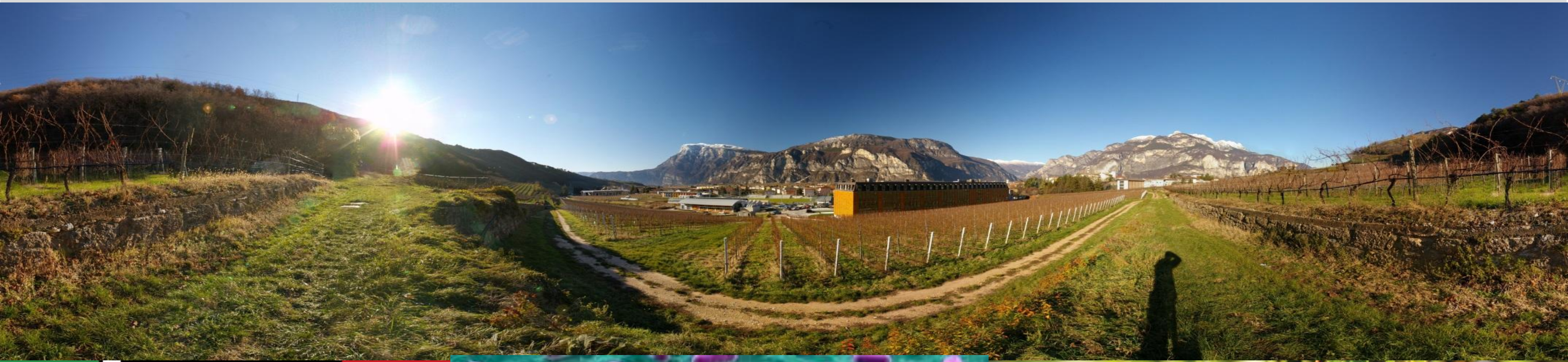
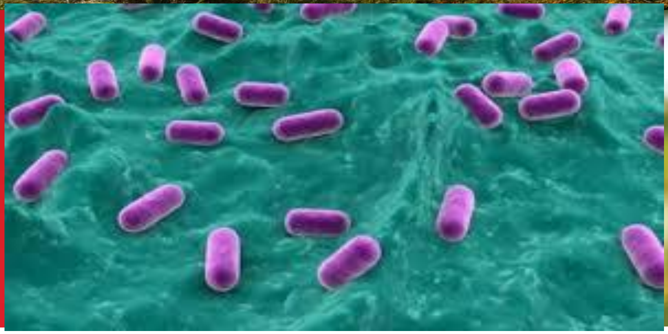
Modulating the human gut microbiome for improved health – is there a role for wine?





Kieran Tuohy

Fondazione Edmund Mach, San Michele all’Adige, Trento, Italy

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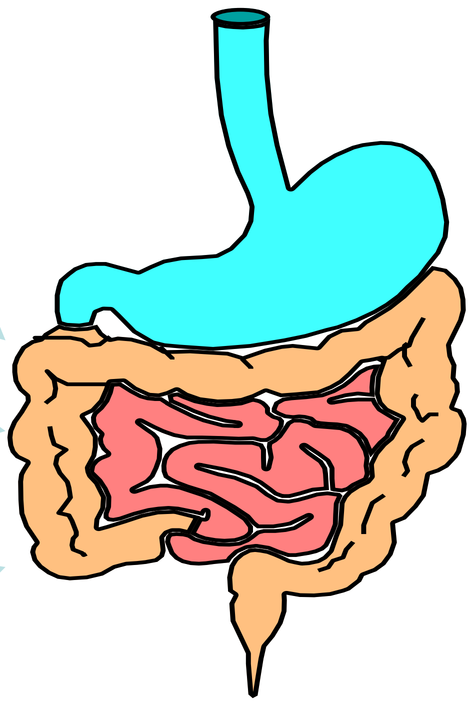
The human gut microbiome

Up to 1000 species

70% unculturable

Closely co-evolved microbial partners



Interactions with;

- Diet
- Drugs
- Immune system
- Gut physiology
- Bile acids/liver
- Systemic metabolism
- Adipose tissue
- Brain development & function

The human gut microbiome

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Up to 1000 species

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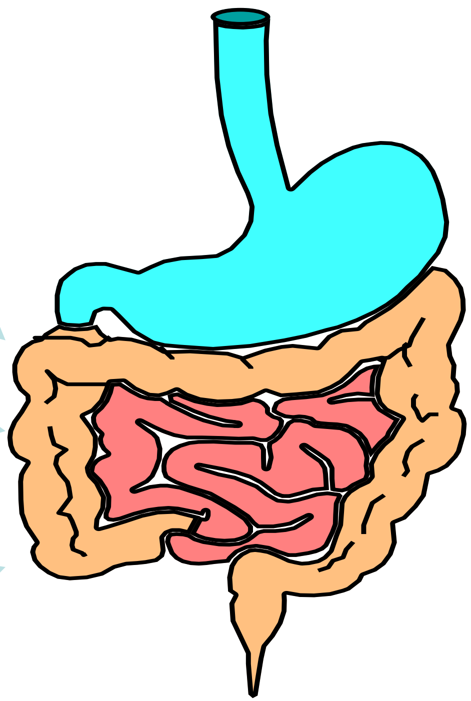
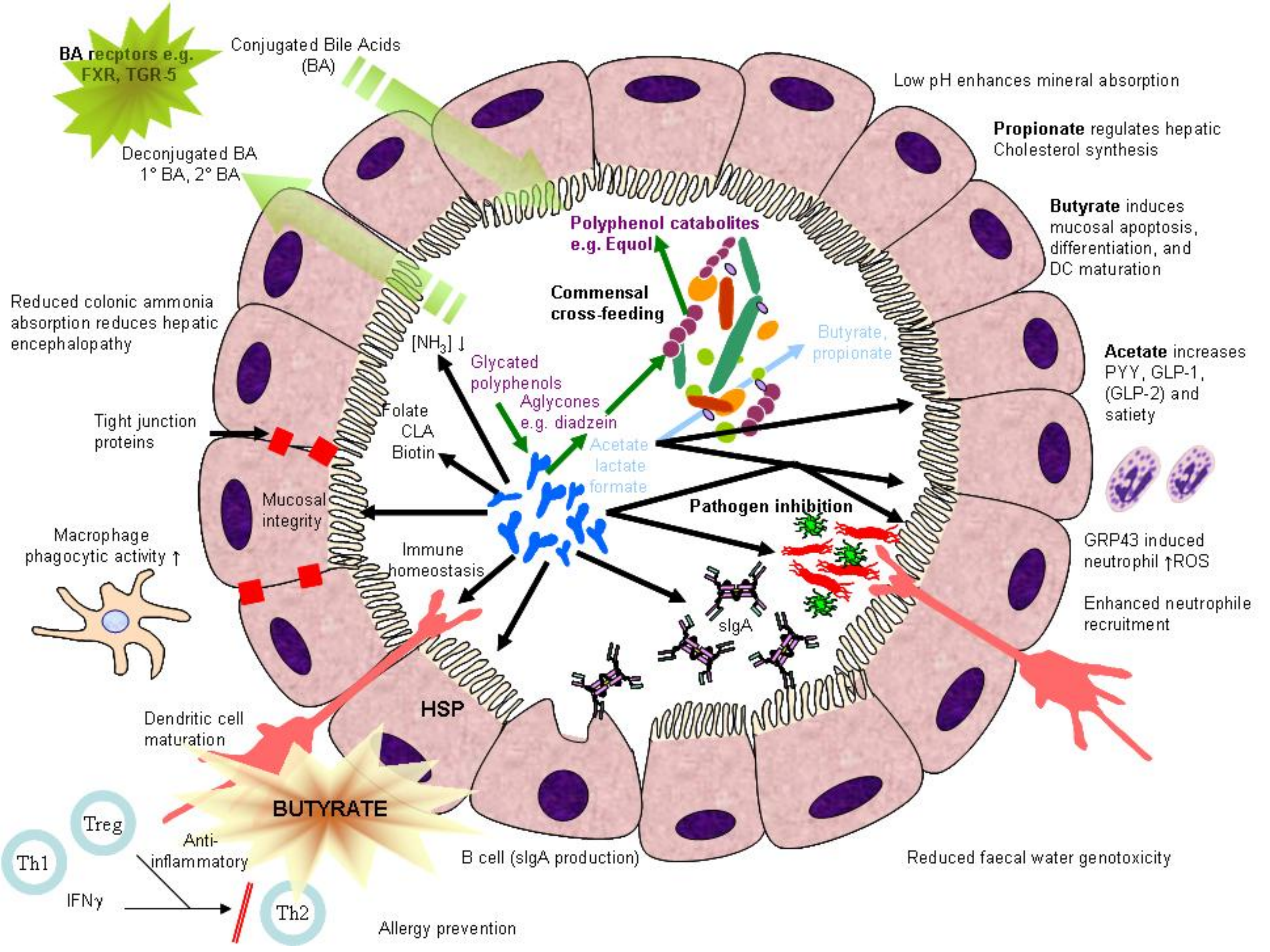


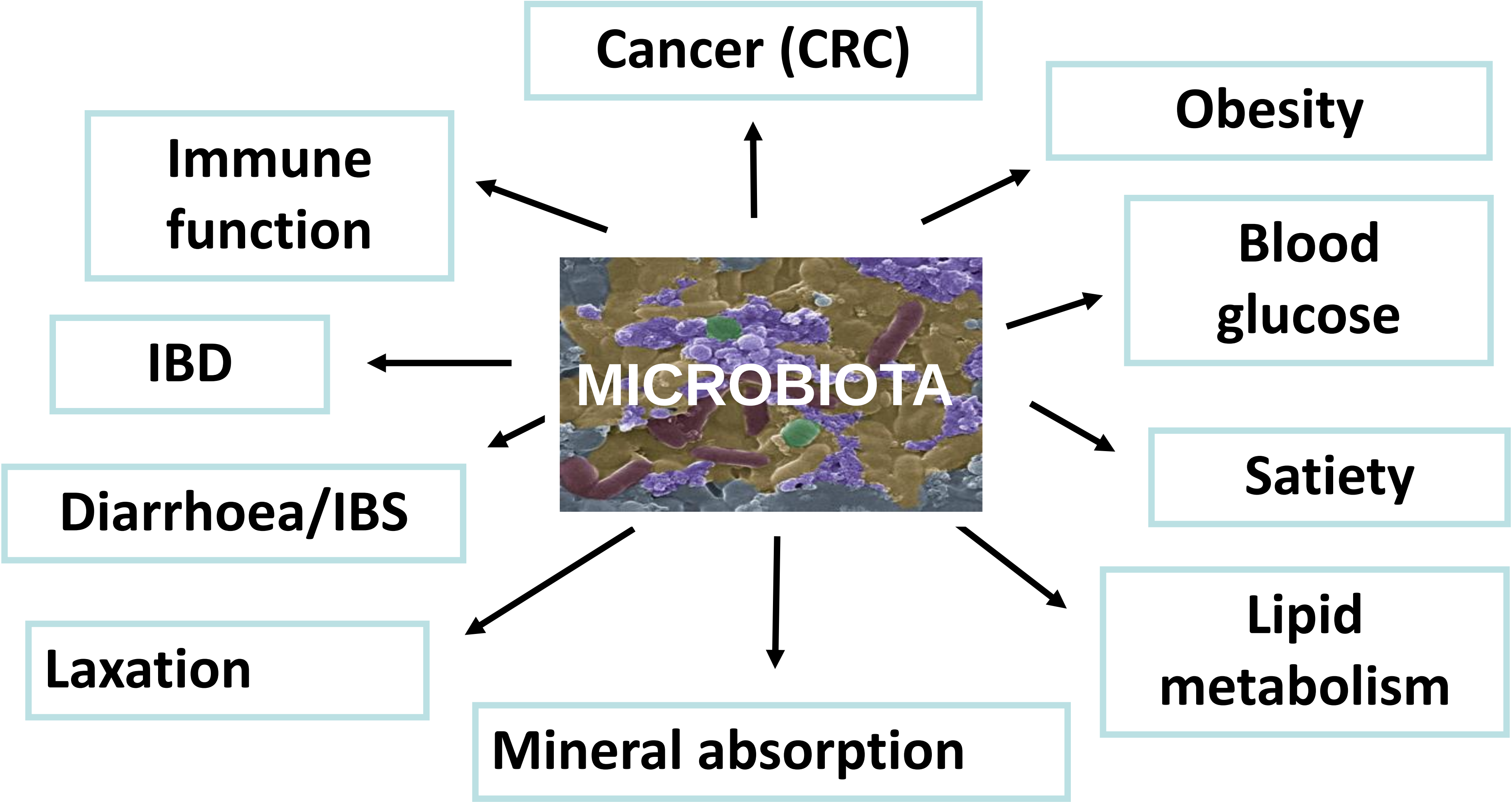
Interactions with;

- Diet
- Drugs
- Immune system
- Gut physiology
- Bile acids/liver
- Systemic metabolism
- Adipose tissue
- Brain development & function

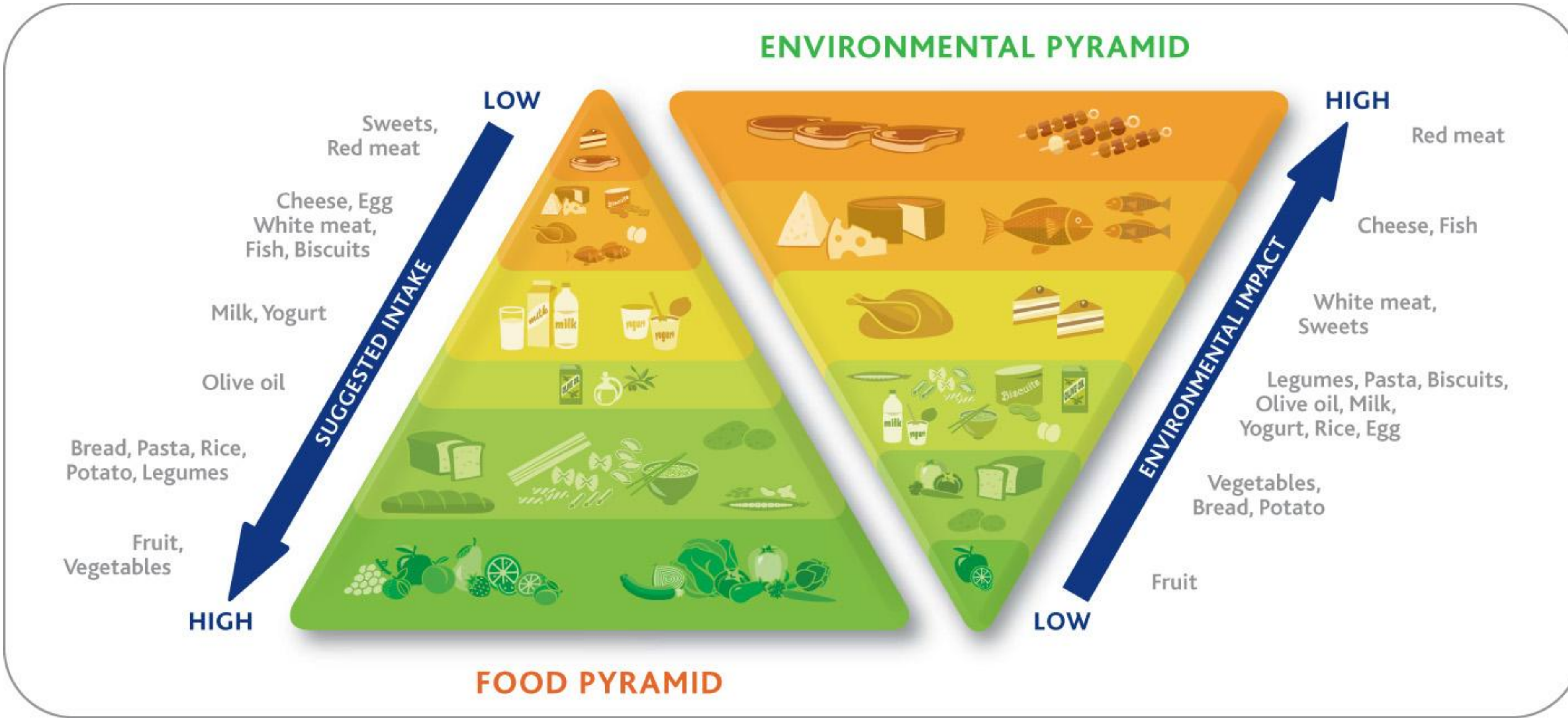
Gut microbiota and essential organ within the human system – we have become an ecosystem


BA recptors e.g. FXR, TGR-5
Conjugated Bile Acids (BA)
Low pH enhances mineral absorption
Propionate regulates hepatic Cholesterol synthesis
Deconjugated BA 1° BA, 2° BA
Butyrate induces mucosal apoptosis, differentiation, and DC maturation
Polyphenol catabolites e.g. Equol
Commensal cross-feeding
Reduced colonic ammonia absorption reduces hepatic encephalopathy
[NH3] ↓
Butyrate, propionate
Glycated polyphenols
Aglycones e.g. diadzein
Acetate increases PYY, GLP-1, (GLP-2) and satiety
Folate CLA Biotin
Tight junction proteins
Acetate lactate formate
Mucosal integrity
Pathogen inhibition
Macrophage phagocytic activity ↑
GRP43 induced neutrophil ↑ROS
Immune homeostasis
Enhanced neutrophile recruitment
sIgA
HSP
Dendritic cell maturation
Treg
BUTYRATE
Anti-inflammatory
Th1
B cell (sIgA production)
Reduced faecal water genotoxicity
IFNγ
Th2
Allergy prevention

Gut microbiota and systemic health



Dietary patterns – Mediterranean diet



INRAN, FAO Double Pyramid

Barilla Centre for Food Nutrition: Double Pyramid: healthy food for people, sustainable food for the planet

http://www.barillacfn.com/en/position-paper/pp-doppia-piramide-alimentazione/

Open Access Research

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BMJ open

Adherence to a Mediterranean diet is associated with a better health-related quality of life: a possible role of high dietary antioxidant content

Marialaura Bonaccio,[1,2] Augusto Di Castelnuovo,[1] Americo Bonanni,[1,3] Simona Costanzo,[1] Francesca De Lucia,[1] George Pounis,[1] Francesco Zito,[1] Maria Benedetta Donati,[2] Giovanni de Gaetano,[2] Licia Iacoviello,[2,4] on behalf of the Moli-sani project Investigators*

Table 2 Multivariate regression coefficients (95% CI) for the association of Mediterranean diet scores or other dietary patterns with mental and physical component scores and further adjustment for food antioxidant content (FAC) or dietary fibre

	β*	95% CI	p Value**	β* Further adjusted for FAC	95% CI	p Value**	B* Further adjusted for dietary fibre	95% CI	p Value**
Mental component score									
Mediterranean diet	0.33	0.18 to 0.49	<0.0001	0.08	−0.09 to 0.25	0.35	0.13	−0.04 to 0.29	0.13
Italian Mediterranean index	0.36	0.20 to 0.51	<0.0001	0.03	−0.14 to 0.22	0.67	0.15	−0.01 to 0.32	0.07
Olive oil and vegetables pattern	0.50	0.34 to 0.65	<0.0001	0.19	−0.003 to 0.38	0.05	0.32	0.15 to 0.50	0.0004
Meat and pasta pattern	0.07	−0.10 to 0.24	0.44	0.05	−0.12 to 0.21	0.59	0.14	−0.03 to 0.31	0.11
Eggs and sweets pattern	−0.33	−0.52 to −0.14	0.001	−0.18	−0.39 to 0.01	0.06	−0.16	−0.36 to 0.04	0.11
Physical component score									
Mediterranean diet	0.15	0.06 to 0.24	0.001	0.13	0.03 to 0.21	0.01	0.16	0.07 to 0.26	0.001
Italian Mediterranean index	0.08	−0.003 to 0.16	0.06	0.06	−0.04 to 0.15	0.26	0.08	−0.01 to 0.17	0.09
Olive oil and vegetables pattern	0.15	0.06 to 0.24	0.001	0.15	0.04 to 0.26	0.01	0.17	0.06 to 0.27	0.0010
Meat and pasta pattern	−0.11	−0.20 to −0.02	0.02	−0.12	−0.22 to −0.03	0.01	−0.11	−0.20 to −0.01	0.03
Eggs and sweets pattern	−0.02	−0.13 to 0.08	0.71	0.004	−0.11 to 0.12	0.94	−0.01	−0.12 to 0.10	0.90

*Regression coefficients represent the variation in mental or physical component scores for a one standard deviation change in MDS, IMI or dietary patterns.
**p for trend values obtained from fully adjusted model for age, sex, BMI, total energy intake, total physical activity, education, income, total socioeconomic status, smoking, diabetes, hypertension, hypercholesterolemia.

“**Conslusions:** Adherence to an MD pattern is associated with better HRQL. The association is stronger with mental health than with physical health. Dietary total antioxidant and fibre content independently explain this relationship”.

Calorie restricted & traditional diets increase life-span and protect against age-associated disease

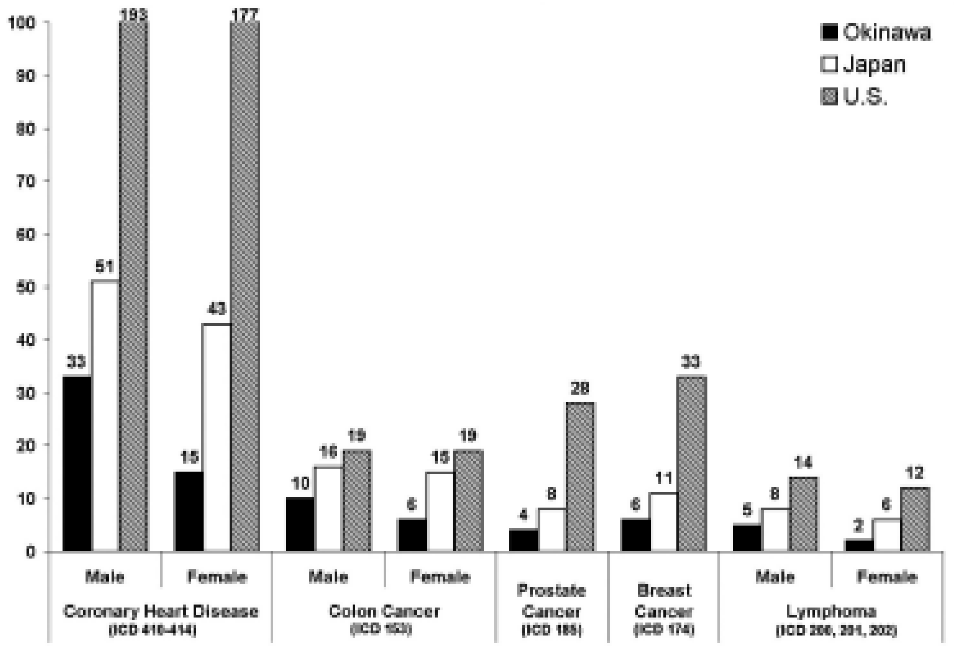

FIGURE 5. Mortality from age-associated diseases in Okinawans versus Americans. Numbers represent age-adjusted mortality rate in deaths per hundred thousand persons per year for 1995. Coding was according to ICD-9 codes; populations were age-adjusted to World Standard Population. These data show markedly lower mortality risk from age-related diseases in Okinawans versus other Japanese and Americans.

- Average life span: Okinawa, 83.8 years; Japan 82.3 years, US 78.9 years

- Traditional Japanese diet: high in vegetables, fruit, soy, fish, fibre

- Low calorie intake, negative energy balance at young age, little weight gain with age, life-long low BMI, low risk of age associated diseases contribute to longevity in Okinawans

Wilcox et al., 2008 Ann NY Acad Sci

Bioactivity of plant based foods against CVD involves the gut microbiota

- **EPIC-elderly study:** (74,607 healthy over 60 year olds (no history of CVD, stroke, or cancer)
  - greater adherence to a plant based (**Mediterranean diet**) in elders was associated with **lower all-cause mortality** (Bamia et al., 2006 Pub Hlth Nutr.)
- **Boyd Orr cohort:** having a vegetable rich diet in childhood was associated with healthy diet in old age (Maynard et al., 2005 Eur J Pub Hlth)
- Diets rich in whole plant foods protect against the diseases of old age especially CVD and may promote longevity and healthy ageing
- Dietary fibre includes **fermentable carbohydrates and prebiotics** which can modulate the composition and activity of the gut **microbiota** and **90% of dietary plant polyphenols** reach the colon

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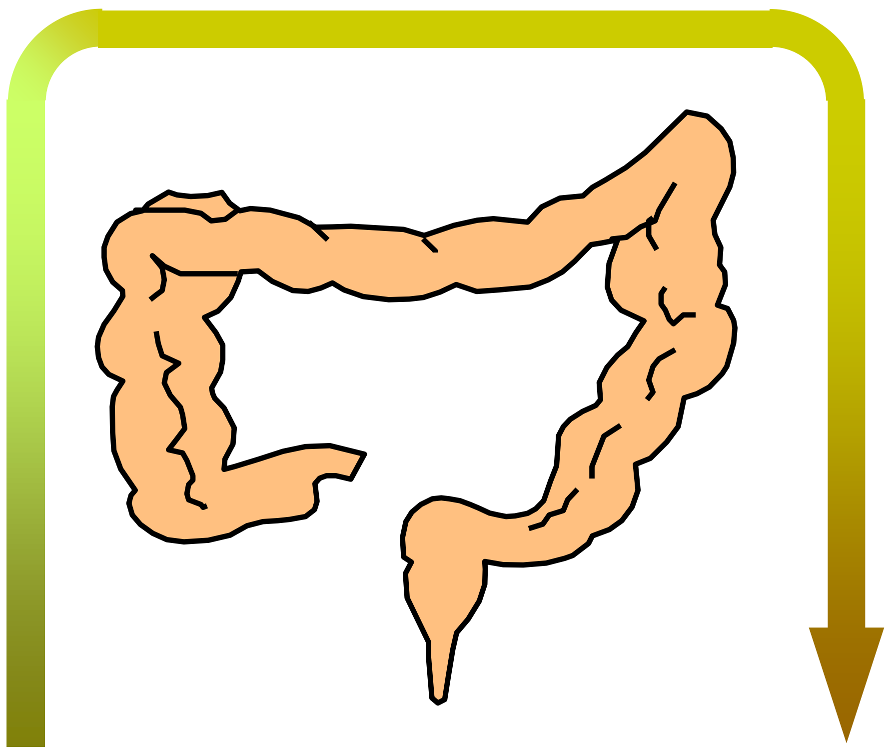
Impact of traditional diets rich in fiber on colonic fermentation

Proximal colon
~ saccharolytic

SCFA
Acetate
Propionate
Butyrate

Energy source
Apoptosis
Differentiation
Epigenetics
Gene expression
Gut hormones
Gut permeability



Distal colon
~ proteolytic

Amines
Indoles
Ammonia
Sulphides
N-nitroso

DNA damage
Tumours
Cytotoxicity
Leaky gut
Liver disease

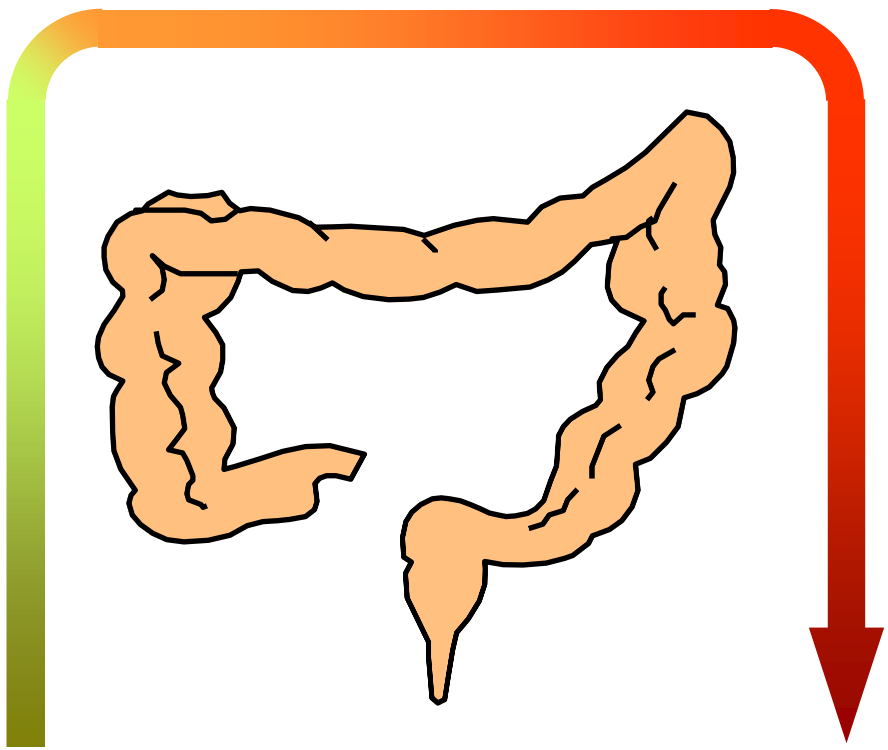
Modified from George Macfarlane

Impact of Western style diet on colonic fermentation

Proximal colon
~ saccharolytic

SCFA
Acetate
Propionate
Butyrate

Energy source
Apoptosis
Differentiation
Epigenetics
Gene expression
Gut hormones
Gut permeability



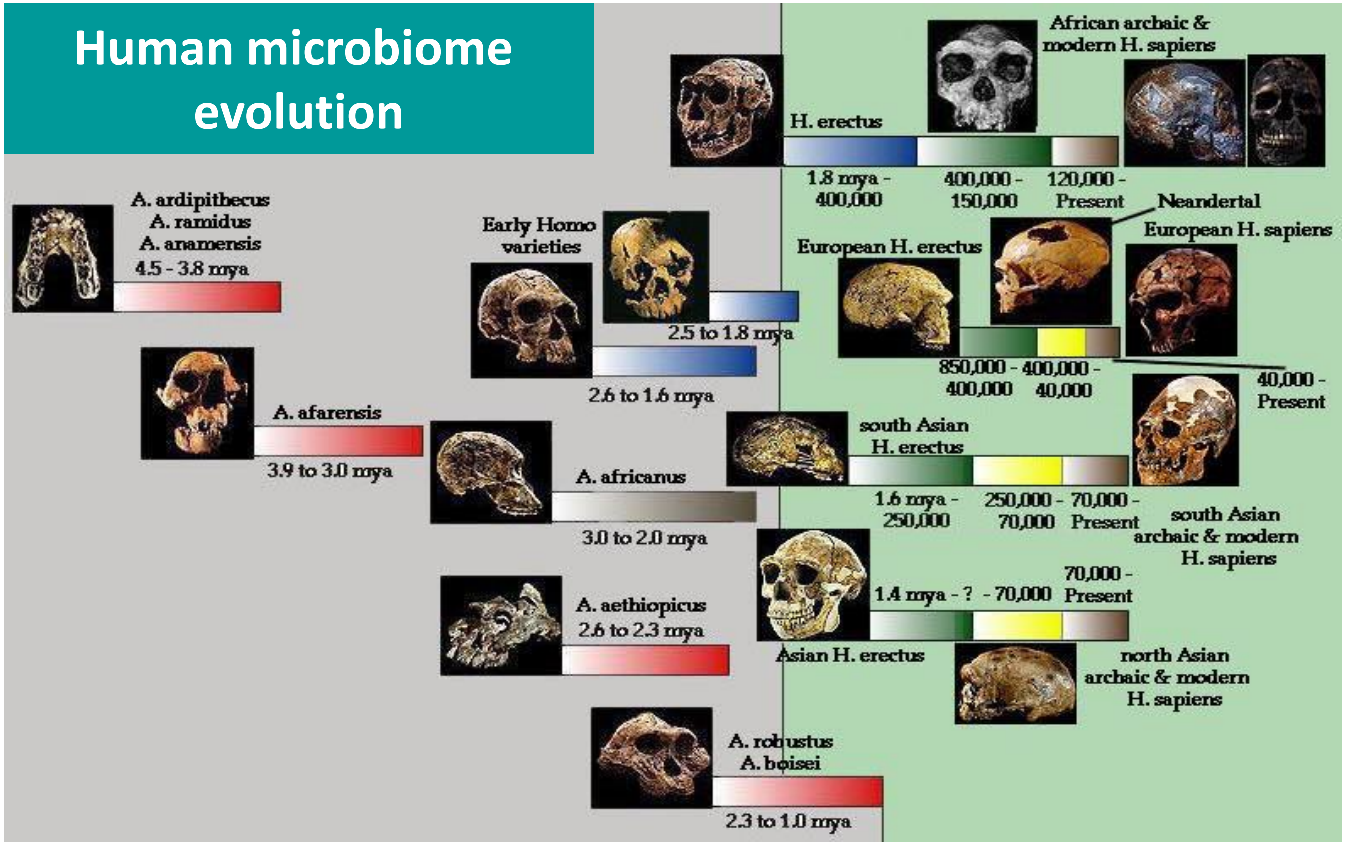
Distal colon
~ proteolytic

Amines
Indoles
Ammonia
Sulphides
N-nitroso

DNA damage
Tumours
Cytotoxicity
Leaky gut
Liver disease

Modified from George Macfarlane

Human diet shaped our closely co-evolved human:microbe ecosystem



Dietary evolution

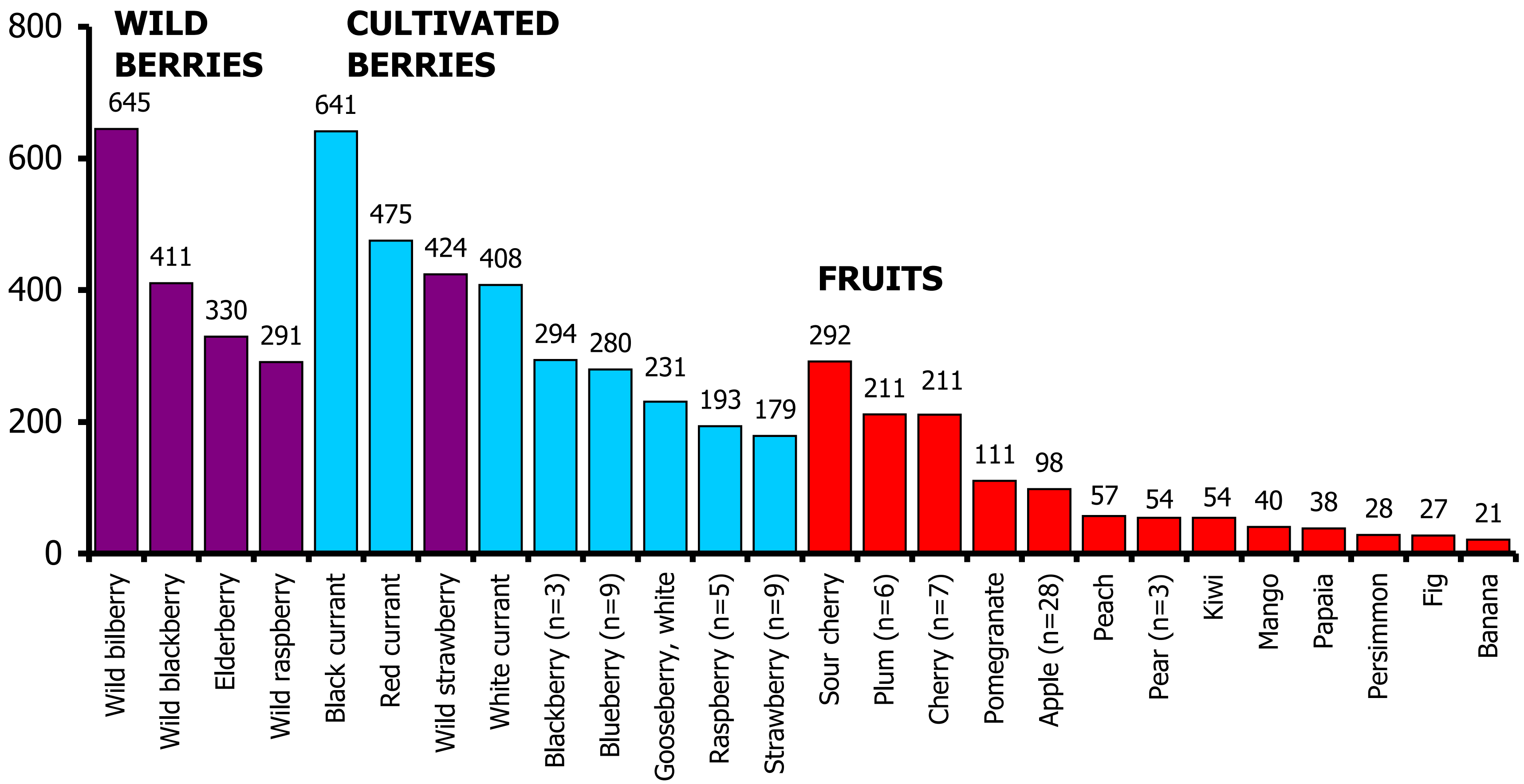
- Neolithic times: ~10,000 yrs BP (birth of agriculture)
- Agricultural/Industrial revolutions: Late 18th and early 19th century
- Green revolution: Over the last 70 yrs (Western-style diet)

Estimated daily fiber intake in Palaeolithic /Traditional diets and Modern diet

Dietary pattern	Fiber content
Palaeolithic diet first reported in 1985 (Eaton SB)	45.7g
Palaeolithic diet modified in 1990 (Eaton SB)	>100g
Palaeolithic diet reported in 1996/1997 (Eaton SB)	104g
Rural Chinese diet	77g
Rural African diet	120g
Current US diet	10-20g
Recommended fiber content in US	25-38g
Current UK diet	12g
Recommended fiber content in UK	18g

(Tuohy et al. Current Pharmaceutical Design, 2009)

Total polyphenols (catechin equivalents, mg/100 g)

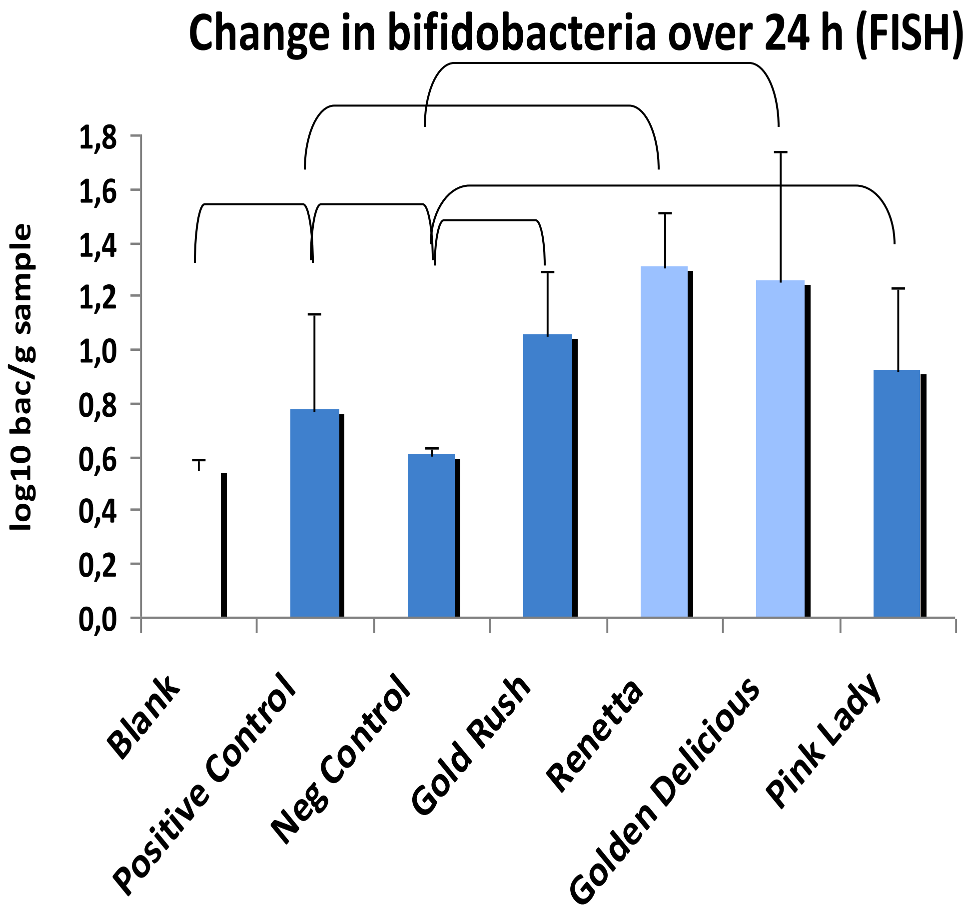


Redrawn from: Mattivi F., Dietas Mediterráneas: La evidencia científica, 2004, 99-111

Microbiota modulation - *in vitro* faecal batch cultures

- 4 commercial apples
- Simulated gastric and small intestinal digestion
- Fermentation pH and temperature controlled anaerobic faecal batch cultures
- FISH microbial enumeration
- Profile of microbial polyphenol catabolites

In vitro bifidogenic effect of apples



Targeting Microbiota Polyphenol metabolism

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JOURNAL OF AGRICULTURAL AND FOOD CHEMISTRY

Article

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A Versatile Targeted Metabolomics Method for the Rapid Quantification of Multiple Classes of Phenolics in Fruits and Beverages

Urska Vrhovsek,* Domenico Masuero, Mattia Gasperotti, Pietro Franceschi, Lorenzo Caputi, Roberto Viola, and Fulvio Mattivi

- Targeted MS based quantitative metabolite analysis
- 139 fruit polyphenols
- UPLC/QqQ-MS/MS
- Modified to accurately quantitify about 150 common fruit polyphenols and their catabolites

Polyphenols/Catabolites after 24h apple faecal fermentation (n=3)

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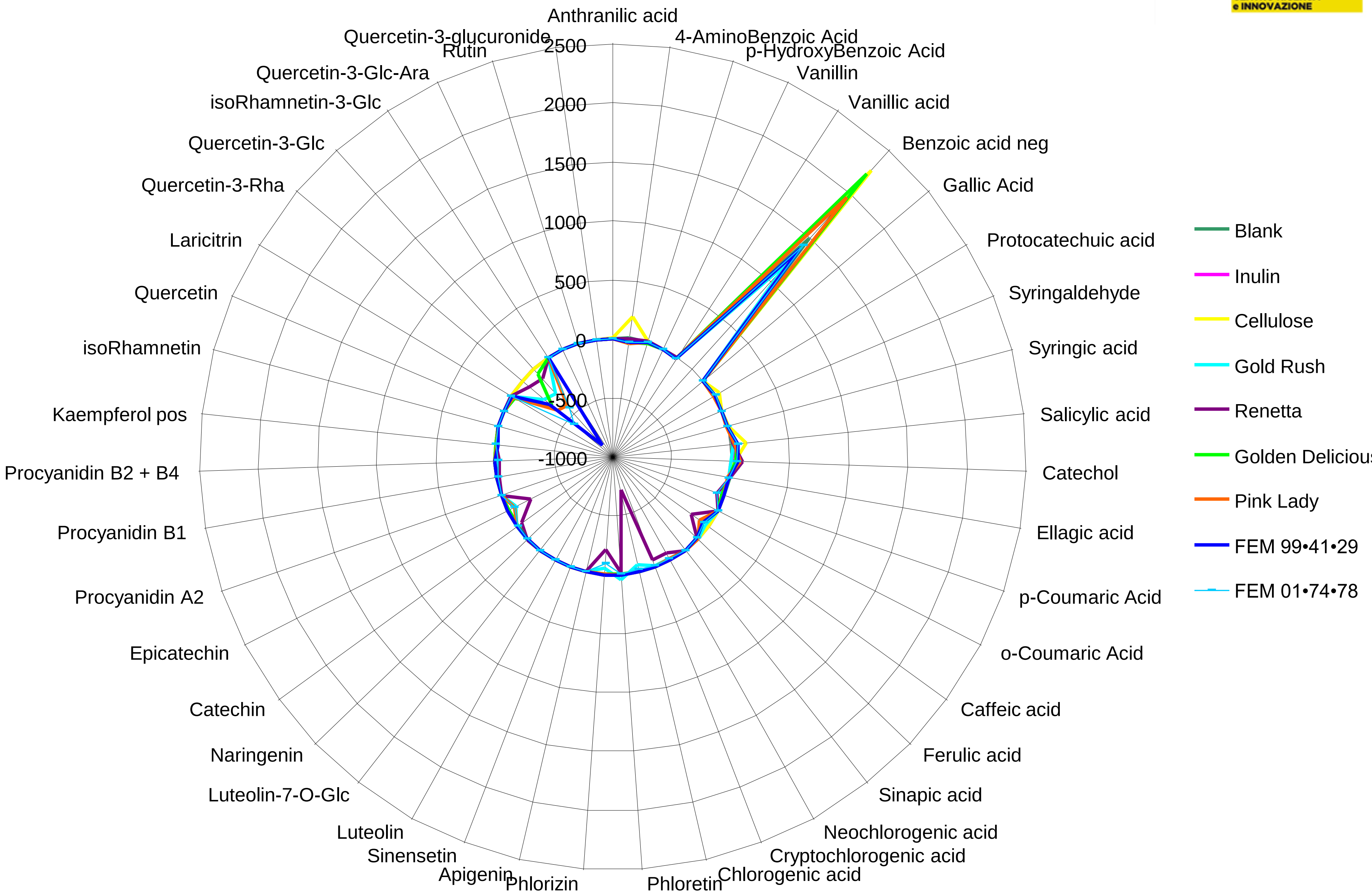
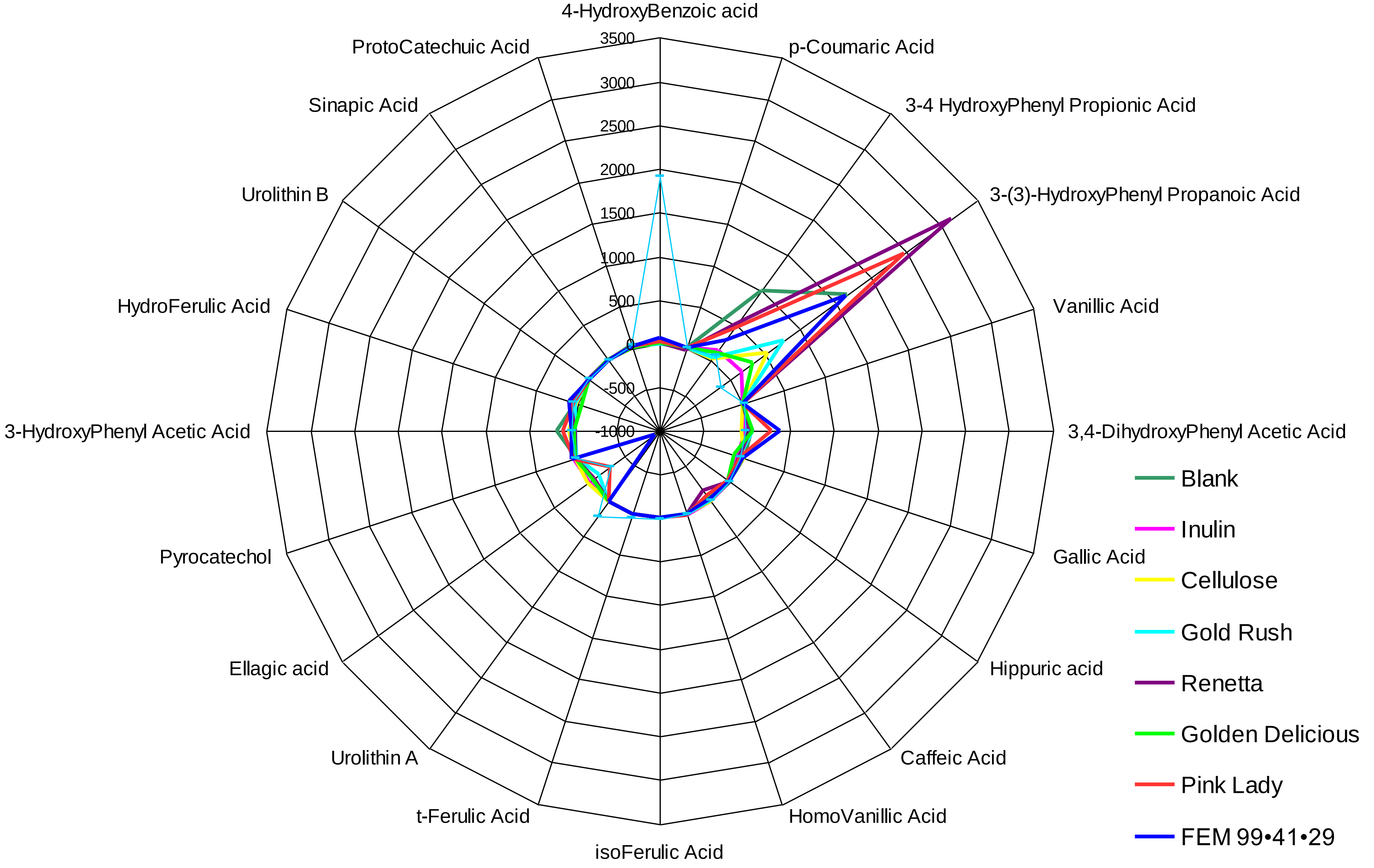


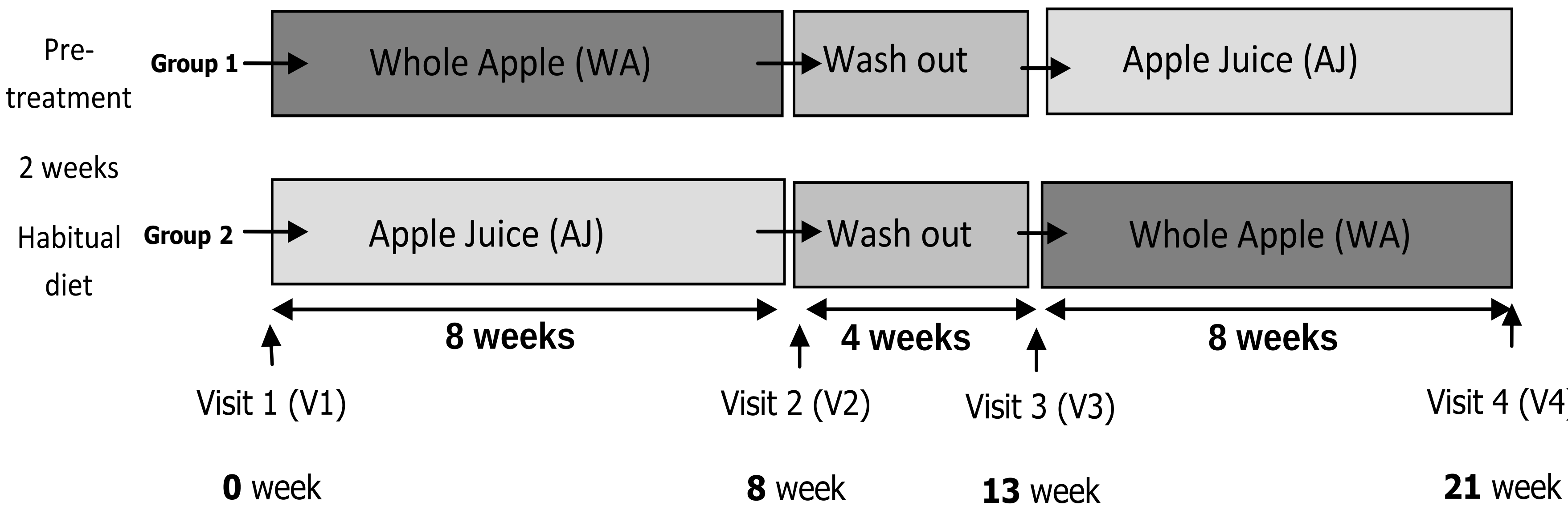
Polyphenols/Catabolites after 24h apple faecal fermentations (n=3)



Measuring the effect of apples (2 per day) on the gut microbiome and heart health.

...from Trentino with love!

Effect of apples consumption on lipid levels, gut health and vascular function in a group of 40 hypercholesterolemic subjects.



Biological samples

- Blood
- Urine
- Faecal sample

Measurements

- anthropometrical
- % body fat composition,
- blood pressure,
- vascular stiffness (pulse wave analysis, PWA)
- and vascular reactivity (laser Doppler imaging, LDI).

University of Reading

Athanasios Koutsos, Joint PhD student

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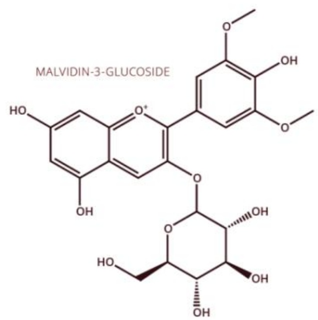
CHEMICAL COMPONENTS
RED WINE

86%	12%	1%	0.4%	0.1%	0.5%
WATER	ETHANOL	GLYCEROL	ORGANIC ACIDS	TANNINS & PHENOLICS	OTHER COMPOUNDS

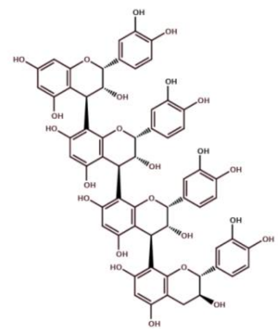
NOTE THAT THESE FIGURES ARE FOR AN AVERAGE COMPOSITION - EXACT PERCENTAGES WILL VARY DEPENDING ON THE PARTICULAR WINE

MALVIDIN-3-GLUCOSIDE



ANTHOCYANINS

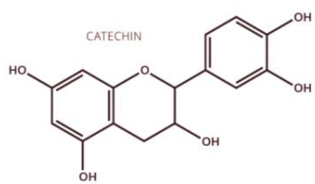
Anthocyanins are found in the skin of grapes. As soon as the grapes are crushed, they can react with other chemicals in wine to produce polymeric pigments. Anthocyanins on their own are also coloured, but the colour varies depending on pH.



TANNINS

Tannins are polymers of other chemicals within wine. Condensed tannins are polymers of flavan-3-ols, and give red wine its astringency, causing a dry feeling in the mouth after drinking. Changes in tannin structure over time are an important factor in wine aging.

CATECHIN

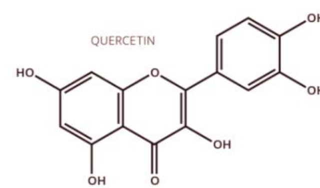


FLAVAN-3-OLS

Flavan-3-ols originate in the seeds of grapes, and are known for their bitterness. In red wine, the amount present can reach up to 800mg/L. 20mg/L is the amount required in order for a bitter taste to be imparted.

OVER 1000 DIFFERENT COMPOUNDS

QUERCETIN



FLAVONOLS

Flavonols can help enhance the colour of red wine via a process called 'co-pigmentation'. They have potential anti-oxidant and anti-carcinogenic effects; however, their concentration in red wine is likely too low to confer significant health benefits.

Red wine polyphenols influence carcinogenesis, intestinal microflora, oxidative damage and gene expression profiles of colonic mucosa in F344 rats

Piero Dolara[a,*], Cristina Luceri[a], Carlotta De Filippo[a], Angelo Pietro Femia[a], Lisa Giovannelli[a], Giovanna Caderni[a], Cinzia Cecchini[b], Stefania Silvi[b], Carla Orpianesi[b], Alberto Cresci[b]

[a] *Department of Pharmacology, University of Florence, Viale G. Pieraccini 6, 50139 Florence, Italy*
[b] *Department of Comparative Morphology and Biochemistry, University of Camerino, Via Emilio 3, 62032 Camerino, Italy*

Mutation Research 591 (2005) 237–246

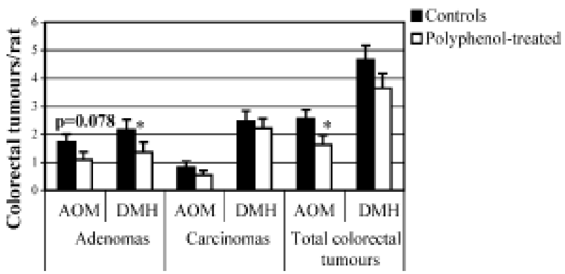


Fig. 1. Number of colorectal tumours/rat in animals induced with two different colon carcinogens (AOM: 7.4 mg/kg × 10; DMH: 30 mg/kg × 10), fed a high fat-low fibre diet (controls) or the same diet containing 50 mg/kg polyphenols (polyphenol-treated) and sacrificed 16 weeks after the last carcinogen injection. Values are mean ± S.E. ($n = 24$ in the control group of DMH experiment; $n = 22$ in all other groups). *Significantly different as compared to control groups by Poisson regression analysis ($p < 0.05$).

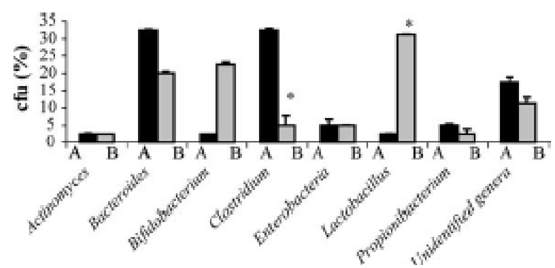


Fig. 2. Bacterial genera predominantly identified in the faecal content of rats induced with DMH (30 mg/kg × 10), fed a high fat-low fibre diet (controls, A) or the same diet containing 50 mg/kg polyphenols (polyphenol treated, B) after 15 weeks of feeding following the last carcinogen injection. Values are expressed as means of three replicates ± S.D. The reported values are percentages calculated on the total number of anaerobic microorganisms. *$p < 0.05$ compared to the control group (A) with unpaired Student's t-test.

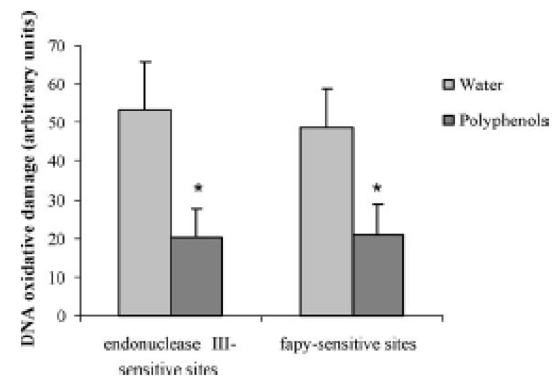


Fig. 3. Effect of wine polyphenol treatment on oxidative DNA damage in colon mucosa in rats treated by oral gavage of polyphenols (0.5 ml per day, 57 mg/kg in water) or water alone, by gavage for 10 days). Pyrimidine (endonuclease III-sensitive sites) and purine (fapy-sensitive sites) oxidation are expressed in arbitrary units (AU). Values (mean ± S.E.M. of nine animals per group) are the difference between DNA damage detected before and after endonuclease III (endo III) or formamido-pyrimidine-glycosylase (fapy) digestion. *$p < 0.05$ compared to the control group (Student's t-test).

Red wine prevents the postprandial increase in plasma cholesterol oxidation products: a pilot study

F. Natella[1]*, A. Macone[2], A. Ramberti[1], M. Forte[1], F. Mattivi[3], R. M. Matarese[2] and C. Scaccini[1]

[1]National Research Institute on Food and Nutrition, Via Ardeatina, 546, 00178 Rome, Italy

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NS British Journal of Nutrition

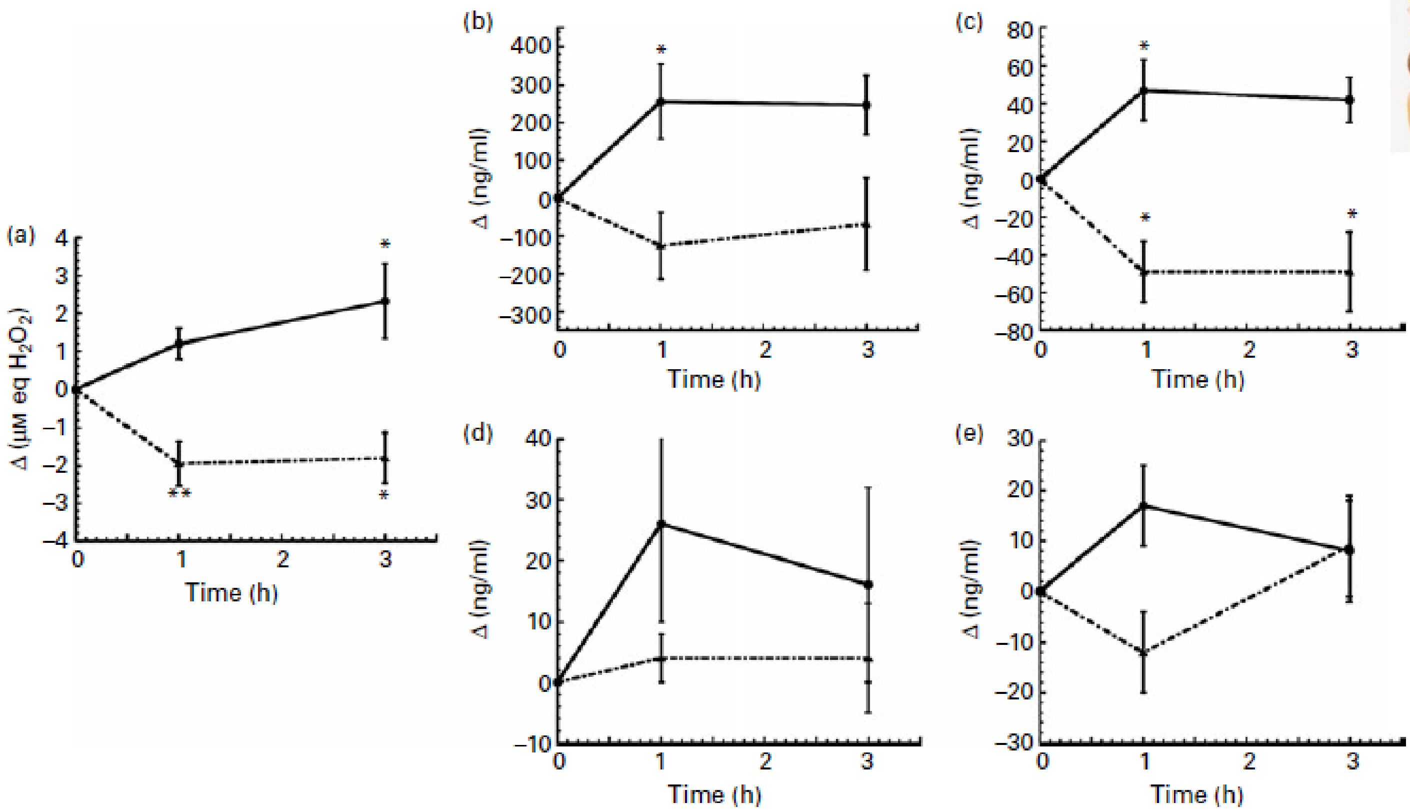

Fig. 1. Time course of plasma (a) lipid hydroperoxides and oxycholesterols ((b) 7-ketocholesterol, (c) 7-β-hydroxycholesterol, (d) 5α,6α-epoxycholesterol and (e) 5β,6β-epoxycholesterol) after the administration of the control meal (—) or wine meal (···). Values are means, with standard errors represented by vertical bars (n 12). Mean values were significantly different from those of homologous time 0: * $P<0.05$ and ** $P<0.01$ (by repeated-measures ANOVA, followed by Tukey's test).

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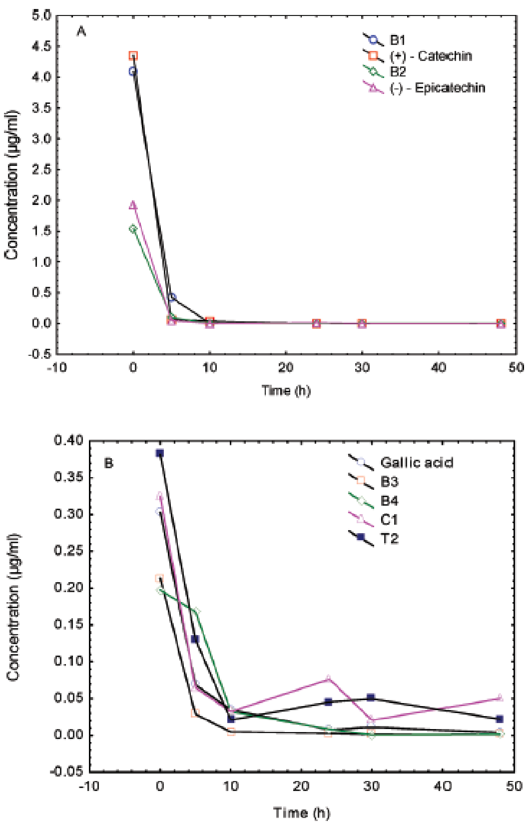
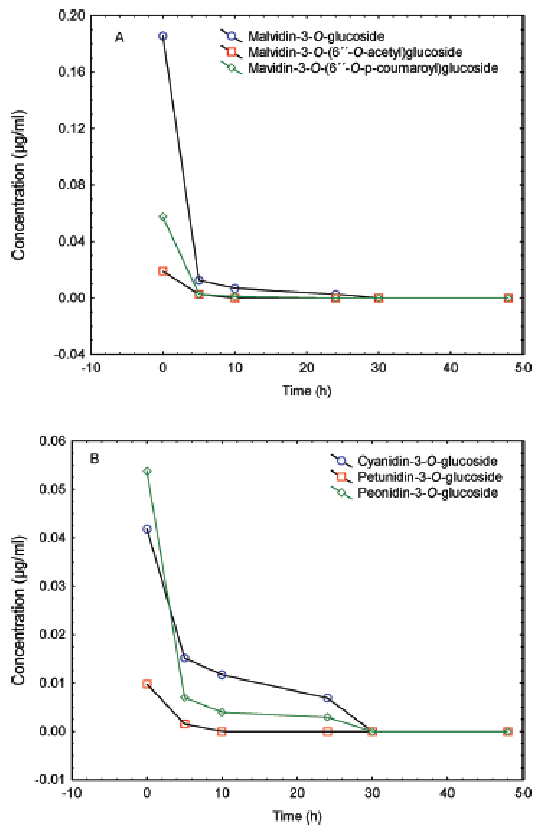
In Vitro Fermentation of a Red Wine Extract by Human Gut Microbiota: Changes in Microbial Groups and Formation of Phenolic Metabolites

Fernando Sánchez-Patán,[†] Carolina Cueva,[†] Maria Monagas,[†] Gemma E. Walton,[‡] Glenn R. Gibson M.,[‡] Jesús E. Quintanilla-López,[§] Rosa Lebrón-Aguilar,[∥] P. J. Martín-Álvarez,[†] M. Victoria Moreno-Arribas,[†] and Begoña Bartolomé*,[†]





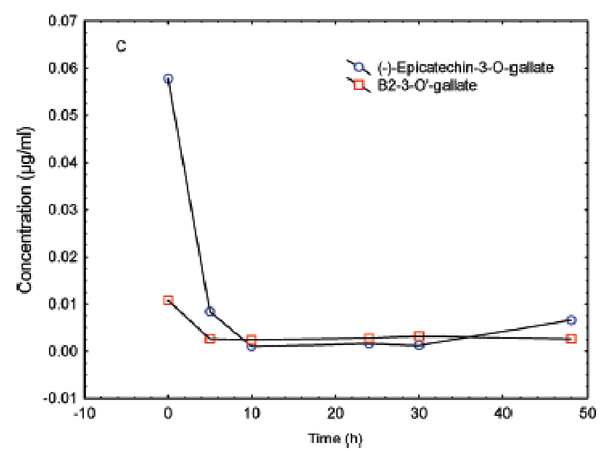


Figure 3. Changes in gallic acid and flavan-3-ols during fecal fermentation (volunteer V1) of the red wine extract: (A) catechin, epicatechin, and procyanidins B1 and B2; (B) gallic acid and procyanidins B3, B4, C1, and T2; (C) epicatechin-3-*O*-gallate and procyanidin B2-3′-*O*-gallate.

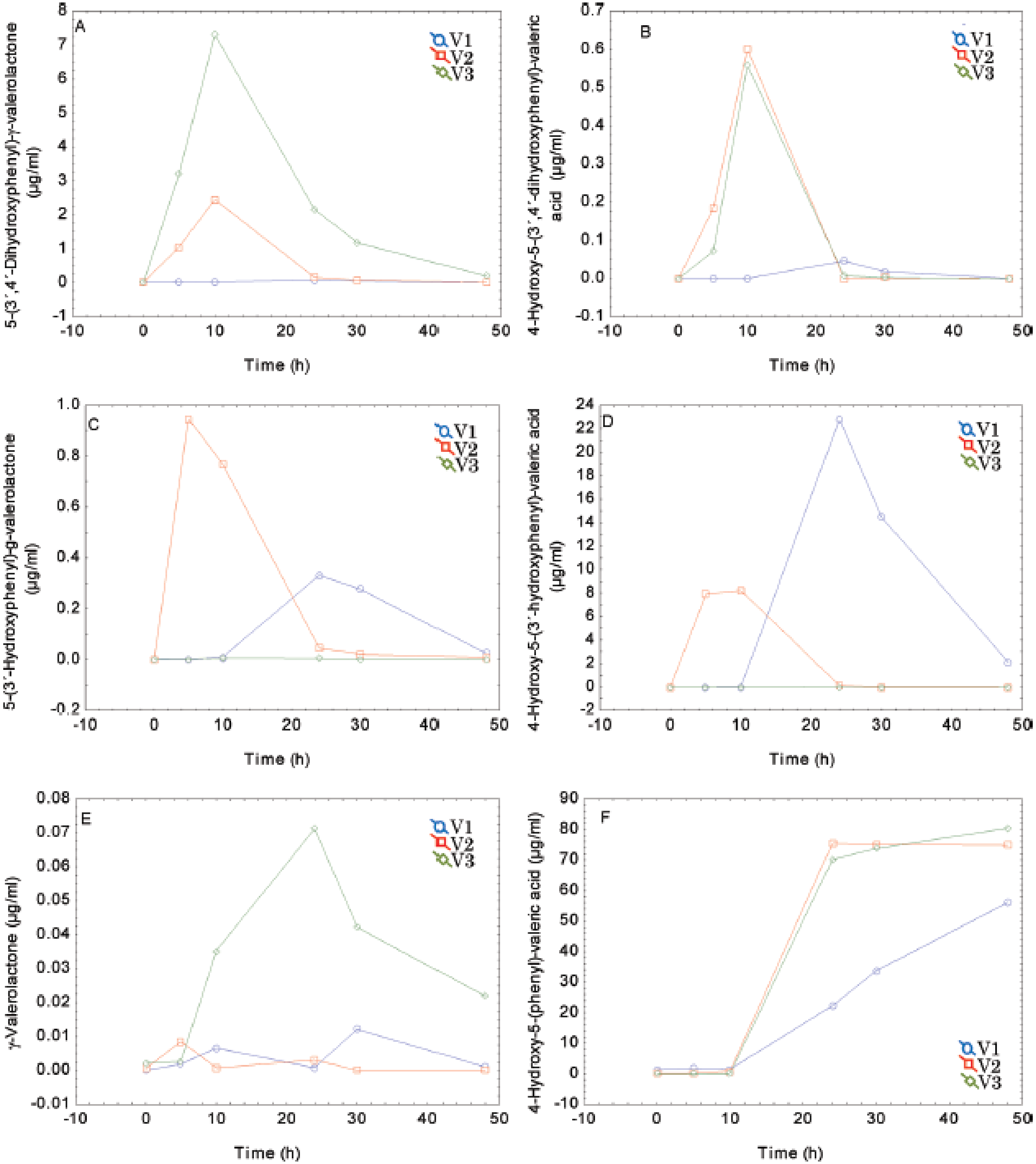


Figure 5. Changes in phenyl-γ-valerolactone and 4-hydroxy-5-(phenyl)-valeric acid derivatives during fecal fermentation (volunteers V1, V2, and V3) of the red wine extract. (A) 5-(3′,4′-Dihydroxyphenyl)-γ-valerolactone; (B) 4-hydroxy-5-(3′,4′-dihydroxyphenyl)-valeric acid; (C) 5-(3′-hydroxyphenyl)-γ-valerolactone; (D) 4-hydroxy-5-(3′-hydroxyphenyl)-valeric acid; (E) γ-valerolactone; (F) 4-hydroxy-5-(phenyl)-valeric acid.

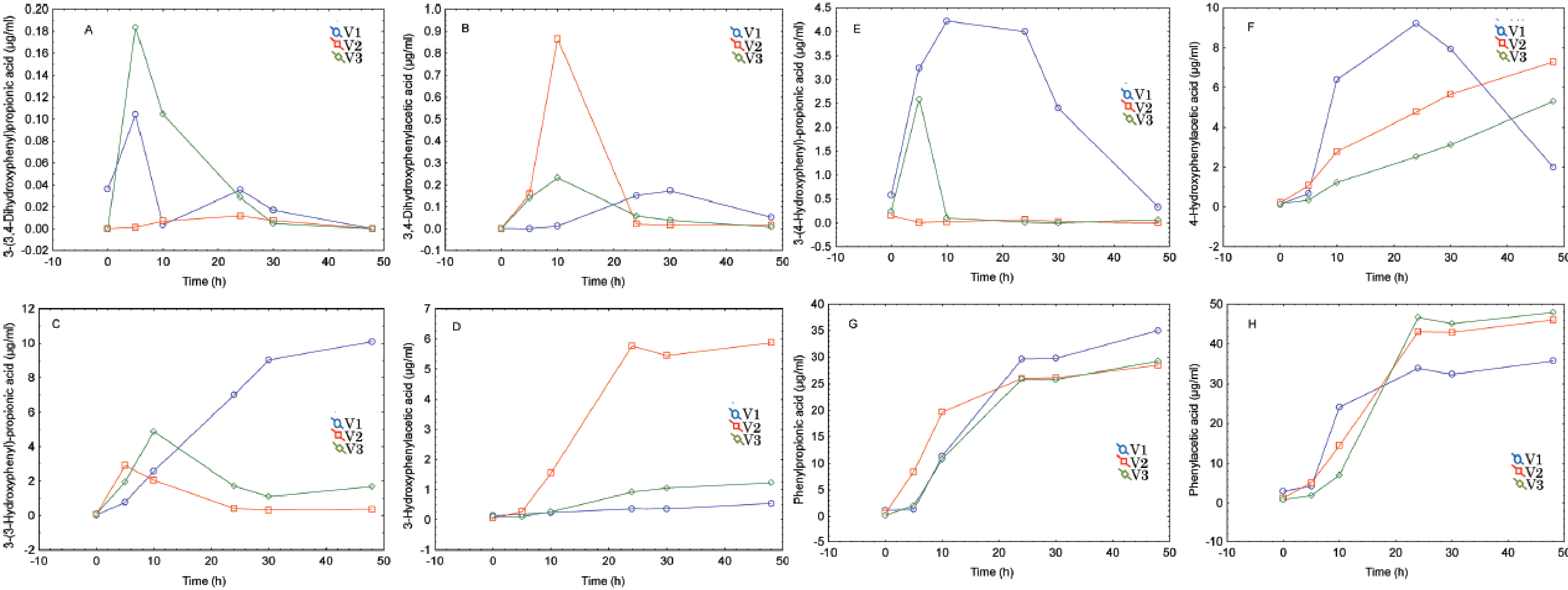


Figure 6. Changes in phenylpropionic and phenylacetic acid derivatives during fecal fermentation (volunteers V1, V2, and V3) of the red wine extract. (A) 3-(3,4-Dihydroxyphenyl)-propionic acid; (B) 3,4-dihydroxyphenylacetic acid; (C) 3-(3-hydroxyphenyl)-propionic acid; (D) 3-hydroxyphenylacetic acid; (E) 3-(4-hydroxyphenyl)-propionic acid; (F) 4-hydroxyphenylacetic acid; (G) phenylpropionic acid; (H) phenylacetic acid.

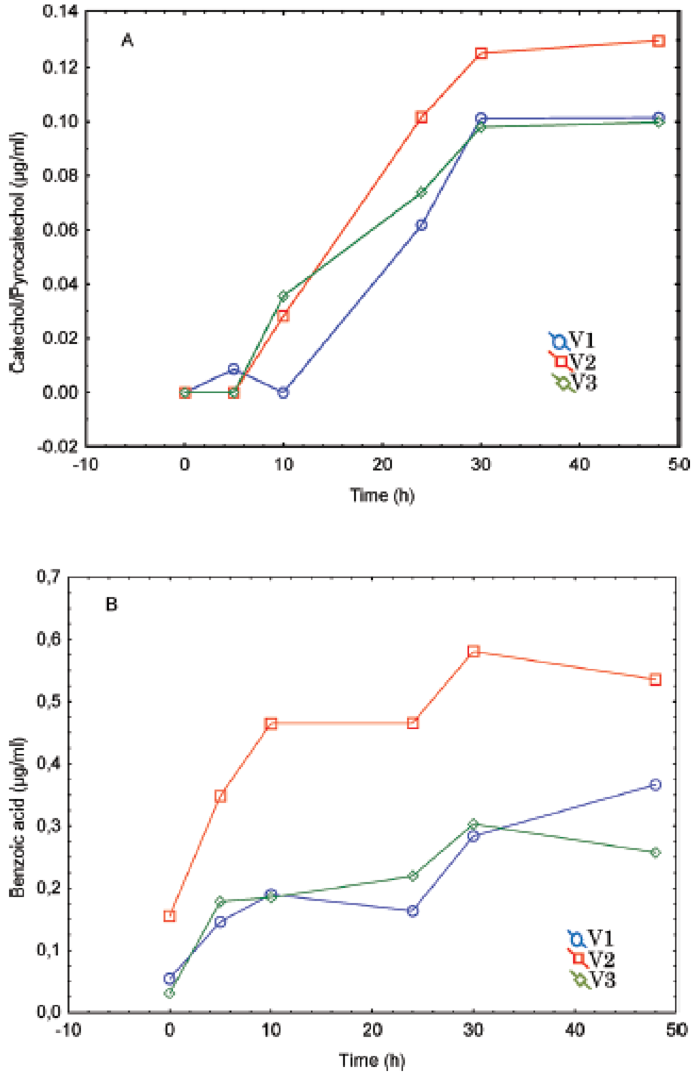


Figure 7. Changes in simple phenols and benzoic acid derivatives during fecal fermentation (volunteers V1, V2, and V3) of the red wine extract. (A) Catechol/pyrocatechol; (B) benzoic acid.

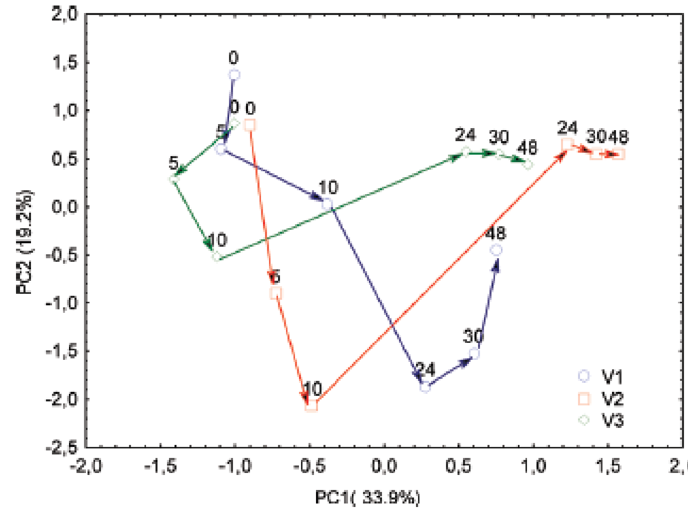


Figure 8. Representation of the samples in the plane defined by the first two principal components (PC1 and PC2) resulting from a PCA of microbial-derived phenolic metabolites (n = 16) for the three volunteers (V1, V2, and V3) at different incubation times (0, 5, 10, 24, 30, and 48 h).

Influence of red wine polyphenols and ethanol on the gut microbiota ecology and biochemical biomarkers[1–4]

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TABLE 2
Daily polyphenol and alcohol consumption from 272 mL red wine, 272 mL de-alcoholized red wine, and 100 mL gin used in this study[1]

	De-alcoholized red wine	Red wine	Gin	P^2
Total phenols (mEq GA)	733.02 ± 23.61[3]	797.86 ± 102.63	ND	0.426
Phenolic compounds (mg/dose)				
Anthocyanins				
Delphinidin-3-glucoside	4.00 ± 0.44	4.15 ± 0.24	ND	0.589
Petunidin-3-glucoside	3.27 ± 0.31	3.34 ± 0.29	ND	0.755
Peonidin-3-glucoside	1.82 ± 0.16	1.84 ± 0.17	ND	0.797
Malvidin-3-glucoside	13.56 ± 1.16	13.28 ± 1.21	ND	0.787
Malvidin-(6-acetyl)-3-glucoside	2.83 ± 0.33	2.98 ± 0.26	ND	0.563
Malvidin-(6-coumaroyl)-3-glucoside	0.96 ± 0.09	1.13 ± 0.07	ND	0.066
Flavonols				
Quercetin-3-glucuronide	3.06 ± 0.39	3.23 ± 0.38	ND	0.770
Quercetin	6.48 ± 0.64	7.25 ± 0.21	ND	0.161
Isorhamnetin	0.80 ± 0.04	0.91 ± 0.07	ND	0.114
Stilbenes				
trans-Resveratrol	0.74 ± 0.06	0.79 ± 0.10	ND	0.352
cis-Resveratrol	0.75 ± 0.04	0.76 ± 0.04	ND	0.761
trans-Piceid	2.86 ± 0.26	2.56 ± 0.31	ND	0.160
cis-Piceid	1.93 ± 0.24	2.10 ± 0.09	ND	0.226
Flavan-3-ols				
Catechin	34.39 ± 3.63	33.60 ± 3.07	ND	0.786
Epicatechin	19.20 ± 2.24	18.46 ± 2.11	ND	0.699
Procyanidin B1	17.50 ± 2.10	17.52 ± 1.52	ND	0.712
Procyanidin B2	12.92 ± 1.44	12.41 ± 0.74	ND	0.502
Procyanidin B3	7.48 ± 0.08	6.85 ± 0.08	ND	0.526
Procyanidin B4	13.19 ± 1.35	13.33 ± 1.54	ND	0.934
Hydroxybenzoic acids				
GA acid	19.90 ± 1.91	18.63 ± 1.74	ND	0.306
Protocatechuic acid	1.59 ± 0.14	1.42 ± 0.17	ND	0.246
Hydroxycinnamic acids				
2-*S*-Glutathionylcaftaric	2.93 ± 0.34	2.80 ± 0.27	ND	0.956
trans-Caftaric	5.23 ± 0.44	5.06 ± 0.39	ND	0.595
trans-Caffeic	3.31 ± 0.25	3.13 ± 0.22	ND	0.246
trans-Coutaric	1.53 ± 0.14	1.42 ± 0.12	ND	0.182
Tyrosols				
Tyrosol	13.01 ± 1.06	11.86 ± 1.29	ND	0.298
Alcoholic content (g)	<1	30	30	

[1] GA, gallic acid; ND, not detected.
[2] Reflects the comparison between red wine and de-alcoholized red wine polyphenols (Student's *t* test for independent samples).
[3] Mean ± SD (all such values; $n = 2$).

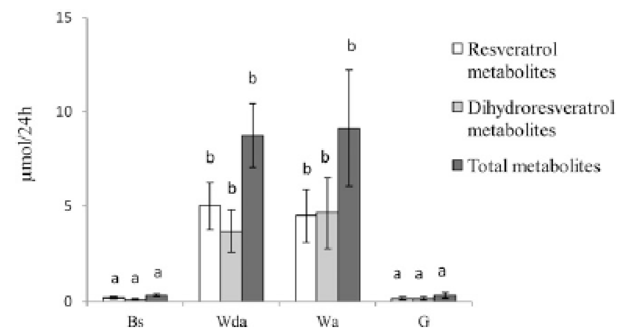

FIGURE 1. Mean (±SEM) resveratrol metabolites, dihydroresveratrol metabolites, and total metabolites (resveratrol and dihydroresveratrol) quantified in 24-h urine samples from 10 volunteers at Bs, Wda, Wa, and G. The changes between the intervention treatments were analyzed by using the Friedman test. Wilcoxon's signed-rank test was used to compare the treatments with one another. Values in a box of the same shade of gray with different lowercase letters are significantly different, $P < 0.05$ (Bonferroni post hoc test). Bs, baseline sample; G, sample after gin consumption; Wa, sample after red wine consumption; Wda, sample after de-alcoholized red wine consumption.

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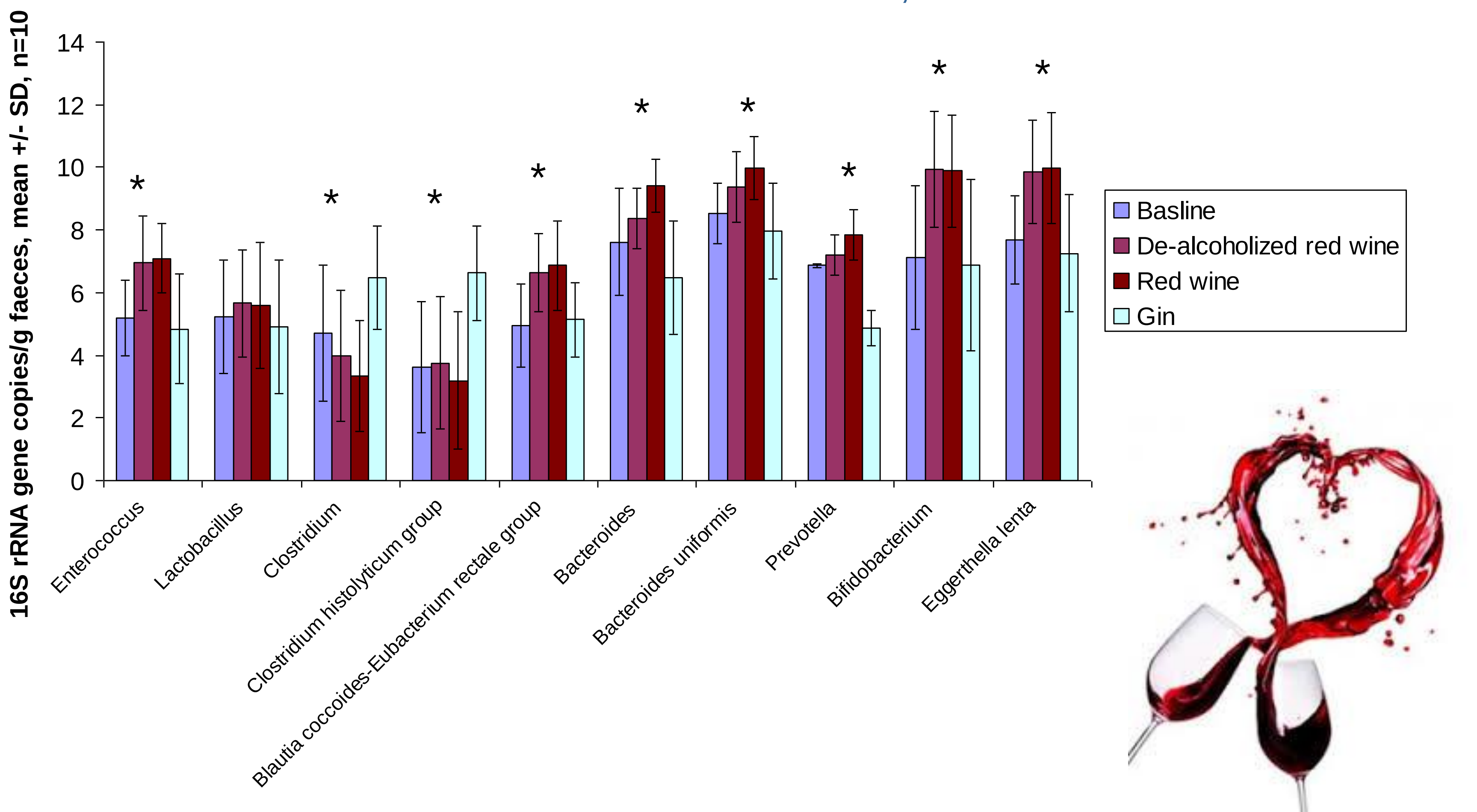

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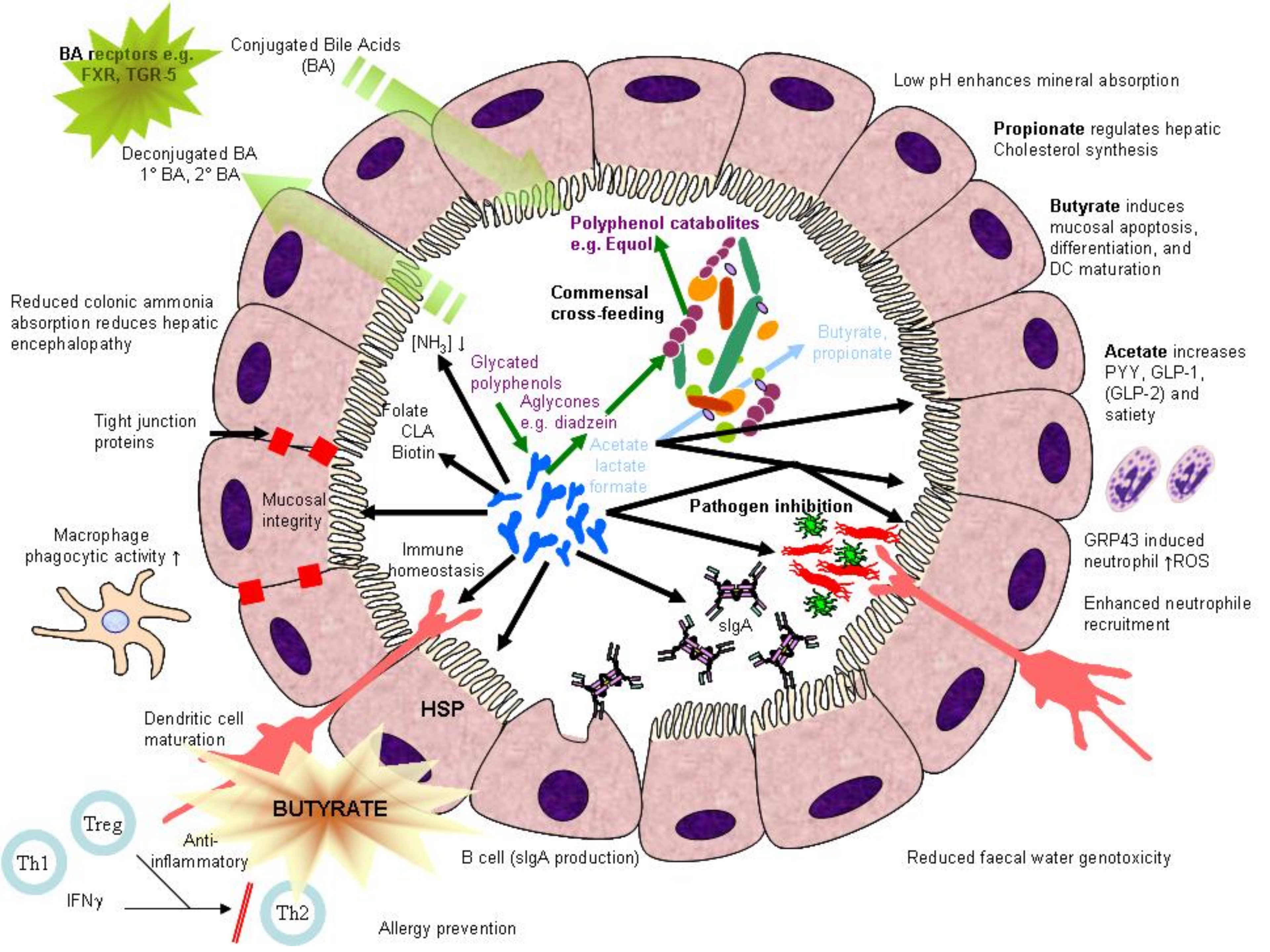
TABLE 4
Anthropometric and biochemical variables during the study[1]

	Baseline (washout period)	De-alcoholized red wine period	Red wine period	Gin period	P^2
Weight (kg)	97.8 ± 21.3	97.8 ± 19.4	96.4 ± 20.6	97.2 ± 19.6	0.306
Waist (cm)	106.7 ± 14.3	106.5 ± 14.4	105.1 ± 14.5	105.7 ± 13.5	0.392
Hip (cm)	111.0 ± 10.4	109.0 ± 12.8	110.2 ± 11.1	110.8 ± 10.3	0.908
DBP (mm Hg)	97.4 ± 15.2[a]	91.0 ± 12.9[a]	86.5 ± 11.6[b]	98.4 ± 14.3[a]	0.026
SBP (mm Hg)	145.4 ± 23.9[a]	135.1 ± 24.6[b]	129.5 ± 17.6[b]	142.7 ± 22.3[a]	0.026
BMI (kg/m^2)	27.6 ± 3.2	27.6 ± 3.1	27.5 ± 2.9	27.6 ± 2.8	0.241
Glucose (mg/dL)	111.3 ± 23.1	104.5 ± 24.2	108.5 ± 16.4	108.8 ± 17.2	0.772
Uric acid (mg/dL)	5.7 ± 1.1[a]	5.3 ± 1.0[a]	5.0 ± 0.8[b]	5.4 ± 1.5[a]	0.018
GOT (mg/dL)	22.0 ± 7.3[a]	14.3 ± 4.0[b]	17.6 ± 13.4[b]	19.1 ± 8.0[a]	0.021
GPT (mg/dL)	46.4 ± 12.6	41.2 ± 7.7	42.0 ± 9.3	43.1 ± 6.9	0.888
GGT (mg/dL)	36.9 ± 25.6[a]	30.1 ± 13.5[b]	36.1 ± 16.3[b]	38.0 ± 27.7[a]	0.012
Triglycerides (mg/dL)	245.4 ± 231.7[a]	171.7 ± 206.7[b]	179.4 ± 177.1[b]	190.1 ± 222.5[b]	0.001
Cholesterol (mg/dL)	257.5 ± 88.6[a]	241.2 ± 94.9[a]	188.6 ± 61.6[b]	235.3 ± 91.4[a]	0.008
LDL cholesterol (mg/dL)	129.6 ± 41.9	123.5 ± 28.1	125.7 ± 30.3	130.6 ± 22.0	0.266
HDL cholesterol (mg/dL)	58.5 ± 16.7[a]	48.8 ± 17.1[b]	49.7 ± 14.3[b]	52.3 ± 16.5[a]	0.001
CRP (mg/L)	6.9 ± 2.6[a]	4.3 ± 2.3[b]	4.6 ± 2.5[b]	6.8 ± 3.7[a]	0.001

[1] All values are means ± SDs; n = 10 subjects. Means in a row with different superscript letters are significantly different, $P < 0.05$ (Wilcoxon's signed-rank test with post hoc Bonferroni test). CRP, C-reactive protein; DBP, diastolic blood pressure, GGT, γ-glutamyl transferase; GOT, glutamic oxaloacetic transaminase; GPT, glutamic pyruvic transaminase; SBP, systolic blood pressure.

[2] Derived by using the Friedman test.


BA recptors e.g. FXR, TGR-5
Conjugated Bile Acids (BA)
Low pH enhances mineral absorption
Propionate regulates hepatic Cholesterol synthesis
Deconjugated BA 1° BA, 2° BA
Butyrate induces mucosal apoptosis, differentiation, and DC maturation
Polyphenol catabolites e.g. Equol
Commensal cross-feeding
Reduced colonic ammonia absorption reduces hepatic encephalopathy
[NH3] ↓
Butyrate, propionate
Glycated polyphenols
Aglycones e.g. diadzein
Acetate increases PYY, GLP-1, (GLP-2) and satiety
Tight junction proteins
Folate CLA Biotin
Acetate lactate formate
Mucosal integrity
Pathogen inhibition
Macrophage phagocytic activity ↑
GRP43 induced neutrophil ↑ROS
Immune homeostasis
sIgA
Enhanced neutrophile recruitment
HSP
Dendritic cell maturation
BUTYRATE
Treg
Th1
Anti-inflammatory
IFNγ
Th2
B cell (sIgA production)
Reduced faecal water genotoxicity
Allergy prevention

Summary

- **Gut microbiota:** an important contributor to human health and disease
- **Microbiota modification by diet:** foods and compounds which comprise a large part of the Mediterranean diet, foods rich in fiber and polyphenols influence both the relative composition and metabolic output of the gut microbiota
- **Wine**, a distinctive part of the **Mediterranean diet** is rich in polyphenols, many of which are antioxidants, escape digestion in the upper gut, and are rendered biologically available and/or biologically active by the gut microbiota
- **Red wine and red wine polyphenols** appear to have a direct effect on relative abundance of bacteria within the gut, **increasing beneficial microorganisms**
- **Red wine microbiota modulation** occurs in parallel with improvements in **markers of metabolic health.**
- **Wine:microbiota interactions** may be involved the observed protection from chronic disease associated with modest wine intake

Fondazione Edmund Mach

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