Flavanols in Health and Disease

Pre-Meeting workshop II, 3:00-5:00 p.m., November 14, 2012

SFRBM, San Diego, CA

Chairs

Helmut Sies, Düsseldorf, Germany

Alan Crozier, Glasgow, U.K.

Carl L. Keen, UC Davis

Blueberry

Cocoa

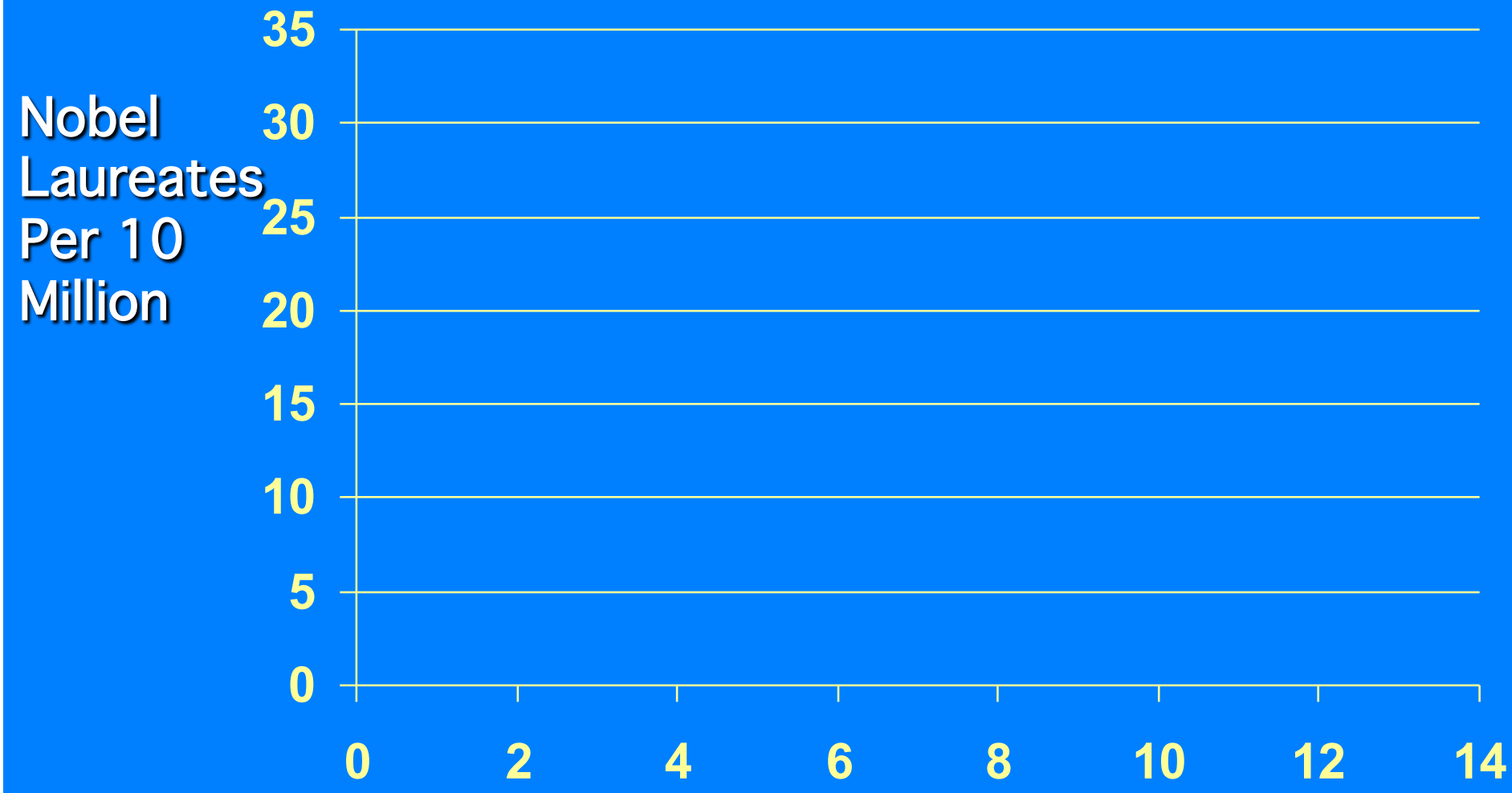
Cranberry

Grapes

Pomegranate

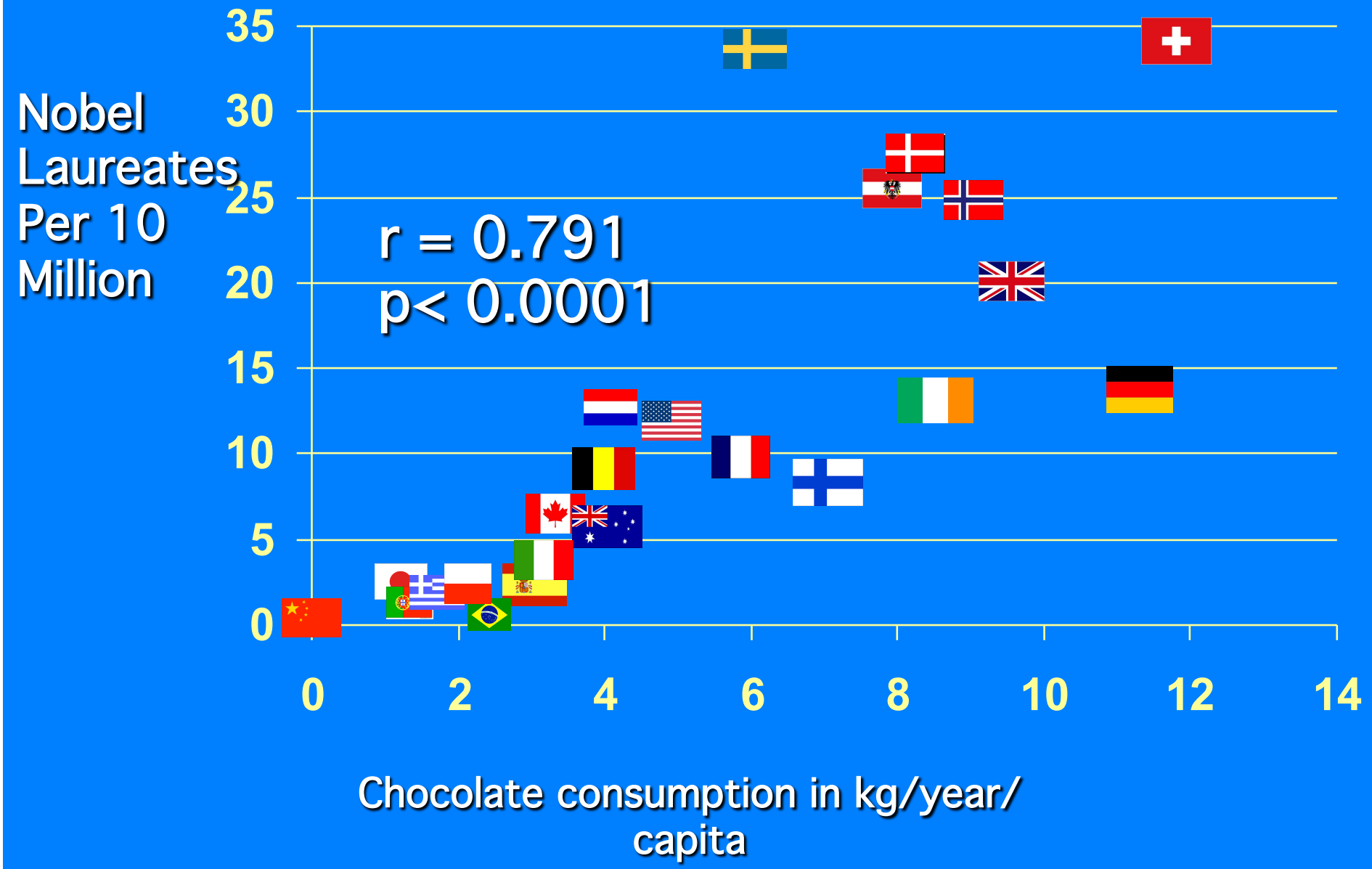
Tea (Green/Black)

Chocolate and the Nobel Prize



Messerli, F. (2012) *NEJM* **367**, 1562-1564

Chocolate and the Nobel Prize



Flavanols in Health and Disease

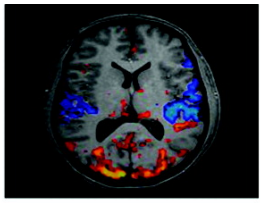
EU 7th Framework Programme:

‘Flaviola’

“Targeted delivery of dietary flavanols for optimal human cell function: Effect on cardiovascular health”

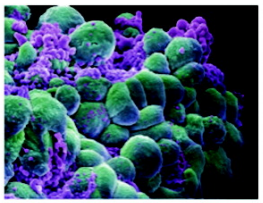
www.flaviola.org

A summary of the potential health benefits of dietary (poly)phenols



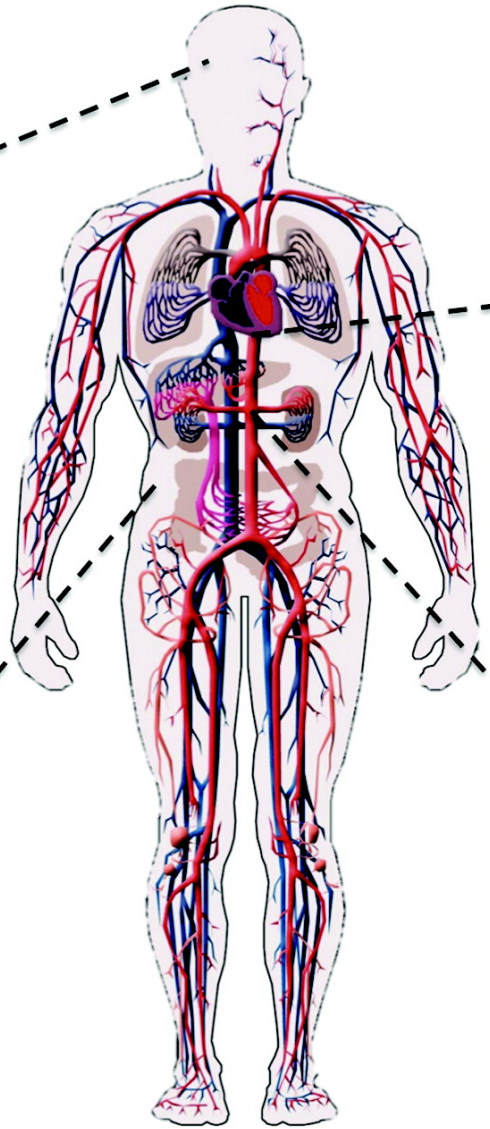
Brain

- Memory and learning
- Cognitive performance
- Cerebral blood flow
- Psychomotor activity
- Inhibition of Neurodegeneration
- Neurogenesis



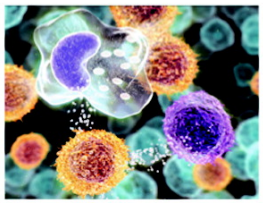
Cancer

- Inhibition of tumor development
- Detoxification of cancer precursors
- Cancer cell apoptosis
- Inhibition of DNA oxidation



Vascular function

- Reduction of Hypertension
- Increased blood perfusion
- Endothelial homeostasis
- Beneficial lipid profile
- Inhibition of Platelet activation

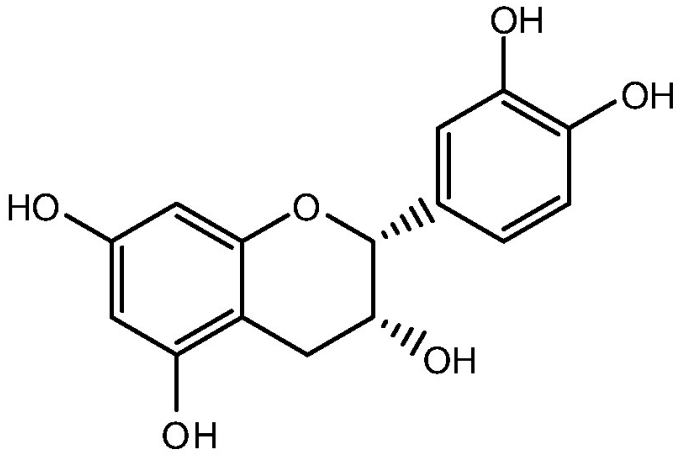


Inflammation

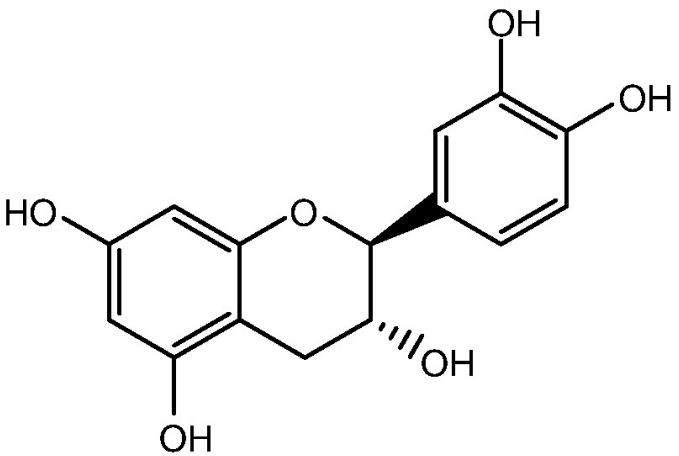
- Inhibition of cytokine/chemokine production mediators
- Reduced of adhesion molecule expression
- Inhibition of Neuroinflammation

Del Rio, D. *et al* (2012) *Antioxidants & Redox Signaling, doi:10.1089/ars.2012.4581*

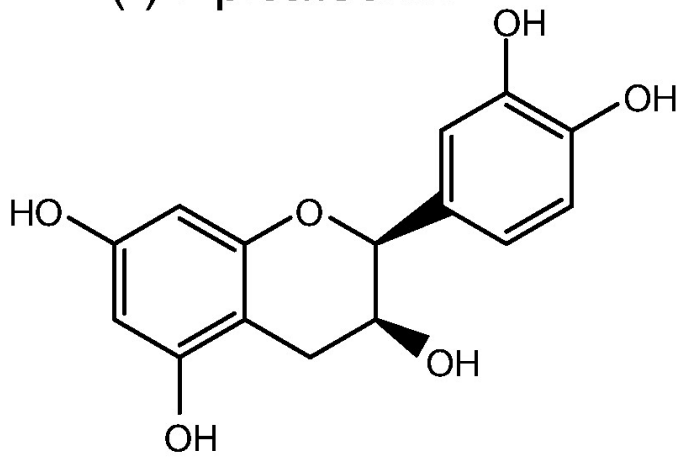
Chemical structure of flavanol stereoisomers



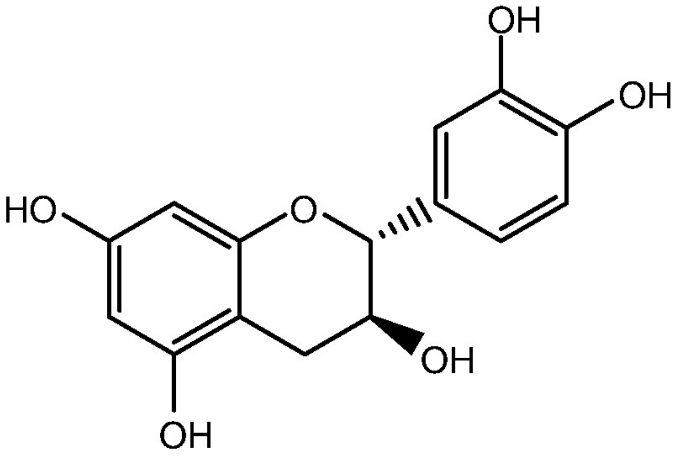
(-)-Epicatechin



(-)-Catechin



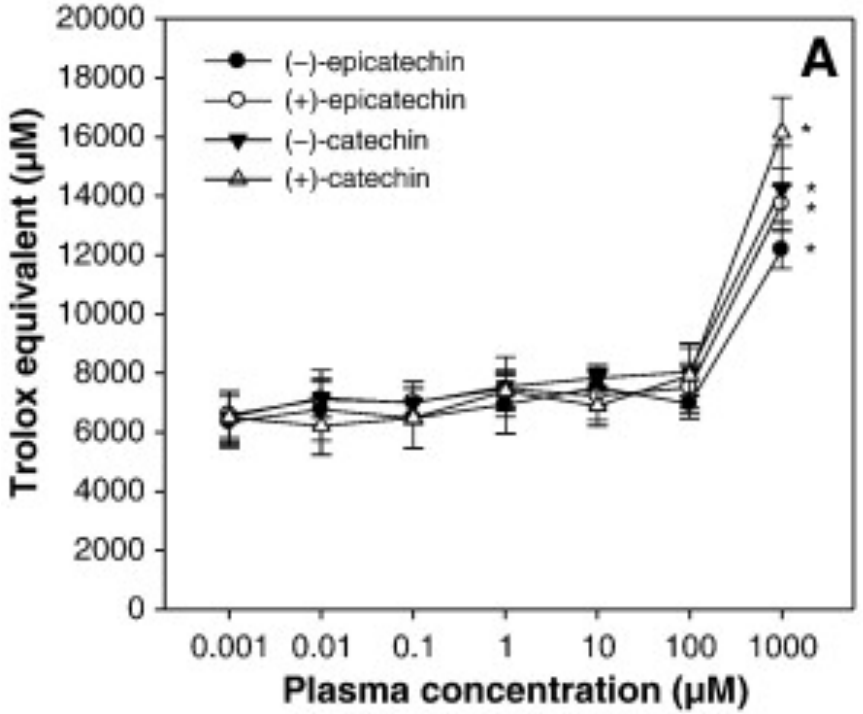
(+)-Epicatechin



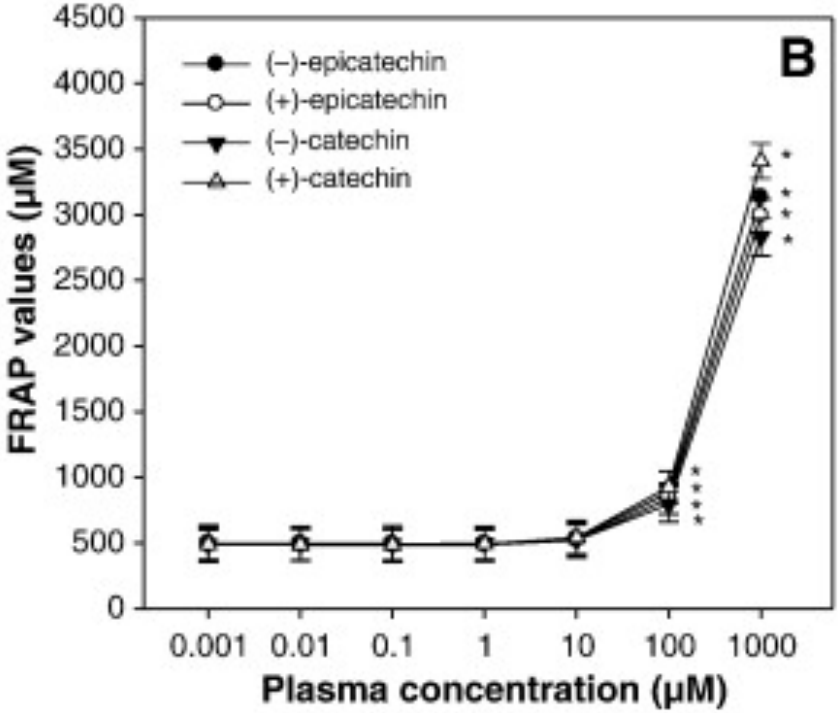
(+)-Catechin

„Total antioxidant capacity“ of flavanol stereoisomers in rat plasma spiked *ex vivo*

ORAC

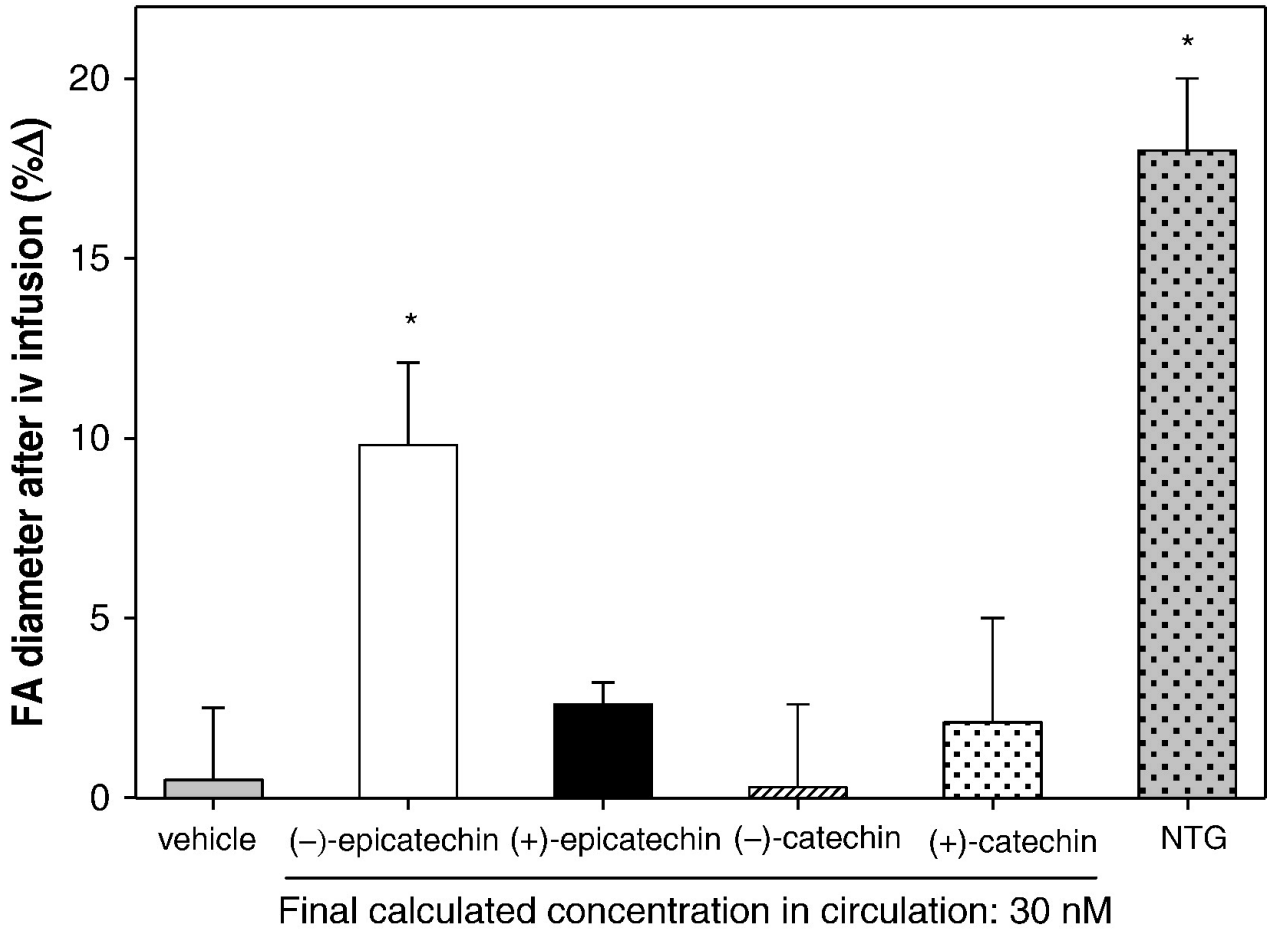


FRAP



Ottaviani JI *et al* (2011) *Free Rad Biol Med* **50**, 237-244

Vasodilatory effect of (−)-epicatechin, (+)-epicatechin, (−)-catechin, and (+)-catechin on femoral artery (FA) in living rats. FA diameter was measured before and 60 s after the iv injection of each flavanol stereoisomer



NTG, nitroglycerin, (positive control)

Ottaviani JI *et al* (2011) *Free Rad Biol Med* **50**, 237-244

Conclusion from these simple observations:

-Polyphenols exert their biological effects NOT by their capacity as ‚antioxidants' *sensu strictu*,

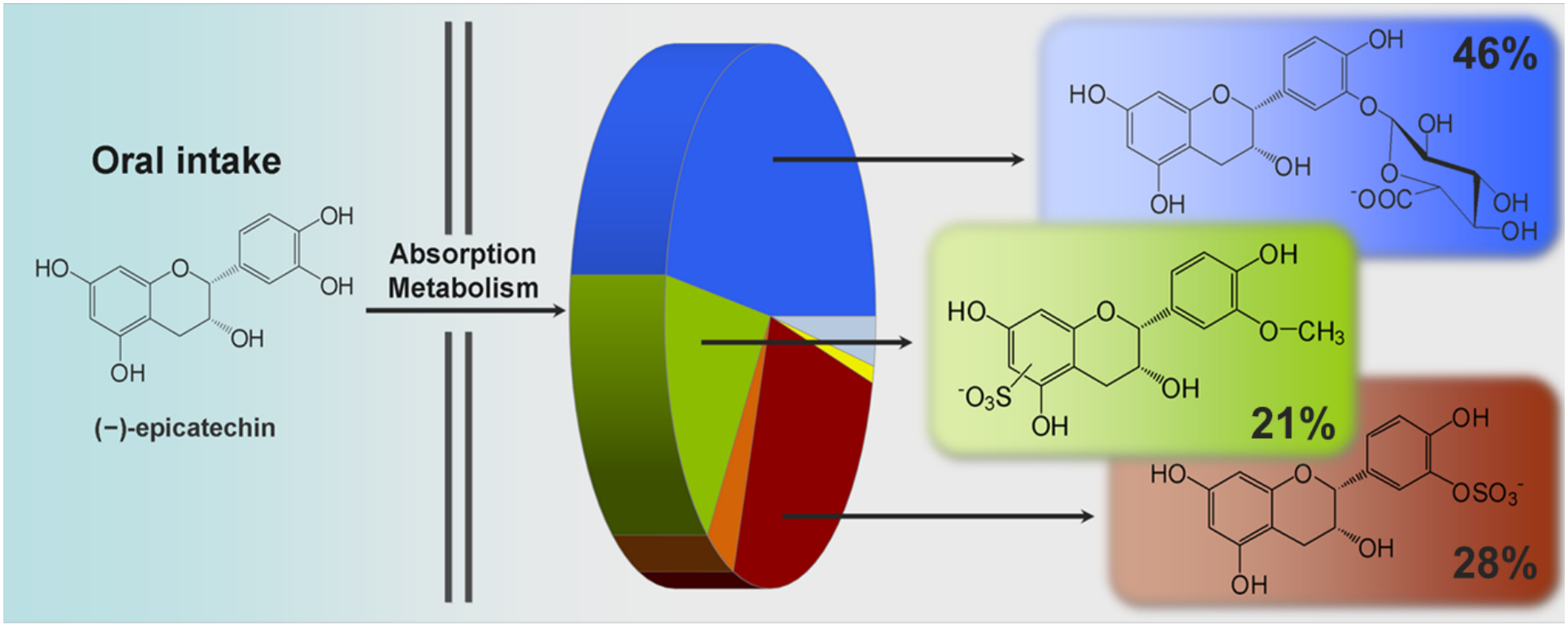
-Their bioactivity is largely mediated through other molecular effects,

-*e.g.* binding to proteins and modifying their function (inhibiting prooxidant enzymes, activating antioxidant enzymes)

-In vivo: Flavanols act as *‚Bioactives' rather than only as ‚Antioxidants'*

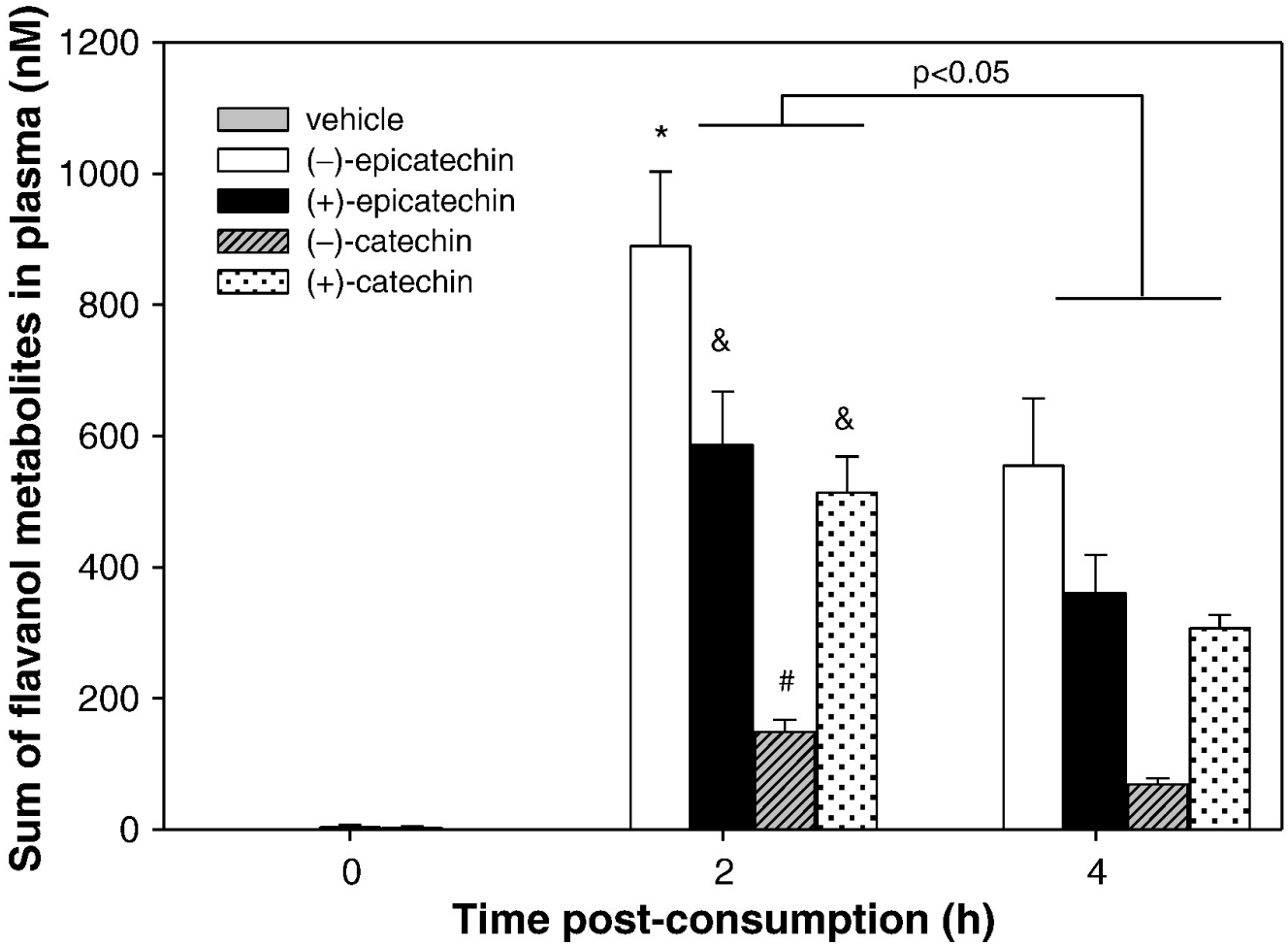
Profile of (−)-epicatechin metabolites in plasma

Very low, if any, free (-)-epicatechin detected in plasma



Structurally related (-)-epicatechin metabolites in humans: Assessment using de novo chemically synthesized authentic standards. Ottaviani JI, Momma TY, Kuhnle GK, Keen CL, Schroeter H. *Free Radic Biol Med.* 2011 Dec 23.

Sum of flavanol metabolites in plasma after the consumption of vehicle (control) or vehicle containing 1.5 mg/kg bw of (−)-epicatechin, (+)-epicatechin, (−)-catechin, or (+)-catechin

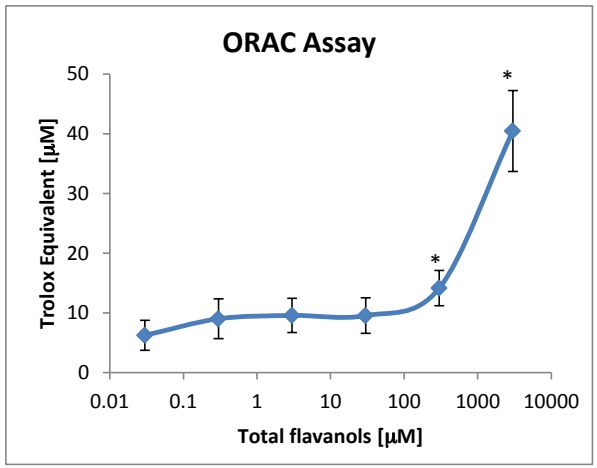


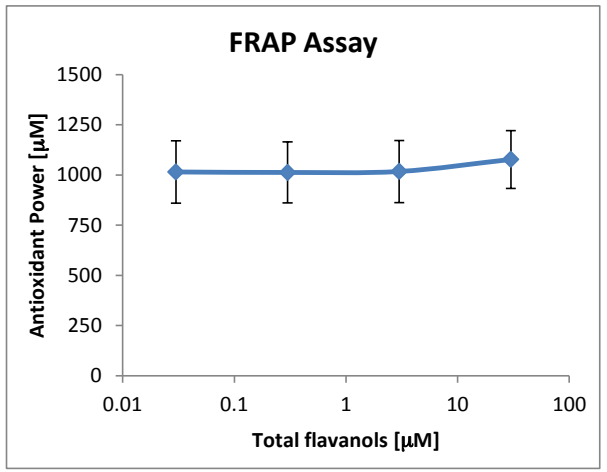
Study with human volunteers

Ottaviani JI *et al* (2011) *Free Rad Biol Med* **50**, 237-244

Postprandial plasma antioxidant capacity

Plasma samples were spiked with a mixture of flavanol metabolites





Result: No detectable change in ORAC or FRAP up to 100 µM flavanol metabolites in plasma (unpubl.)

May 16, 2012:

USDA's Nutrient Data Laboratory (NDL) removed the USDA ORAC Database for Selected Foods from the NDL website

due to mounting evidence that the values indicating antioxidant capacity have no relevance to the effects of specific bioactive compounds, including polyphenols on human health

„The data for antioxidant capacity of foods generated by *in vitro* (test-tube) methods cannot be extrapolated to *in vivo* (human) effects and the clinical trials to test benefits of dietary antioxidants have produced mixed results.

We know now that antioxidant molecules in food have a wide range of functions, many of which are unrelated to the ability to absorb free radicals.

For these reasons the ORAC table, previously available on this web site has been withdrawn.“

http://www.ars.usda.gov/services/docs.htm?docid=15866

Upshot on Flavanols

- *Keywords*: ‚**Bioactives**' rather than (only) ‚Antioxidants'
- *Active Compounds*: Flavanol *Metabolites*
- *Health and Disease Parameters*: measure chemical compounds involved (not ORAC ‚Kit-ology'); *Nitric Oxide, Nitrite,* functional biomarkers (e.g. *Flow-Mediated Dilation (FMD*), *blood pressure*);
- *Mechanism of Action*: targeted control of prooxidant enzymes in inflammation and cardiovascular biology (specificity); master switches: *Nrf2, NFkappaB*
- *Cardiovascular Health*: Short-term/Long-term; Young/Old
-

Take-home Message: ***Flavanols Session***

- ‚**Bioactives**‘ rather than (only) ‚Antioxidants‘
- *Active Compounds*: Flavanol *Metabolites from Monomer, (-)-Epicatechin; Oligomers (Procyanidins) do NOT contribute*
- *Epidemiology: blood pressure lowering in human intervention studies at >50 mg flavanol (monomer)/day*
-

• *Mechanism of Action*: prooxidant enzymes, reactive oxygen species (*in vitro*, cell culture expts); inflammatory markers; master switches: *Nrf2, NFkappaB*

• *Cardiovascular Health*:
Short-term (2 hr)/Long-term (>30 days); *Adaptive* Response

•*Young/Old*; acute (2 hr) response restricted in elderly after longer-term intake