A mechanistic view on heath-promoting effects of fermented Foods

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USDA

ars

Beer/Wine







Yogurt
Yogurt
+Honey=
Food of
God

The wonderful world of fermented foods



Kifer



Cheese



Kombucha



Kimchi

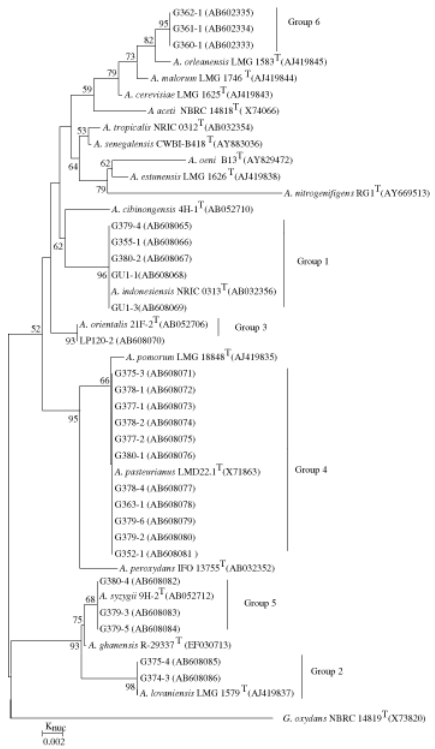
Picture from Wikipedia

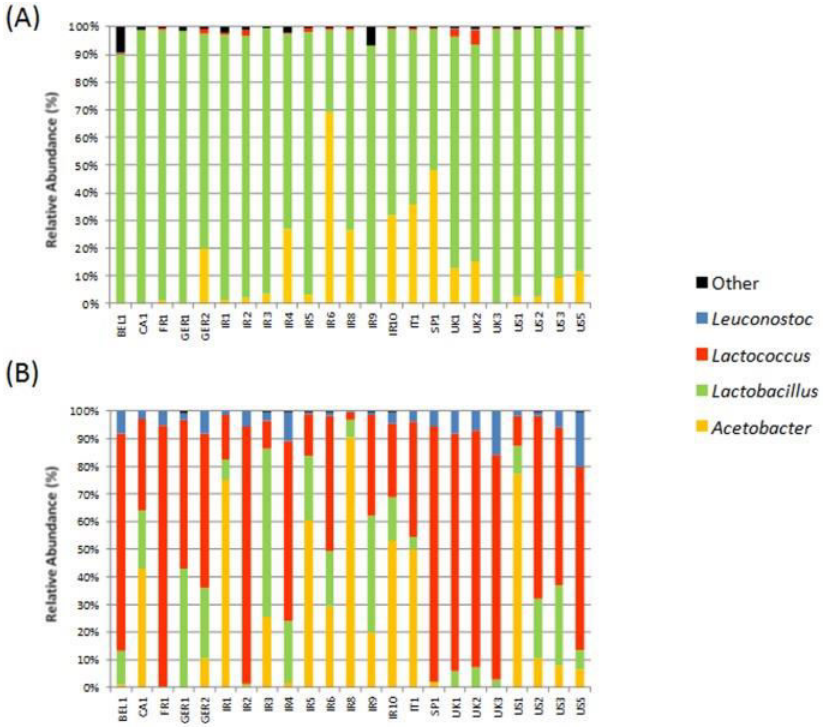
What's New?

Advance in technologies

- PCR: Sensitivity, throughput, time.
- Microarray: nucleic acid, protein, examination of multiple pathways.
- High-through-put sequencing: expanded genomic studies, splicing, methylation, SNPs.
- Multiplex assay.
- Bioinformatics. Analysis tool, Databases.

Bacteria composition maybe different





Identification of Acetobacter strains from Thai fermented rice products based on the 16S rRNA gene sequence and 16S–23S rRNA gene internal transcribed spacer restriction analyses. Journal of the Science of Food and Agriculture Volume 91, Issue 14, pages 2652-2659, 29 JUN 2011 DOI: 10.1002/jsfa.4506 http://onlinelibrary.wiley.com/doi/10.1002/jsfa.4506/full#fig1

Marsh AJ1, O'Sullivan O, Hill C, Ross RP, Cotter PD. Sequencing-based analysis of the bacterial and fungal composition of kefir grains and milks from multiple sources. PLoS One. 2013 Jul 19;8(7):e69371. doi: 10.1371/journal.pone.0069371.

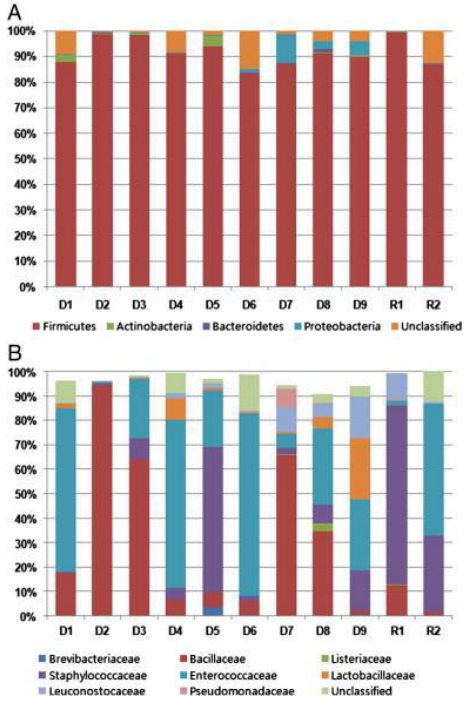


Fig. 2. Relative abundance of bacterial 16S rRNA genes from doenjang samples at the phylum level (A) and family level (B) identified with a modified 16S rRNA database from the Ribosomal Database Project (RDP).

Young-Do Nam, So-Young Lee, Seong-Il Lim

Microbial community analysis of Korean soybean pastes by next-generation sequencing

International Journal of Food Microbiology, Volume 155, Issues 1–2, 2012, 36–42

http://dx.doi.org/10.1016/j.ijfoodmicro.2012.01.013

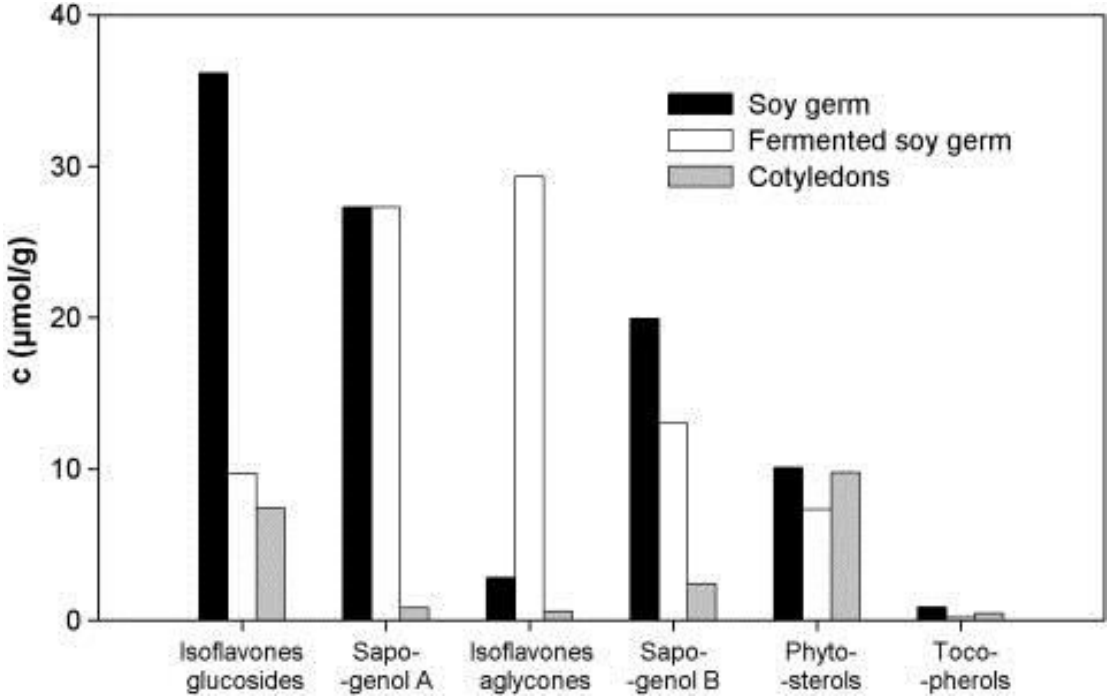


Fig. 6. Comparison of antioxidant phytochemical composition in raw soy germ, fermented soy germ and soy cotyledons. Concentration values related to fermented soy germ correspond to the results obtained with the lactic acid strain B.

Jane Hubert, Monique Berger, Françoise Nepveu, François Paul, Jean Daydé

Effects of fermentation on the phytochemical composition and antioxidant properties of soy germ

Food Chemistry, Volume 109, Issue 4, 2008, 709–721

http://dx.doi.org/10.1016/j.foodchem.2007.12.081

Human microbiome/gut microbiome

human body contains ~ 10^{14} bacteria cells vs. ~ 3.72 * 10^{13} human cells .

~ 3,000,000 genes compared with ~30,000 in the human genome.

500 to 1,000 species of bacteria live in the human gut, 99% of the bacteria come from about 30 or 40 species. Bacteria make up most of the flora in the colon and 60% of the dry mass of feces.

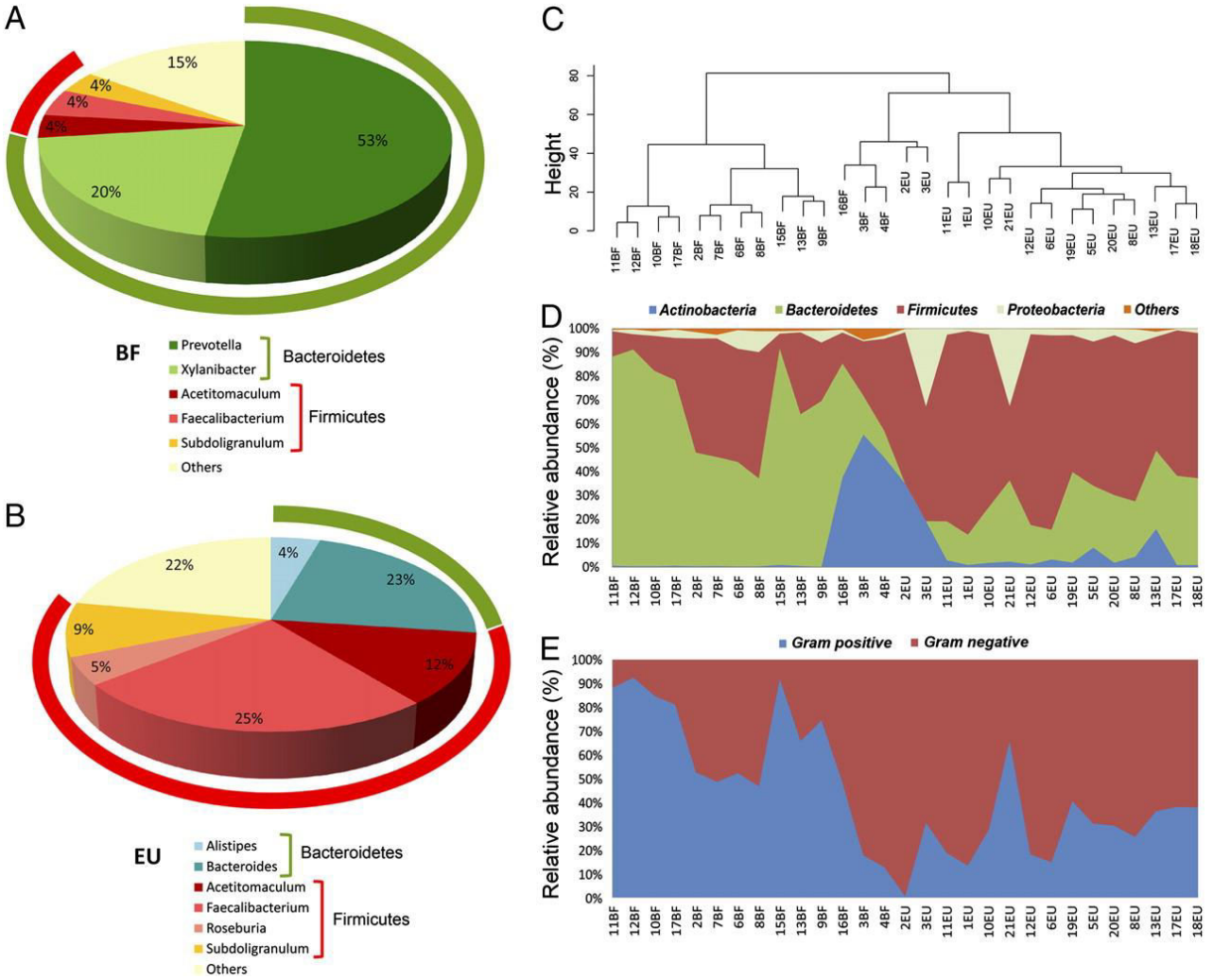
Interaction with host : (1) modulating the inflammatory response, (2) synthesizing small molecules and proteins that are taken up by the host, and (3) changing the amount of available energy in the diet.



http://discovermagazine.com/galleries/zen-photo/m/microbiome

16S rRNA gene surveys reveal a clear separation of two children populations investigated.

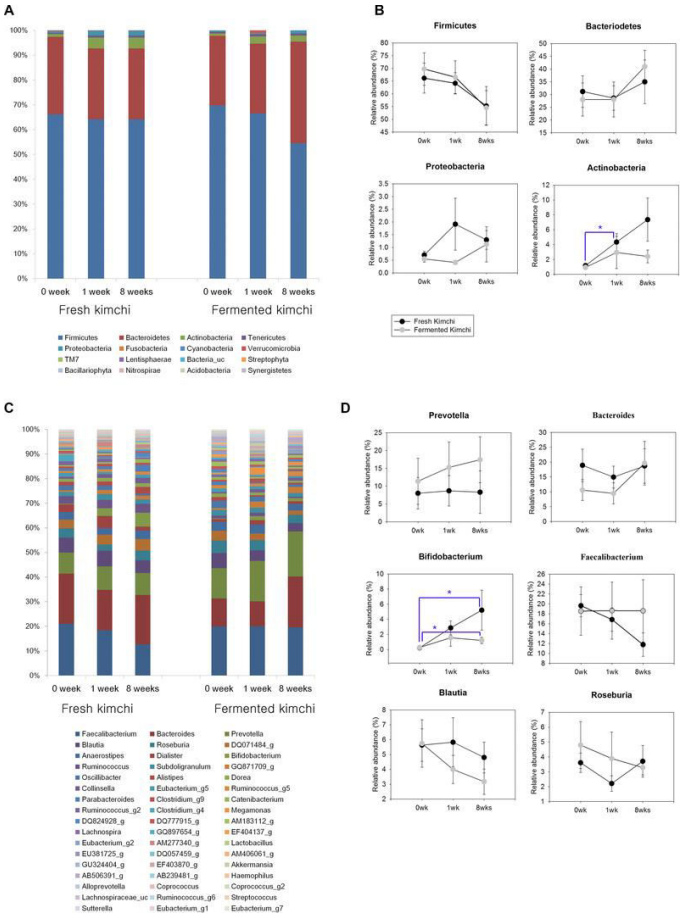
Burkina Faso



Carlotta De Filippo et al. PNAS 2010;107:14691-14696

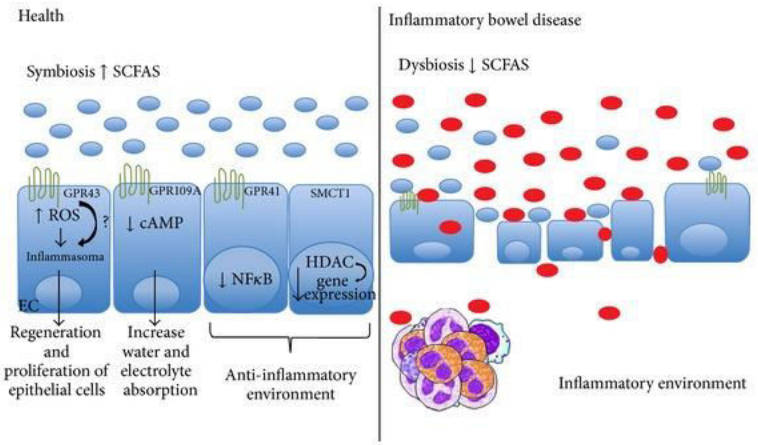
©2010 by National Academy of Sciences

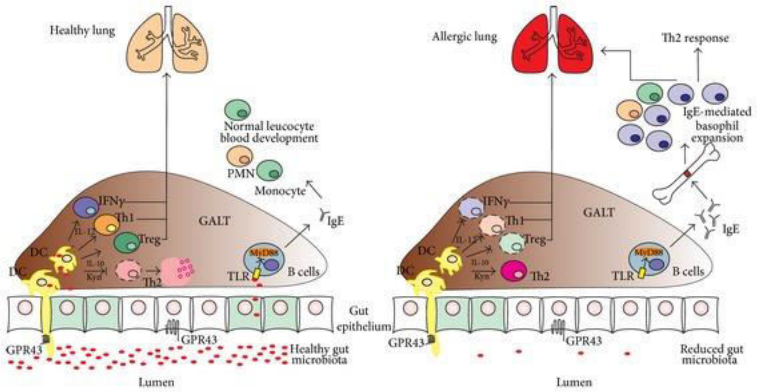
Contrasting effects of fresh and fermented kimchi consumption on gut microbiota composition and gene expression related to metabolic syndrome in obese Korean women

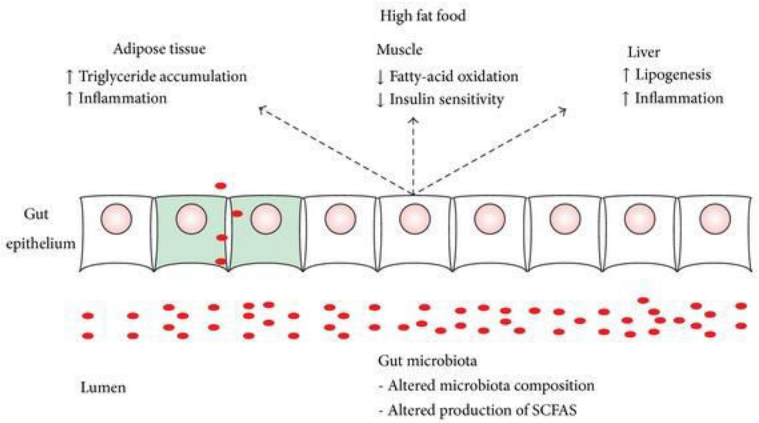


Molecular Nutrition & Food Research
Volume 59, Issue 5, pages 1004-1008, 23 MAR 2015 DOI: 10.1002/mnfr.201400780
http://onlinelibrary.wiley.com/doi/10.1002/mnfr.201400780/full#mnfr2359-fig-0001

Modulation of host immune system





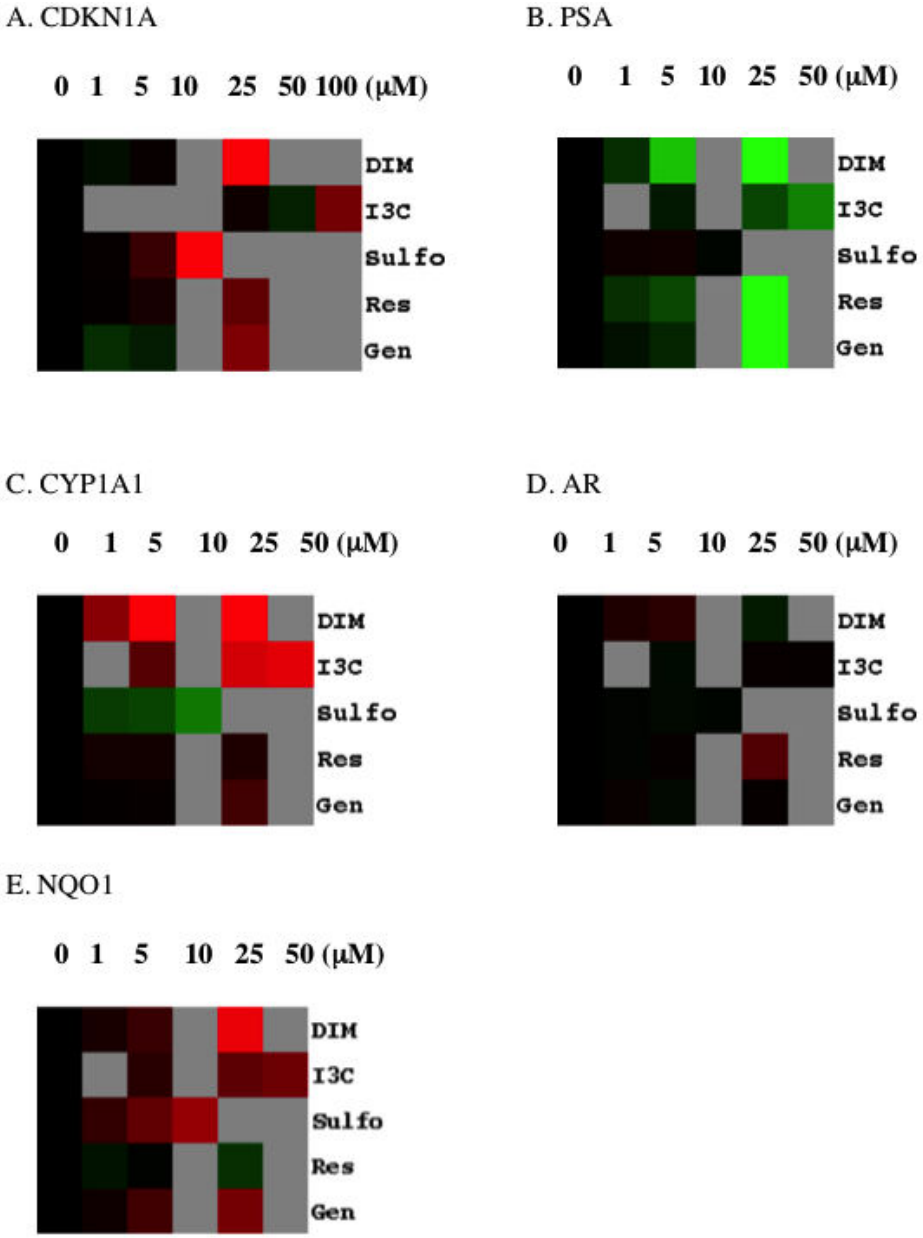


J Immunol Res. 2014;2014:689492. doi: 10.1155/2014/689492. Epub 2014 Sep 18. Review.

Diet/Nutrients Gene Interaction

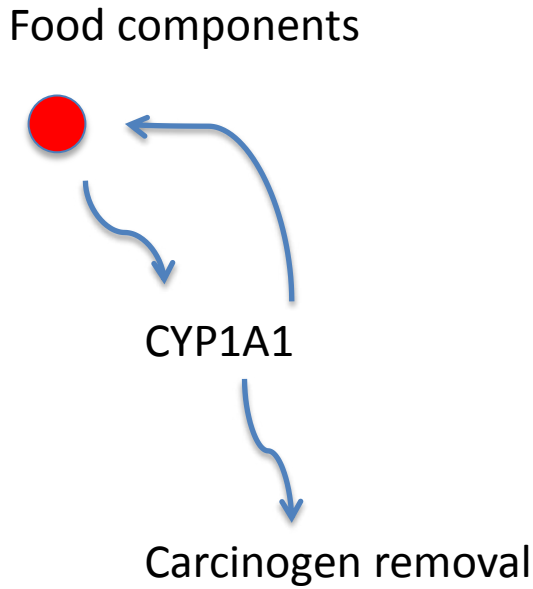
- Gene as on-off switch for pathways and efficacies.
- Nutrients induce gene(s) involved in critical cellular pathways such as hormone, cytokines, cell number homeostasis, xenobiotic metabolism.
- Genes can confer or modulate nutrient efficacies.
- You are what you eat.

Genetic regulation: Regulation of transcriptome



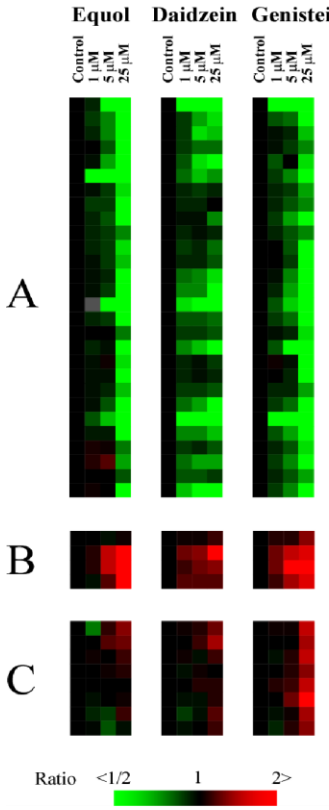
Green, down regulated. Red, up regulated. Black, Zero. Gray, no data. Scale –3 to 3.

- Diet-gene, gene-diet interaction



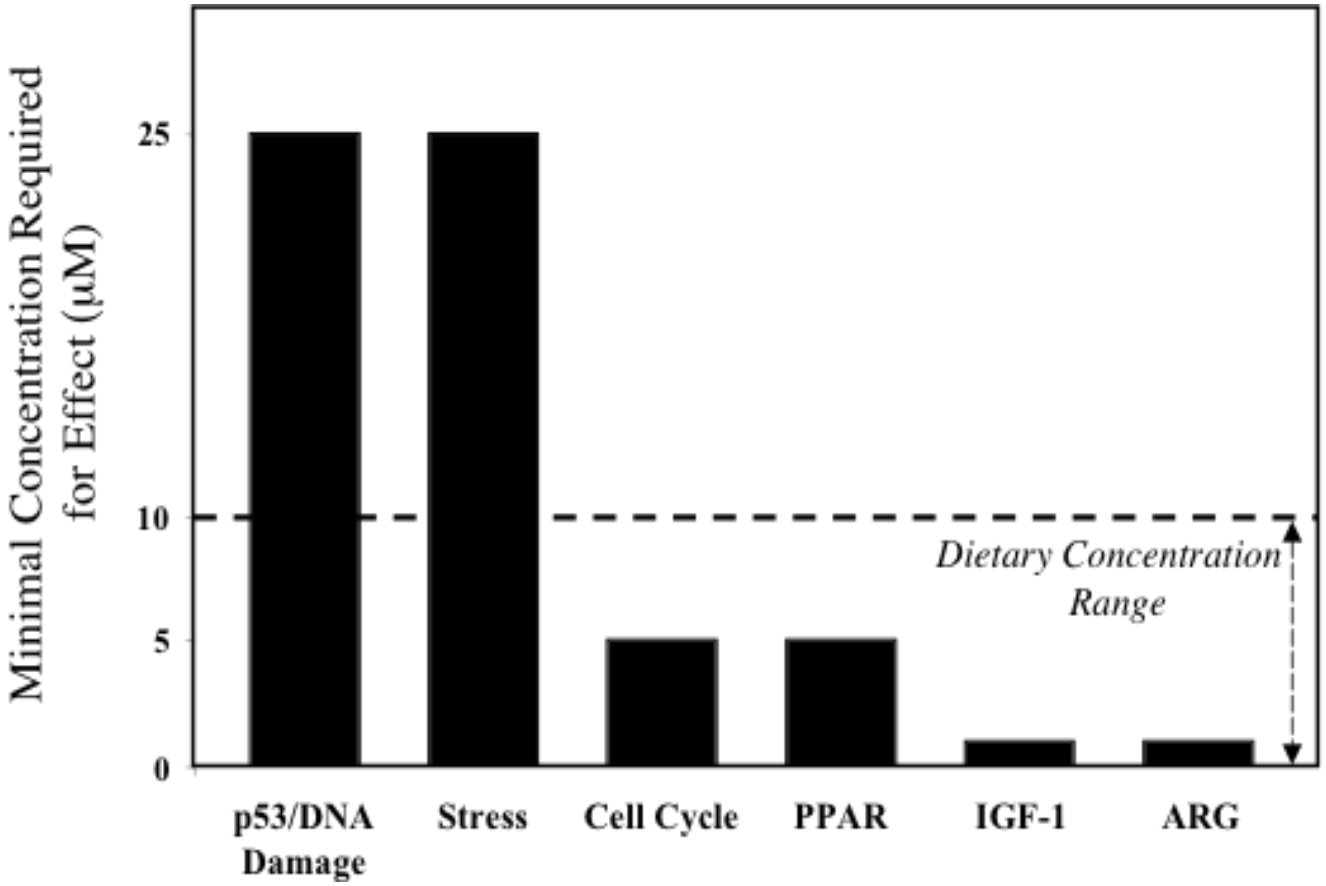
- A compound can act on multiple pathways
- Identify a target tissue/system

Effects of equol, daidzein and genistein on androgen responsive genes



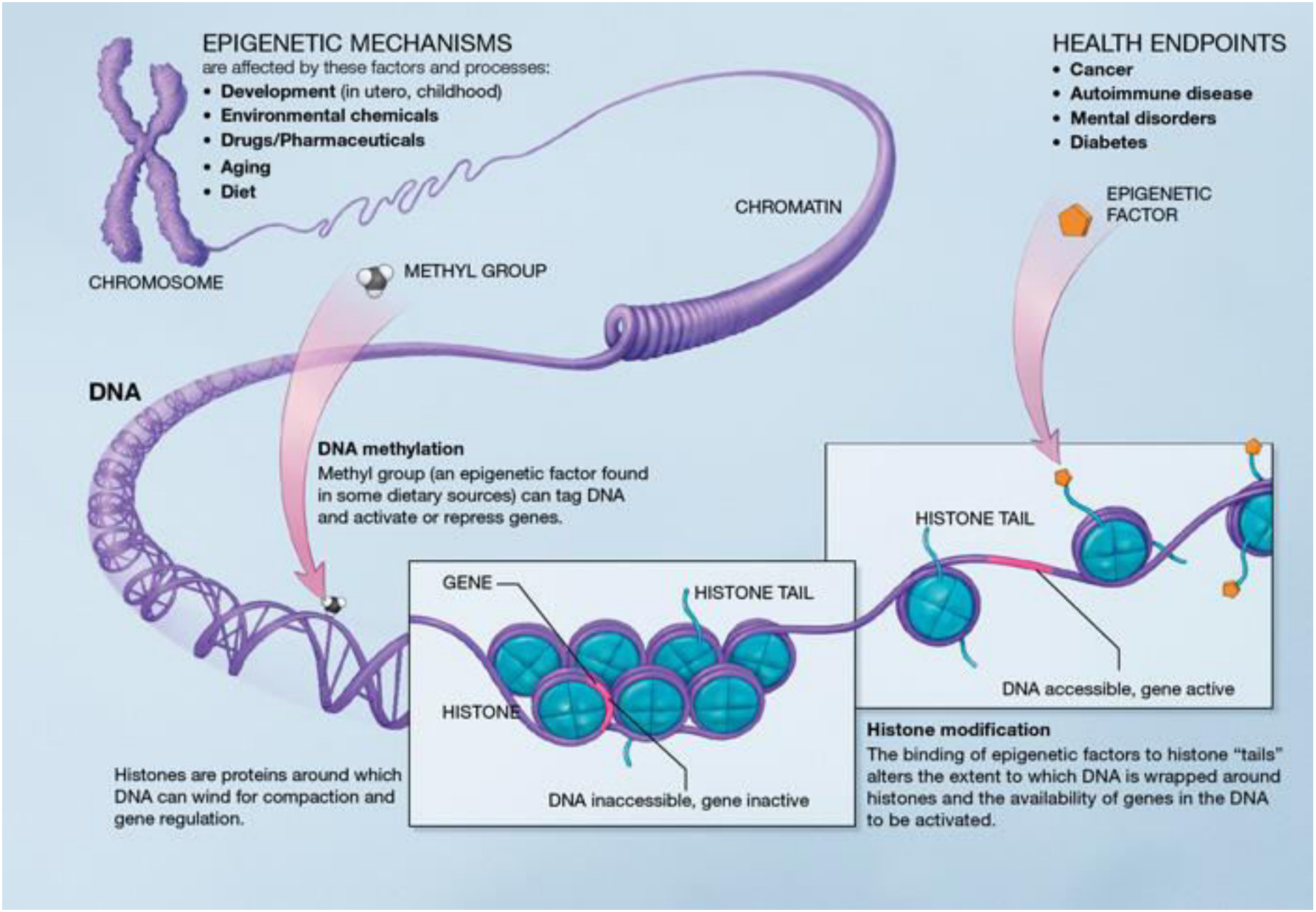
	GeneBank Accession	Gene	Equol/Control ratio			Daidzein/Control ratio			Genistein/Control ratio		
			1 μM	5 μM	25 μM	1 μM	5 μM	25 μM	1 μM	5 μM	25 μM
A	AF055376	MAF	0.871	0.500	0.406	0.435	0.379	0.435	0.406	0.308	0.268
	NM_013233	STK39	0.812	0.660	0.308	0.812	0.616	0.536	0.758	0.707	0.500
	NM_023929	ZBTB10	0.871	0.660	0.354	0.812	0.536	0.574	0.933	0.871	0.574
	NM_014350	TNFAIP8	1.000	0.758	0.500	0.812	0.707	0.707	0.933	0.812	0.660
	NM_003866	INPP4B	0.933	0.616	0.287	0.758	0.536	0.435	0.758	1.000	0.536
	AF140507	CAMKK2	0.467	0.500	0.268	0.707	0.574	0.637	0.812	0.660	0.435
	AL136939	ELOVL5	0.933	0.812	0.536	0.871	0.812	0.871	0.871	0.812	0.616
	NM_014762	DHCR24	0.812	0.812	0.500	0.871	0.871	1.000	0.871	0.758	0.660
	Y19026	HOMER2	0.871	0.758	0.435	0.933	0.933	0.660	0.812	0.616	0.435
	NM_003104	SORD	0.871	0.812	0.660	0.871	0.933	0.871	0.871	0.758	0.660
	NM_012391	SPDEF	0.871	0.812	0.536	0.812	0.871	0.707	1.000	0.758	0.406
	AI745526	SPDEF	0.933	0.812	0.574	0.871	0.871	0.758	1.000	0.812	0.500
	BC005196	KLK2	0.933	0.871	0.218	0.707	0.660	0.536	0.933	0.660	0.177
	AA595465	KLK2	0.933	0.812	0.154	0.660	0.660	0.406	0.871	0.616	0.117
	AF249669	NKX3-1		0.500	0.088	0.536	0.500	0.467	0.758	0.555	0.051
	AF247704	NKX3-1	0.871	0.812	0.379	0.758	0.758	0.707	0.812	0.707	0.233
	AI435670	SPDEF	1.000	1.000	0.683	0.812	0.812	0.758	0.933	0.871	0.536
	AF270487	TMPRSS2	0.871	0.933	0.287	0.660	0.574	0.500	0.758	0.500	0.177
	U17040	KLK3	0.933	1.072	0.536	0.871	0.933	0.812	1.072	0.933	0.435
	NM_001648	KLK3	0.933	0.933	0.467	0.871	0.933	0.871	1.000	0.871	0.406
	S73498	UAP1	0.933	0.871	0.574	0.812	0.812	0.758	0.871	0.871	0.616
	NM_000693	ALDH1A3	0.933	0.758	0.379	0.707	0.616	0.500	0.812	0.707	0.308
	NM_020182	TMEPAI	0.758	0.574	0.134	0.500	0.467	0.177	0.467	0.241	0.077
	AF249671	NKX3-1	0.901	0.901	0.467	0.660	0.660	0.574	0.758	0.616	0.406
	AA181179	CAMKK2	1.110	1.072	0.683	0.812	0.871	0.758	0.871	0.758	0.536
	NM_005656	TMPRSS2	1.149	1.320	0.616	0.707	0.616	0.616	0.812	0.660	0.406
	AK024748	CAMKK2	1.000	1.000	0.758	0.758	0.758	0.812	0.871	0.758	0.616
	NM_006633	IQGAP2	1.072	1.000	0.467	0.574	0.500	0.467	0.812	0.660	0.308
B	BE622627	PIK3R3	1.000	0.933	1.072	1.072	1.072	1.231	1.149	1.149	1.516
	NM_000790	DDC	1.149	1.741	3.249	1.414	1.516	2.000	1.414	1.741	1.866
	NM_000055	BCHE	1.149	1.741	2.639	1.231	1.414	1.516	1.414	2.144	2.297
	R59697	CDK8	0.933	1.320	2.297	1.320	1.320	1.320	1.231	1.625	1.866
C	BC005807	SCD	0.683	1.189	1.516	1.072	1.149	1.414	1.072	1.072	1.741
	AA678241	SCD	1.000	1.320	1.414	1.000	1.231	1.625	1.000	1.000	1.625
	AL080081	DNAJB9	1.072	1.000	1.231	1.072	0.933	1.231	0.933	1.149	1.741
	BC005247	IDI1	1.000	1.072	1.149	0.933	1.072	1.000	1.000	1.149	1.516
	NM_004508	IDI1	1.000	1.000	1.000	1.000	1.149	1.149	1.149	1.231	1.741
	NM_003359	UGDH	0.933	1.000	1.072	0.933	0.933	1.149	1.000	1.414	2.000
	NM_012328	DNAJB9	0.871	0.812	1.231	0.812	0.933	1.320	0.933	1.072	1.625
	NM_014822	SEC24D	0.966	0.758	0.933	0.933	1.000	1.231	0.871	1.149	1.516

Effects of genistein on cellular pathways in LNCaP cells



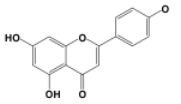
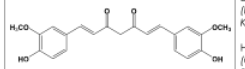
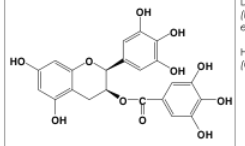
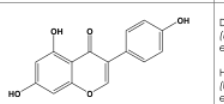
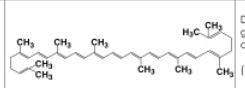
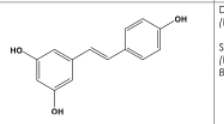
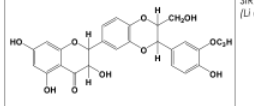
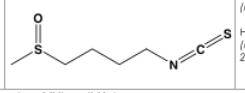
Epigenetics/Epigenomics

In 2008, a consensus definition of the epigenetic trait, "stably heritable phenotype resulting from changes in a chromosome without alterations in the DNA sequence", was made at a Cold Spring Harbor meeting. Wiki.


EPIGENETIC MECHANISMS
are affected by these factors and processes:
• Development (in utero, childhood)
• Environmental chemicals
• Drugs/Pharmaceuticals
• Aging
• Diet
HEALTH ENDPOINTS
• Cancer
• Autoimmune disease
• Mental disorders
• Diabetes
CHROMOSOME
CHROMATIN
METHYL GROUP
EPIGENETIC FACTOR
DNA
DNA methylation
Methyl group (an epigenetic factor found in some dietary sources) can tag DNA and activate or repress genes.
HISTONE TAIL
GENE
HISTONE TAIL
HISTONE
DNA accessible, gene active
DNA inaccessible, gene inactive
Histones are proteins around which DNA can wind for compaction and gene regulation.
Histone modification
The binding of epigenetic factors to histone "tails" alters the extent to which DNA is wrapped around histones and the availability of genes in the DNA to be activated.

wiki

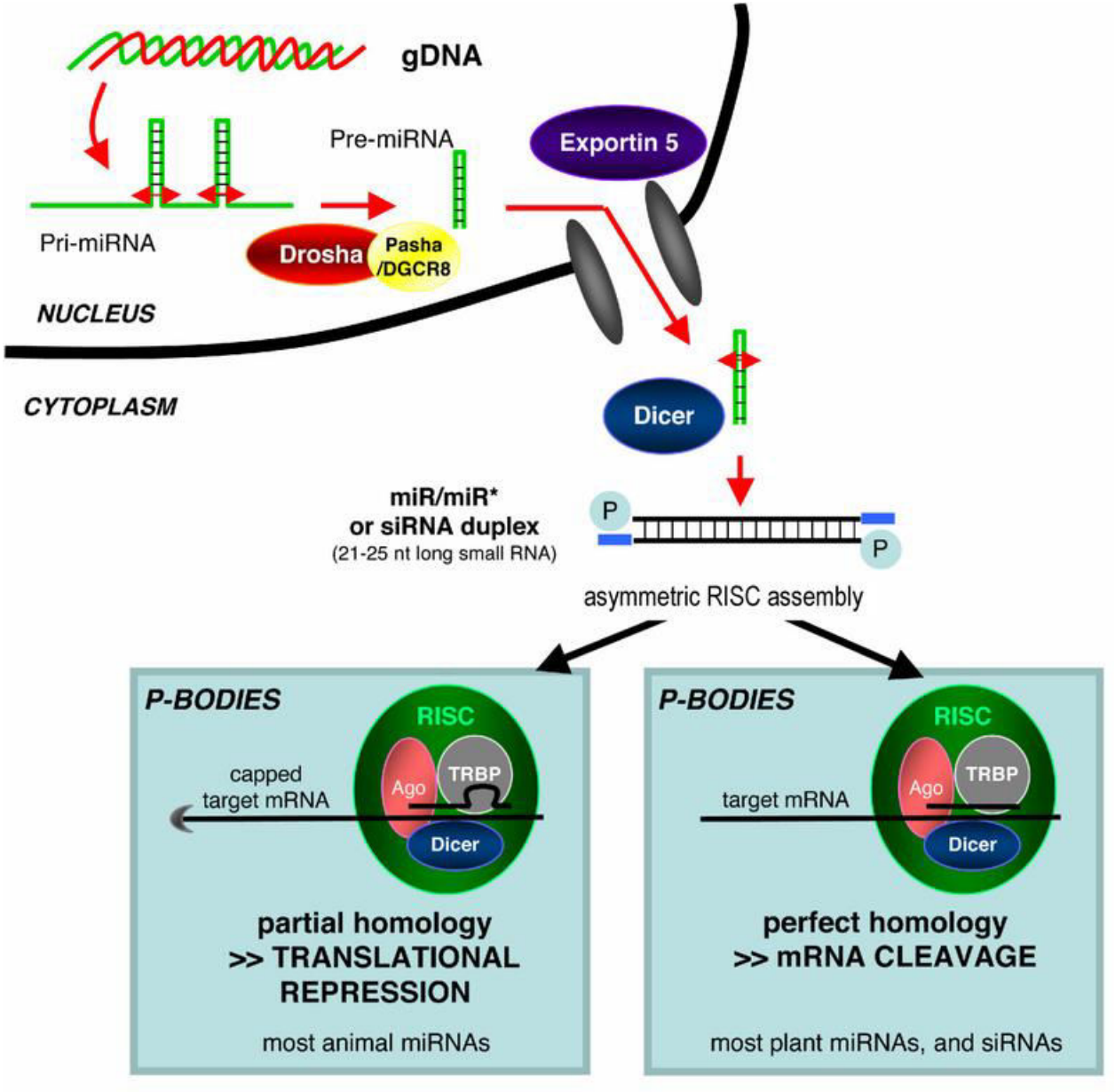
Table 1 Bioactive dietary compounds—their source, molecular structure, and epigenetic targets

Dietary agents	Structure	Epigenetic effect on Cancer*	Picture of the sources
Apigenin (Parsley)[1] (*Petroselinum*)[2]		DNMT inhibitor *(Fang M et al 2007)*	
Allyl Mercaptan (Garlic)[1] (*Allium sativum*)[2]		HDAC inhibitor *(Lea et al 2001; Druesne et al 2004)*	
Curcumin (Turmeric)[1] (*Curcuma longa*)[2]		DNMT inhibitor *(Liu et al 2009; Fang et al 2007; Fu and Kurzrock 2010)* HDAC and HAT inhibitor *(Chen et al 2007; Liu et al 2005; Kang et al 2006; Cui et al 2007; Balasubramanyam et al 2004)*	
Epigallocatechin-3-gallate (EGCG) (Green tea)[1] (*Camellia sinensis*)[2]		DNMT inhibitor *(Fang et al 2003; Kato et al 2008; Pandey et al 2010; Lee et al 2005)* HAT inhibitor *(Choi et al 2009)*	
Genistein (Soybean)[1] (*Glycine max*)[2]		DNMT inhibitor *(Majid et al 2008; Kikuno et al 2008; Fang et al 2005; Li et al 2009)* HDAC inhibitor and HAT activator *(Fang et al 2005; Li et al 2009; King-Batoon et al 2008; Majid et al 2008)*	
Lycopene (Tomatoes)[1] (*Solanum lycopersicum*)[2]		Demethylates the *GSTP1, RARβ2 and HIN-1* genes in breast cancer cells (MDA-MB-231 and MCF10A) *(King-Batoon et al 2008)*	
Resveratrol (Red grapes)[1] (*Vitis vinifera*)[2]		DNMT inhibitor *(Papoutsis et al 2010; Stefanska et al 2010)* SIRT1 activator *(Kaeberlein et al 2008; Wang et al 2008; Baily et al 2009)*	
Silymarin (Milk thistle)[1] (*Silybum marianum L.*)[2]		SIRT1 activator *(Li et al 2007)*	
Sulforaphane (Cruciferous vegetables)[1] (*Brassicaceae*)[2]		DNMT inhibitor *(Meeran et al 2010; Traka et al 2005)* HDAC inhibitor *(Myzak et al 2007; Dashwood and Ho 2007; Ho et al 2009; Myzak et al 2004)*	

*limited references given, full list available in text
[1] Source
[2] Botanical name

Epigenetic targets of bioactive dietary components for cancer prevention and therapy
Syed M. Meeran & Amiya Ahmed & Trygve O. Tollefsbol
Clin Epigenet (2010) 1:101–116

miRNA


gDNA
Pre-miRNA
Exportin 5
Pri-miRNA
Drosha
Pasha /DGCR8
NUCLEUS
CYTOPLASM
Dicer
miR/miR*
or siRNA duplex
(21-25 nt long small RNA)
P
P
asymmetric RISC assembly
P-BODIES
RISC
capped
target mRNA
Ago
TRBP
Dicer
partial homology
>> TRANSLATIONAL
REPRESSION
most animal miRNAs
P-BODIES
RISC
target mRNA
Ago
TRBP
Dicer
perfect homology
>> mRNA CLEAVAGE
most plant miRNAs, and siRNAs

Wiki

TABLE 2 Representative dietary components that can modulate microRNA (miRNA) using in vivo models[1]

Dietary component	Animal model	Concentration	miRNA Upregulated	miRNA Downregulated	Reference
Essential nutrients					
Folate, methionine, choline	Male weaning Fisher 344 rats	Low in L-methionine (0.18%), devoid of choline and folic acid (Dyets, Inc.)	let-7a, miR-21, miR-23, miR-130, miR-190 and miR-17–92	miR-122a	(58)
Folate, methionine, choline	Male weaning Fisher 344 rats	Low in L-methionine (0.18%), devoid of choline and folic acid (Dyets, Inc.)		miR-34a, miR-16a, miR-127, miR-181a, miR-20a, and miR-200b	(60)
Choline	C57BL/6 mice	Lombardi's choline-deficient (0 g/kg), low-methionine (1.7 g/kg), and amino acid-defined diet (Dyets, Inc.)	miR-155, miR-221/222, and miR-21	miR-122	(61)
Vitamin E	Weaned male Fisher 344 rats	Diets deficient in vitamin E (VE-free vitamin premix, E15313–2;ssniff Spezialdiaeten)		miR-122a and miR-125b	(67)
Phytochemicals					
EGCG	Athymic nude mice implanted with androgen-sensitive human prostate carcinoma CWR22Rv1 cells	EGCG for 6 wk (1 mg/d 3×/wk)	miR-330	miR-21	(71)
Curcumin	Chicken-embryo-metastasis CAM assay (RKO and HCT116 cells inoculated into 10-d-old chicken embryos)	20 μmol/L		miR-21	(76)
I3C	Adult male Sprague-Dawley rats	2.5 g/kg diet; mean intake 62.5 mg/rat/d	miR-34b, miR-26a, miR-125a-p, and miR-10a		(78)
I3C	Female A/J mice	70 μmol I3C/g diet		miR-21, miR-31, miR-130a, miR-146b and miR-377	(79)
PEITC	Adult male Sprague-Dawley rats	500 mg/kg diet; mean intake 9.6 mg/rat/d	miR125b, miR-26a, miR-146-p, let-7a, let-7c, miR-192, miR-99b, miR-123-p, and miR-222-p		(78)
Other bioactive food components					
(n-3) PUFA	Weanling male Sprague-Dawley rats	11.5 g fish oil/100 g diet; total fat content diet 15%	let-7d, miR-15b, miR-107, miR-191 and miR-324–5p		(98)
(n-3) PUFA	Weanling male Sprague-Dawley rats	11.5 g fish oil/100 g diet; total fat content diet 15%	miR-19b, miR26b, miR-27b, and miR-203		(99)

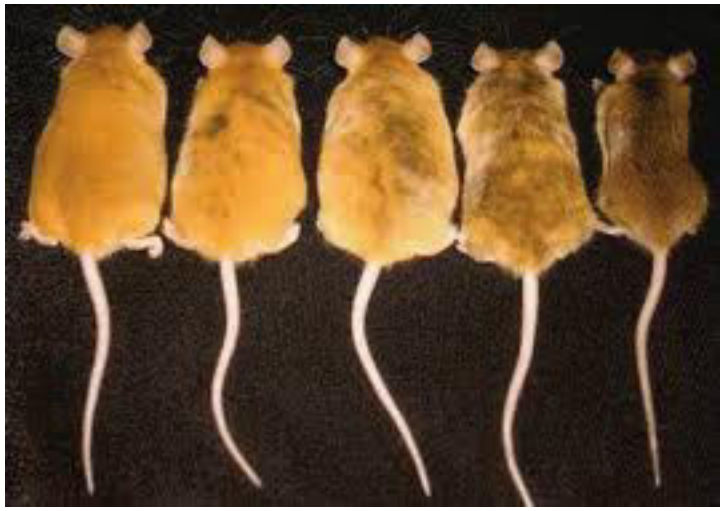
[1] CAM, chorionallantoic membrane assay; EGCG, epigallocatechin gallate; I3C, indole-3-carbinol; PEITC, phenethyl isothiocyanate.

MicroRNA, Nutrition, and Cancer Prevention
Sharon A. Ross and Cindy D. Davis
Adv. Nutr. 2: 472–485, 2011

Epigenetic, In-utero and trans-generation effects

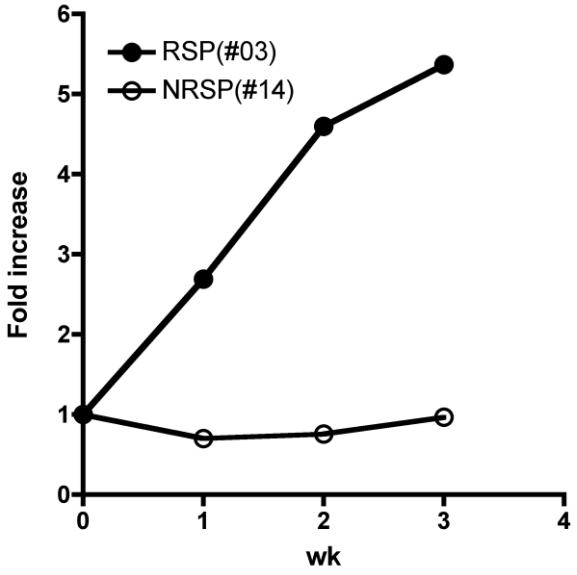
Maternal genistein alters coat color and protects Avy mouse offspring from obesity by modifying the fetal epigenome. Environ Health Perspect. 2006 Apr;114(4):567-72.

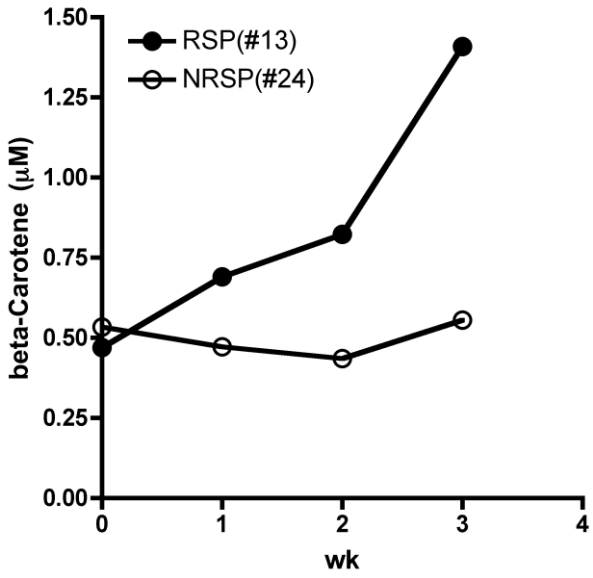
High-fat or ethinyl-oestradiol intake during pregnancy increases mammary cancer risk in several generations of offspring
Nature Communications 3, 11 September 2012.



Individual differences

Individual respond of beta-carotene





Wang TT, Edwards AJ, Clevidence BA. Strong and weak plasma response to dietary carotenoids identified by cluster analysis and linked to beta-carotene 15,15'-monooxygenase 1 single nucleotide polymorphisms.
J Nutr Biochem. 2013 Aug;24(8):1538-46. doi: 10.1016/j.jnutbio.2013.01.001. Epub 2013 Mar 18.

Timing and physiological concentration

Timing Appears to Influence the Response (*Apc*+/- *Msh*2-/- mouse)

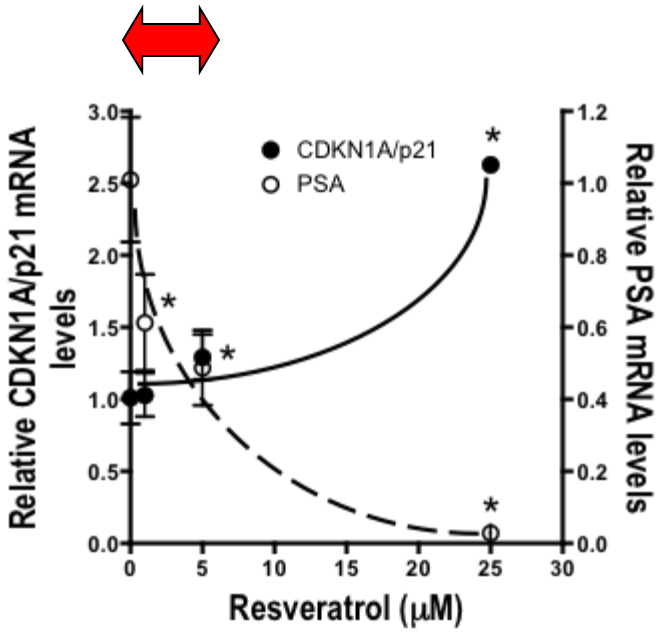
Start Diet	3 weeks	3 weeks	6 weeks	6 weeks
Dietary folate (mg folate/kg diet)	0 (*n* = 7)	8 (*n* = 7)	0 (*n* = 10)	8 (*n* = 7)
Duration of folate intervention (weeks)	8	8	5	5
Serum folate (ng/ml)	15.0 ± 2.6	63.5 ± 7.7**	19.8 ± 3.2	95.6 ± 27.0**
Average number of total small intestinal adenomas per mouse	299.4 ± 27.4	**110.3 ± 5.2****	70.0 ± 17.1	**295.3 ± 59.6****

Song et al. (2000) Cancer Res 2000;60: 3191

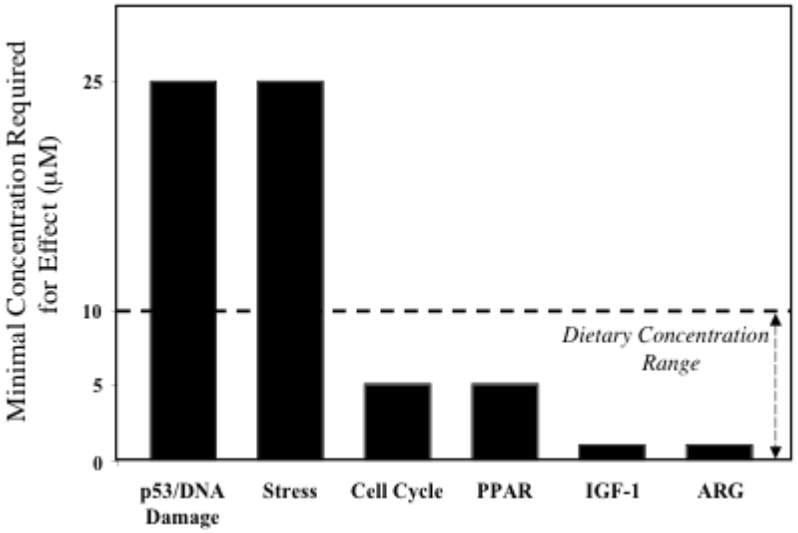
Replicated in the *Apc* min mouse: *Cancer Res* 2000;60: 5434

Physiological achievable concentration consideration

Plasma and tumor concentration range of resveratrol



Soy isoflavones circulating concentration



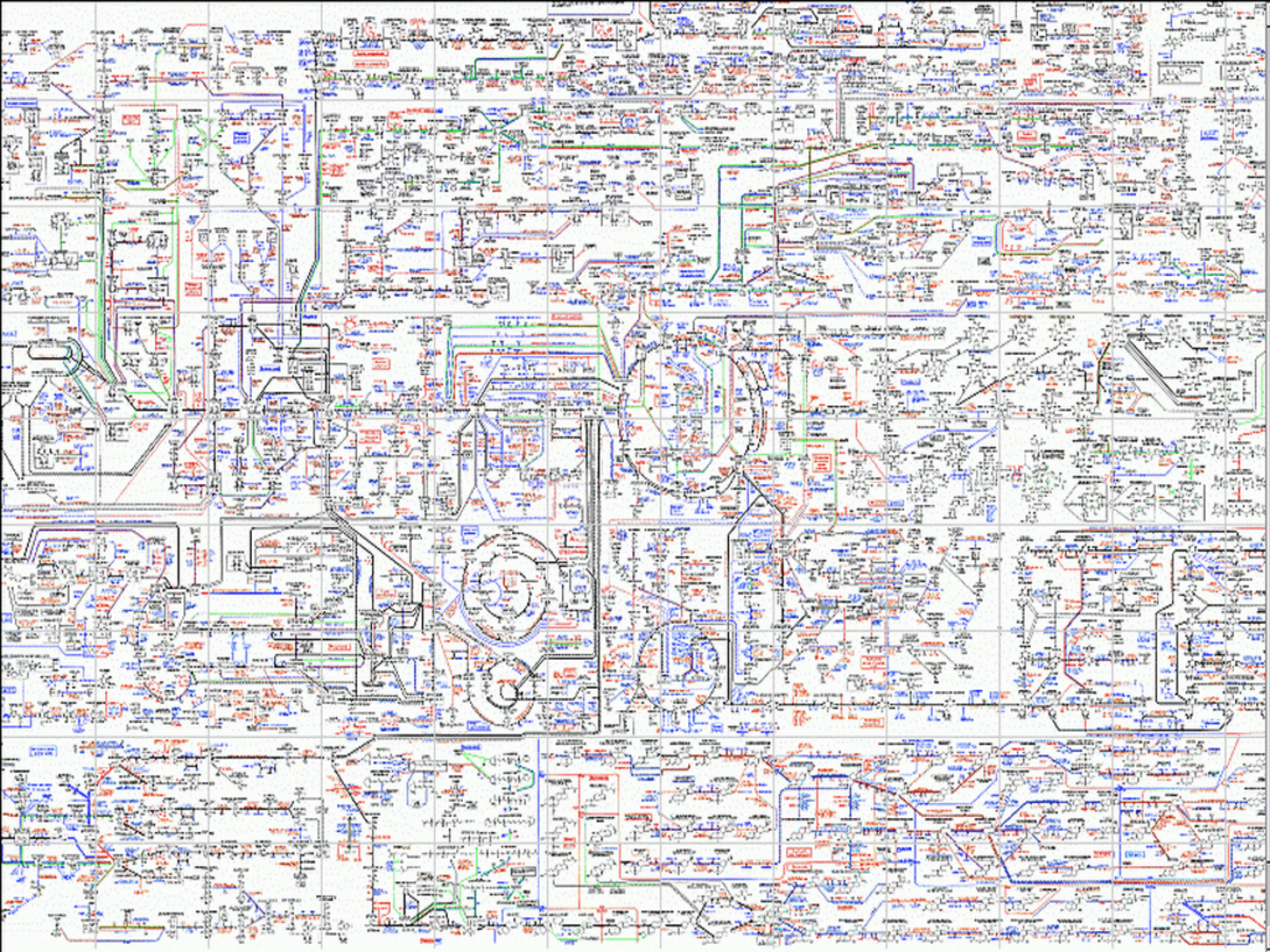
Summary

- Diet or diet-derived compounds can regulate microbiome, regulate gene at genomic/epigenomic level that may affect cellular pathways include, hormone/cytokines, xenobiotic meatbolsisms, inflammation etc.

- Multiple mechanisms may be involved.

- Individual may respond to nutrient differently and genotype may influence bioavailability, efficacies, susceptibilities.

- Timing, and physiological concentration are important variables to consider.



My view of 21st Century Nutrition Research
4P Nutrition

4 New Ps in Nutrition

1.Predictive Nutrition refers to the development of a probabilistic health projection for a person based on their DNA and protein expression.
2.Preventative Nutrition denotes the creation of Dietary practice that will prevent a disease/excess/deficiency that a person is assessed to have a high probability of developing.
3.Personalized Nutrition refers to treating an individual based on their unique human genetic variation, complementing the predictive and preventative efforts above
4.Participatory Nutrition denotes a patient's active, informed involvement in their medical choices and care, acting in partnership with their health providers.

Hood L, Friend SH. 2011. Predictive, personalized, preventive, participatory (P4) cancer medicine. Nat Rev Clin Oncol. 8:184-7.

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