is most common.
Challenges with NP-drug interaction predictions

• Compositional variability of NPs
  ◦ Seasonal changes, manufacturing variability

• Constitutional complexity of NPs
  ◦ Multiple bioactive constituents, isomers

• Scarce human pharmacokinetic data for NP constituents

• Lack of harmonized approaches

Paine et al. (2018) Drug Metab Dispos, in press
Center of Excellence for Natural Product-Drug Interaction Research
Mission of the NaPDI Center

Provide leadership in the study of NP-drug interactions, with the ultimate goal of developing a set of Recommended Approaches to determine the clinical relevance of pharmacokinetic interactions between NPs and conventional drugs.

NaPDI Center: Natural Product-Drug Interaction Research Center

Paine et al. (2018) Drug Metab Dispos, in press
Objectives of the NaPDI Center

• Identify, prioritize, source, and characterize 4-6 NPs as potential precipitants of clinically significant interactions with commonly used medications. Pharmacology Core and Analytical Core

• Design in vitro and clinical studies for each NP that address existing gaps in the scientific literature and definitively assess the clinical relevance of any pharmacokinetic interaction. Pharmacology Core

• Develop and maintain a repository and public access portal for the data and resources generated to facilitate improved design of future research. Informatics Core

• Develop a set of Recommended Approaches to address the unique challenges related to the study of NP-drug interactions. All Cores

NaPDI Center: Natural Product-Drug Interaction Research Center

Paine et al. (2018) Drug Metab Dispos, in press
## Anticipated Recommended Approaches

<table>
<thead>
<tr>
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RA, Recommended Approach  
Paine et al. (2018) Drug Metab Dispos, in press
NP selection process

40 from HerbalGram → 47 NPs → 7 from DIDB

DIDB, Drug Interaction Database (UW)
target = drug metabolizing enzyme or transporter

Johnson et al. (2018) Drug Metab Dispos, in press
<table>
<thead>
<tr>
<th>Rank</th>
<th>Natural Product</th>
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<th>Rank</th>
<th>Natural Product</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Horehound</td>
<td>17</td>
<td>Ginkgo</td>
<td>33</td>
<td>Fennel</td>
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<tr>
<td>2</td>
<td>Cranberry</td>
<td>18</td>
<td>Plant sterols</td>
<td>34</td>
<td>Horsetail</td>
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<tr>
<td>3</td>
<td><em>Echinacea</em></td>
<td>19</td>
<td>Red yeast rice</td>
<td>35</td>
<td>Tribulus</td>
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<tr>
<td>4</td>
<td>Black cohosh</td>
<td>20</td>
<td>Elderberry</td>
<td>36</td>
<td>White kidney bean</td>
</tr>
<tr>
<td>5</td>
<td>Flaxseed/flaxseed oil</td>
<td>21</td>
<td>Guarana</td>
<td>37</td>
<td>Evening primrose oil</td>
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<tr>
<td>6</td>
<td>Valerian</td>
<td>22</td>
<td>Coconut oil</td>
<td>38</td>
<td>Kelp</td>
</tr>
<tr>
<td>7</td>
<td>Yohimbe</td>
<td>23</td>
<td>Senna</td>
<td>39</td>
<td>Gymnema</td>
</tr>
<tr>
<td>8</td>
<td>Bioflavonoid complex</td>
<td>24</td>
<td>Ivy leaf</td>
<td>40</td>
<td>Grass</td>
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<tr>
<td>9</td>
<td>Saw palmetto</td>
<td>25</td>
<td>Chia seed/chia oil</td>
<td>-</td>
<td>Berberine</td>
</tr>
<tr>
<td>10</td>
<td>Ginger</td>
<td>26</td>
<td>Turmeric</td>
<td>-</td>
<td>Cannabinoids</td>
</tr>
<tr>
<td>11</td>
<td>Aloe vera</td>
<td>27</td>
<td>Maca</td>
<td>-</td>
<td>Feverfew</td>
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<tr>
<td>12</td>
<td>Milk thistle</td>
<td>28</td>
<td>Fenugreek</td>
<td>-</td>
<td>Glycyrrhizin</td>
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<tr>
<td>13</td>
<td>Garlic</td>
<td>29</td>
<td>Isoflavones</td>
<td>-</td>
<td>Goldenseal</td>
</tr>
<tr>
<td>14</td>
<td>Cinnamon</td>
<td>30</td>
<td>Ginseng</td>
<td>-</td>
<td><em>Shisandra</em> spp.</td>
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<tr>
<td>15</td>
<td>Rhodiola</td>
<td>31</td>
<td>St. John’s wort</td>
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<td>Resveratrol</td>
</tr>
<tr>
<td>16</td>
<td>Horny goat weed</td>
<td>32</td>
<td>Green tea</td>
<td>-</td>
<td></td>
</tr>
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</table>
NP selection process

DIDB, Drug Interaction Database (UW)

47 NPs

40 from HerbalGram

7 from DIDB

In vivo interaction documented in DIDB?

YES

25 NO

22 NPs

• High number of positive interactions,
• All interactions negative,
• Lack of in vitro targets, OR
• Negative:positive interactions ≥3:1

11 YES

Gap analysis based on targets and experimental systems

11 NPs

Positive: ≥20% change in object drug AUC
Negative: <20% change in object drug AUC

Gap analysis based on targets and experimental systems

11 NPs

Johnson et al. (2018) Drug Metab Dispos, in press
# Gap analysis

<table>
<thead>
<tr>
<th></th>
<th>Inhibition</th>
<th>Induction</th>
<th>Gaps</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CYPs</strong> (1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recombinant enzymes</td>
<td>Nonessential</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Human liver microsomes</td>
<td>Essential</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Human hepatocytes</td>
<td>Nonessential</td>
<td>Essential</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>UGTs</strong> (2B7, 1A9, 1A1, 1A4, 1A6, 2B15, 1A3, 2B10, 1A8, 1A10)</td>
<td></td>
<td></td>
<td></td>
</tr>
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<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Transporters</strong> (OATP1B1, OATP1B3, OATP2B1, OAT1, OAT3, OCT1, OCT2, P-gp, BCRP, BSEP, NTCP, MRP2, MRP3, MATE1, MATE2K)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transfected cell lines</td>
<td>Essential</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Human hepatocytes</td>
<td>Nonessential</td>
<td>Essential</td>
<td></td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>Nuclear receptors</strong> (PXR, CAR, AhR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human hepatocytes</td>
<td>N/A</td>
<td>Essential</td>
<td></td>
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</table>

Johnson et al. (2018) *Drug Metab Dispos*, in press
NP selection process

DIDB, Drug Interaction Database (UW)

target = drug metabolizing enzyme or transporter

Johnson et al. (2018) Drug Metab Dispos, in press
Final high priority NPs using the ‘fulcrum model’

Unbalanced Minor to Moderate Gaps
- Overstudied
- Preponderence of mechanistic data
- Unlikely to yield substantial or novel NPDI findings

Cannabinoids
Goldenseal
Green tea
Licorice
Turmeric

Balanced Major Gaps
- Understudied
- Minimal evidence of NPDI
- Required studies infeasible during the funding period

Cannabinoids
Goldenseal
Green tea
Licorice
Turmeric

Balanced Minor Gaps
- Overstudied
- Minimal evidence of NPDI
- Unlikely to yield substantial or novel NPDI findings

NPDI, natural product-drug interaction

Johnson et al. (2018) Drug Metab Dispos, in press
Green tea consumption patterns and uses

• Infusions of green tea leaves are among the most commonly consumed beverages worldwide.

• Green tea supplements were ranked 4th in sales by HerbalGram in September, 2017.

• Green tea products are promoted for cardioprotection, chemoprevention, and weight loss.

• Medicinal effects have been attributed to polyphenols known as catechins, which constitute 30-42% of solid green tea.

Tian et al. (2018) Drug Metab Dispos
Major catechins in green tea

(-)-epicatechin (EC)  
(-)-gallocatechin (GC)  
(-)-epigallocatechin (EGC)

(-)-epicatechin-3-O-gallate (ECG)  
(-)-epigallocatechin-3-O-gallate (EGCG)

Tian et al. (2018) Drug Metab Dispos
Potential green tea-drug interaction targets

• Transporters
  ◦ Green tea constituents inhibited OATP1B1, OATP1B3, OCT1, OCT2, MATE1, MATE2-K, and P-gp activity in transfected cell systems (IC$_{50}$, 8-130 µM).
  ◦ Green tea (as a canned beverage) reduced systemic exposure (AUC and C$_{max}$) to nadolol by 85% in human subjects, which was attributed to inhibition of the intestinal uptake transporter, OATP1A2 (existence questioned).

• Cytochromes P450 (CYPs)
  ◦ Well-studied both *in vitro* and *in vivo*
  ◦ No effects on the pharmacokinetics of probe substrates for CYP1A2 (caffeine), CYP2C9 (losartan), CYP2D6 (dextromethorphan), and CYP3A4 (alprazolam, buspirone) in human subjects

Maximum reported catechin concentrations in human plasma ≤4 µM

Tian et al. (2018) *Drug Metab Dispos*
Potential green tea-drug interaction targets, cont’d

- **Sulfotransferases**
  - A green tea extract (1.25 mg/mL) nearly abolished ritodrine sulfation in recombinant SULT1A1 and SULT1A3 systems.

- **UDP-glucuronosyltransferases (UGTs)**
  - IC$_{50}$ for EGCG against UGT1A1, UGT1A4, UGT1A6, and UGT2B17 activity in human liver microsomes or recombinant enzyme ranged from 17-400 µM.
  - IC$_{50}$ for EGCG against 4-methylumbelliferone (4-MU) glucuronidation in human intestinal microsomes was 46 µM.
  - EGCG at 100 µM inhibited 4-MU glucuronidation by 40-80% in UGT1A1-, UGT1A8-, and UGT1A10-expressing cell lysates.

Intestinal UGTs were prioritized as targets for the green tea interaction project.
Hypothesis: green tea inhibits intestinal UGTs
Green tea product selection for *in vitro* and clinical studies

• Steeped green tea was selected based on typical use and lack of need for dissolution of bioactive constituents.
Product selection

Courtesy of Nadja B. Cech, PhD
Green tea product selection for *in vitro* and clinical studies

• Steeped green tea was selected based on typical use and lack of need for dissolution of bioactive constituents.

• The **Analytical Core** used a state-of-the-art chemometrics approach to select the green tea product for *in vitro* and clinical studies.
  ◦ A variety commercially available products – teas, powders, and supplements – (n=45) were selected based on consumer sales and product quality reports.
  ◦ Reference materials from the NIST and a non-green tea were used as positive and negative controls, respectively.
  ◦ Metabolomic data collection approaches were compared to characterize the chemical composition of all green tea products.
  ◦ Green tea products that were most chemically similar to the NIST reference material were selected for testing as inhibitors of intestinal UGT activity.

NIST, National Institute of Standards and Technology

Kellogg et al. (2017) *J Natr Prod*
Effects of green tea extracts/fractions on intestinal UGT activity

UGT activity = 4-MU glucuronidation
Test system = human intestinal microsomes

Tian et al. (2018) Drug Metab Dispos
Effects of major green tea catechins on intestinal UGT activity

All NP constituents were tested at 100 μM; nicardipine was tested at 400 μM. Bars and error bars denote means ± SDs, respectively, of triplicate incubations. Test system = human intestinal microsomes

Tian et al. (2018) Drug Metab Dispos
IC$_{50}$ for ECG and EGCG

The data suggest a potential interaction between green tea and intestinal UGT drug substrates.

**Concentration in cup**$^a$ **of hot tea**$^b$ (µM)

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>EC</td>
<td>86.1 ± 29.1</td>
<td></td>
</tr>
<tr>
<td>ECG</td>
<td>104 ± 14.9</td>
<td></td>
</tr>
<tr>
<td>EGC</td>
<td>241 ± 38.9</td>
<td></td>
</tr>
<tr>
<td>EGCG</td>
<td>210 ± 37.3</td>
<td></td>
</tr>
<tr>
<td>GC</td>
<td>227 ± 38.2</td>
<td></td>
</tr>
</tbody>
</table>

$^a$240 mL

$^b$Prepared from NIST leaf reference material.

Test system = human intestinal microsomes

IC$_{50}$ determined via nonlinear regression analysis using Phoenix WinNonlin

Tian et al. (2018) Drug Metab Dispos
Raloxifene as a clinically relevant intestinal UGT substrate

- Selective estrogen receptor modulator indicated for osteoporosis and breast cancer risk reduction
- Low oral bioavailability (<2%) due primarily to extensive intestinal glucuronidation by UGT1As
- Inhibition of intestinal UGT1As could increase systemic exposure (AUC) to raloxifene, leading to adverse effects (e.g., hot flashes, venous thromboembolism).
Raloxifene intestinal glucuronidation

Raloxifene

UGT1A1
UGT1A8
UGT1A10

Raloxifene 4′-glucuronide (R4G)

Raloxifene 6-glucuronide (R6G)

UGT1A8 and UGT1A10 expressed in intestine but not liver
$K_i$ for ECG and EGCG

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>$K_i$</th>
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<tr>
<td>R4G</td>
<td>0.81</td>
</tr>
<tr>
<td>R6G</td>
<td>0.95</td>
</tr>
<tr>
<td>ECG (μM)</td>
<td>1.99</td>
</tr>
<tr>
<td>EGCG (μM)</td>
<td>2.02</td>
</tr>
</tbody>
</table>

Velocity vs. substrate concentration data were described best by the simple competitive inhibition model.

$K_i$'s were determined via nonlinear least-squares regression analysis using Phoenix WinNonlin (v6.4).

The $K_i$'s for ECG and EGCG were 100x lower than concentrations measured in a cup of hot tea prepared from the NIST product.

Test system = human intestinal microsomes
R4G, raloxifene-4'-glucuronide; R6G, raloxifene-6-glucuronide

Tian et al. (2018) Drug Metab Dispos
**In vitro-in vivo prediction**

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>$I_g$ (μM)</th>
<th>Predicted AUC$_i$ / AUC</th>
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<tr>
<td><strong>ECG</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gut lumen concentration$^a$</td>
<td>4.4</td>
<td>4.4</td>
</tr>
<tr>
<td>Enterocyte concentration$^b$</td>
<td>0.18</td>
<td><strong>1.2</strong></td>
</tr>
<tr>
<td><strong>EGCG</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gut lumen concentration$^a$</td>
<td>15.2</td>
<td>6.1</td>
</tr>
<tr>
<td>Enterocyte concentration$^b$</td>
<td>0.54</td>
<td><strong>1.3</strong></td>
</tr>
</tbody>
</table>

$^a$Calculated according to $F_a x k_a x \text{Dose}/Q_{ent}$

$^b$Simulated using Simcyp

\[
\frac{\text{AUC}_i}{\text{AUC}} = \frac{1}{(1-F_g)} \times \frac{1}{\left(1 + \frac{I_g \times f_{u,g}}{K_i \times f_{u,mic}}\right)} + F_g
\]

- $I_g$, inhibitor concentration in gut
- $F_g$, fraction of oral drug dose that escapes gut extraction (literature: 0.054)
- $f_{u,g}$, unbound fraction of inhibitor in gut ($\sim 1$)$^b$
- $K_i$, experimentally determined using HIM (1 or 2 μM)
- $f_{u,mic}$, unbound fraction of inhibitor in HIM ($\sim 1$)$^b$
- $F_a$, fraction of inhibitor dose absorbed into enterocytes ($\sim 0.65$)$^b$
- $k_a$, first-order absorption rate constant (default: 0.1 min$^{-1}$)
- $Q_{ent}$, blood flow through enterocytes (literature: 248 ml/min)

Tian et al. (2018) Drug Metab Dispos
Clinical study design and procedures

- Healthy volunteers (8 men, 8 women)
  - Sample size was based on 80% power to detect a 25% change in the primary endpoint with a Type I error of 0.05.
  - Primary endpoint: log-transformed raloxifene AUC ratio (green tea/baseline)

- Raloxifene (60 mg po) was administered alone (baseline), with green tea on 1 day (acute), or upon a 5-day treatment with green tea (chronic) in a fixed-sequence fashion.

- Plasma and urine were collected from 0-96 and 0-24 h, respectively.

- The pre-defined no effect range was 0.75-1.33.

<table>
<thead>
<tr>
<th>Phase</th>
<th>Washout</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (baseline)</td>
<td>≥1 week washout</td>
</tr>
<tr>
<td>II (acute green tea)</td>
<td>≥1 week washout</td>
</tr>
<tr>
<td>III (chronic green tea)</td>
<td></td>
</tr>
</tbody>
</table>

McCune et al. (2018) Clin Pharmacol Ther Suppl S1
Slides 36-42 redacted
Summary and conclusion

• **Green tea**, one of four NPs selected to study as a precipitant of NP-drug interactions, was the first to be advanced to an interaction project.

• Based on a gap analysis, **intestinal UGTs** were prioritized as targets for the *in vitro* and clinical green tea-drug interaction studies.

• A pharmacokinetic interaction occurred between a well-characterized green tea and the intestinal UGT substrate raloxifene, as the geometric mean raloxifene AUC lay **below** the pre-defined no effect range.

• The greater decrease in raloxifene geometric mean $C_{max}$ relative to AUC, combined with a minimal change in terminal half-life, suggested that green tea alters primarily processes in the **intestine**, which could include permeability, transport, and/or physicochemical processes involved in raloxifene absorption.
Slides 44-48 redacted
Acknowledgements

Dandan Tian, PhD (Pharmacology Core, WSU)
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Allan Rettie, PhD (Pharmacology Core, UW)
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Nadja Cech, PhD (Analytical Core, UNCG)
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