Modulation of gut microbiota by plant polyphenols: A Paradigm Shift in Understanding their Effects on Diseases

Québec City, 22 October 2014

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Laval University
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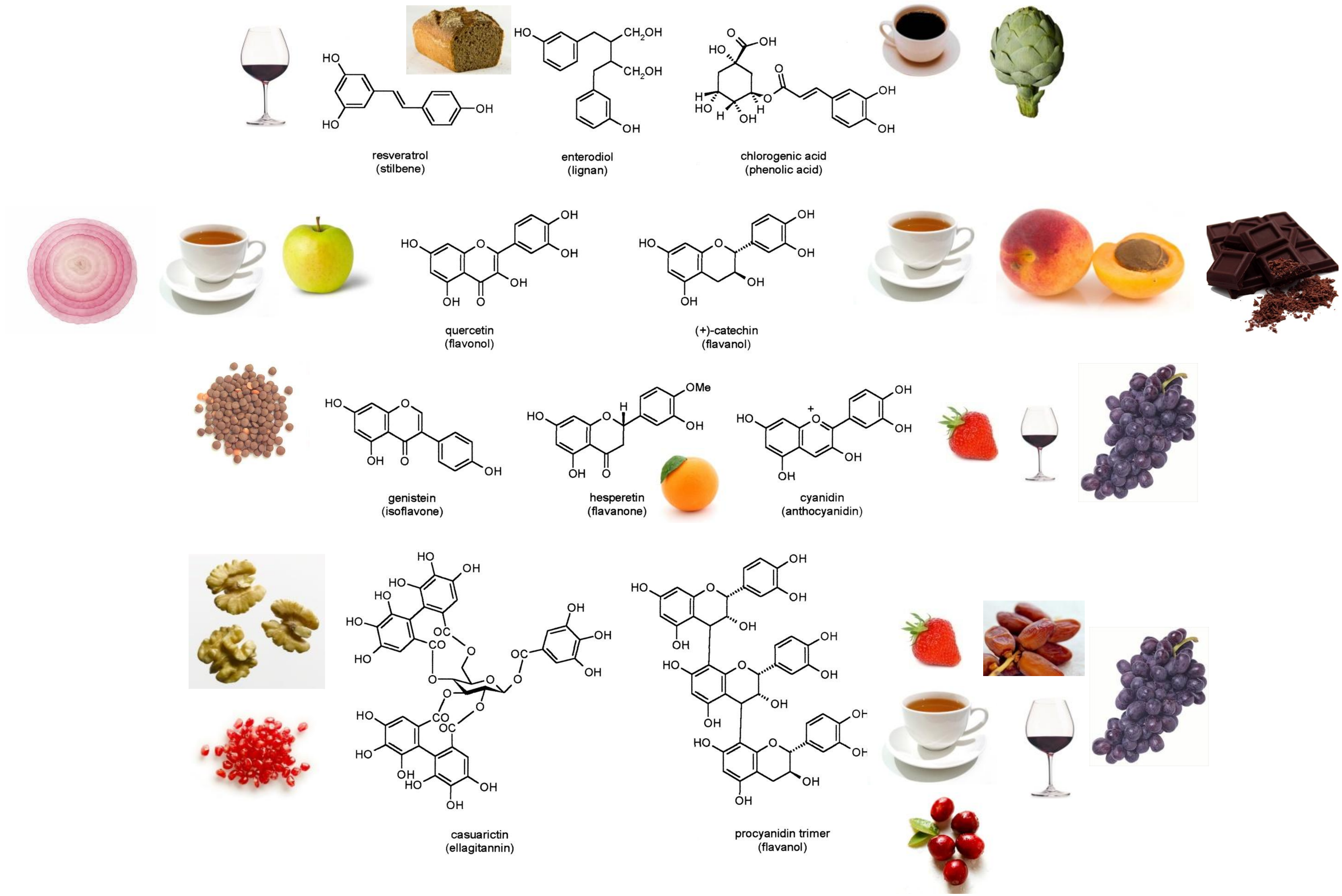
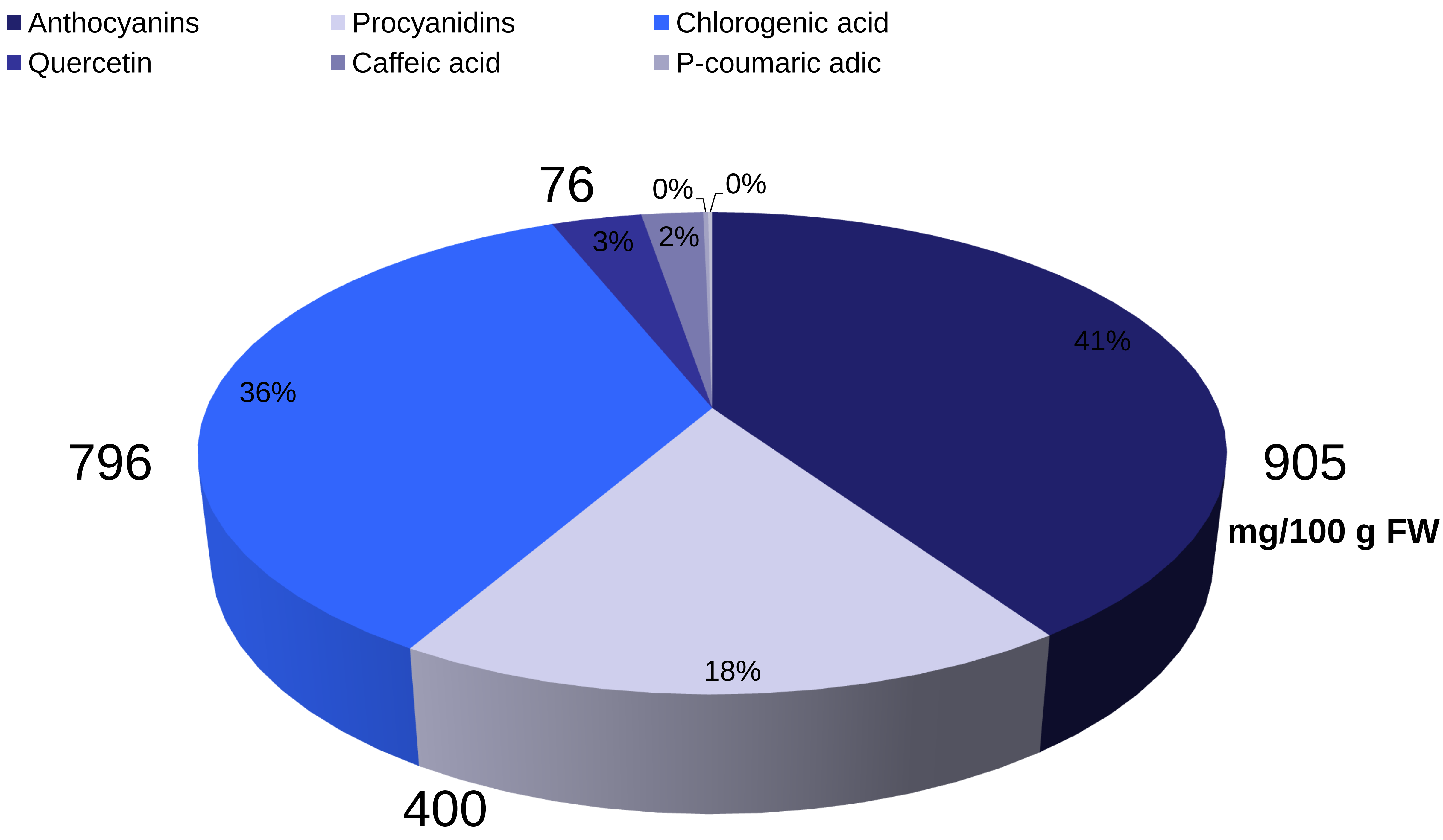
Why is bear poop blue ???

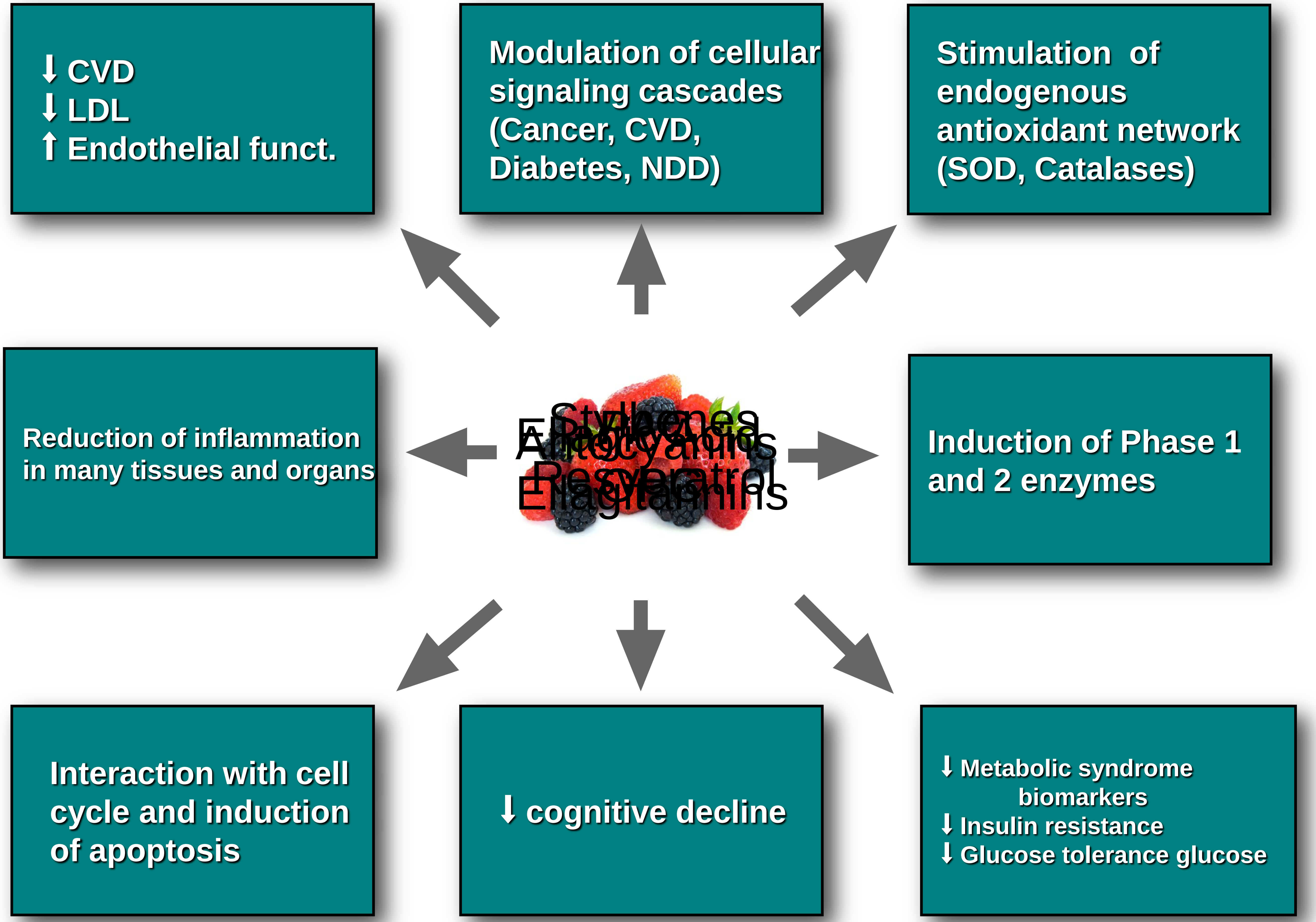
Health effects have been attributed to phenolic compounds



Blueberry Polyphenols

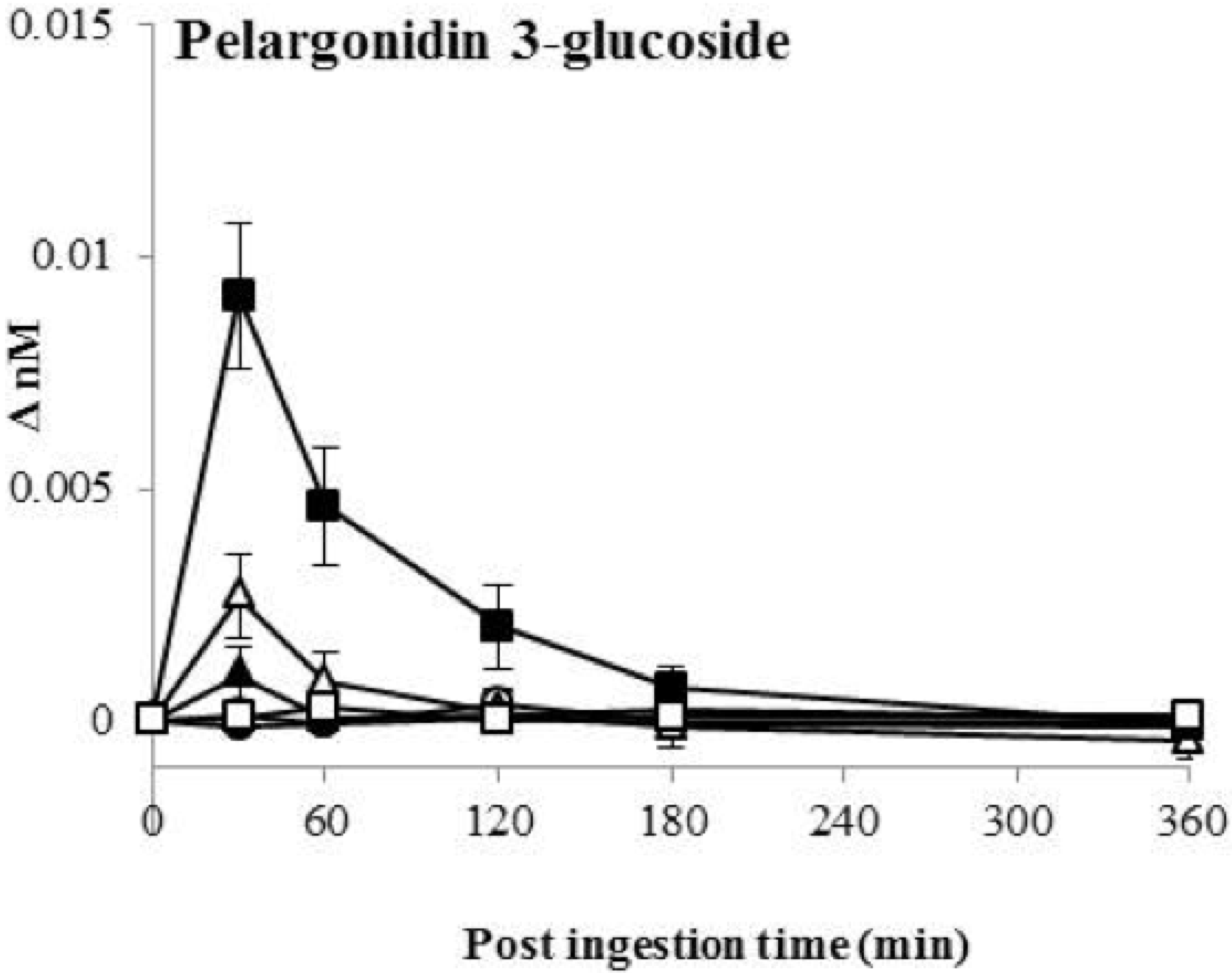


Rodrigues-Mateos et al. (2013) Amer. J. Clin Nutr. 98: 1179 .


↓ CVD
↓ LDL
↑ Endothelial funct.
Modulation of cellular signaling cascades (Cancer, CVD, Diabetes, NDD)
Stimulation of endogenous antioxidant network (SOD, Catalases)
Reduction of inflammation in many tissues and organs
Induction of Phase 1 and 2 enzymes
Interaction with cell cycle and induction of apoptosis
↓ cognitive decline
↓ Metabolic syndrome biomarkers
↓ Insulin resistance
↓ Glucose tolerance glucose

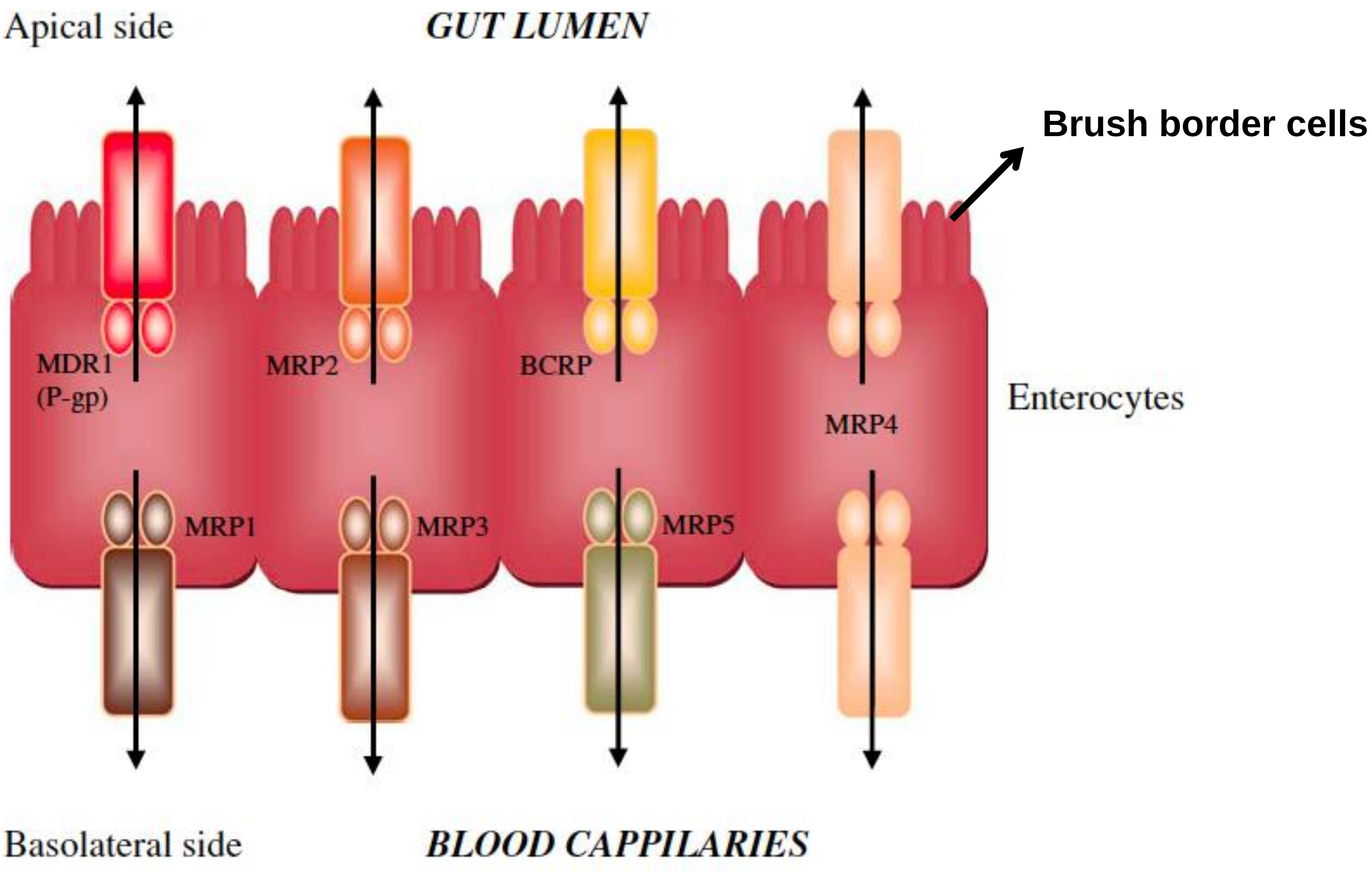
Bioavailability of polyphenols is very low

100 mg quercetin	→	0.3 - 0.7 µmol/l
150 mg catechin	→	0.1 µmol/l
200 mg hesperin	→	1.1 µmol/l
200 mg naringenin	→	6 µmol/l
200 mg anthocyanin	→	~ 10 nmol/l
25 mg secoislariceresinol	→	~ 30 nmol/l



Residence time in the body is relatively short

Polyphenols are recognized by the body as xenobiotics and are rapidly eliminated

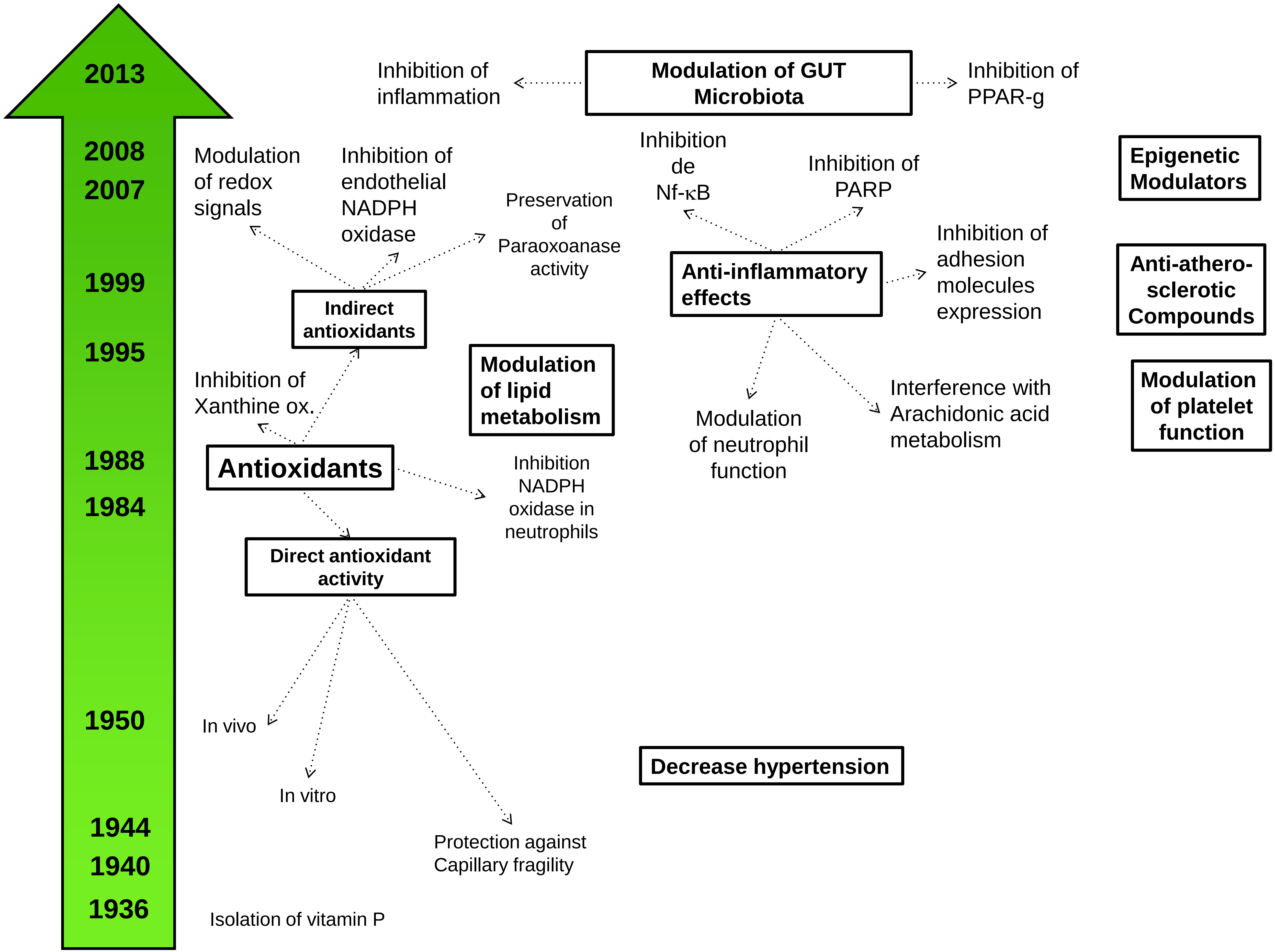


The Journal of Nutrition
Supplement: Antioxidant Activity of Polyphenols and Cardiovascular Risk—Application of the PASSCLAIM Criteria

The Biological Relevance of Direct Antioxidant Effects of Polyphenols for Cardiovascular Health in Humans Is Not Established[1–4]

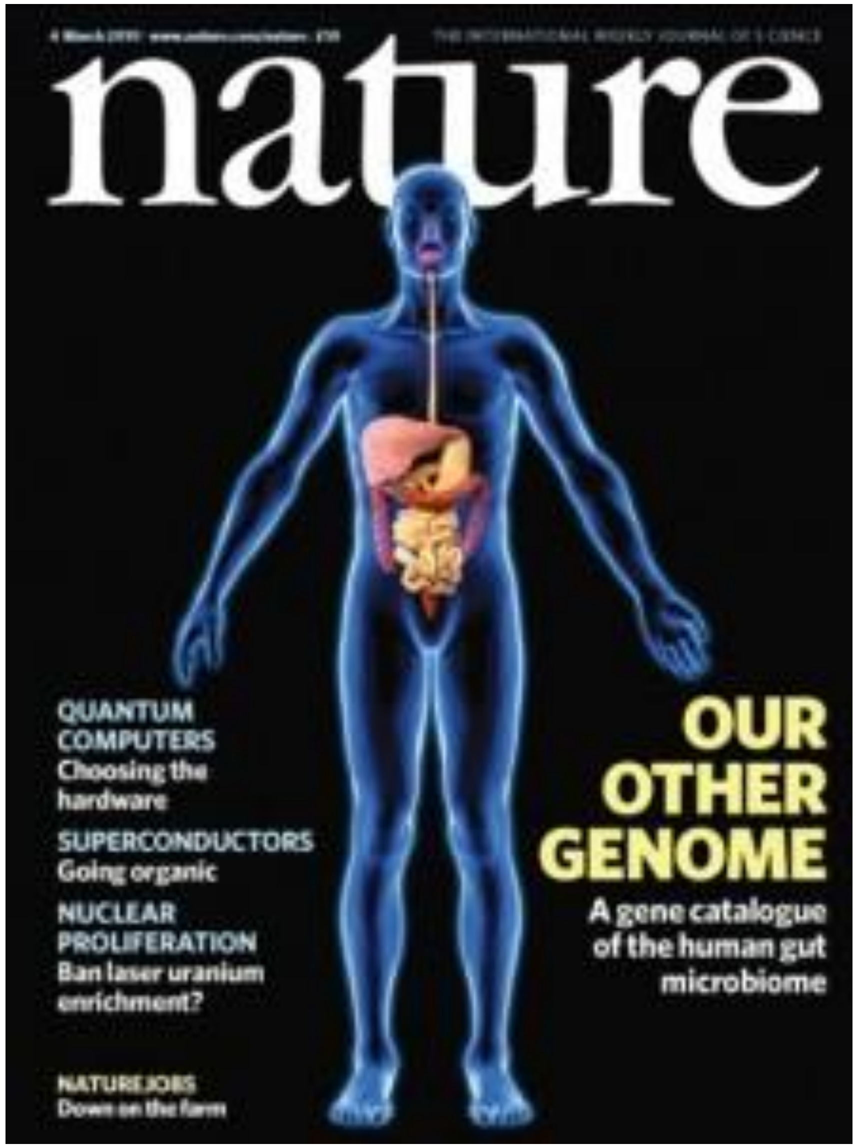
Peter C. H. Hollman,[5] Aedin Cassidy,[6] Blandine Comte,[3] Marina Heinonen,[8] Myriam Richelle,[9] Elke Richling,[10] Mauro Serafini,[11] Augustin Scalbert,[7] Helmut Sies,[12] and Stéphane Vidry[13]*

First published online March 30, 2011; doi:10.3945/jn.110.131490.



Adapted de Weseler et al., 2012. JAFC

Our genome: the microbiome



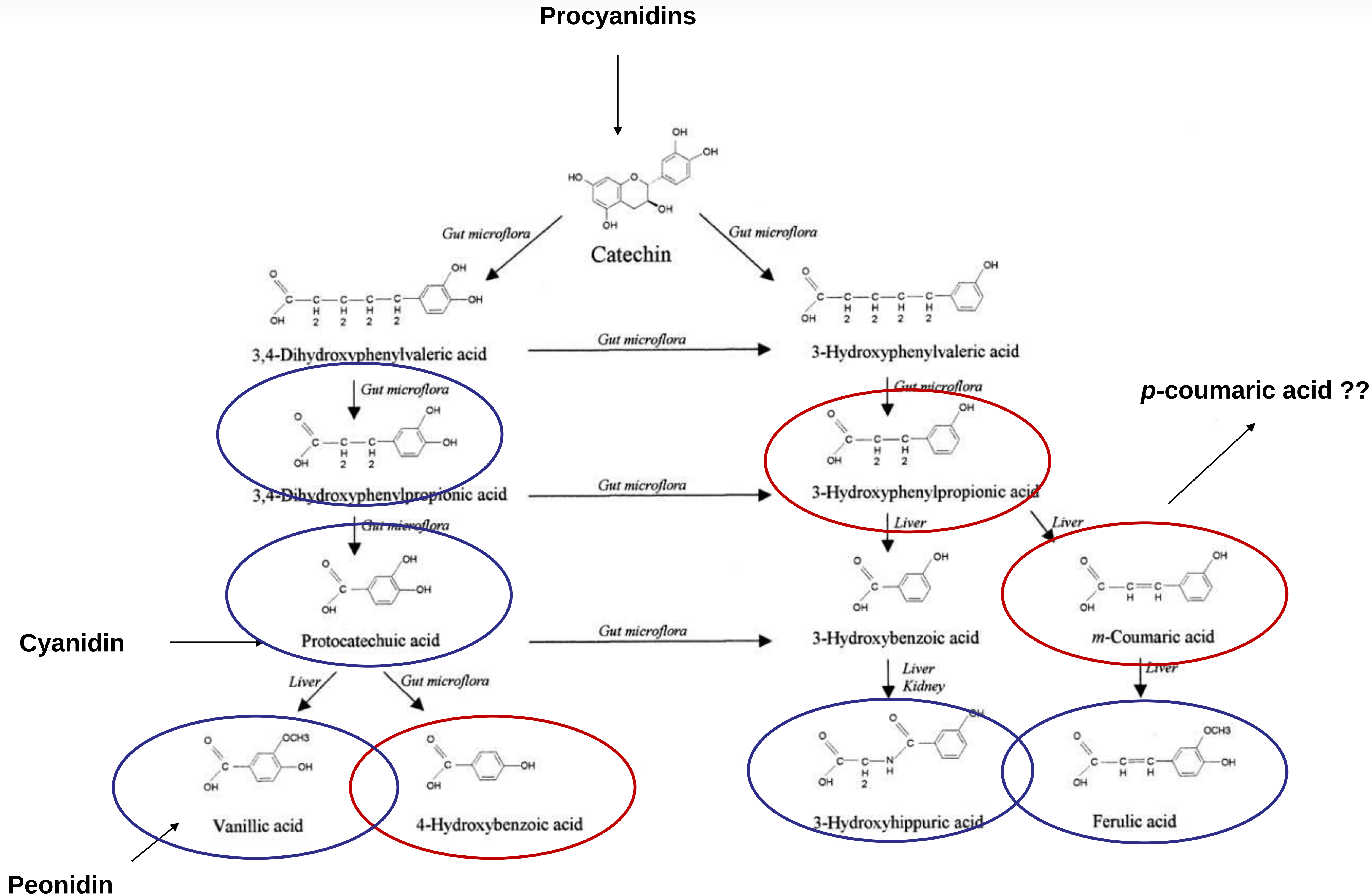
Adapted from Backehed et al. Science 307, 1915-1920.

Metagenomic analysis of the colon microbiome

- **10X more bacterial cells than our body**
- **100 more genes than our own genome.**
- **1.5-2.0 kg microorganisms**
- **100 trillion bacteria in our gut…**

Microbial degradation of polyphenols

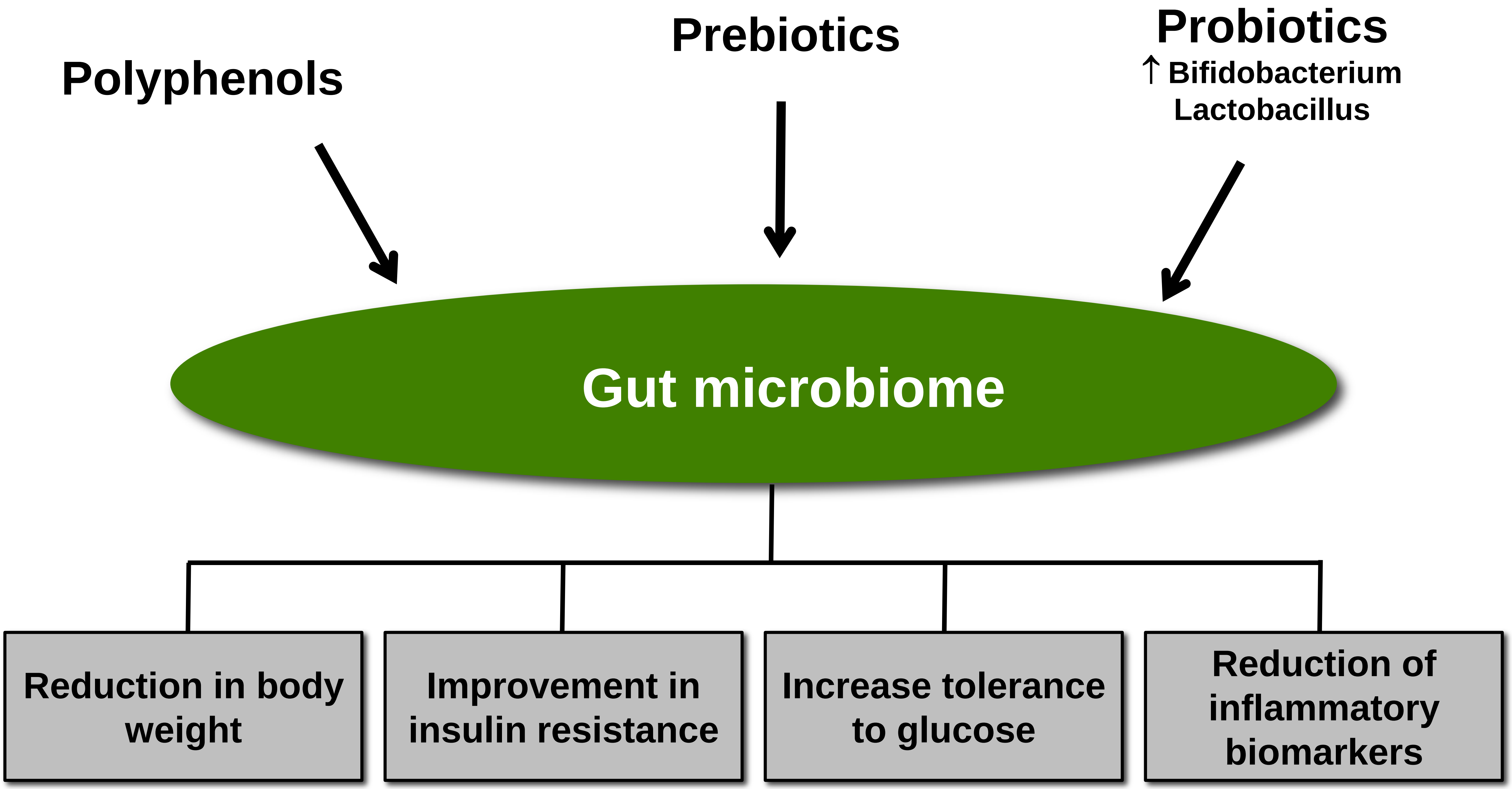
Flavonols	→	Hydroxyphenyl acetic acid
Flavanones	→	Hydroxyphenyl propionic acid
Flavanols	→	Phenyl valerolactone
Catechins	→	Hyppuric accid, Catecuic acid
Lignans	→	Enterodiol
Isoflavones	→	Equol



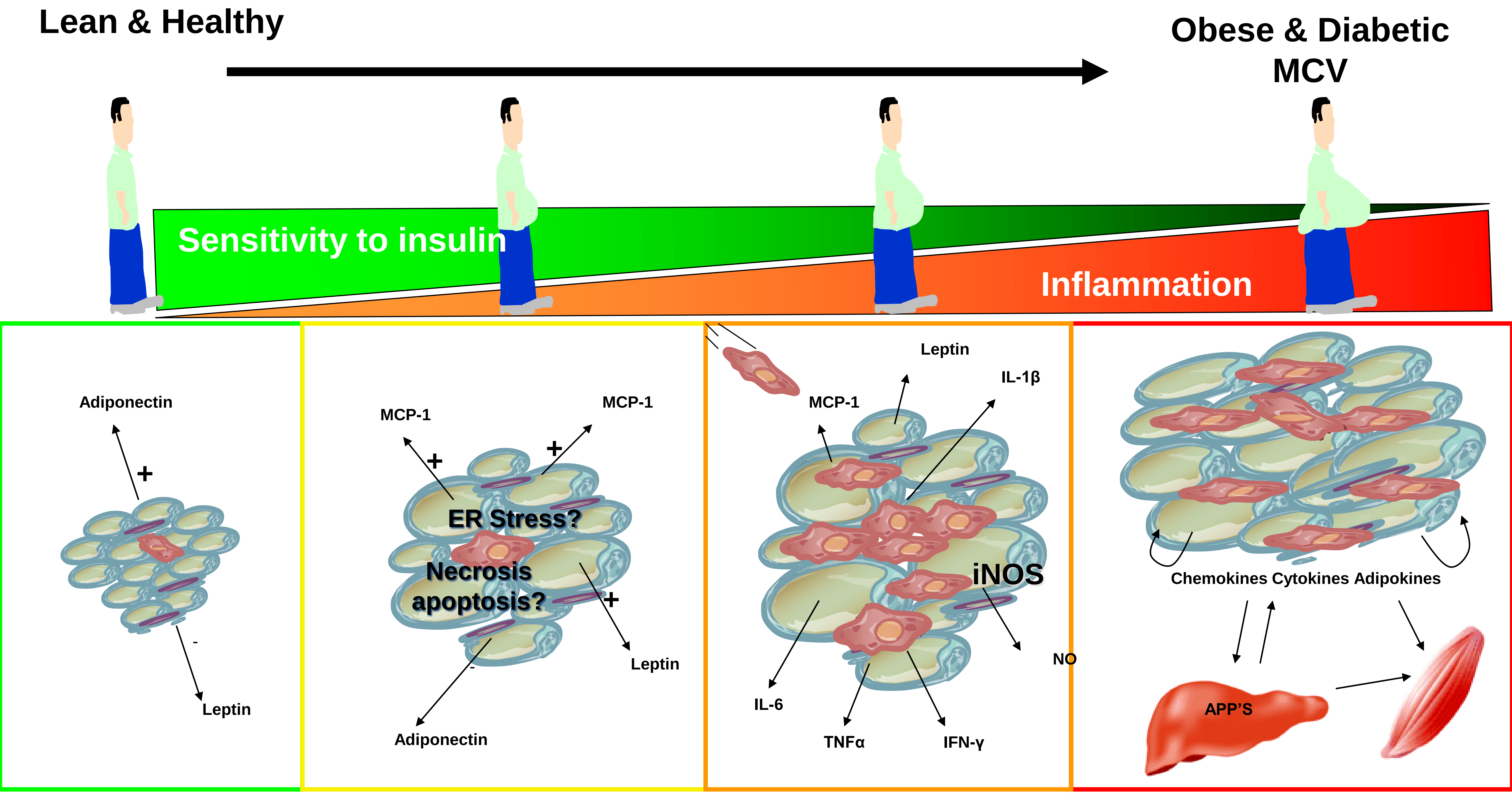
Gonthier *et al.* 2003, Free Radical Biology & Medicine

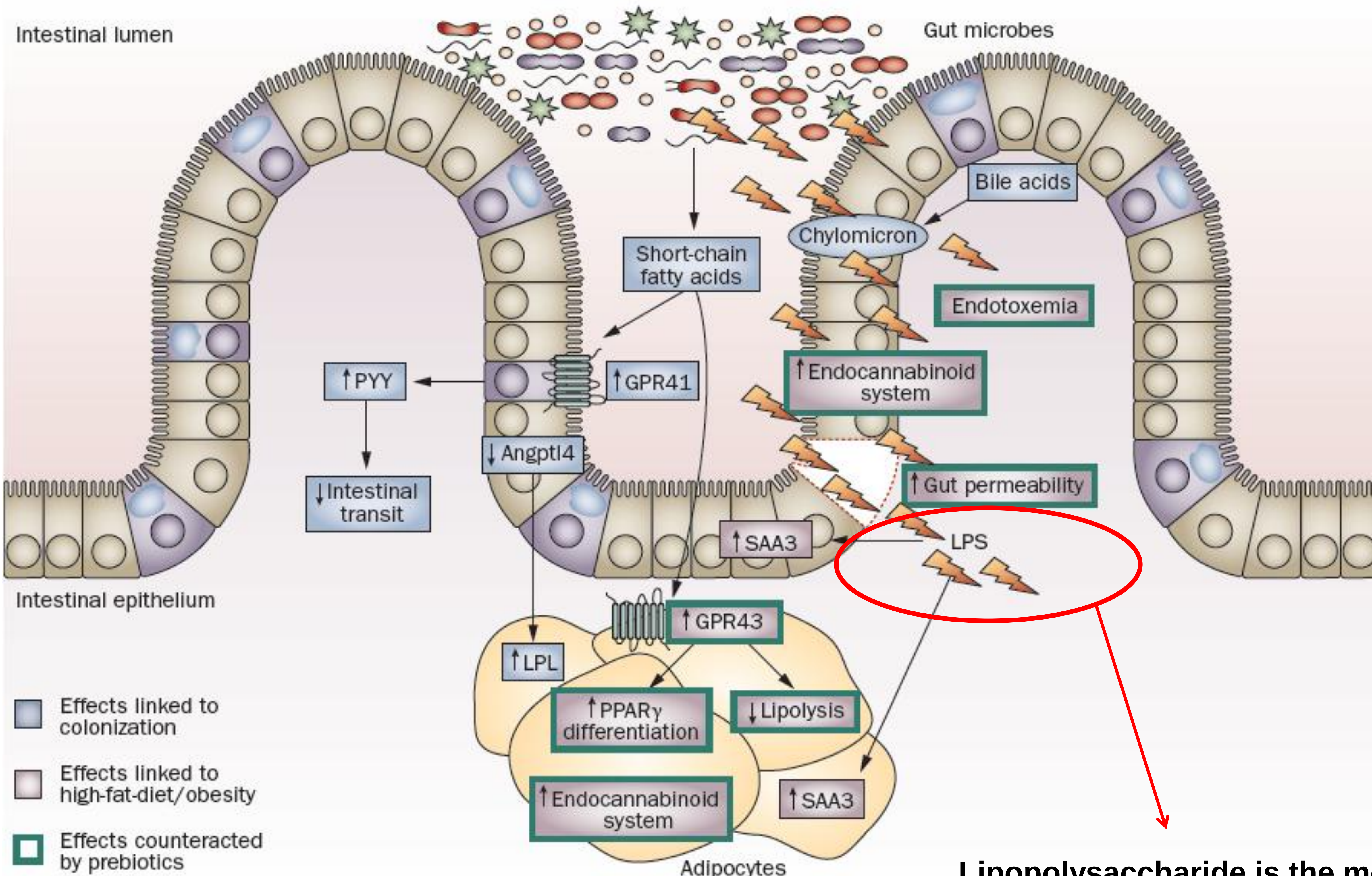
Link between the microbiome and diabetes

(Esteves *et al.* 2011 Curr. Op. Clin. Nutr.)



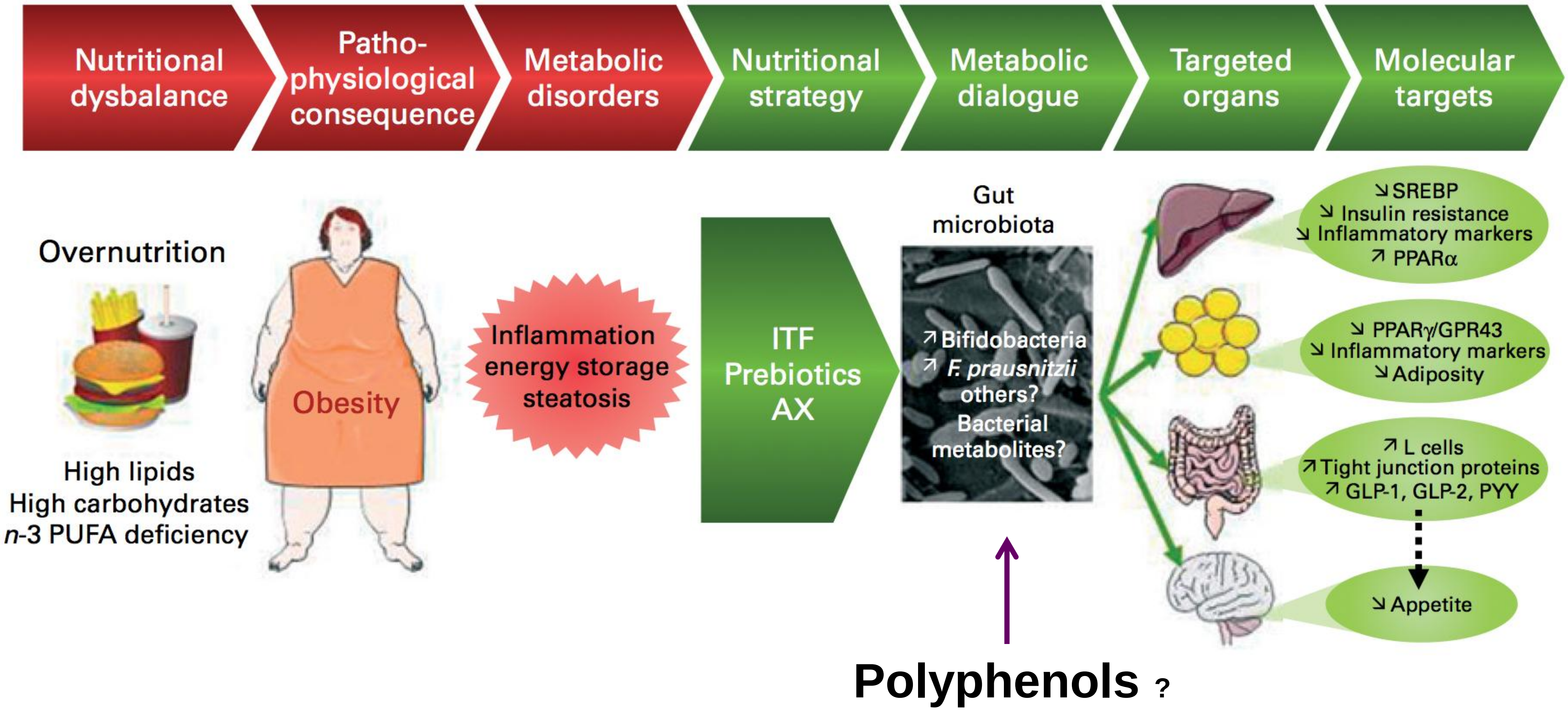
Evolution of inflammation associated chronic deseases





Lipopolysaccharide is the most inflammatory molecule recognized by the body

Delzenne, N. M. *et al. Nat. Rev. Endocrinol.* 7, 639–646 (2011); published online 9 August 2011; doi:10.1038/nrendo.2011.126



Gut microbiota and metabolic disorders: how prebiotic can work?

Nathalie M. Delzenne*, Audrey M. Neyrinck and Patrice D. Cani

British Journal of Nutrition (2013), **109**, S81–S85

Effect of polyphenols on gut microbes

Journal of Applied Microbiology 2001, **90**, 494–507

Antimicrobial properties of phenolic compounds from berries

R. Puupponen-Pimiä[1], L. Nohynek[1], C. Meier[1], M. Kähkönen[2], M. Heinonen[2], A. Hopia[2] and K.-M. Oksman-Caldentey[1]

[1]VTT Biotechnology, and [2]University of Helsinki, Department of Applied Chemistry and Microbiology, Food Chemistry Division, University of Helsinki, Finland

Table 6 Antimicrobial activity of selected pure phenolic compounds and berry extracts in liquid culture. (▨) No inhibition: plate counts differ by $< 5 \times 10^1$; (▩) clear inhibition: plate counts differ by 5×10^1–5×10^2; (▦) strong inhibition: plate counts differ by 5×10^2–5×10^4; (■) very strong inhibition: plate counts differ by $> 5 \times 10^4$; (□) not tested

Berry extracts 1 mg ml^{-1}	*Lactobacillus rhamnosus* E-800	*Lact. rhamnosus* E-666	*Lact. reuteri* E-849	*Lact. paracasei* E-510	*Lact. johnsonii* E-797	*Lact. crispatus* E-725	*Lact. plantarum* E-076	*E. coli* 50	*E. coli* CM871	*Salmonella enterica* SH-5014	*Enterococcus faecalis* E-203	*Bifidobacterium lactis* E-508
Blueberry	No inhibition	No inhibition	No inhibition	No inhibition	No inhibition	No inhibition	No inhibition	Clear inhibition	Strong inhibition	No inhibition	No inhibition	No inhibition
Raspberry	No inhibition	No inhibition	No inhibition	No inhibition	No inhibition	No inhibition	No inhibition	Clear inhibition	Very strong inhibition	Very strong inhibition	Clear inhibition	Clear inhibition
Lingonberry	No inhibition	No inhibition	No inhibition	No inhibition	No inhibition	No inhibition	No inhibition	Clear inhibition	Very strong inhibition	Strong inhibition	No inhibition	No inhibition
Black currant	No inhibition	No inhibition	No inhibition	No inhibition	No inhibition	No inhibition	No inhibition	No inhibition	Clear inhibition	Clear inhibition	No inhibition	No inhibition
Strawberry	No inhibition	No inhibition	No inhibition	No inhibition	No inhibition	No inhibition	No inhibition	Clear inhibition	Strong inhibition	Very strong inhibition	Clear inhibition	Clear inhibition
Cranberry	No inhibition	No inhibition	No inhibition	Not tested	Not tested	Not tested	Not tested	Clear inhibition	Strong inhibition	Strong inhibition	No inhibition	No inhibition
Buckthorn berry	No inhibition	No inhibition	No inhibition	Not tested	Not tested	Not tested	Not tested	Clear inhibition	Clear inhibition	Strong inhibition	No inhibition	No inhibition
Cloudberry	No inhibition	No inhibition	No inhibition	Not tested	Not tested	Not tested	Not tested	Strong inhibition	Very strong inhibition	Very strong inhibition	No inhibition	Clear inhibition

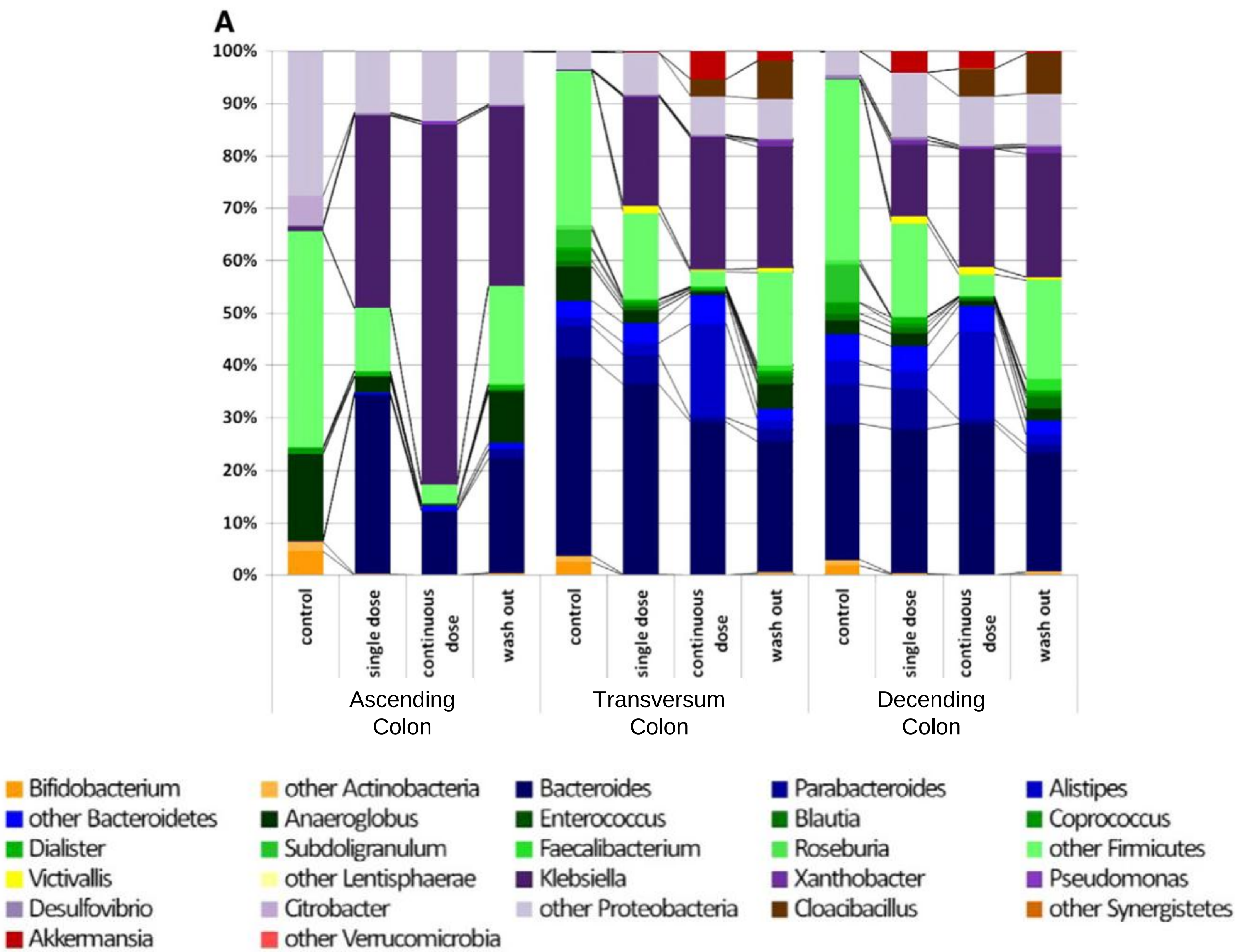
Effect of polyphenols on gut microbes

Impact of polyphenols from black tea and red wine/grape juice on a gut model microbiome

Robèr A. Kemperman [a,*,1], Gabriele Gross [a,b,1], Stanilas Mondot [c], Sam Possemiers [b], Massimo Marzorati [b], Tom Van de Wiele [b], Joël Doré [c], Elaine E. Vaughan [a]

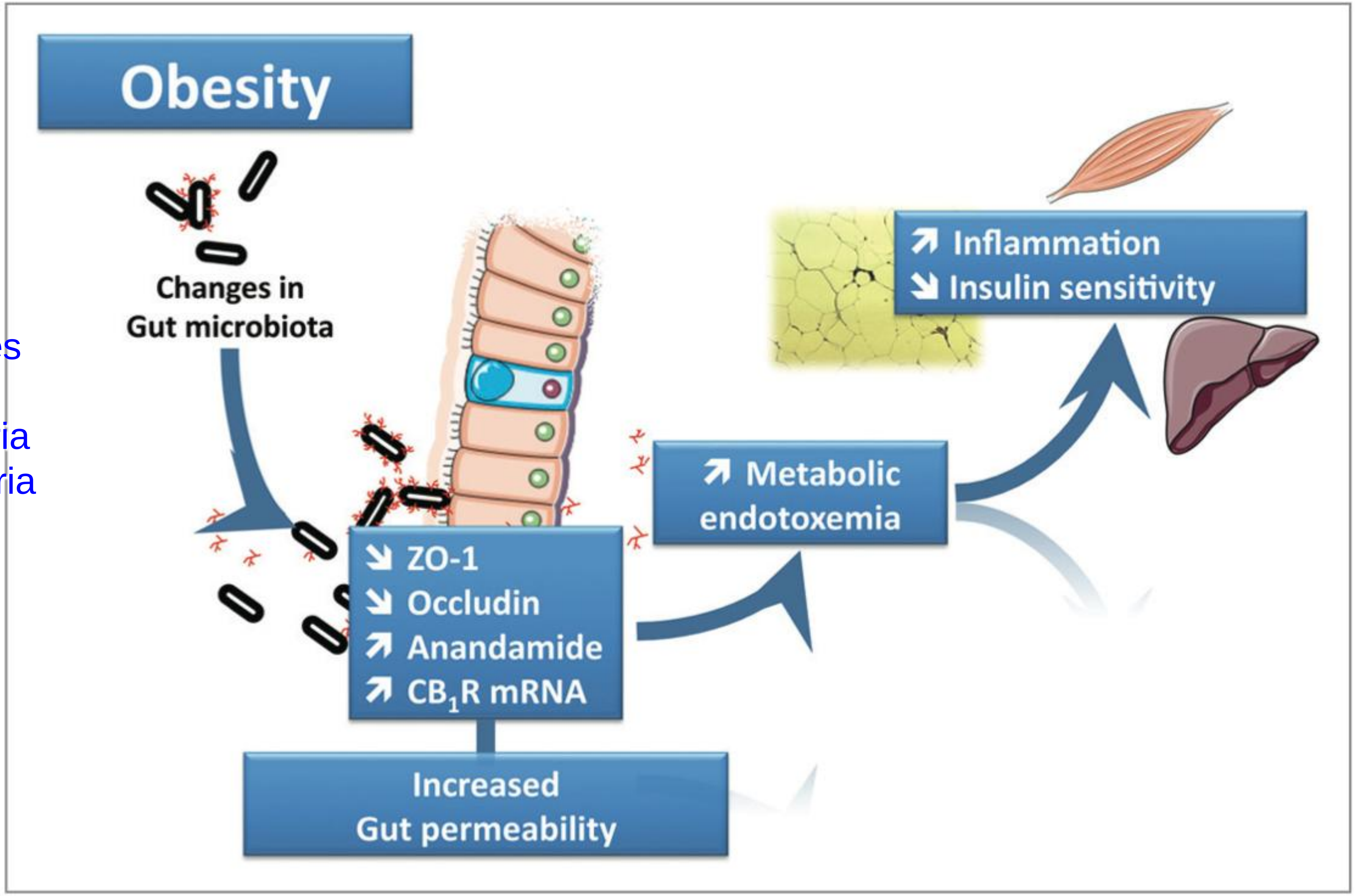
[a] *Unilever R&D, Olivier van Noortlaan 120, 3133 AT, Vlaardingen, The Netherlands*
[b] *Laboratory of Microbial Ecology and Technology (LabMET), Coupure Links 653, Ghent University, B-9000 Gent, Belgium*
[c] *Institut National de la Recherche Agronomique, Unite Ecologie Physiologie Systeme Digestif, Batiment 440 - CRJ — INRA, 78352 Jouy-en-Josas, Cedex, France*

Food Research International, 2013. DOI: 10.1016/j.foodres.2013.01.034



The gut microbiota plays an essential role in the low-grade inflammation

Bacteroidetes
Firmicutes
Actinobacteria
Proteobacteria



Patrice D. Cani,* Melania Osto, Lucie Geurts and Amandine Everard

Gut Microbes 3:4, 279-288; July/August 2012; © 2012 Landes Bioscience

Involvement of gut microbiota in the development of low-grade inflammation and type 2 diabetes associated with obesity

Gastrophénol Projet

Yves Desjardins
André Marette
Denis Roy
Emile Levy
Stéphanie Dudonné
Geneviève Pilon
Sébastien Matamoros

Experimental design

MiceC57Bl6 N=12 per group
8 weeks of chow diet or HFHS

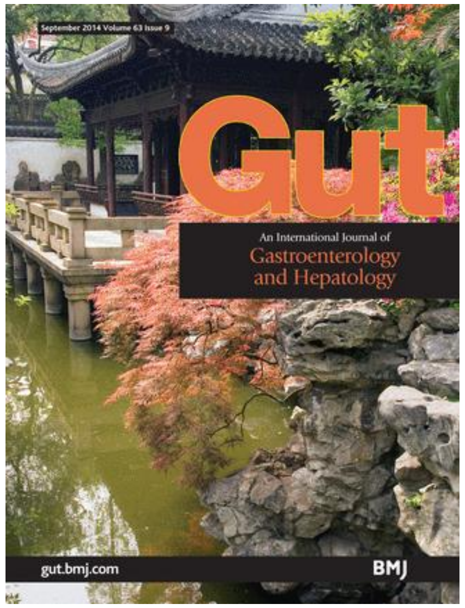
Chow	HFHS	HFHS
Gavage: **vehicle**	Gavage: **vehicle**	Gavage: **300 mg Cranberry**
Drink: **water**	Drink: **water**	Drink:**Water**

Weight gain
Food intake
Gtt / Itt

Modulation of microbiota

Inflammation

Bioavailability



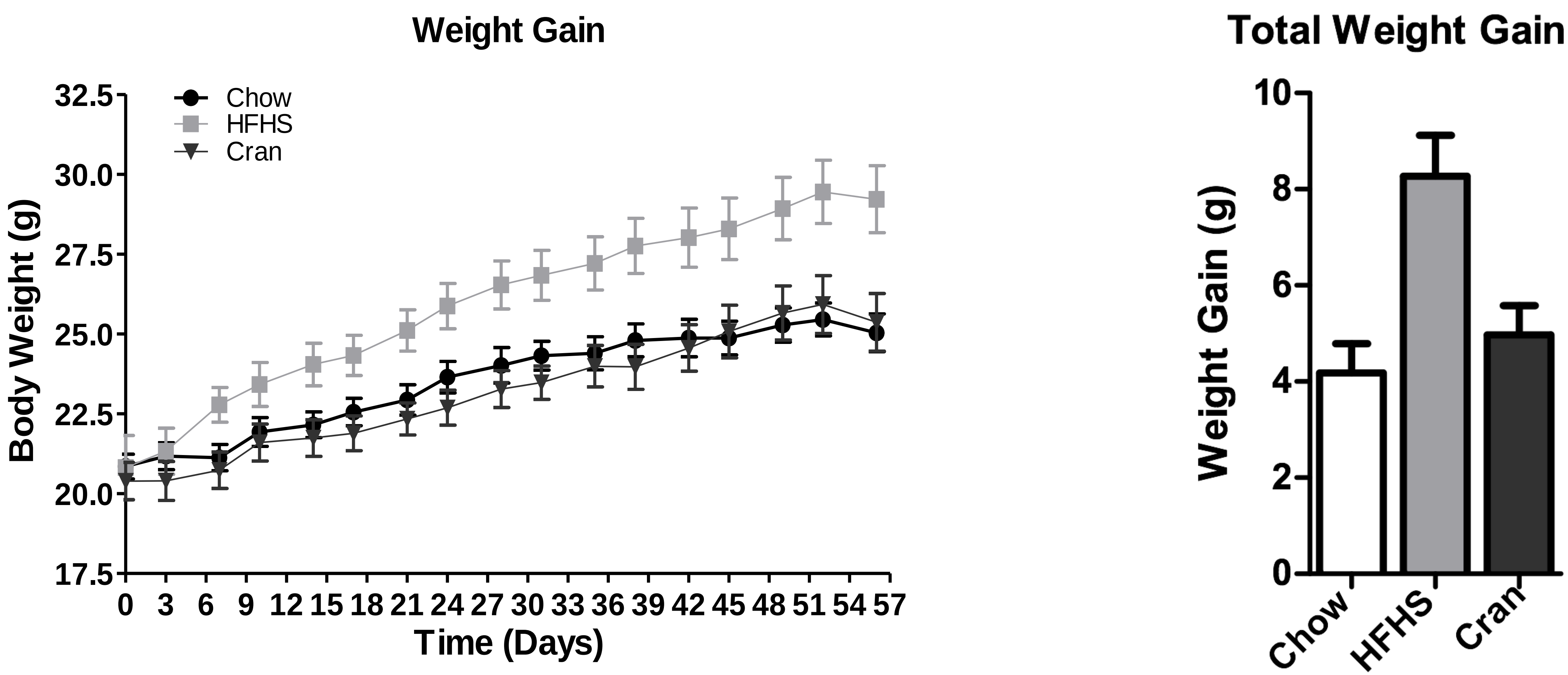
Gut Online First, published on July 30, 2014 as 10.1136/gutjnl-2014-307142

ORIGINAL ARTICLE

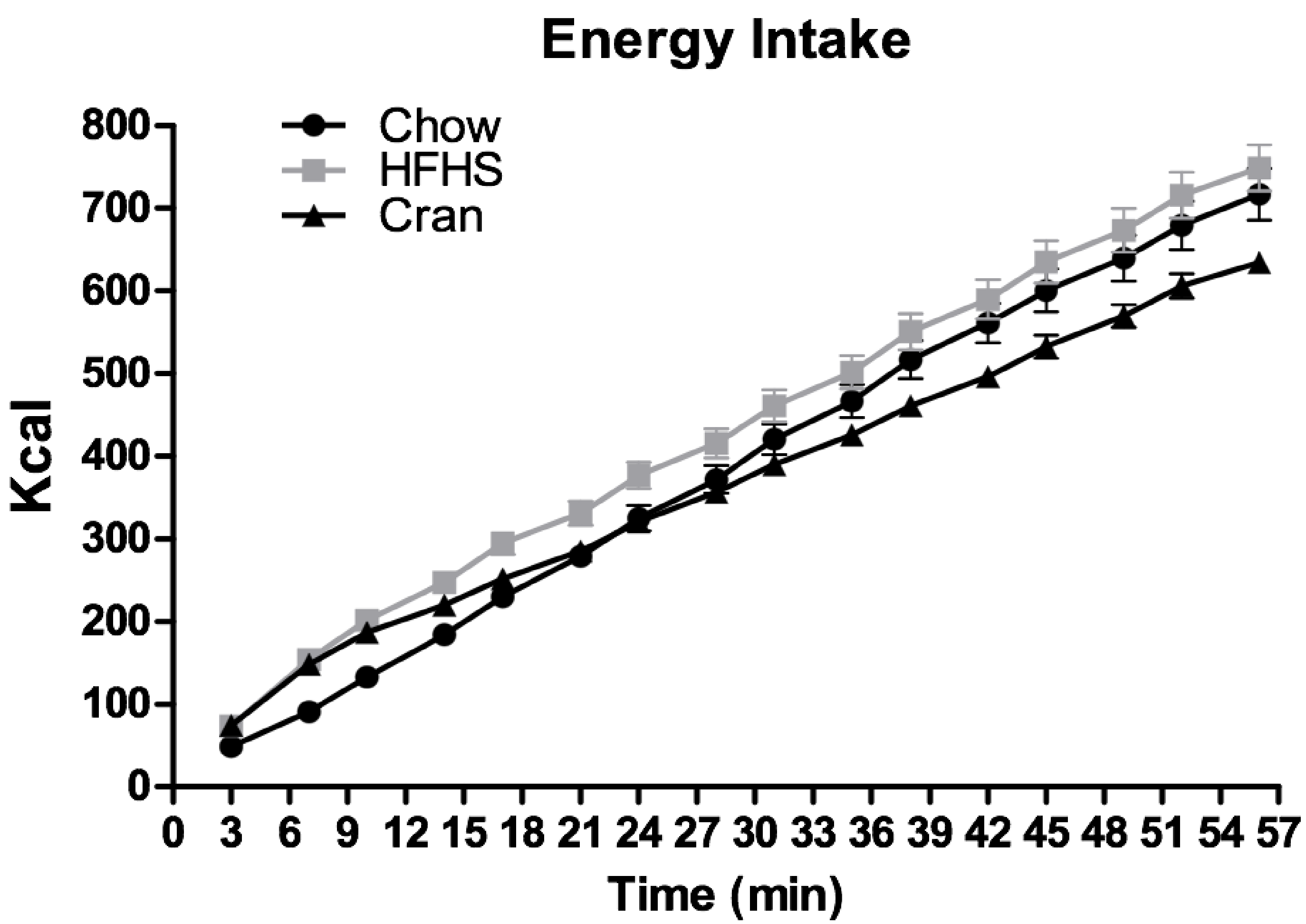
A polyphenol-rich cranberry extract protects from diet-induced obesity, insulin resistance and intestinal inflammation in association with increased *Akkermansia* spp. population in the gut microbiota of mice

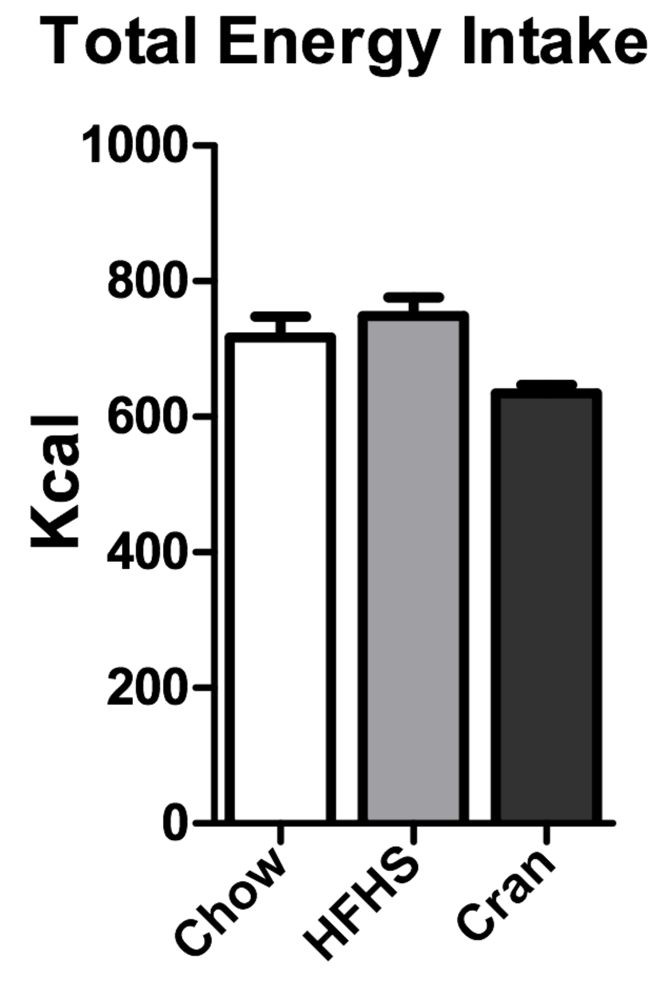
Fernando F Anhê,[1,2] Denis Roy,[2] Geneviève Pilon,[1,2] Stéphanie Dudonné,[2] Sébastien Matamoros,[2] Thibault V Varin,[2] Carole Garofalo,[3] Quentin Moine,[3] Yves Desjardins,[2] Emile Levy,[3,4] André Marette[1,2]

Effect of cranberry extract on Weight Gain

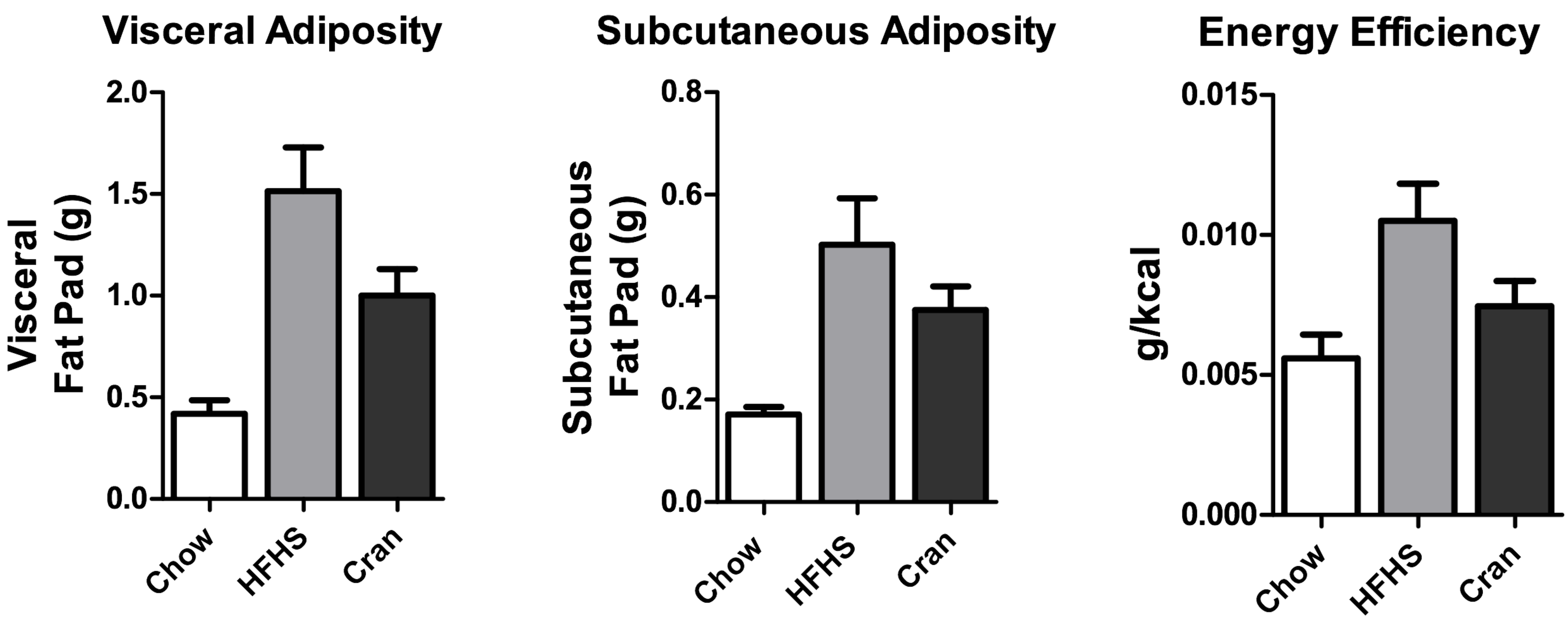


Effect of cranberry extract on Total Energy Intake

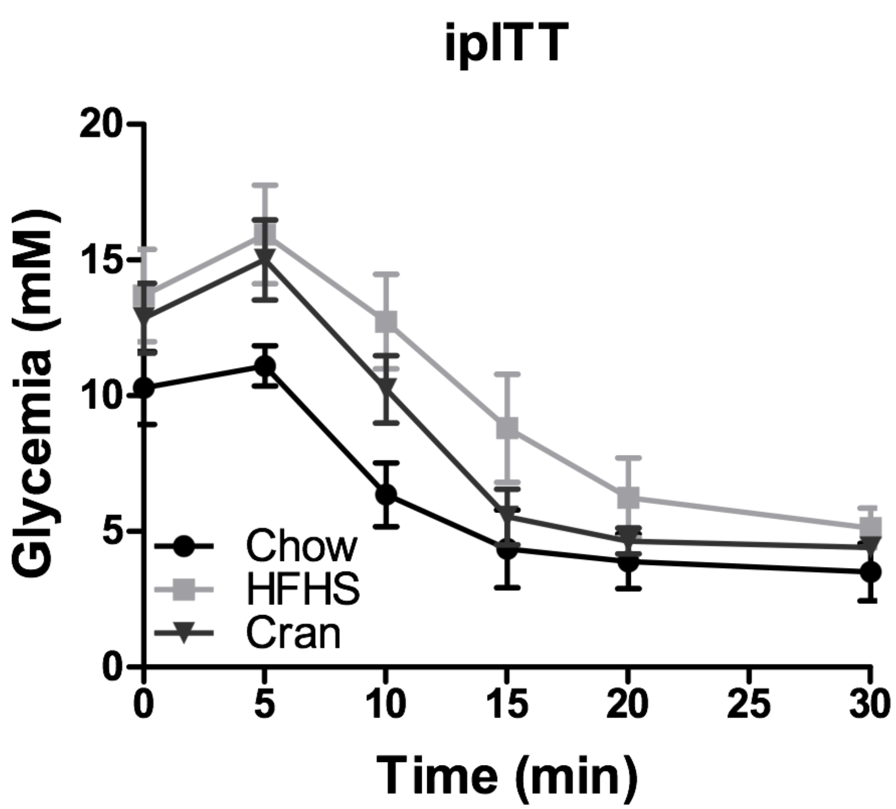


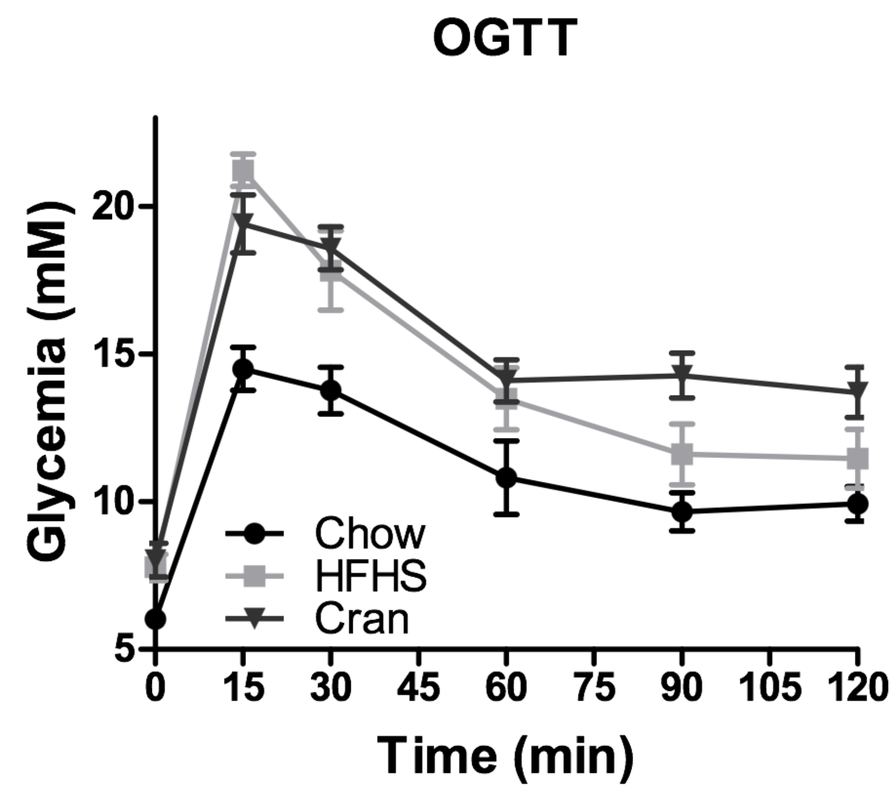


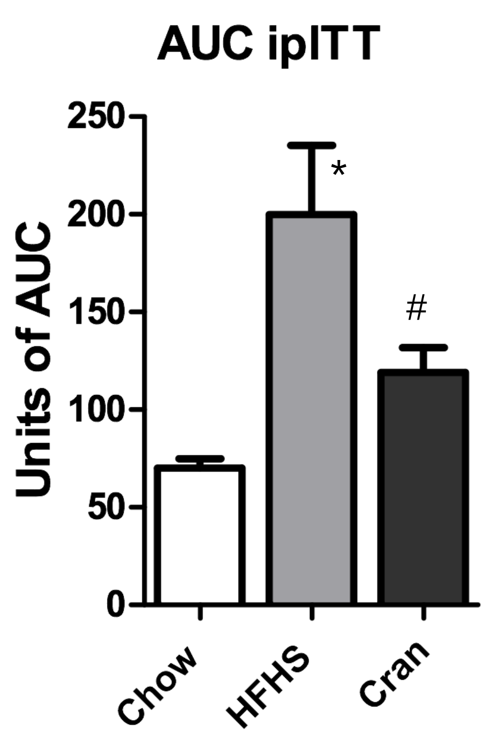
Effect of cranberry extract on viceral adiposity

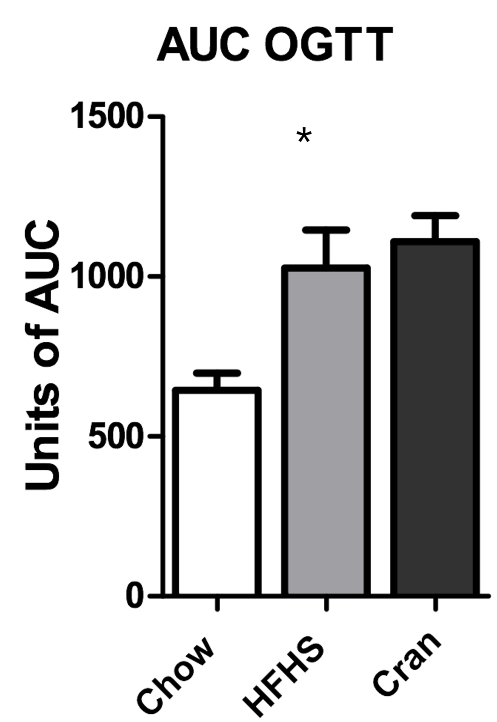


Effect of cranberry extract on glucose and insulin tolerance

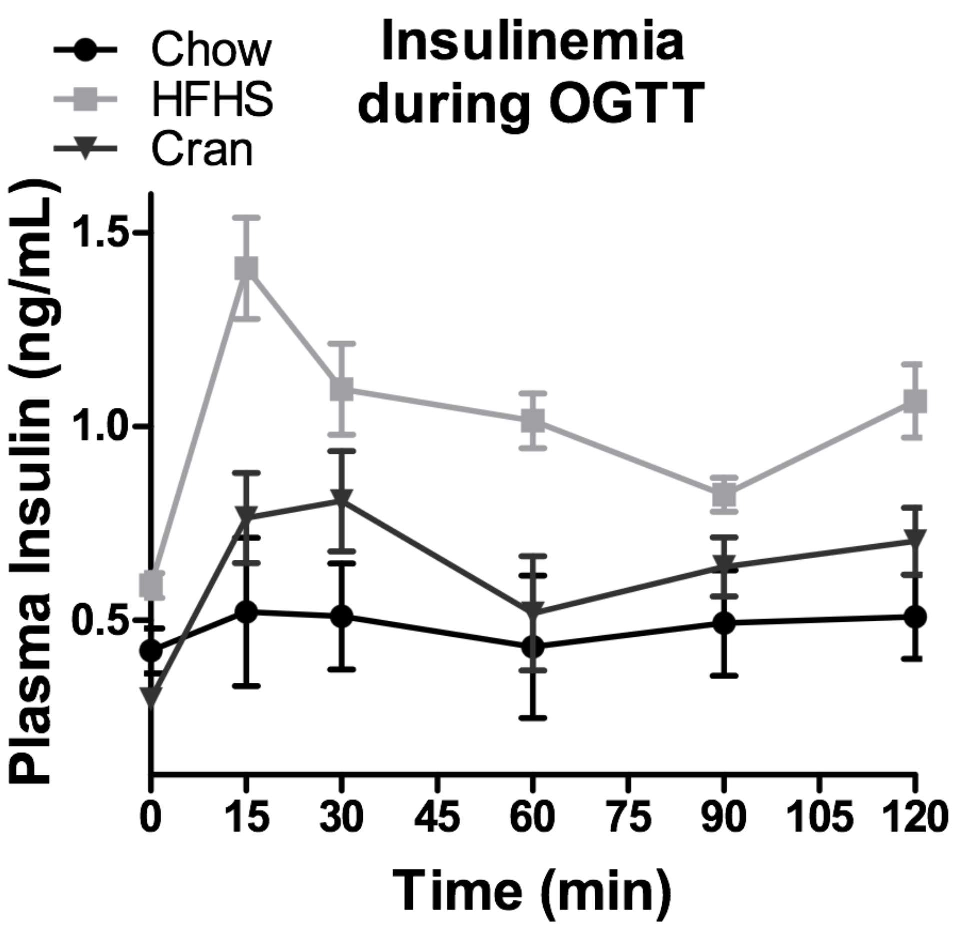


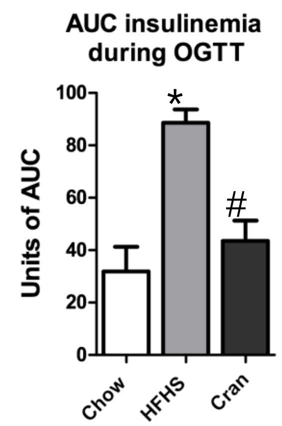


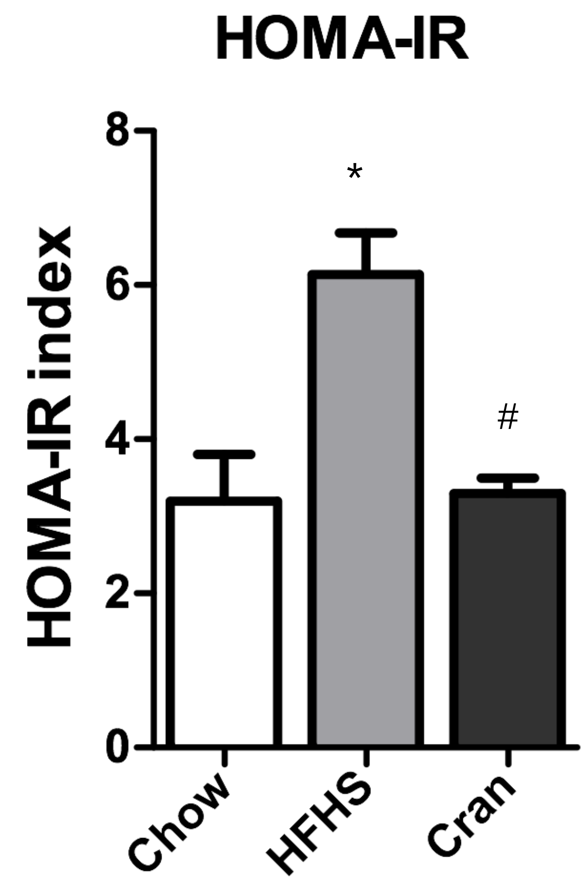




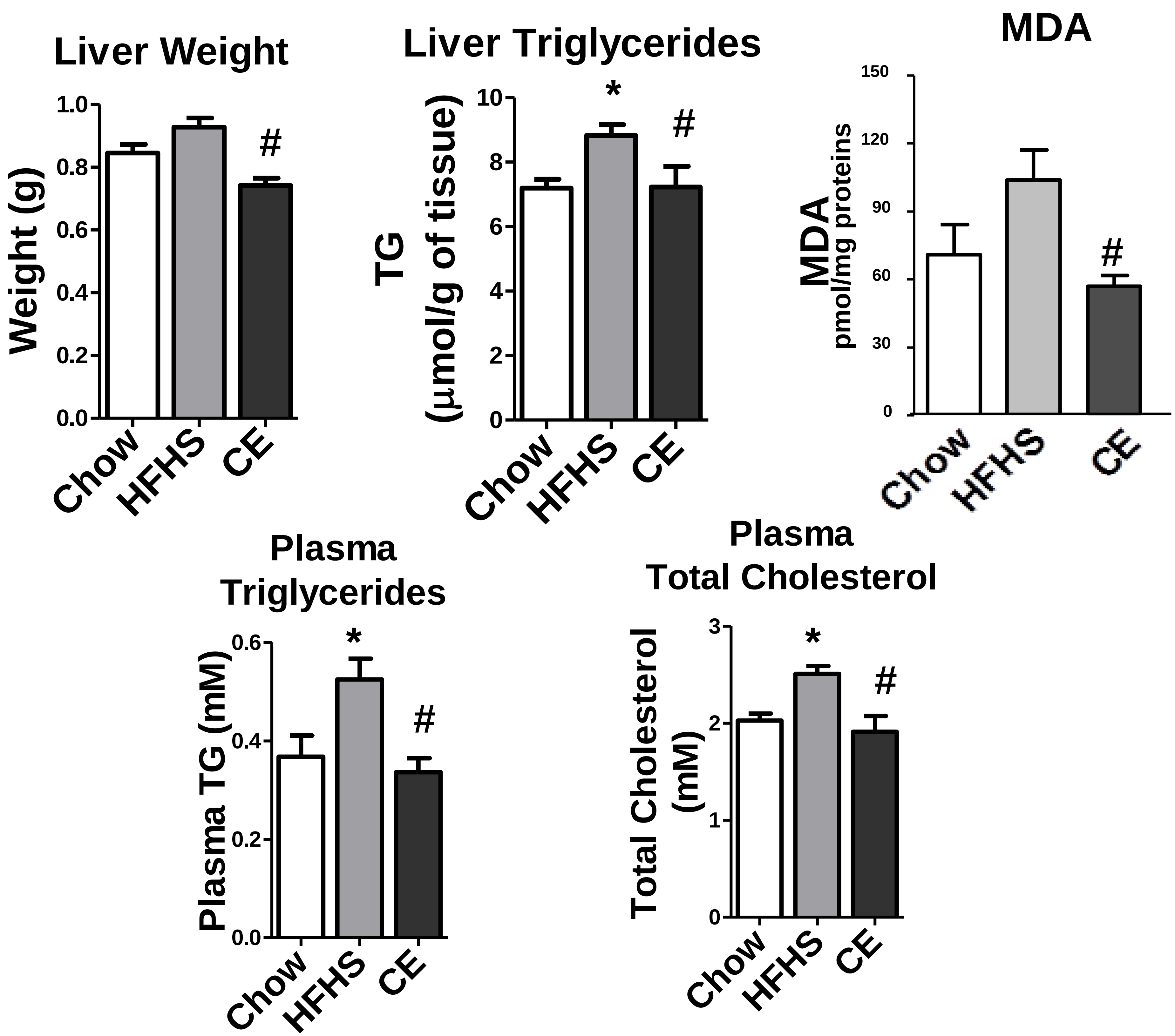
Effect of cranberry extract on glucose and insulin tolerance during OGTT







Effect of cranberry extract on liver weight, triglycerides, lipid peroxydation, plasma triglycerides and cholesterol



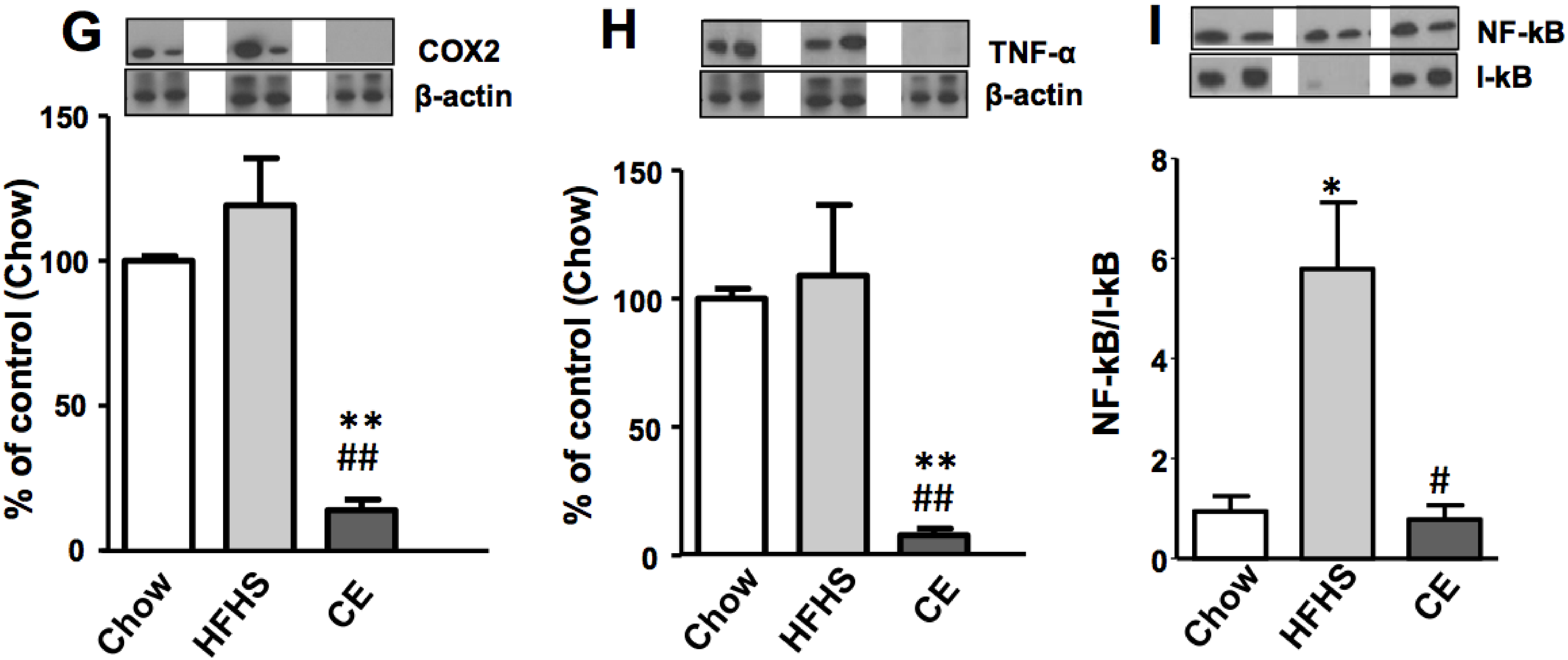
Effect of a cranberry extract on hepatic steatosis

Chow

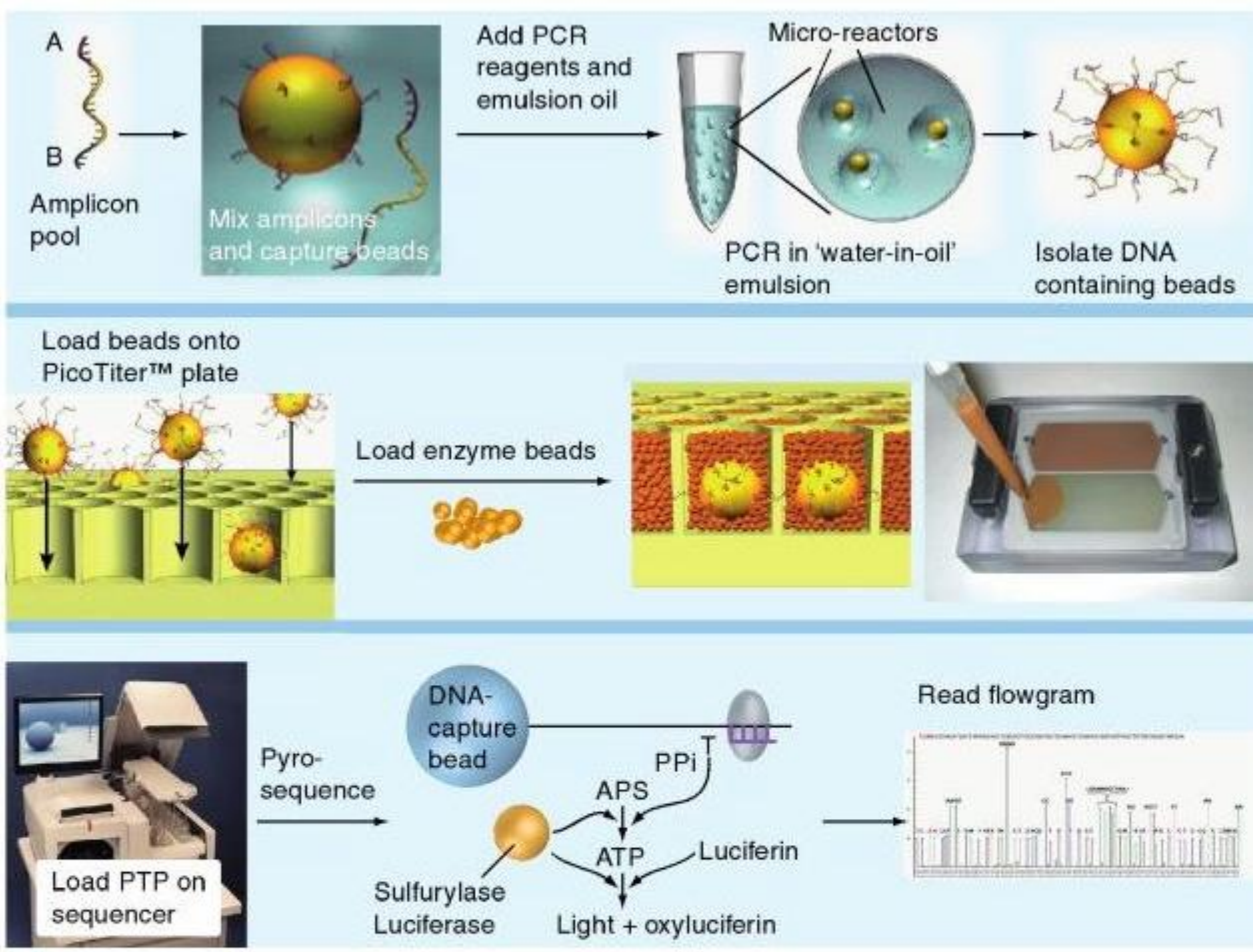
HFHS

HFHS
+
Cranberry

Effect of cranberry extract on Intestinal inflammatory reaction



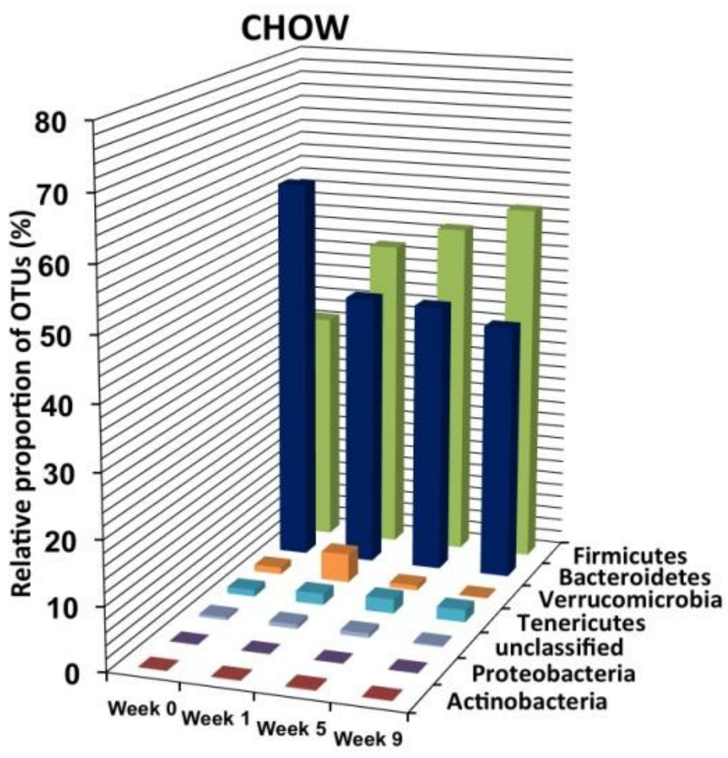
454 Pyrosequencing of the gut metagenome

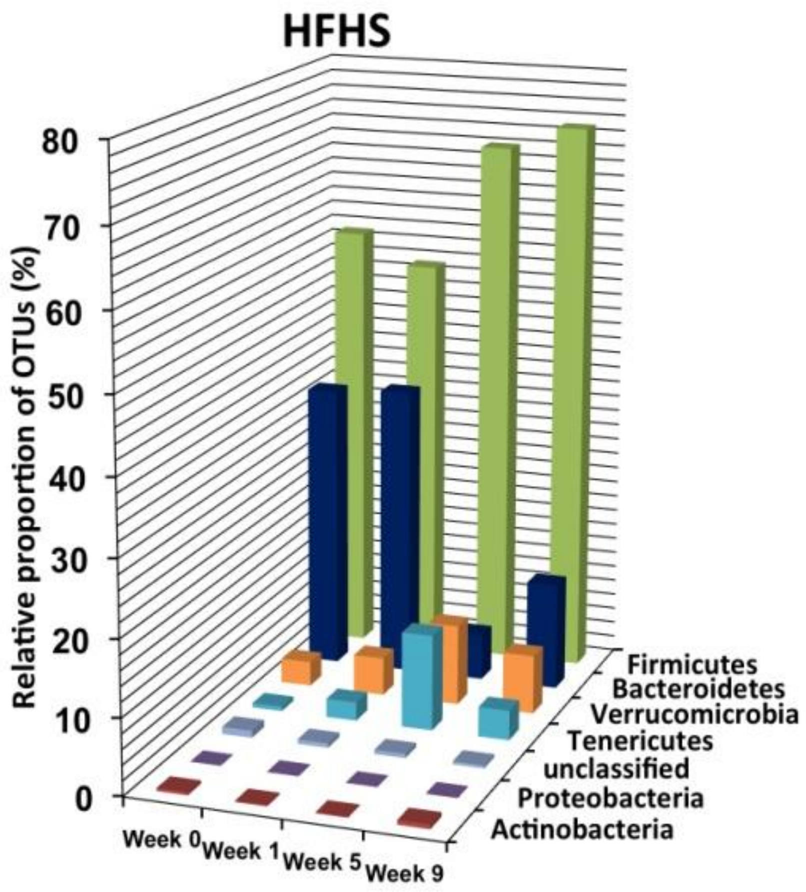


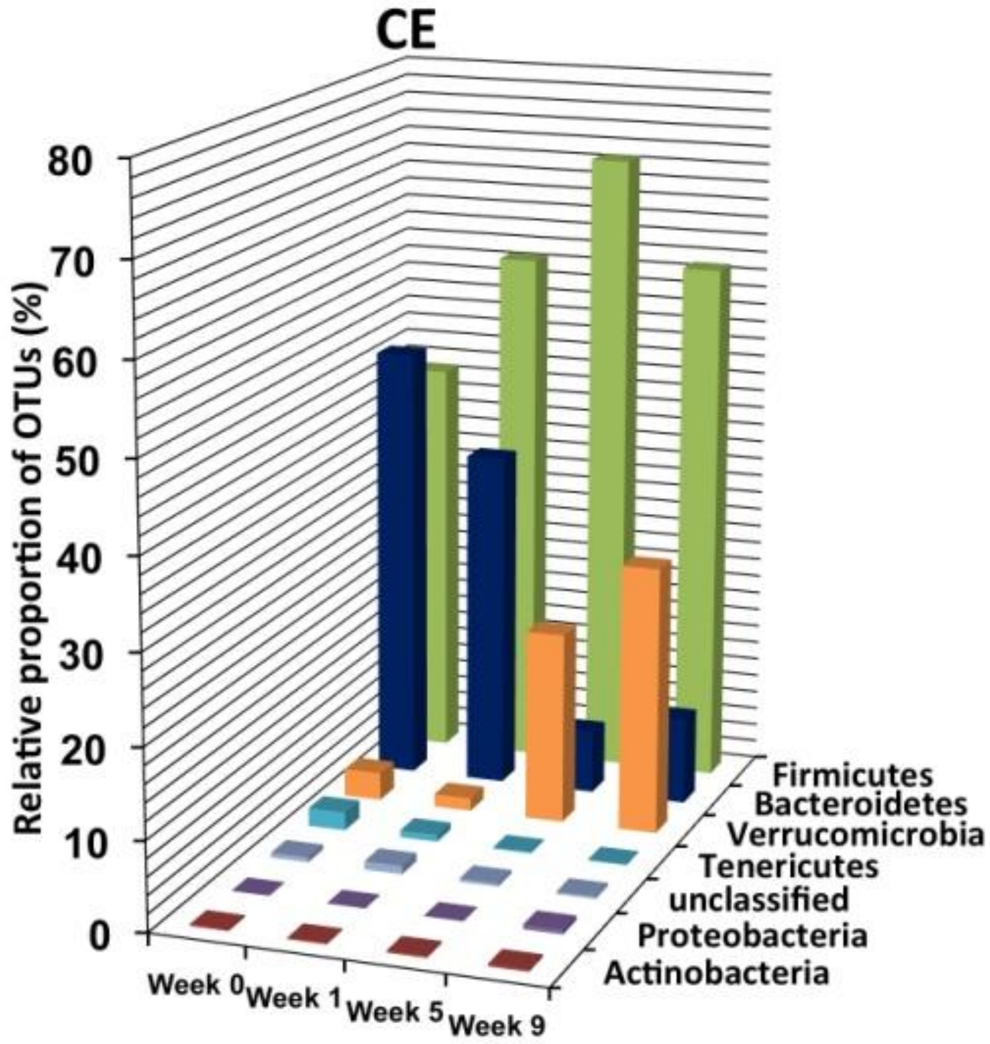
- Analysis of the V6-V8 region of the 16S rRNA bacterial genes by high-throughput pyrosequencing
- (~ 100,000 reads on 1/8 plate)
- 20 samples sequenced
- (Mice DNA was pooled for each diet and each week)
- A bar-code per sample allowed to assign the obtained sequences
- 2566 sequences were obtained per sample (after clean-up)

Evolution of the gut microbiota under a HFHS diet or a diet supplemented with cranberry extract.

CHOW	HFHS	HFHS + cranberry







Cross-talk between *Akkermansia muciniphila* and intestinal epithelium controls diet-induced obesity

Amandine Everard[a], Clara Belzer[b], Lucie Geurts[a], Janneke P. Ouwerkerk[b], Céline Druart[a], Laure B. Bindels[a], Yves Guiot[c], Muriel Derrien[b], Giulio G. Muccioli[d], Nathalie M. Delzenne[a], Willem M. de Vos[b,e], and Patrice D. Cani[a,1]

[a]Metabolism and Nutrition Research Group, Walloon Excellence in Life sciences and BIOtechnology (WELBIO), Louvain Drug Research Institute, Université catholique de Louvain, B-1200 Brussels, Belgium; [b]Laboratory of Microbiology, Wageningen University, 6703 HB, Wageningen, The Netherlands. [c]Department of Pathology, Cliniques Universitaires Saint-Luc, Université catholique de Louvain, B-1200 Brussels, Belgium; [d]Bioanalysis and Pharmacology of Bioactive Lipids Research Group, Louvain Drug Research Institute, Université catholique de Louvain, B-1200 Brussels, Belgium; and [e]Departments of Bacteriology and Immunology and Veterinary Biosciences, University of Helsinki, 00014 Helsingin yliopisto, Helsinki, Finland

Edited* by Todd R. Klaenhammer, North Carolina State University, Raleigh, NC, and approved March 28, 2013 (received for review November 8, 2012)

NATURE | NEWS

Gut microbe may fight obesity and diabetes

Bacterium helps to regulate metabolism in mice.

Brian Owens

13 May 2013

The Buzz About *Akkermansia muciniphila*: It's More Than Just Weight Loss

May 17, 2013 by Terri Sundquist

3 Votes

The bacterium *Akkermansia muciniphila* is creating quite a stir in science news, with people calling it the "weight loss bacterium". While it's exciting to think about a bacterium that has the ability to reduce body weight with no change in food intake, there's another reason to get excited: The potential to treat obesity-related metabolic disorders such as type-2

The ISME Journal (2012) 6, 1449–1458

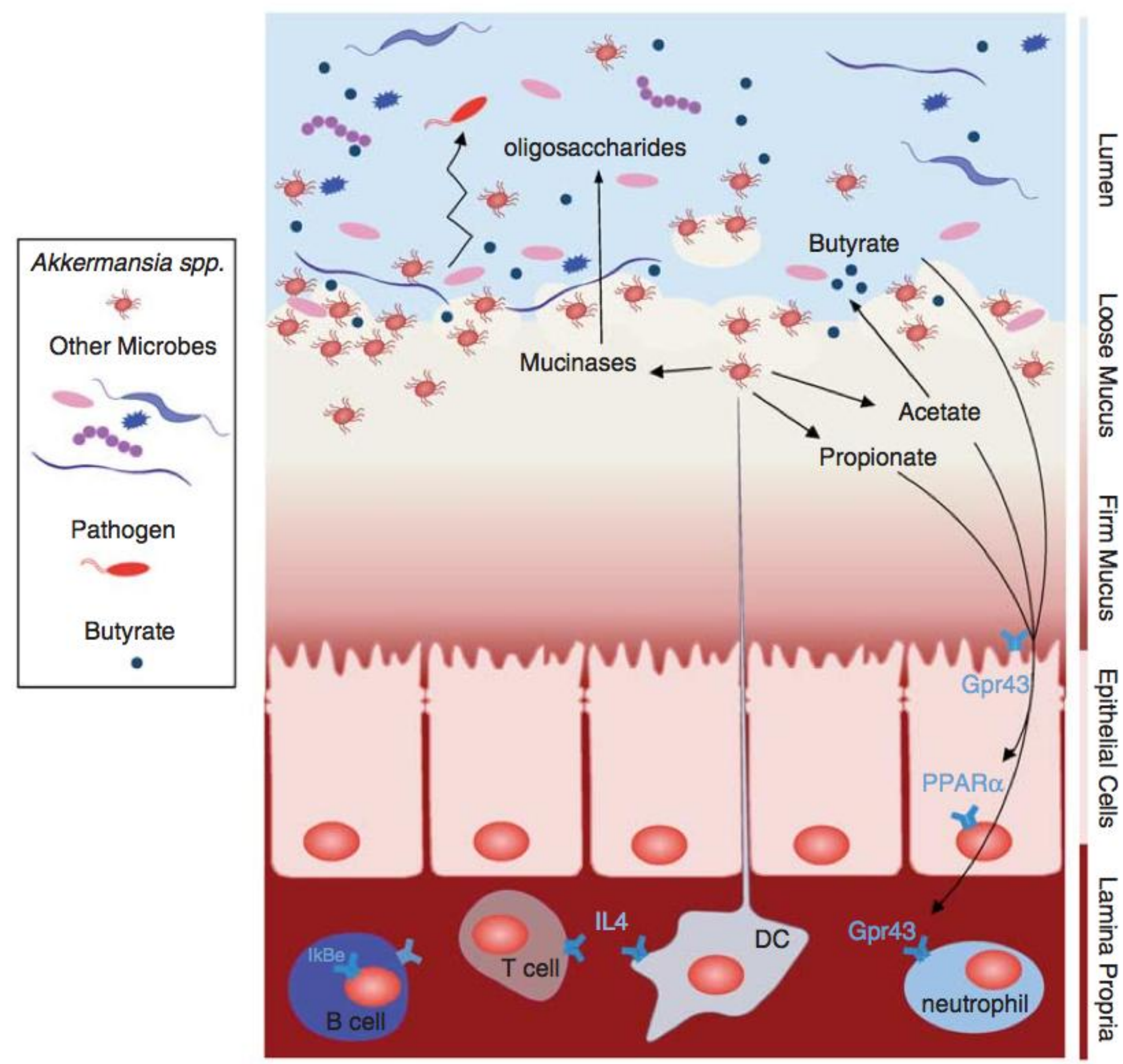
www.nature.com/ismej

WINOGRADSKY REVIEW

Microbes inside—from diversity to function: the case of *Akkermansia*

Clara Belzer[1] and Willem M de Vos[1,2,3]
[1]*Laboratory of Microbiology, Wageningen University, Wageningen, The Netherlands;* [2]*Department of Veterinary Biosciences, Helsinki University, Helsinki, Finland;* [3]*Department of Bacteriology and Immunology, Helsinki University, Helsinki, Finland*

- True symbiont of humans
  - Represent 1-4% of intestinal bacterial population
  - Mucus degrading bacteria
  - Produces SCFA – immunological signals
  - Linked to obesity and low-grade inflammation



Cross-talk between *Akkermansia muciniphila* and intestinal epithelium controls diet-induced obesity

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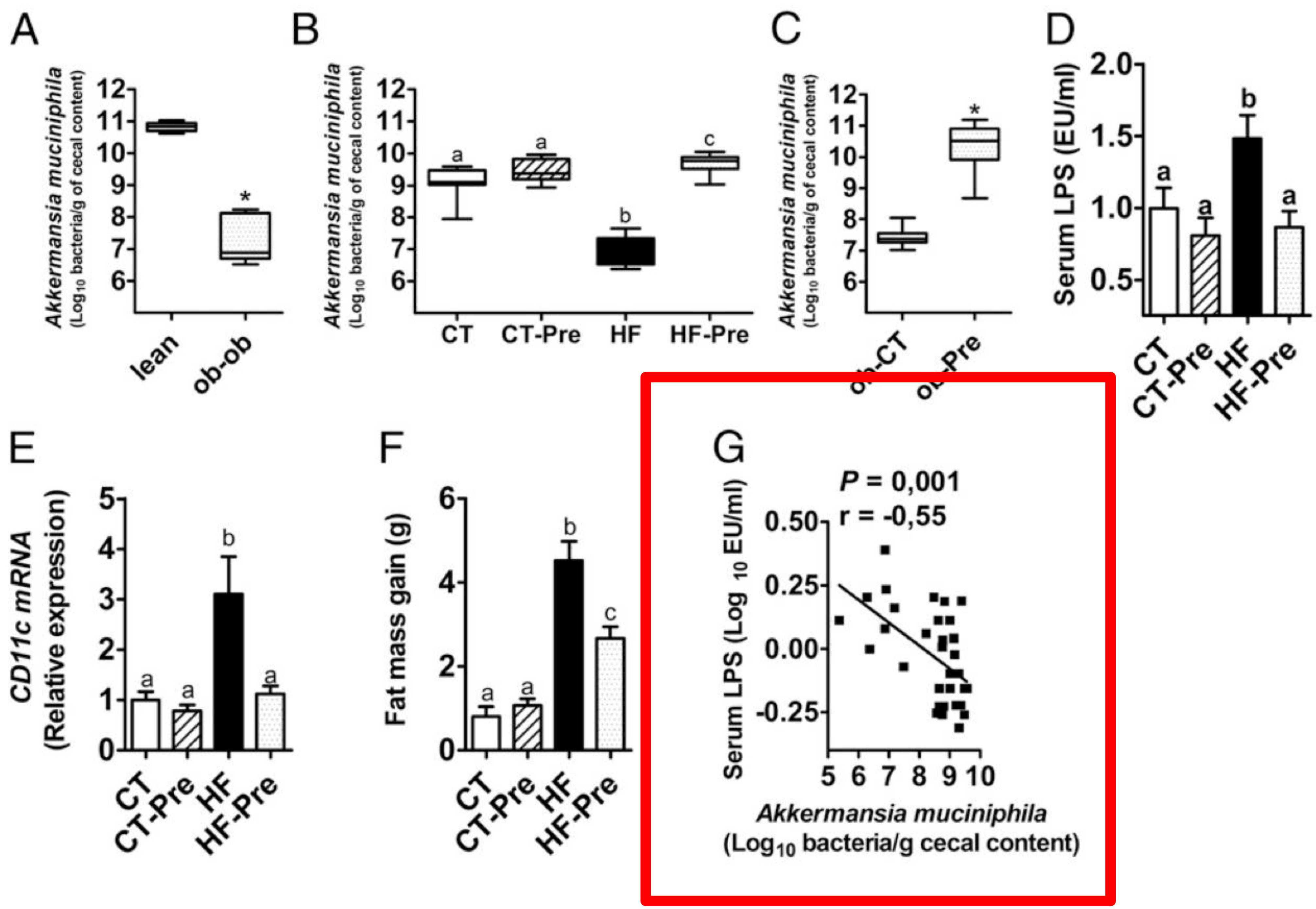
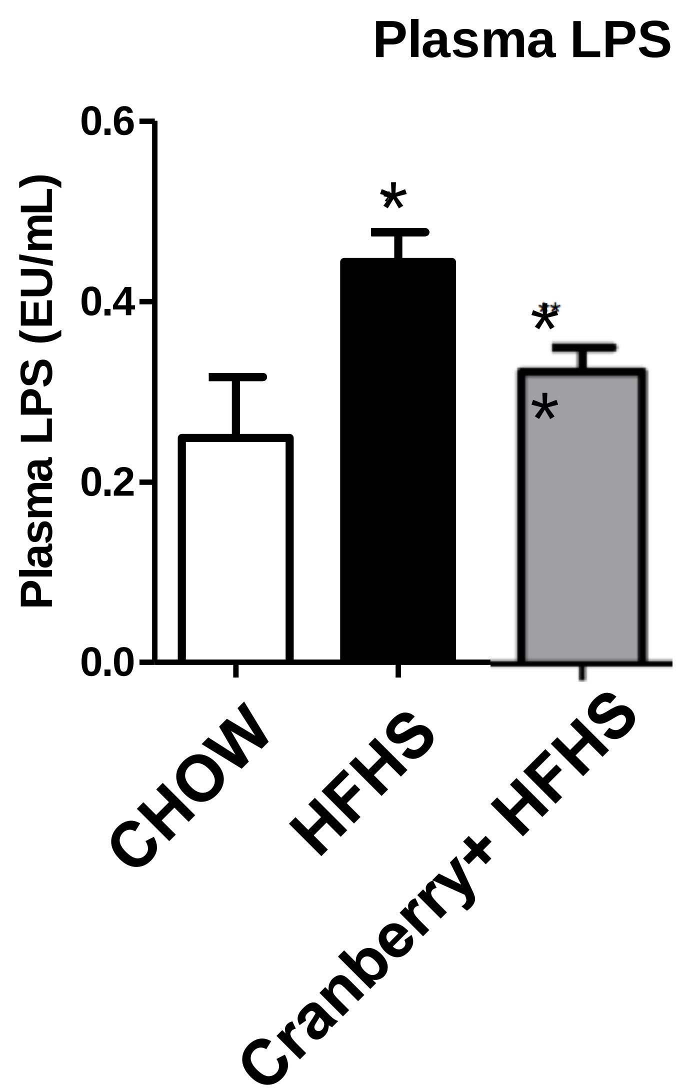
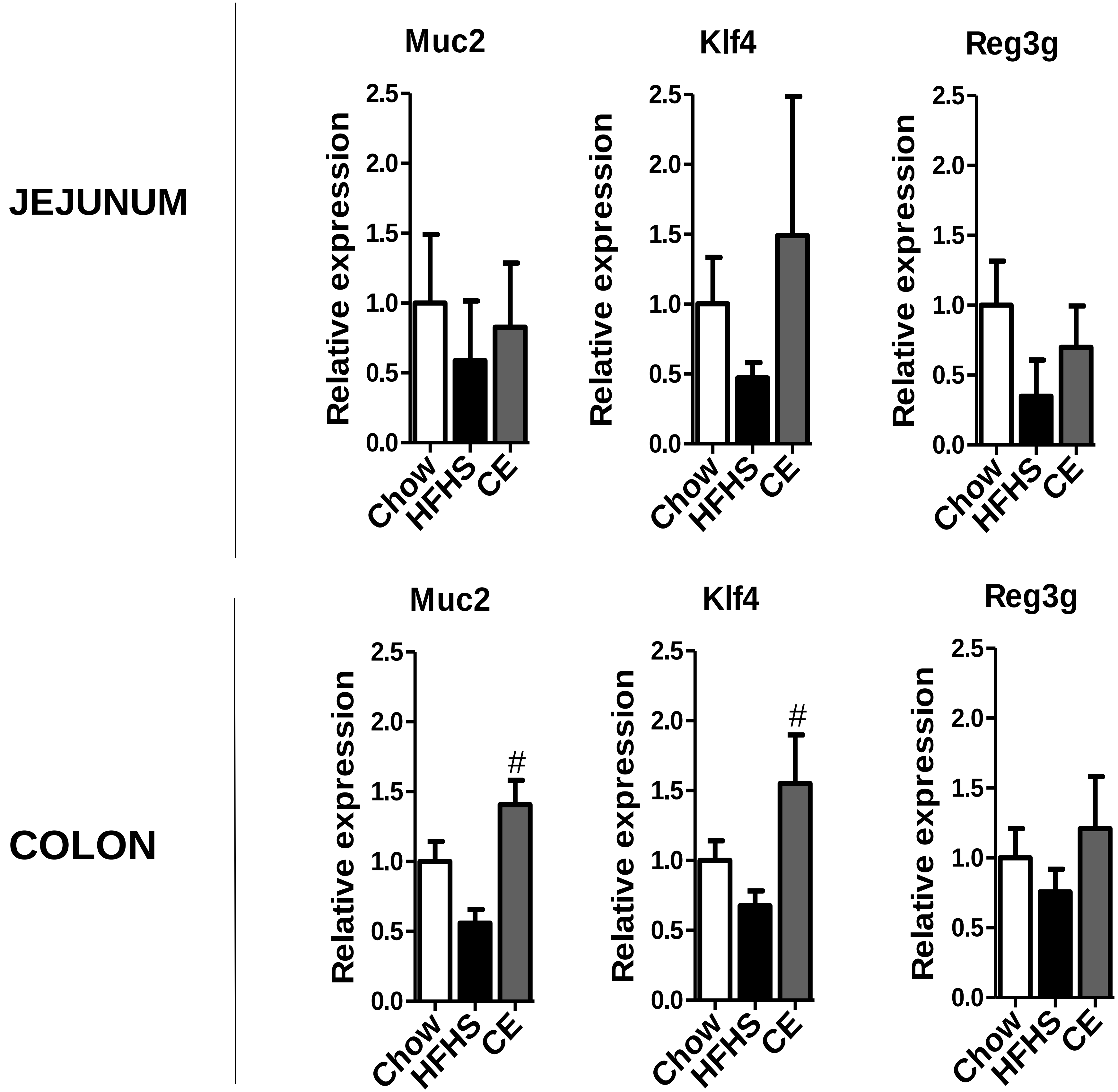


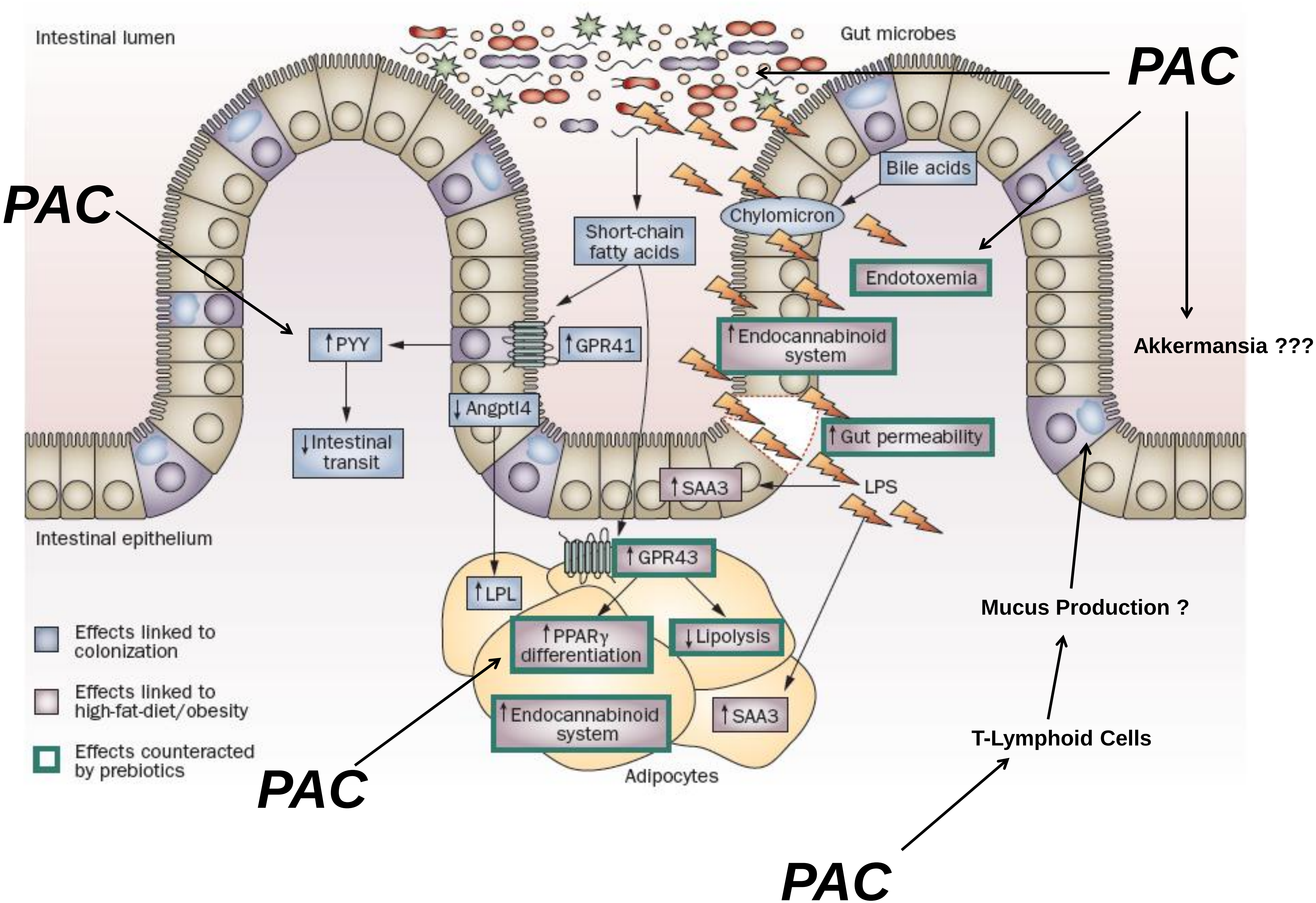
Effect of cranberry extract on metabolic endotoxemia induced by the HFHS diet



N= 6 for the Chow, HFHS et HFHS + Cranberry
*p < 0.05 vs. Chow; **p < 0.05 vs. HFHS

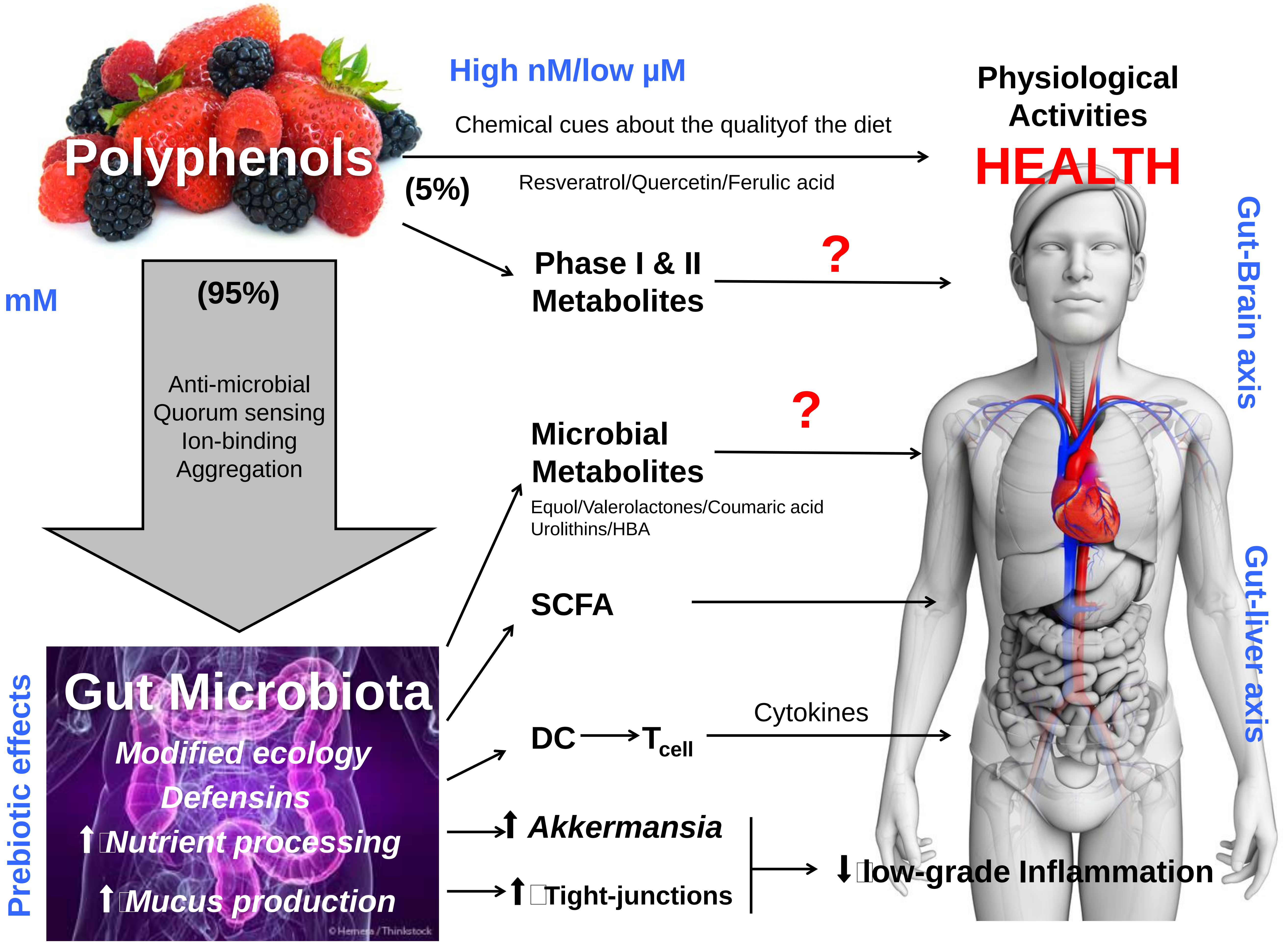
Figure S3


JEJUNUM
COLON
Muc2
Klf4
Reg3g
Relative expression
2.5
2.0
1.5
1.0
0.5
0.0
Chow
HFHS
CE
#



Delzenne, N. M. *et al. Nat. Rev. Endocrinol.* 7, 639–646 (2011); published online 9 August 2011; doi:10.1038/nrendo.2011.126

Why is bear poop blue ???



Polyphenols
High nM/low µM
Chemical cues about the qualityof the diet
Resveratrol/Quercetin/Ferulic acid
(5%)
Physiological Activities
HEALTH
Phase I & II Metabolites
?
mM
(95%)
Anti-microbial
Quorum sensing
Ion-binding
Aggregation
Microbial Metabolites
?
Equol/Valerolactones/Coumaric acid
Urolithins/HBA
SCFA
Gut-Brain axis
Gut-liver axis
Gut Microbiota
Modified ecology
Defensins
↑ Nutrient processing
↑ Mucus production
Prebiotic effects
DC → T cell
Cytokines
↑ Akkermansia
↑ Tight-junctions
↓ low-grade Inflammation
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Stéphanie Dudonné
Pascale Dubé
Véronique Richard

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