Green tea effects on pharmacokinetics and pharmacodynamics

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Topics to be covered

• Green tea and catechins
• Clinical pharmacokinetics of catechins
• Green tea-drug interactions in humans
  ✓ CYP-mediated interactions
  ✓ Drug transporter-mediated interactions
Green tea

Consumption of green tea in Japan and the USA

• Tea is the most widely consumed beverage in the world next to water.

• About 15% of Japanese (older than 40 y.o., male 17.9% and female 13.1%) consumed more than 10 cups of green tea in a day (>1800 mL).

  (Imai et al., Prev Med 1997, 26:769–75)

• “Tea sales in the U.S. have increased five-fold in 25 years, to more than $10 billion dollars.”

Green tea catechins (flavan-3-ol)

Reported health benefits
✓ Cancer prevention
✓ Reducing cardiovascular risk
✓ Anti-obesity
✓ Anti-infection
✓ Anti-oxidative stress

Naturally occurring catechins (cis-type)

- Epigallocatechin gallate (EGCG)
- Epigallocatechin (EGC)
- Epicatechin (EC)
- Epicatechin gallate (ECG)

- 50-80% of total catechins
- Most bioactive

Heat-epimerized catechins: gallocatechin gallate (GCG), gallocatechin (GC), catechin (C), catechin gallate (CG)
Contents of catechins in Japanese green tea

Catechin concentrations

<table>
<thead>
<tr>
<th>Catechin</th>
<th>Min</th>
<th>Average</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGC</td>
<td></td>
<td></td>
<td>1.3 (0.6–1.8) mM</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.3 (0.2–0.7) mM</td>
</tr>
<tr>
<td>EC</td>
<td></td>
<td>1.4 to 4.0-fold</td>
<td>2.3 (1.7–2.8) mM</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.4 (0.1–1.1) mM</td>
</tr>
<tr>
<td>ECG</td>
<td></td>
<td></td>
<td>0.6 (0.4–0.8) mM</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.1 (0.04–0.2) mM</td>
</tr>
<tr>
<td>EGCG</td>
<td></td>
<td></td>
<td>0.2 (0.07–0.3) mM</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.07 (0.03–0.2) mM</td>
</tr>
</tbody>
</table>

A cup of brewed green tea contains approx. 100 mg of EGCG

Caffeine

<table>
<thead>
<tr>
<th>Type</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brewed GT</td>
<td>1.8 (0.5–2.4) mM</td>
<td></td>
</tr>
<tr>
<td>Bottled GT</td>
<td>0.8 (0.5–1.1) mM</td>
<td></td>
</tr>
</tbody>
</table>

(modified from Mizukami et al., J Agric Food Chem, 2007)
Topics to be covered

- Green tea and catechins
- Clinical pharmacokinetics of catechins
- Green tea-drug interactions in humans
  - CYP-mediated interactions
  - Drug transporter-mediated interactions
Pharmacokinetics of catechins after green tea intake

- Subjects received 700 mL of green tea (350 mL × 2 at 0 and 0.5 hr)

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>EGC</th>
<th>ECG</th>
<th>EGCG</th>
<th>0.3 μM</th>
</tr>
</thead>
<tbody>
<tr>
<td>168</td>
<td>37.8 (34.7–40.9)</td>
<td>49.4 (30.0–68.7)</td>
<td>141.2 (111.5–171.0)</td>
<td>322</td>
</tr>
<tr>
<td>91</td>
<td>1.0 (0.5–2)</td>
<td>1.0 (0.5–2)</td>
<td>1.0 (1–2)</td>
<td></td>
</tr>
<tr>
<td>322</td>
<td>1.5 (1.3–1.8)</td>
<td>1.6 (1.3–1.8)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Geometric mean (90% CI); n = 10

(Misaka et al., Clin Pharmacol Ther, 2014)
Pharmacokinetics of EGCG in humans

EGCG dose vs. $C_{\text{max}}$

- $r^2 = 0.5812$
- $P = 0.0463$

- Log $P$: $1.41 \pm 0.03$
- $P_{\text{app,a-b}}$: $0.83 \pm 0.24$ (× $10^{-7}$ cm/s, Caco-2 cells)
- $C_{\text{max}}$: 50 ng/mL (0.11 μM) after 100 mg dose
- $t_{\text{max}}$: $1.6 \pm 0.4$ (h)
- $t_{1/2}$: $1.5 \pm 0.9$ (h)
- EGCG appears unconjugated in the blood.

Absorption of EGCG

Intestine is the main site of green tea-drug interactions.

EGCG dose: 100 mg (218 μmol)
Assumed GI fluid (0.5 – 11 L)

EGCG conc. in the intestine may reach 20 – 436 μM.

Reference:
Topics to be covered

• Green tea and catechins
• Clinical pharmacokinetics of catechins
• Green tea-drug interactions in humans
  ✓ CYP-mediated interactions
  ✓ Drug transporter-mediated interactions
Possible two different mechanisms

OATPs: OATP1A2 and OATP2B1; P-gp: P-glycoprotein; BCRP: breast cancer resistance protein
In vitro inhibitory effect of catechins on human CYPs

<table>
<thead>
<tr>
<th>CYP</th>
<th>$K_i$ (μM)</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP1A1</td>
<td>16.6</td>
<td>Mixed</td>
</tr>
<tr>
<td>CYP1A2</td>
<td>9.5</td>
<td>Noncompetitive</td>
</tr>
<tr>
<td>CYP2A6</td>
<td>41.1</td>
<td>Mixed</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>18.0</td>
<td>Noncompetitive</td>
</tr>
<tr>
<td>CYP2E1</td>
<td>57.8</td>
<td>Mixed</td>
</tr>
<tr>
<td>CYP3A4</td>
<td>13.0</td>
<td>Noncompetitive</td>
</tr>
</tbody>
</table>

Substrate: 7-Ethoxycoumarin (CYP1A1), 7-Ethoxyresorufin (CYP1A2), Coumarin (CYP2A6), Diclofenac (CYP2C9), 4-Nitrophenol (CYP2E1), Midazolam (CYP3A4)

(Muto S. et al., Mutat Res, 2001)
Case report suggesting green tea-simvastatin interaction

![Graphs showing Simvastatin lactone and Simvastatin acid (active metabolite) plasma concentrations over time with and without green tea.]

**Table. Pharmacokinetic Parameters of Simvastatin Lactone and Simvastatin Acid after Oral Administration of 20 mg of Simvastatin**

<table>
<thead>
<tr>
<th>Substance</th>
<th>$C_{\text{max}}, \text{ ng/mL}$ No Green Tea</th>
<th>$C_{\text{max}}, \text{ ng/mL}$ Green Tea</th>
<th>$T_{\text{max}}, \text{ h}$ No Green Tea</th>
<th>$T_{\text{max}}, \text{ h}$ Green Tea</th>
<th>AUC $0-t, \text{ ng/mL} \times \text{h}^{-1}$ No Green Tea</th>
<th>AUC $0-t, \text{ ng/mL} \times \text{h}^{-1}$ Green Tea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simvastatin lactone</td>
<td>3.70</td>
<td>7.21</td>
<td>1</td>
<td>2</td>
<td>6.3</td>
<td>12.5</td>
</tr>
<tr>
<td>Simvastatin acid</td>
<td>1.41</td>
<td>1.73</td>
<td>2</td>
<td>2.5</td>
<td>2.1</td>
<td>2.2</td>
</tr>
</tbody>
</table>

AUC = area under the curve; $C_{\text{max}}$ = maximum plasma concentration; $T_{\text{max}}$ = time to $C_{\text{max}}$.

(Werba et al., Ann Internal Med, 2008)
In vitro inhibitory effect of catechins on human CYPs

**IC\textsubscript{50} of EGCG**

<table>
<thead>
<tr>
<th>Organ</th>
<th>IC\textsubscript{50} of EGCG (μM)</th>
<th>Mean with 95% CI</th>
<th>Human liver microsome</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2B6 Liver</td>
<td>8.3 (4.8–14.5)</td>
<td></td>
<td>Human liver microsome</td>
</tr>
<tr>
<td>CYP2C8 Liver</td>
<td>10.9 (7.3–16.0)</td>
<td></td>
<td>Human liver microsome</td>
</tr>
<tr>
<td>CYP2C19 Liver, intestine</td>
<td>101.3 (29.8–343.6)</td>
<td></td>
<td>Human liver microsome</td>
</tr>
<tr>
<td>CYP2D6 Liver</td>
<td>68.5 (44.5–105.4)</td>
<td></td>
<td>Human liver microsome</td>
</tr>
<tr>
<td>CYP3A4/5 Intestine, liver</td>
<td>23.3 (15.0–36.1)</td>
<td></td>
<td>Human liver microsome</td>
</tr>
</tbody>
</table>

Substrate: Bupropion (CYP2BA6), Amodiaquine (CYP2C8), Diclofenac (CYP2C9), Fluvastatin (CYP2C9), S-mephenytoin (CYP2C19), Dextromethorphan (CYP2D6), Midazolam (CYP3A).
GT affects simvastatin disposition (Japanese)

Randomized crossover study in healthy volunteers

- Green tea contained EGCG of 46 mg/100 mL.

Simvastatin lactone

- Mean ± SD (n = 12)

Simvastatin acid (active metabolite)

- C<sub>max</sub> 1.6-fold
- AUC 1.5-fold

(Werba et al., Curr Pharm Des, 2015)
Possible mechanism underlying GT-simvastatin interaction

SL: Simvastatin lactone, SA: Simvastatin acid
Pie chart of CYPs in human intestine and liver

Small intestine
- CYP2C19
- CYP2D6
- CYP2J2
- CYP2C9
- CYP3A

Liver
- CYP1A2
- CYP2E1
- CYP2B6
- CYP2A6
- CYP2D6
- CYP3A
- CYP2C

(Shimada et al., J Pharmacol Exp Ther, 1994; Paine et al., Drug Metab Dispos, 2006)
Inhibition of diclofenac metabolism by EGCG and GT

- Recombinant human CYP2C9 bactosome
- CYP2C9 substrate: Diclofenac (4’-hydroxylation) CYP2C9

**IC$_{50}$** = 1.9 (0.5-6.7) μM for EGCG

**IC$_{50}$** = 0.5 (0.2-1.3)% for Green tea

(Misaka et al., unpublished data)
Inhibition of fluvastatin metabolism by EGCG and GT

\[ IC_{50} = 44.8 \ (1.2-1687) \ \mu M \]

(Misaka et al., unpublished data)
Fluvastatin

• Acid-type statin

• Bioavailability: 29%

• Plasma protein binding: more than 98%

• BCS and BDDCS class I drug

• Metabolism: CYP2C9 (major), CYP3A (minor)

• Drug transporter
  Efflux: BCRP (major), P-gp and MRP2 (minor)
  Uptake: OATP1B1, OATP1B3, OATP2B1

• Drug interaction
  Fluconazole (CYP2C9 inhibitor) increased fluvastatin AUC by 84%.

(Kantola et al., Eur J Clin Pharmacol 2000)
Green tea-fluvastatin interaction study

- Randomized open 3-phase crossover design
- Subject: healthy volunteers
- Fluvastatin dose: 20 mg with 300 mL of water or green tea
- Green tea (Harada Tea Processing Co., Ltd., Shizuoka, Japan)
  - Brewed (2.2 g/100 mL water) before fluvastatin dosing
  - EGCG concentration: 50 mg/dL
  - EGCG dose: 150 mg (300 mL)
- Green tea extract (Sunphenon®-EGCG, Taiyo Kagaku, Yokkaichi, Japan)
  - Total catechin content: 97.4%
  - EGCG: 92.5%
  - ECG: 3.8%
  - Caffeine: not detected
  - EGCG dose: 150 mg
→ EGCG dose was the same both in green tea and GTE
Effect of green tea on fluvastatin pharmacokinetics

- Green tea → AUC 14%
- GTE → AUC 4%

(Misaka et al., unpublished data)
Summary of CYP-mediated drug-green tea interaction

✓ Catechins can inhibit CYPs such as CYP3A and CYP2C9 in vitro

✓ Clinical studies suggest that green tea increases simvastatin exposure
  → The interaction is less pronounced compared with grapefruit juice

✓ Green tea and GTE may not affect fluvastatin pharmacokinetics
Topics to be covered

• Green tea and catechins
• Clinical pharmacokinetics of catechins
• Green tea-drug interactions in humans
  ✓ CYP-mediated interactions
  ✓ Drug transporter-mediated interactions
Inhibitory effects of catechins on drug transporters in vitro

P-glycoprotein

(Jodoin et al., Biochim Biophys Acta, 2002)

OATP1A2

OATP2B1

(Roth et al., Drug Metab Dispos 2011)
Nadolol

- Nonselective $\beta$-blocker
- Bioavailability: less than 30%
- Plasma protein binding: 24%
- Metabolism: negligible
- Excretion: urine
- Drug transporter
  Efflux: P-glycoprotein
  Influx: OATP1A2
- Drug interactions
  Itraconazole (P-gp inhibitor) increased nadolol AUC by 224%.

(Misaka et al., J Clin Phramacol, 2013)
Clinical study

- Randomized, open-label, 2-way crossover study
- Subjects: 10 healthy Japanese male volunteers
  Age: 23.8 y.o. (range 20–30)
  Male: 8; female: 2
  BMI: 21.2 kg/m² (range 18.3–23.9)
- Subjects received 700 mL/day of green tea or water for 14 days.
- On day 15, nadolol (30 mg) was administered orally with 350 mL of green tea or water.
- Subjects drank another 350 mL of green tea or water 30 min after nadolol administration.
- Green tea contained EC, EGC, ECG and EGCG of 80, 240, 130 and 460 μg/mL, respectively, determined by UPLC/ESI-MS.
Green tea greatly reduces nadolol exposure

![Graph showing nadolol plasma concentration over time with and without green tea]

**AUC 85%**

<table>
<thead>
<tr>
<th>Water</th>
<th>Green tea</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td>55.7 (24.8–86.5)</td>
</tr>
<tr>
<td>$\text{AUC}_{0-48}$ (ng·h/mL)</td>
<td>708.9 (569.8–848.0)</td>
</tr>
</tbody>
</table>

**,** **,** $P < 0.01$, $0.001$ vs. Water

Mean ± SD ($n=10$)

(Misaka et al., Clin Pharmacol Ther, 2014)
Effect of green tea on nadolol urinary excretion

Green tea did not influence nadolol renal clearance

Green tea may affect nadolol intestinal absorption

** $P<0.01$ vs. water

(Misaka et al., Clin Pharmacol Ther, 2014)
Possible mechanism underlying GT-nadolol interaction

NDL: Nadolol

NDL

Catechin

OATP1A2

OATP2B1

P-gp

Intestinal lumen

Enterocyte

Blood vessel

Hepatocyte

(Misaka et al., Clin Pharmacol Ther, 2014)
Further questions regarding nadolol-green tea interaction

- Even a single intake of green tea could cause the interaction?
- Catechins such as EGCG are causative substances?
- How much catechin is required to clinically relevant interaction?
- How long does the interaction last?
- How about the other drugs (drug transporter-mediated interaction)?
GTE-nadolol interaction study

- Randomized, open 3-phase crossover study
- Subject: healthy volunteers
- Nadolol dose: 30 mg with 300 mL of water with GTE
- Green tea extract (Sunphenon®-EGCG, Taiyo Kagaku)
  - EGCG dose:
    - 50 mg (16.7 mg/dL)
    - 150 mg (50 mg/dL)
  - GTE was dissolved in water prior to administration

EGCG concentration in Japanese green tea preparations

![Graph showing EGCG concentration in different green tea preparations](image-url)
Effect of EGCG on nadolol concentrations

Nadolol plasma concentrations in healthy volunteers

Mean ± SD

Nadolol + EGCG 50 mg → AUC 38%

Nadolol + EGCG 150 mg → AUC 46%

(Misaka et al., Unpublished data)
Further questions regarding nadolol-green tea interaction

- Even a single intake of green tea could cause the interaction?
  → Yes, in case of nadolol.

- Catechins such as EGCG are causative substances?
  → Yes, at least EGCG.

- How much catechin is required to clinically relevant interaction?
  → Our data suggest 50 mg of EGCG could cause interaction.

- How long does the interaction last?
  → Unknown, but we will plan to address this question.

- How about the other drugs (drug transporter-mediated interaction)?
  → Unknown, but should be tested.
Summary

Green tea catechins

- Hydrophilic, poor permeable, and low bioavailability.
- Interaction with drugs could mainly occur in the intestine.

CYP-mediated green tea-drug interactions

- Catechins can inhibit CYPs including CYP3A and CYP2C9 in vitro.
- Green tea slightly increases simvastatin acid concentration in vivo.
- Green tea and GTE may not affect fluvastatin pharmacokinetics in vivo.

Drug transporter-mediated green tea-drug interactions

- Catechins can inhibit several influx and efflux transporters in vitro.
- Green tea significantly decreases nadolol concentration in vivo.
- EGCG is the one of causative component in green tea.
- Single intake of 50 mg EGCG could influence nadolol pharmacokinetics.
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