CiBari
il cibo della salute

edizione 3ª

Nutri Previeni

Dimmi cosa fa il tuo microbiota e ti dirò chi sei!

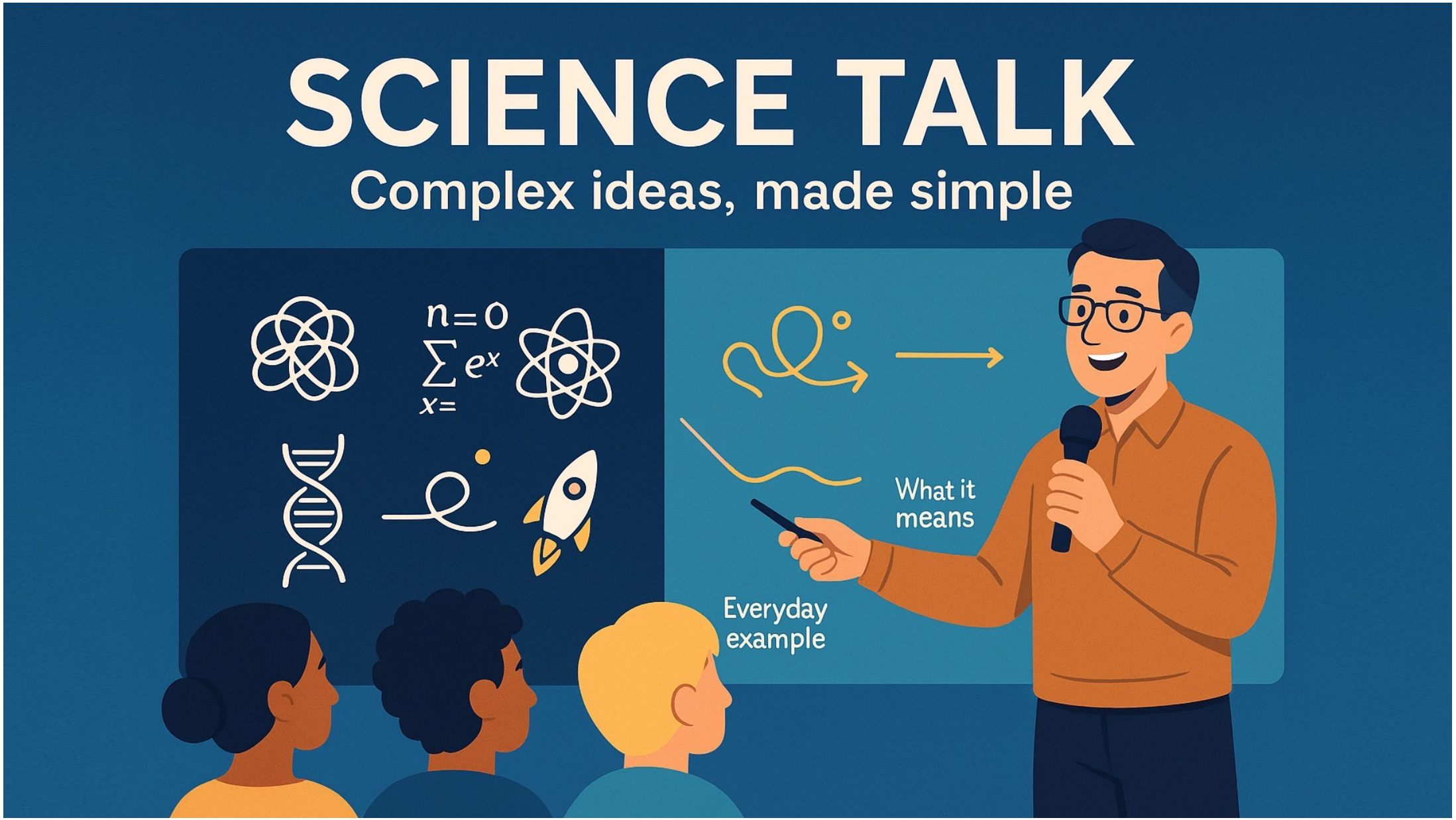
Un esempio di nutrizione di precisione

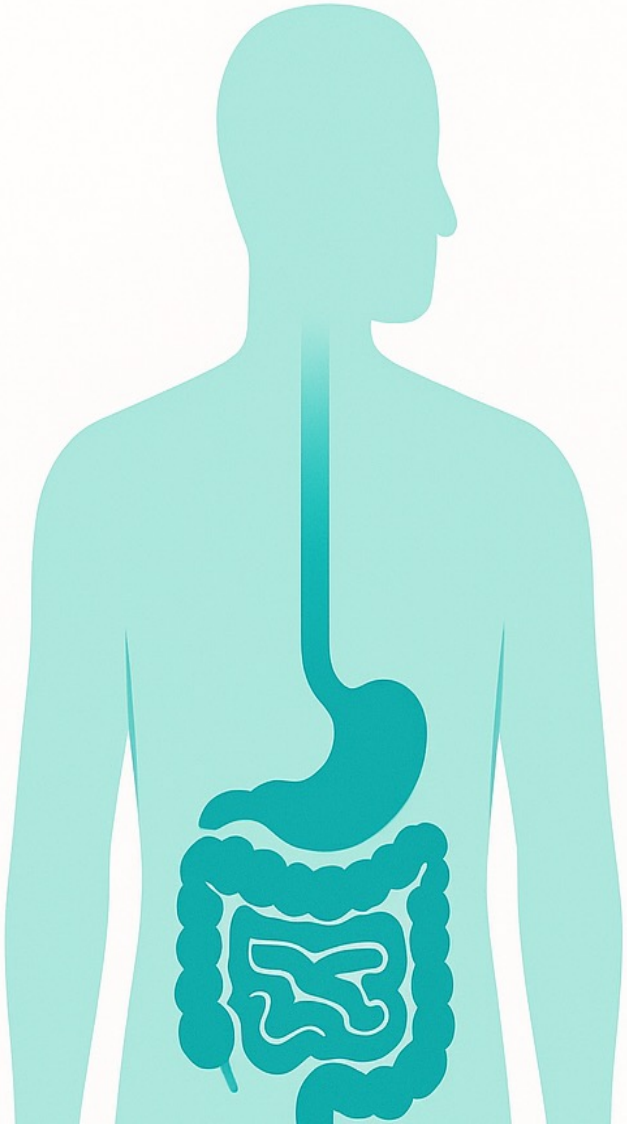
Daniele Del Rio

Università di Parma
Fondazione OnFoods

No Conflicts of Interest

UN CONFLITTO CON LA SCIENZA...


SCIENCE TALK
Complex ideas, made simple
What it means
Everyday example



What is the gut microbiota?

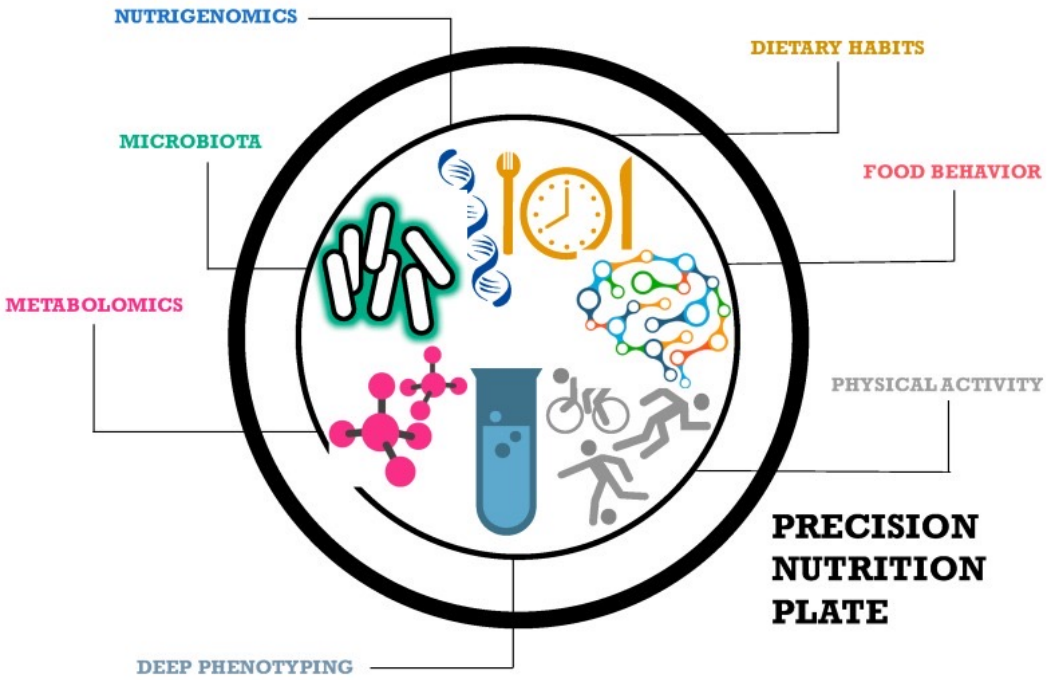
Il **microbiota intestinale** è la comunità di microrganismi, principalmente batteri, ma anche archei, virus e funghi, che vivono nel tratto gastrointestinale, in particolare nel colon. Come ecosistema, aiutano a scomporre composti altrimenti indigeribli (la fibra), **producono metaboliti**, modellano lo sviluppo immunitario e la funzione della barriera intestinale e forniscono resistenza contro i patogeni. **La sua composizione e attività variano tra le persone e nel tempo**, influenzate da fattori come età, dieta, farmaci (ad esempio antibiotici) e malattie, ma anche in funzione della genetica dell'ospite. Le alterazioni di questo equilibrio sono associate a diversi disturbi.

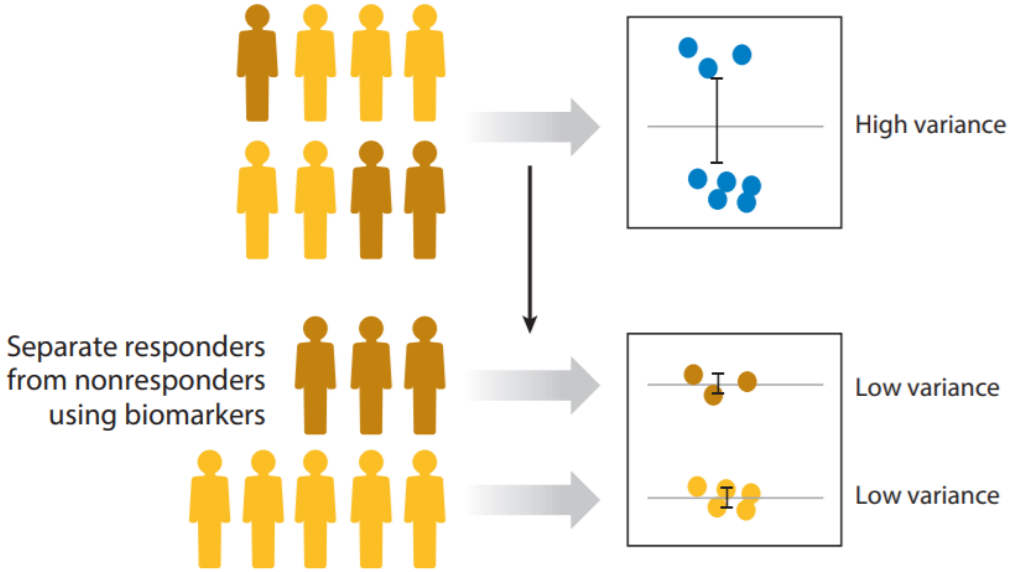
WHAT IS PRECISION NUTRITION?

La **nutrizione di precisione** è un approccio basato sull'evidenza scientifica che personalizza le raccomandazioni nutrizionali in base alla composizione genetica unica, al metabolismo, **al microbiota**, allo stile di vita e allo stato di salute di ciascuno, al fine di ottimizzare i risultati per la salute.

Personalizza l'alimentazione a livello molecolare e metabolico!

Precision nutrition



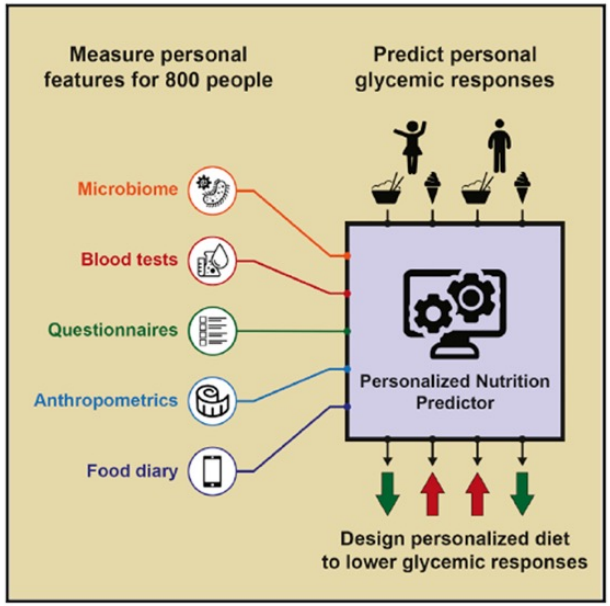


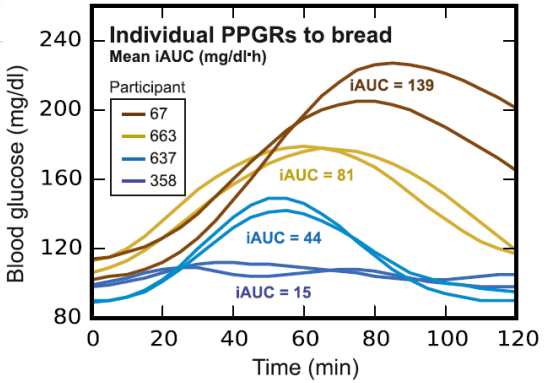
de Toro-Martín et al. (2017). Nutrients 9(8): 913.

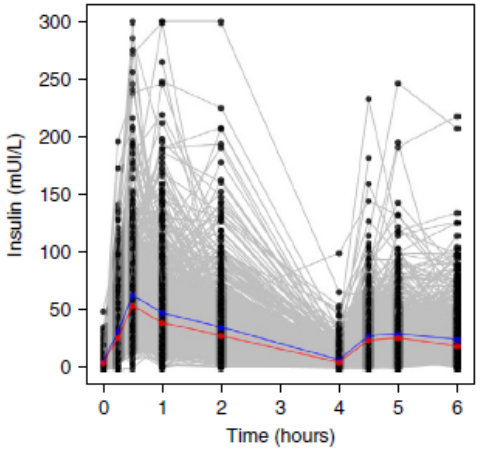
Nutrizione di precisione (esempi?)

Personalized Nutrition by Prediction of Glycemic Responses

David Zeevi,[1,2,8] Tal Korem,[1,2,8] Niv Zmora,[3,4,5,8] David Israeli,[6,8] Daphna Rothschild,[1,2] Adina Weinberger,[1,2] Orly Ben-Yacov,[1,2] Dar Lador,[1,2] Tali Avnit-Sagi,[1,2] Maya Lotan-Pompan,[1,2] Jotham Suez,[3] Jemal Ali Mahdi,[3] Elad Matot,[1,2] Gal Malka,[1,2] Noa Kosower,[1,2] Michal Rein,[1,2] Gili Zilberman-Schapira,[3] Lenka Dohnalová,[3] Meirav Pevsner-Fischer,[3] Rony Bikovsky,[1,2] Zamir Halpern,[5,7] Eran Elinav,[3,9,*] and Eran Segal[1,2,9,*]



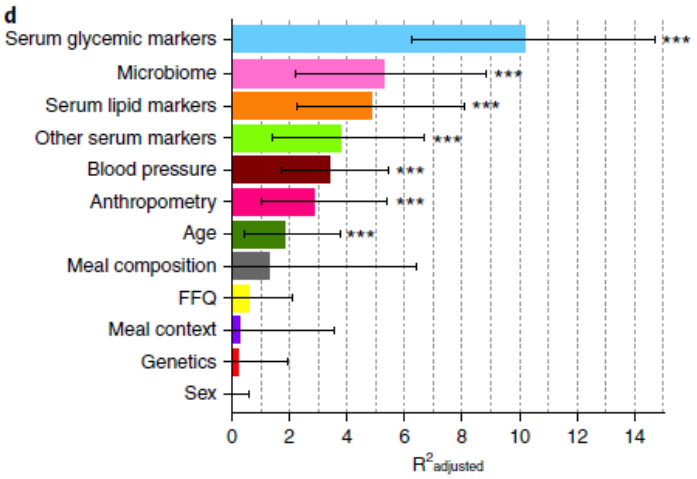




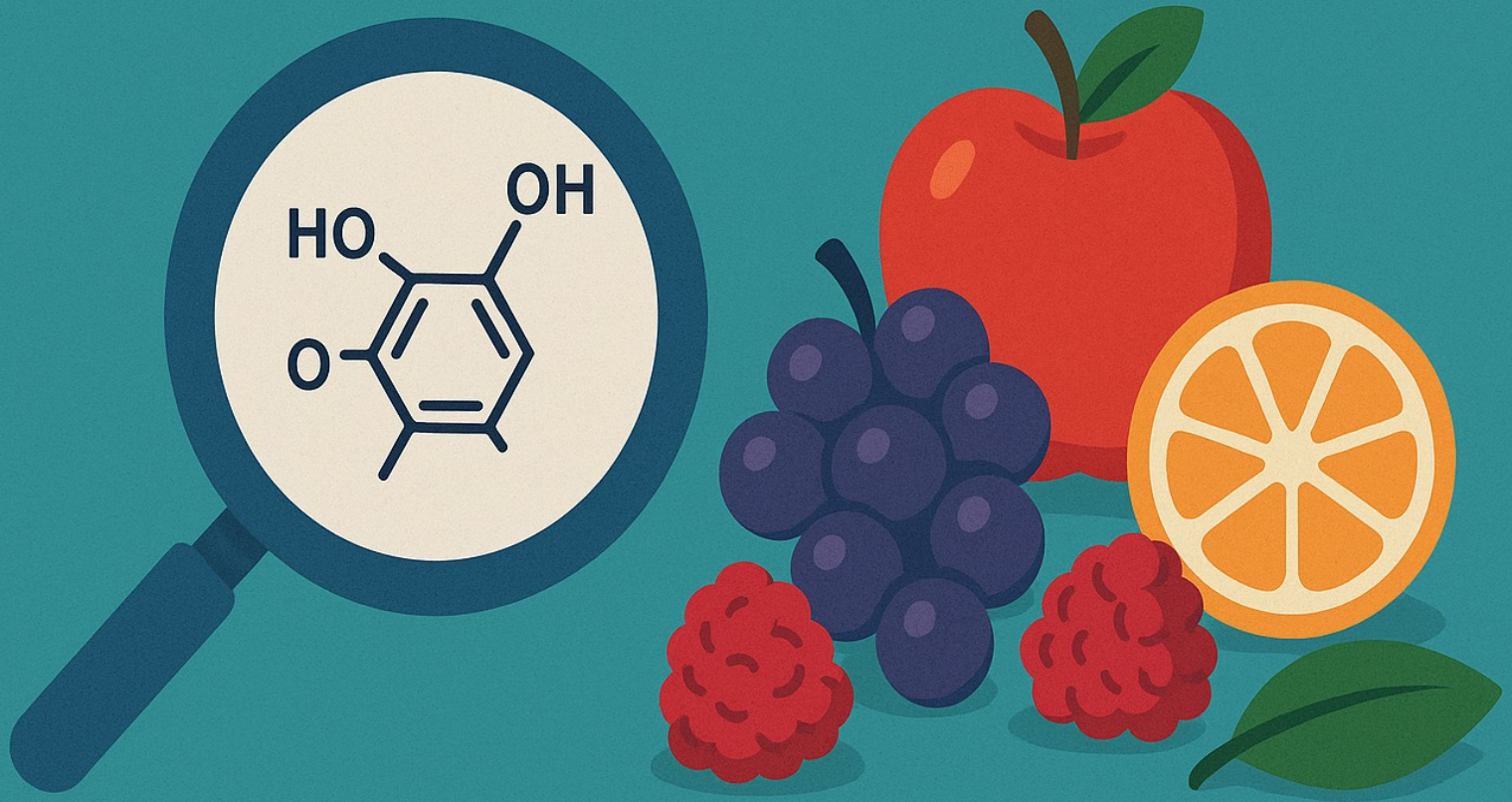
nature medicine
ARTICLES
https://doi.org/10.1038/s41591-020-0934-0
Check for updates

Human postprandial responses to food and potential for precision nutrition

Sarah E. Berry[1,15], Ana M. Valdes[2,3,15] ✉, David A. Drew[4], Francesco Asnicar[5], Mohsen Mazidi[6], Jonathan Wolf[7], Joan Capdevila[7], George Hadjigeorgiou[7], Richard Davies[7], Haya Al Khatib[1,7], Christopher Bonnett[7], Sajaysurya Ganesh[7], Elco Bakker[7], Deborah Hart[6], Massimo Mangino[6], Jordi Merino[4,8,9], Inbar Linenberg[7], Patrick Wyatt[7], Jose M. Ordovas[10,11], Christopher D. Gardner[12], Linda M. Delahanty[4], Andrew T. Chan[4], Nicola Segata[5,15], Paul W. Franks[6,13,14,15] and Tim D. Spector[6,15] ✉

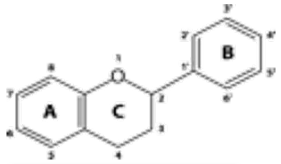


What Are Polyphenols?



(Poly)phenols

Flavonoids



- A. Flavones
- B. Flavonols
- C. Flavan-3-ols and Proanthocyanidins
- D. Flavanones
- E. Isoflavones
- F. Anthocyani(di)ns







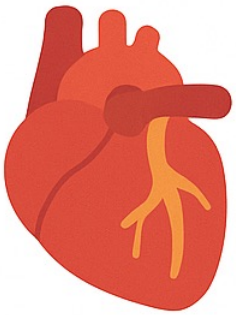
Non Flavonoids

- Phenolic Acids
- Stilbenes
- Lignans



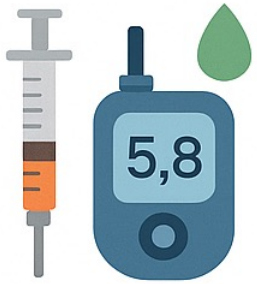

DIETARY POLYPHENOLS

Protective health contexts

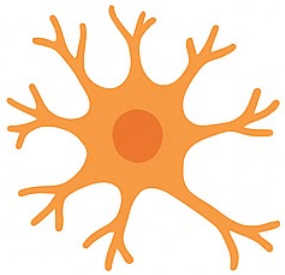


Cardiovascular

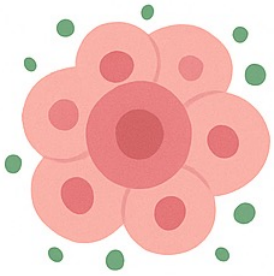
Cerebrovascular



Diabetes

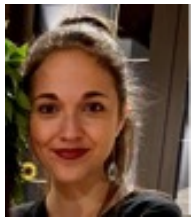


Neurodegenerative



Cancer

Phenolic compounds: human metabolism and bioavailability



Nicole Tosi

(Poly)phenol intake

Ingestion

Oral cavity

Esophagus

Liver

Kidney

Stomach

Pancreas

Small intestine

Large intestine

Rectum

Anus

Esophageal and gastric transit: stability

Gut microbiota catabolism:
- hydrolysis
- ring fission (A/C rings)
- demethylation
- dehydroxylation
- oxidation of the lateral chain
- reduction of double bonds
- isomerization
- decarboxylation

LPH, CBG, MRP2/3, P-gp, BCRP, GLUT2

Deglycosylation + absorption (<5%)

Microbial catabolism + absorption

Excretion of undigested/ unabsorbed compounds

Structurally-related (poly)phenol metabolites

Ring-fission catabolites

SULTs, UGTs, COMT

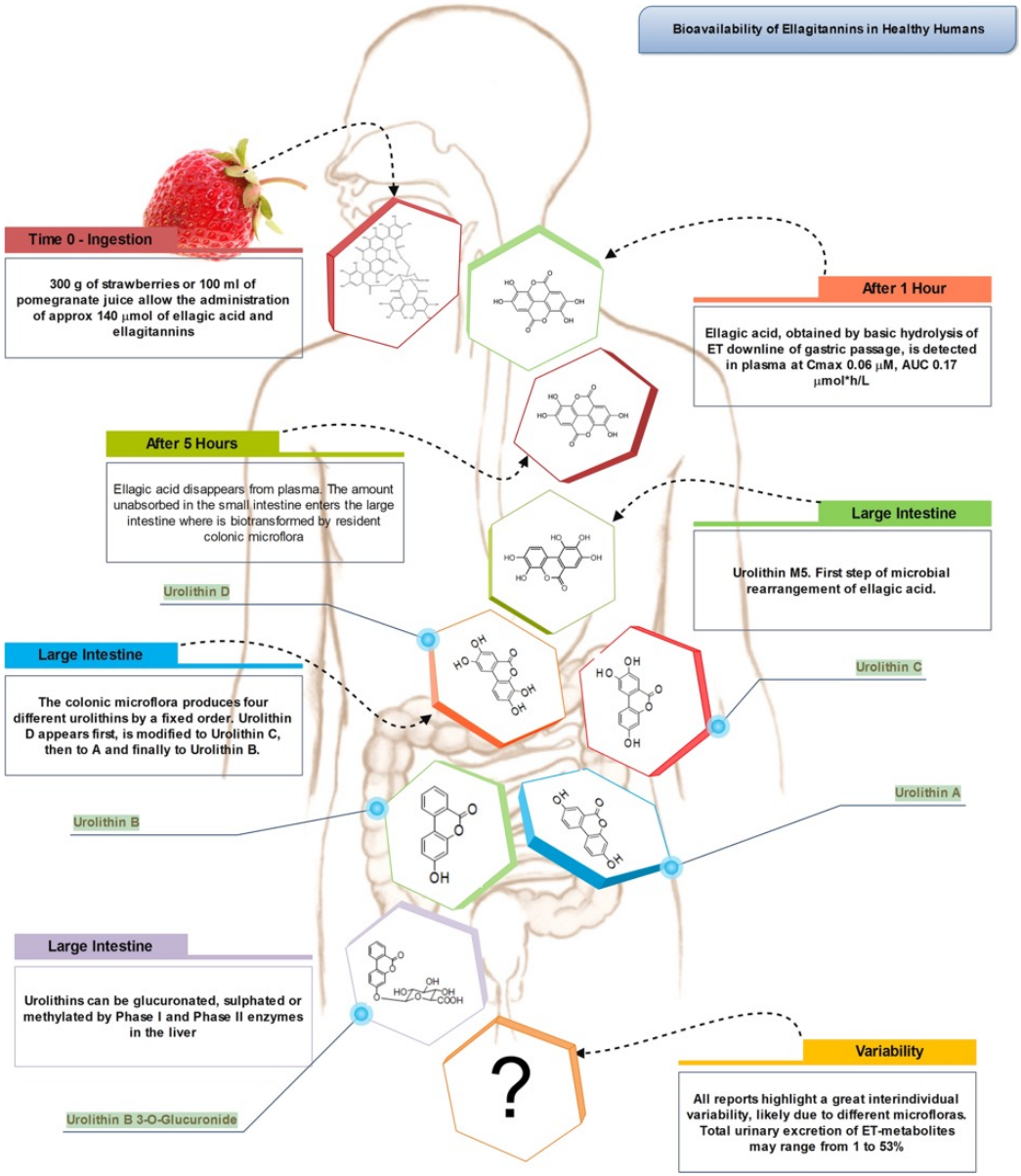
Human phase II metabolism

Target cells

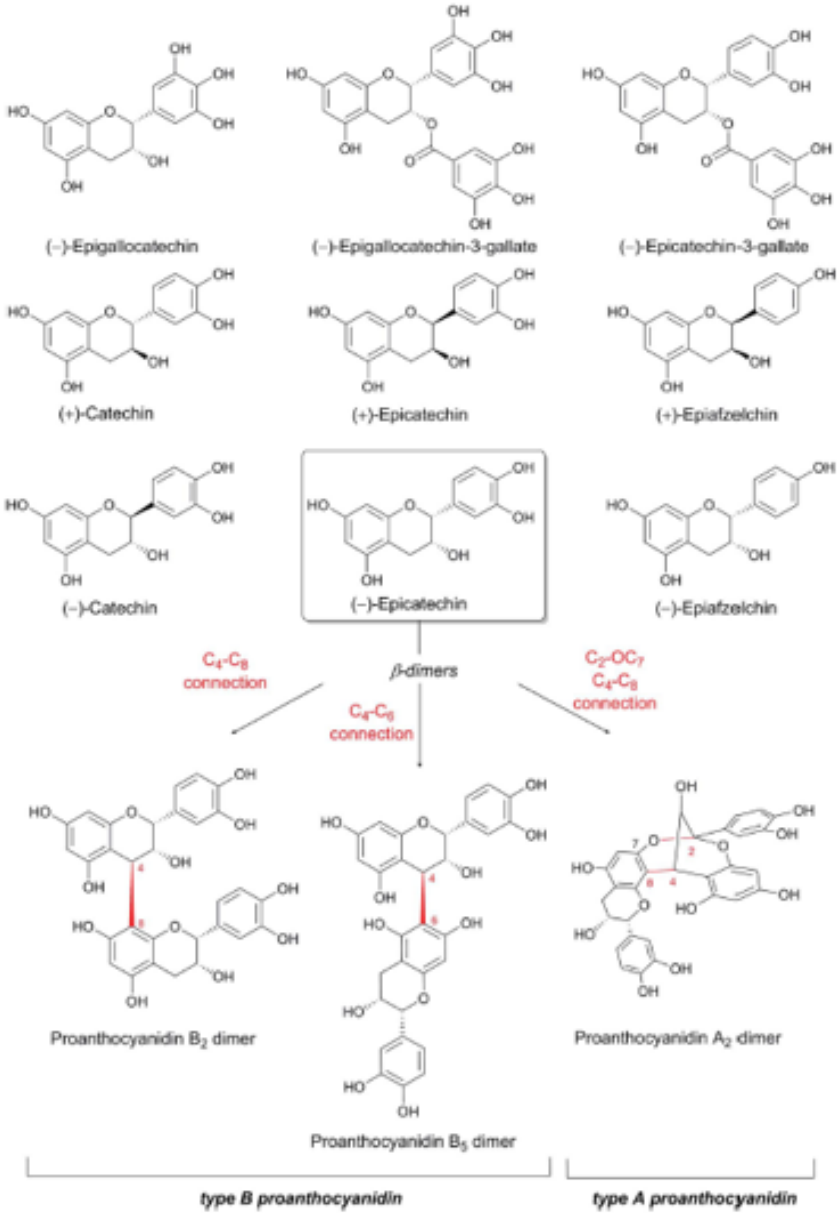
OATs, OATPs, MRPs

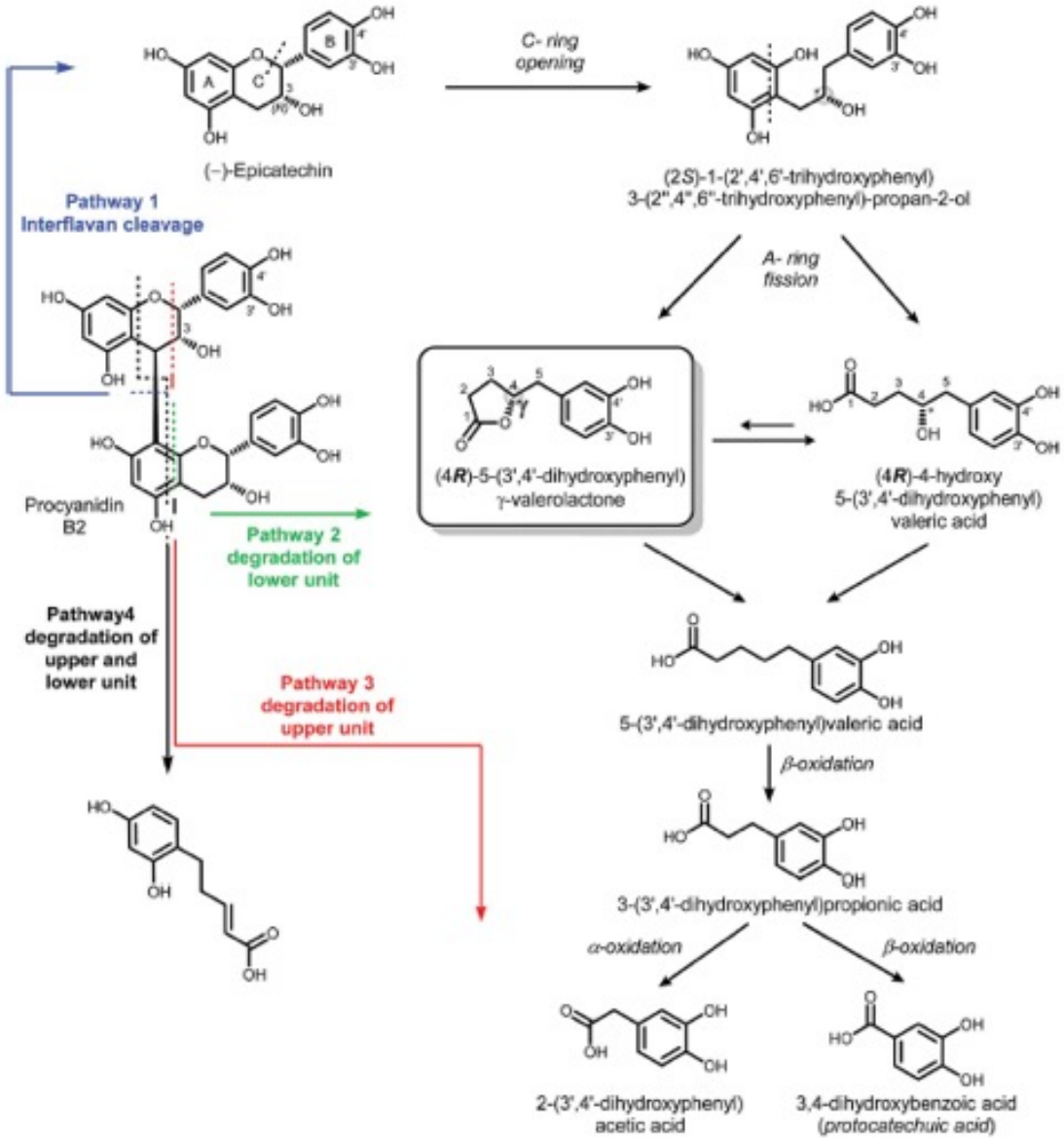
Renal excretion of **phenolic metabolites**

Crozier et al., Molecular Aspects of Medicine. 2010
Liu et al., Current Pharmacology Reports. 2017
Manach et al., The American Journal of Clinical Nutrition. 2004

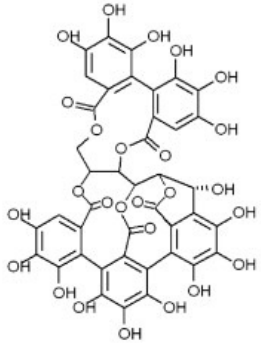

Bioavailability of Ellagitannins in Healthy Humans
Time 0 - Ingestion
300 g of strawberries or 100 ml of pomegranate juice allow the administration of approx 140 μmol of ellagic acid and ellagitannins
After 1 Hour
Ellagic acid, obtained by basic hydrolysis of ET downline of gastric passage, is detected 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
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 C
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%

Flavan-3-ols?

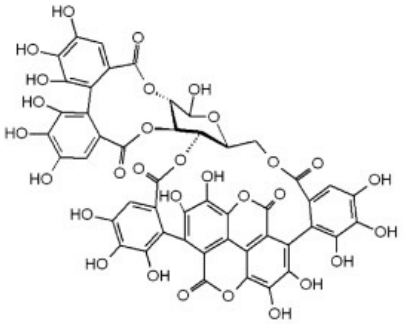

(−)-Epigallocatechin
(−)-Epigallocatechin-3-gallate
(−)-Epicatechin-3-gallate
(+)-Catechin
(+)-Epicatechin
(+)-Epiafzelchin
(−)-Catechin
(−)-Epicatechin
(−)-Epiafzelchin
β-dimers
C4-C8 connection
C4-C6 connection
C2-OC7 C4-C8 connection
Proanthocyanidin B2 dimer
Proanthocyanidin B5 dimer
Proanthocyanidin A2 dimer
type B proanthocyanidin
type A proanthocyanidin


(−)-Epicatechin
C- ring opening
(2S)-1-(2',4',6'-trihydroxyphenyl) 3-(2'',4'',6''-trihydroxyphenyl)-propan-2-ol
Pathway 1 Interflavan cleavage
A- ring fission
Procyanidin B2
Pathway 2 degradation of lower unit
(4R)-5-(3',4'-dihydroxyphenyl) γ-valerolactone
(4R)-4-hydroxy 5-(3',4'-dihydroxyphenyl) valeric acid
Pathway4 degradation of upper and lower unit
Pathway 3 degradation of upper unit
5-(3',4'-dihydroxyphenyl)valeric acid
β-oxidation
3-(3',4'-dihydroxyphenyl)propionic acid
α-oxidation
β-oxidation
2-(3',4'-dihydroxyphenyl) acetic acid
3,4-dihydroxybenzoic acid (protocatechuic acid)

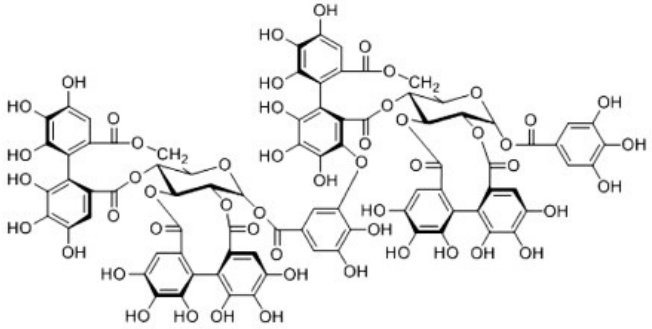
Ellagitannins?



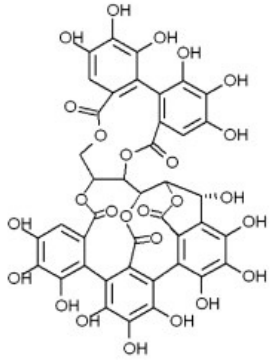
Vescalagin



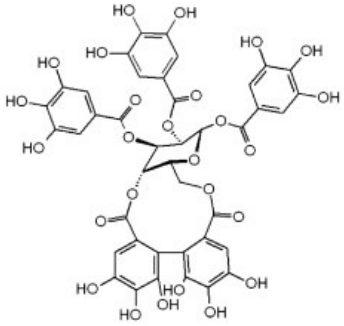
Punicalagin



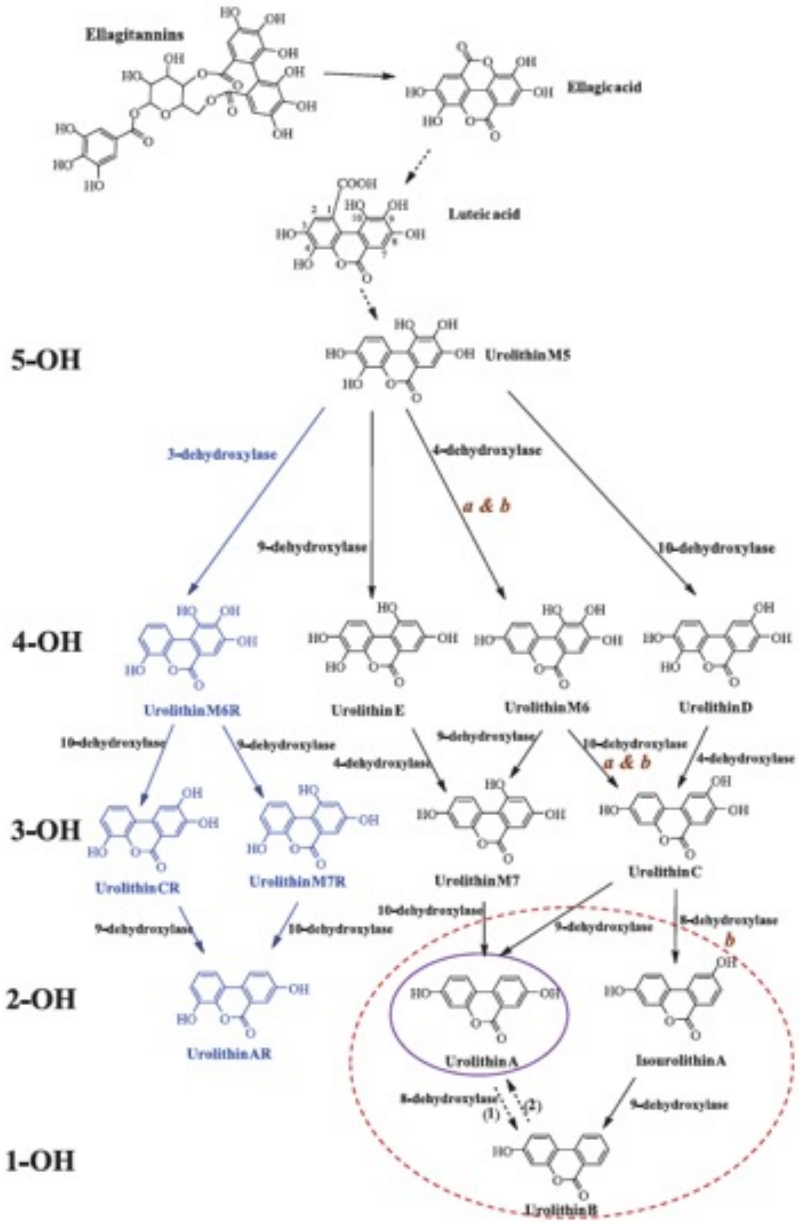
Sanguiin H-6



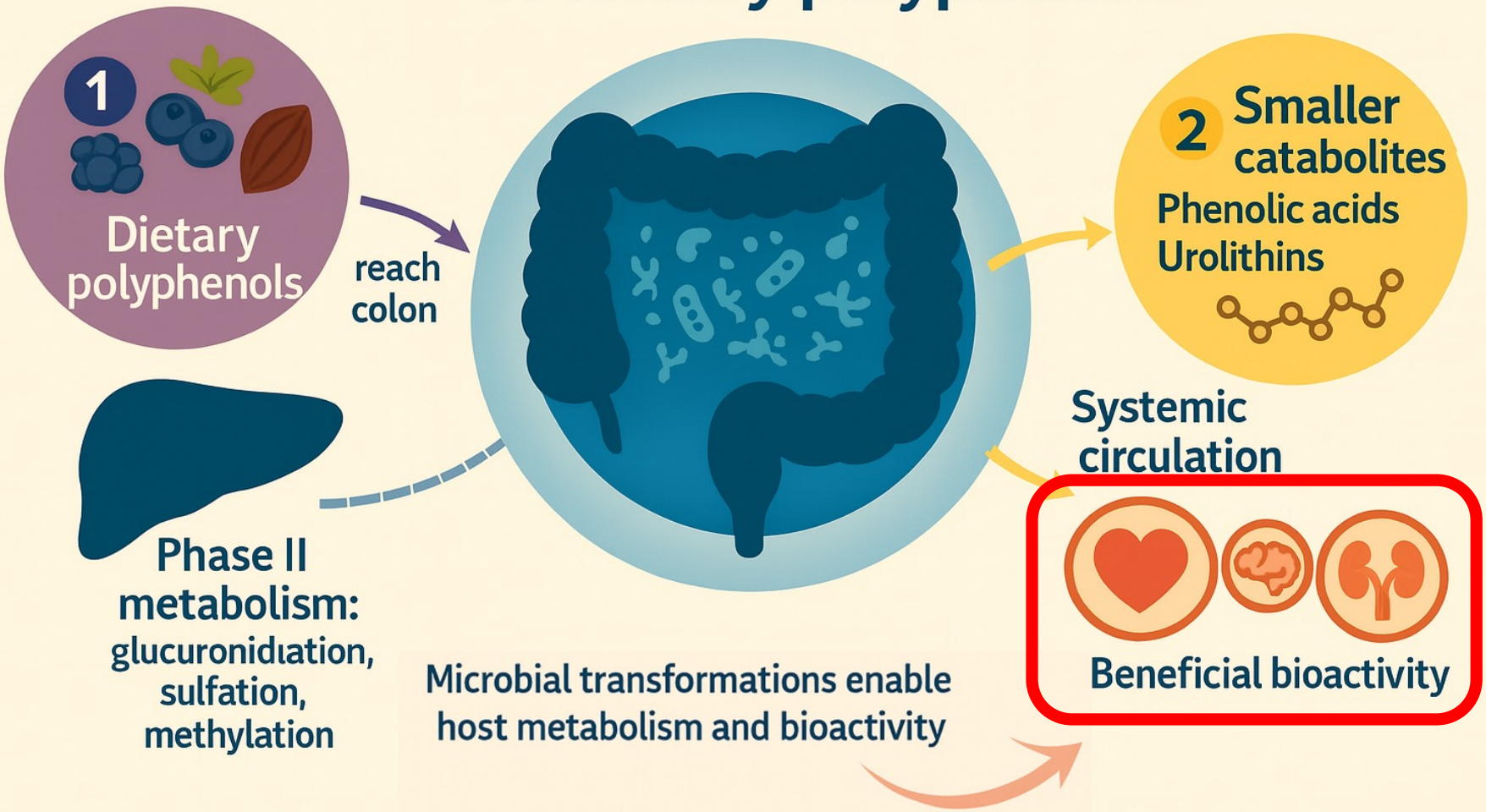
Castalagin



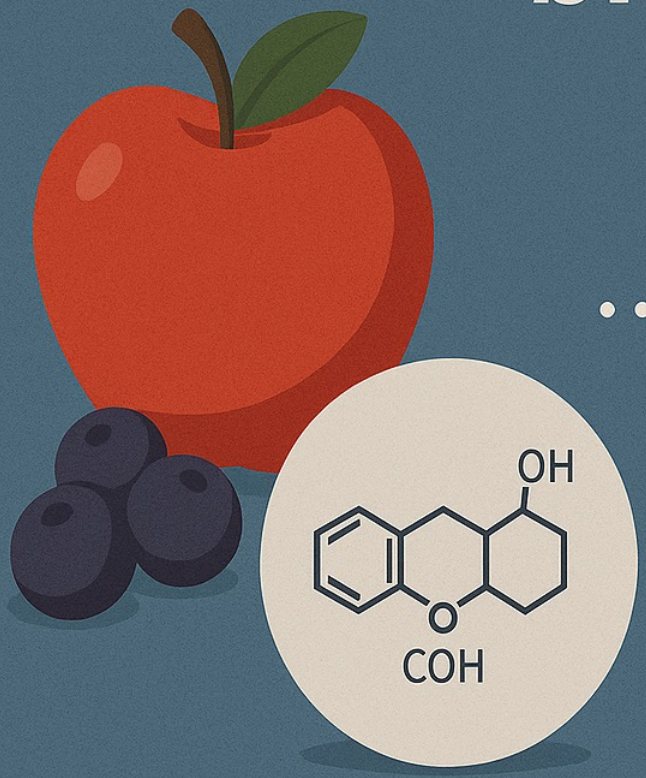
Tellimagradin II

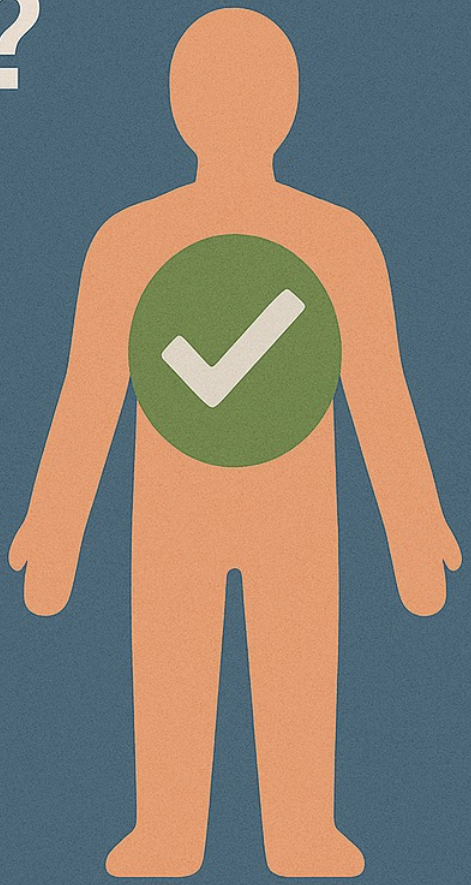

Ellagitannins
Ellagic acid
Luteic acid
5-OH
Urolithin M5
3-dehydroxylase
4-dehydroxylase
a & b
9-dehydroxylase
10-dehydroxylase
4-OH
Urolithin M6R
Urolithin E
Urolithin M6
Urolithin D
10-dehydroxylase
9-dehydroxylase
4-dehydroxylase
9-dehydroxylase
10-dehydroxylase
a & b
4-dehydroxylase
3-OH
Urolithin CR
Urolithin M7R
Urolithin M7
Urolithin C
10-dehydroxylase
9-dehydroxylase
9-dehydroxylase
10-dehydroxylase
8-dehydroxylase
b
2-OH
Urolithin AR
Urolithin A
Isourolithin A
8-dehydroxylase
(1)
(2)
9-dehydroxylase
1-OH
Urolithin B

Gut microbiota: central biotransformer of dietary polyphenols

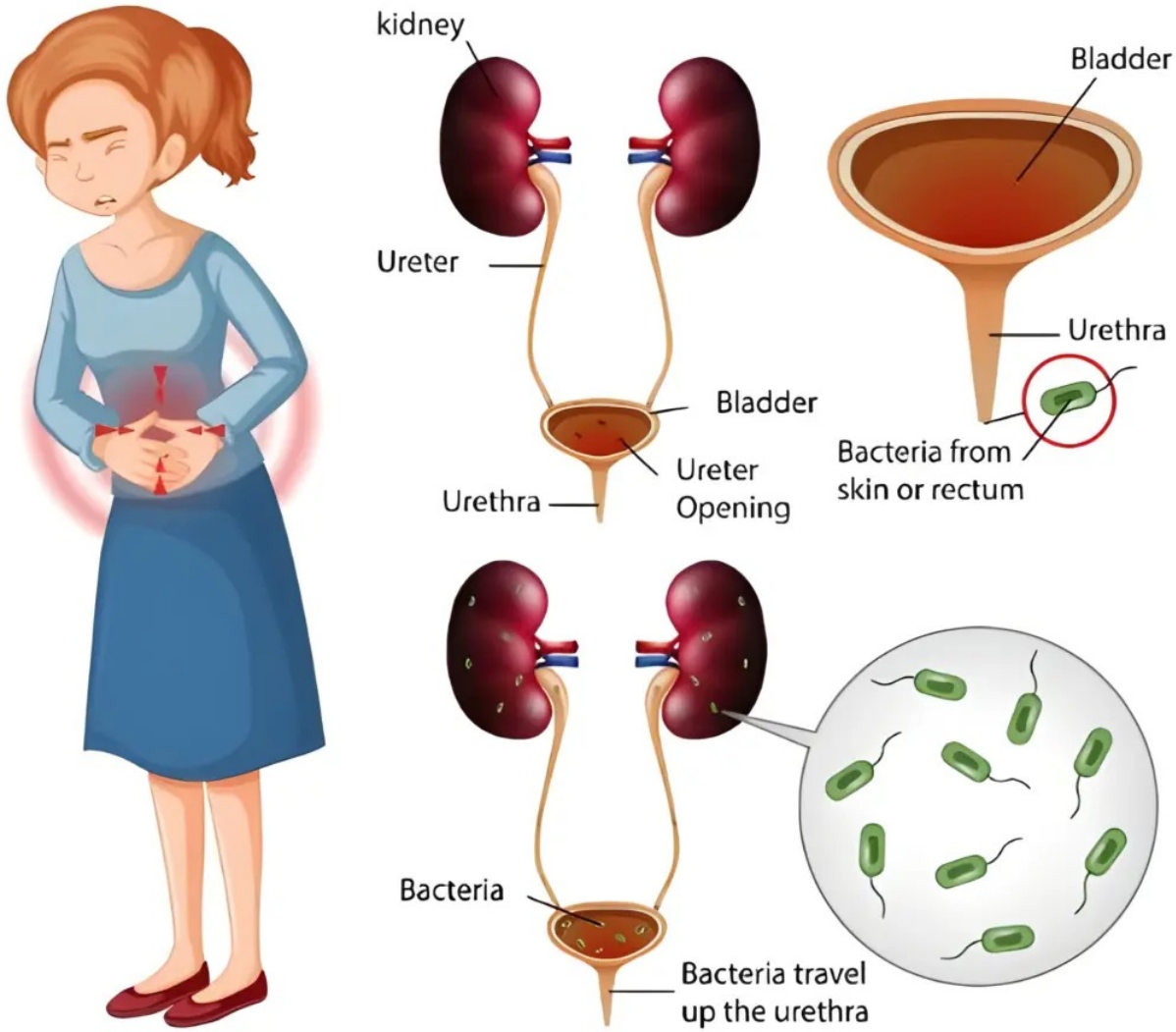


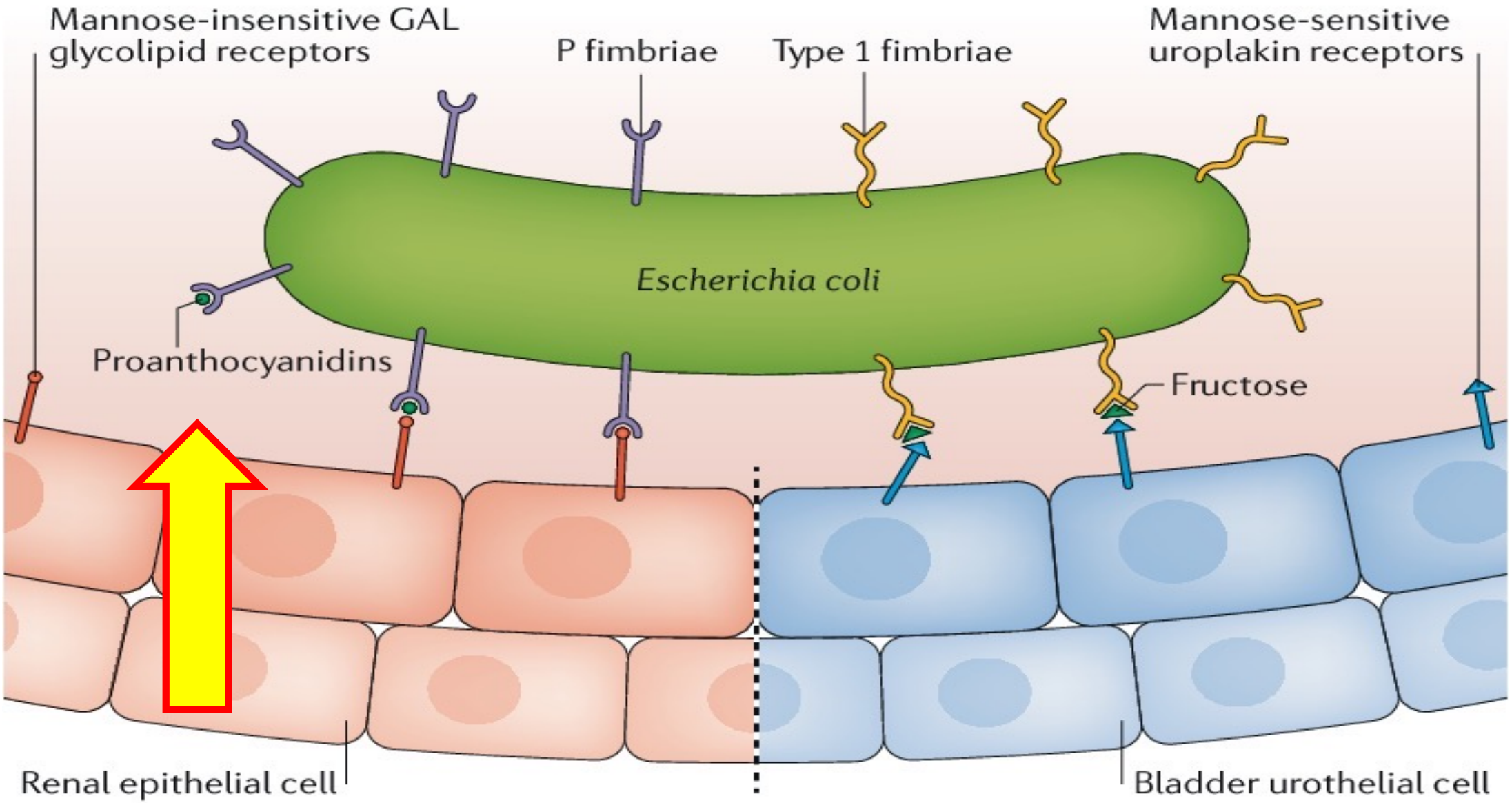
Are polyphenol metabolites bioactive?





Urinary tract infections




Mannose-insensitive GAL glycolipid receptors
P fimbriae
Type 1 fimbriae
Mannose-sensitive uroplakin receptors
Escherichia coli
Proanthocyanidins
Fructose
Renal epithelial cell
Bladder urothelial cell

Journal of Functional Foods 29 (2017) 275–280

Contents lists available at ScienceDirect

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journal homepage: www.elsevier.com/locate/jff

5-(3′,4′-Dihydroxyphenyl)-γ-valerolactone and its sulphate conjugates, representative circulating metabolites of flavan-3-ols, exhibit anti-adhesive activity against uropathogenic *Escherichia coli* in bladder epithelial cells

Pedro Mena[a,1], Dolores González de Llano[b,1], Nicoletta Brindani[c], Adelaida Esteban-Fernández[b], Claudio Curti[c], María Victoria Moreno-Arribas[b], Daniele Del Rio[a,*], Begoña Bartolomé[b,*]

Acting Post-Doc (now Associate Professor!): Dr. Pedro Mena

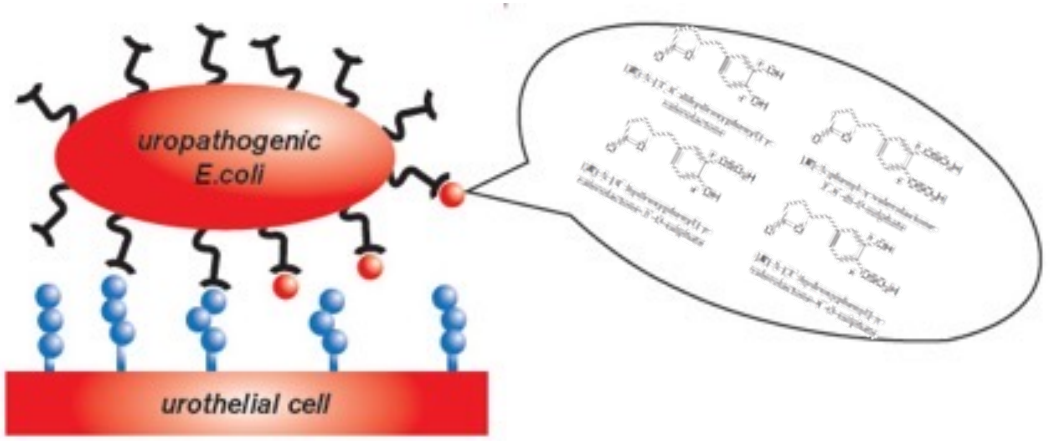
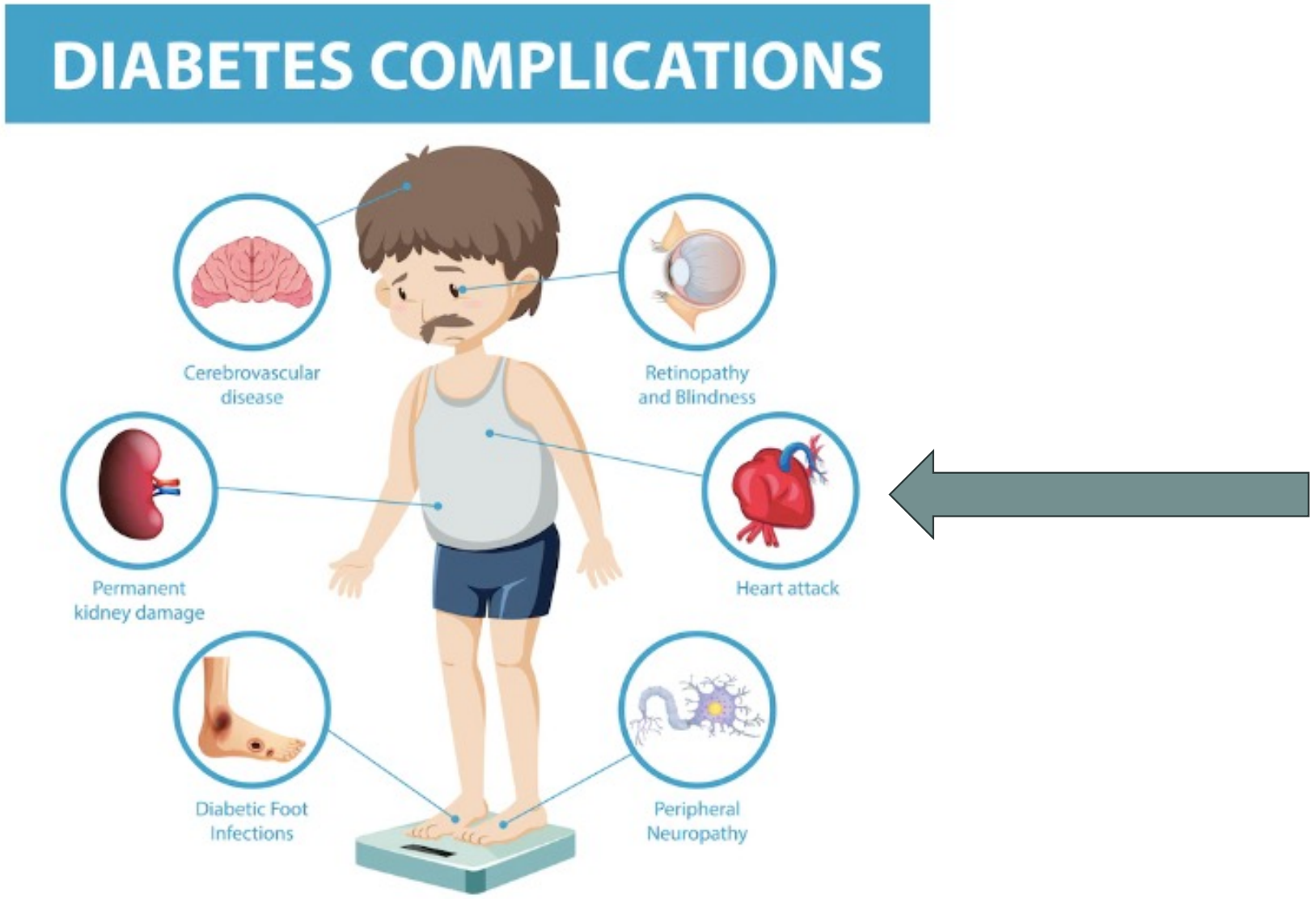


Table 1
Inhibition (%) of the adherence of *E. coli* ATCC® 53503™ to bladder epithelial cells by dihydroxyphenyl-γ-valerolactones.

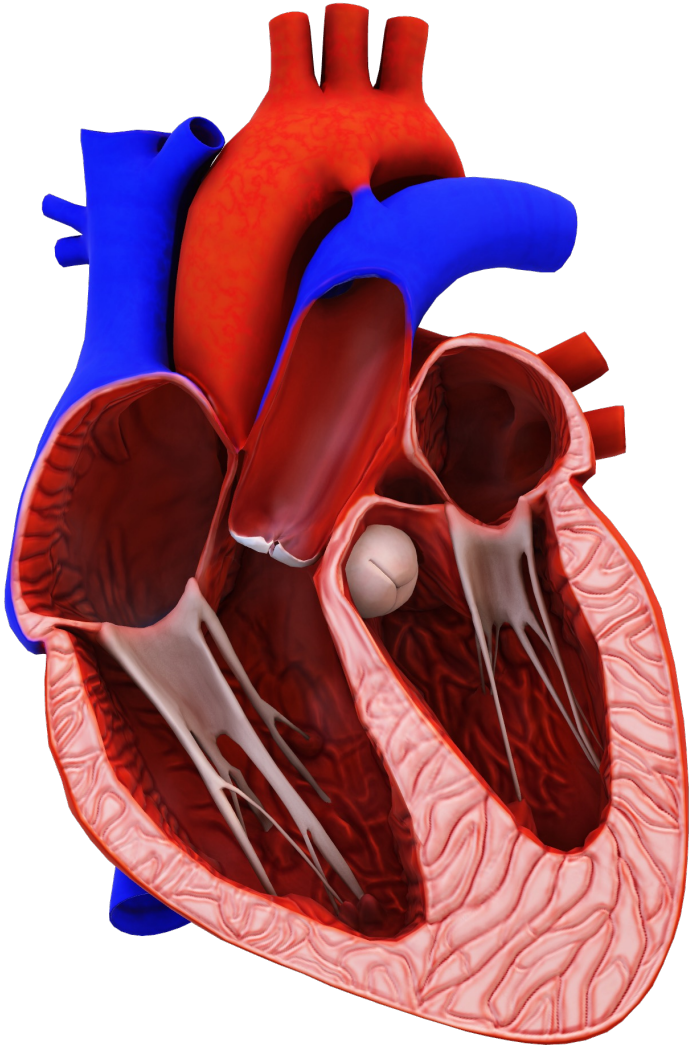
Compound	Concentration (μM)		
	10	50	100
5-(3′,4′-Dihydroxyphenyl)-γ-valerolactone	6.79 ± 3.92	9.95 ± 8.28	19.4 ± 10.3*
5-Phenyl-γ-valerolactone-3′,4′-di-*O*-sulphate	−0.22 ± 0.71	14.7 ± 1.5	30.3 ± 3.6**
5-(4′-Hydroxyphenyl)-γ-valerolactone-3′-*O*-sulphate	11.9 ± 1.7	10.2 ± 3.9	22.2 ± 5.9**
5-(3′-Hydroxyphenyl)-γ-valerolactone-4′-*O*-sulphate	10.1 ± 3.1	16.1 ± 6.1*	24.2 ± 3.1**

* Mean significantly different from zero ($p < 0.05$) using one-sample *t*-test.
** Mean significantly different from zero ($p < 0.01$) using one-sample *t*-test.

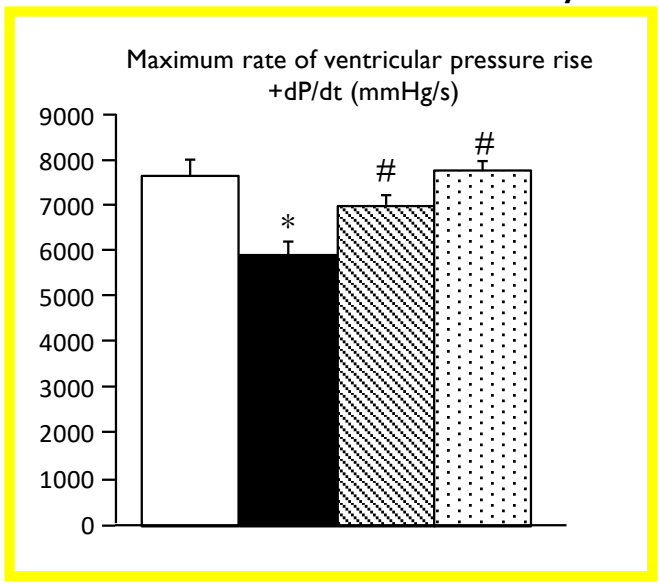
To sum up: Light on the flavan-3-ol metabolites behind the prophylactic effect of cranberries against UTI

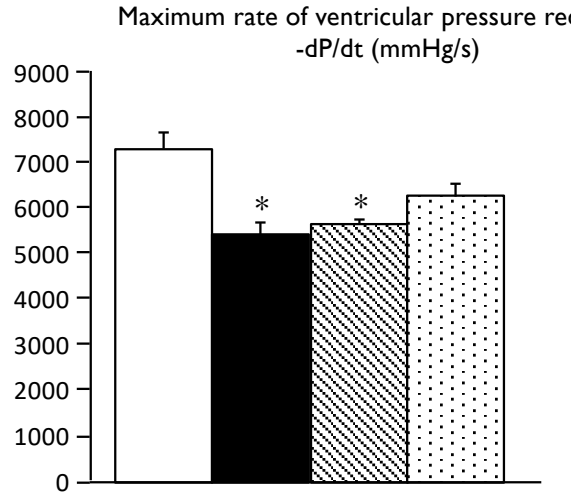

DIABETES COMPLICATIONS
Cerebrovascular disease
Retinopathy and Blindness
Permanent kidney damage
Heart attack
Diabetic Foot Infections
Peripheral Neuropathy

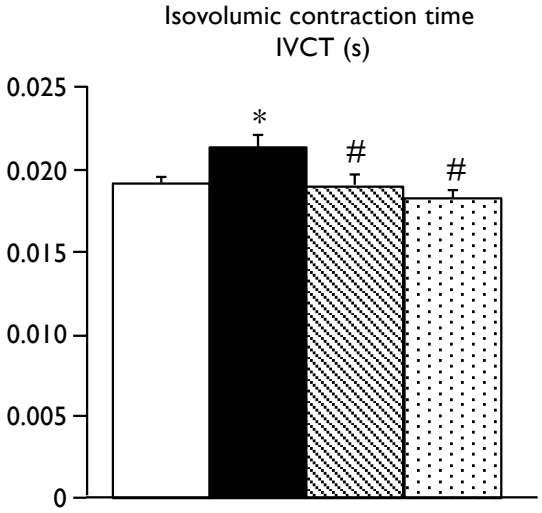
Hemodynamic measurements?

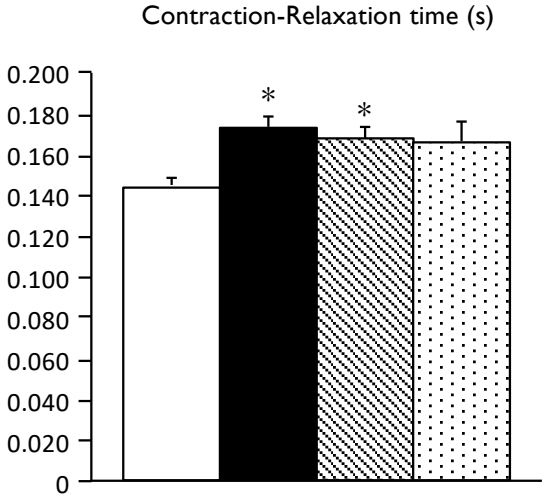


Results: Hemodynamic measurements (Contraction rate)









CTRL (n=10)

D3 (n=9)

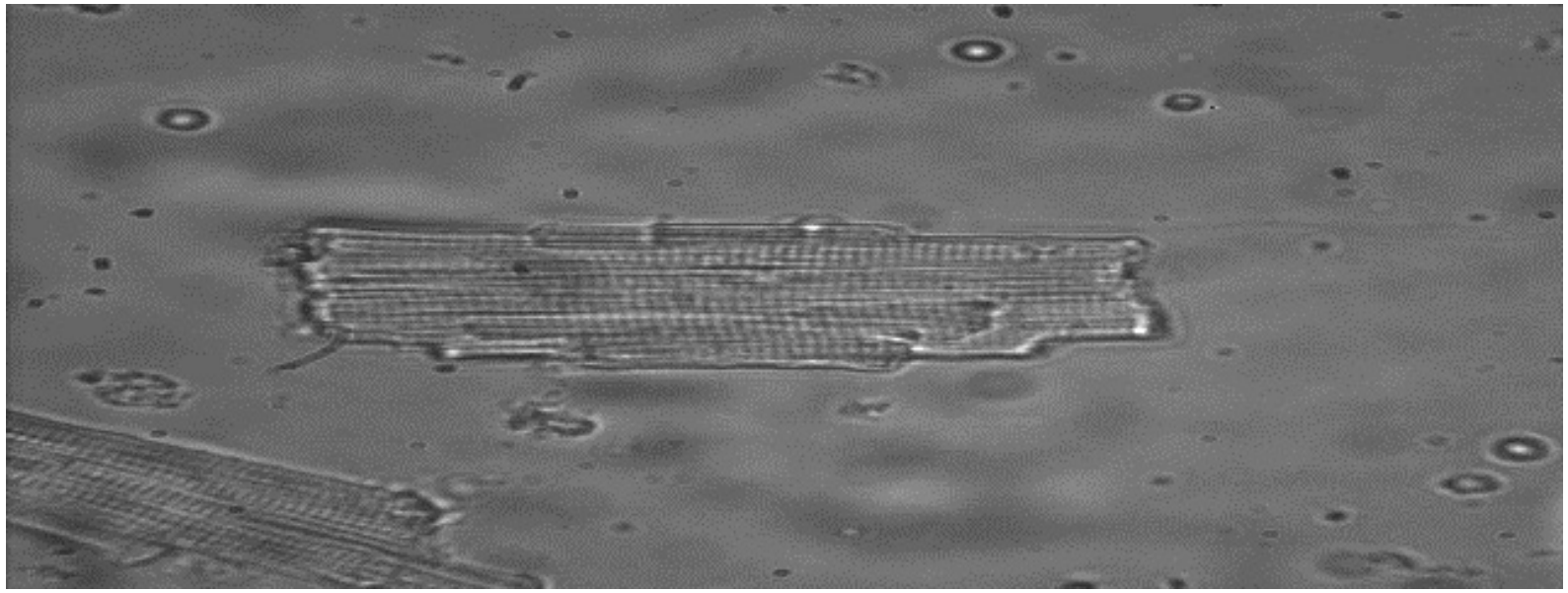
D3_UA (n=8)

D3_UB (n=9)

* p<0.05 vs CTRL

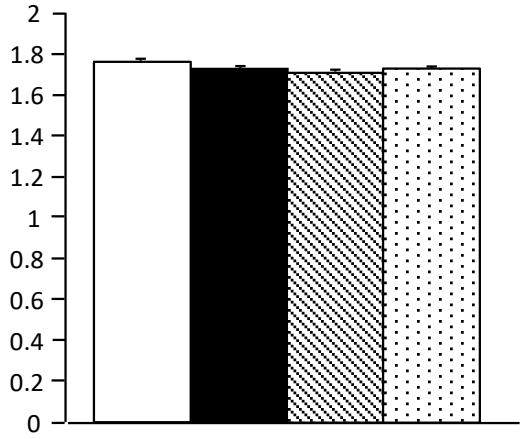
# p<0.05 vs D3

Cardiomyocytes isolation, cell mechanics

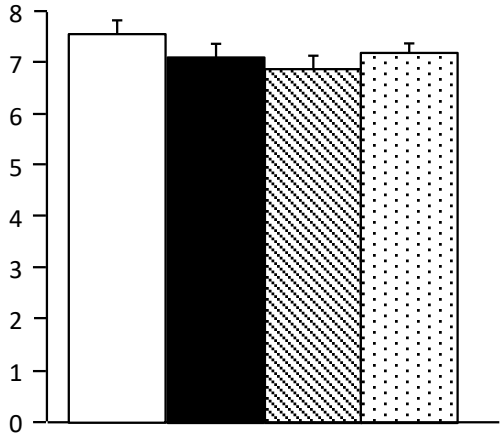


Results: Cell mechanics

Mean diastolic sarcomere length (µm)



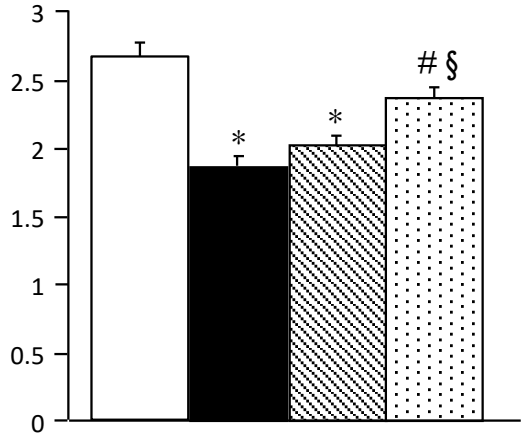
Fraction of Shortening (%)



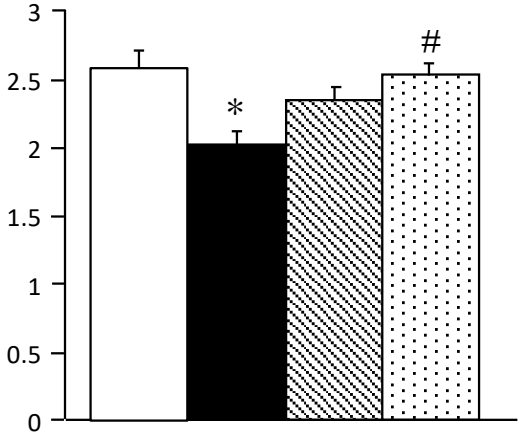
CTRL (n=66)
D3 (n=91)
D3_UA (n=100)
D3_UB (n=102)

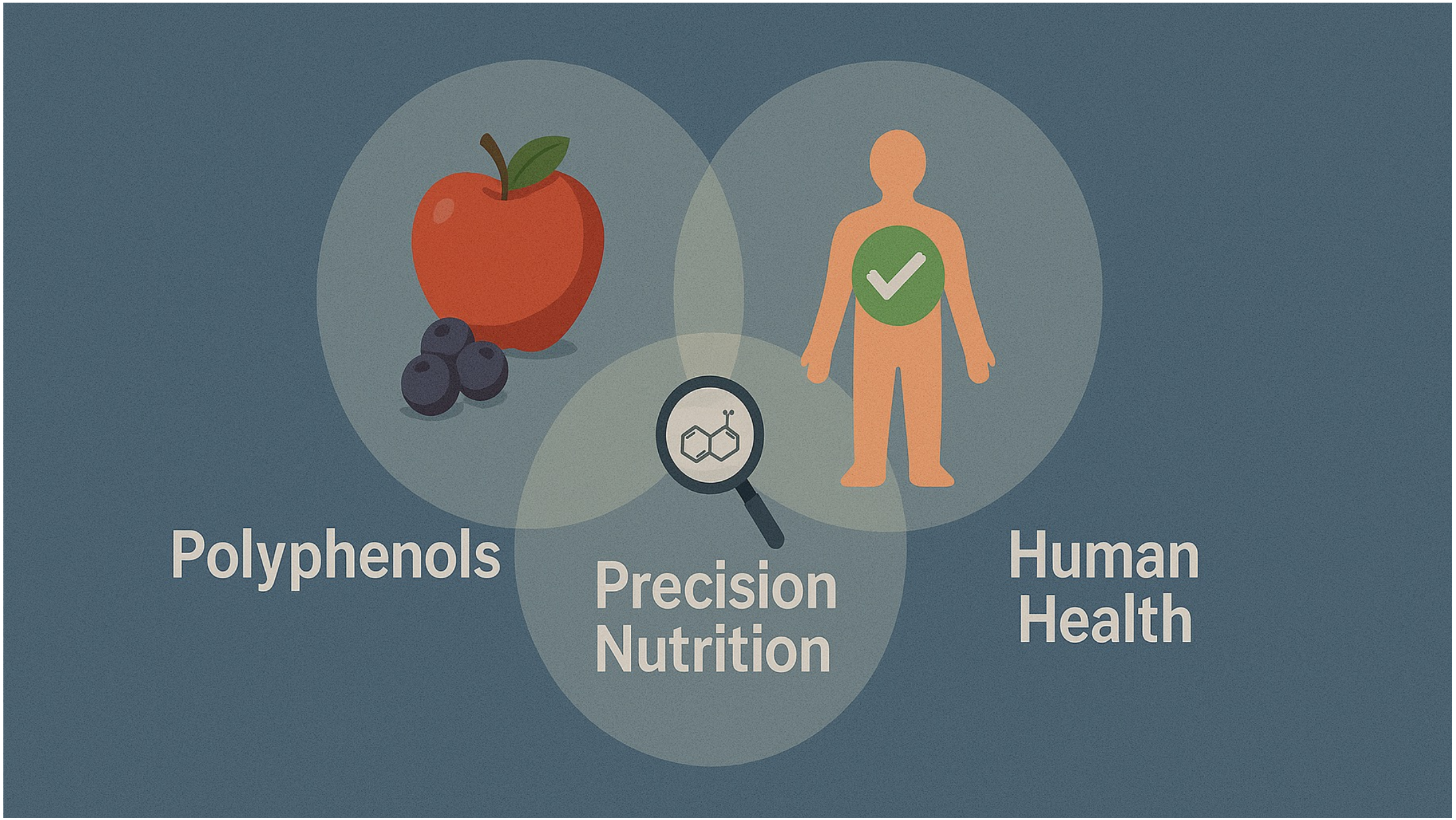
* p<0.01 vs CTRL
# p<0.01 vs D3
§ p<0.01 vs D3_UA

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



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




Polyphenols
Precision Nutrition
Human Health

Polifenoli & nutrizione di precisione?

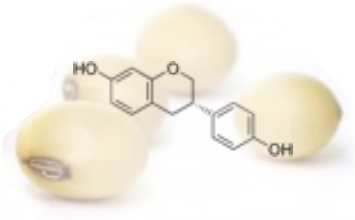
Metabotyping
classificazione di individui in sottogruppi in base al loro profilo metabolico

Metabolic profiles

Clustering

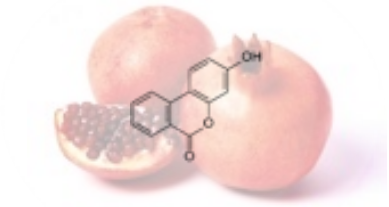
(Poly)phenols & metabotypes

Isoflavones



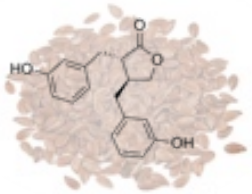
Equol & co.

Ellagitannins



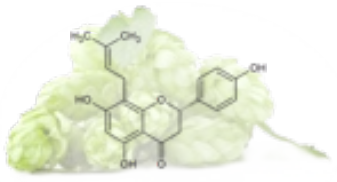
Urolithins

Lignans



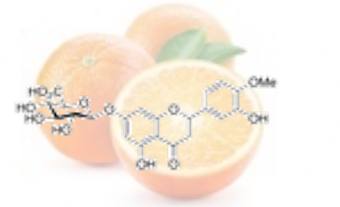
Enterolactone

Prenylflavonoids



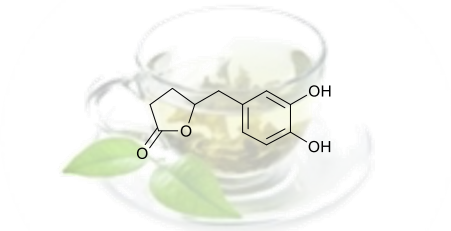
8-prenylnaringenin

Flavanones



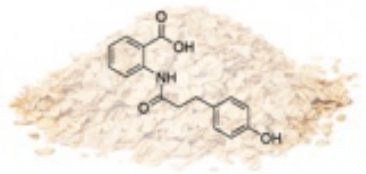
Phase II metabolites, phenolic acids

Flavan-3-ols



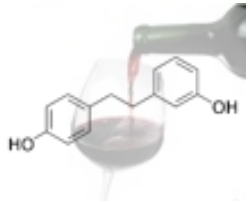
Phenyl-γ-valerolactones

Avenanthramides



Dihydro-avenanthramides

Resveratrol

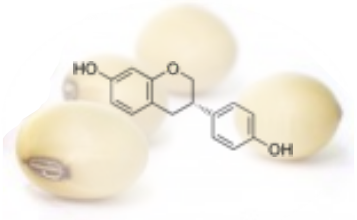


Lunularin

(Poly)phenols & metabotypes

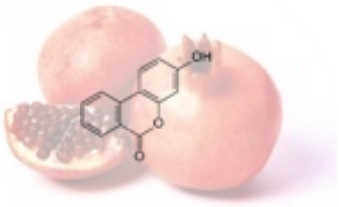
Qualitatively distinguished metabolic phenotypes

Isoflavones



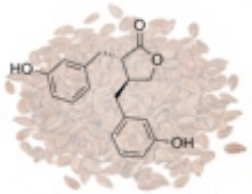
Equol & co.

Ellagitannins



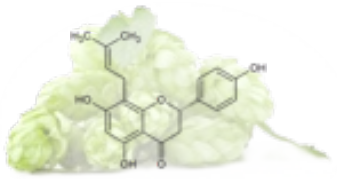
Urolithins

Lignans



Enterolactone

Prenylflavonoids



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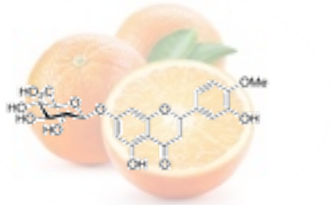
Flavanones



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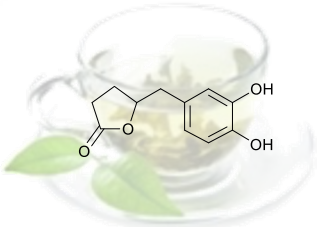
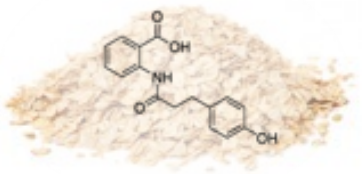


Phenyl-γ-valerolactones

Avenanthramides



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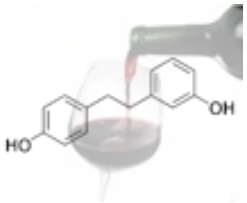


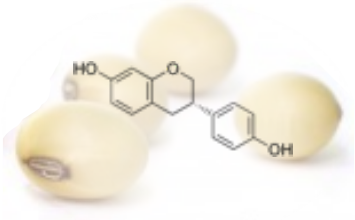
Lunularin

(Poly)phenols & metabotypes

Metabolite concentration gradients

Quali-quantitative metabolic phenotypes

Isoflavones



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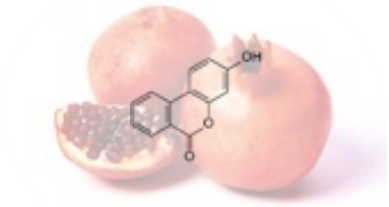
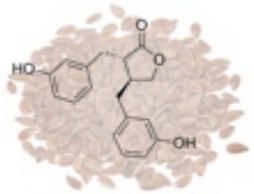


Urolithins

Lignans



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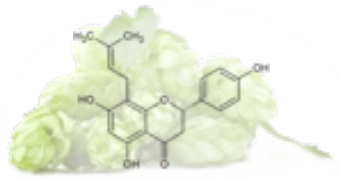
Prenylflavonoids



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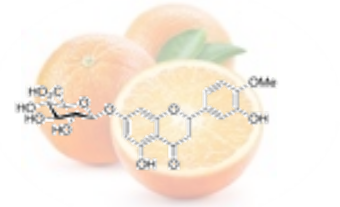

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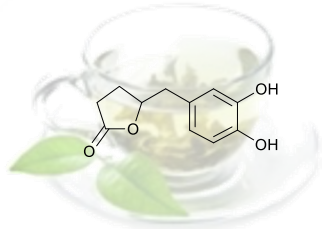

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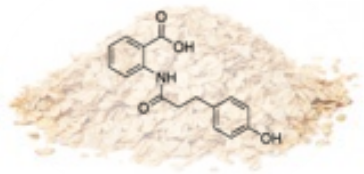

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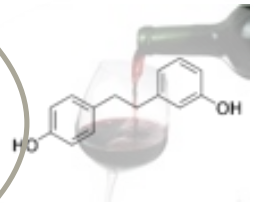
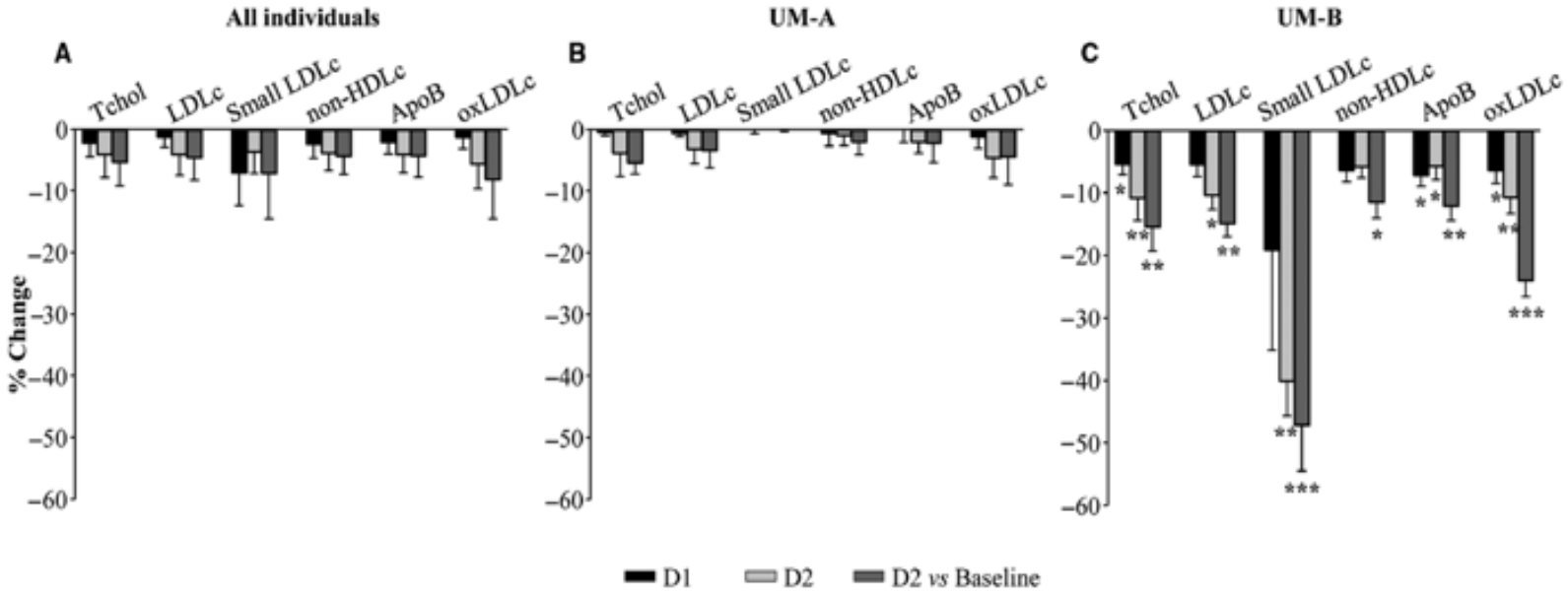


Lunularin

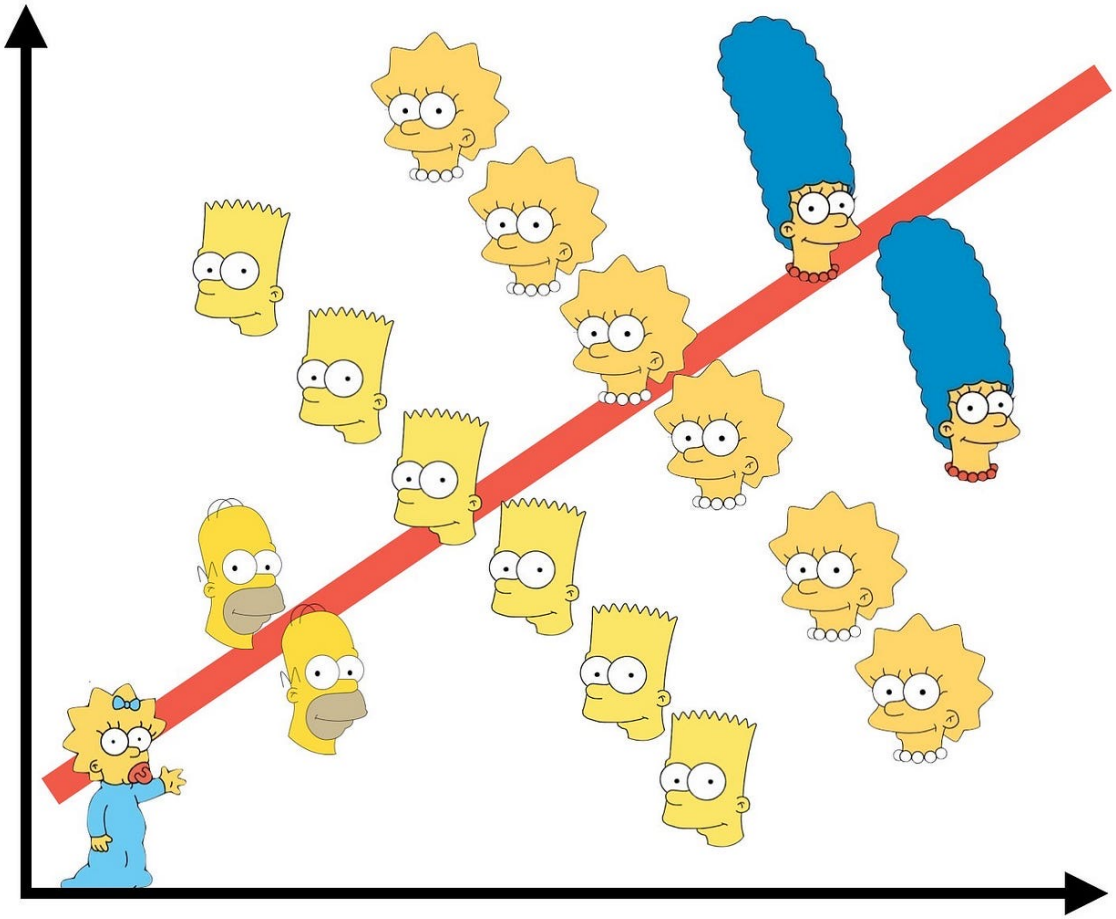
Clustering according to urolithin metabotype explains the interindividual variability in the improvement of cardiovascular risk biomarkers in overweight-obese individuals consuming pomegranate: A randomized clinical trial

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]



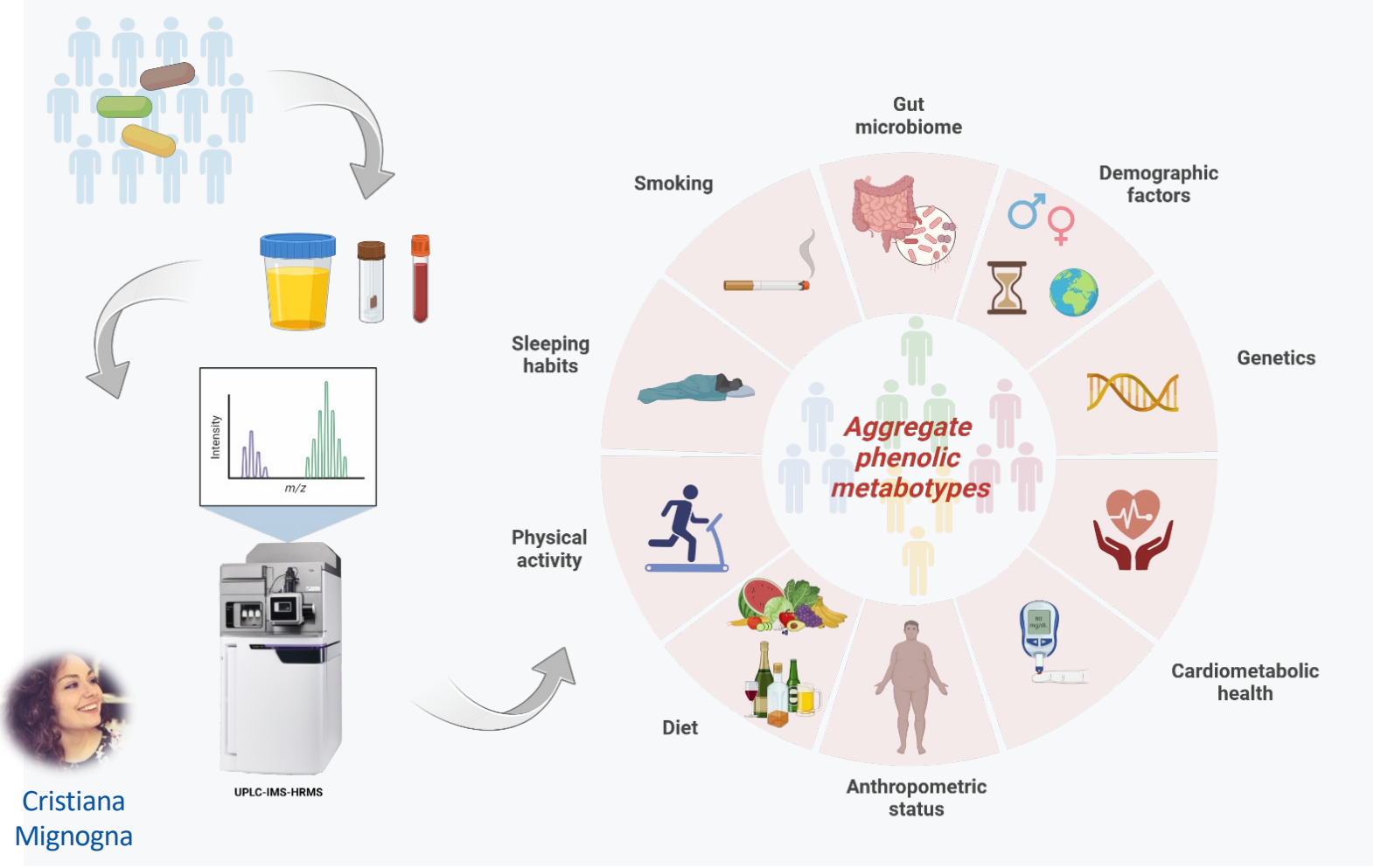
Potremmo trovarci di fronte a un caso di **«paradosso di Simpson»?**



"The Simpson's Paradox", referenced from twitter account of RJ Andrews

Nuove ricerche in corso presso **l'Unità di Nutrizione Umana dell'Università di Parma**...

Oral (Poly)phenol Challenge Test (OPCT)



Cristiana Mignogna

PREDICT-CARE

@PredictCare_ERC

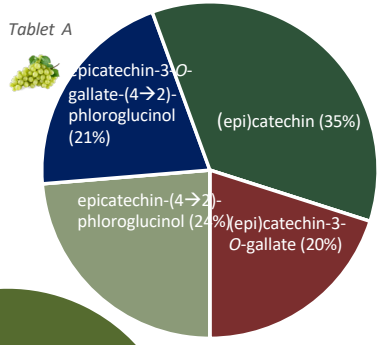
Aims

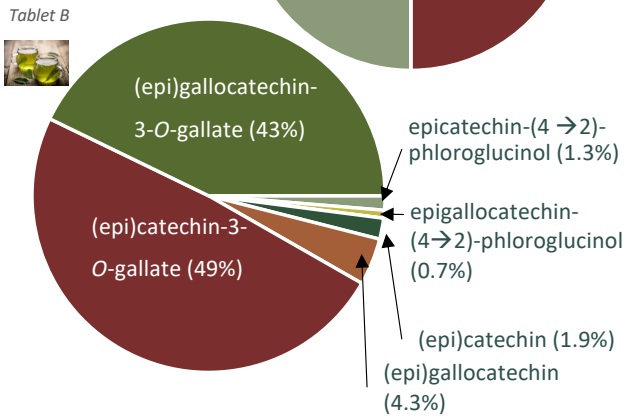
Identificazione dei fenotipi metabolici aggregati per i principali (poli)fenoli alimentari

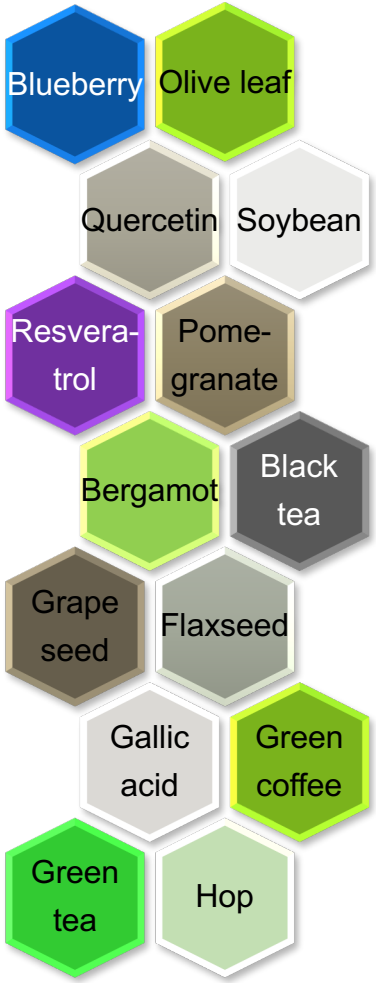
Valutazione dei determinanti della variazione interindividuale che porta a diversi profili fenotipici

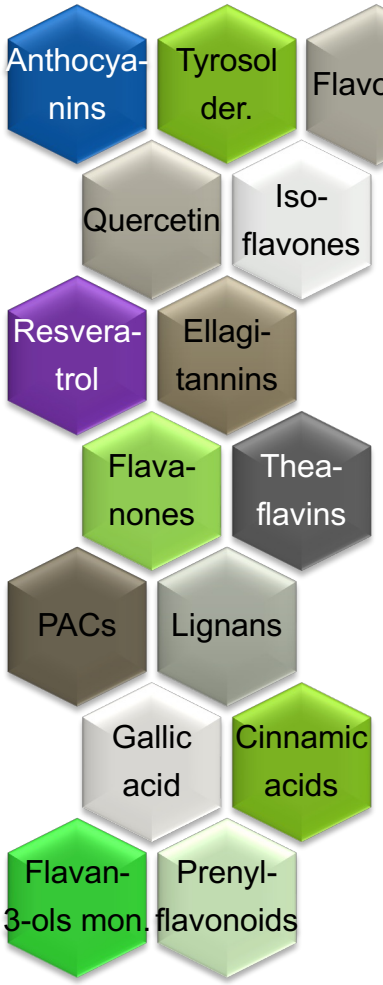
Valutazione dell'associazione tra metabotipi e lo stato di salute cardiometabolico

Oral (Poly)phenol Challenge Test (OPCT)









305 compounds quantified

Cristiano Negro

Vicente Agulló

José F. Rinaldi de Alvarenga

Bianca Romanelli

Oral (Poly)phenol Challenge Test (OPCT)


Cristina del Burgo


Cristiano Negro


José F. Rinaldi de Alvarenga

Determining (poly)phenol metabolites

24 h

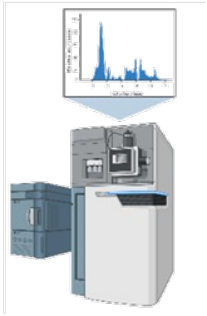
Spot urine in fasting conditions

Option A

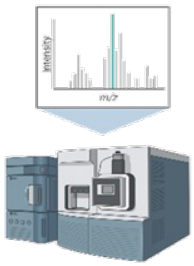
The "(poly)phenolome"

436 compounds monitored

HYBRID LC-MS-based Targeted Metabolomics Approach



LC-IMS-qToF-HRMS



LC-QqQ-MS/MS

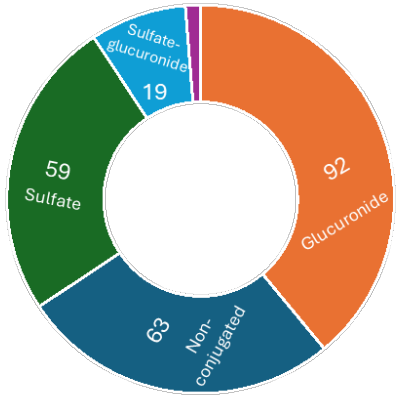
23 new unusual phase II conjugated

Glycine

Carnitine

Taurine

236 metabolites identified and quantified, **208** final data set



Oral (Poly)phenol Challenge Test (OPCT)


Cristina del Burgo


Cristiano Negro


José F. Rinaldi de Alvarenga

Determining (poly)phenol metabolites

Spot urine in fasting conditions

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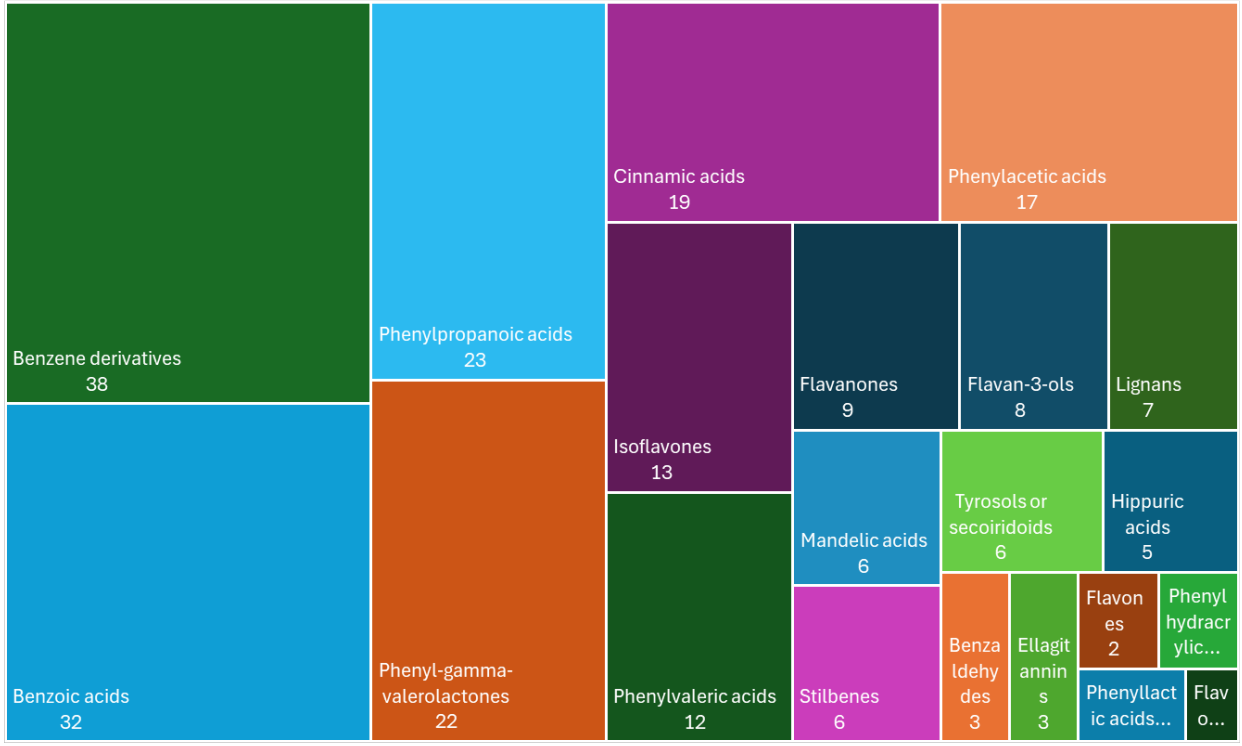
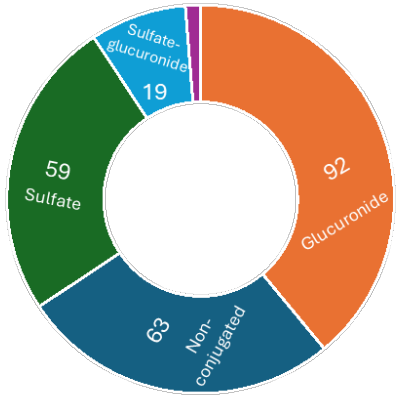
The "(poly)phenolome"

436 compounds monitored



236 metabolites identified and quantified, **208** final data set



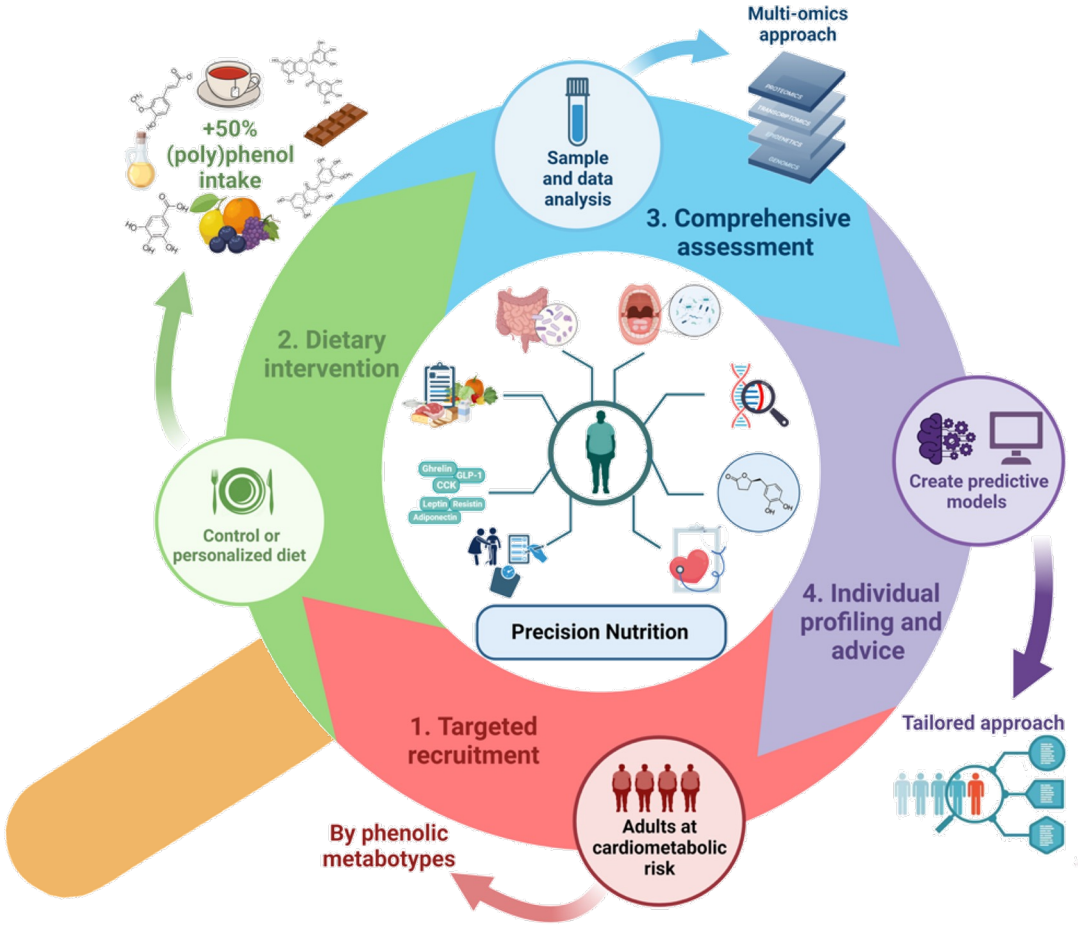
Precision nutrition to improve cardiometabolic health with dietary (poly)phenols (PRE-*CARE*-DIET)

Joana Rebelo

M. Sole Morandini

Sharon Zaffuto

Elisa Monica



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Precision nutrition to improve cardiometabolic health with dietary (poly)phenols (PRE-*CARE*-DIET)

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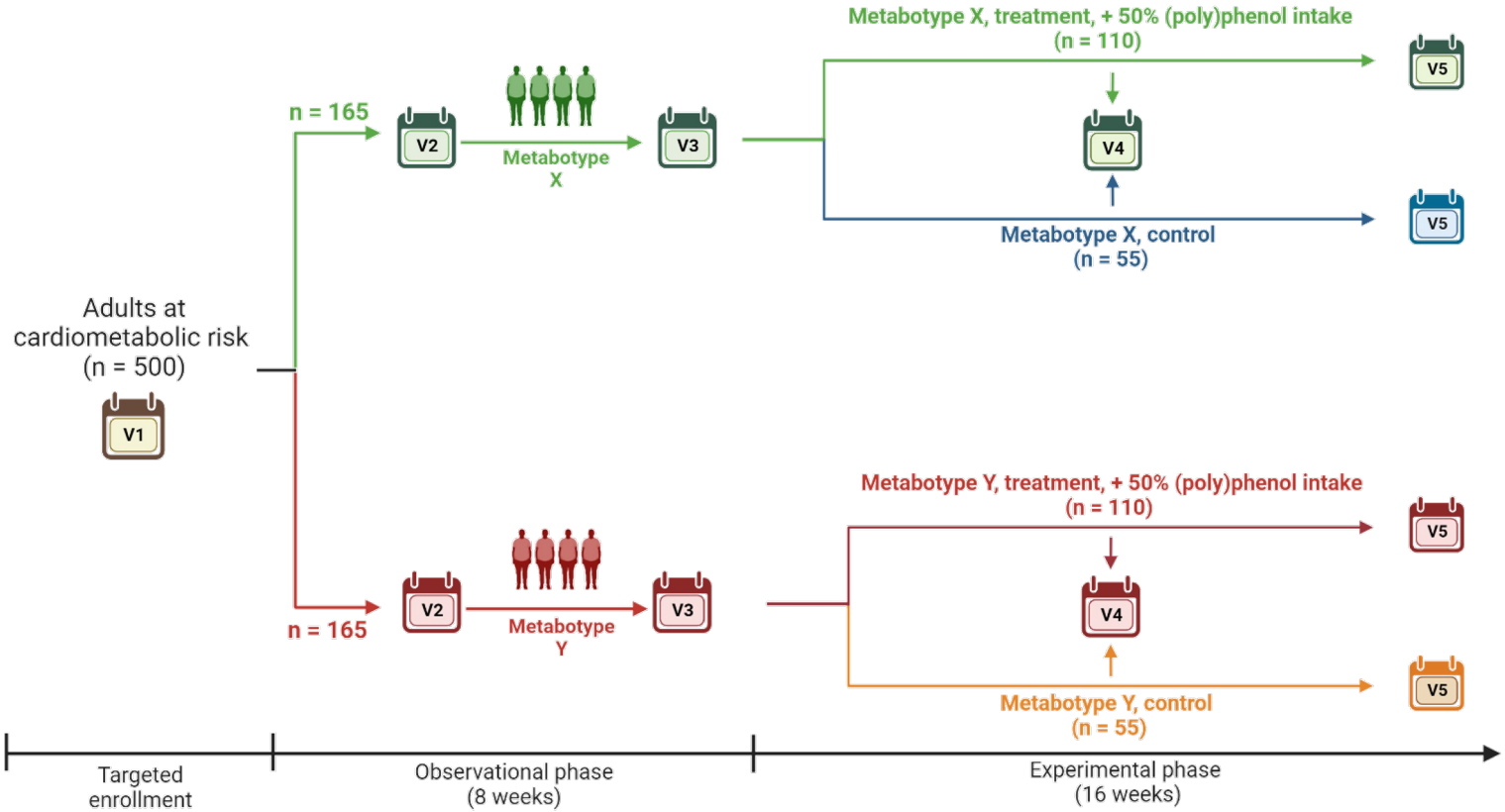


STAY
TUNED
OH
OH
HO
OH
OH
OH

In conclusion:

- In base alla capacità del microbiota intestinale di trasformare i polifenoli alimentari, un soggetto potrebbe ottenere maggiori o minori benefici da alimenti vegetali specifici (e dai loro derivati);
- Questa differenza potrebbe dipendere da fattori aggiuntivi…
- Questa condizione potrebbe non essere stabile, ma cambiare nel tempo e in funzione della dieta;
- **È complicato! Ma molto interessante!**

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Bolton Food

Rio

CIRFOOD Feed the future

DēLonghi Group

SACCO system

TECNOALIMENTI

CONFCOOPERATIVE Confederazione Cooperative Italiane

Thanks!

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Leonardo Mancabelli
Christian Milani
Gabriele Andrea Lugli
Federico Fontana
Chiara Tarracchini
(Microbiome Research Hub)

Valeria Barili
(Genetics)

Francesco Potì
(Pharmacology)

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de Alvarenga
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Luca Calani
Nicola Bragazzi
Mirko Treccani
Cristina del Burgo
Elisabetta Viale
Nicole Tosi
Sara Dobani
Costanza Michelini
Laila Zeraik
Elisa Monica
Cristiano Negro
M. Sole Morandini
Joana Santos Rebelo
Sharon Zaffuto
Marco Codeluppi
Angeliki Sofroniou
Federica Bergamo
Lucia Ghiretti
Bianca Romanelli
Arianna Gallina
Marta Berzaghi
Carmen Carrieri
… the whole team
… former colleagues

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Patrizia Riso
Monica Laureati

Cristian Del Bò
Camilla Cattaneo

J. Alfredo Martínez
Victor de la O-Pascual

Jan Stautemas

Michele Vacca

Marialaura Bonaccio
Emilia Ruggiero

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