Green tea effects on pharmacokinetics and pharmacodynamics

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ASCPT 2016 annual meeting
ASCPT-Asia Pacific Joint Symposium

March 9, 2016

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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.”

(“Matcha madness sparks new tea craze”, *CBS News*, April 14, 2015)

抹茶 *Matcha*

煎茶 *Sencha*

Bottled teas

Green tea catechins (flavan-3-ol)

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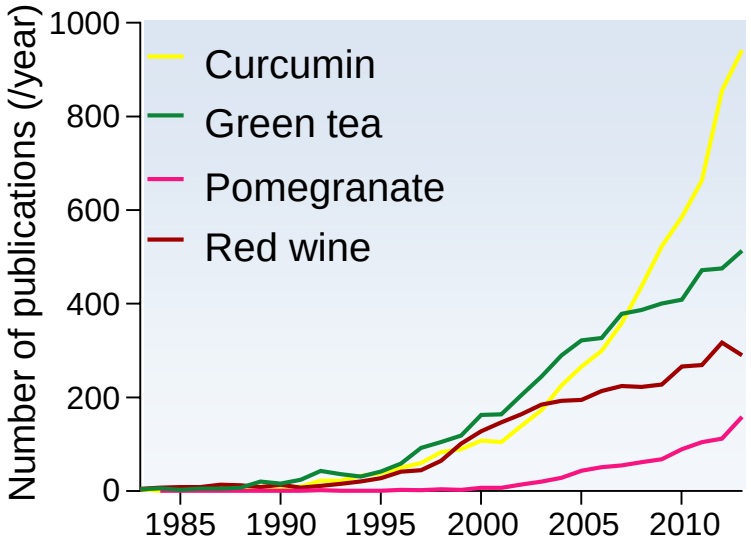
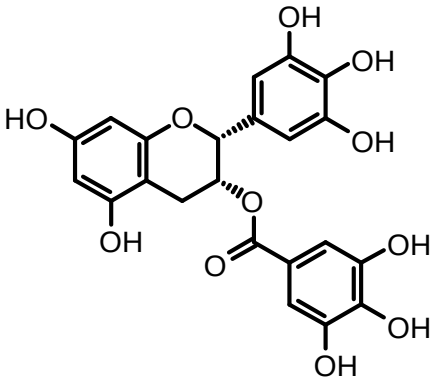
Reported health benefits

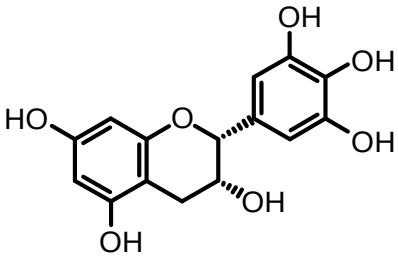
- ✓ Cancer prevention
- ✓ Reducing cardiovascular risk
- ✓ Anti-obesity
- ✓ Anti-infection
- ✓ Anti-oxidative stress



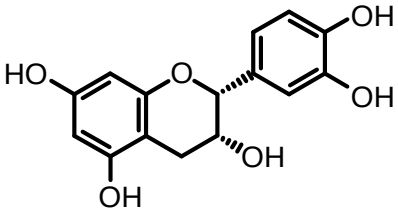
Naturally occuring catechins (*cis*-type)



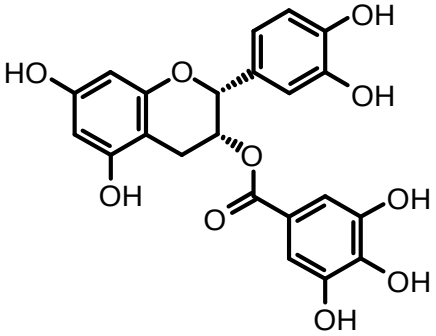
Epigallocatechin gallate (EGCG)



Epigallocatechin (EGC)



Epicatechin (EC)



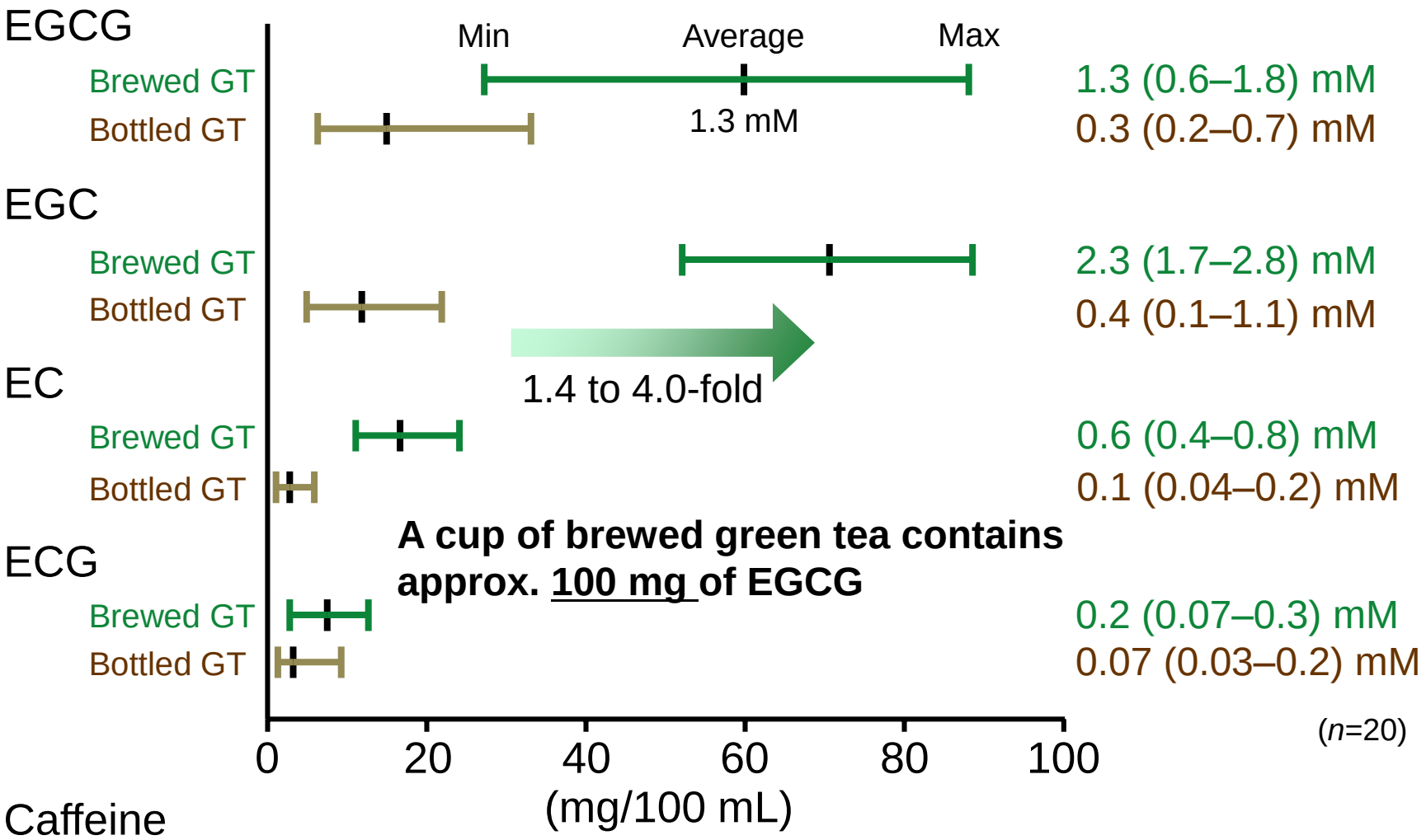
Epicatechin gallate (ECG)

- ➢ 50-80% of total catechins
- ➢ most bioactive

Heat-epimerized catechins: gallocatechin gallate (GCG), gallocatechin (GC), catechin (C), catechin gallte (CG)

Contents of catechins in Japanese green tea

Catechin concentrations



(modified from Mizukami *et al*., *J Agric Food Chem*, 2007)

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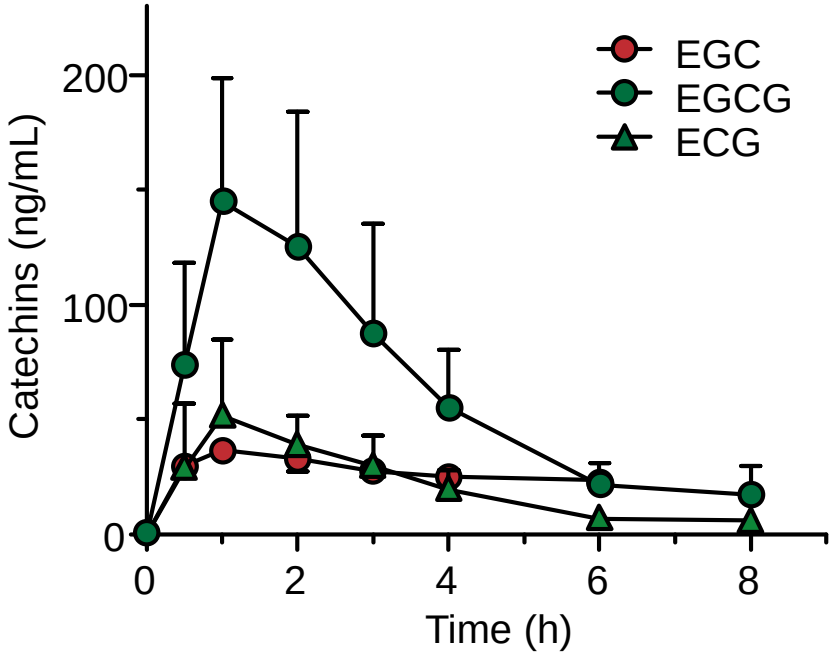
Pharmacokinetics of catechins after green tea intake

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



	EGC	ECG	EGCG
Dose (mg)	168	91	322
C_{max} (ng/mL)	37.8 (34.7–40.9)	49.4 (30.0–68.7)	141.2 (111.5–171.0)
T_{max} (h)	1.0 (0.5–2)	1.0 (0.5–2)	1.0 (1–2)
$t_{1/2}$ (h)	-	1.5 (1.3–1.8)	1.6 (1.3–1.8)

0.3 μM

Geometric mean (90% CI); *n* =10

(Misaka *et al*., *Clin Pharmacol Ther,* 2014)

Pharmacokinetics of EGCG in humans

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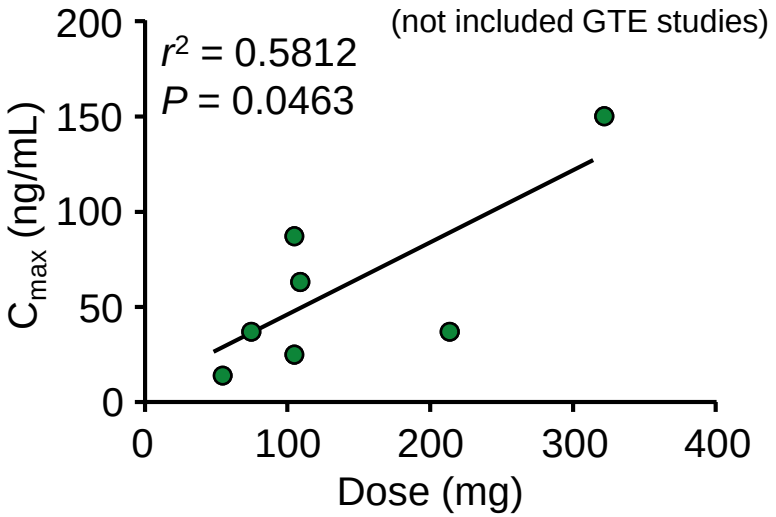
EGCG dose *vs.* C_{max}



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

Mean±SD

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.

Blood

EGCG

EGC and its sulfate or glucuronide

Trihydroxyphenyl-γ-valerolactone and its further metabolites

abolism

nno *et al*., *Biosci Biotechnol Biochem* 1996; Henning *et al*., *Am J Clin Nutr* 004; Zhang *et al*., *Int J Pharm*, 2004; Masukawa *et al*., *J Chromatogr B* 2006; Stalmach *et al*., *Mol Nutr Food Res* 2009; Del Rio *et al*., *Nutrition* 2010; Müller *et al*., *Mol Nutr Food Res* 2010; Misaka *et al*., *Clin Pharmacol Ther,* 2014)

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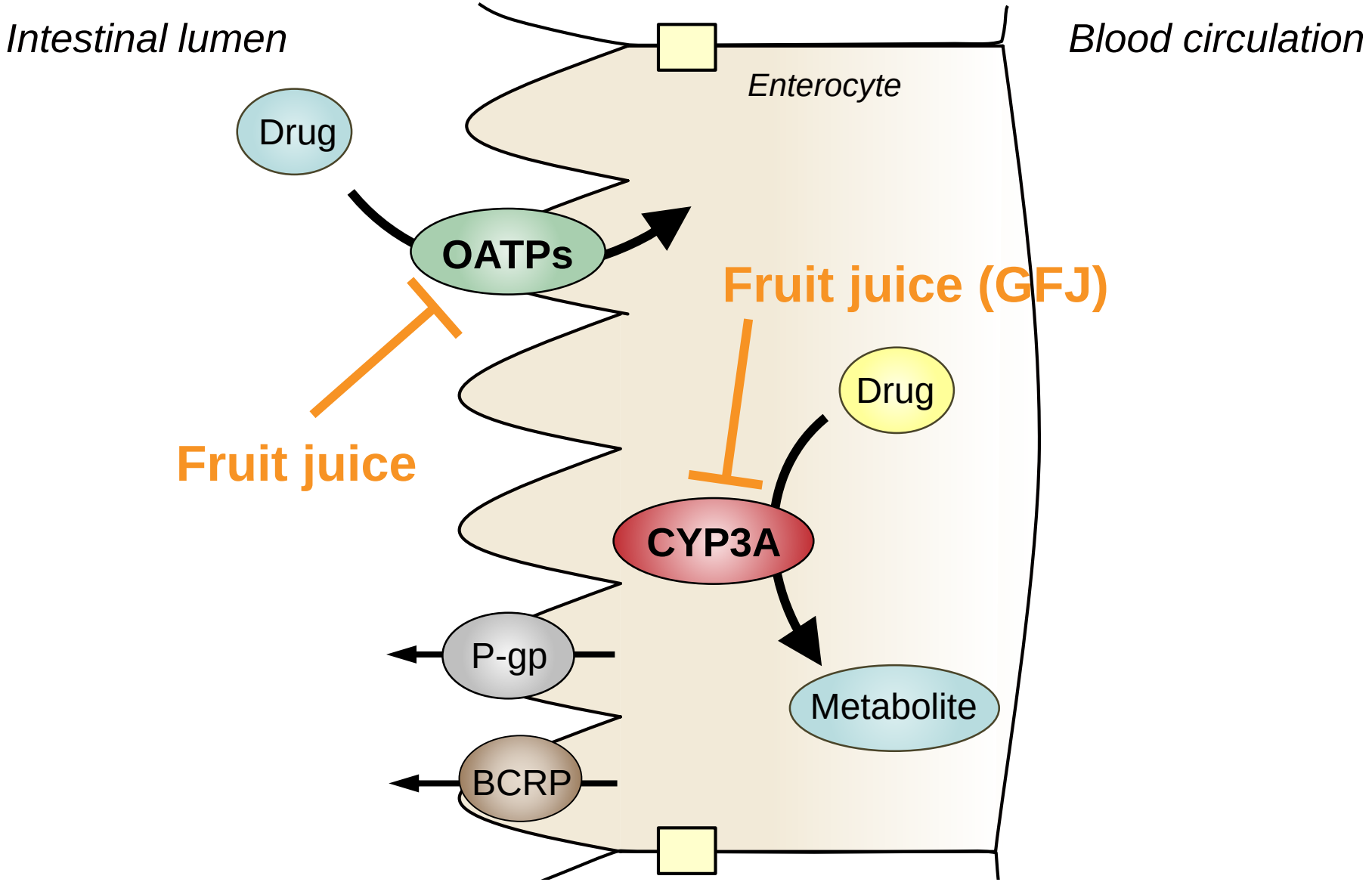
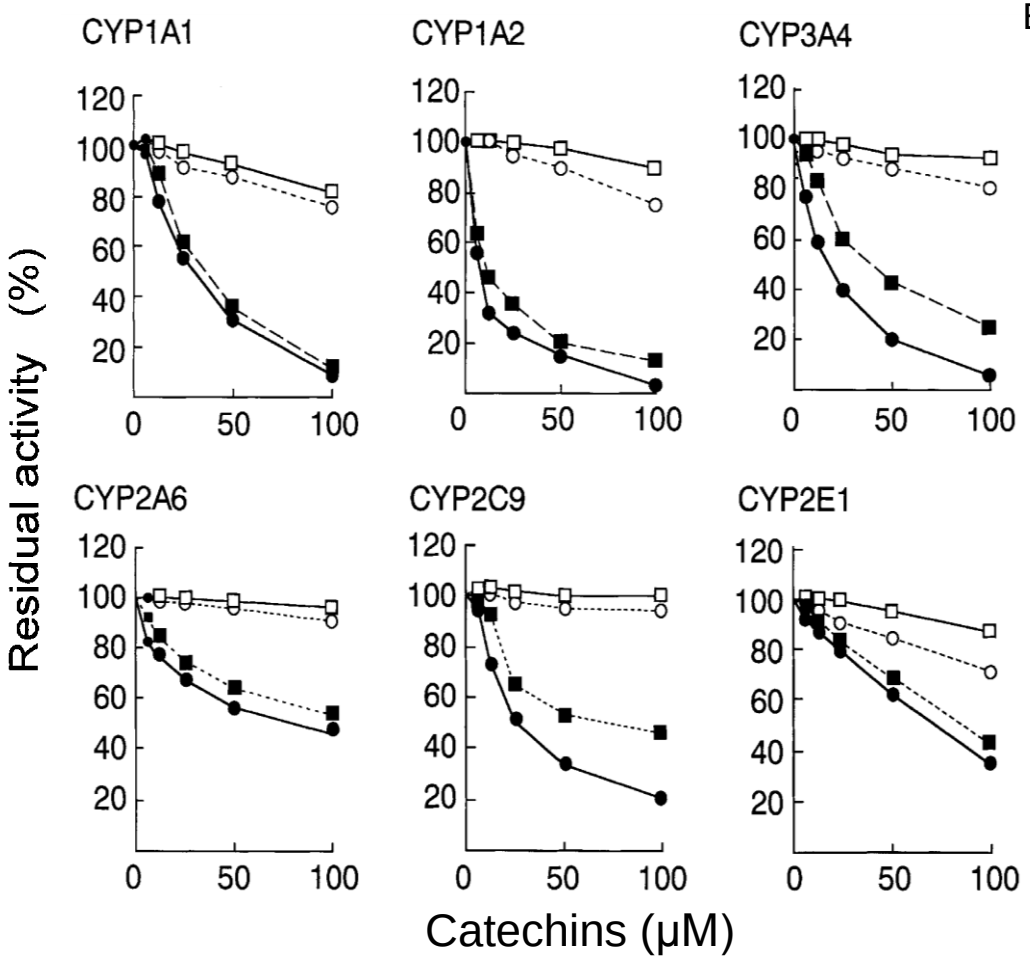
Possible two different mechanisms



OATPs: OATP1A2 and OATP2B1; P-gp: P-glycoprotein; BCRP: breast cancer resistance protein

In vitro inhibitory effect of catechins on human CYPs



EC (○); EGC (□); ECG (●); EGCG (■)

Inhibition of CYPs by EGCG

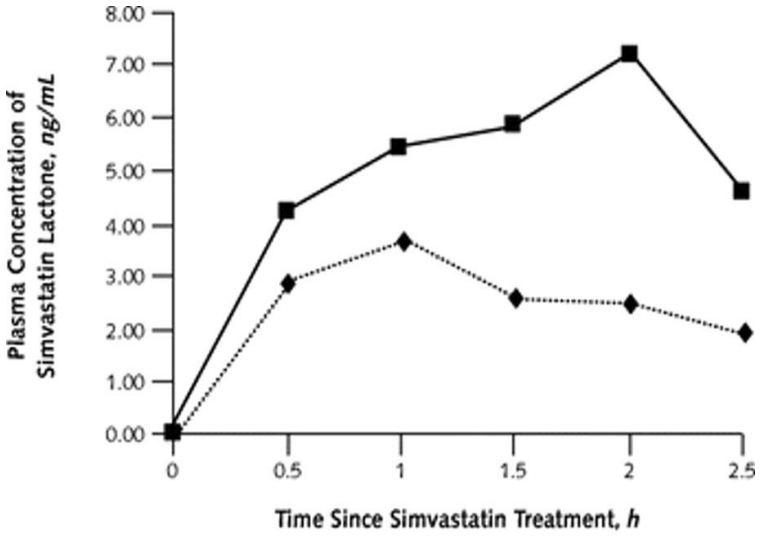
	K_i (μM)	Type
CYP1A1	16.6	Mixed
CYP1A2	9.5	Noncompetitive
CYP2A6	41.1	Mixed
CYP2C9	18.0	Noncompetitive
CYP2E1	57.8	Mixed
CYP3A4	13.0	Noncompetitive

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

Simvastatin lactone



Simvastatin acid (active metabolite)

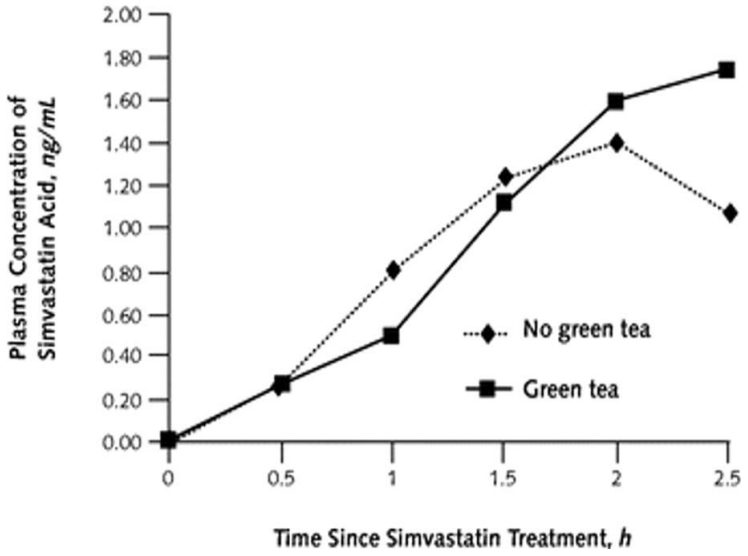


Table. **Pharmacokinetic Parameters of Simvastatin Lactone and Simvastatin Acid after Oral Administration of 20 mg of Simvastatin**

Substance	C_{max}, *ng/mL*		T_{max}, *h*		AUC 0–*t*, *ng/mL* × h^{-1}	
	No Green Tea	Green Tea	No Green Tea	Green Tea	No Green Tea	Green Tea
Simvastatin lactone	3.70	7.21	1	2	6.3	12.5
Simvastatin acid	1.41	1.73	2	2.5	2.1	2.2

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

(Werba *et al*., *Ann Internal Med*, 2008)

In vitro inhibitory effect of catechins on human CYPs

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IC_{50} of EGCG

	Organ	IC_{50} of EGCG (μM)	
CYP2B6	Liver	8.3 (4.8–14.5)	Human liver microsome
CYP2C8	Liver	10.9 (7.3–16.0)	Human liver microsome
CYP2C19	Liver, intestine	101.3 (29.8–343.6)	Human liver microsome
CYP2D6	Liver	68.5 (44.5–105.4)	Human liver microsome
CYP3A4/5	Intestine, liver	23.3 (15.0–36.1)	Human liver microsome

Mean with 95% CI

Substrate: Bupropion (CYP2BA6), Amodiaquine (CYP2C8), Diclofenac (CYP2C9), Fluvastatin (CYP2C9), *S*-mephenytoin (CYP2C19), Dextromethorphan (CYP2D6), Midazolam (CYP3A).

(Misaka *et al*., *Drug Metab Pharmacokinet*, 2013)

GT affects simvastatin disposition (Japanese)

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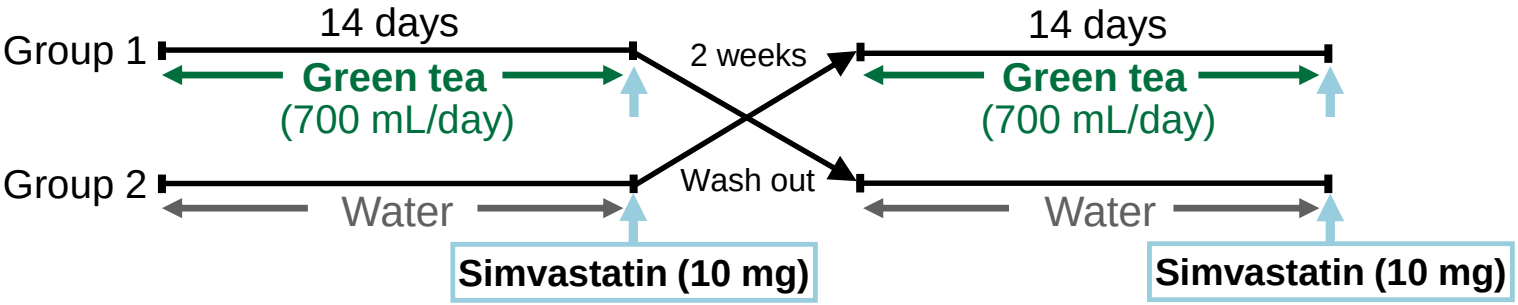
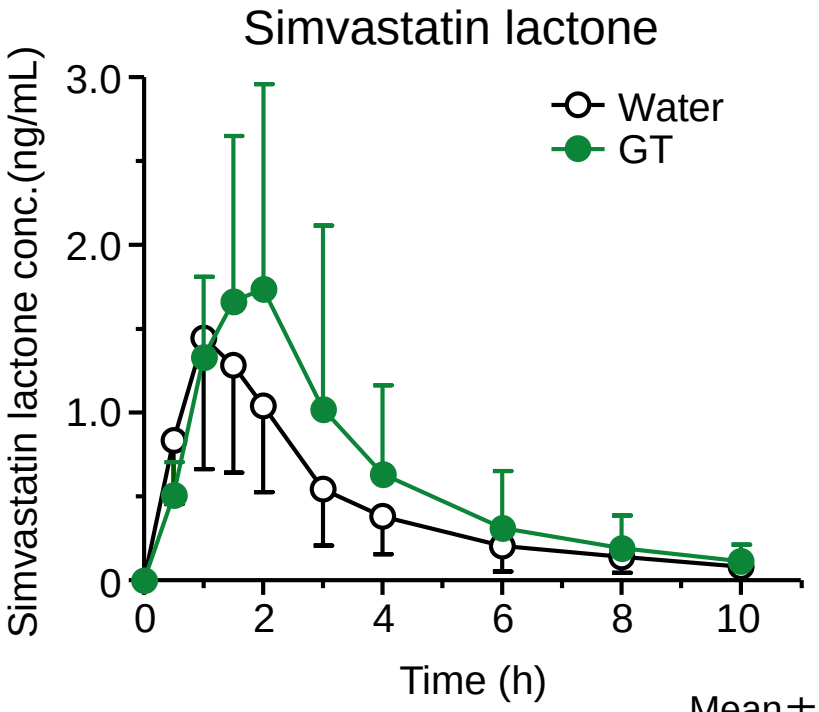
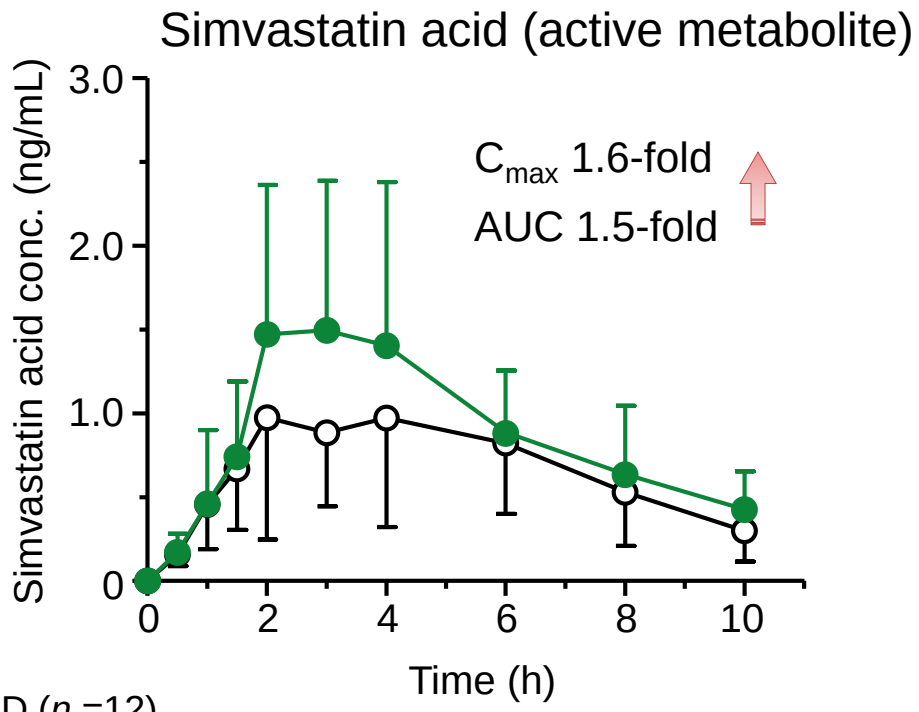
Randomized crossover study in healthy volunteers



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

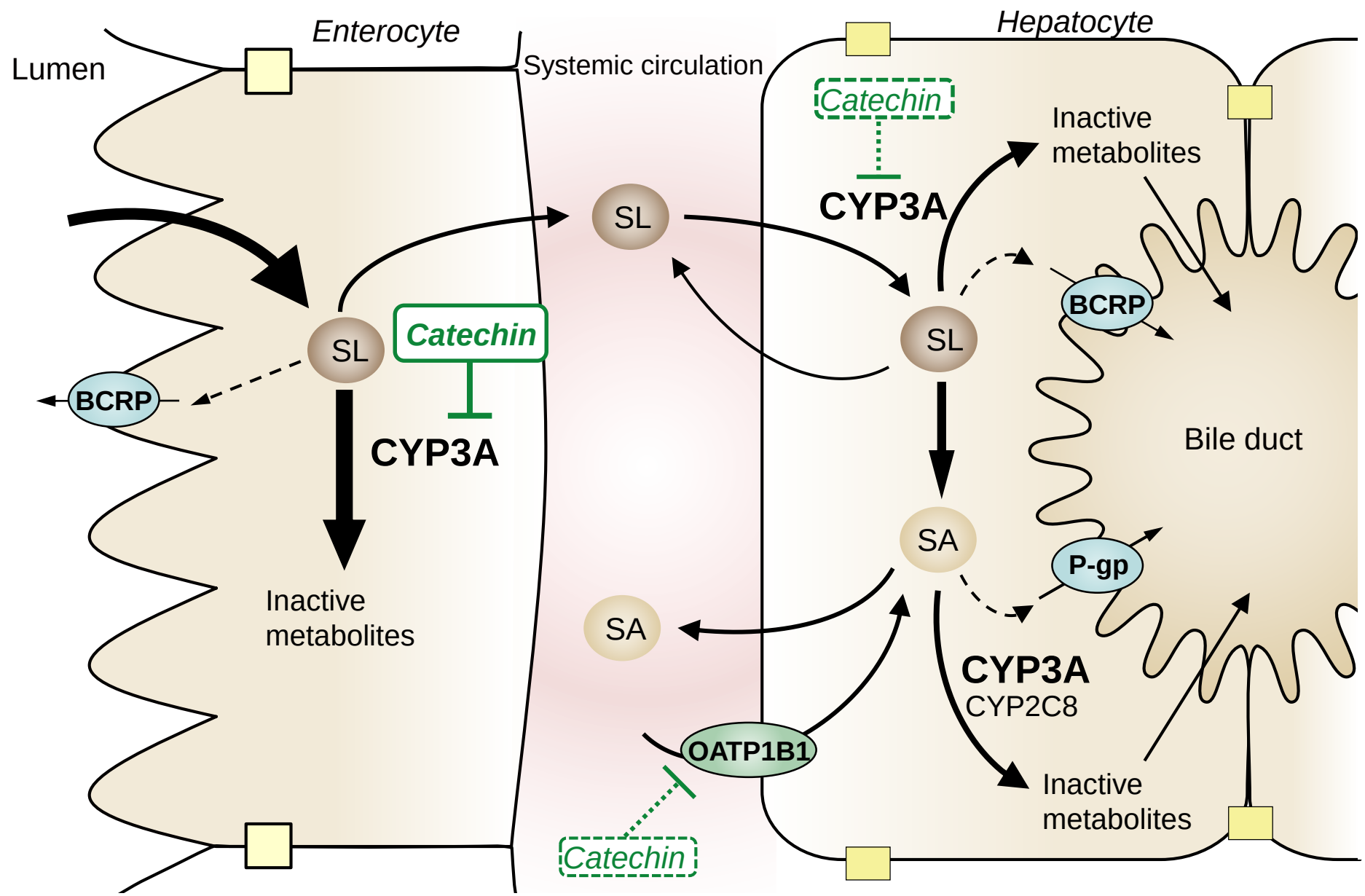




Mean±SD (*n* =12)

(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

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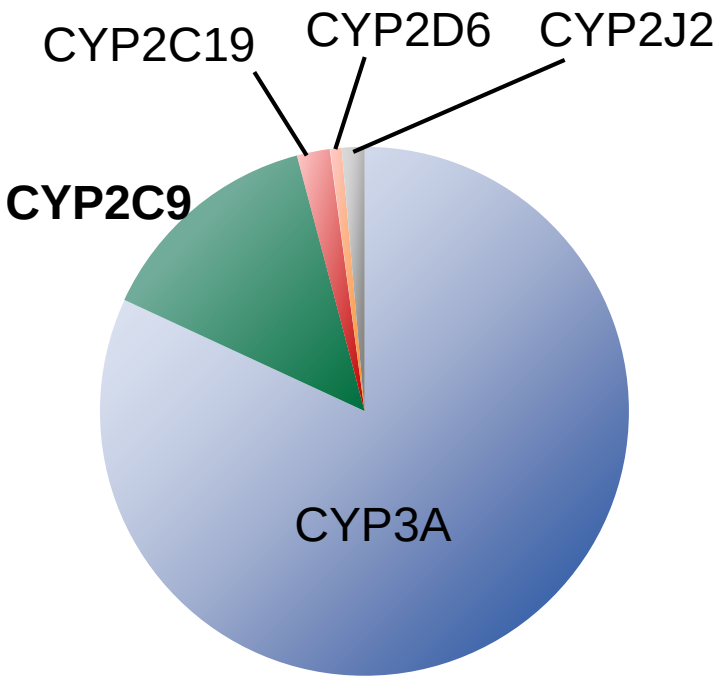
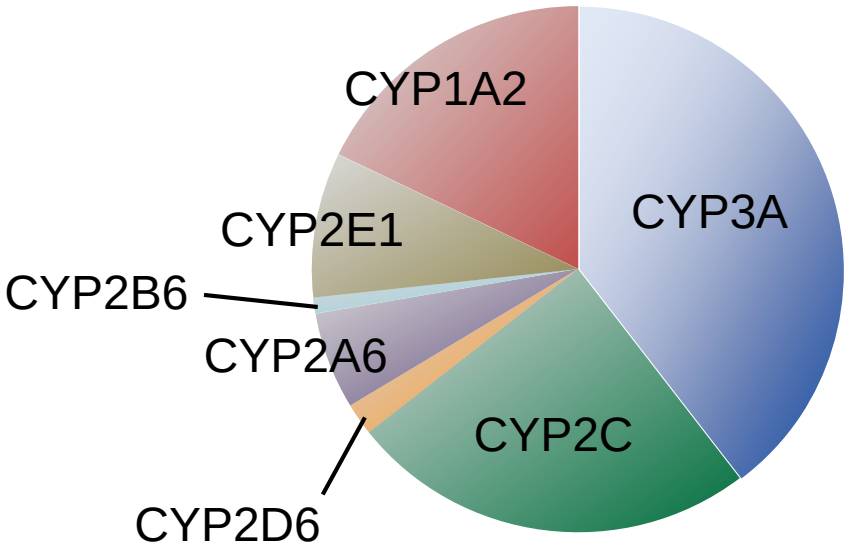
Small intestine



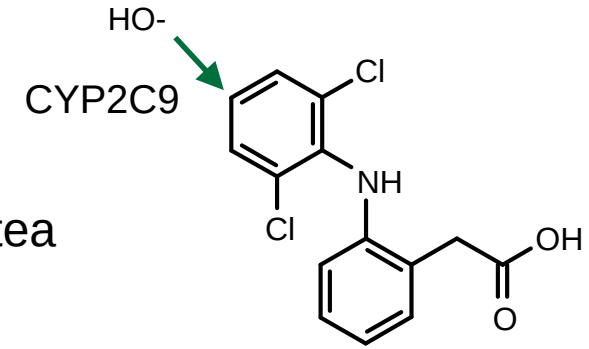
Liver



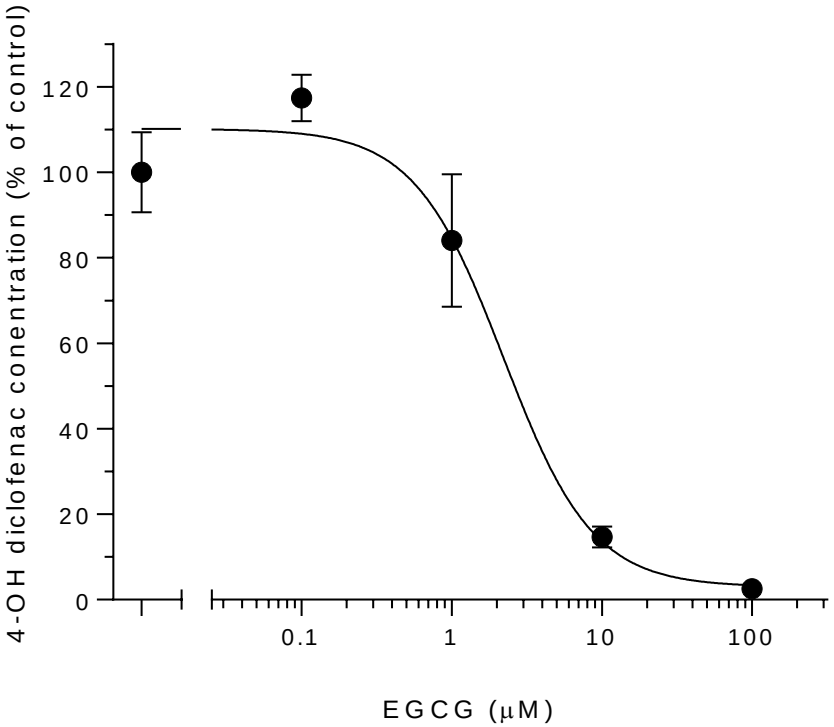
(Shimada *et al*., *J Pharmacol Exp Ther, 1994;* Paine *et al*., *Drug Metab Dispos*, 2006)

Inhibition of diclofenac metabolism by EGCG and GT

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

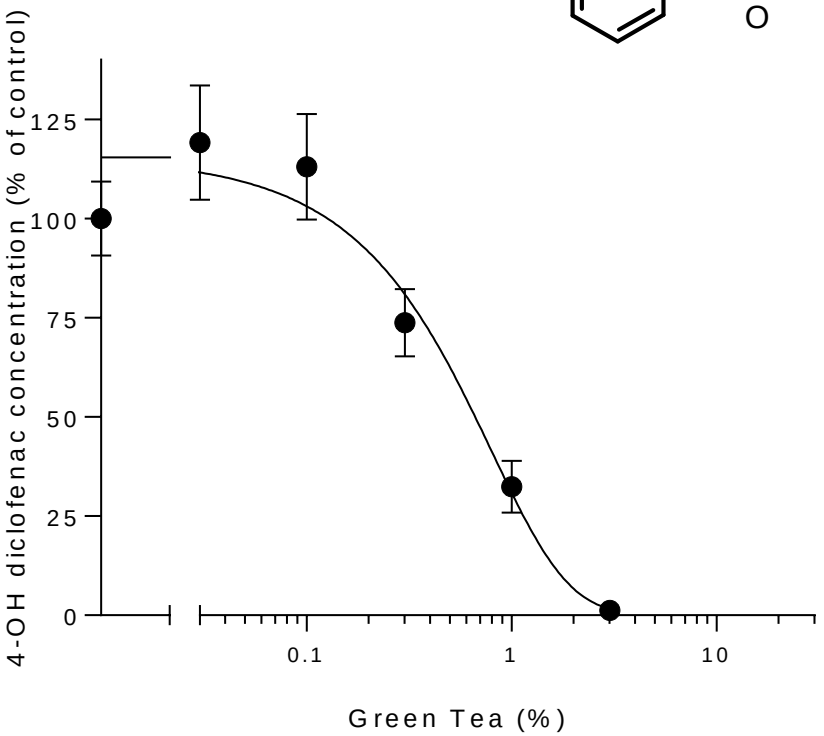


EGCG



IC_{50} = 1.9 (0.5-6.7) μM

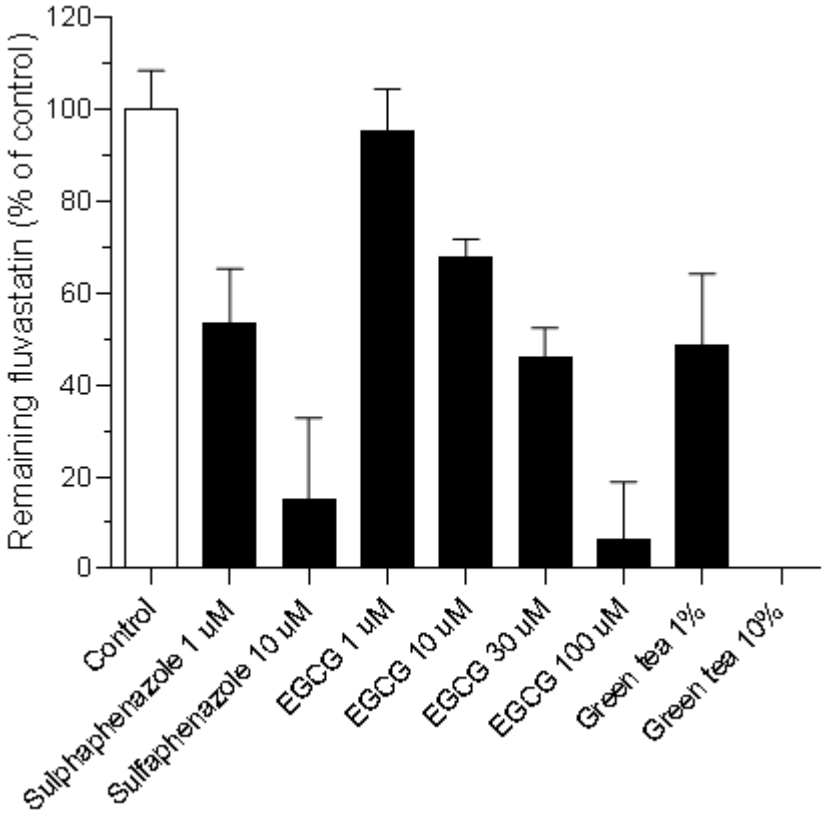
Green tea

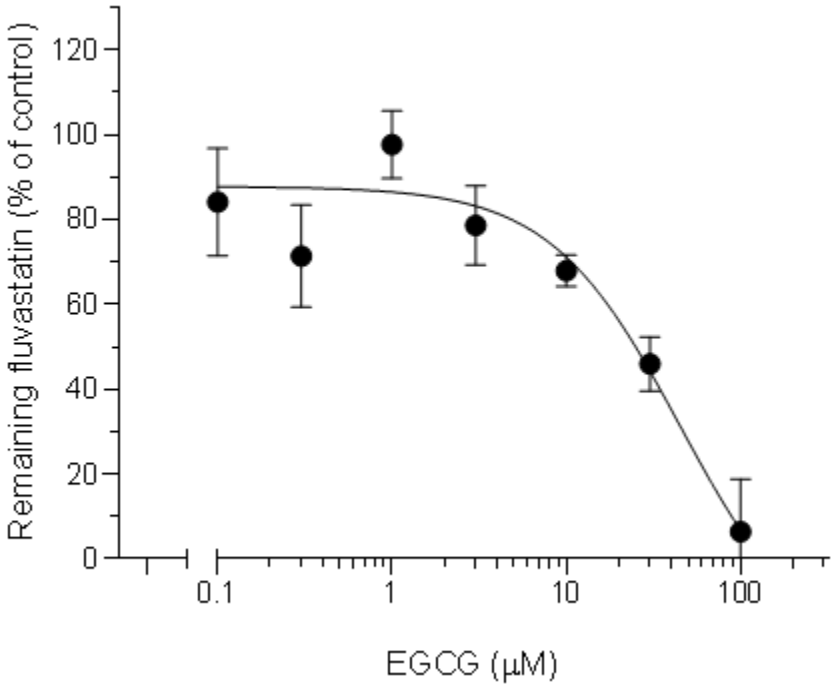


IC_{50} = 0.5 (0.2-1.3)%

(Misaka *et al.*, unpublised data)

Inhibition of fluvastatin metabolism by EGCG and GT

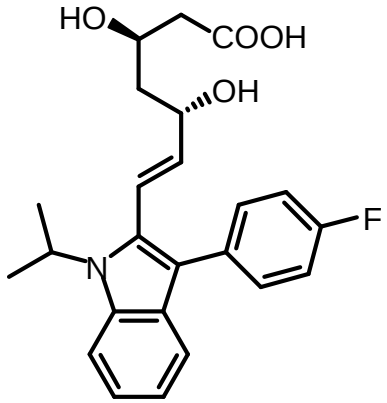




IC_{50} = 44.8 (1.2-1687) μM

(Misaka *et al*., unpublised 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 Phramacol* 2000)

Green tea-fluvastatin interaction study

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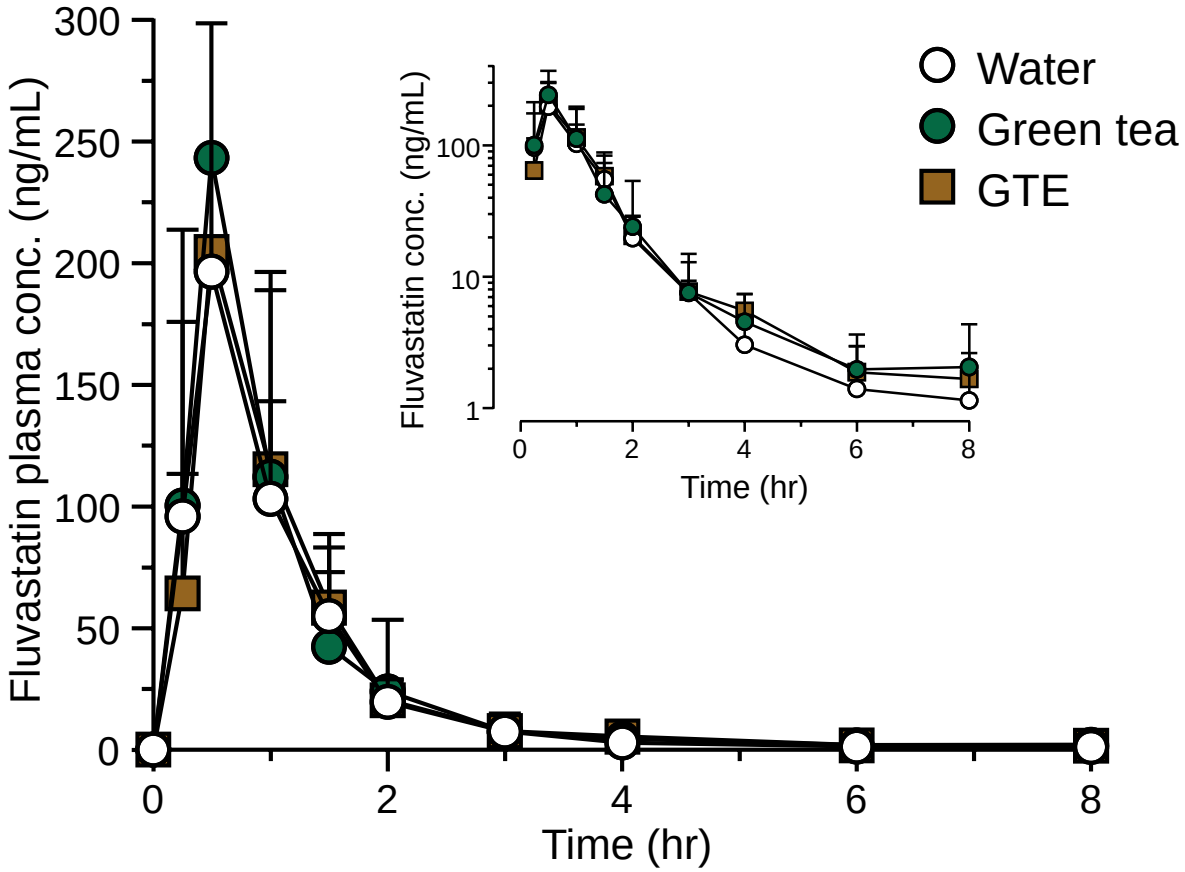
- Randomized open 3-phase crossover design
- Subject: healthy volunteers
- Fluvastatin dose: 20 mg with 300 mL of water or green tea
- Green tea (Harada Tea Processing Co., Ltd., Shizuoka, Japan)
  - Brewed (2.2 g/100 mL water) before fluvastatin dosing
  - EGCG concentration: 50 mg/dL
  - EGCG dose: 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



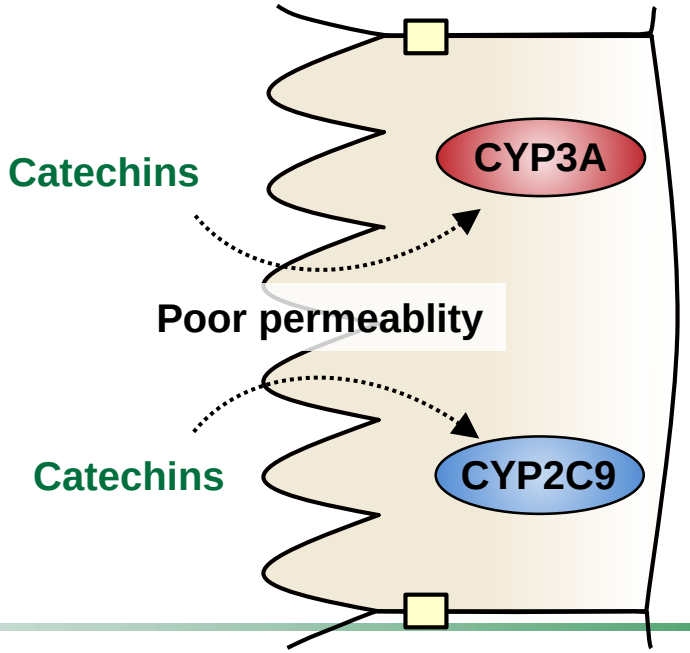
- Green tea → AUC 14% ↑
- GTE → AUC 4% ↑

(Misaka *et al*., *unpublised 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



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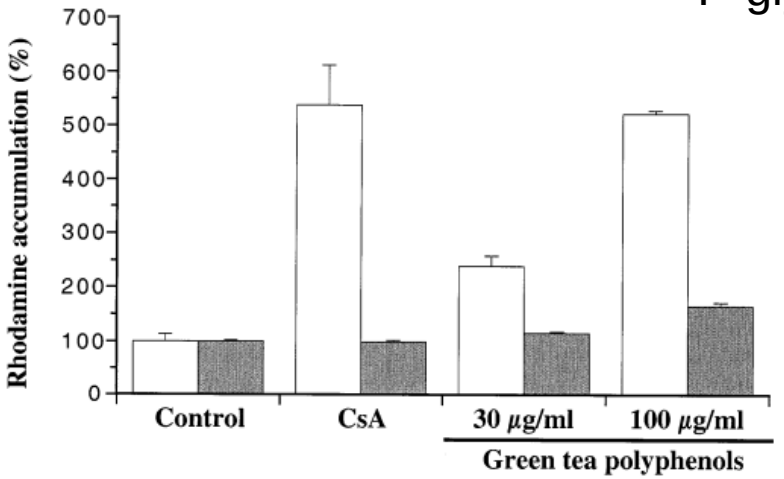
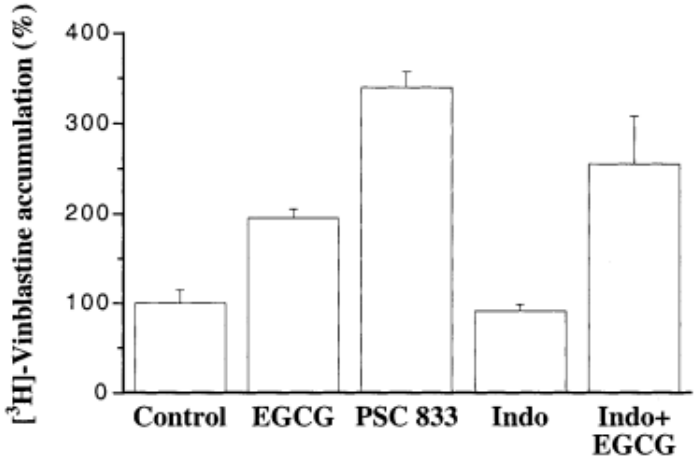
Inhibitory effects of catechins on drug transporters in vitro

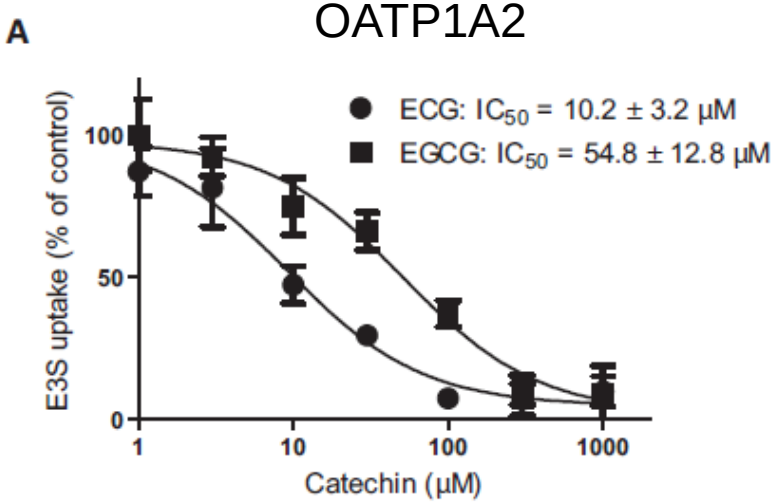
P-glycoprotein



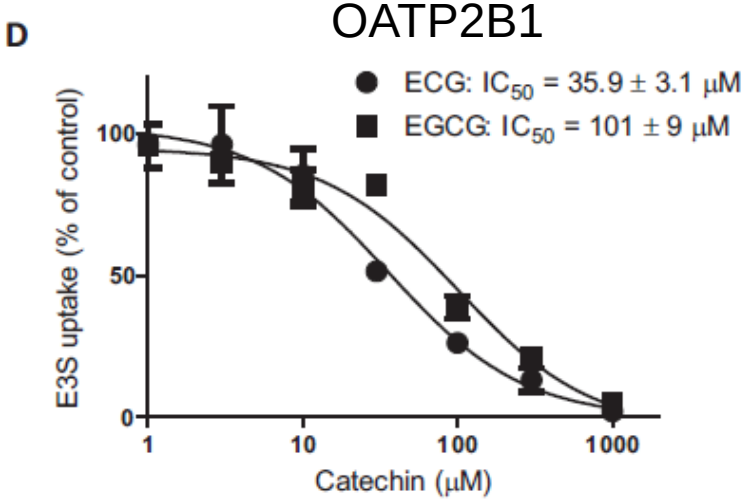


(Jodoin *et al*., *Biochim Biophys Acta,* 2002)

OATP1A2

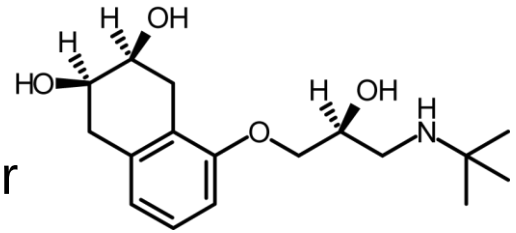


OATP2B1



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

Nadolol



- Nonselective *β*-blocker
- Bioavailability: less than 30%
- Plasma protein binding: 24%
- Metabolism: negligible
- Excretion: urine
- Drug transporter
  Efflux: P-glycoprotein
  Influx: OATP1A2
- Drug interactions

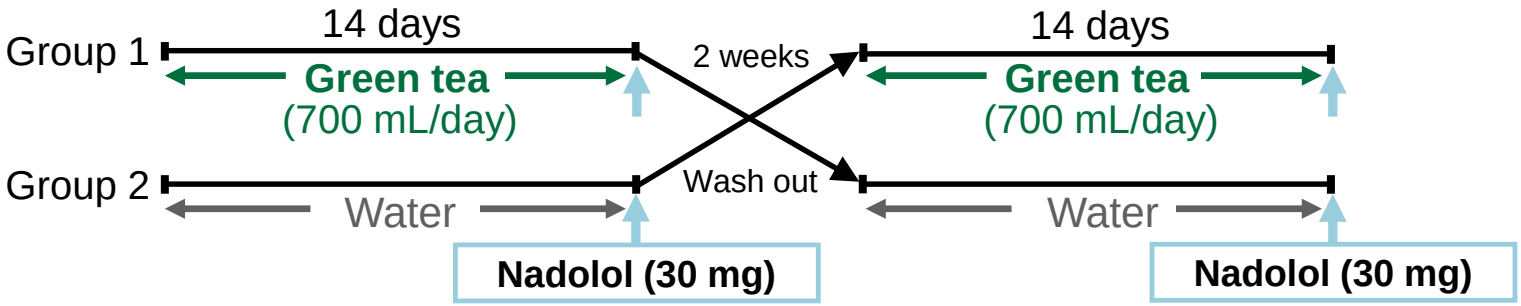
  Itraconazole (P-gp inhibitor) increased nadolol AUC by 224%.

		cLogP
Hydrophilic ↑	Atenolol	0.02
	Nadolol	**0.07**
	Carteolol	0.2
	Acebutolol	0.7
	Pindolol	0.8
	Metoprolol	1.0
	Bisoprolol	2.6
Lipophilic ↓	Betaxolol	4.0
	Labetalol	11.5
	Propranolol	20.2

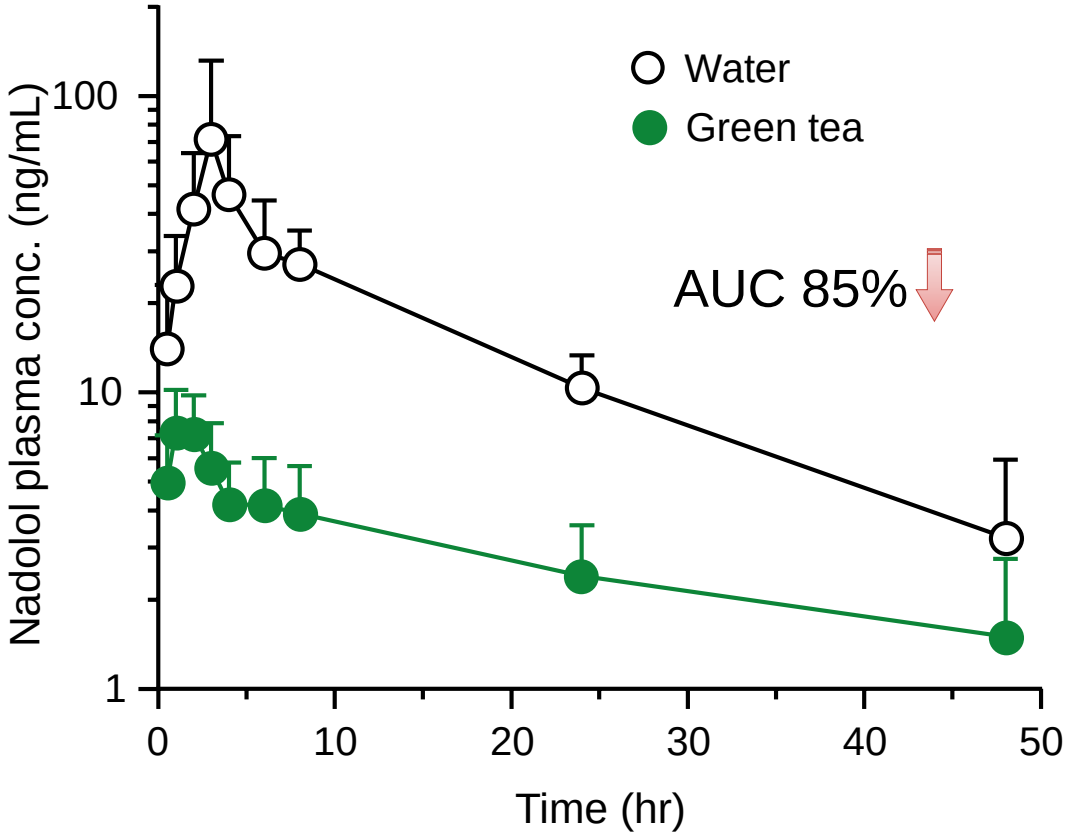
(Misaka *et al.*, *J Clin Phramacol,* 2013)

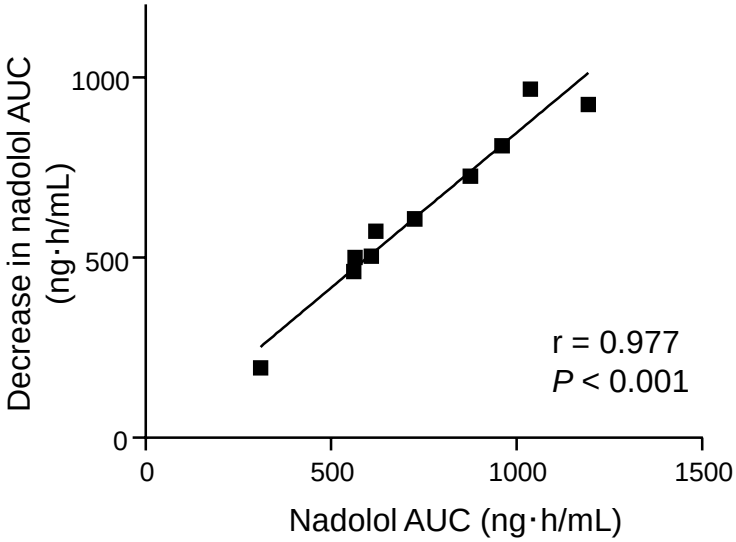
Clinical study

- 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/m^2（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



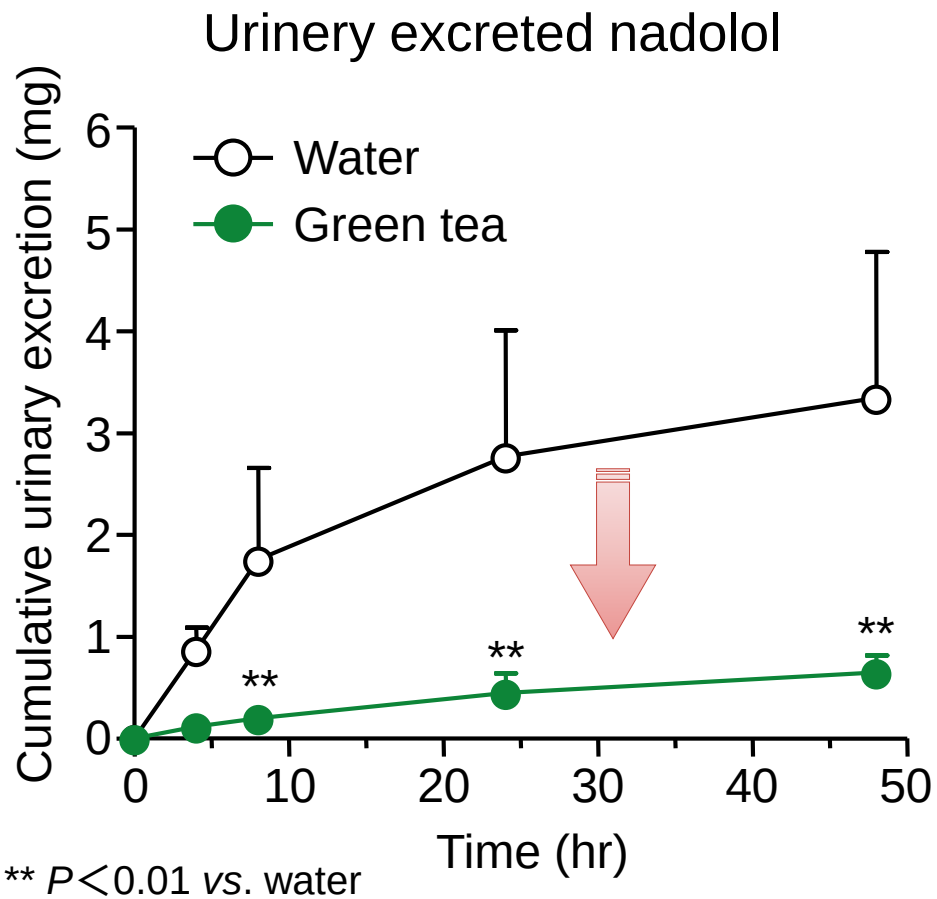


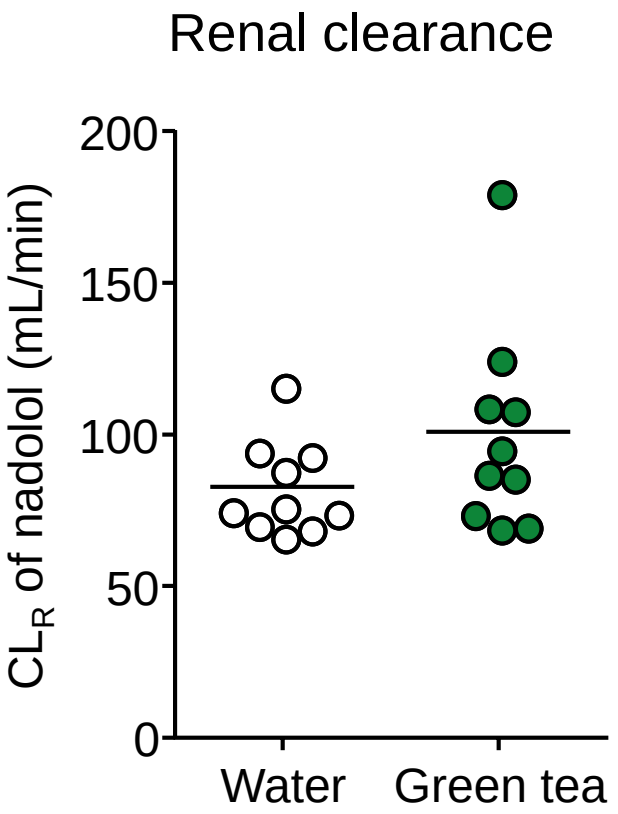
	Water	Green tea
C_{max} (ng/mL)	55.7 (24.8–86.5)	8.2 (6.7–9.6)**
$AUC_{0\text{-}48}$ (ng·h/mL)	708.9 (569.8– 848.0)	106.6 (67.8–145.5)***

,*; $P < 0.01$, 0.001 *vs*. Water
Mean±SD (n=10)

(Misaka *et al*., *Clin Pharmacol Ther,* 2014)

Effect of green tea on nadolol urinary excretion





** $P < 0.01$ *vs*. water

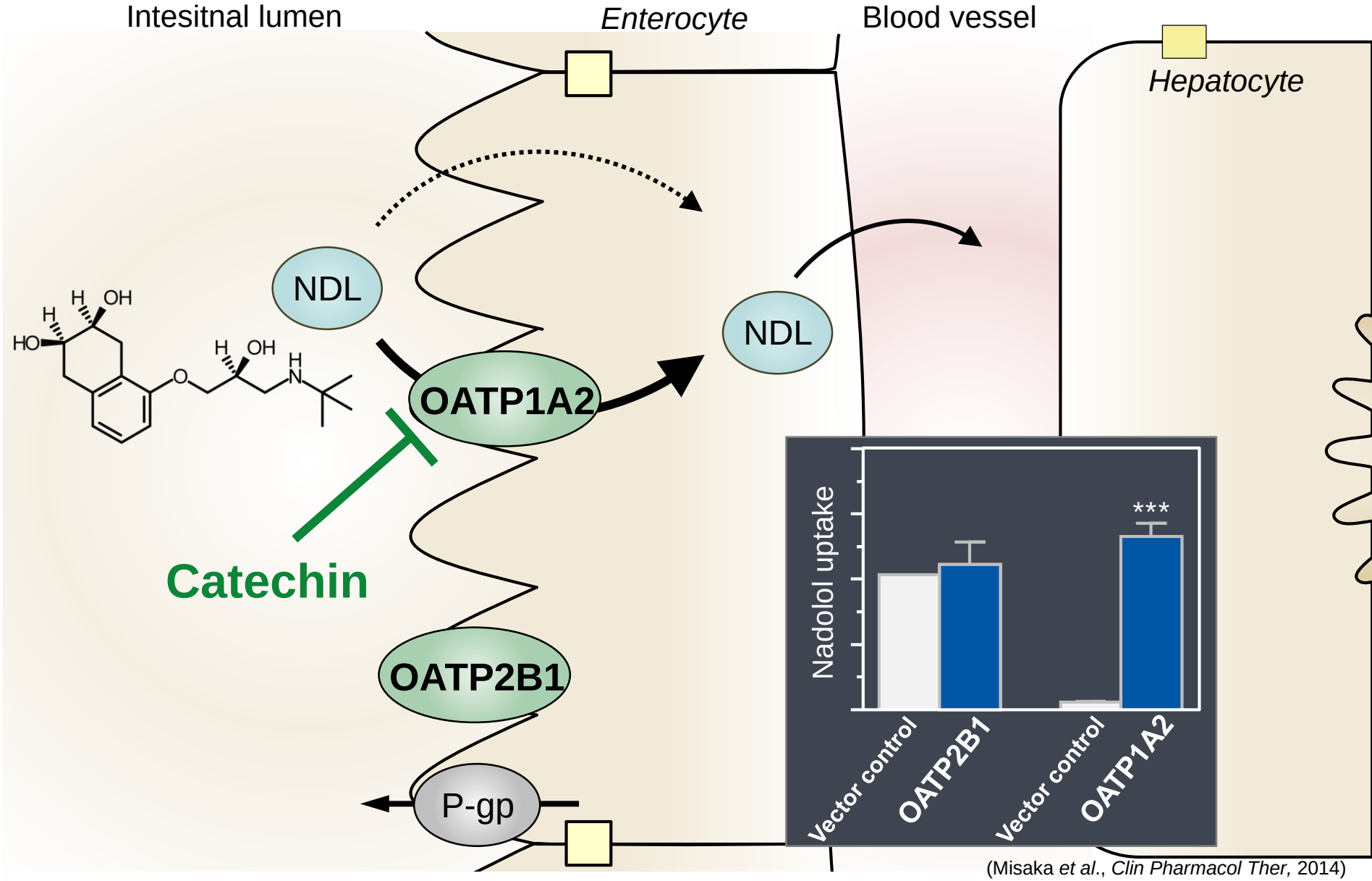
(Misaka *et al*., *Clin Pharmacol Ther,* 2014)

Green tea did not influence nadolol renal clearance

↓

Green tea may affect nadolol intestinal absorption

Possible mechanism underlying GT-nadolol interaction



(Misaka *et al*., *Clin Pharmacol Ther,* 2014)

NDL: Nadolol

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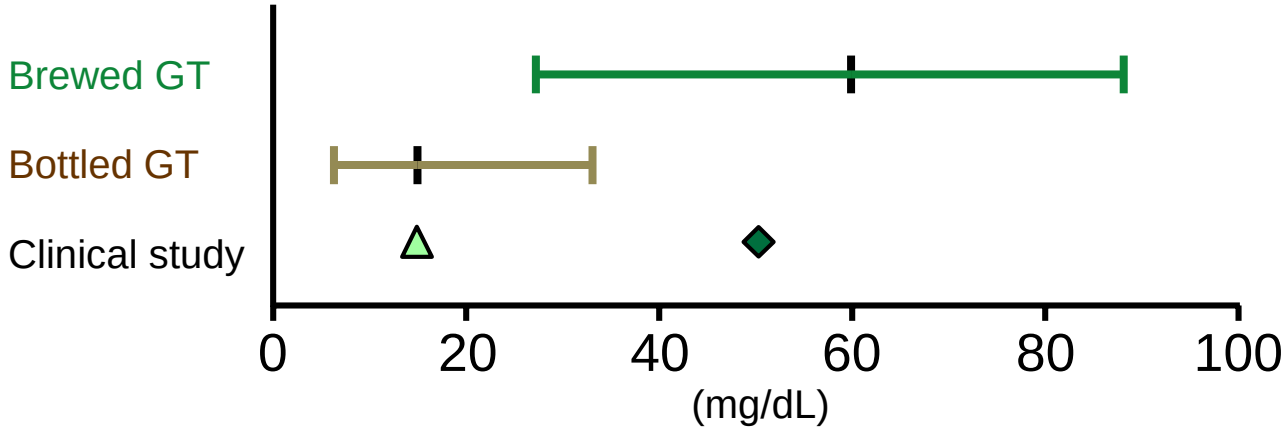
Further questions regarding nadolol-green tea interaction

- ✓ 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

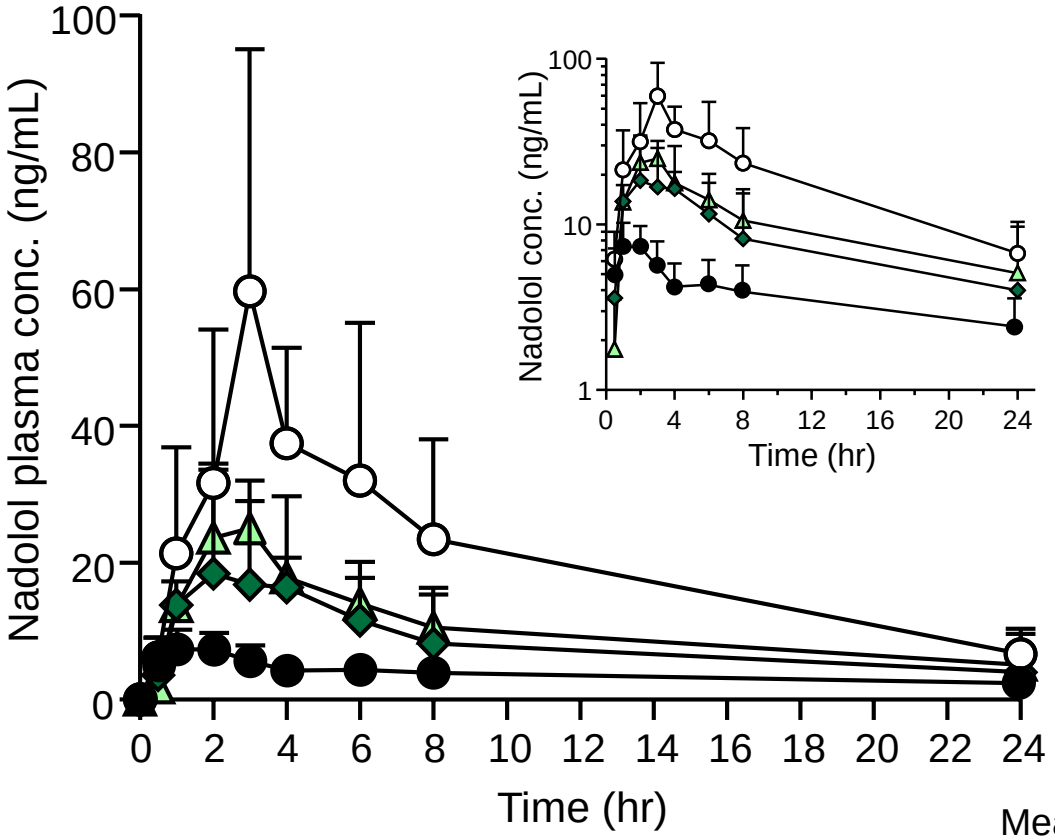
- Randomized, open 3-phase crossover study
- Subject: healthy volunteers
- Nadolol dose: 30 mg with 300 mL of water with GTE
- Green tea extract (Sunphenon®-EGCG, Taiyo Kagaku)
  - EGCG dose:
    - 50 mg (16.7 mg/dL)
    - 150 mg (50 mg/dL)
  - GTE was dissolved in water prior to administration

EGCG concentration in Japanese green tea preparations



Effect of EGCG on nadolol concentrations

Nadolol plasma concentrations in healthy volunteers



Water
EGCG 50 mg
EGCG 150 mg
Green tea
(Misaka *et al*., CPT, 2014)

Mean±SD

Nadolol + EGCG 50 mg → AUC 38% ↓

Nadolol + EGCG 150 mg → AUC 46% ↓

(Misaka *et al*., Unpublished data)

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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

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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.

Acknowledgements

公立大学法人
福島県立医科大学
FUKUSHIMA MEDICAL UNIVERSITY

Prof. Junko Kimura
Prof. Yayoi Shikama
Dr. Osamu Abe
Dr. Yuko Ono
Dr. Junichi Yatabe
Dr. Midori S. Yatabe

FAU FRIEDRICH-ALEXANDER UNIVERSITÄT ERLANGEN-NÜRNBERG
MEDIZINISCHE FAKULTÄT

Prof. Dr. Martin F. Fromm
Prof. Dr. Jörg König
Dr. Hartmut Glaeser
Dr. Fabian Müller
Dr. Jana Knop

静岡県公立大学法人
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HAMAMATSU UNIVERSITY SCHOOL OF MEDICINE

Prof. Hiroshi Watanabe

Centro Cardiologico
Monzino

Dr. José Pablo Werba

ふくしまから
はじめよう。

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