FLAVIOLA

Targeted delivery of dietary flavanols for optimal human cell function: Effects on cardiovascular health

SFRBM Annual Meeting, Pre-meeting Workshop II

Flavanols in Health and Disease

Flavanols and Procyanidins: Absorption, Distribution, Metabolism, and Excretion

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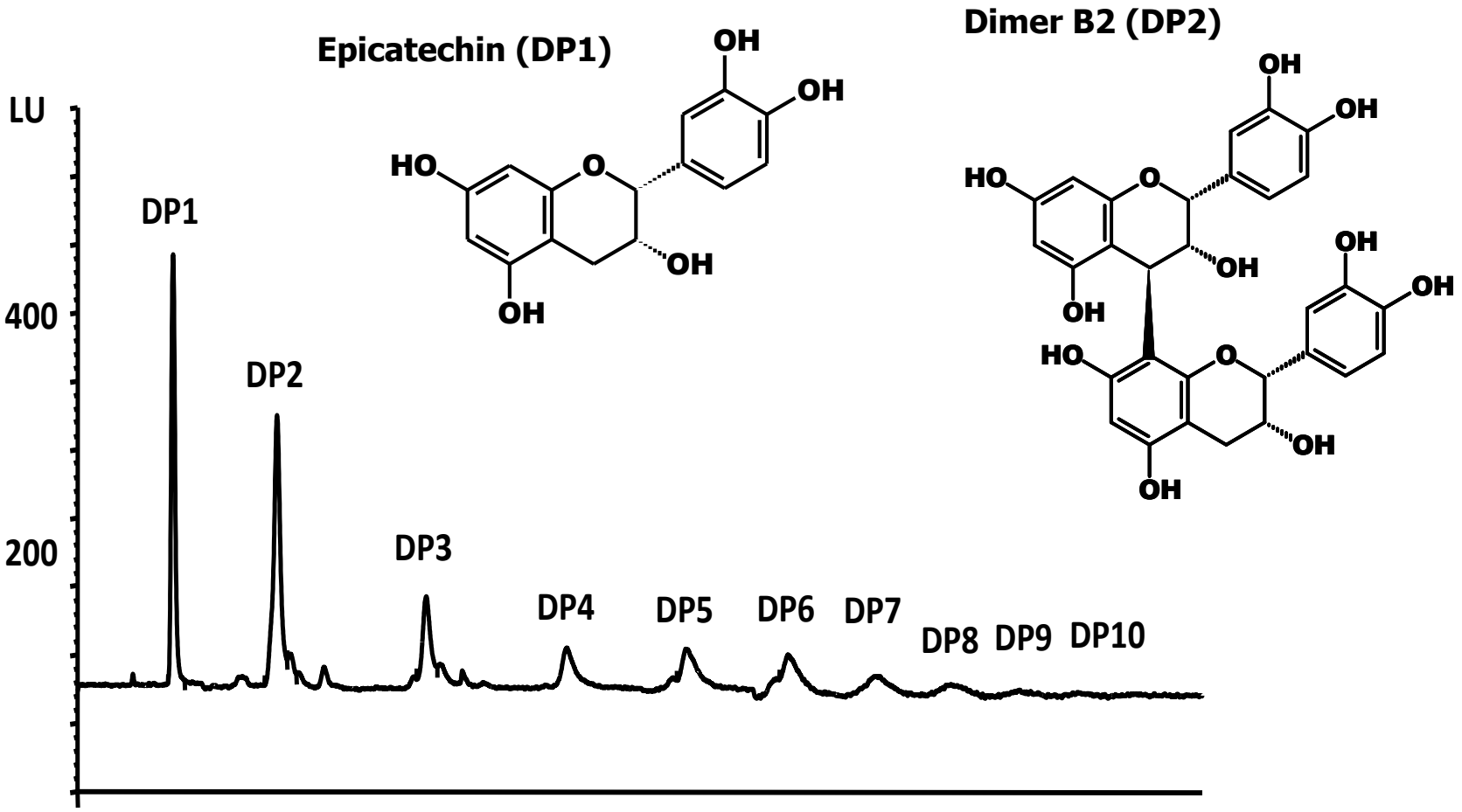
San Diego, 14 November 2012

Flavanols and procyanidins present in cocoa



Hammerstone et al., J. Agr. Food Chem., 47, 490-496

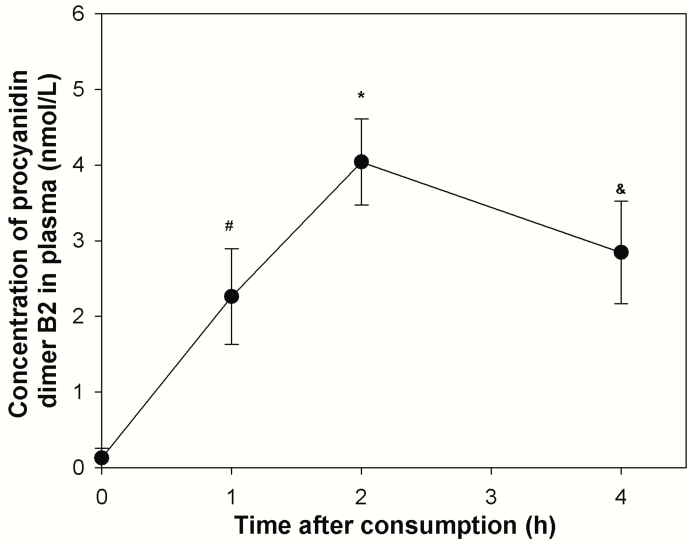
Are procyanidins absorbed and do they contribute to the pool of circulating flavanols in humans?

Procyanidins higher than DP2 are not absorbed following cocoa flavanol intake

Flavanols and procyanidins ingested with each test drink (mg/kg BW)

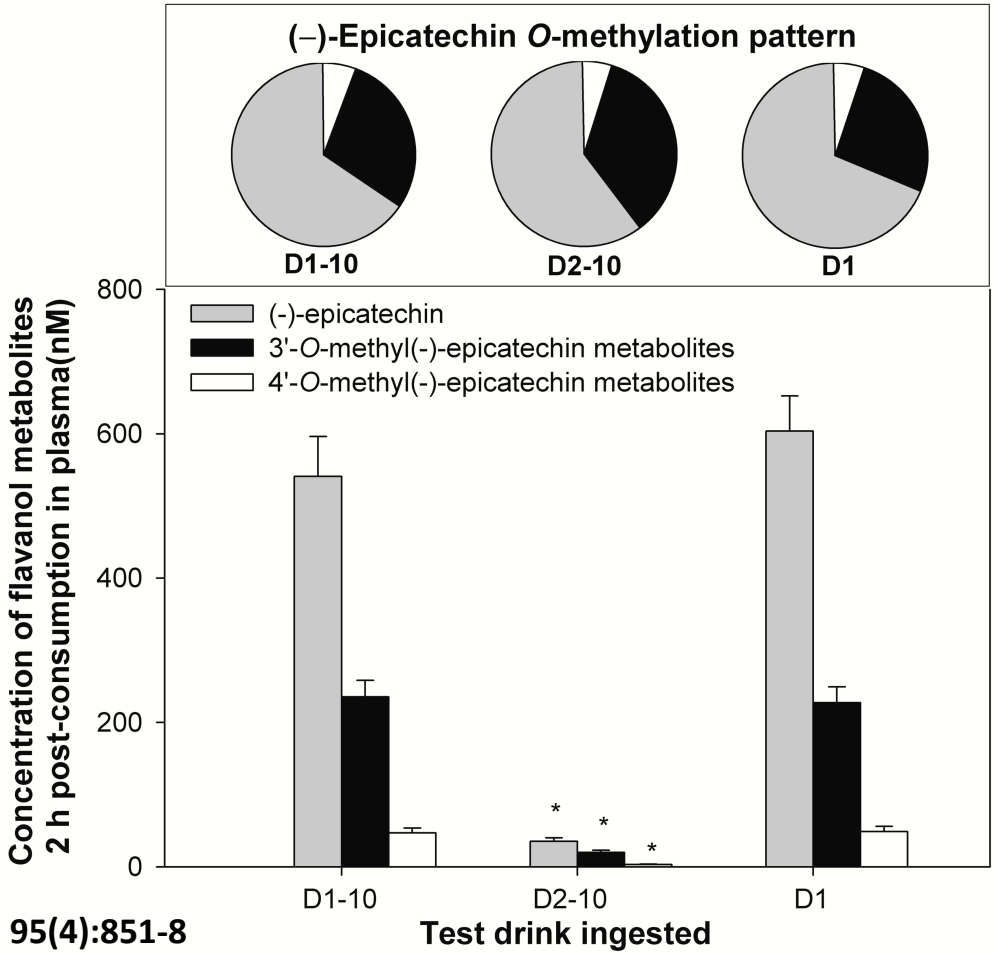
Flavanols + Procyanidins	DP 1-10	DP2-DP10	DP1
Flavanols (1 unit)	2.10	0.16	1.8
(-)-epicatechin	1.80	0.14	1.8
(+)-catechin	0.28	0.02	0
Procyanidins	9.91	9.91	0
Dimers	1.8	1.8	0
Trimers	1.6	1.6	0
Tetramers to decamers	6.5	6.5	0

There was no evidence for the absorption of procyanidins higher than DP 2



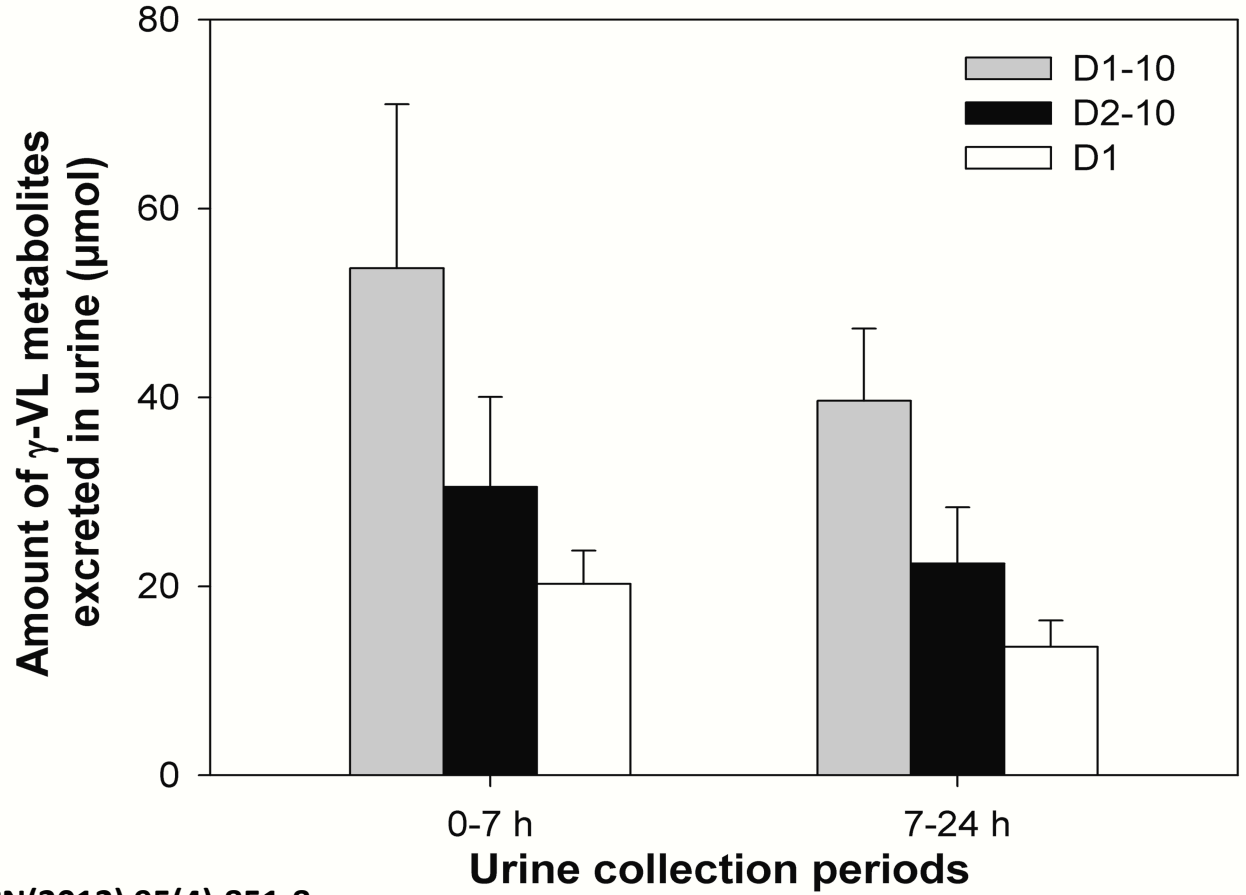
Ottaviani et al. AJCN(2012) 95(4):851-8

Procyanidin intake does not contribute to the pool of circulating flavanols in humans



Ottaviani et al. AJCN(2012) 95(4):851-8

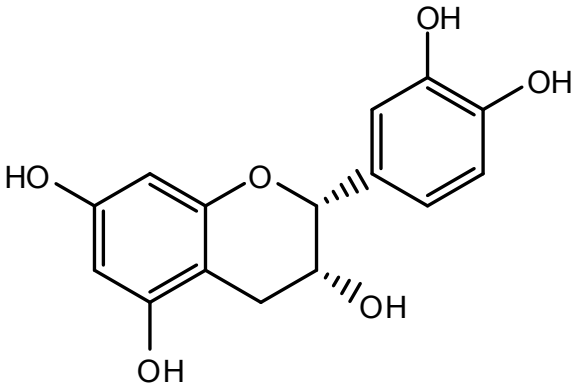
Consumption of flavanol monomer (DP1) and procyanidins (DP 2-10) give rise to γ-valerolactone metabolites



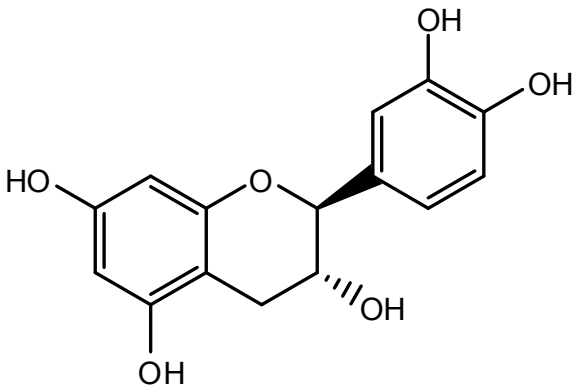
Ottaviani et al. AJCN(2012) 95(4):851-8

What about the monomeric flavanols?

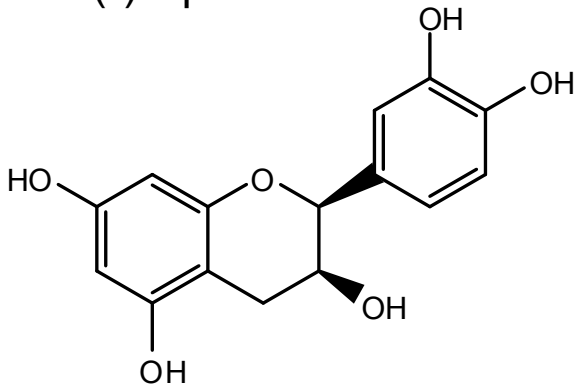
Chemical structure of flavanol stereoisomers (−)epicatechin, (+)epicatechin, (−)catechin, and (+)catechin



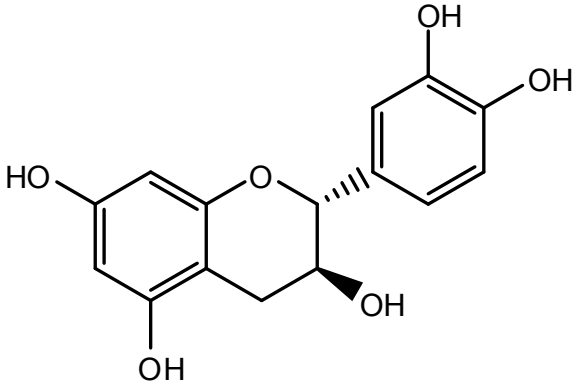
(-)-Epicatechin



(-)-Catechin

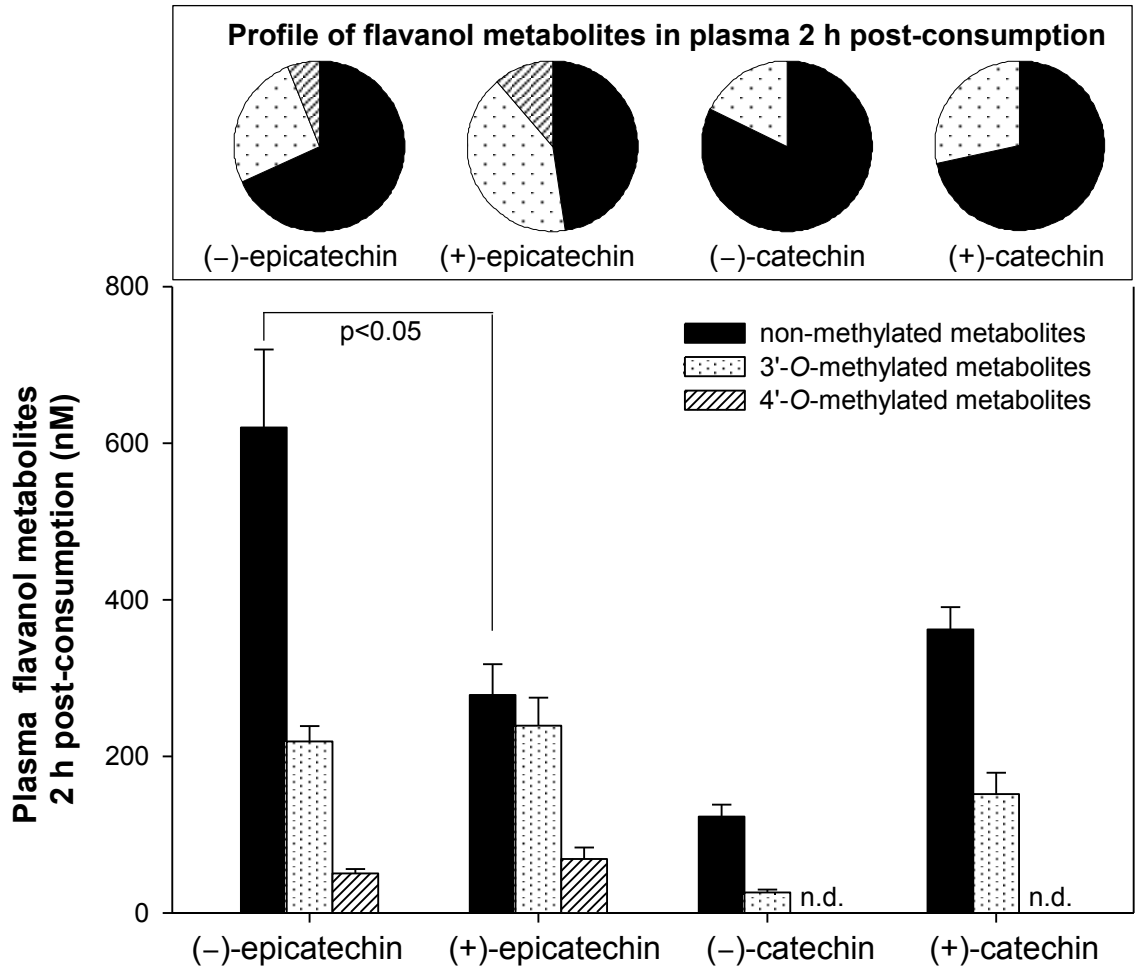


(+)-Epicatechin



(+)-Catechin

Plasma levels of flavanols after consumption of (−)epicatechin, (+)epicatechin, (−)catechin, or (+)catechin (1.5 mg/kg BW)



Ottaviani et al. FRBM (2011) 50, 237-244

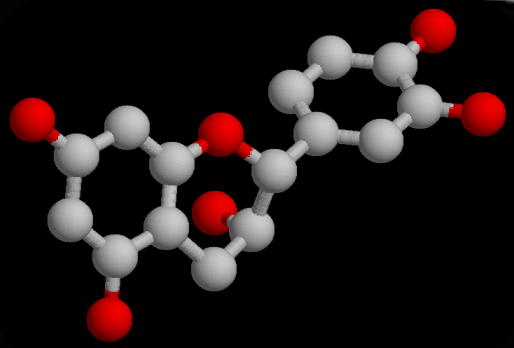
Standard food manufacture processes decrease flavanol contents

Heat

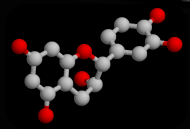
Oxidation

pH

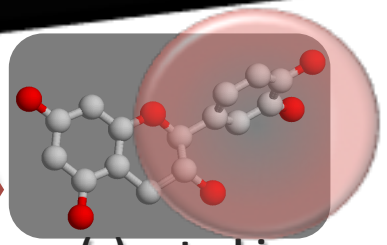
Isomerisation
(change in chemical structure)



(−)-epicatechin



(−)-epicatechin

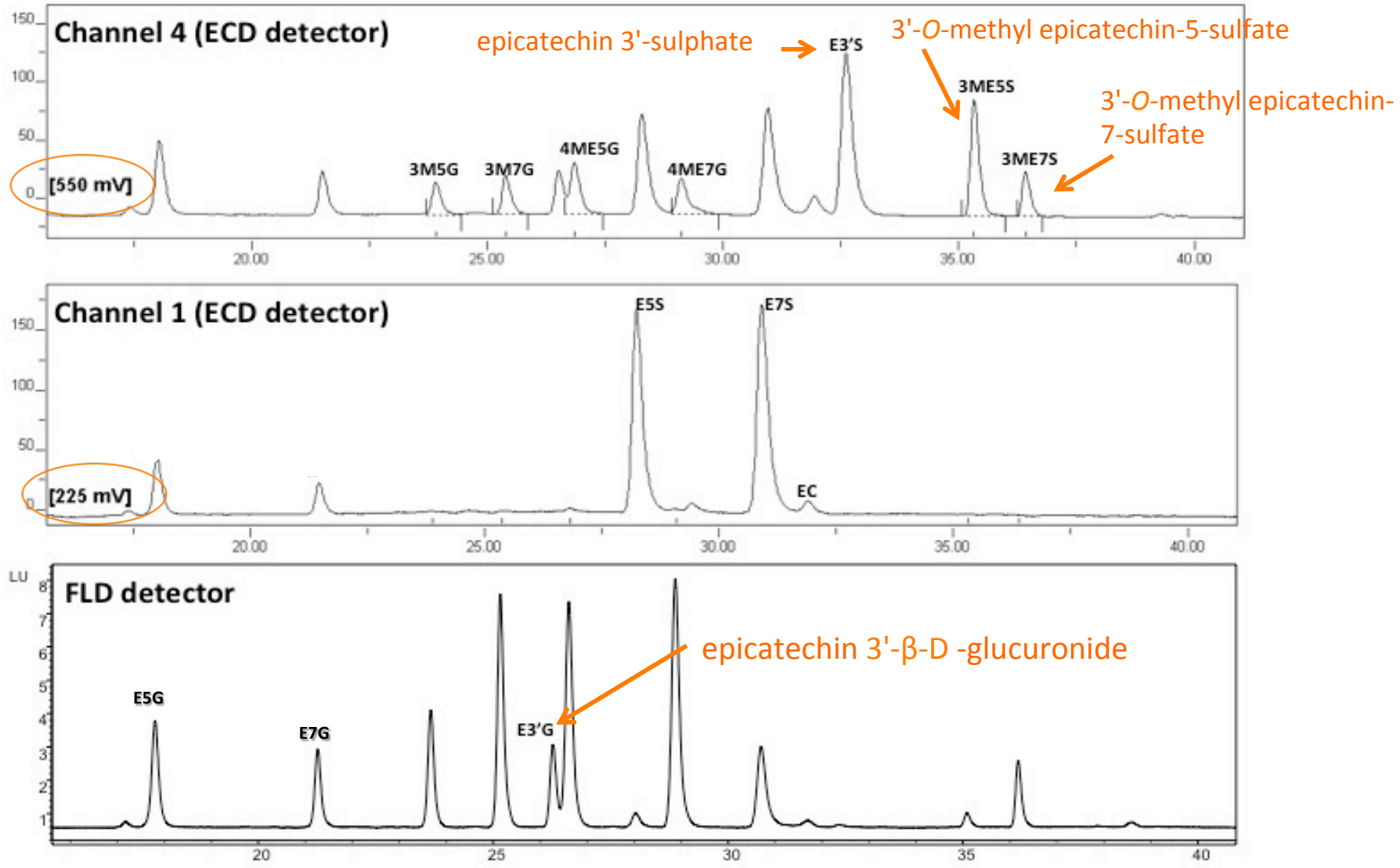


(−)-catechin

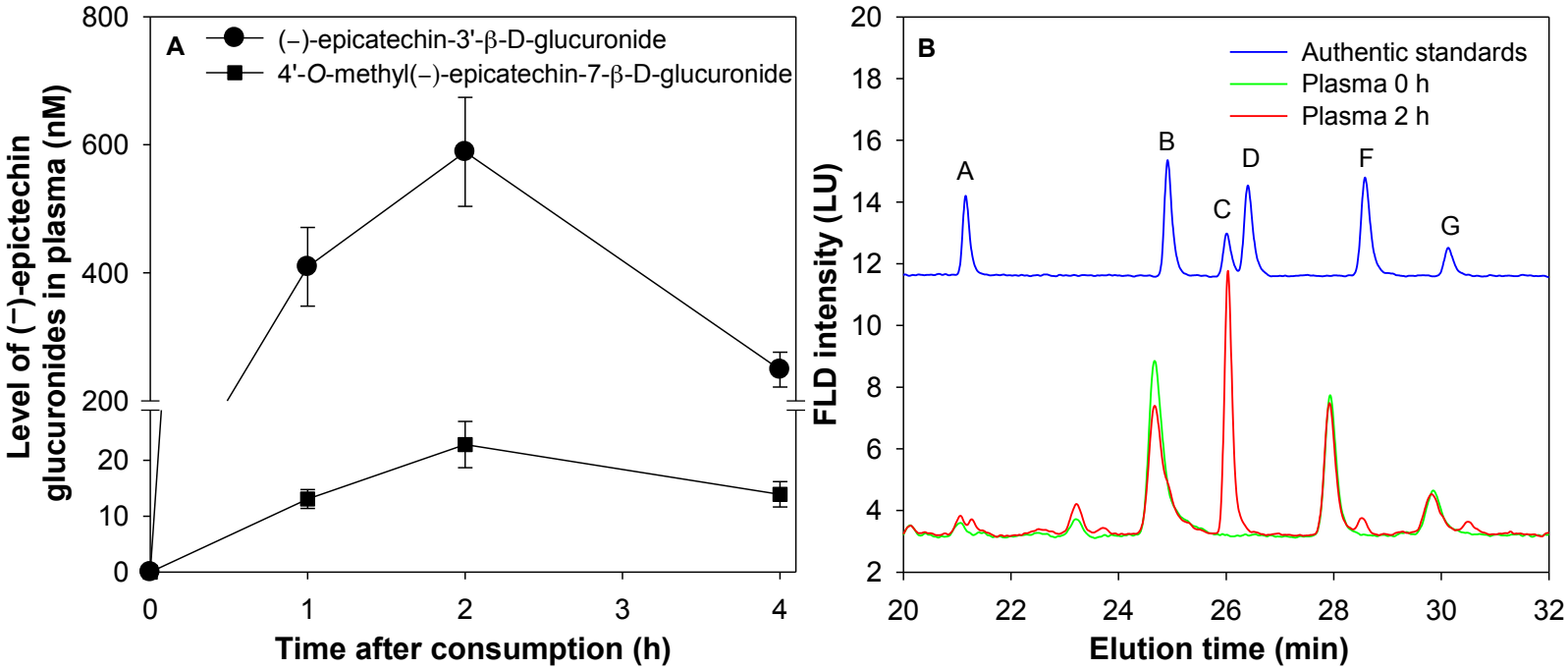
Based on these findings, we created technologies that preserve the flavanols naturally present in cocoa during food manufacture, making flavanols available in the final food product.

What are the major circulating flavanol metabolites in humans?

HPLC chromatogram trace of de novo synthesized (-)-epicatechin metabolites

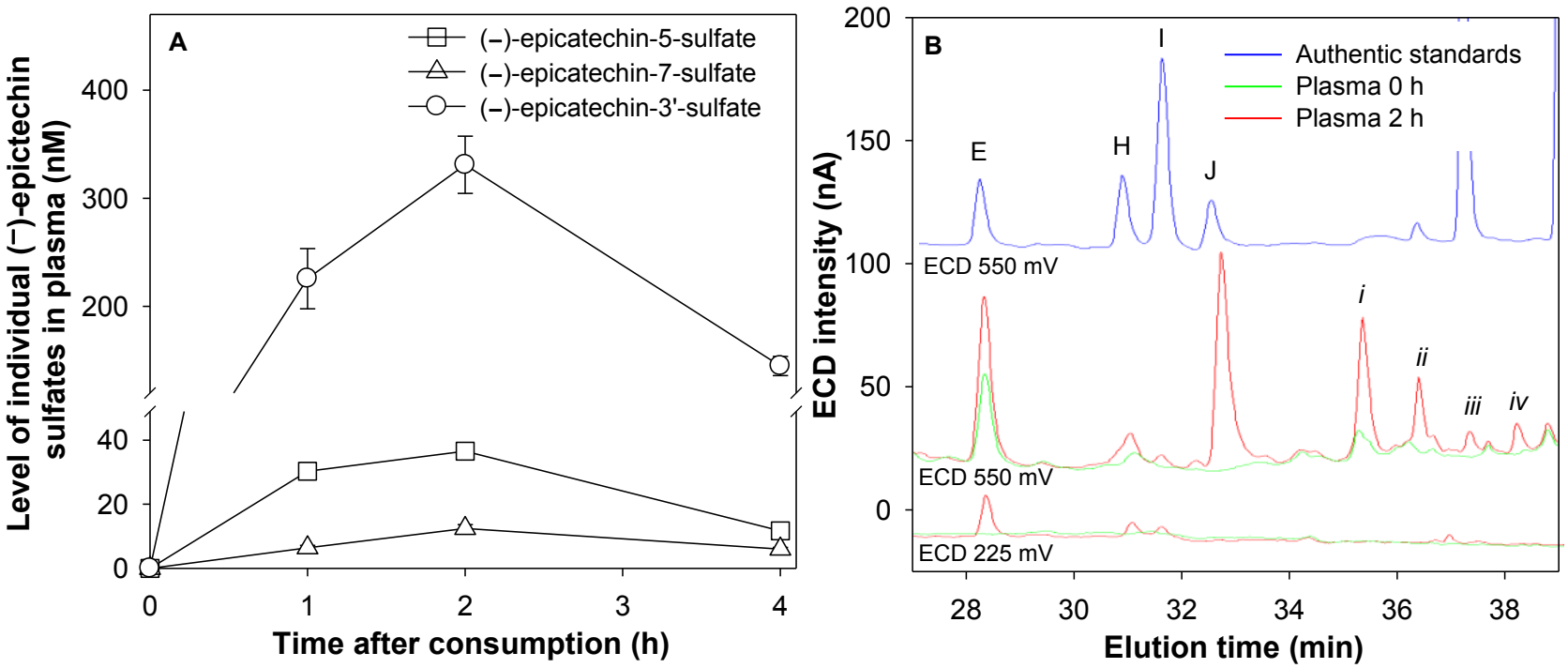


Circulating levels of (-)-epicatechin glucuronides following intake of the Flaviola test drink



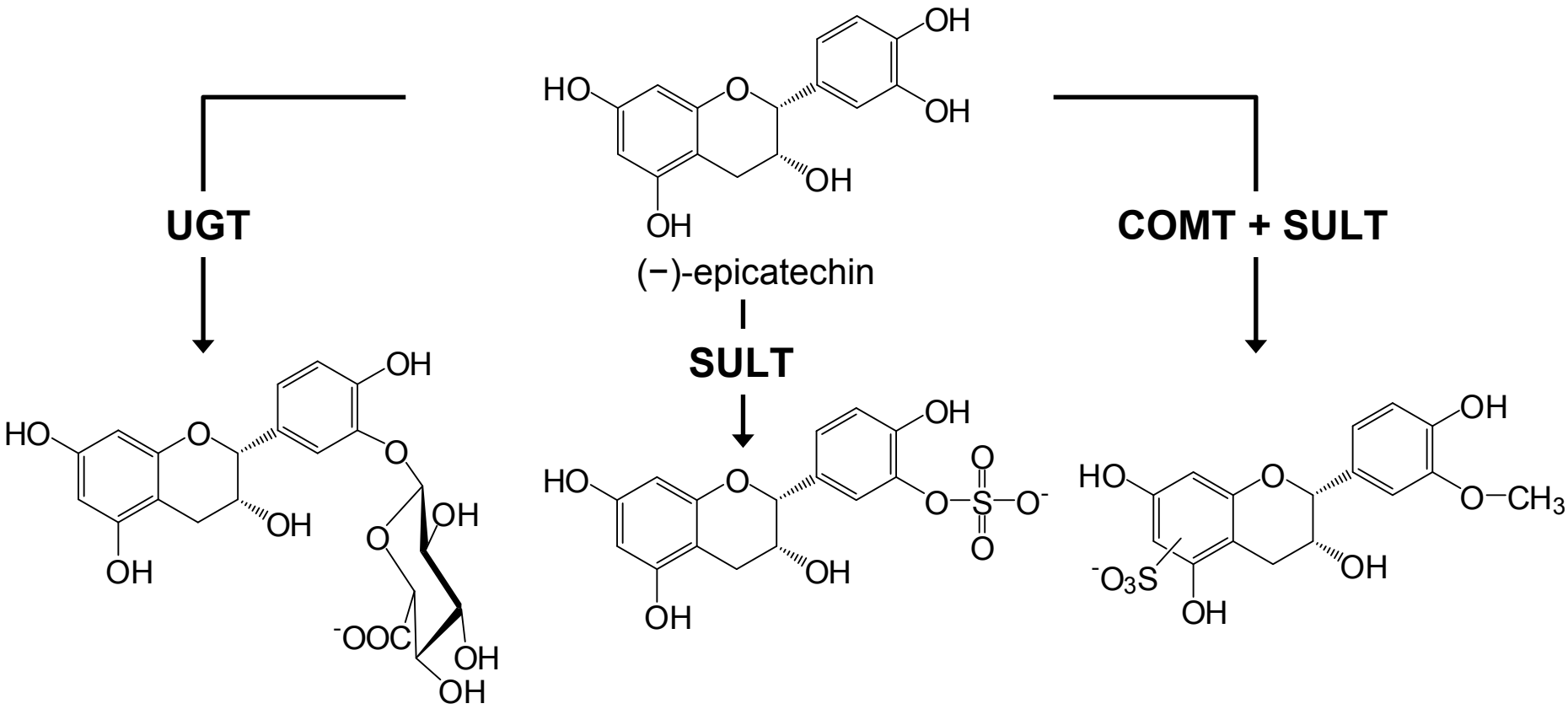
Ottaviani et al. FRBM (2012) 52(8):1403-12

Circulating levels of (-)-epicatechin sulfates following intake of the Flaviola test drink

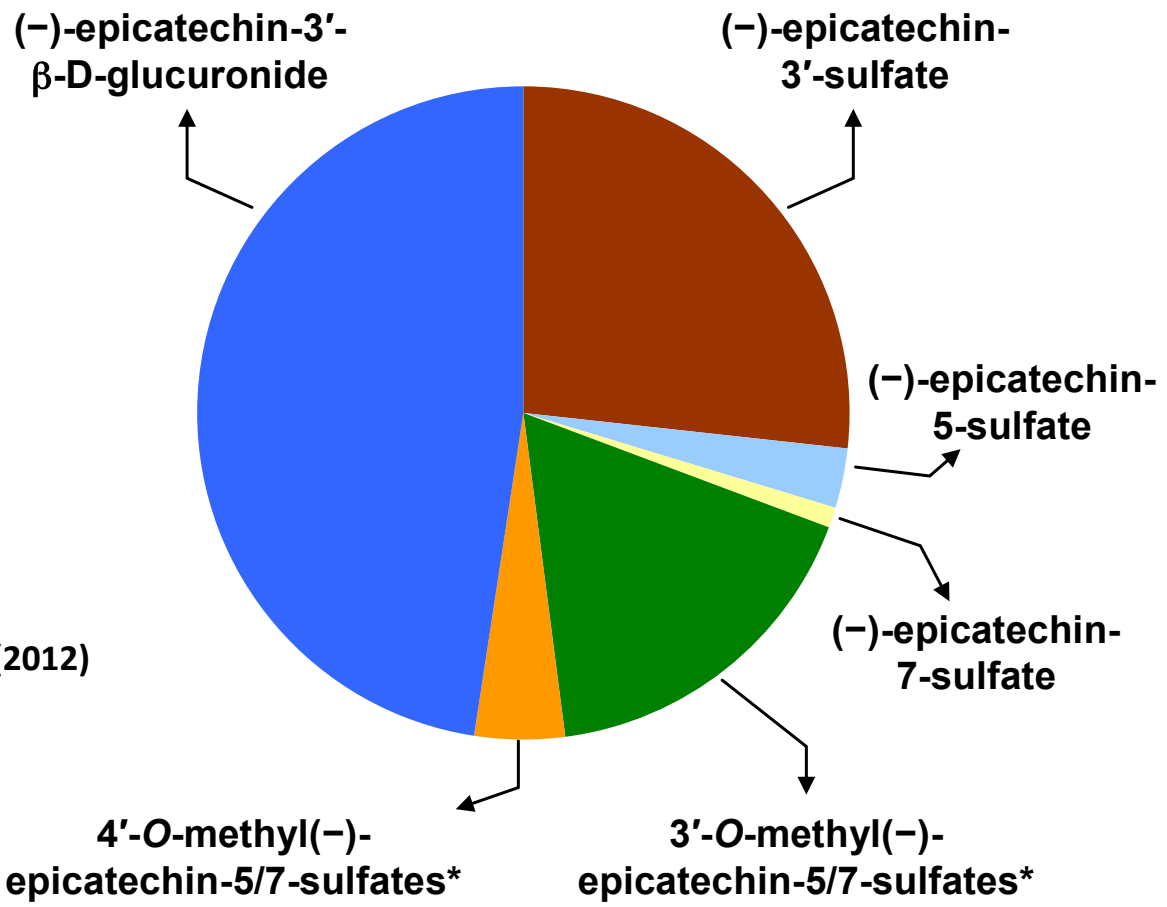


Ottaviani et al. FRBM (2012) 52(8):1403-12

(-)-epicatechin metabolism in humans



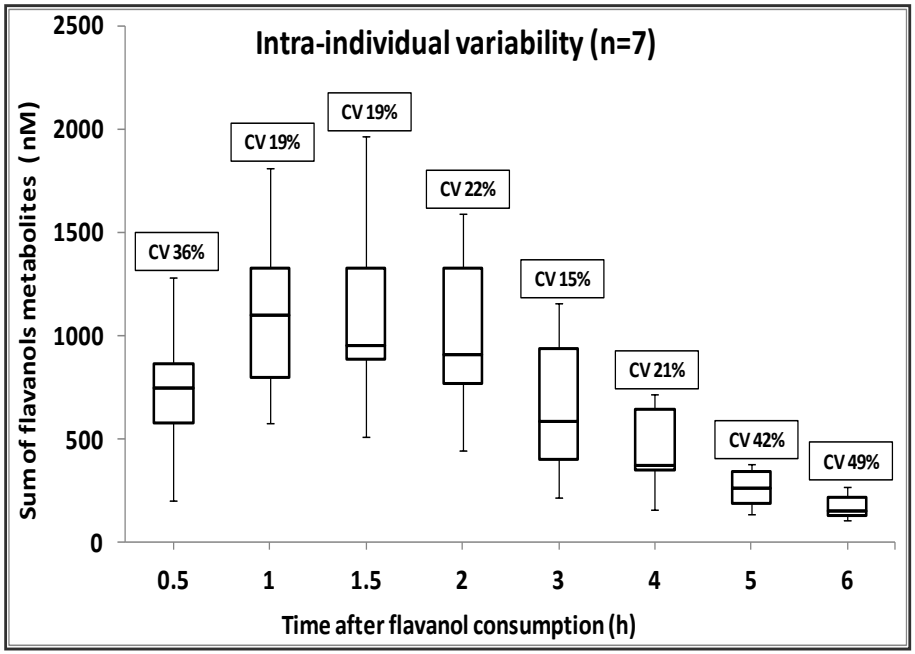
Relative amounts of individual (−)-epicatechin metabolites in the circulation



Ottaviani et al. FRBM (2012) 52(8):1403-12

Factors affecting flavanol absorption, distribution, metabolism and excretion

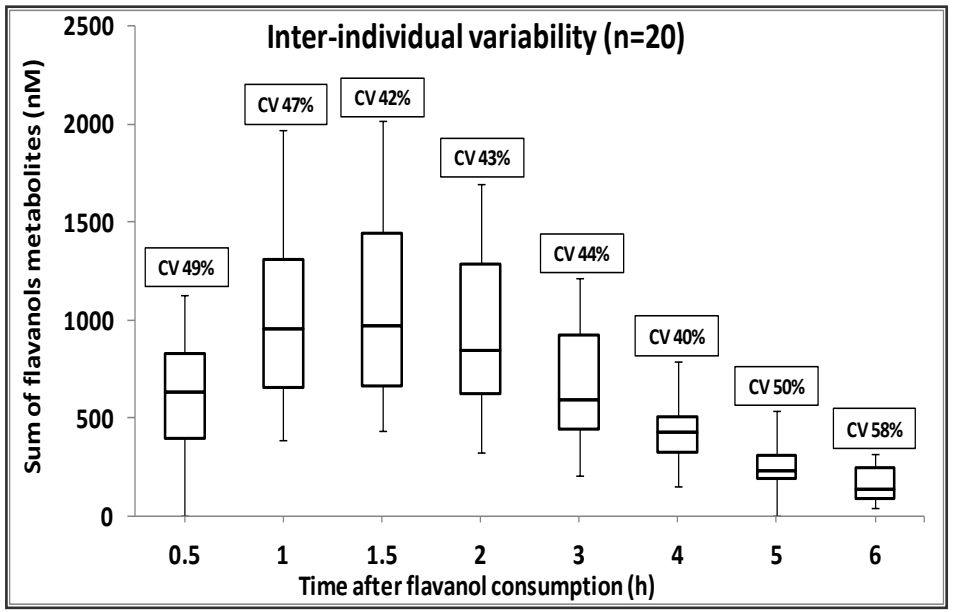
Intra-individual absorption and metabolism (n=9; 2 visits; 1 week washout)



CV %	C_{max}	T_{max}	$AUC_{(0\text{-}6h)}$
E3'G	30.1	21.7	26.0
E3'S	25.3	33.4	32.8
3ME5S	18.9	11.5	24.4
3ME7S	25.7	24.2	32.0
Total flavanols	***16.6***	***13.9***	***15.8***

– According to FDA, drugs exhibiting intra-subject variability greater than ***30%*** in AUC or Cmax are considered **highly variable drugs**

Inter-individual absorption and metabolism



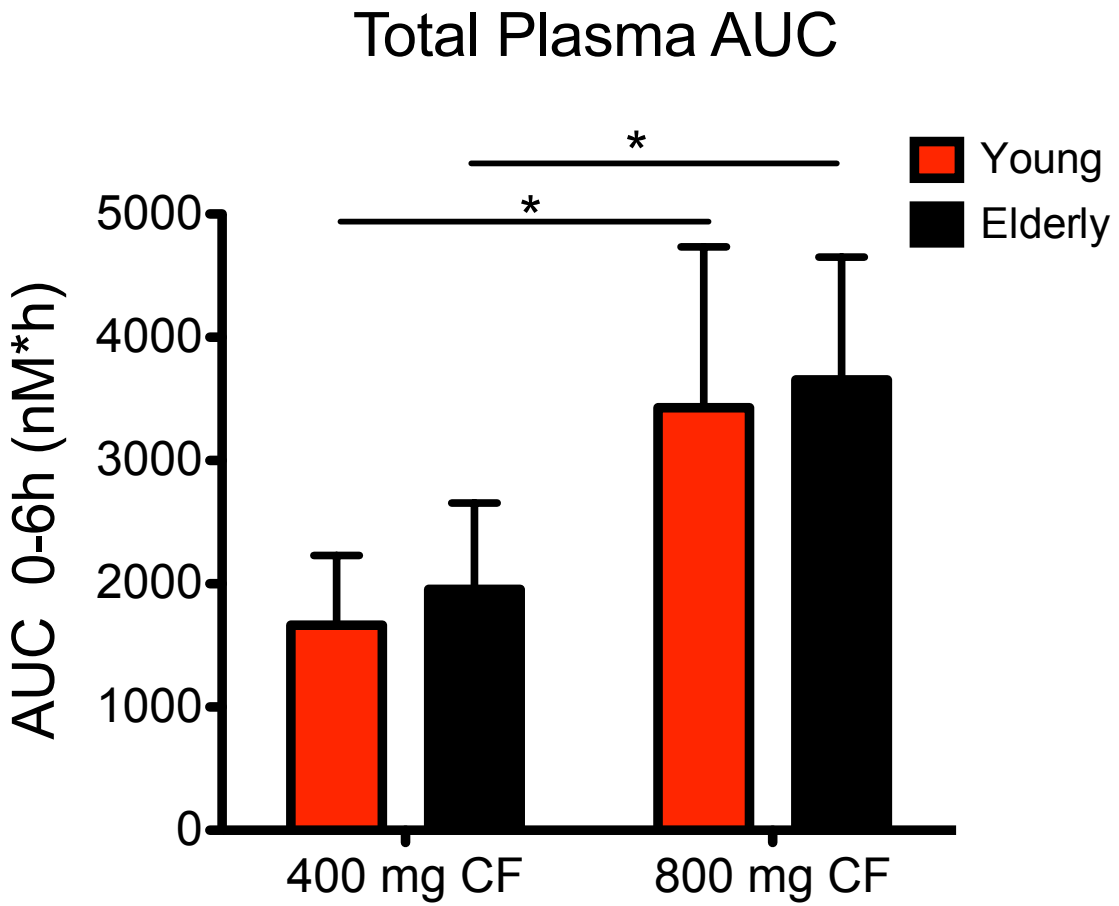
CV %	C_{max}	T_{max}	$AUC_{(0-6h)}$
E3'G	54.2	23.7	50.0
E3'S	36.4	34.4	43.5
3ME5S	34.9	46.2	39.0
3ME7S	50.6	38.2	46.4
Total flavanols	**38.6**	**26.0**	**38.1**

CV %	C_{max}	T_{max}	$AUC_{(0-6h)}$
Acetaminophen glucuronide	48.8	33.0	55.4
Acetaminophen sulfate	54.4	34.4	56.1
Acetaminophen	27.1	47.1	25.2
Total acetaminophen	40.9	41.4	**39.0**

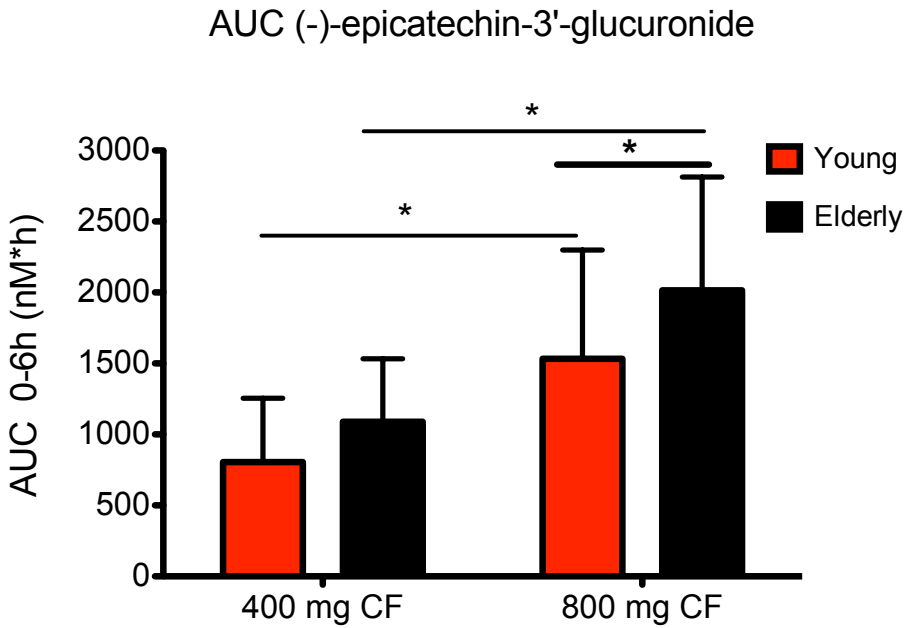
Influence of age on the absorption and metabolism of flavanols

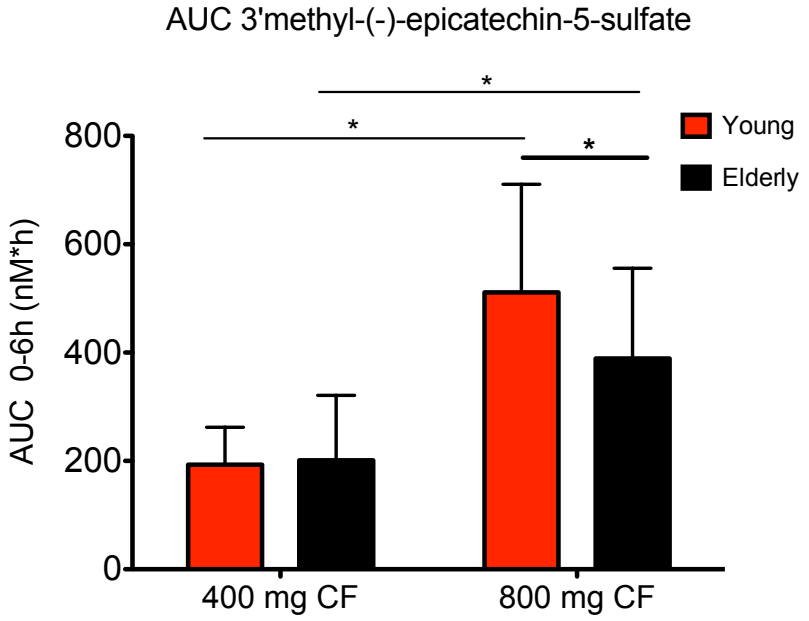
Characteristics	Elderly (n=20)	Young (n=20)
Age (years)	70 ± 4[a]	26 ± 6[b]
Weight (kg)	81 ± 10	79 ± 9
BMI (kg/m^2)	27 ± 3	24 ± 2
GFR (mL/min/1.73m^2)	72 ± 12	114 ± 22
Cholesterol (mM)	4.6 ± 1.0	4.4 ± 1.2
Triglycerids (mM)	1.0 ± 0.4	0.8 ± 0.4
Glucose (mM)	5.1 ± 0.5	4.7 ± 0.4
Creatinine (µM)	96.2 ± 14.2	97.4 ± 14.4
Bilirubin (µM)	17.0 ± 9.1	14.9 ± 5.5
Uric acid (µM)	341.1 ± 46.7	344.2 ± 74.1
ALT (U/L)	21.7 ± 7.7	20.6 ± 6.3
GGT-L (U/L)	25.0 ± 9.9	22.5 ± 8.0
ALP (U/L)	61.7 ± 14.8	75.9 ± 15.4
On medication	7	-

Age does not influence total levels (AUC: 0-6h) of circulating flavanol metabolites



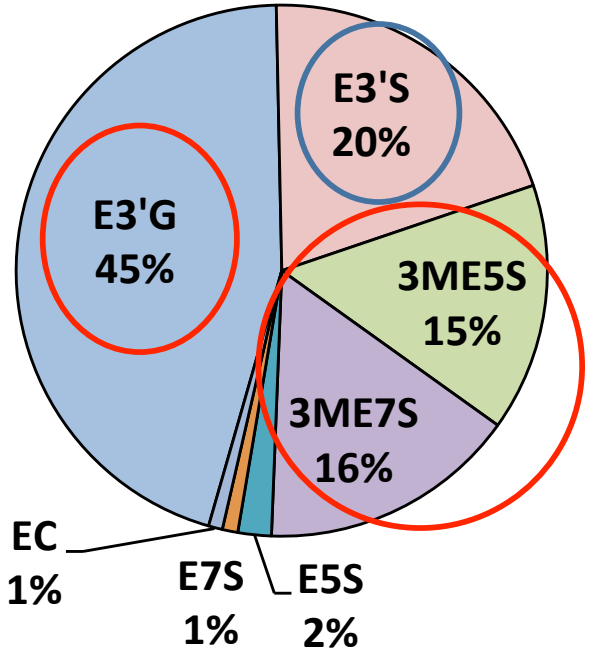
Plasma levels (AUC: 0-6h) of (-)-epicatechin metabolites in young and old



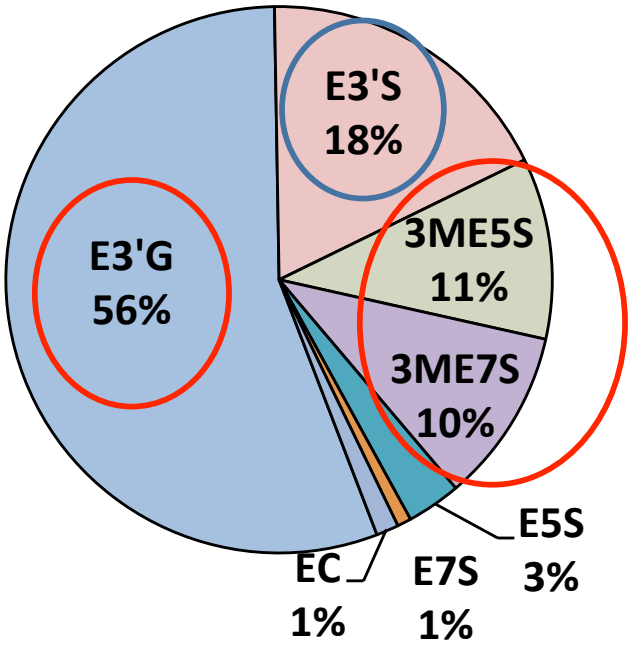


Influence of age on (-)-epicatechin metabolism

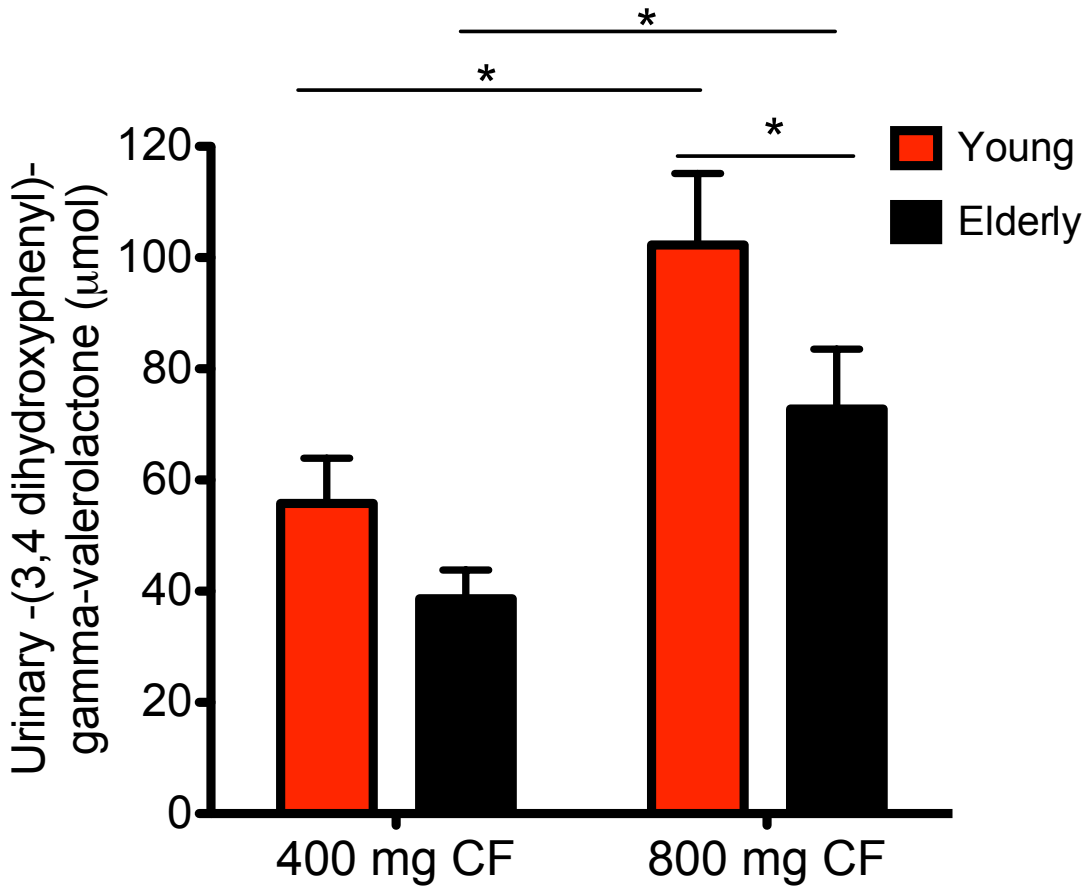
AUC (0-6h) in Young individuals



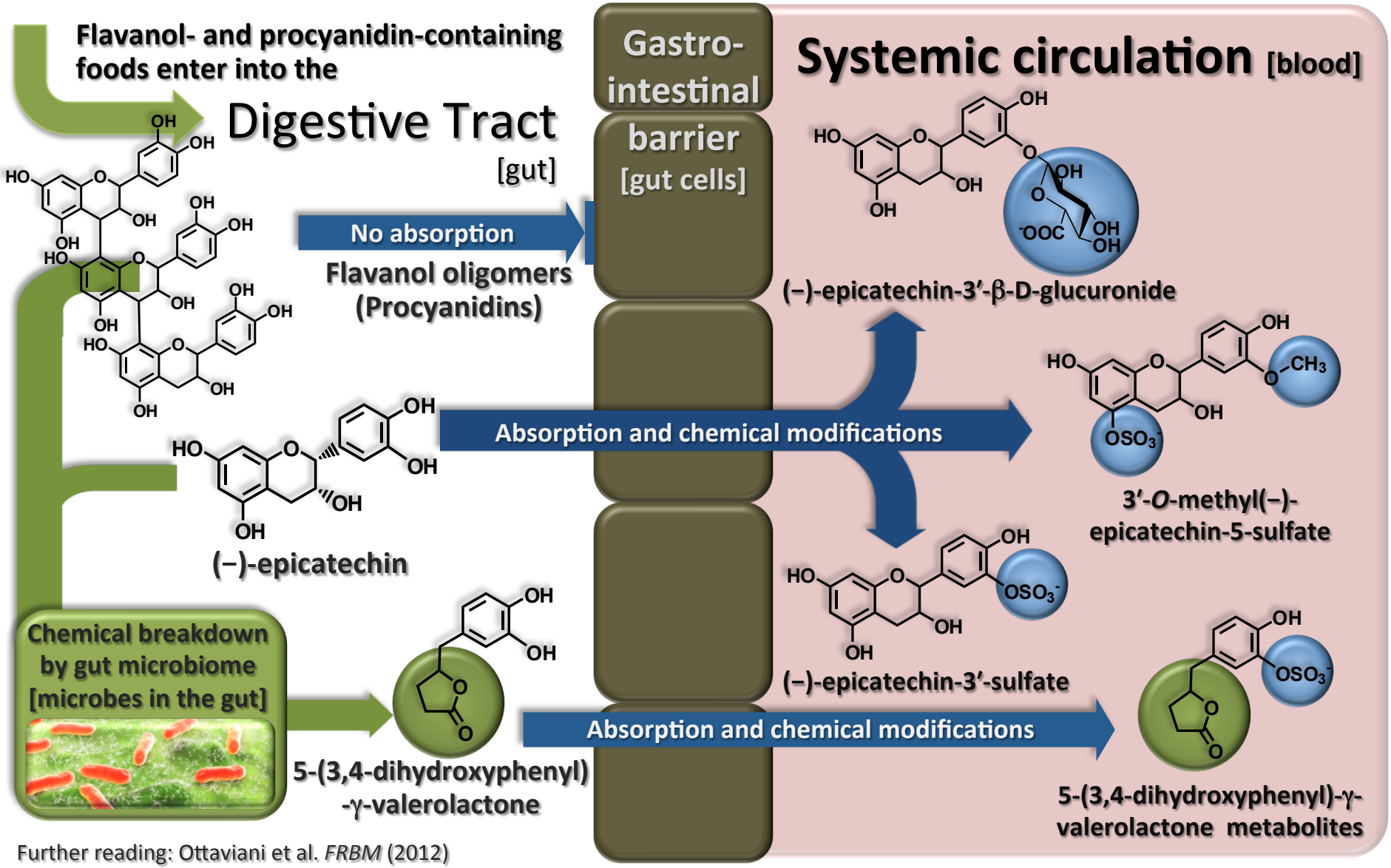
AUC(0-6h) in Elderly individuals



Urinary excretion of γ-valerolactones in young and old individuals



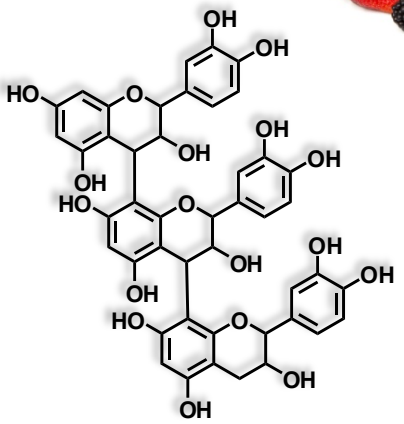
Summary of the metabolism of flavanols following consumption



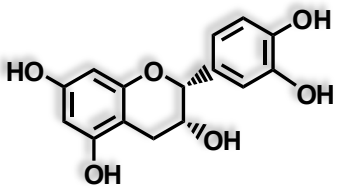
Further reading: Ottaviani et al. *FRBM* (2012)

Relevance for mechanistic assessment of flavanol function

Flavanols in plants and foods



Flavanol oligomers (Procyanidins)



Flavanol (–)-epicatechin

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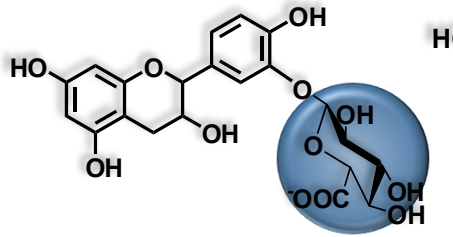
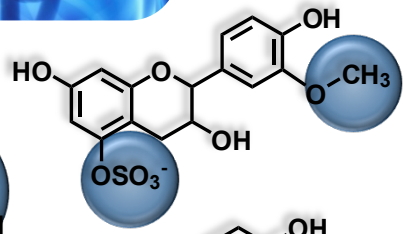
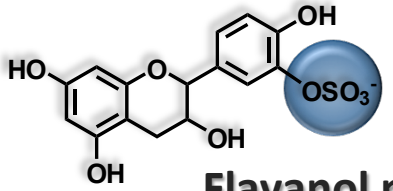
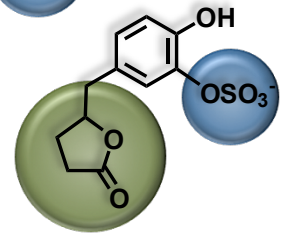
Flavanols in humans









Flavanol metabolites

These findings are important, as they inform us about the chemical structure of the flavanols present in the human body, which enables research aimed at understanding the mechanisms by which flavanol-rich diets mediate cardiovascular health benefits.