Dietary polyphenols in the prevention of cardiovascular diseases: facts, fiction and prospective mechanisms of action

Daniele Del Rio

The Laboratory of Phytochemicals in Physiology
&
The Micriobiome Research Hub

***University of Parma**, Italy*

The Need for Nutrition Education/Innovation Programme (NNEdPro)

Wolfson College
Cambridge

Thanks to….


efsa
European Food Safety Authority


Red
RASPBERRIES


Barilla


PROGETTO Ager
AGROALIMENTARE E RICERCA
FONDAZIONI IN RETE
PER LA RICERCA
AGROALIMENTARE

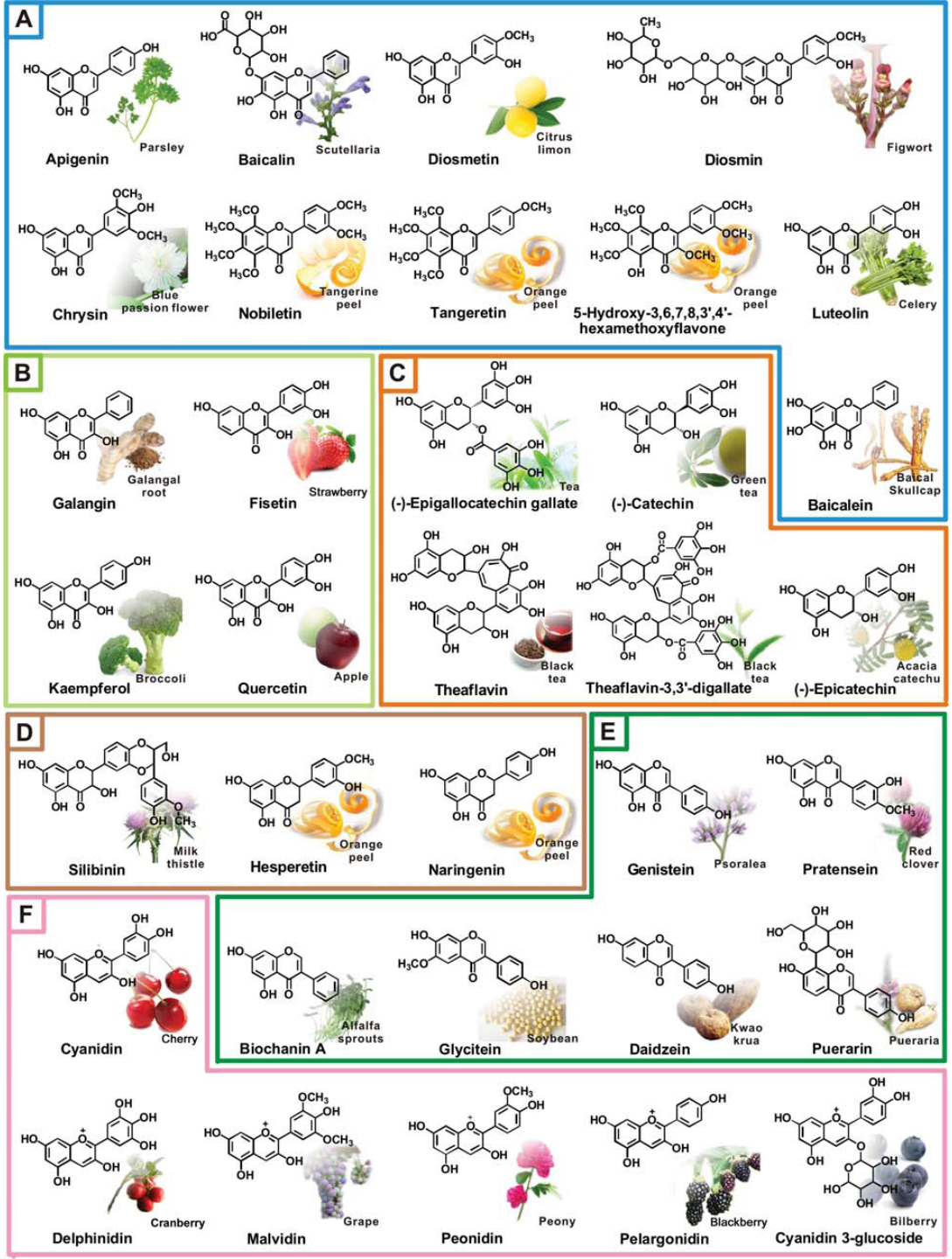

FERRERO


Fytexia

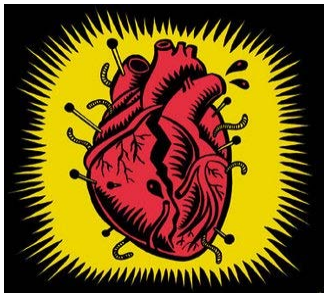

POSITIVe

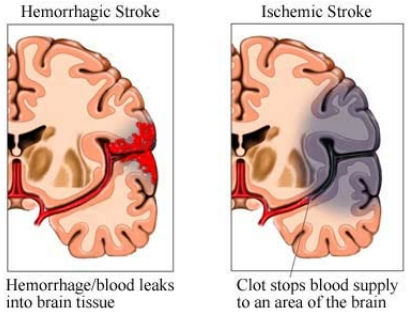

Juice
PLUS+

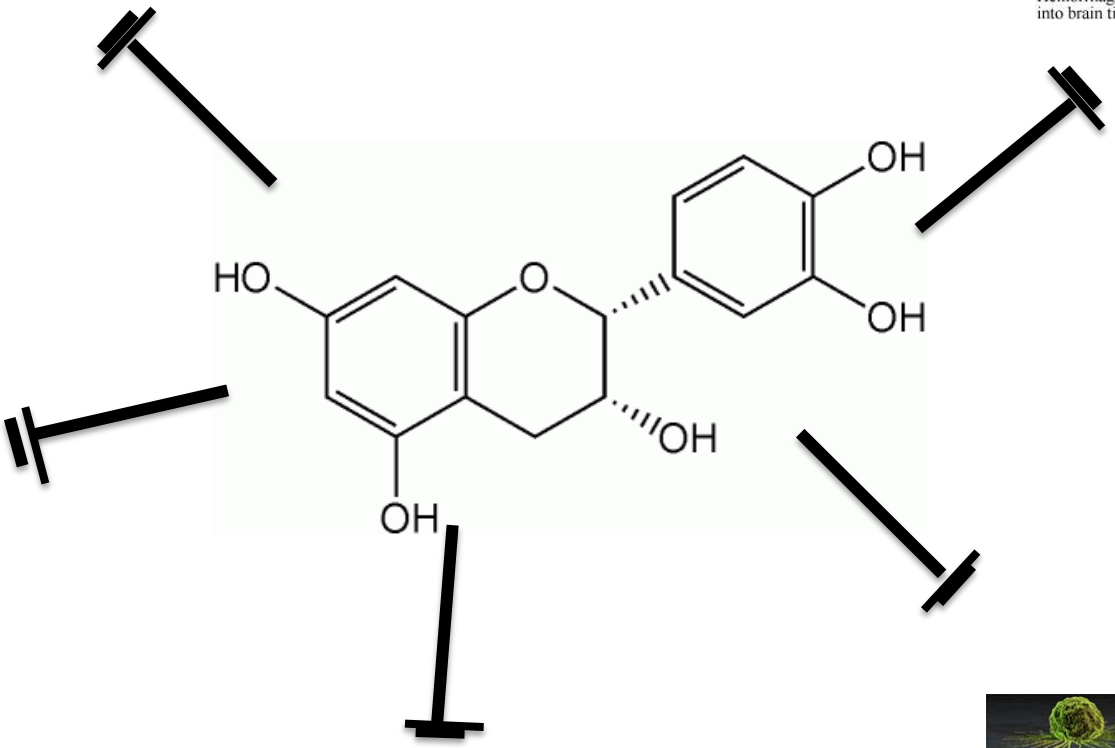

JPI
a healthy diet
for a healthy life

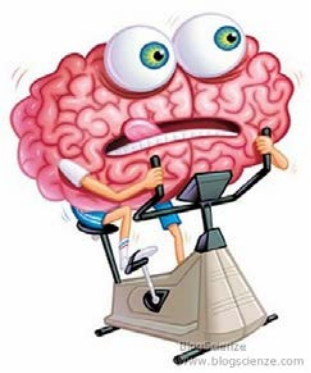

A
Apigenin
Parsley
Baicalin
Scutellaria
Diosmetin
Citrus limon
Diosmin
Figwort
Chrysin
Blue passion flower
Nobiletin
Tangerine peel
Tangeretin
Orange peel
5-Hydroxy-3,6,7,8,3',4'-hexamethoxyflavone
Orange peel
Luteolin
Celery
B
Galangin
Galangal root
Fisetin
Strawberry
Kaempferol
Broccoli
Quercetin
Apple
C
(-)-Epigallocatechin gallate
Tea
(-)-Catechin
Green tea
Baicalein
Baical Skullcap
Theaflavin
Black tea
Theaflavin-3,3'-digallate
Black tea
(-)-Epicatechin
Acacia catechu
D
Silibinin
Milk thistle
Hesperetin
Orange peel
Naringenin
Orange peel
E
Genistein
Psoralea
Pratensein
Red clover
F
Cyanidin
Cherry
Biochanin A
Alfalfa sprouts
Glycitein
Soybean
Daidzein
Kwao krua
Puerarin
Pueraria
Delphinidin
Cranberry
Malvidin
Grape
Peonidin
Peony
Pelargonidin
Blackberry
Cyanidin 3-glucoside
Bilberry

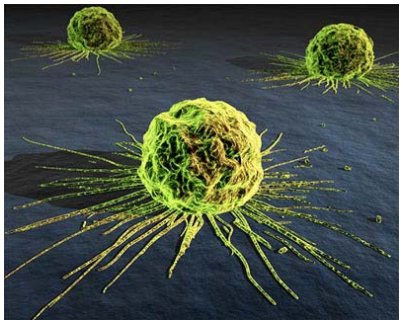
They prevent!!?



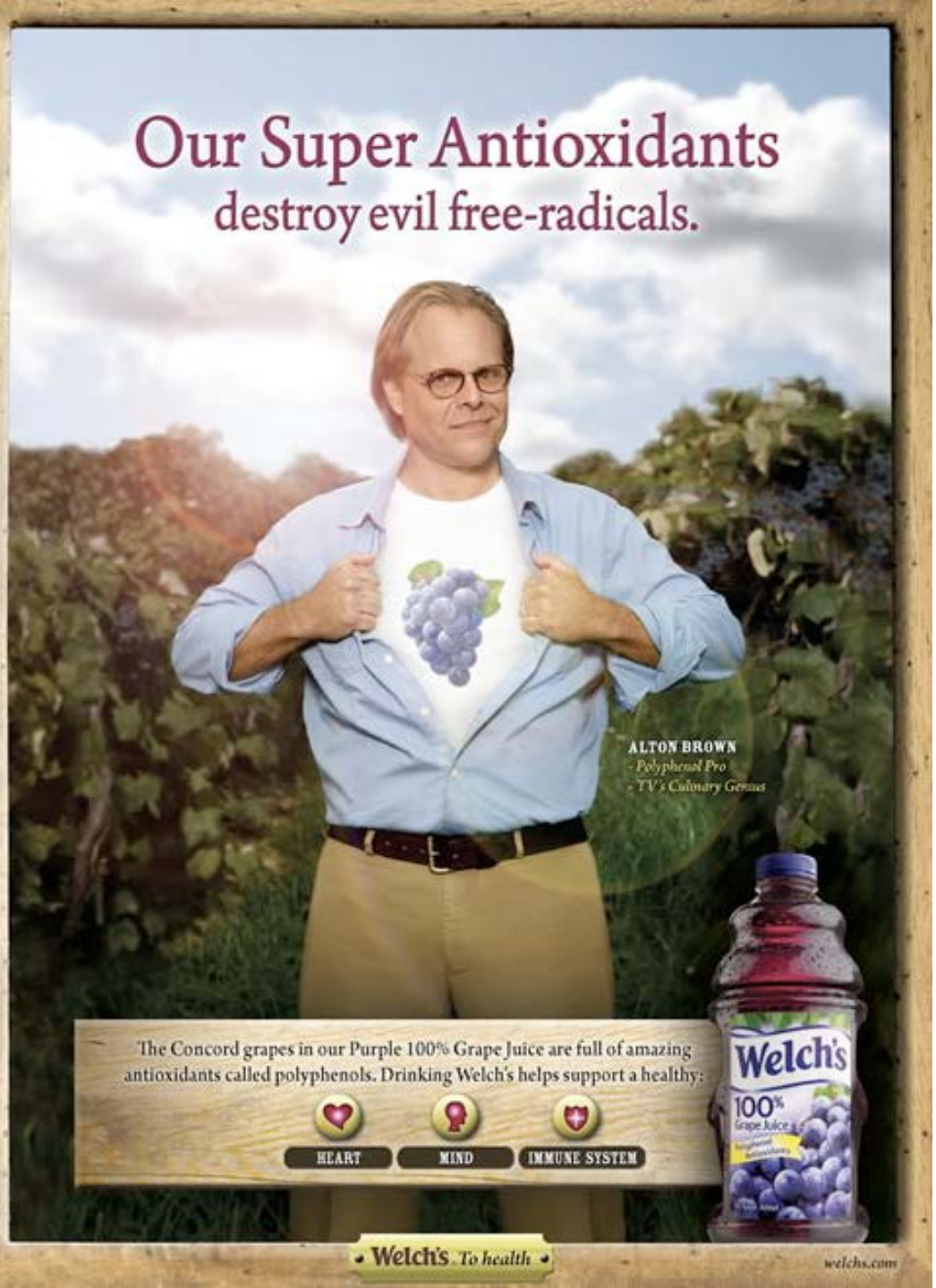








Companies are riding the wave…..


Our Super Antioxidants
destroy evil free-radicals.
ALTON BROWN
- Polyphenol Pro
- TV's Culinary Genius
The Concord grapes in our Purple 100% Grape Juice are full of amazing antioxidants called polyphenols. Drinking Welch's helps support a healthy:
HEART
MIND
IMMUNE SYSTEM
Welch's
100%
Grape Juice
Welch's. To health.
welchs.com

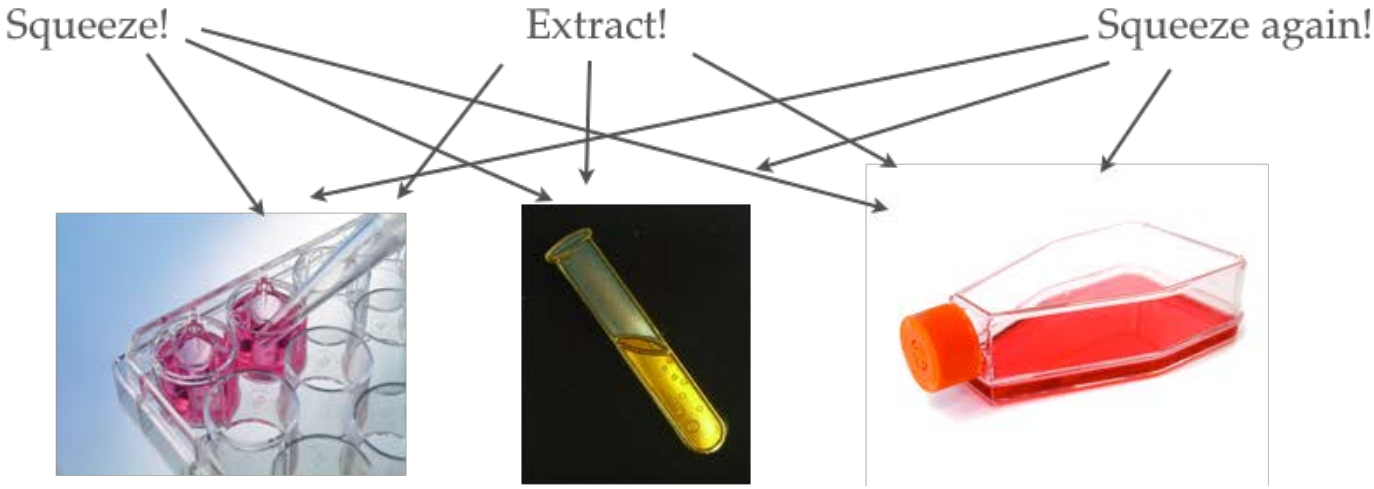
Life support.

The antioxidant power of pomegranate juice.

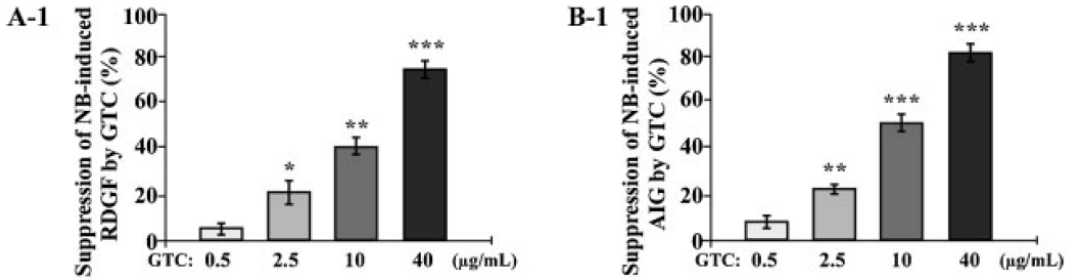
But the best comes from Japan!


HaloHalo.ph

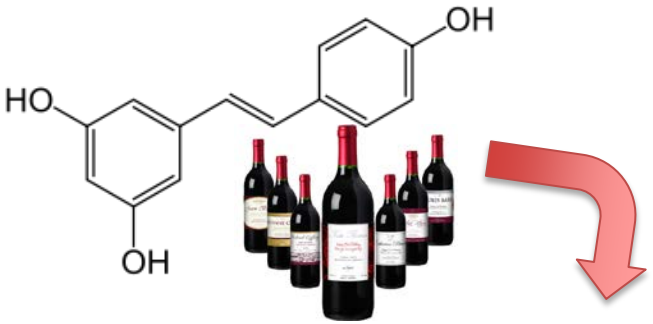
Unfortunately…



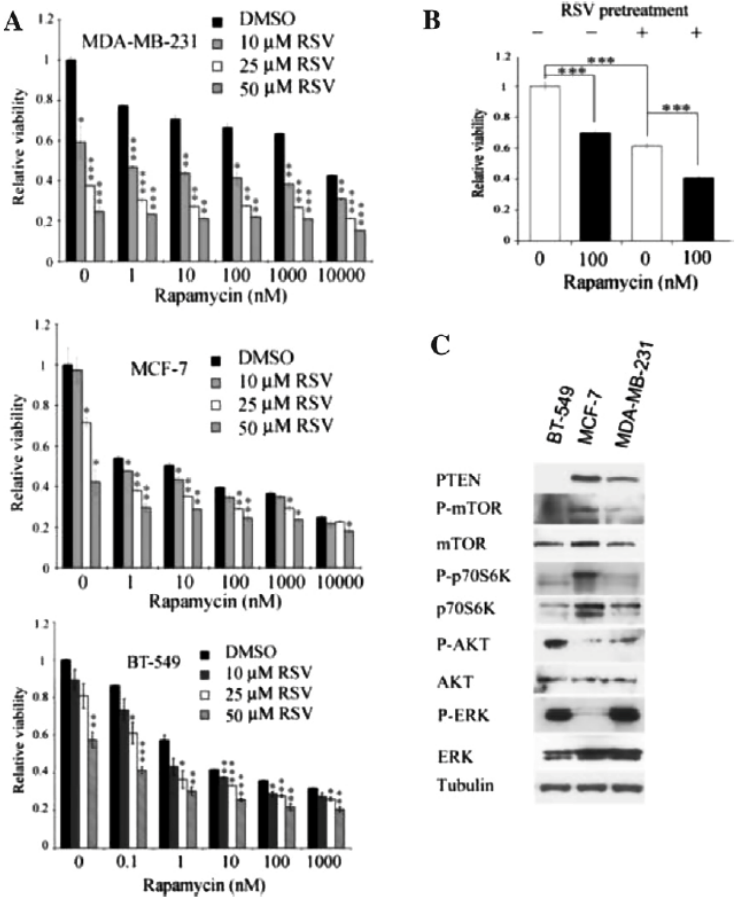
MOLECULAR CARCINOGENESIS 51:280–289 (2012)



GTC suppression of cellular carcinogenesis.

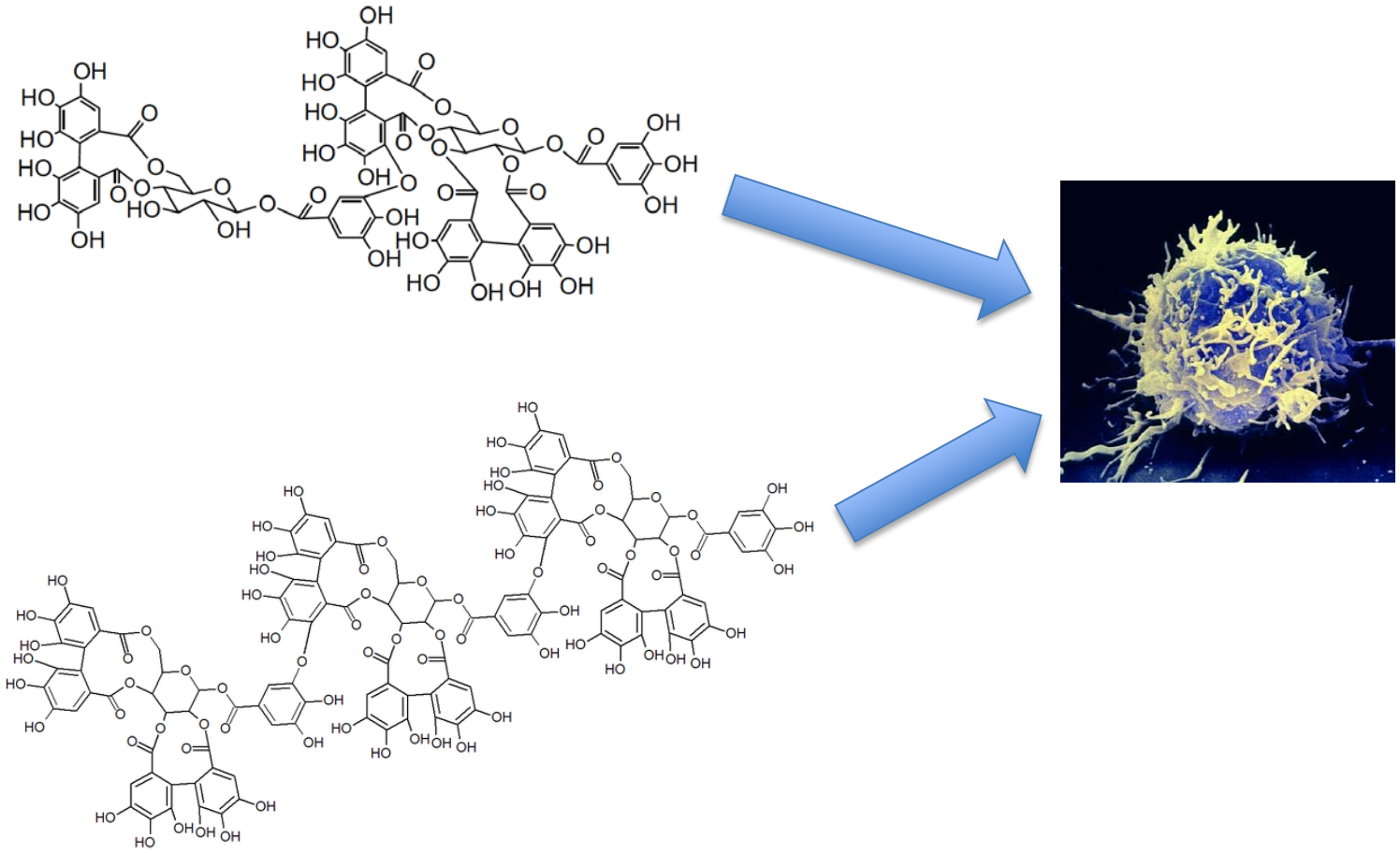


X. He et al./Cancer Letters 301 (2011) 168–176



Blackberry Seed Extracts and Isolated Polyphenolic Compounds Showing Protective Effect on Human Lymphocytes DNA

Dejan Gođevac, Vele Tešević, Vlatka Vajs, Slobodan Milosavljević, and Miroslava Stanković



Vol. 76, Nr. 7, 2011 • Journal of Food Science

At low concentrations (**< 50 µM**), resveratrol appears to activate AMPK without decreasing energy (Dasgupta and Milbrandt, 2007; Suchankova et al., 2009)

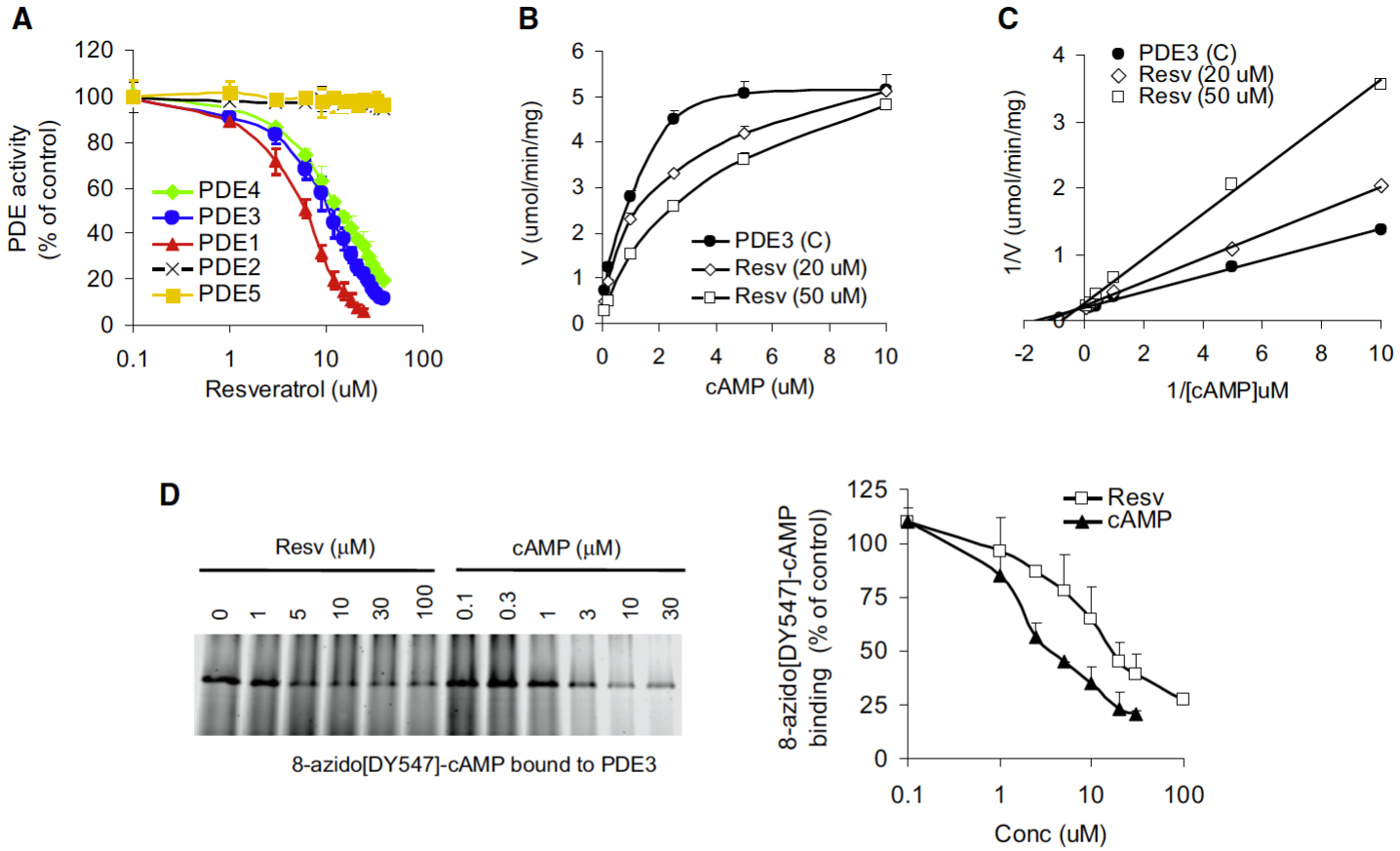


Figure 4. Resveratrol Is a PDE Inhibitor

(A) The effect of resveratrol on the activities of recombinant PDEs 1–5.

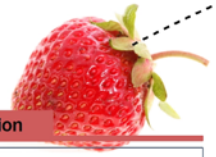
(B) Velocity of recombinant PDE3 activity as a function of cAMP and resveratrol concentration.

(C) Lineweaver-Burk plot of (B).

(D) Recombinant PDE3 was photoaffinity labeled with the fluorescent cAMP analog 8-azido-[DY-547]-cAMP in the presence of resveratrol or cAMP. 8-azido-[DY-547]-cAMP bound to PDE3 was visualized by fluorescence imaging (left). Quantification of 8-azido-[DY-547]-cAMP binding is shown in the right panel (n = 3).

Work out more physiological models!

Bioavailability of Ellagitannins in Healthy Humans



Time 0 - Ingestion

300 g of strawberries or 100 ml of pomegranate juice allow the administration of approx 140 μmol of ellagic acid and ellagitannins

After 1 Hour

Ellagic acid, obtained by basic hydrolysis of ET downline of gastric passage, is detected in plasma at Cmax 0.06 μM, AUC 0.17 μmol*h/L

After 5 Hours

Ellagic acid disappears from plasma. The amount unabsorbed in the small intestine enters the large intestine where is biotransformed by resident colonic microflora

Large Intestine

Urolithin M5. First step of microbial rearrangement of ellagic acid.

Urolithin D

Urolithin C

Large Intestine

The colonic microflora produces four different urolithins by a fixed order. Urolithin D appears first, is modified to Urolithin C, then to A and finally to Urolithin B.

Urolithin B

Urolithin A

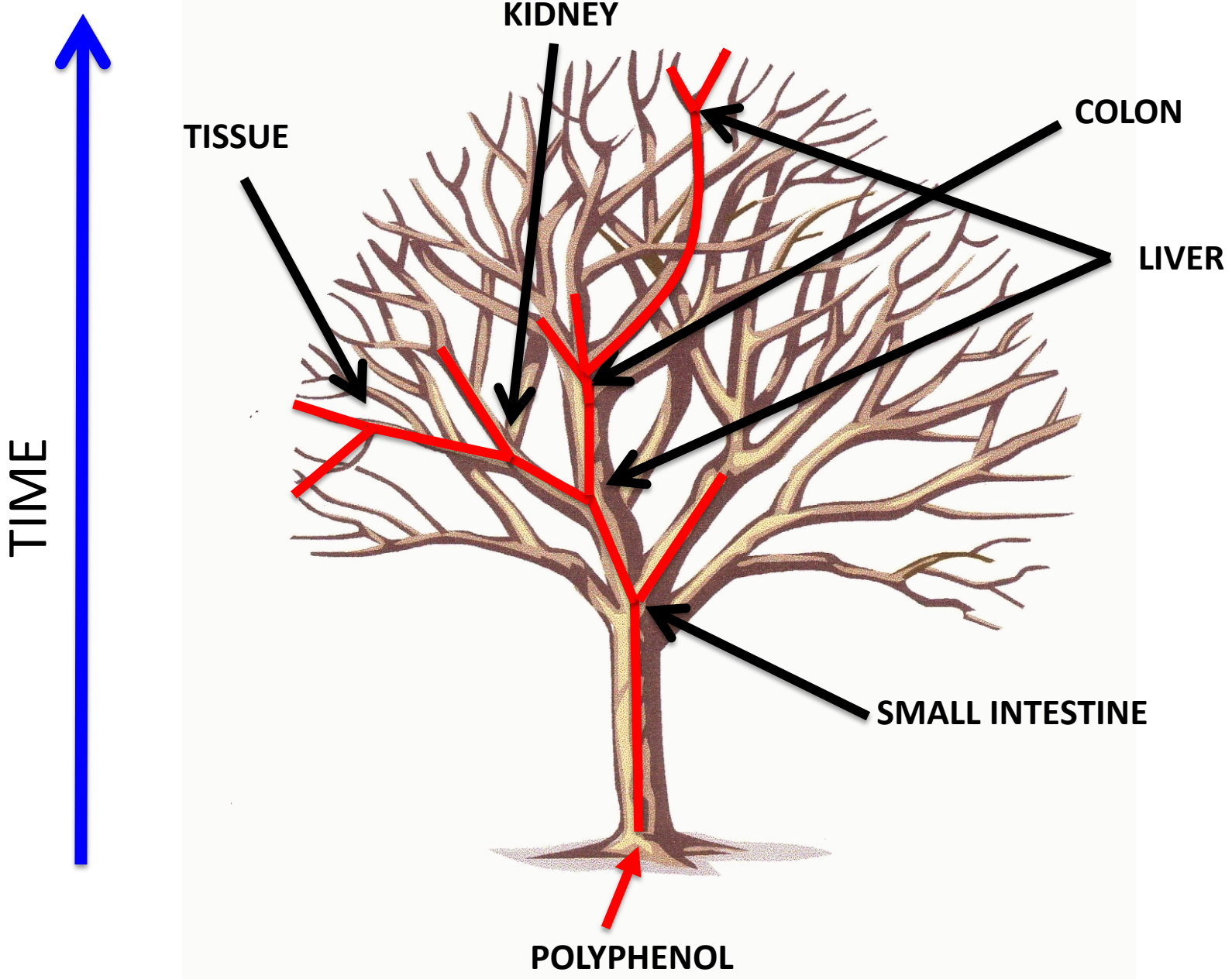
Large Intestine

Urolithins can be glucuronated, sulphated or methylated by Phase I and Phase II enzymes in the liver

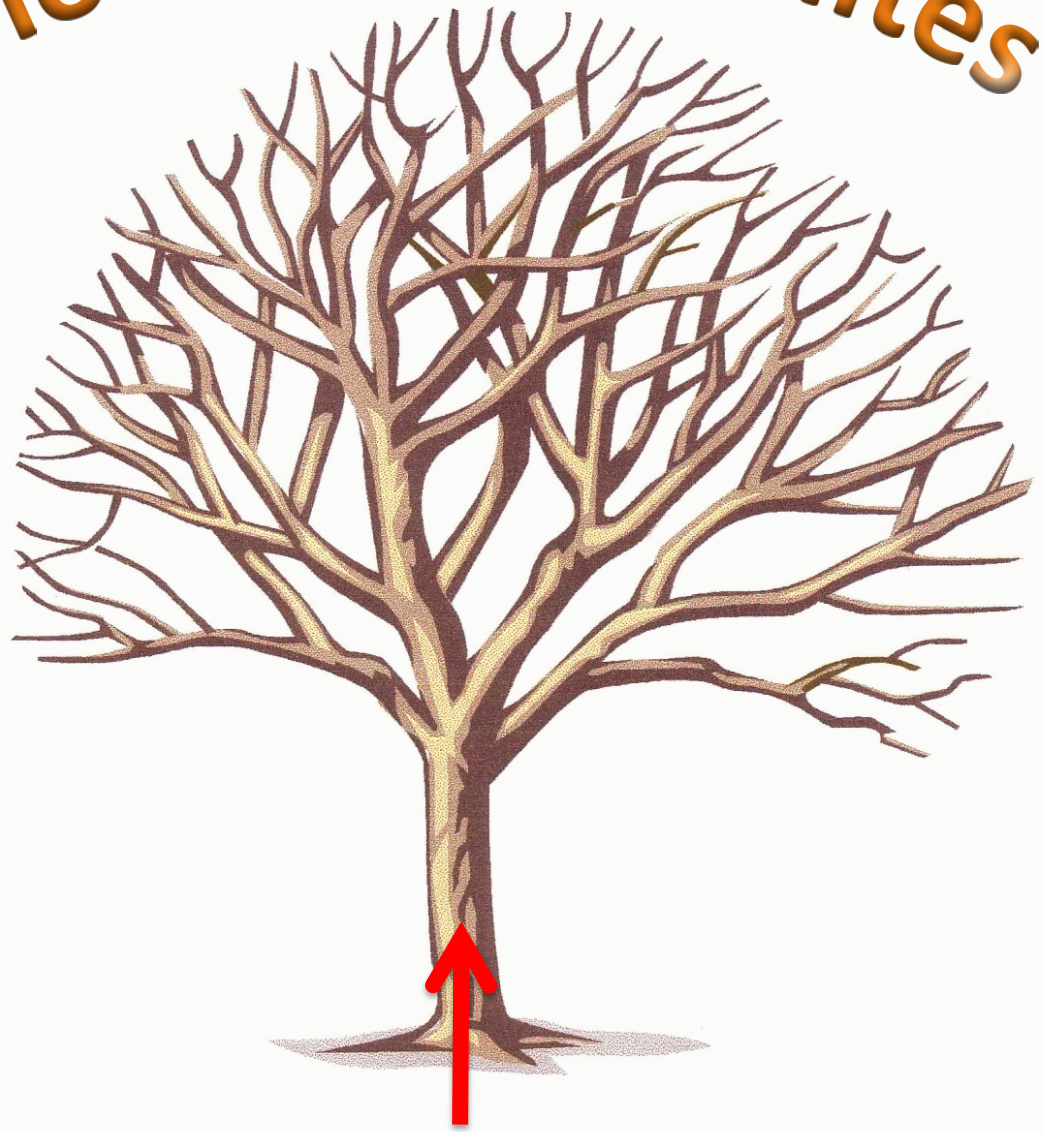
Urolithin B 3-O-Glucuronide

Variability

All reports highlight a great interindividual variability, likely due to different microfloras. Total urinary excretion of ET-metabolites may range from 1 to 53%


TIME
KIDNEY
TISSUE
COLON
LIVER
SMALL INTESTINE
POLYPHENOL

A lot of metabolites



A FEW PLANT POLYPHENOLS

Isourolithin A

Urolithin B-3-O-glucuronide

Ellagitannins

Ellagic acid

Urolithin D

Urolithin C

Urolithin A

Urolithin B

3,8-*O*-Dimethylellagic acid-2-*O*-glucuronide

Urolithin A-3-*O*-glucuronide

C3'dehydroxylation

4'-Hydroxyphenylacetic acid

Ring fission of upper monomeric unit

3',4'-Dihydroxyphenylacetic acid

C4'dehydroxylation

3'-Hydroxyphenylacetic acid

Procyanidin B2

Cleavage of interflavan bond

(–)-Epicatechin

Reductive cleavage of C-ring

1-(3',4'-dihydroxyphenyl)-3-(2'',4'',6''-trihydroxyphenyl)propan-2-ol

Ring fission

Ring fission of lower monomeric unit

5-(3',4'-dihydroxyphenyl)-γ-valerolactone

Hydrolysis

5-(3',4'-dihydroxy)phenylvaleric acid

C4'dehydroxylation

C4'dehydroxylation

C3'dehydroxylation

5-(4'-hydroxyphenyl)-γ-valerolactone

5-(3'-hydroxyphenyl)-γ-valerolactone

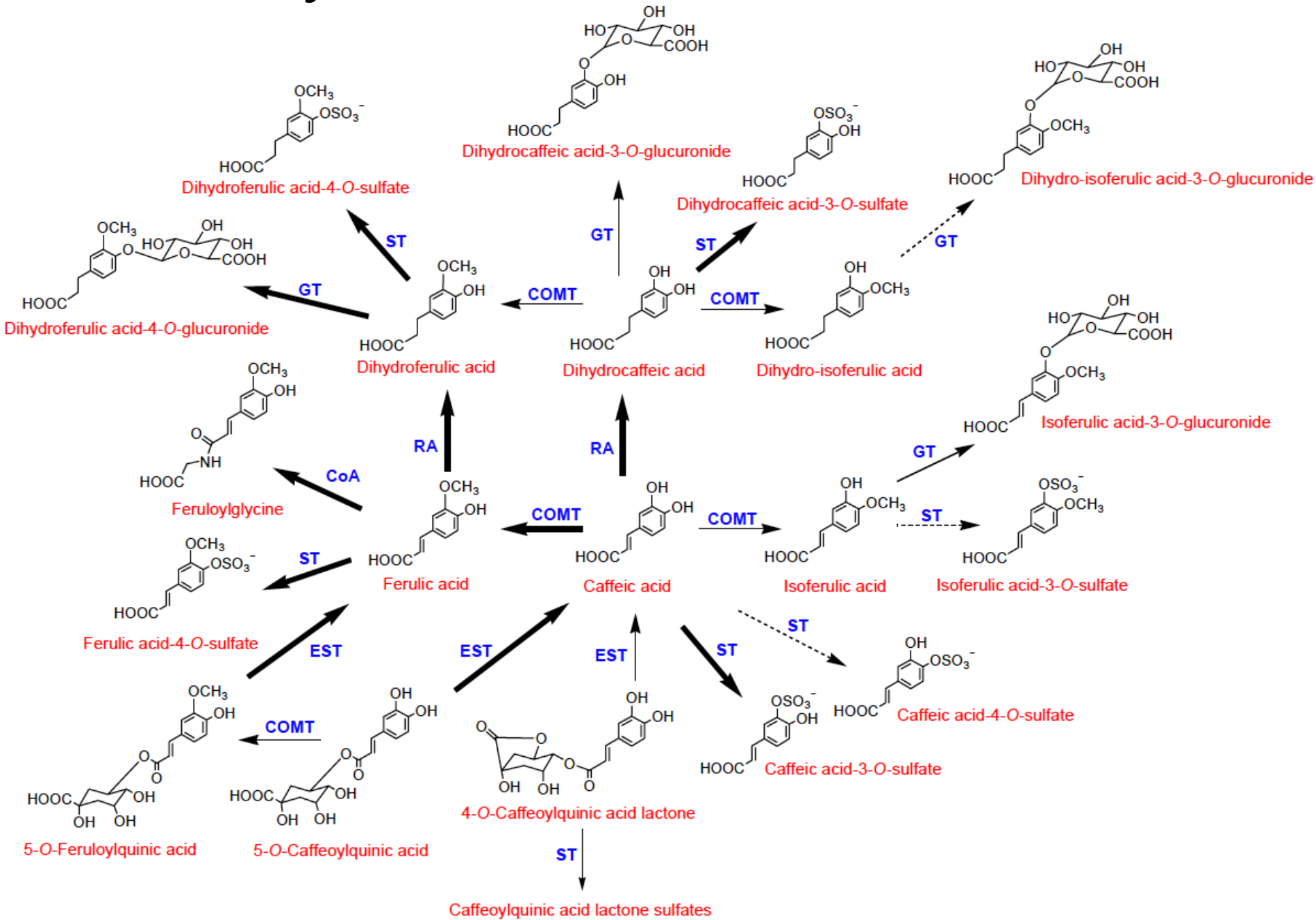
Hydrolysis

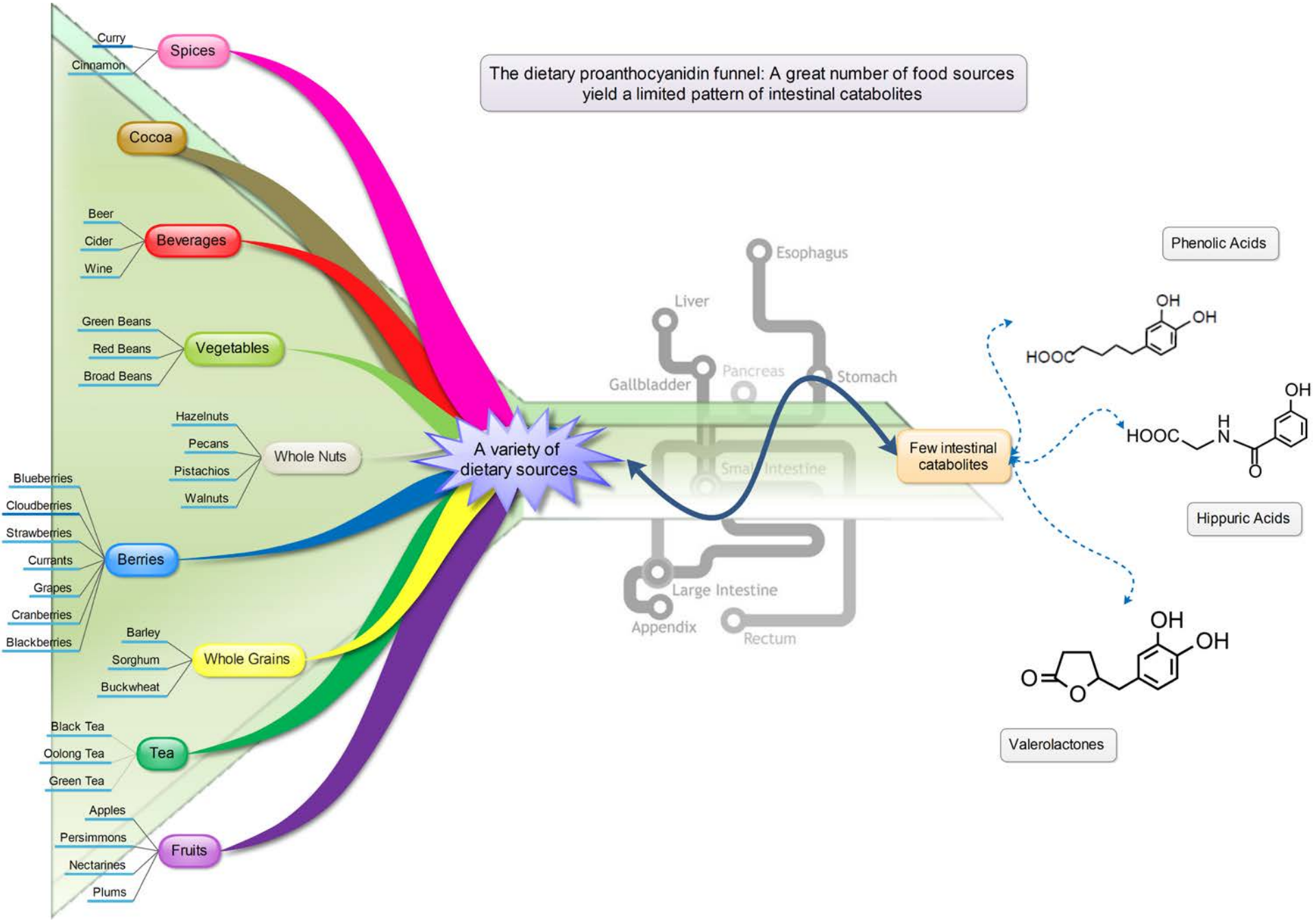
5-(3'-hydroxy)phenylvaleric acid

3-(3'-hydroxyphenyl)propionic acid

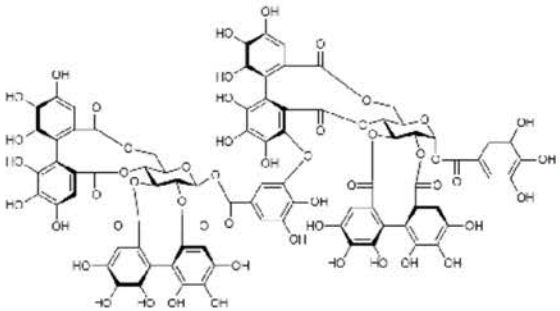
β-oxidation

You fancy a coffee?

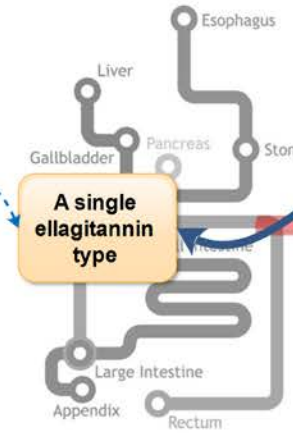



The dietary proanthocyanidin funnel: A great number of food sources yield a limited pattern of intestinal catabolites
Curry
Cinnamon
Spices
Cocoa
Beer
Cider
Wine
Beverages
Green Beans
Red Beans
Broad Beans
Vegetables
Hazelnuts
Pecans
Pistachios
Walnuts
Whole Nuts
Blueberries
Cloudberries
Strawberries
Currants
Grapes
Cranberries
Blackberries
Berries
Barley
Sorghum
Buckwheat
Whole Grains
Black Tea
Oolong Tea
Green Tea
Tea
Apples
Persimmons
Nectarines
Plums
Fruits
A variety of dietary sources
Esophagus
Liver
Gallbladder
Pancreas
Stomach
Small Intestine
Large Intestine
Appendix
Rectum
Few intestinal catabolites
Phenolic Acids
OH
OH
HOOC
OH
HOOC
H
N
O
Hippuric Acids
OH
OH
O
O
Valerolactones

The phytochemical fan of ellagitannins: A single molecule yields a wide range of intestinal catabolites

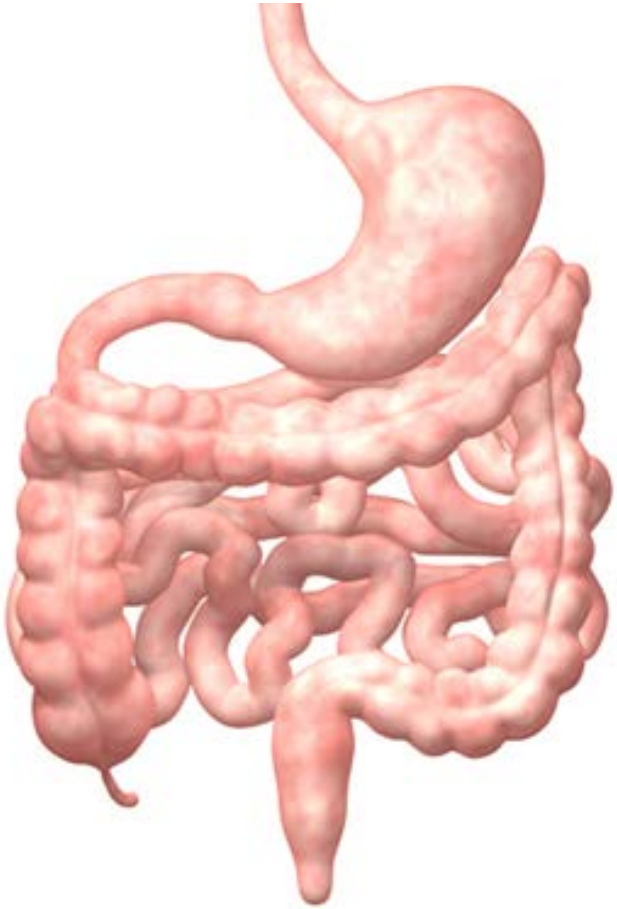


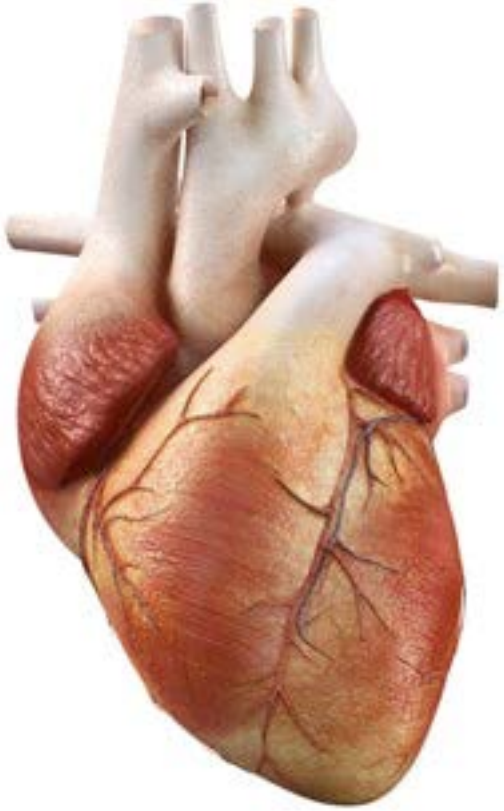
Sanguiin H-6



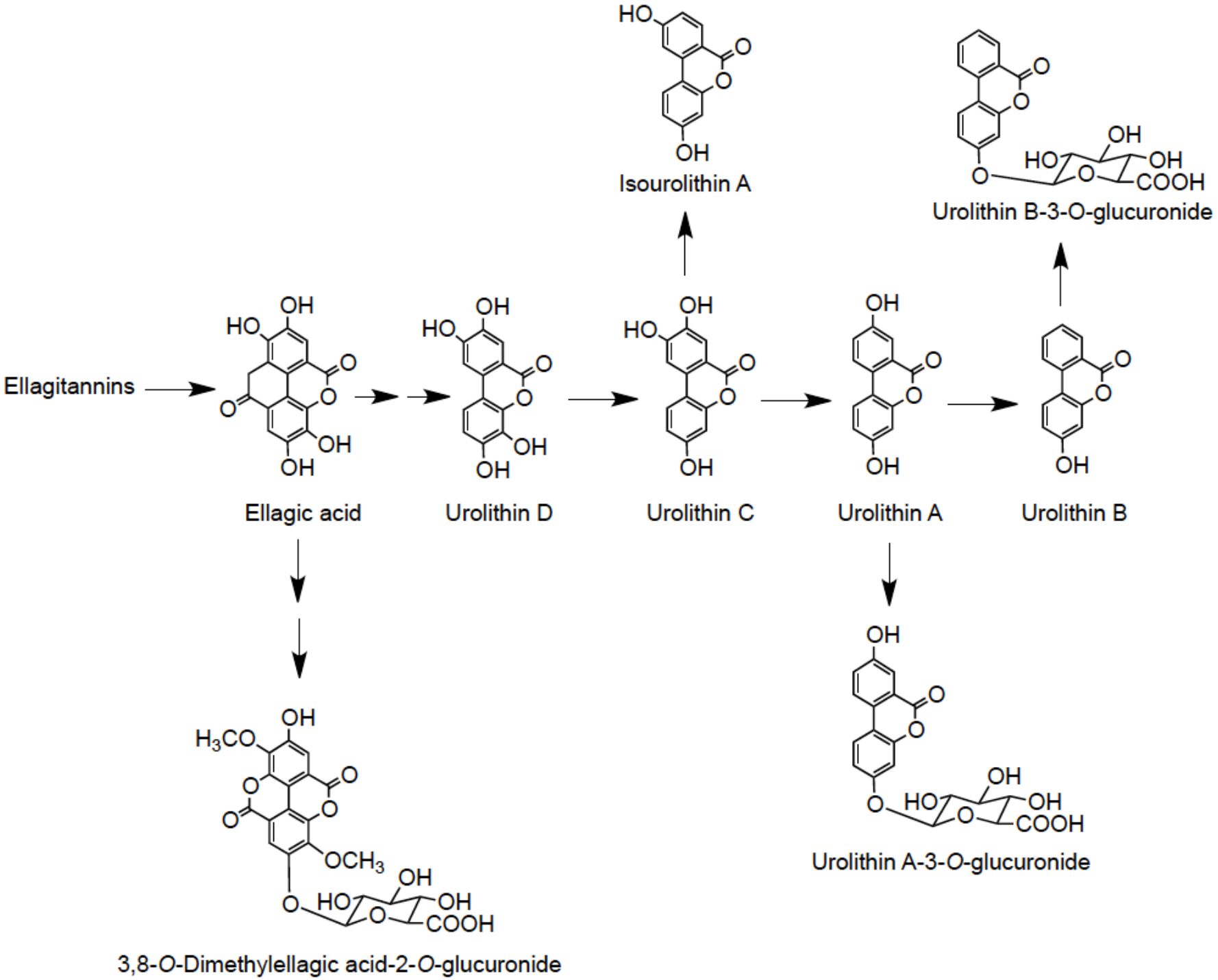
A number of catabolic endpoints

- Ellagic acid
- Gallic acid derivatives
- Urolithins
- Simple Phenols
  - Pyrogallol
  - Catechol





GUT – CV AXIS


Ellagitannins
Ellagic acid
Urolithin D
Urolithin C
Urolithin A
Urolithin B
Isourolithin A
Urolithin B-3-O-glucuronide
Urolithin A-3-O-glucuronide
3,8-O-Dimethylellagic acid-2-O-glucuronide

Savi *et al. Cardiovasc Diabetol (2017) 16:80*
DOI 10.1186/s12933-017-0561-3

Cardiovascular Diabetology

ORIGINAL INVESTIGATION Open Access

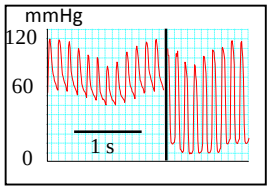
In vivo administration of urolithin A and B prevents the occurrence of cardiac dysfunction in streptozotocin-induced diabetic rats

Monia Savi[1,2†], Leonardo Bocchi[2†], Pedro Mena[1†], Margherita Dall'Asta[1], Alan Crozier[3], Furio Brighenti[1], Donatella Stilli[2*] and Daniele Del Rio[1*]

EXPERIMENTAL PROTOCOL

1. Hemodynamic measurements

CTRL, n=10
D3, n=9
D3_UA, n=8
D3_UB, n=9



2. Cardiomyocytes isolation, cell mechanics and Ca2+ transients

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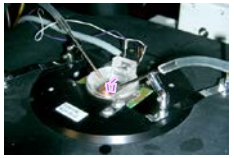
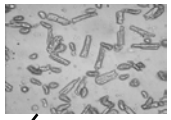
D3, n=8
D3_UA, n=5
D3_UB, n=4



Ion Optix system



Vehicle i.p. injection *(CTRL, n=10)*

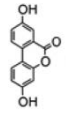
STZ i.p. injection (60mg/Kg; D3, n=29)

Glucose blood level measurement

48 hours

3 weeks

time



Uro A

UROLITHIN A i.p. ***daily injection*** (2.5mg/kg/gg) *(D3_UA, n=10)*

Uro B

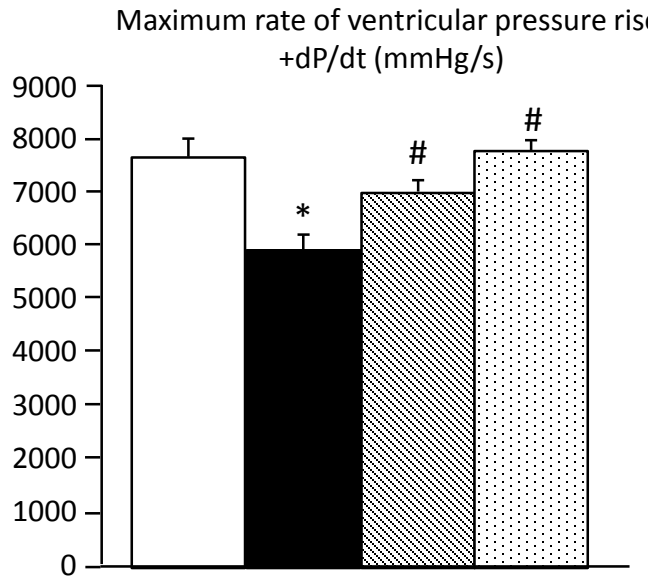
UROLITHIN B i.p. ***daily injection*** (2.5mg/kg/gg) *(D3_UB, n=10)*

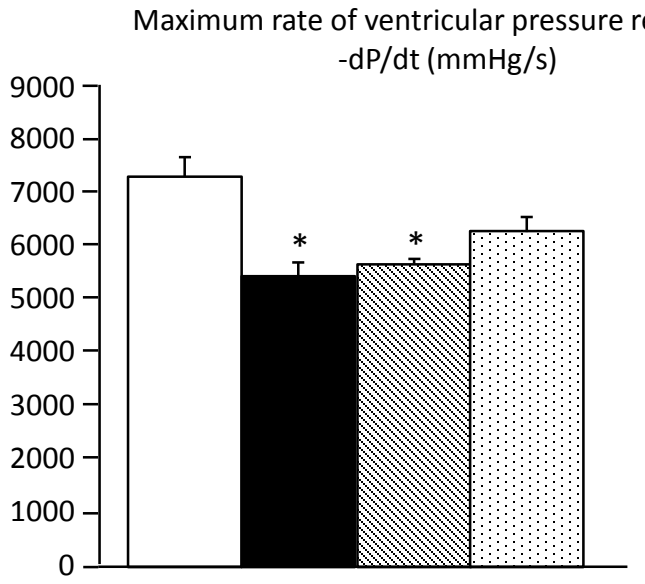
DIABETIC UNTREATED RATS
(D3, n=9)

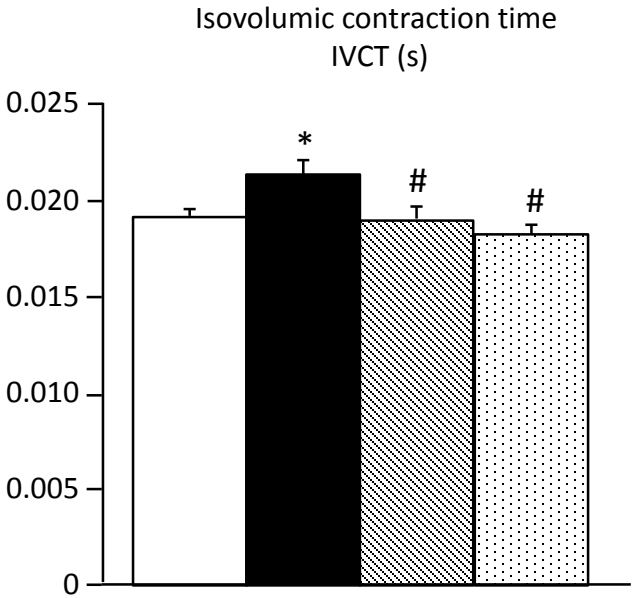
Savi *et al. Cardiovasc Diabetol (2017) 16:80*

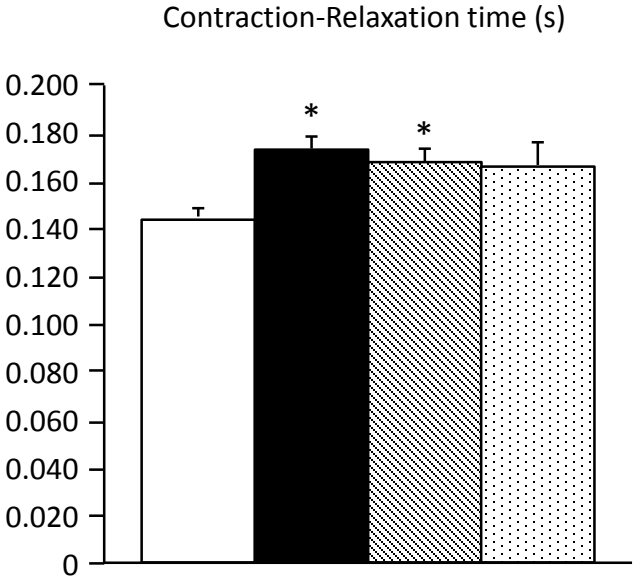
Acting Post-Doc: Dr. Monia Savi

Results: Hemodynamic measurements (Contraction rate)









CTRL (n=10)

D3 (n=9)

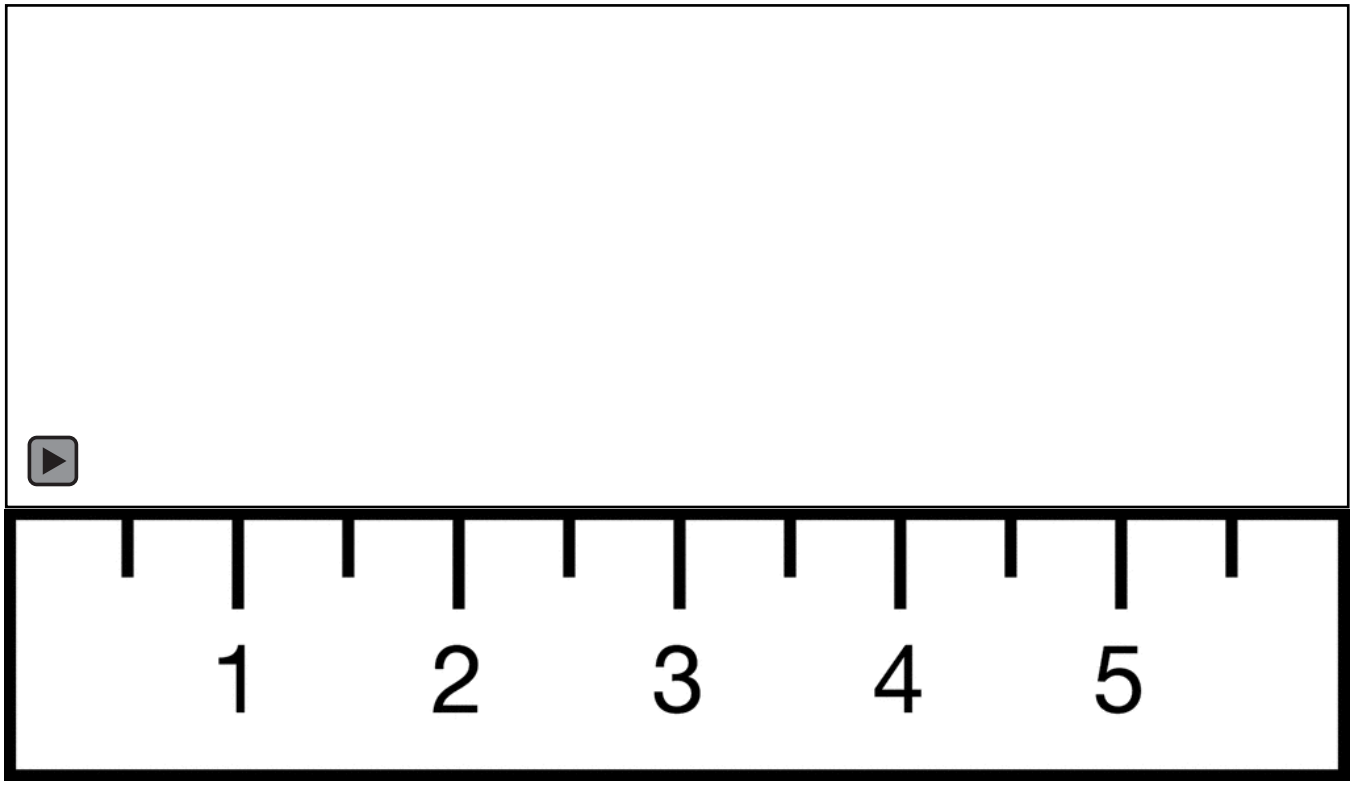
D3_UA (n=8)

D3_UB (n=9)

* p<0.05 vs CTRL

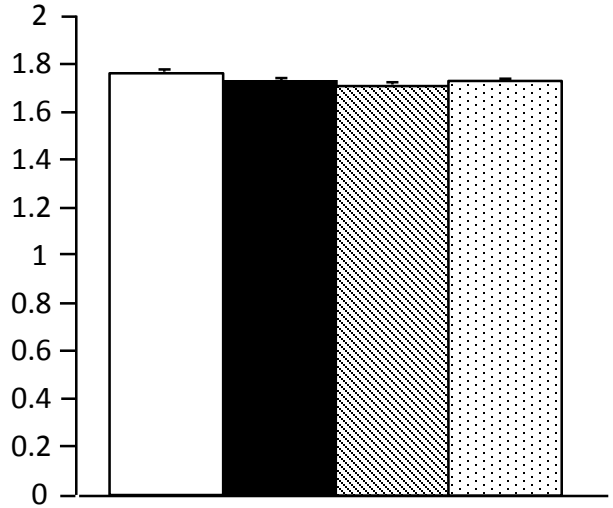
# p<0.05 vs D3

Cardiomyocytes isolation, cell mechanics

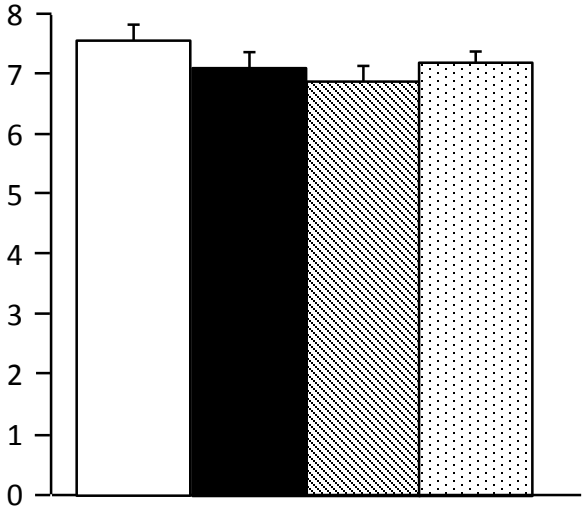


Results: Cell mechanics

Mean diastolic sarcomere length (µm)



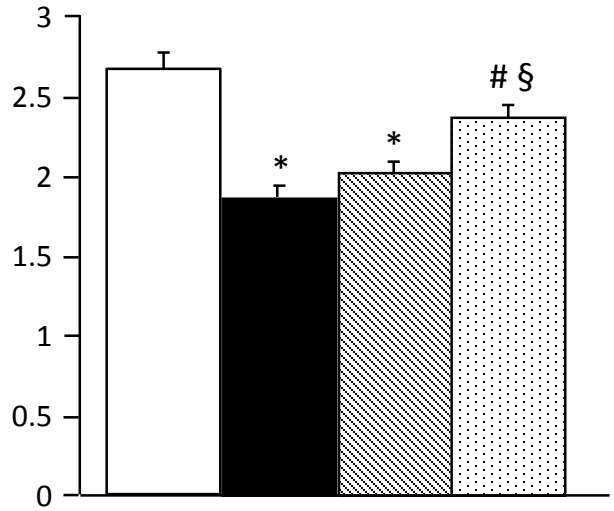
Fraction of Shortening (%)



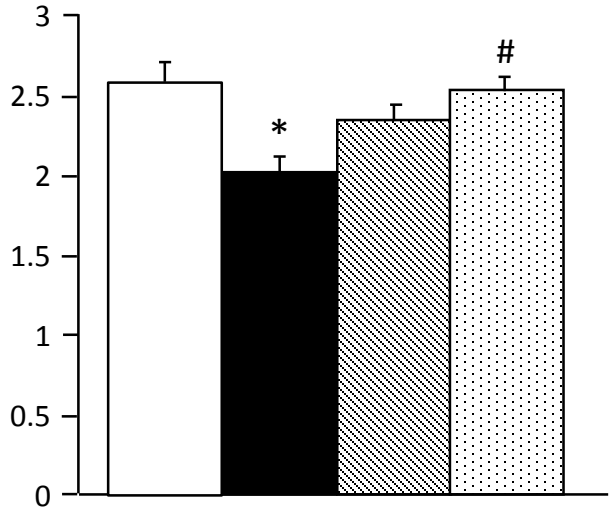
CTRL (n=66)
D3 (n=91)
D3_UA (n=100)
D3_UB (n=102)

* p<0.01 vs CTRL
# p<0.01 vs D3
§ p<0.01 vs D3_UA

-dL/dt (µm/s) (MAX RATE OF SHORTENING)



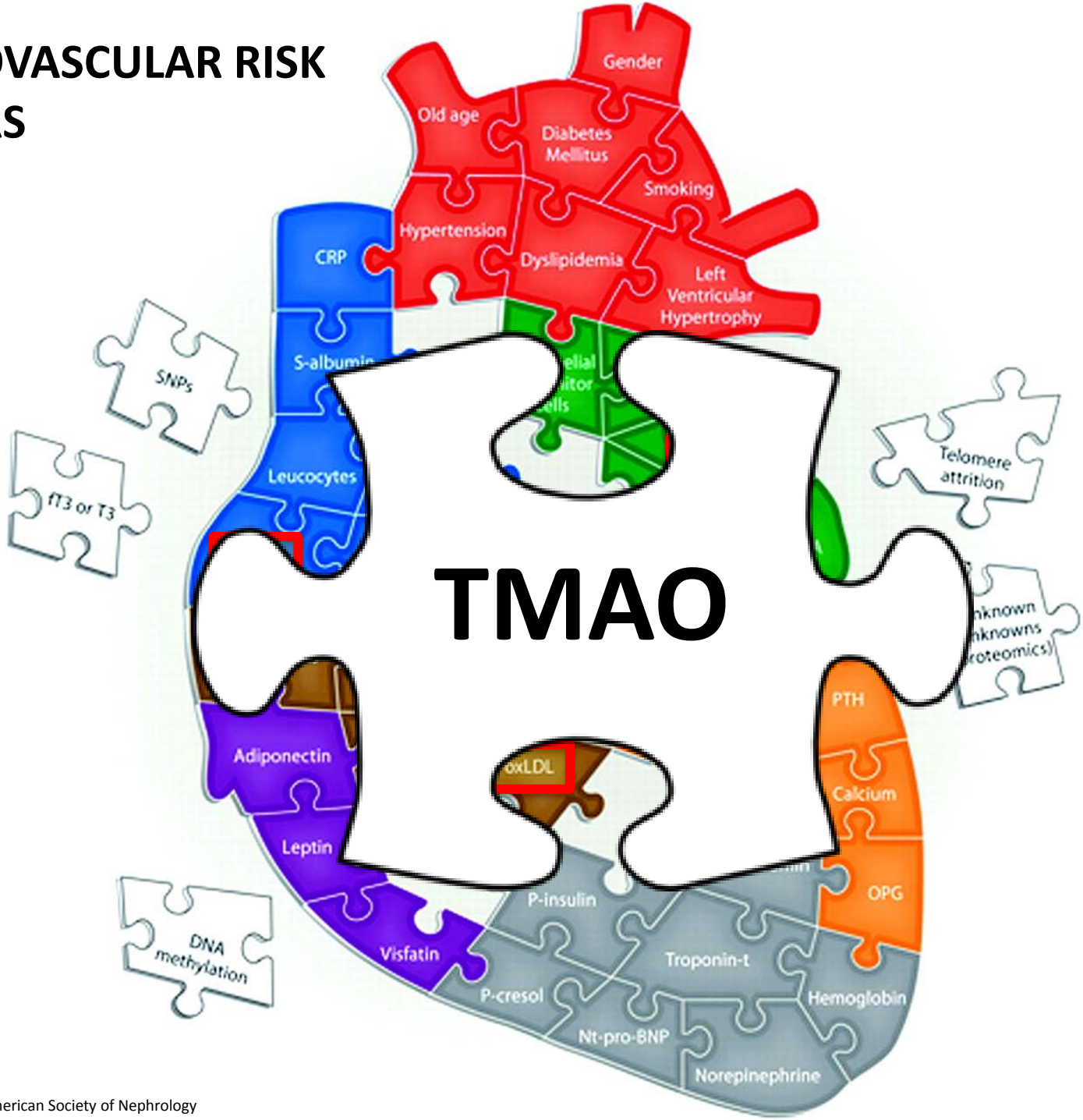
+dL/dt (µm/s) (MAX RATE OF RE-LENGTHENING)

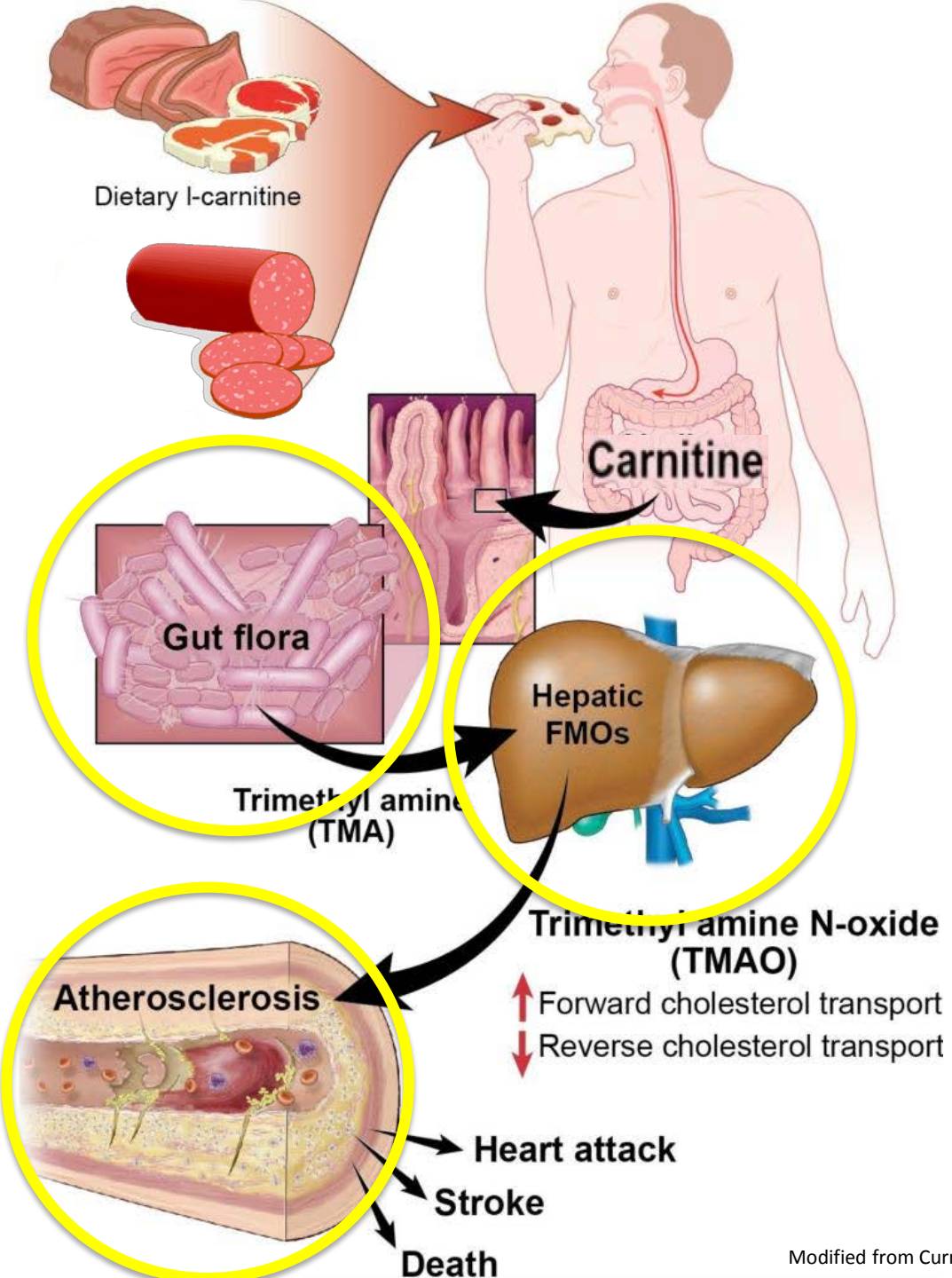


To sum up:

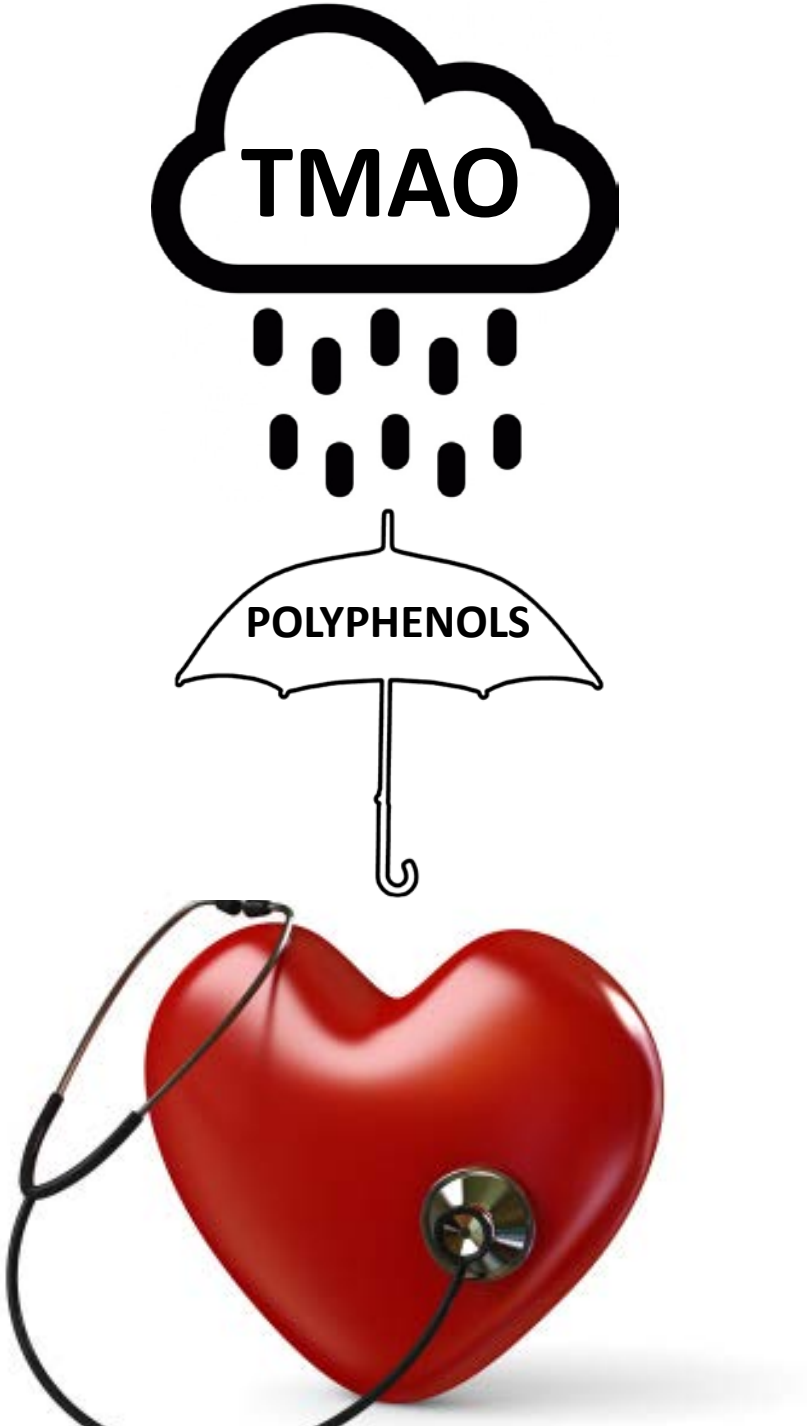
- Urolithin A and B contribute to a remarkable recovery of heart muscle function after DCM is induced.
- This effect involves calcium transient (as expected)
- ....possibly through actions involving SERCA phosphorilation and PLB
- ....with inflammation potentially involved in the model (Fractalkine).

CARDIOVASCULAR RISK FACTORS



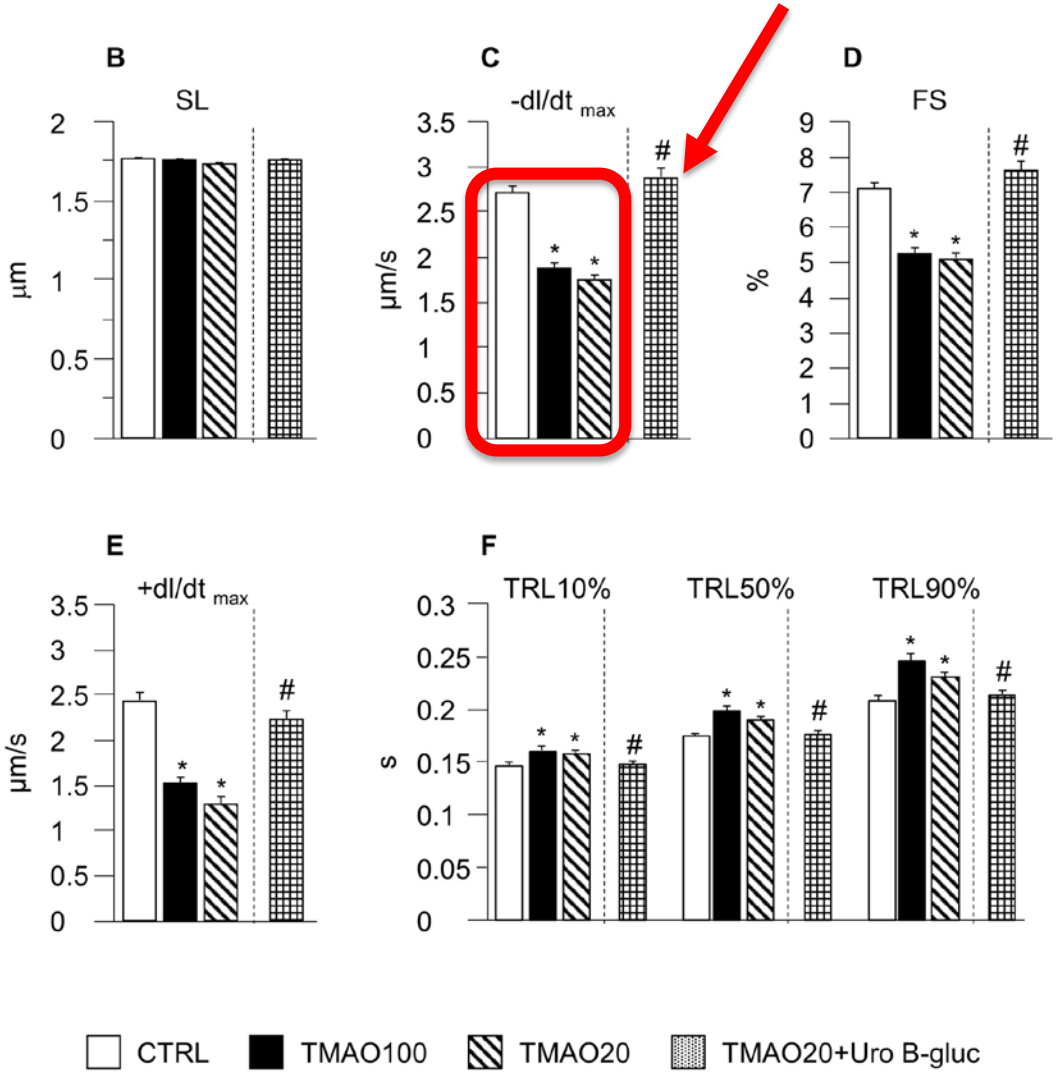


Modified from Curr Opin Lipidol. 2014 Feb; 25(1): 48–53.


TMAO
POLYPHENOLS

Trimethylamine-N-oxide (TMAO)-induced impairment of cardiomyocyte function and the protective role of urolithin B-glucuronide

Monia Savi[1,2‡], Leonardo Bocchi[2,‡], Letizia Bresciani[1], Angela Falco[3], Federico Quaini[3], Pedro Mena[1], Furio Brighenti[1], Alan Crozier[4], Donatella Stilli[2,*], Daniele Del Rio[1,*]



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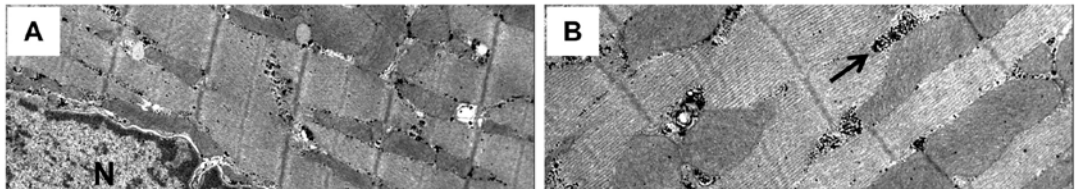
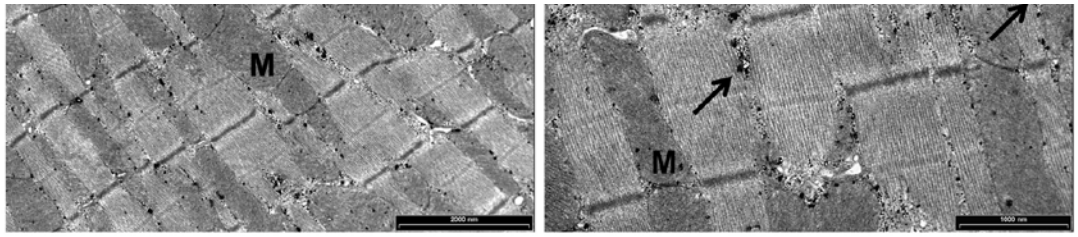




WORLD VIEW A personal take on events

Publish houses of brick, not mansions of straw

Papers need to include fewer claims and more proof to make the scientific literature more reliable, warns **William G. Kaelin Jr.**

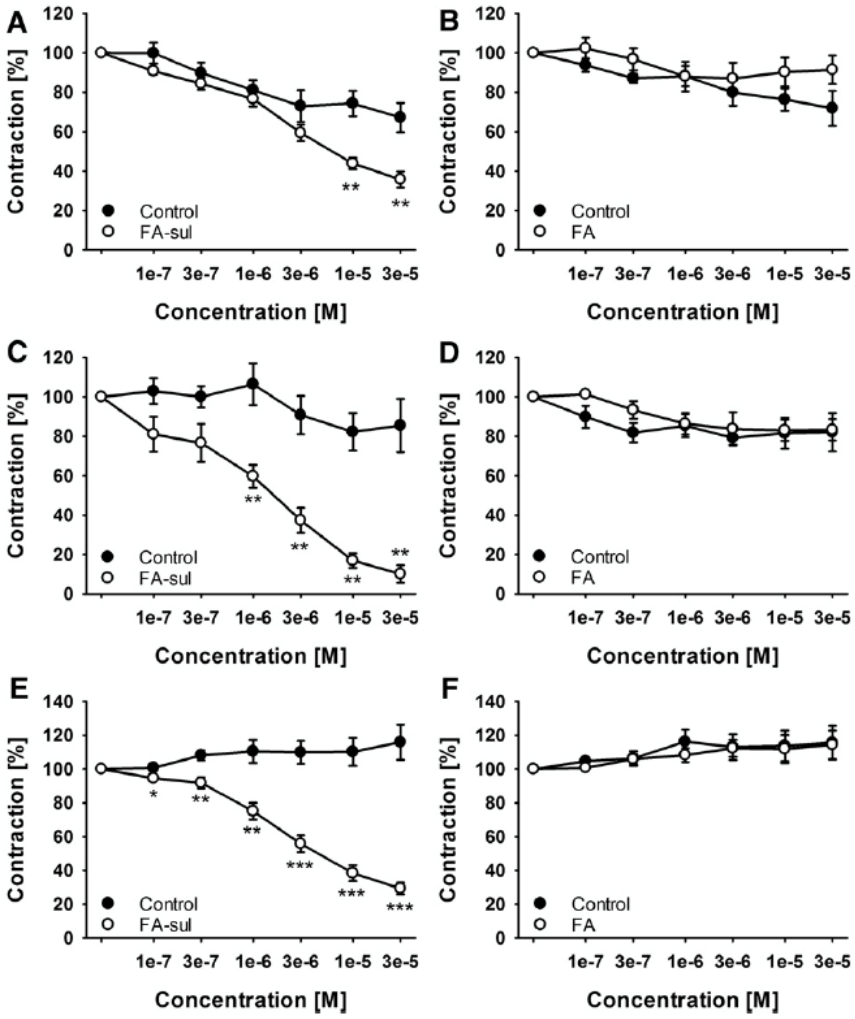
25 MAY 2017 | VOL 545 | NATURE | 387

"*the papers leading to [his] 2016 Lasker prize (with Gregg Semenza and Peter Ratcliffe, for discovering how cells sense oxygen) were published more than a decade ago. Most would be considered quaint, preliminary and barely publishable today. […] Fortunately, an experienced editor intervened, arguing that publication would open the search for the enzyme to other groups; such reprieves seem less common today.*".

Ferulic acid-4-*O*-sulfate rather than ferulic acid relaxes arteries and lowers blood pressure in mice☆,☆☆

Evelien Van Rymenant[a], John Van Camp[a], Bart Pauwels[b], Charlotte Boydens[b], Laura Vanden Daele[b], Katrijn Beerens[a], Peter Brouckaert[c], Guy Smagghe[d], Asimina Kerimi[e], Gary Williamson[e], Charlotte Grootaert[a], Johan Van de Voorde[b,*]

Journal of Nutritional Biochemistry 44 (2017) 44–51



Mouse saphenous artery

Mouse femoral artery

Mouse aorta

Human interventions…

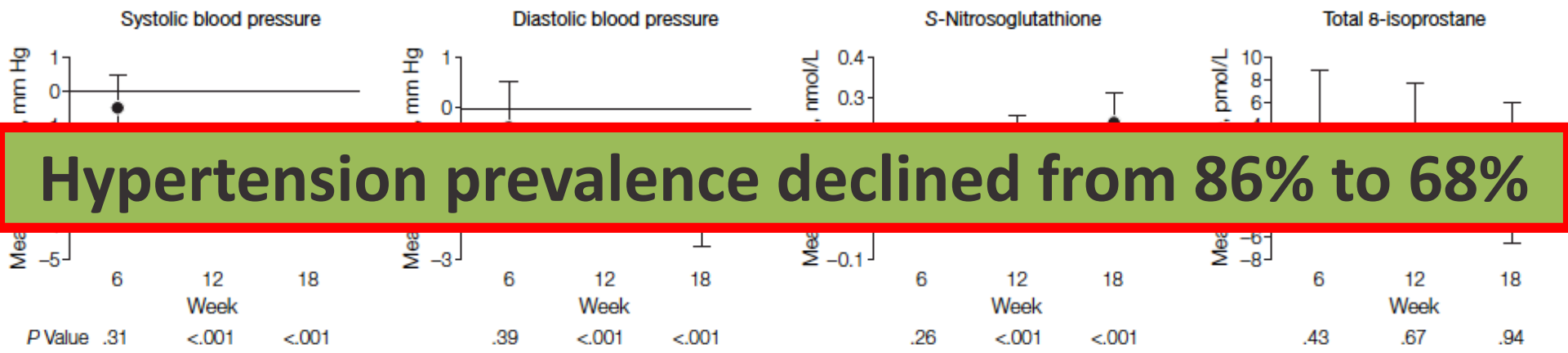
Effects of Low Habitual Cocoa Intake on Blood Pressure and Bioactive Nitric Oxide

A Randomized Controlled Trial

JAMA, July 4, 2007—Vol 298, No. 1

Dirk Taubert, MD, PhD
Renate Roesen, PhD
Clara Lehmann, MD
Norma Jung, MD
Edgar Schömig, MD

Figure 3. Between-Group Comparisons of Blood Pressure, *S*-Nitrosoglutathione, and Total 8-Isoprostane Levels After Dark and White Chocolate



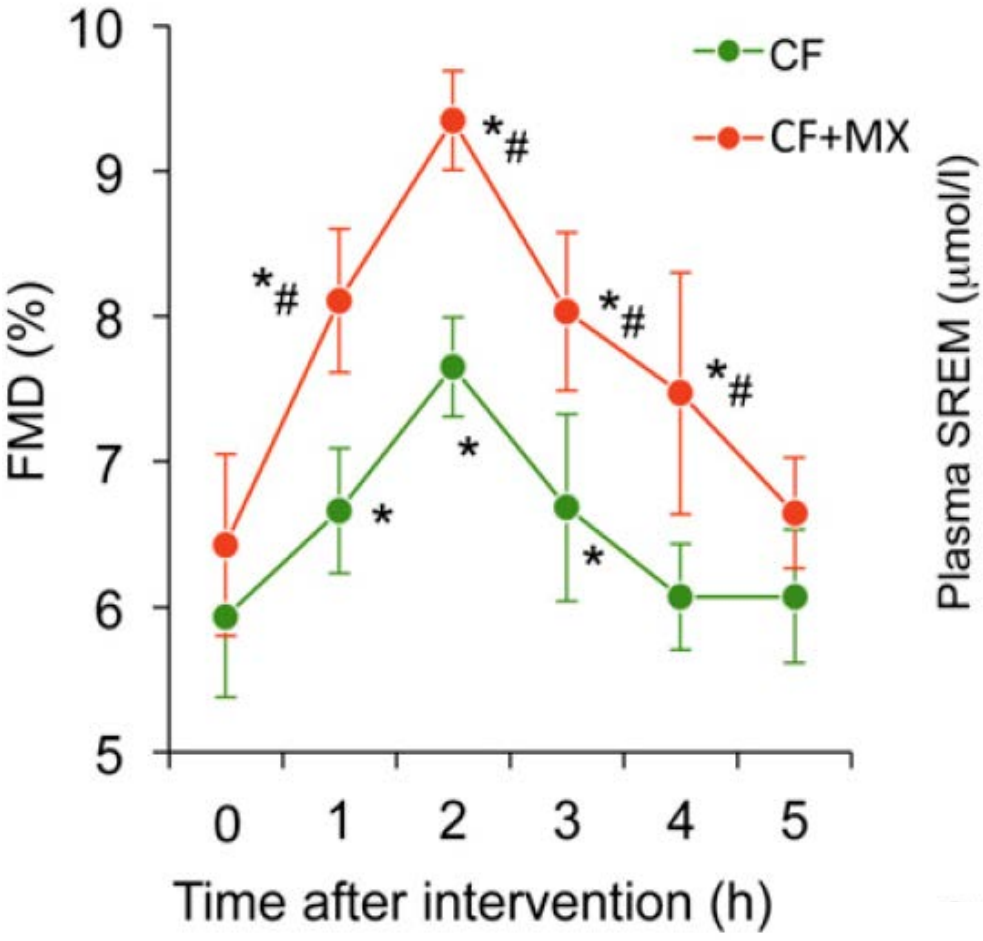
Hypertension prevalence declined from 86% to 68%

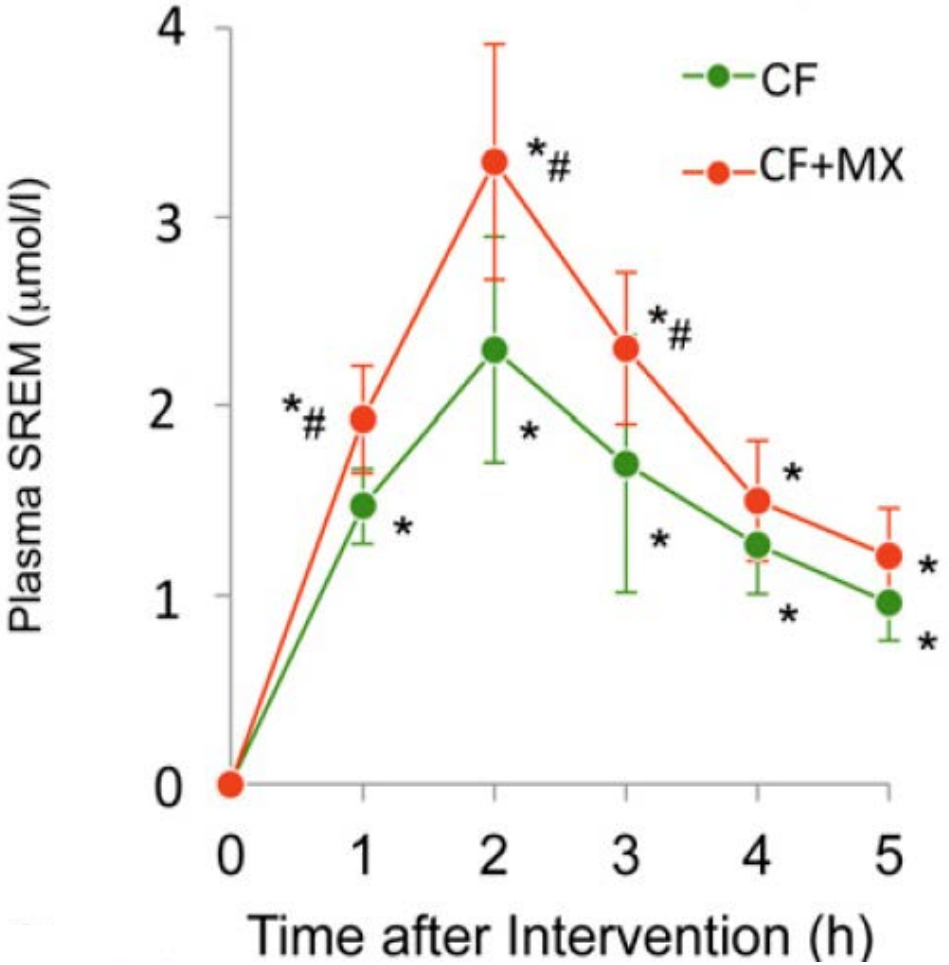
Error bars indicate 95% confidence intervals of differences in mean change scores. Nominal *P* values were calculated for pairwise between-group differences in change by 2-tailed *t* test.

Methylxanthines enhance the effects of cocoa flavanols on cardiovascular function: randomized, double-masked controlled studies[1]

*Roberto Sansone,[2] Javier I Ottaviani,[3] Ana Rodriguez-Mateos,[2,4] Yvonne Heinen,[2] Dorina Noske,[2] Jeremy P Spencer,[5] Alan Crozier,[6] Marc W Merx,[2] Malte Kelm,[2] Hagen Schroeter,[3] and Christian Heiss[2]**

Am J Clin Nutr 2017;105:352–60.

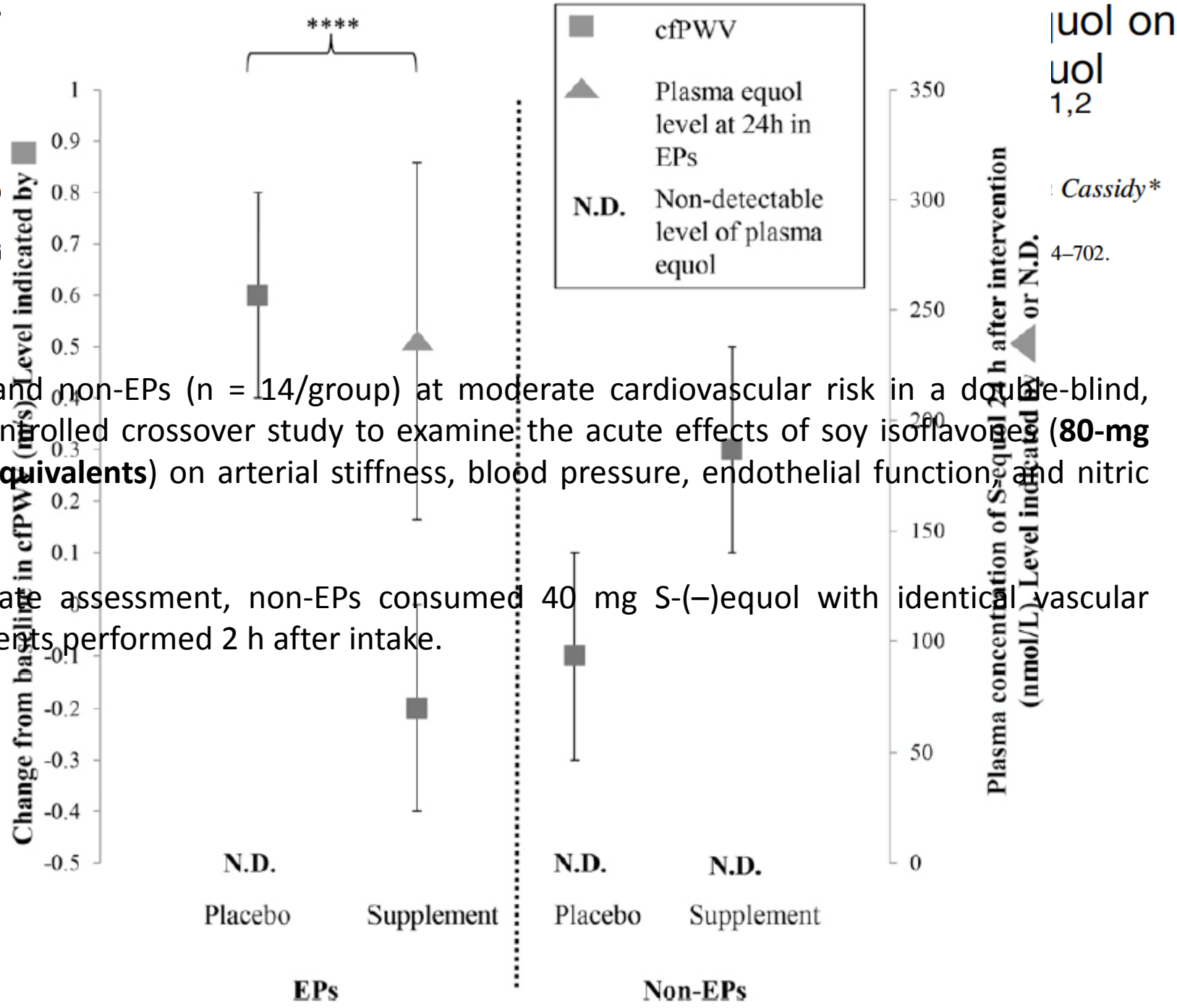




Acute ber … uol on
arterial sti … uol
producer … 1,2

*Sara Hazim,[3] Pet … Cassidy**

Department of Nutriti … 4–702.



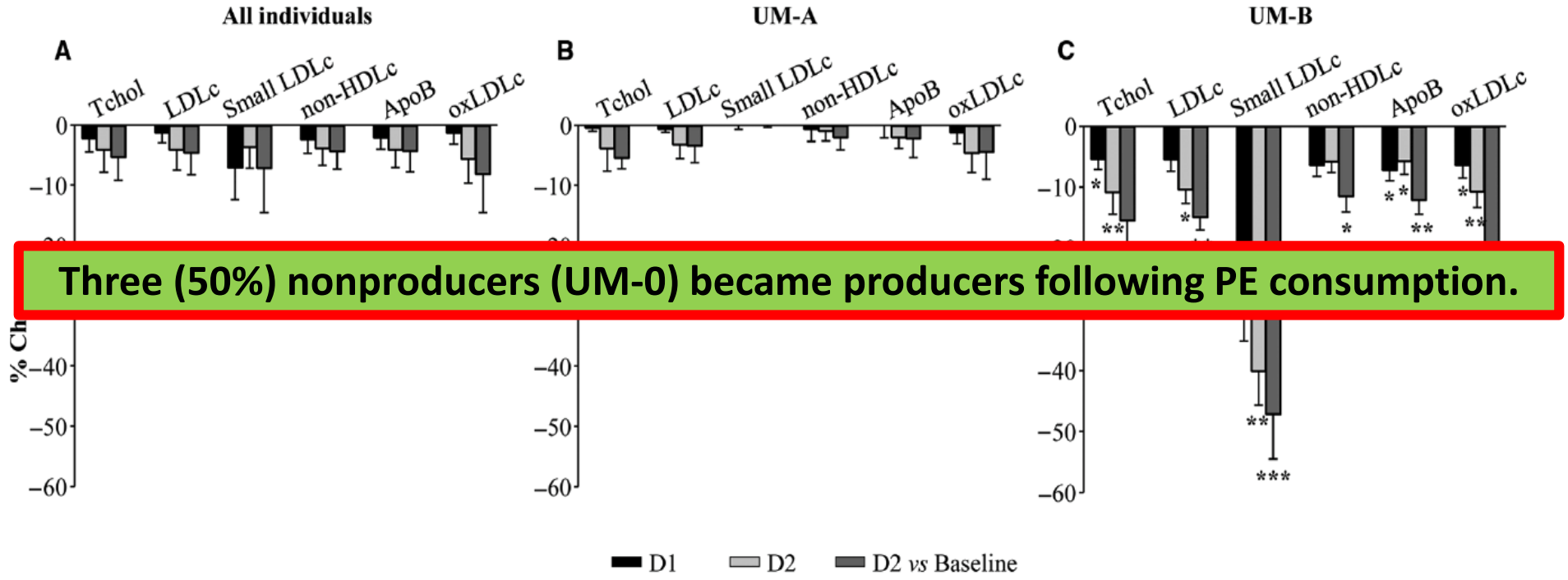
Male EPs and non-EPs (n = 14/group) at moderate cardiovascular risk in a double-blind, placebo controlled crossover study to examine the acute effects of soy isoflavones (**80-mg aglycone equivalents**) on arterial stiffness, blood pressure, endothelial function and nitric oxide.

In a separate assessment, non-EPs consumed 40 mg S-(–)equol with identical vascular measurements performed 2 h after intake.

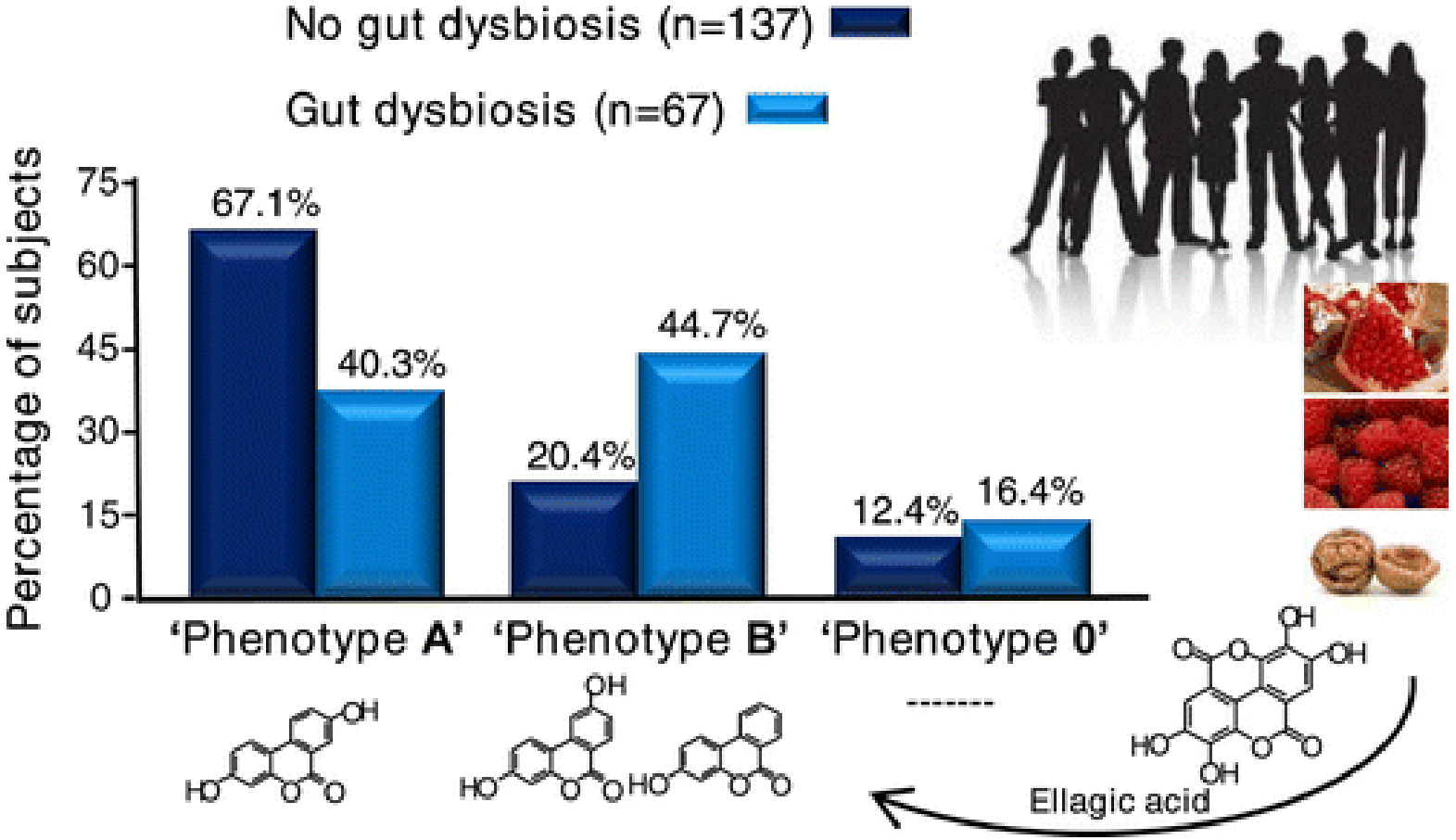
Clustering according to urolithin metabotype explains the interindividual variability in the improvement of cardiovascular risk biomarkers in overweight-obese individuals consuming pomegranate: A randomized clinical trial

Mol. Nutr. Food Res. 61, 5, 2017, 1600830

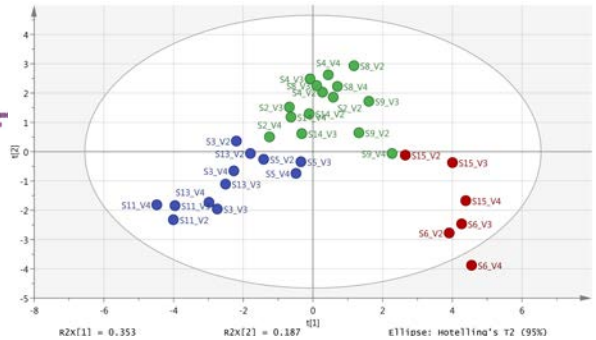
Antonio González-Sarrías[1], Rocío García-Villalba[1], María Romo-Vaquero[1], Cesarettin Alasalvar[2], Asim Örem[3], Pilar Zafrilla[4], Francisco A. Tomás-Barberán[1], María V. Selma[1] and Juan Carlos Espín[1]



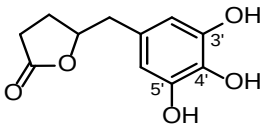
Three (50%) nonproducers (UM-0) became producers following PE consumption.

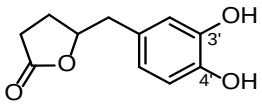


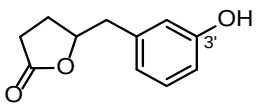
J. Agric. Food Chem., **2014**, *62* (28), pp 6535–6538 **DOI:** 10.1021/jf5024615

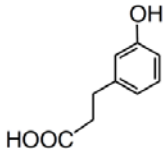


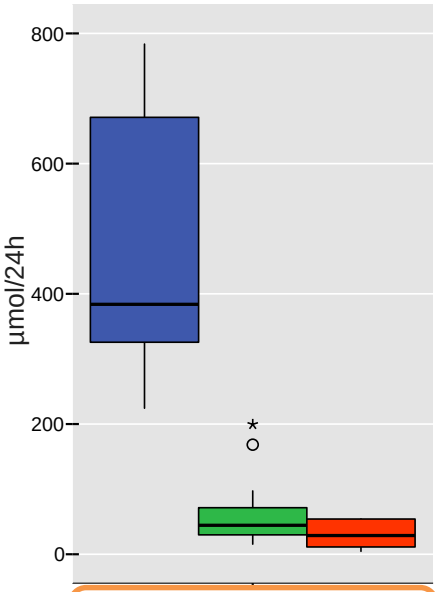
Subjects 2, 4, 8, 9, & 14 (n=15)
Subjects 3, 5, 11, & 13 (n=12)
Subjects 6 & 15 (n=6)





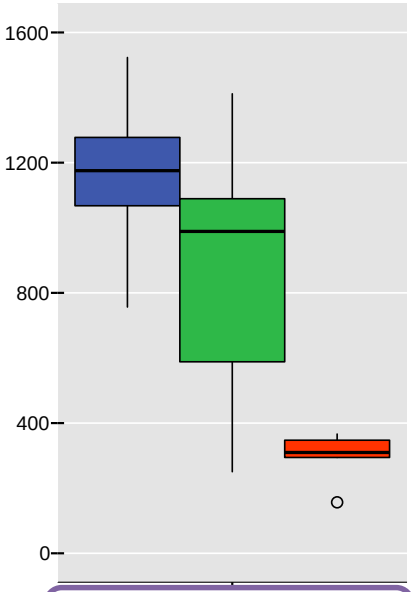






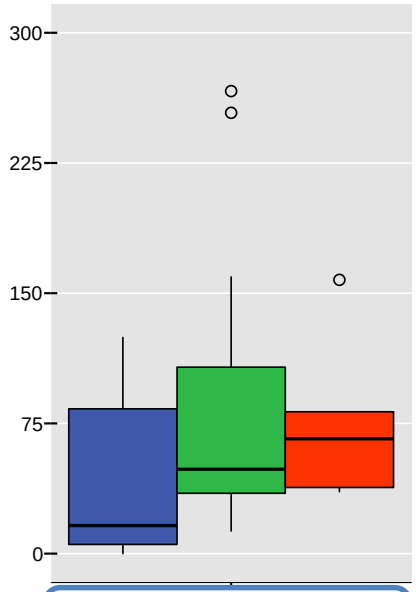
Trihydroxyphenyl-γ-valerolactone

-glucuronide
-methyl-sulfate



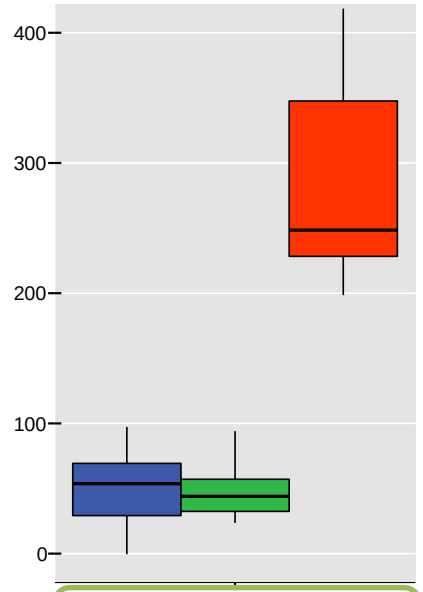
Dihydroxyphenyl-γ-valerolactone

-glucuronide
-disulfate
-sulfate-glucuronide



Monohydroxyphenyl-γ-valerolactone

-glucuronide
-sulfate



Hydroxyphenyl propionic acid

-sulfate

- *Plausible mechanisms of actions!*
- *Critical mass of observational results*
- *Well designed and well conducted intervention studies!*

- ***<u>Better understanding of the involvement of the gut microbiota</u>***

&

- ***<u>Interindividual variability clear in mind!!</u>***

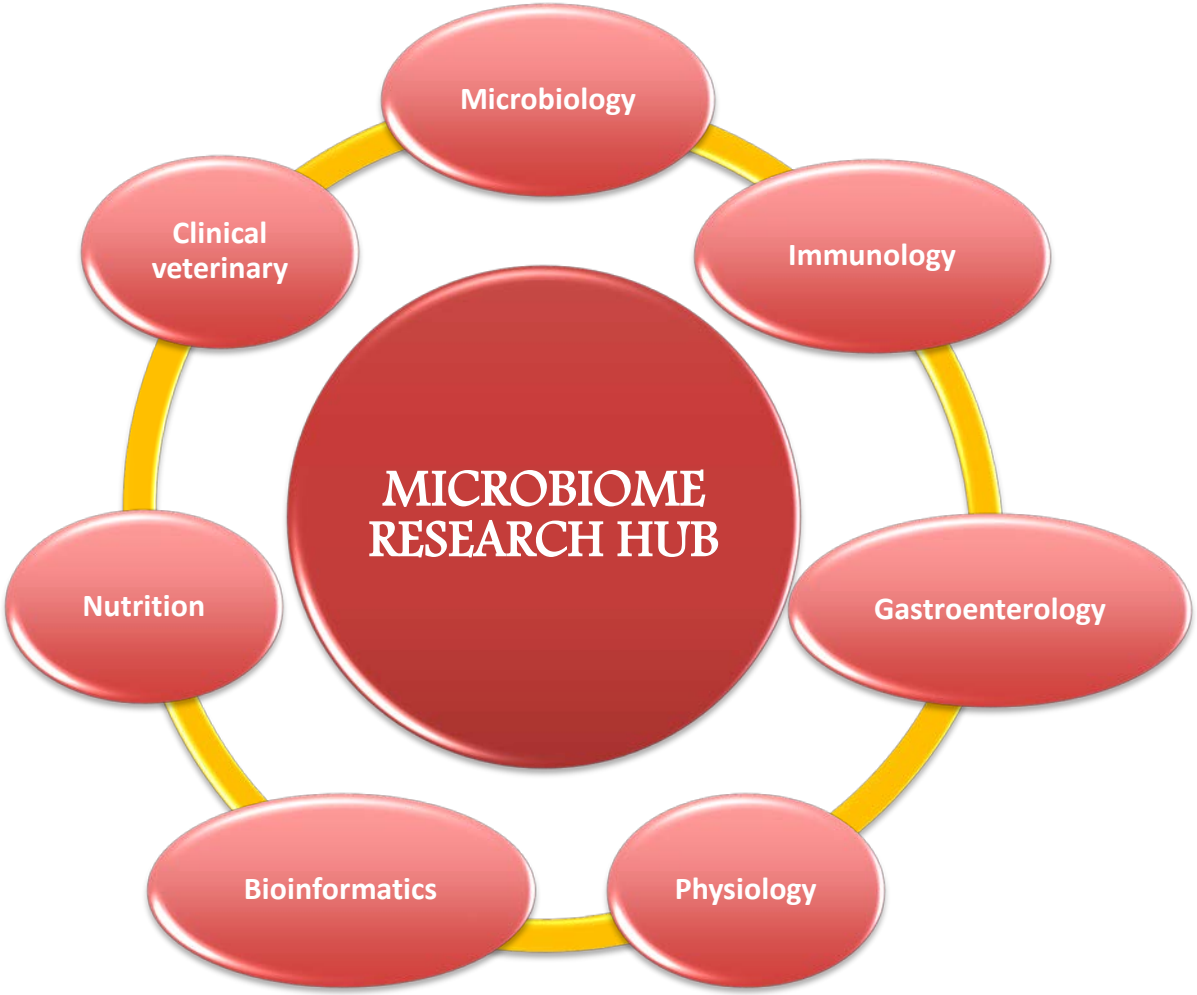
Despite the very bad science performed to date….

It could work!

Microbiome Research Hub

A new Microbiome Research Centre at the University of Parma

MICROBIOME
Research Hub



Thanks to….my personal microbiota!