“Unimportant” Molecules

Dr. Joseph Pizzorno, ND

Editor, *Integrative Medicine: A Clinician’s Journal*

Co-Author, *Clinical Environmental Medicine*

President Emeritus, Bastyr University

Treasurer, Board of Directors, IFM

Chair, Scientific Advisory Board, Bioclinic Naturals

President, SaluGenecists, Inc.

mail2@DrPizzorno.com

Outline

1. Simplification of research to make sense of complexity left out important physiological functions
2. Vitamins in natural foods have many variants (vitamers)
3. Many “unimportant” molecules physiologically active
4. Much of the disease association with SNPs due to loss of “unimportant” molecules from the food supply
5. Modern agriculture has resulted in loss of UMs
6. Increasing consumption of UMs has many health benefits

Simplification of Research Left Out a Lot of Physiology

Nature is Extremely Complex

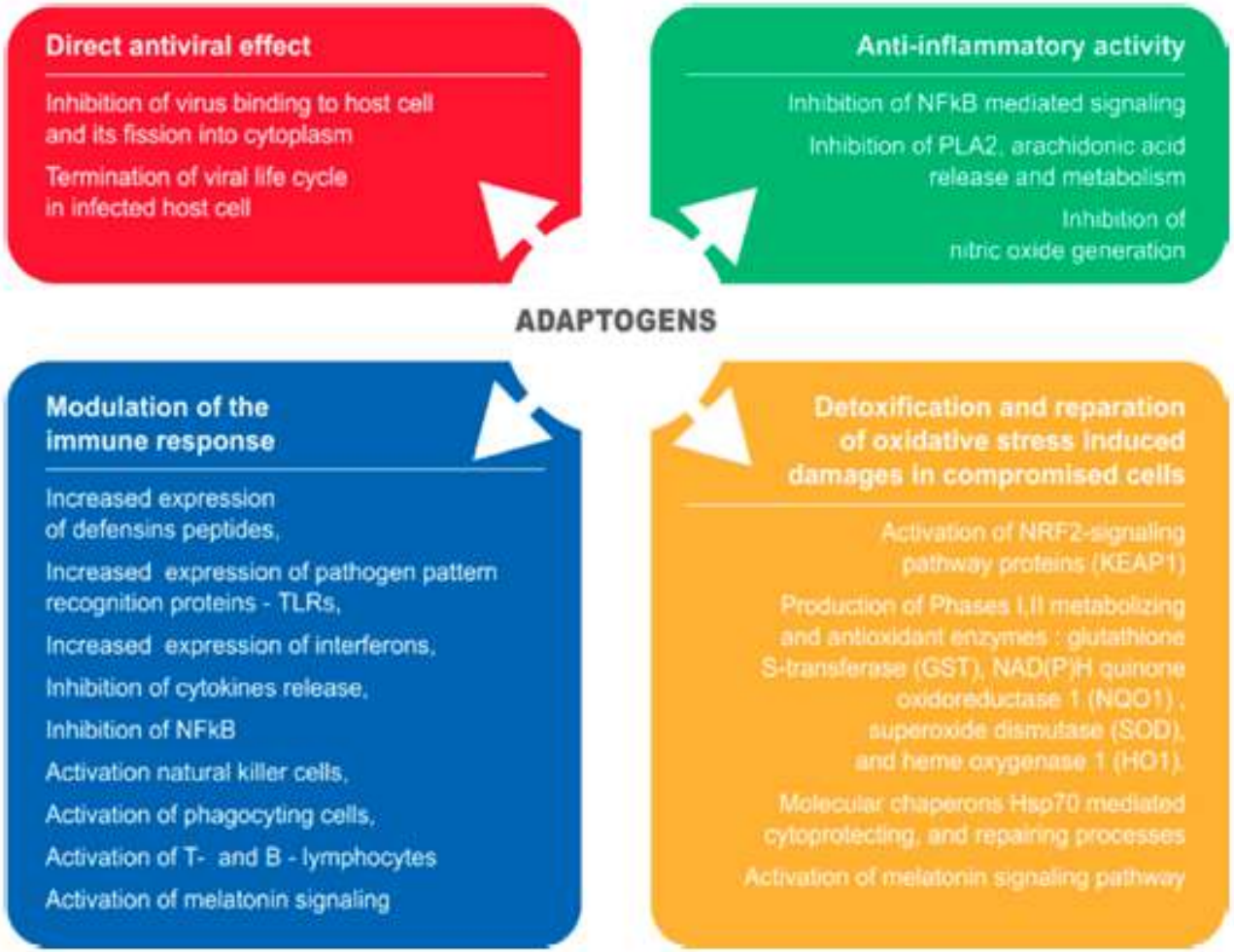
- In order to understand and manipulate nature researchers have virtually always simplified as much as possible
- In health and medicine, this was done by prioritizing major pathways and focusing on those with the greatest physiological effects
- This means a lot of physiology was either not considered important enough to study or was simply missed

Simplification Misses A Lot

- While simplification has helped understand physiology immensely and supported the single agent/single drug model of medicine, it also resulted in unexplained phenomena
- This was so obvious in herbal medicine that the concept of Adaptogens was introduced
- Many adaptogens work through mechanisms that are poorly, if at all, understood

Adaptogens

- Example is protection from viruses
- Many benefits of herbal medicine appear due to replaced lost UMs
- Could this indicate early recognition of non-nutritional effects?



Panossian A, Brendler T. The Role of Adaptogens in Prophylaxis and Treatment of Viral Respiratory Infections. Pharmaceuticals (Basel). 2020 Sep 8;13(9):236. PMID: 32911682

Orphan CYPs

- Examples of unelicited physiological functions
- CYPs without any clear connection to metabolism are called "orphans“
- Many "orphan" CYPs are over-expressed in tumor tissues
- Many CYPs hugely impacted by “unimportant” molecules

Molecules and Elements in Food

- Conventionally required (until recently)
  - Vitamins: 12
  - Minerals: 10
  - Amino acids: 9
    - Conditional: 6
  - Fatty acids: 5
  - **Total: 43**
- The technology of the time determined what was found
- Over time, others eventually became recognized as clinically important, such as fiber

How Many Molecules in Food?

- Humans consume many grams everyday of molecules in food not considered “important”
- Many of these phytochemicals are bioactive beyond our current understanding because they:
  1. Are difficult to detect in vitro
  2. Act through weak biological feedback mechanisms
  3. Considered involved in minor unimportant pathways
- **50,000** molecules identified in plants; 200,000 projected

Hounsome N, Hounsome B, Tomos D, Edwards-Jones G. Plant metabolites and nutritional quality of vegetables. J Food Sci. 2008 May;73(4):R48-65 PMID: 18460139

Foods Contain Multiple Variants of Many Nutrients

The Vitamin E Story

Vitamin E

- Discovered by Herbert Evans and Katherine Bishop in 1922 through rat studies
- Labelled the “fertility” vitamin as fetuses died when pregnant rats fed purified diet
- Fertility reestablished with wheat germ oil
- Name from Greek tokos ”childbirth or offspring” and pherein ”to bring forth” ending in ol since an alcohol
- Purified from wheat germ oil in 1936

Shute Brothers

- The 2 MDs discovered in 1940s wheat germ oil effective in treating cardiovascular disease
- Huge opposition from medical establishment
- Professionally and personally ostracized

THE_FIGHT_OVER_VITAMIN_E_1954_Special_Reprint_4-54.pdf (seleneriverpress.com)

Fetal Reabsorption Assay

- Used to measure vitamin E in food
- Later discovered that alpha tocopherol was most active variant for rat fertility, so only one considered important
- For decades all human research was on synthetic DL alpha tocopherol
- BIG MISTAKE!
  - **Huge variations according to animal species**

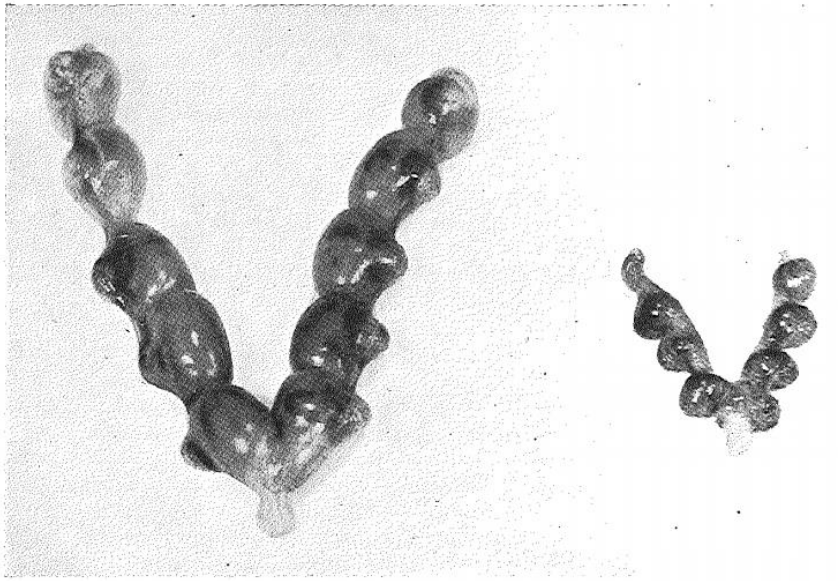
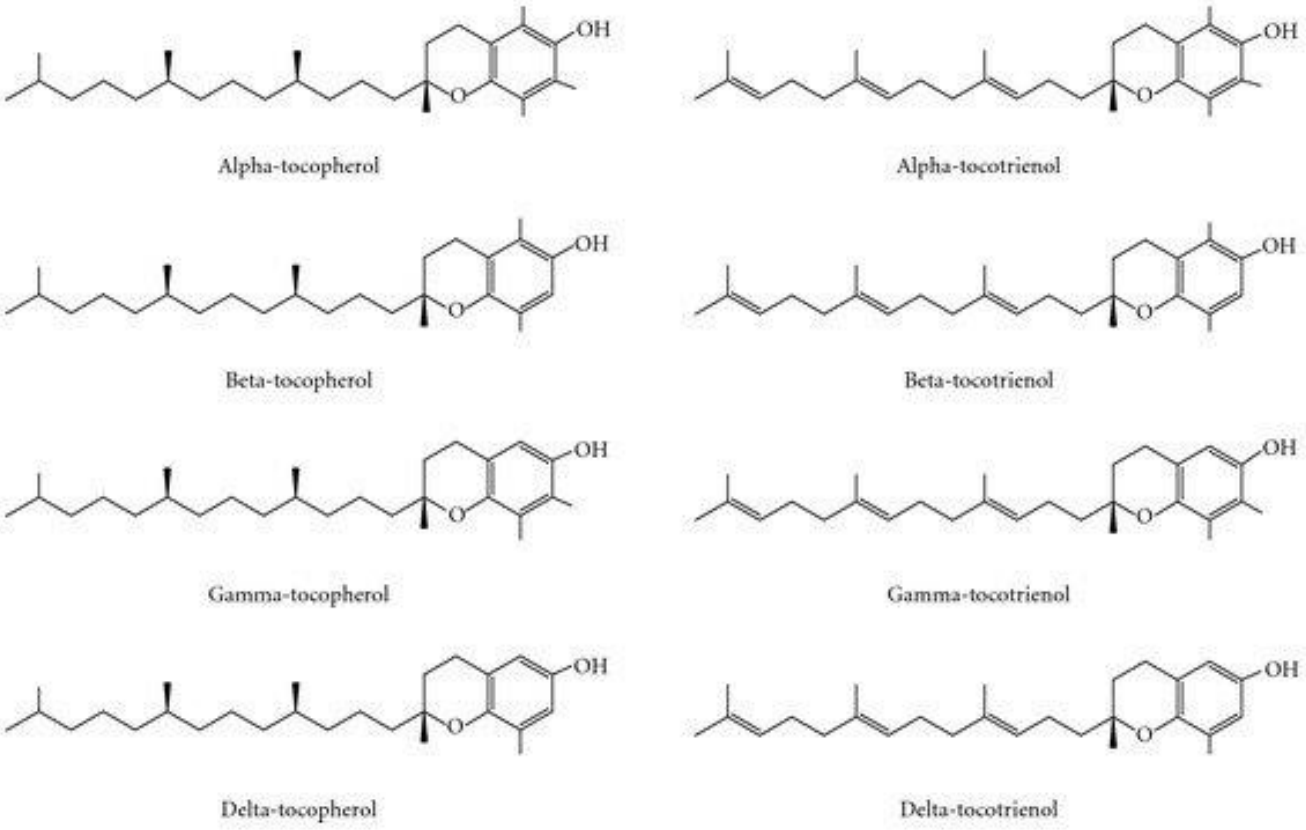


FIG. 210. The uterus on the left is from a pregnant rat on a normal diet, while that on the right is from a pregnant rat on a diet deficient in vitamin E. Note the smaller number of embryos within the latter, and their arrested development.

The Real Vitamin E



Chin KY, Ima-Nirwana S. Vitamin E as an Antiosteoporotic Agent via Receptor Activator of Nuclear Factor Kappa-B Ligand Signaling Disruption: Current Evidence and Other Potential Research Areas. Evid Based Complement Alternat Med. 2012;2012:747020. PMID: 22919420

Early Studies with Wheat Germ Oil

- Early clinical studies with wheat germ oil not in PubMed
- Benefit from wheat germ oil:
  - Infertility
  - Recurrent abortions
  - Toxemia of pregnancy
  - Muscular dystrophy
  - Dupuytren's & other contractures
  - Cardiovascular disease
  - Intermittent claudication
  - Clotting from surgery
  - Atrophic lateral sclerosis (ALS)
- Most negative results were from using synthetic vitamin E, typically DL alpha tocopherol

Franklin Bicknell, MD, and Frederick Prescott, MD. The Vitamins in Medicine. 1948

Recent Study with Wheat Germ Oil

- Not just vitamin E variants, but also policosanol and other molecules since discovered beneficial
- Study in Russia:
  - 30g/d wheat germ oil for 30 days
    - HDL cholesterol increased 3-24%
    - LDL cholesterol decreased by 4-21%
    - Triglycerides decreased by 12-24%
    - Atherogenic factor improved 10-25%.
  - Benefits continued for 30 days after discontinuation

Rodionova NS, Isaev VA, Vishnyakov AB, et al. [Investigation of the effect of oil and flour from wheat germ meal on lipid metabolism of students and teachers of the university]. Vopr Pitan. 2016;85(6):57-63. Russian. PMID: 29376309.

Problems with Alpha Tocopherol

- D active, mirror L version not only ineffective, competes with effective variant
- Other variants far more important for human health
- Displaces the other tocopherols!

Gamma Tocopherol

- Major form of vitamin E in human diet
- Anti-inflammatory
  - More effective protecting lipids from oxidation
- Supplementation with alpha lowers levels

y-Tocopherol, but Not a-Tocopherol, Improves Anti-Inflammatory; Decreases Adverse Effects of Aspirins | Longevity Medicine Review (lmreview.com)

Gamma Tocopherol

- Antiproliferative
- Serum levels inversely correlate with cardiovascular disease
  - Alpha levels not correlated
  - Alpha supplementation studies inconsistent and many negative
- Serum levels inversely correlate with many cancers
  - Men in top 20% serum level have 80% decreased risk of prostate cancer

Jiang Q, Christen S, Shigenaga MK, Ames BN. gamma-tocopherol, the major form of vitamin E in the US diet, deserves more attention. Am J Clin Nutr. 2001 Dec;74(6):714-22. PMID: 11722951

Policosanol

- Could the vitamin centric bias have caused missing possibly the most important wheat germ molecule?
- Mixture of long-chain alcohols extracted plant waxes
- Whole wheat contains 3.0-56.0 mg/kg, lost when refined
- Clinical benefits from 5-20 mg/d:
  - Lowers LDL cholesterol (19-31%)
  - Increases HDL cholesterol (6-29%)
  - Reduces platelet aggregation
  - Reduces cholesterol oxidation
  - Lowers total cholesterol similar statins

Serna-Saldivar SO, Janet A. Gutiérrez-Uribe JA, García-Lara S. Phytochemical Profiles and Nutraceutical Properties of Corn and Wheat Tortillas. In Tortillas, Wheat Flour and Corn Products. AACC, 2015

Varady KA, Wang Y, Jones PJ. Role of policosanols in the prevention and treatment of cardiovascular disease. Nutr Rev. 2003 Nov;61(11):376-83. PMID: 14677572.

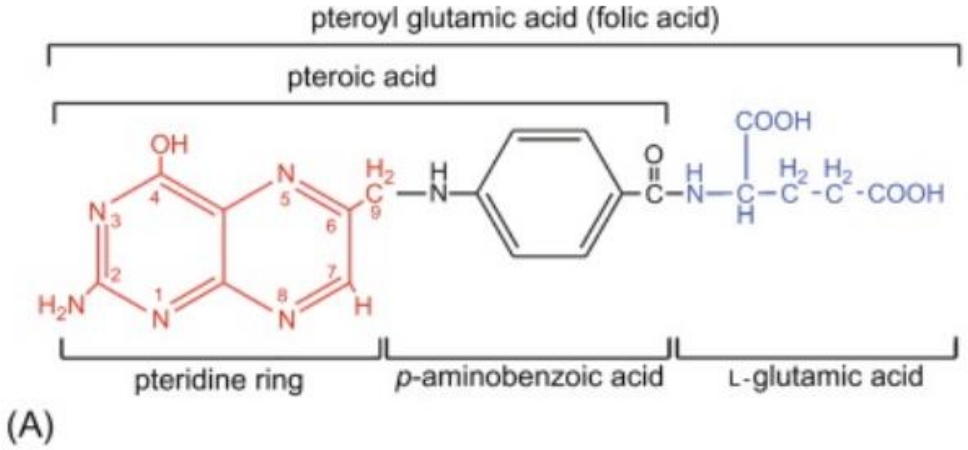
Vitamers

Folates

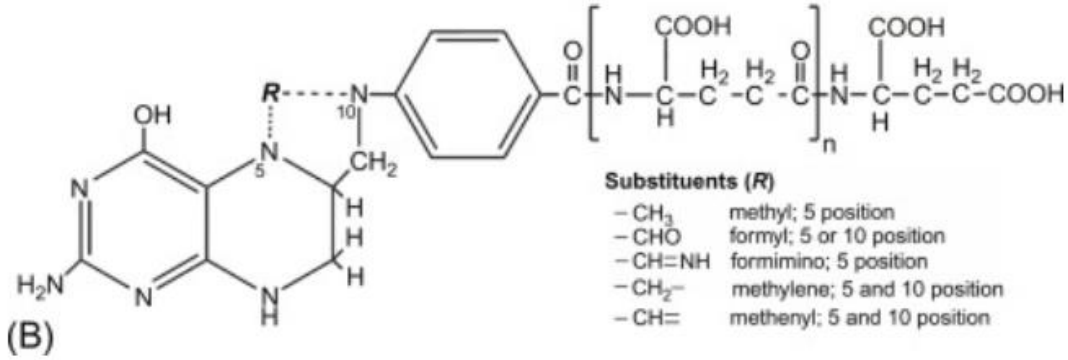
- Foods contain folates, not folic acid
- Response to NATURAL folate deficiency hugely impacted by MTHFR polymorphisms

Types of Folates

Folic acid

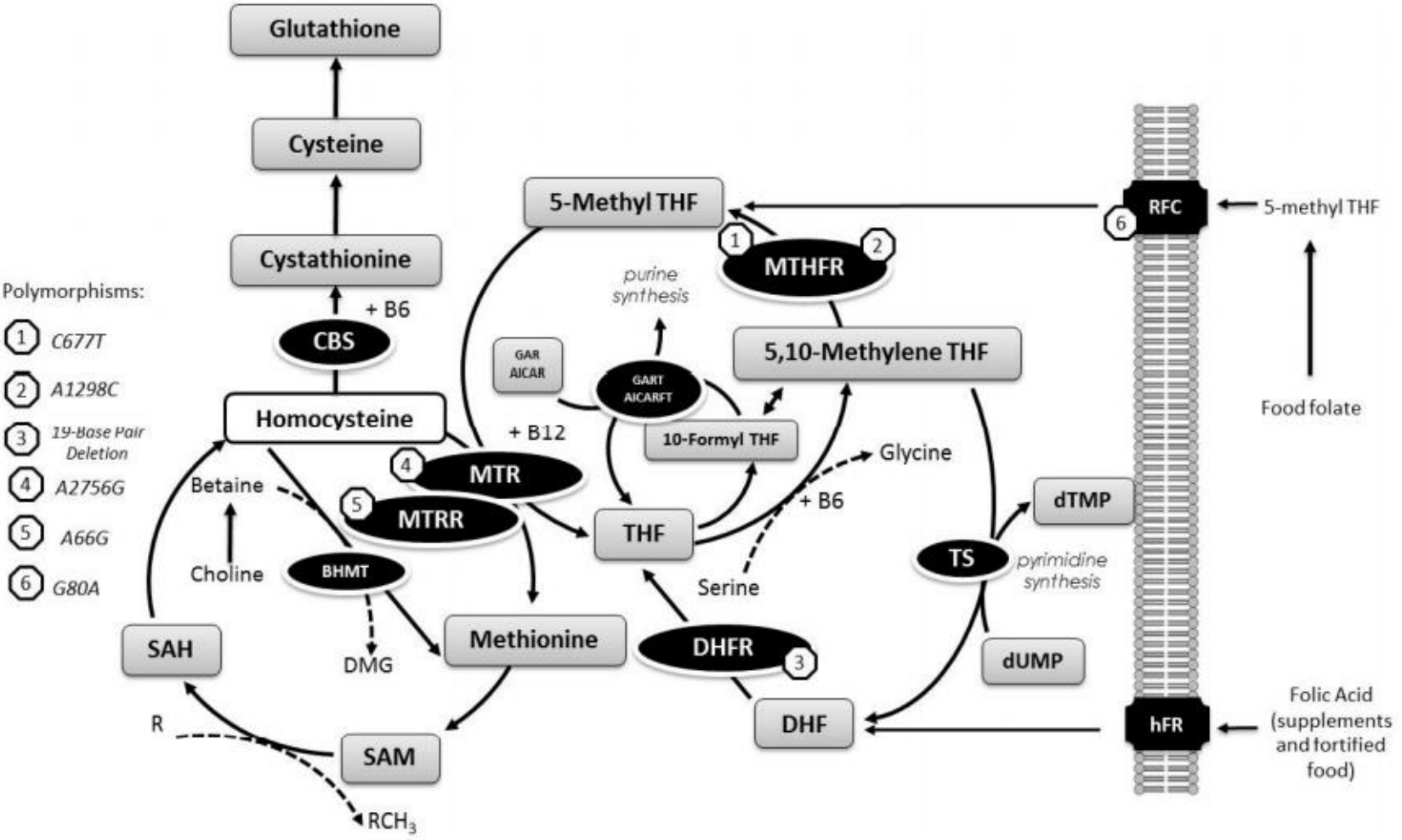


Natural folates



Savoy de GioriJean G, LeBlanc G. Folate Production by Lactic Acid Bacteria. In Polyphenols in the prevention and treatment of vascular and cardiac disease and cancer. 2018, Academic Press

Folic Acid NOT Same as Food Folate



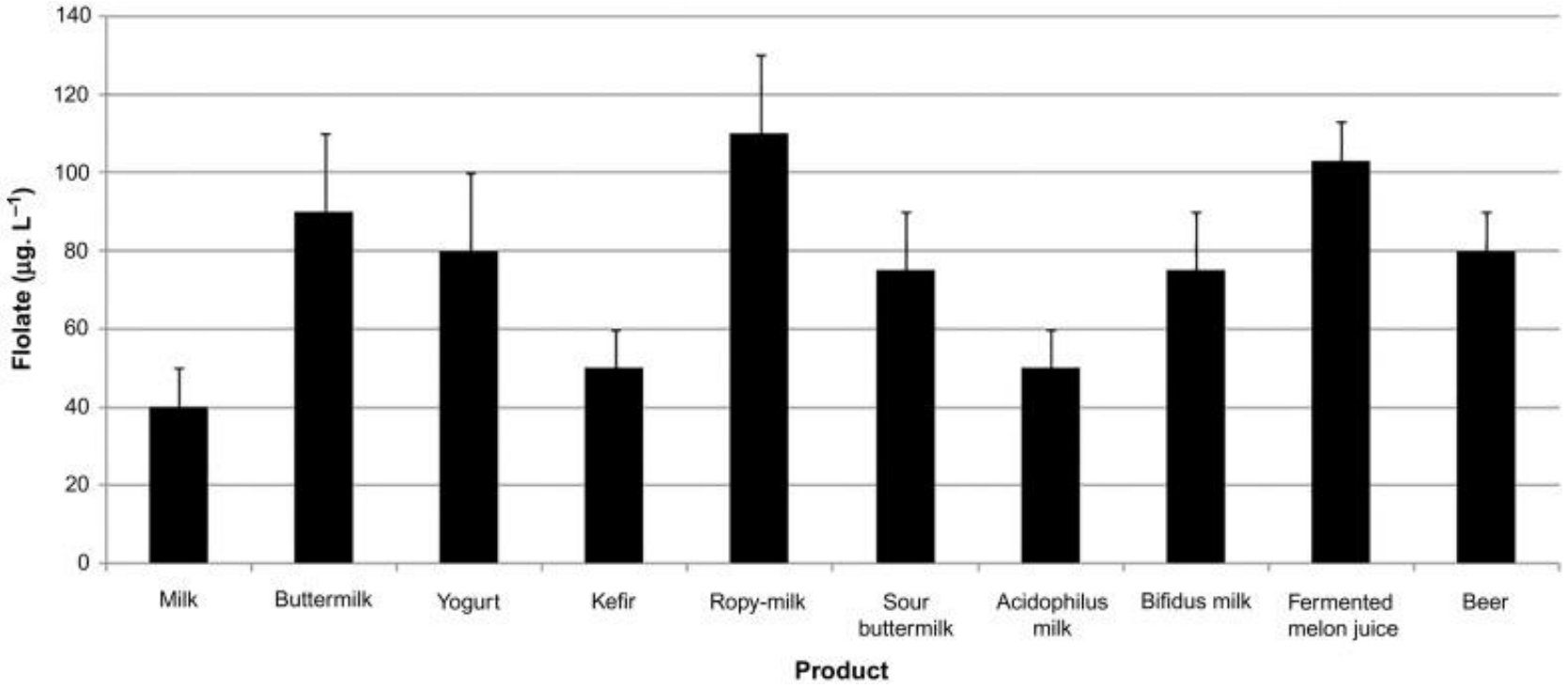
Steluti J, Carvalho AM, Carioca AAF, et al. Genetic Variants Involved in One-Carbon Metabolism: Polymorphism Frequencies and Differences in Homocysteine Concentrations in the Folic Acid Fortification Era. Nutrients. 2017 May 25;9(6):539. PMID: 28587068

Sources of Active Folates

- Primarily in:
  - Green leafy vegetables
  - Liver
  - Berries
  - Many kinds of beans
- Fermentation increases active folates
- Easily denatured by heat, light, oxygen and time
- Methyl folates protected from degradation by vitamin C

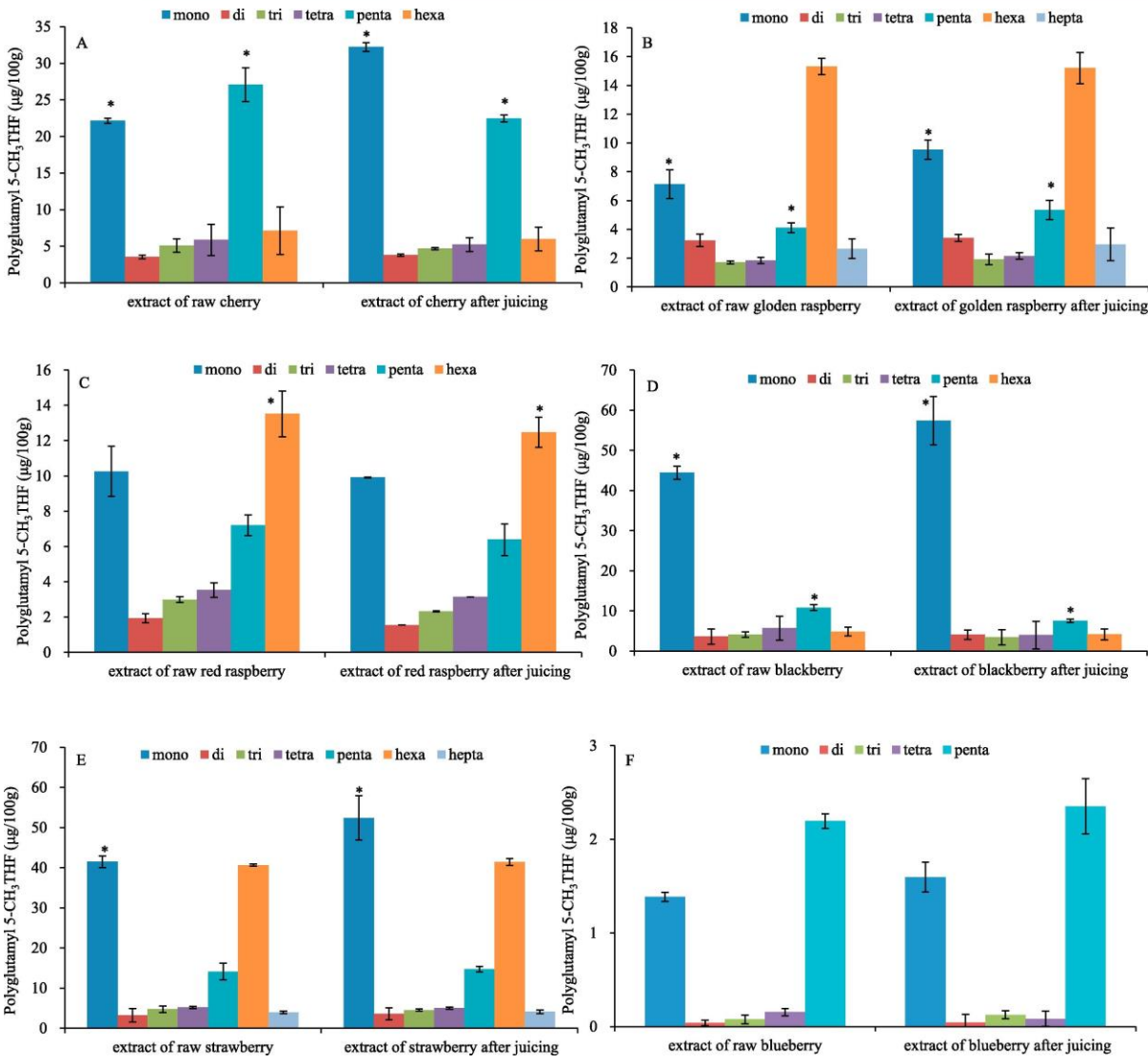
Indrawati, Arroqui C, Messagie I, et al. Comparative study on pressure and temperature stability of 5-methyltetrahydrofolic acid in model systems and in food products. J Agric Food Chem. 2004 Feb 11;52(3):485-92. PMID: 14759137.

Fermentation Increases Active Folates



Savoy de GioriJean G, LeBlanc G. Folate Production by Lactic Acid Bacteria. In Polyphenols in the prevention and treatment of vascular and cardiac disease and cancer. 2018, Academic Press

BERRIES ARE FULL OF NATURAL FOLATES



Zou Y, Duan H, Li L, Chen X, Wang C. Quantification of polyglutamyl 5-methyltetrahydrofolate, monoglutamyl folate vitamers, and total folates in different berries and berry juice by UHPLC-MS/MS. Food Chem. 2019 Mar 15;276:1-8. PMID: 30409571

Dietary Intake of Folates

- Highly variable according to diet
- Even relatively healthier diet found in Netherlands, men consume inadequate natural folates (ug/D)

	Subcohort (*n* = 1,963)
Total folate	225.1 ± 66.2
Monoglutamates	70.6 ± 41.5
Polyglutamates	130.2 ± 38.4
Tetrahydrofolate	18.5 ± 28.9
5-Methyl-tetrahydrofolate	128.7 ± 41.9
5-Formyl-tetrahydrofolate	26.3 ± 9.7
Folic acid	7.2 ± 6.1
10-Formyl-dihydrofolate	10.1 ± 5.1
10-Formyl-folate	20.9 ± 8.6

Keszei AP, Verhage BA, Heinen MM, et al. Dietary folate and folate vitamers and the risk of pancreatic cancer in the Netherlands cohort study. Cancer Epidemiol Biomarkers Prev. 2009 Jun;18(6):1785-91. PMID: 19505911

Folic Acid Controversy

- FA supplementation decreases neural tube defects
- But, may increase cancer death risk
- Food folates do not increase cancer risk

Study or subgroup	Folic acid supplement Events	Total	Control Events	Total	Weight	RR M-H, Random, 95% CI
Charles[29 30]	24	485	69	1977	10.8%	1.42 (0.90 to 2.23)
Zhang (WAFACS)[26]	47	2721	57	2721	13.9%	0.82 (0.56 to 1.21)
Lonn (HOPE-2)[27]	94	2758	95	2764	20.6%	0.99 (0.75 to 1.31)
Ebbing (WENBIT + NORVIT)[12]	136	3411	100	3426	22.9%	1.37 (1.06 to 1.76)
SEARCH[28]	260	6033	252	6031	31.9%	1.03 (0.87 to 1.22)
Total (95% CI)		**15 408**		**16 919**	**100.0%**	**1.09 (0.92 to 1.30)**
Total events	561		573			

Heterogeneity: $\tau^2 = 0.02$; $\chi^2 = 7.22$, df = 4 (p=0.12); $I^2 = 45\%$

Test for overall effect: Z=1.04 (p=0.30)

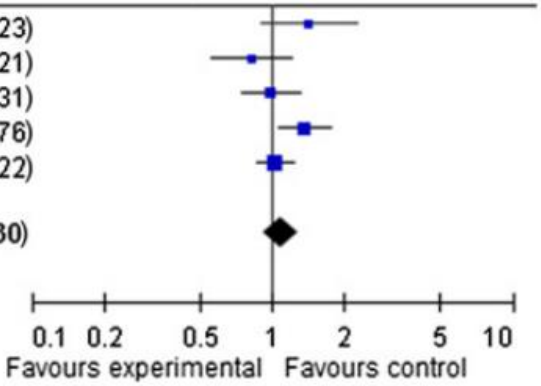


Figure 4 Forest plot of randomised controlled trials that compare folic acid supplements ≥0.4 g/day with placebo/control treatment with respect to total cancer mortality.

Wien TN, Pike E, Wisløff T, et al. Cancer risk with folic acid supplements: a systematic review and meta-analysis. BMJ Open. 2012 Jan 12;2(1):e000653. PMID: 22240654

Folate and Cancer

- Inverse correlation between dietary folate and blood levels of folate and colon cancer
- In tissue culture, natural folates more effective in stopping tumor growth than synthetic folic acid
  - Folic acid only helped if cells first damage by homocysteine

Konings EJ, Goldbohm RA, Brants HA, et al. Intake of dietary folate vitamers and risk of colorectal carcinoma: results from The Netherlands Cohort Study. Cancer. 2002 Oct 1;95(7):1421-33. PMID: 12237910
Akoglu B, Milovic V, Caspary WF, Faust D. Hyperproliferation of homocysteine-treated colon cancer cells is reversed by folate and 5-methyltetrahydrofolate. Eur J Nutr. 2004 Apr;43(2):93-9. PMID: 15083316.

Folate Vitamers and Breast Cancer

- Risk of death from breast cancer
- Dietary folate more protective than synthetic folic acid

Variable	Q1	Q2	Q3	Q4
Plasma total folate, nmol/L		14.04	25.21	40.56
HR (95% CI)	1.0, ref	1.11 (0.60 - 2.07)	0.72 (0.37 - 1.39)	0.41 (0.19 - 0.90)
p-value		0.74	0.33	0.03
5-MethylTHF, nmol/L		11.50	20.40	34.90
HR (95% CI)	1.0, ref	1.09 (0.59 - 2.01)	0.81 (0.41 - 1.56)	0.62 (0.30 - 1.28)
p-value		0.78	0.52	0.20
Folic acid, nmol/L		0.33	0.64	1.27
HR (95% CI)	1.0, ref	0.56 (0.29 - 1.08)	0.78 (0.43 - 1.48)	0.75 (0.39 - 1.43)
p-value		0.08	0.45	0.38
THF, nmol/L		0.84	1.69	2.85
HR (95% CI)	1.0, ref	1.06 (0.58 - 1.94)	1.13 (0.62 - 2.05)	0.51 (0.25 - 1.04)
p-value		0.86	0.69	0.06

McEligot AJ, Ziogas A, Pfeiffer CM, et al. The association between circulating total folate and folate vitamers with overall survival after postmenopausal breast cancer diagnosis. Nutr Cancer. 2015;67(3):442-8. PMID: 25647689

Folic Acid is NOT Natural Folate

- "Folic acid, obtained by chemical synthesis, differs from natural folate in many aspects: (i) oxidation level (not reduced); (ii) no substitutions are present in the pterin and *p*ABA domain; and (iii) it **can cause adverse side effects that currently put in doubt its use in fortification programs**."

Savoy de GioriJean G, LeBlanc G. Folate Production by Lactic Acid Bacteria. In Polyphenols in the prevention and treatment of vascular and cardiac disease and cancer. 2018, Academic Press

MTHFR Polymorphisms

- Increase homocysteine which increases risk for:
  - Cardiovascular disease: aortic aneurysm, atherosclerosis, kidney failure, myocardial infarction, stroke
  - Neurological disease: dementia, epilepsy, multiple sclerosis, neural tube defects, Parkinson's disease
  - Other: diabetes, eclampsia, cancer, hypothyroidism, osteoporosis, rheumatoid arthritis

BUT ONLY IF DIET IS LOW IN NATURAL FOLATES!

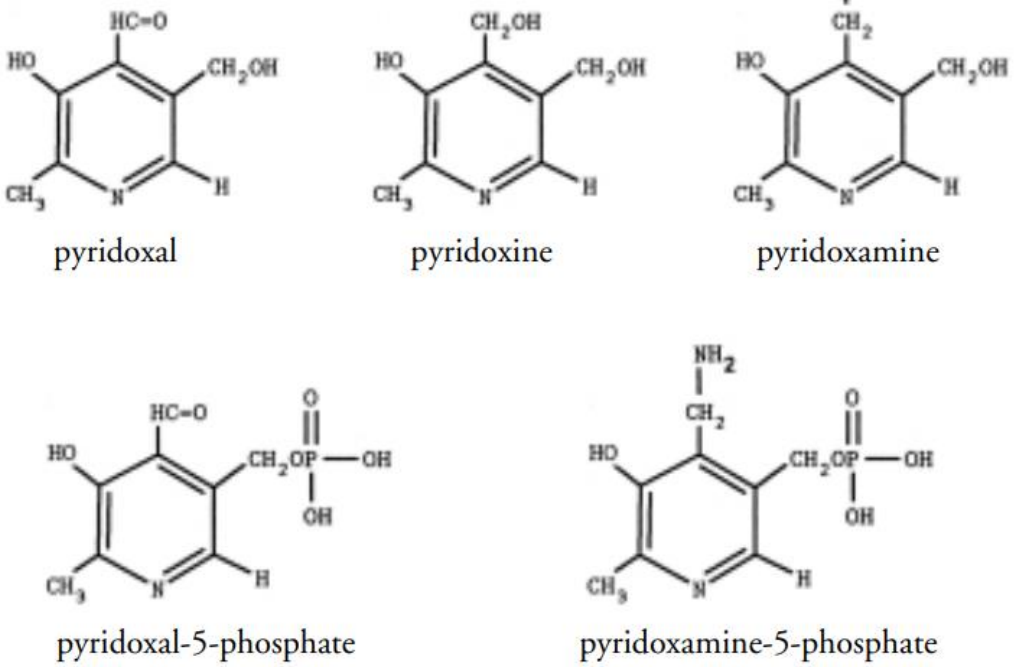
Folates in Wheat

- 70% lost when ground into flour
- Additional 30% lost after 8 months of storage
- Boiling, baking, steaming loses another 11-16%
- Fermenting doughs increases folate levels 50-400%
- Wheat flour bread folate levels
  - Unfortified: 45 ug/cup
  - Fortified: 395 ug/cup (but folic acid, not active folates)

Liang Q, Wang K, Shariful I, et al. Folate content and retention in wheat grains and wheat-based foods: Effects of storage, processing, and cooking methods. Food Chem. 2020 Dec 15;333:127459. PMID: 32683256

VITAMIN B6 VITAMERS

Figure 7.11 Structures of the most common compounds with vitamin B_6 activity



Greenfield H, Southgate DAT. Food composition data production, management and use. Food and Agriculture Organization of the United Nations Rome 2003

Plant Molecules

Subtle and Often Unexpected Impact of “Unimportant” Constituents

- **Concept**: when plants are hybridized to increase one class of molecules, then there is decreased production of the others

- **Concept**: When foods are refined, the levels of many “unimportant” constituents decline

Food Supply has Changed Dramatically

- Changing food choices to higher calorie, lower diversity, lower “unimportant” molecule content
- Hybridization, GMO
- Growth forced with chemicals
- Plants are now so weak they need toxic chemicals to protect from insects, viruses, mold, etc.
- Farming costs decreased by spraying fields with herbicides to control weeds and pesticides to protect against organisms the foods have lost the ability to resist

Plant Molecules

- Anti-bacterial, anti-fungal, anti-viral
- Anti-insect
- Anti-herbivore
- Anti-oxidant
- Etc.

⇒ Organically-grown, heirloom plants are more resilient and need less help against pests

Humans eating these plant molecules are more resilient to disease and less susceptible to pests (infections!)

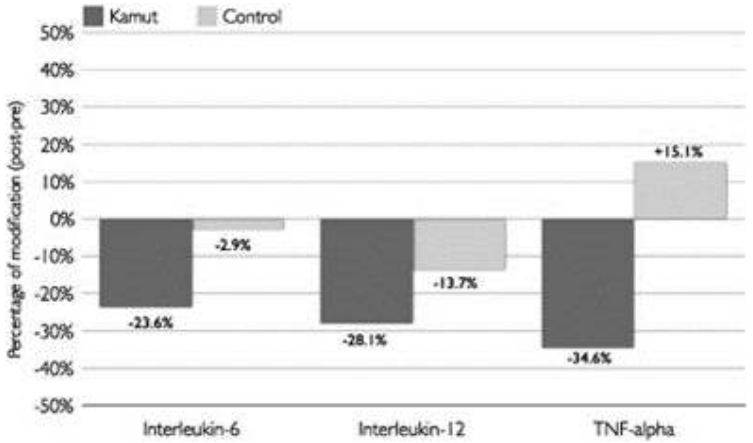
Zaynab M, Fatima M, Abbas S, et al. Role of secondary metabolites in plant defense against pathogens. Microb Pathog. 2018 Nov;124:198-202 PMID: 30145251

Ancient Kamut Versus Current Wheat

- Crossover study
- Higher minerals:
  - Zinc: ↑64.7%
- Much lower inflammation:
  - TNF-alpha ↓49.7%
- Also lower cholesterol, LDL, blood sugar, etc.

Mineral element composition of Kamut and control wheat

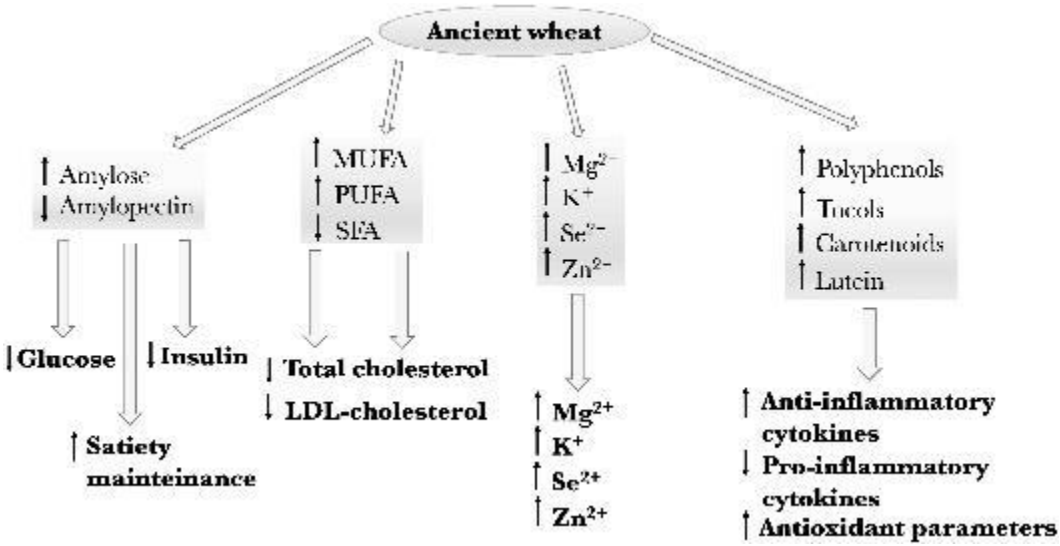
Variable (mg/kg)	*Kamut (Semolina)*	*Control (Semolina)*	P-value	*Kamut (Flour)*	*Control (Flour)*	P-value
Potassium	2817±6.52	2393±0.808	0.006	2663±0.811	1553±6.47	0.001
Magnesium	909.57±58.7	795.58±50.1	0.003	889.03±27.6	542.06±28.9	0.001
Phosphorus	2.98±0.26	2.67±0.62	0.001	2.85±0.62	1.77±0.84	0.02
Zinc	25.19±0.05	25.99±0.09	0.02	24.95±0.02	15.15±0.05	0.001
Iron	29.63±0.24	28.02±0.04	0.06	24.13±0.04	20.42±0.14	0.01
Selenium	0.99±0.04	0.92±0.03	0.2	0.90±0.008	0.74±0.006	0.02
Vanadium, mg/kg	1.01±0.02	0.73±0.008	0.005	0.98±0.008	0.63±0.004	0.0001



Sofi F, Whittaker A, Cesari F, et al. Characterization of Khorasan wheat (Kamut) and impact of a replacement diet on cardiovascular risk factors: cross-over dietary intervention study. Eur J Clin Nutr. 2013 Feb;67(2):190-5 PMID: 23299714

Ancient Wheat Healthier than Modern Wheat

- Emmer, einkorn, spelt, khorasan and various regional Italian varieties
- Higher in multiple nutrients: phytosterols, alkylresorcinols, minerals, etc.
- Real clinical impact (many human studies)



⇒ **Heirloom seeds**

Dinu M, Whittaker A, Pagliai G, et al. Ancient wheat species and human health: Biochemical and clinical implications. J Nutr Biochem. 2018 Feb;52:1-9 PMID: 29065353

EXAMPLE PLANT METABOLITES IMPORTANT TO HUMAN HEALTH

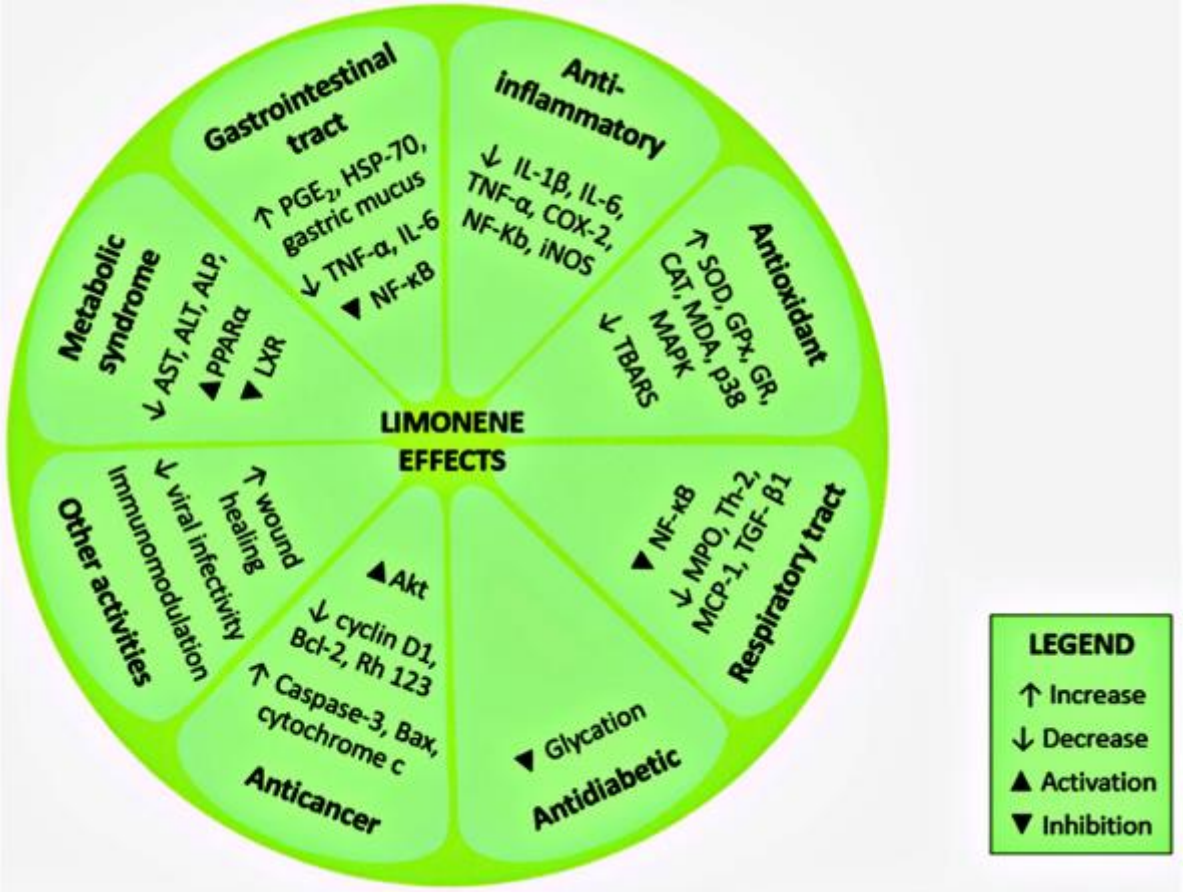
List of plant secondary metabolites against Insects. Listed secondary metabolites are shown their linked to a specific category and their target insect in specific plan.

Secondary Metabolites	Plants	Categories	Resistance against	Reference
Terpenoids	Citrus	Terpenoid Limonene	*Atta cephalotes*	[57]
	Pine and fir	Monoterpenes	*bark beetle*	[58]
Steroids	Common fern	Phytoecdysones	*Insect*	[59]
Terpenoids	Tobbaco	Trans-anethole and thymol, citronellal,	*Spodoptera litura*	[60]
Phenolics	Wheat	Phenolics	*Rhopalosiphum padi*	[61]
Phenolics	Willow plant	Phenolics	*Galerucella lineola*	[62]
Benzoic acid	Salix	Benzoic acid	*Operophtera brumata*	[63]
Phenolics	Strawberry	Phenolics	*Tetranychus urticae*	[64]
Phenolics	Cotton	Gossypol	*Heliothis virescens, Heliothis zea*	[65]
Alkaloids	Nightshade potato	Alkaloid demissine	*Leptinotarsa decemlineata*	[66]
Benzoxazinoides	Gramineae	DIMBOA	*Ostrinia nubilalis*	[67]
Cyanogenic Glucosides	Cassava	CNglcs	*Cyrtomenus bergi*	[68]
Cyanogenic Glucosides	Bitter almond plants	Amygdalin and prunasin	*Capnodis tenebronis*	[69]
Cyanogenic Glucosides	Trifolium repens	Amygdalin and prunasin	*Hypera postica*	[70]
Cyanogenic Glucosides	Lotus	Cyanogenic glucosides	*Zygaena filipendulae*	[71]
Cyanogenic Glucosides	P.lunatus	CNglcs	*Spodoptera eridania*	[73]

Zaynab M, Fatima M, Abbas S, et al. Role of secondary metabolites in plant defense against pathogens. Microb Pathog. 2018 Nov;124:198-202 PMID: 30145251

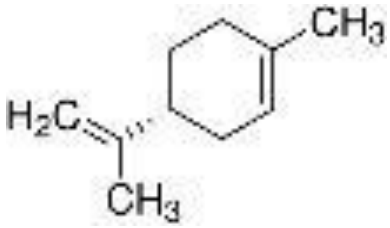
Terpenoids

- Carvacrol, linalool, and limonene
- Limonene most common terpenoid
- MANY beneficial physiological effects
- Terpenes active constituents in many herbal medicines

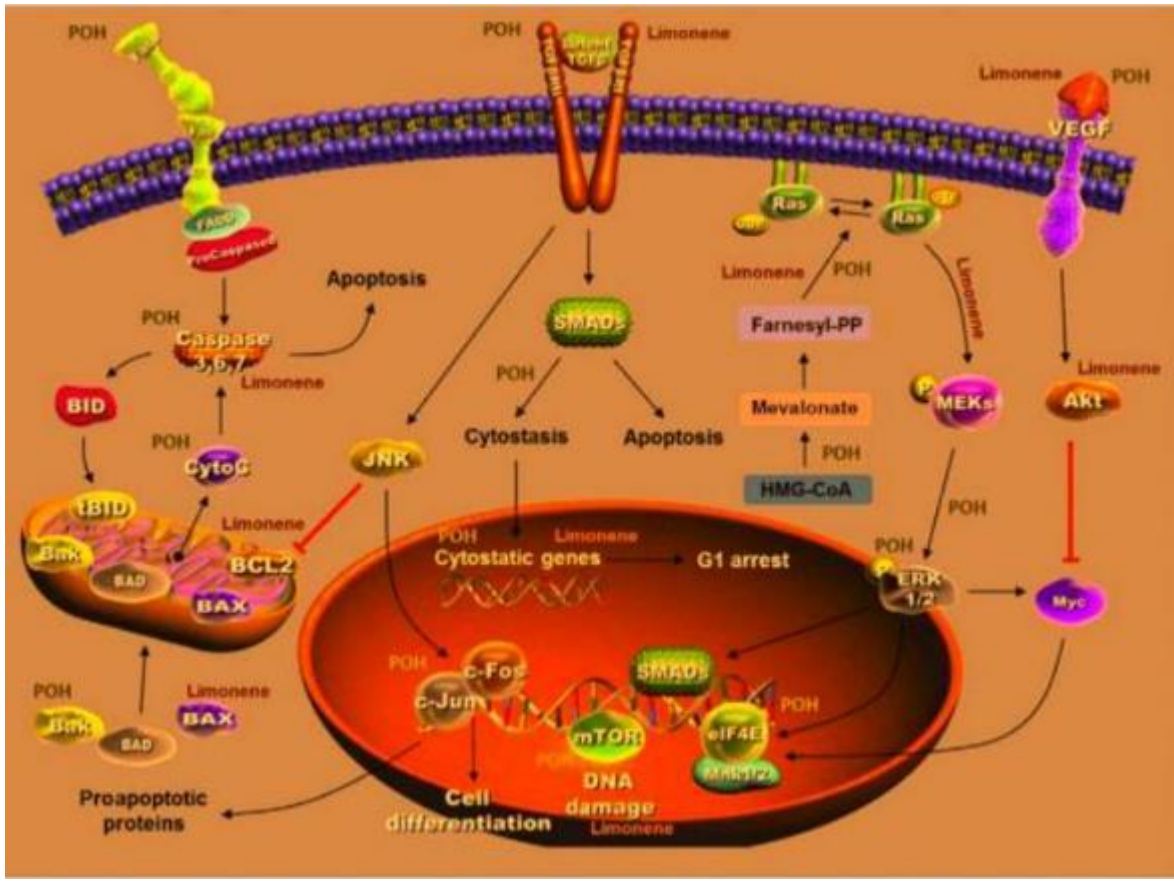


Vieira AJ, Beserra FP, Souza MC, et al. Limonene: Aroma of innovation in health and disease. Chem Biol Interact. 2018 Mar 1;283:97-106 PMID: 29427589

Limonene



- Anticancer—but being lost from the food supply
- Multiple patents on limonene-derived chemotherapy agents

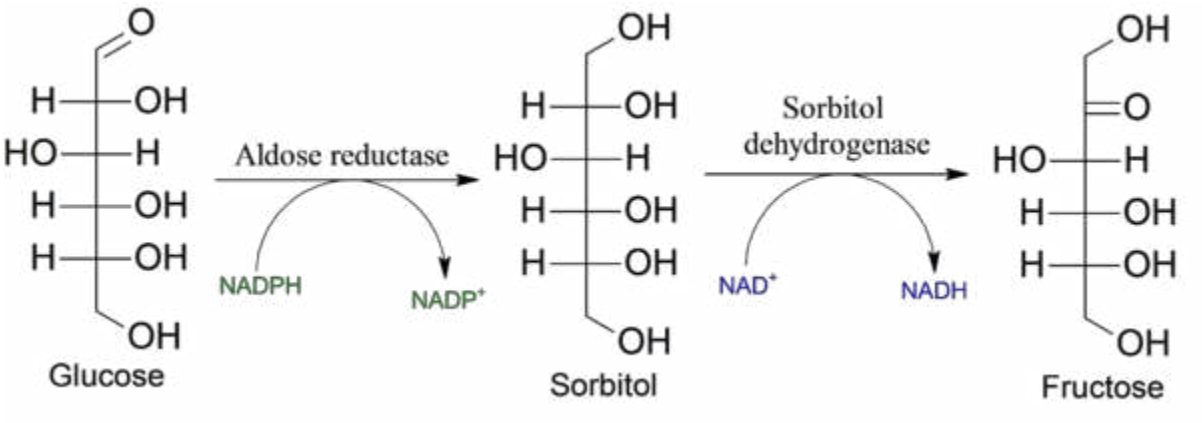


Mukhtar YM, Adu-Frimpong M, Xu X, Yu J. Biochemical significance of limonene and its metabolites: future prospects for designing and developing highly potent anticancer drugs. Biosci Rep. 2018 Nov 13;38(6) PMID: 30287506

Peak Sugar Levels Much More Damaging than Average Blood Sugar

- Polyol and glycation activation greatly increased at higher glucose levels which results in the sequelae of diabetes
- MANY “Unimportant” plant constituents:
  - Decrease peak sugar
  - Inhibit polyol pathway
  - Inhibit glycation of proteins, enzymes, etc.

Polyol Pathway Play Major Role in Complications of Diabetes



- Also called the sorbitol-aldose reductase pathway
- Sorbitol cannot cross cell membranes
- Accumulates producing osmotic stress and increases production of oxidants especially damaging to mitochondria

Polyol pathway – Wikipedia (accessed 2021-02-20)

Hemoglobin A1c

- HbA1c is the standard, but:
- Not just average—the peaks are what cause the damage!
- HbA1c misses daily fluctuations such as postprandial hyperglycemia, which can only be detected with continuous glucose monitoring
- Patient 1 suffers far more diabetes sequelae

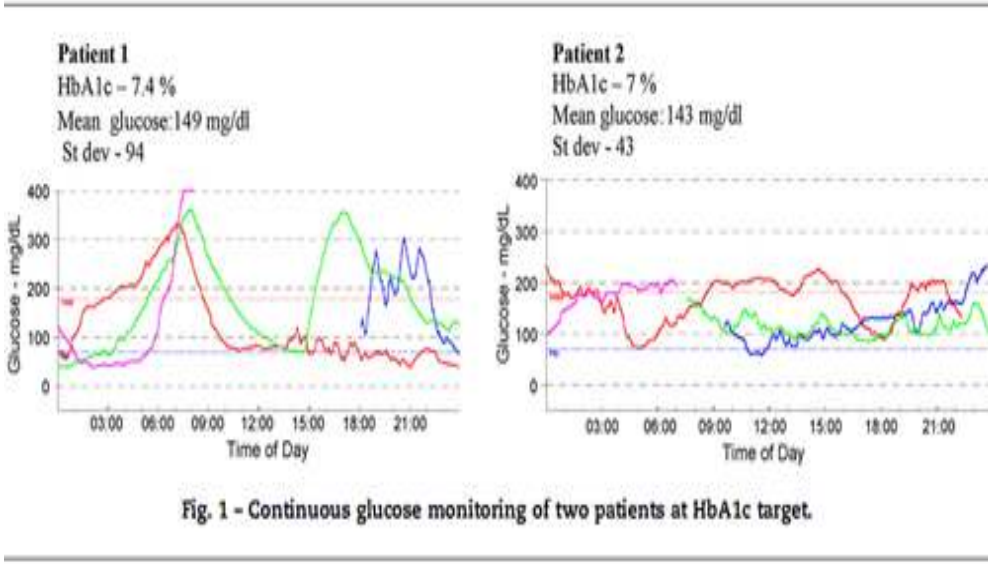


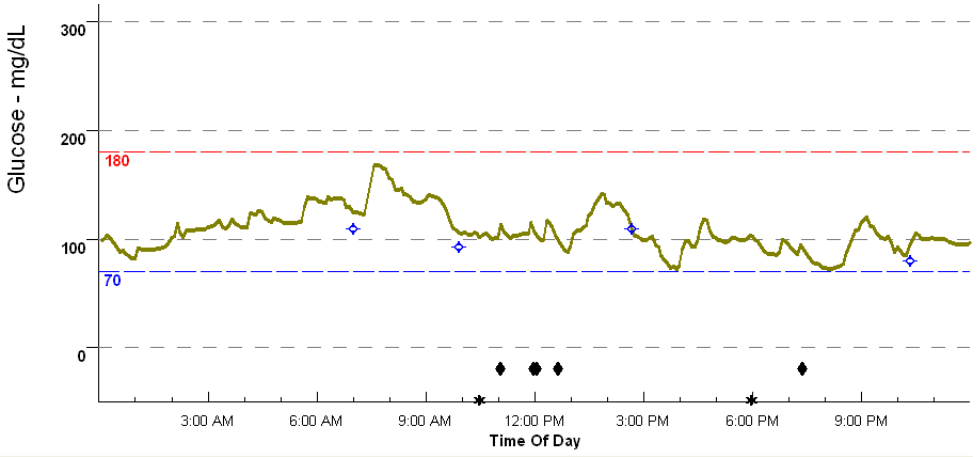
Fig. 1 – Continuous glucose monitoring of two patients at HbA1c target.

PMID: 19027978

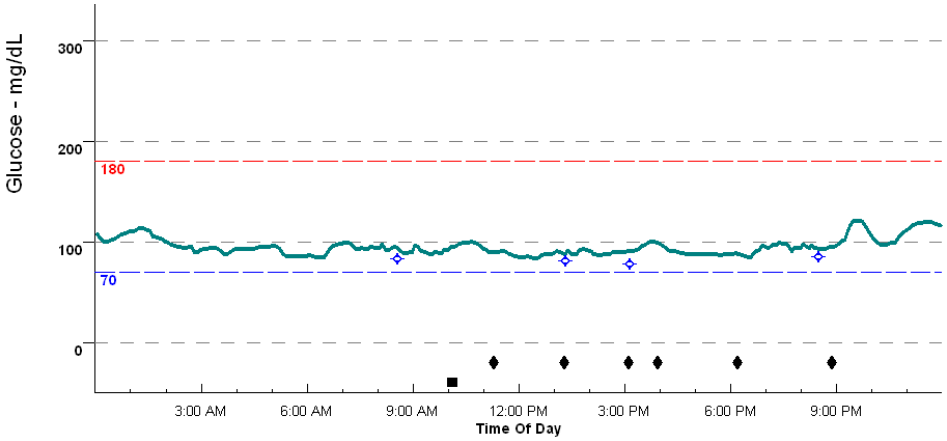
Executive summary: standards of medical care in diabetes--2011. Diabetes Care. 2011 Jan;34 Suppl 1:S4-10

Hoeks LB, et al. Real-time continuous glucose monitoring system for treatment of diabetes: a systematic review. Diabet Med. 2011 Apr;28(4):386-94.

24-Hour Blood Sugar Monitor of Obese Diabetic



Standard diet

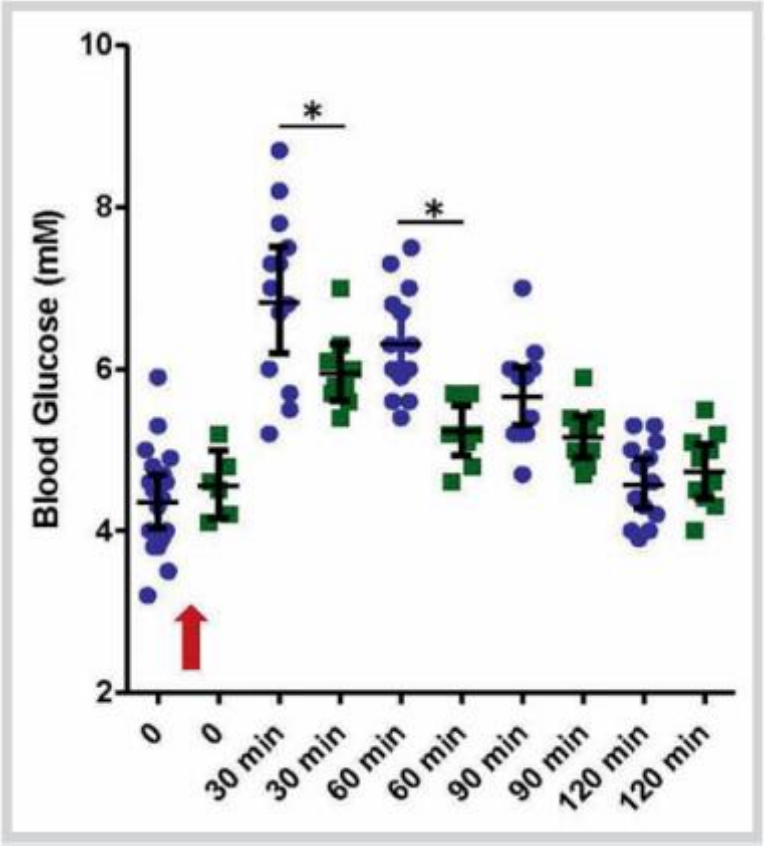


Standard diet + PGX

Personal communications Michael Lyon, MD

Chlorophyll

- Whole foods, plant-based diets have many constituents with unexpected health benefits
- Remember: glucose spikes cause the most damage
- Another benefit for **green** leafy vegetables!



Blue dots: 75g glucose only
Green dots: Plus 1g chlorophyll

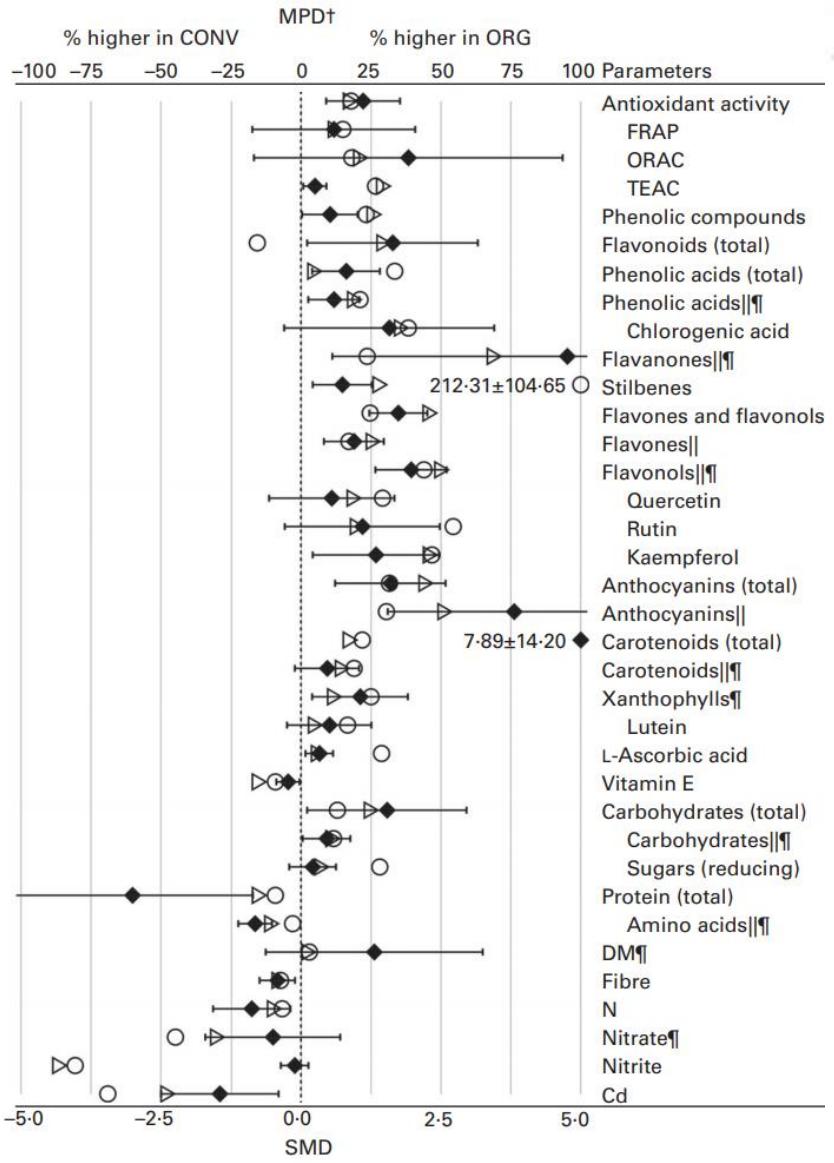
Gertsch J. The Metabolic Plant Feedback Hypothesis: How Plant Secondary Metabolites Nonspecifically Impact Human Health. Planta Med. 2016 Jul;82(11-12):920-9 PMID: 27286339

Modern Agriculture Has Dangerously Distorted the Food Supply

Organically-Grown Foods Much More healthful than Chemically-Grown Foods

Huge Molecular Differences Between Chemically- and Organically Grown Foods

- Metanalysis of 343 studies
- Graph show which has highest % of molecule types
- Organically-grown higher in virtually all the important molecules



Barański M, Srednicka-Tober D, Volakakis N, et al. Higher antioxidant and lower cadmium concentrations and lower incidence of pesticide residues in organically grown crops: a systematic literature review and meta-analyses. Br J Nutr. 2014;112:794-811. PMID: 24968103

JUST THE TIP OF THE ICEBERG

Parameters	Food produce	Organic versus conventional	References
Vitamins: e.g., vitamin C, vitamin E, and carotenoids	Fruit, vegetables	Higher (most studies)	7, 11, 17, 49, 115
Minerals: calcium, potassium, phosphorous, magnesium, iron	Fruit, vegetables, cereals	Higher	11, 14, 28, 49, 93, 99, 118
Nitrate	Fruit, vegetables, cereals	Lower	7, 17, 61, 69, 115, 118
Antioxidant activity	Fruit, vegetables, cereals	Higher	7, 11, 17, 49, 61, 93
Phenolic compounds (total)	Fruit, vegetables, cereals	Higher	7, 18, 99
Protein, amino acids, nitrogen	Fruit, vegetables, cereals	Lower	7, 28
Beneficial fatty acids, i.e., eicosapentaenoic acid, docosapentaenoic acid, docosahexaenoic acid, α-linolenic acid, and conjugated linoleic acid	Milk, meat	Higher	61, 87, 102, 103
Iodine and selenium	Milk	Lower	102, 103
Cadmium	Fruit, vegetables, cereals	Lower in cereals	7
Pesticide residues	Fruits, vegetables, and grains	Lower risk for contamination	6, 14, 61, 69, 99
Fusarium toxins	Cereals	Similar or lower in organic	99
Microorganisms, antibiotic-resistant bacteria	Chicken and pork		99

Brantsæter AL, Ydersbond TA, Hoppin JA, et al. Organic Food in the Diet: Exposure and Health Implications. Annu Rev Public Health. 2017 Mar 20;38:295-313 PMID: 27992727

Many Clinical Benefits

End point	Study population and design	Exposure	Result	References
Preeclampsia	Prospective study in 28,192 first time singleton pregnant mothers in Norway 2002–2008	Organic food in six food groups assessed by FFQ grouped into any versus seldom/never	Lower prevalence of preeclampsia with frequent organic vegetables, no difference for other food groups or any organic consumption	106
Sperm quality	Cross-sectional study in 30 members of organic farming organizations and 73 blue-collar workers as controls in Denmark in 1994	Organic farmers had a high proportion of organic food in their diets	Higher sperm density in organic farmers	1
Sperm quality	Cross-sectional study in 55 members of organic farming organizations (age 20–45 years) and 141 controls working in an airline company (age 23–43 years) in Denmark in 1996	The organic farmers had at least 25% organic food in their diets	Higher sperm quality in organic food consumers	54
Sperm quality	Cross-sectional study in 85 organic (mean age 40 years) and 171 conventional farmers (mean age 38 years) in Denmark in 1995/1996	Organic food consumption assessed by FFQ and grouped into 0%, 1–49%, and 50–100% organic fruits and vegetables	Lower concentration of morphologically normal spermatozoa in the group with no organic food intake. No differences in 14 other parameters	57
Sperm quality	Cross-sectional study in 85 organic (mean age 40 years) and 171 conventional farmers (mean age 38 years) in Denmark in 1995/1996	Comparison of pesticide exposure and sperm quality between organic and conventional farmers	No difference in sperm quality between organic and conventional farmers	62
Cancer incidence, overall and for 17 individual cancer sites	Prospective study in 623,080 British women with follow-up for 9.3 years from 2002 to 2011	Organic consumption (any food group) in four categories; never, sometimes, usually, or always	No differences for all cancer incidence between usually/always versus never organic	15
Risk factors for cardiovascular disease	Intervention study, crossover design with 150 Italian men (100 healthy and 50 patients with chronic liver disease) in 2006–2008. Outcomes: BMI by dexa scan and blood parameters	Two weeks intervention with Mediterranean conventional diet (T1) and Mediterranean organic diet (T2)	Significant reduction in risk factors for cardiovascular disease after the T2 period	30

End point	Study population and design	Exposure	Result	References
Atopy	Cross-sectional study in 295 children from families with anthroposophic lifestyle and 380 children from control families in Sweden	Organic food consumption as part of an anthroposophic lifestyle	Less atopy in the children coming from anthroposophic families	4
Allergies and atopic sensitization	Cross-sectional study including 14,893 children aged 5–13 years from anthroposophic families and reference children from five European countries (Austria, Germany, the Netherlands, Sweden, and Switzerland)	Organic food consumption as part of an anthroposophic lifestyle	Fewer allergies in families with anthroposophic lifestyle	3
Hay fever and asthma-like symptoms	Cross-sectional study in 593 organic and 1,205 conventional farmers in the Netherlands	Organic versus conventional farming practice	No difference in respiratory disease associated with farming practice/organic consumption	98
Eczema and/or wheeze occurrence	Prospective follow-up of 2,700 children in the KOALA birth cohort in the Netherlands. Blood samples from 815 infants at 2 years of age were analyzed for total and specific immunoglobulin-E	Organic consumption in six food groups and proportion of organic within the total diet	No difference in atopic sensitization. Less eczema with consumption of organic dairy products but not with other organic foods or proportion of organic food	60
Allergic sensitization	Prospective study of 330 children from families with anthroposophic, partly anthroposophic, or nonanthroposophic lifestyle in Sweden. Allergen-specific immunoglobulin-E sensitization measured in blood	Organic food consumption as part of an anthroposophic lifestyle	Immunoglobulin-E sensitization to common allergens was lower among children of families with an anthroposophic lifestyle	104
Hypospadias	Case-control study in mothers of 306 boys who were operated on for hypospadias and 306 mothers of healthy boys	Retrospective recall of organic consumption in six food groups during pregnancy	No difference with any organic consumption but higher prevalence with nonorganic milk/dairy combined with frequent consumption of high fat dairy products	23
Hypospadias and cryptorchidism	Prospective study in 35,107 mothers of singleton male infants in Norway 2002–2008	Organic food in six food groups assessed by FFQ grouped into frequent versus sometimes	Lower prevalence of hypospadias with any organic consumption, and in particular organic vegetables. No difference for cryptorchidism	19

Abbreviations: BMI, body-mass index; FFQ, Food Frequency Questionnaire; KOALA, Kind, Ouders en gezondheid: Aandacht voor Leefstijl en Aanleg (Child, parents and health, addressing lifestyle and constitution).

Brantsæter AL, Ydersbond TA, Hoppin JA, et al. Organic Food in the Diet: Exposure and Health Implications. Annu Rev Public Health. 2017 Mar 20;38:295-313 PMID: 27992727

Summary Benefits from Last Slide

Decreased:

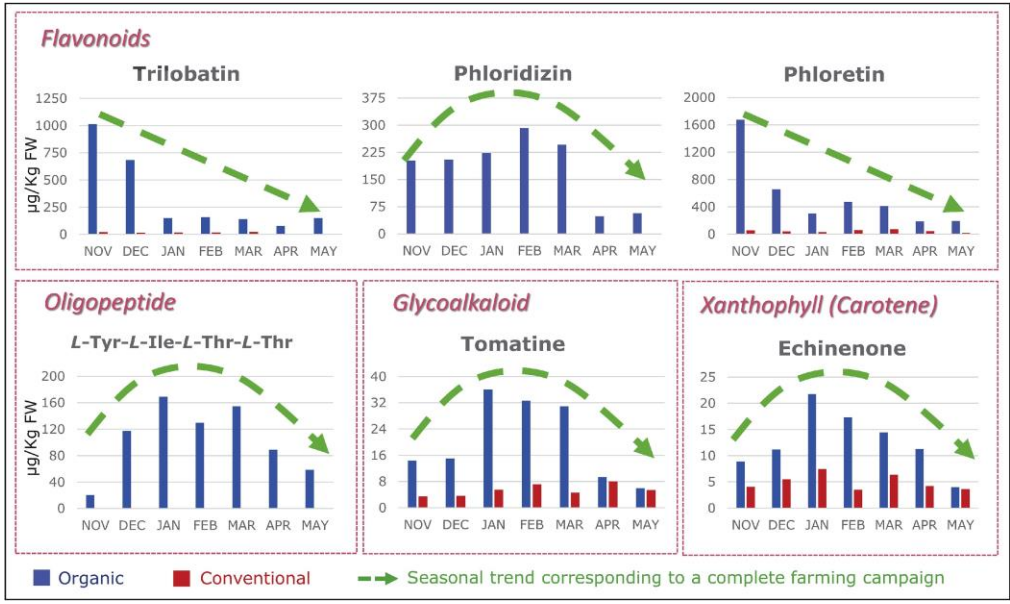
- Cardiovascular disease
- Eczema
- Food allergies
- Preeclampsia

Increased:

- Sperm count
- Sperm quality

Dramatic Differences Between Organic- and Chemically-Grown Foods

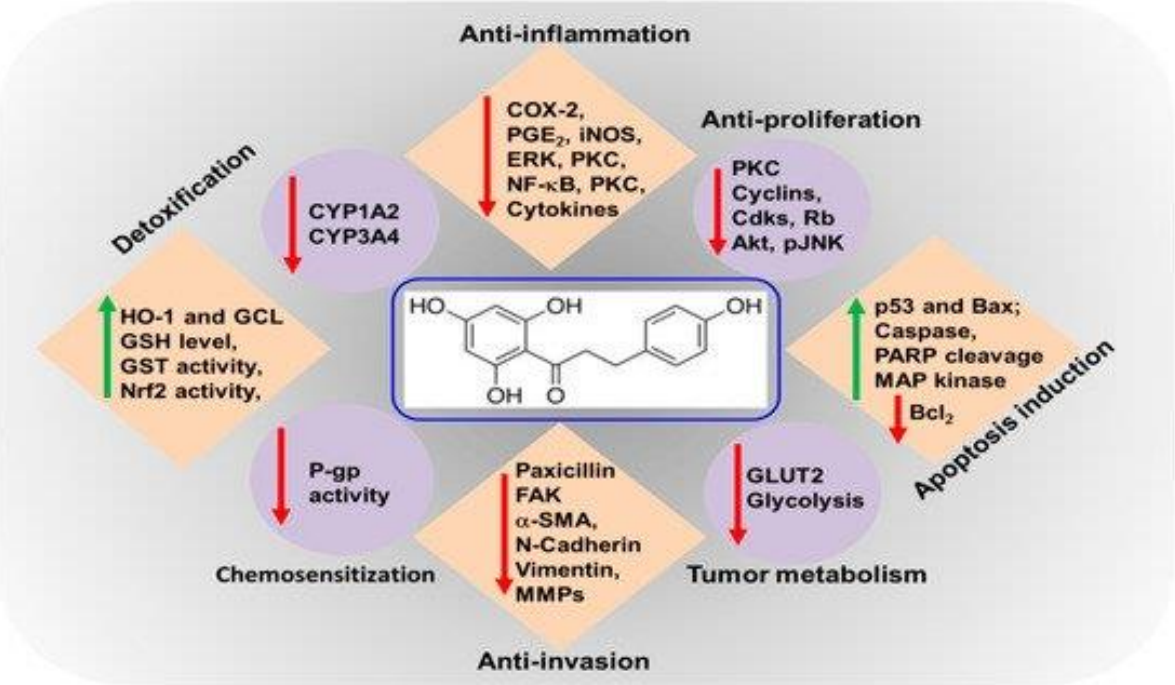
- Tomatoes
- Highly controlled greenhouse
- Shows variation during year
- Dramatic decrease in “unimportant” molecules
- Note: coloring molecules are conserved so food looks normal



Martínez Bueno MJ, Díaz-Galiano FJ, Rajski Ł, et al. A non-targeted metabolomic approach to identify food markers to support discrimination between organic and conventional tomato crops. J Chromatogr A. 2018 Apr 20;1546:66-76 PMID: 29526497

Phloretin

- Polyphenol
- Apples rich source
- Antioxidant, anti-inflammatory, anti-allergic, anti-cancer
- Many cell studies:
  - Induces apoptosis of cancer cells
  - Inhibits angiogenesis



Choi BY. Biochemical Basis of Anti-Cancer-Effects of Phloretin-A Natural Dihydrochalcone. Molecules. 2019 Jan 13;24(2):278. PMID: 30642127

Phloretin: Cholesterol Reduction

- 2 apples a day
  - Marker for apple consumption
  - Virtually no urinary phloretin metabolites if not eating apples
- Serum flavonoids increased: 438 to 1,534 mg/d
- Small but statistically significant decrease in cholesterol
- Phloretin not conserved, so must eat regularly
- One study did not find difference in phloretin levels between organically- and chemically grown apples

Koutsos A, Riccadonna S, Ulaszewska MM, et al. Two apples a day lower serum cholesterol and improve cardiometabolic biomarkers in mildly hypercholesterolemic adults: a randomized, controlled, crossover trial. Am J Clin Nutr. 2020 Feb 1;111(2):307-318. PMID: 31840162

Stracke BA, Rüfer CE, Bub A, et al. No effect of the farming system (organic/conventional) on the bioavailability of apple (Malus domestica Bork., cultivar Golden Delicious) polyphenols in healthy men: a comparative study. Eur J Nutr. 2010 Aug;49(5):301-10. PMID: 20033417

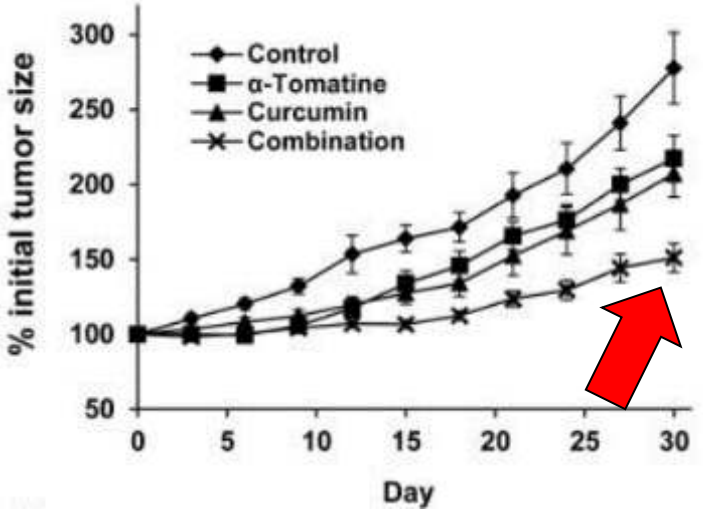
Phloretin: Acne Treatment?

- Cell study
- Blocks growth of *Propionibacterium acnes* which plays major role in acne vulgaris
  - Recently renamed *Cutibacterium acnes* (C. acnes)
  - Comparable activity to Triclosan and benzoyl peroxide
  - Nontoxic to mammalian cells
- Decreases inflammation as well

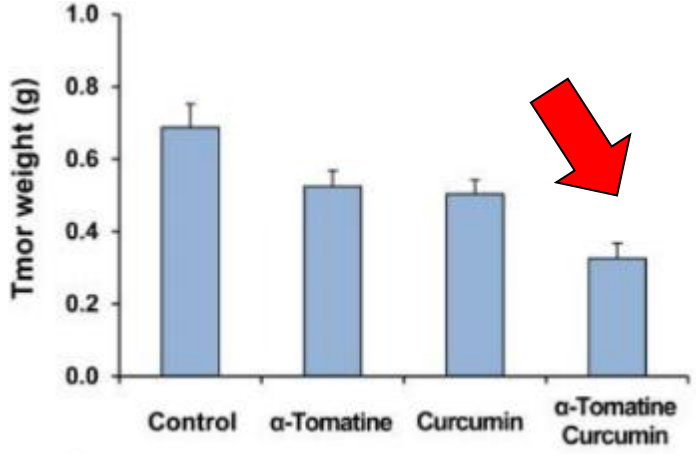
Cheon D, Kim J, Jeon D, Shin HC, Kim Y. Target Proteins of Phloretin for Its Anti-Inflammatory and Antibacterial Activities Against Propionibacterium acnes-Induced Skin Infection. Molecules. 2019 Apr 3;24(7):1319. PMID: 30987239

Tomatine

- The major saponin in tomatoes
- Antitumor, antioxidant, anti-inflammatory
- Suppresses production of pro-inflammatory cytokines in lipopolysaccharide (LPS)-induced macrophages
- Human prostate cancer cells



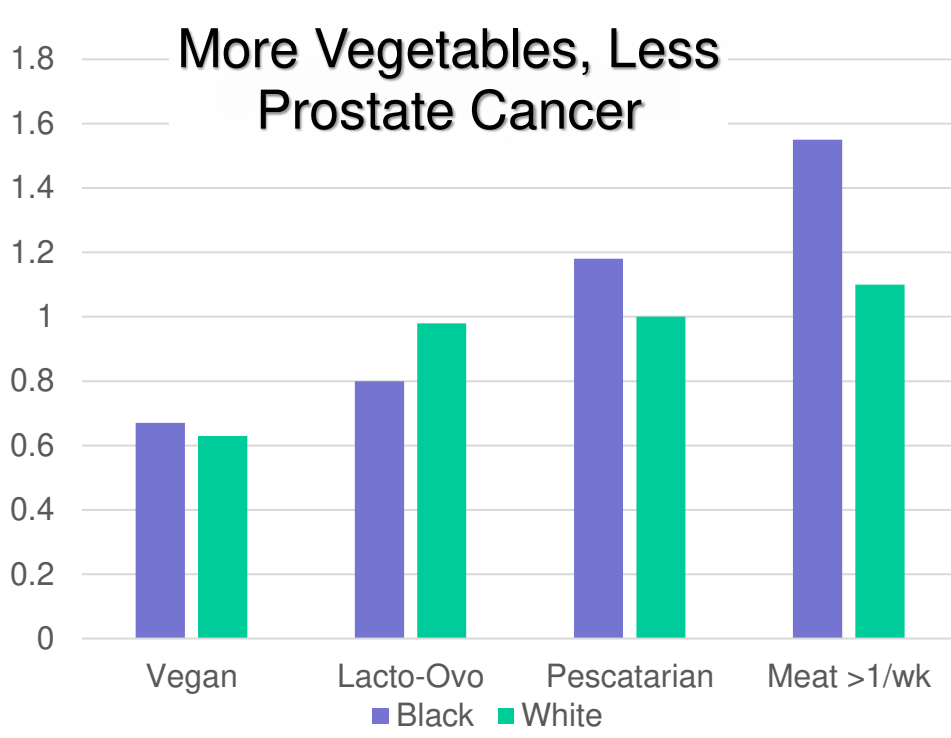
Note synergistic effects



Huang H, Chen X, Li D, et al. Combination of α-Tomatine and Curcumin Inhibits Growth and Induces Apoptosis in Human Prostate Cancer Cells. PLoS One. 2015 Dec 2;10(12) PMID: 26630272

TOMATINE, ET AL. CLINICALLY SIGNIFICANT

- Virtually no direct clinical research on tomatine in humans
- Implied research comparing vegans to other eating patterns
- Research inconsistent ranging from no statistical difference to substantial protection
- Probable cause is uncontrolled variance in genomics of test populations and quality of food



Tantamango-Bartley Y, Knutsen SF, Knutsen R, et al. Are strict vegetarians protected against prostate cancer? Am J Clin Nutr. 2016 Jan;103:153-60

The “Unimportant” Molecules Greatly Impact “Important” Nutrients

Zinc Hugely Impacted by "Unimportant" Molecules, Chemical Farming and Toxins

- Zinc critical for metabolism—**but only if in cells**
- Bioflavonoids increase zinc transport into cells
  - But bioflavonoids are being lost from the food supply
- Foods grown with high phosphates have
  - Less zinc
  - Higher levels of zinc-antagonist cadmium
- Foods depleted in zinc and bioflavonoids and high in cadmium means lower intra-cellular zinc:

  ⇒ Increased susceptibility to viral infections

  ⇒ Impaired function of zinc-dependent enzymes (>100)

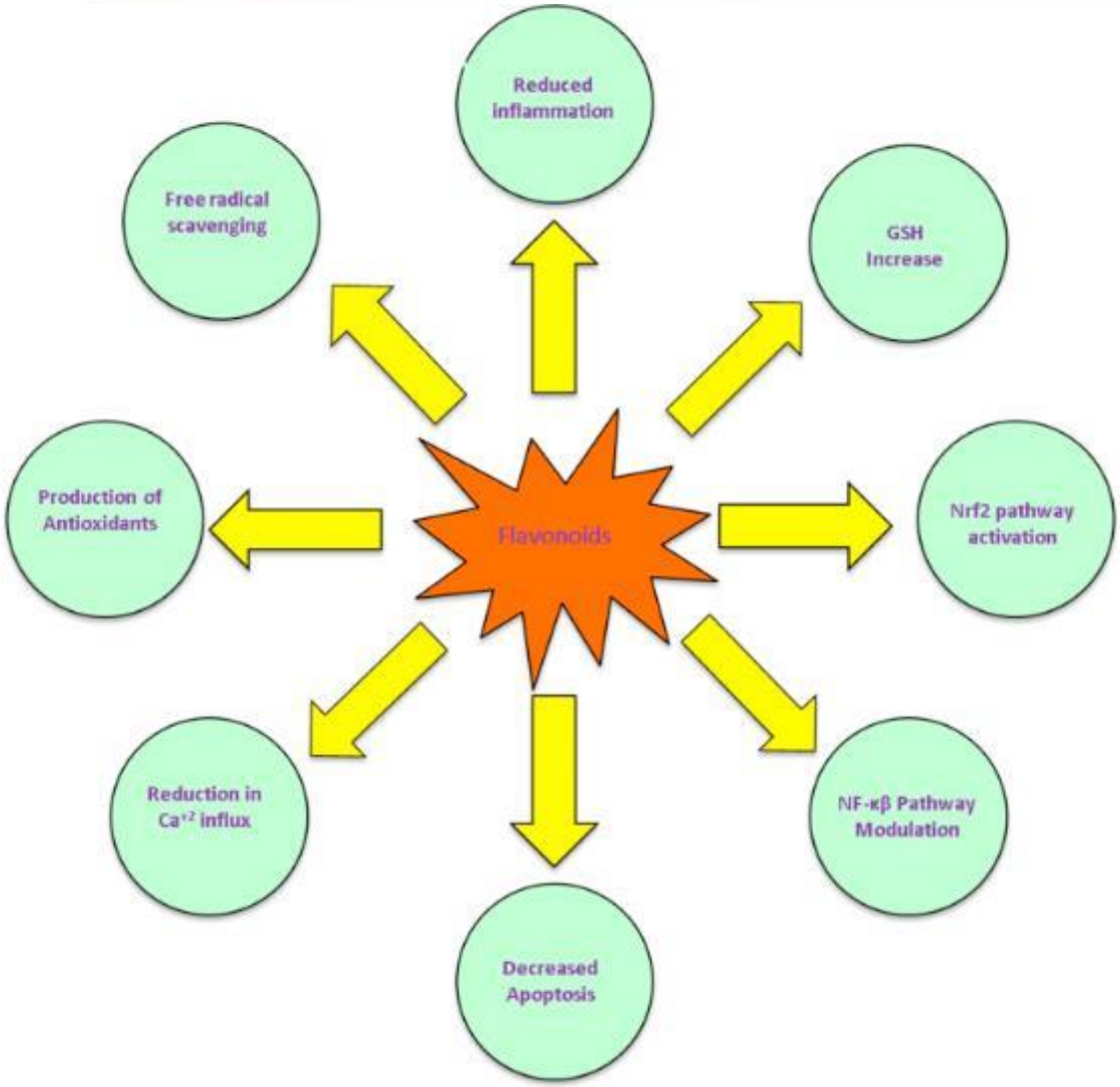
Favonoids Critical to Transport Zinc Into Cells

- Cell study
- Dietary plant polyphenols such as flavonoids quercetin and epigallocatechin-gallate are zinc ionophores
  - Transport zinc cations through the plasma membrane
- Numerous enzymes dependent on zinc are activated by polyphenols
- Combination of zinc and flavonoids dramatically increase zinc levels in cells and metabolic activity of Zn-dependent enzymes

Dabbagh-Bazarbachi H, Clergeaud G, Quesada IM, et al. Zinc ionophore activity of quercetin and epigallocatechin-gallate: from Hepa 1-6 cells to a liposome model. J Agric Food Chem. 2014 Aug 13;62(32):8085-93 PMID: 25050823

The “Unimportant” Molecules Greatly Impact Health and Disease Risk

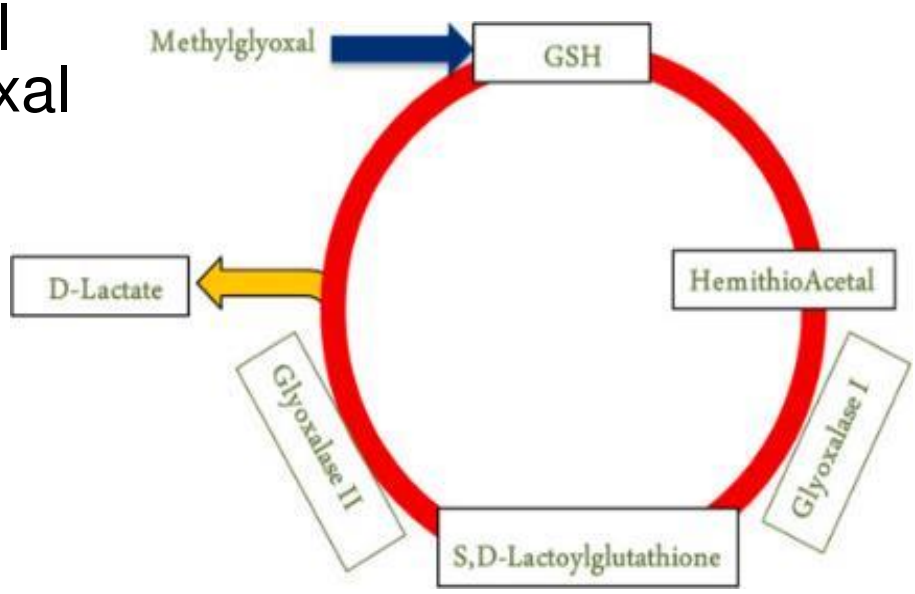
FLAVONOIDS CRITICAL FOR HEALTH



Frandsen JR, Narayanasamy P. Neuroprotection through flavonoid: Enhancement of the glyoxalase pathway. Redox Biol. 2018 Apr;14:465-473 PMID: 29080525

Preserving Our Brains

- Flavonoids enhance glyoxalase pathway
- Detoxifies reactive dicarbonyl compounds, esp. methylglyoxal
- Critical antioxidant neuron protection
- Decreases risk for:
  - Alzheimer's
  - Parkinson's
  - Aging
  - Autism Spectrum Disorder



Frandsen JR, Narayanasamy P. Neuroprotection through flavonoid: Enhancement of the glyoxalase pathway. Redox Biol. 2018 Apr;14:465-473 PMID: 29080525

The Higher Level of "Unimportant" Molecules in Organically-Grown Foods Has Huge Clinical Implications

- Lower risk of cancers
  - All cancers: OR 0.75
  - Lymphomas: OR 0.23!
- Benefit not just lower pesticide levels

Baudry J, Assmann KE, Touvier M, et al. Association of Frequency of Organic Food Consumption With Cancer Risk: Findings From the NutriNet-Santé Prospective Cohort Study. JAMA Intern Med. 2018 Dec 1;178(12):1597-1606 PMID: 30422212

Why Do Organic Foods Taste Better?

- Three strawberry cultivars grown both chemically and organically
- 79% variation in metabolome explained 88% of variation in sensory profiles
- Sensory variations due to flavonoids, tannins and fatty acids
- Organic farming practices enhance accumulation of sensory plant metabolites

⇒ Full taste (not overstimulation of 1 or 2 sensors) = health

Kårlund A, Hanhineva K, Lehtonen M, et al. Nontargeted metabolite profiles and sensory properties of strawberry cultivars grown both organically and conventionally. J Agric Food Chem. 2015 Jan 28;63(3):1010-9 PMID: 25569122

Many Studies Show Organic Foods Higher in "Unimportant" Molecules

- Examples
  - Onions: phenolics, total flavonoids and antioxidant activity
  - Broccoli: indolyl glucosinolates (precursors of I3C)

Ren F, Reilly K, Gaffney M, et al. Evaluation of polyphenolic content and antioxidant activity in two onion varieties grown under organic and conventional production systems. J Sci Food Agric. 2017 Jul;97(9):2982-2990 PMID: 27859352

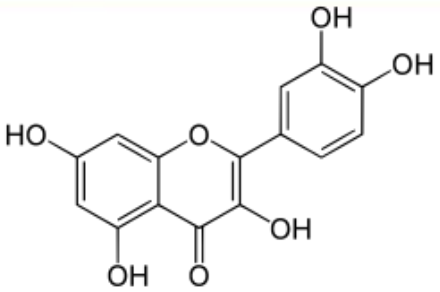
Valverde J, Reilly K, Villacreces S, et al. Variation in bioactive content in broccoli (Brassica oleracea var. italica) grown under conventional and organic production systems. J Sci Food Agric. 2015 Apr;95(6):1163-71 PMID: 24976520

Clinical Application

Specific Supplements

Quercetin

Polyphenol antioxidant found in plant foods
One of most abundant flavonoids in diet



Physiological Effects

- Anti-inflammatory
- Antioxidant
- Antiviral
- Improves insulin sensitivity
- Induces apoptosis
- Induces autophagy
- Protects cholesterol
- Stabilizes cell membranes
- Neuroprotective
- Etc.

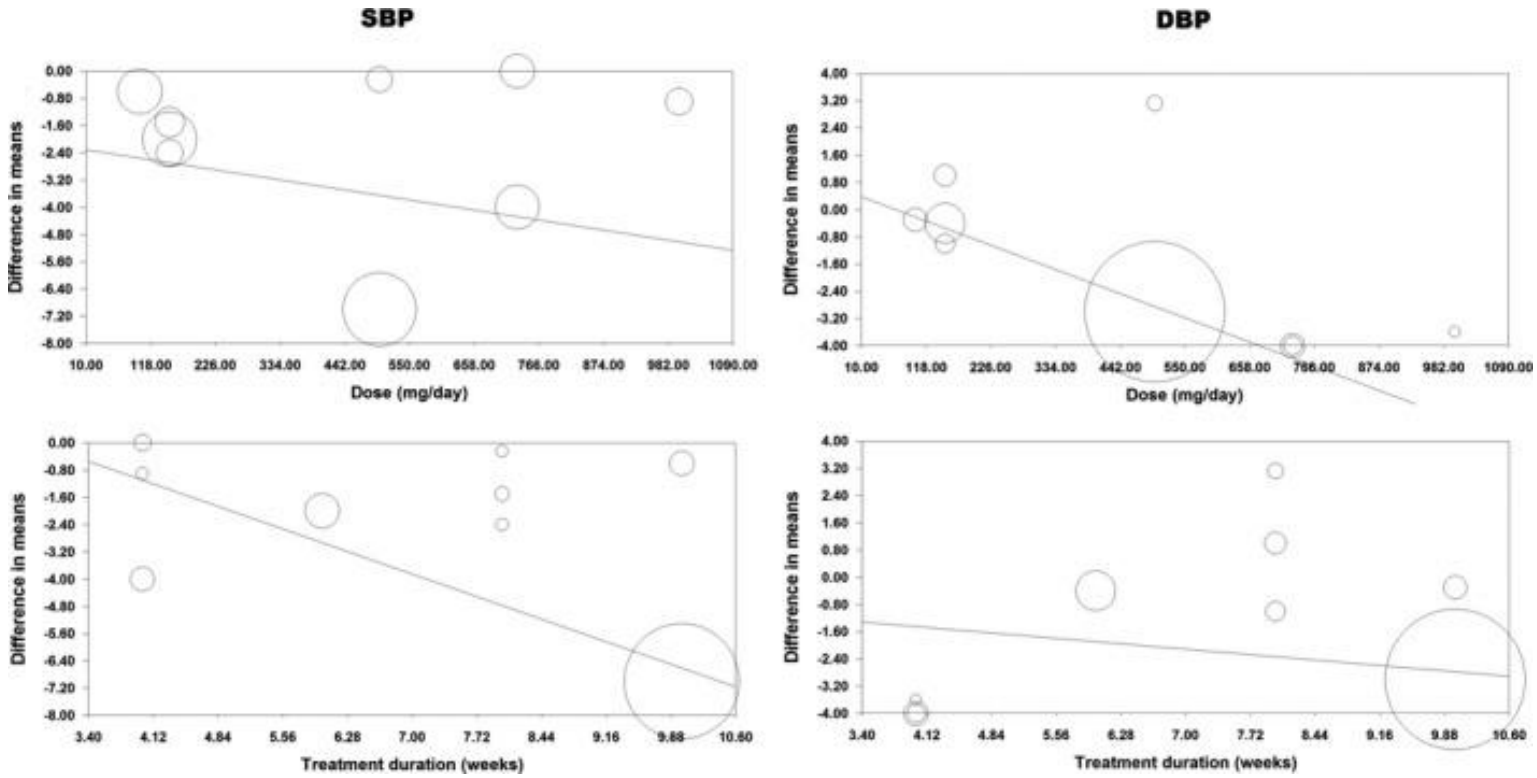
Clinical Impacts

- Decreases dementia risk
- Decreases allergies
- Decreases atopic disease
- Decreases diabetes
- Decreases viral infections
- Decreases cancer risk
- Decreases prostatitis
- Decreases PCOS
- Lowers blood pressure
- Etc.

Quercetin and Blood Pressure

Dosage

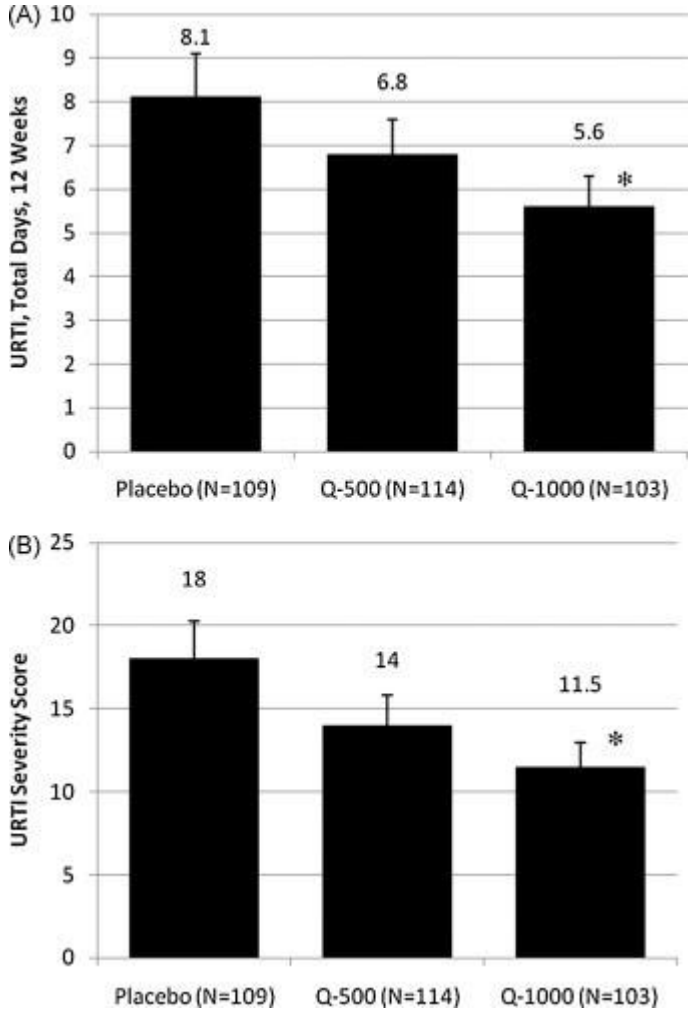
Duration



Serban MC, Sahebkar A, Zanchetti A, et al; Lipid and Blood Pressure Meta-analysis Collaboration (LBPMC) Group. Effects of Quercetin on Blood Pressure: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. J Am Heart Assoc. 2016 Jul 12;5(7):e002713. doi: 10.1161/JAHA.115.002713. PMID: 27405810; PMCID: PMC5015358.

Quercetin Decreases URIs

- 1,000 subjects
- 12-weeks
- Double blind, placebo controlled
- But only beneficial in healthy, fit adults >40 yo

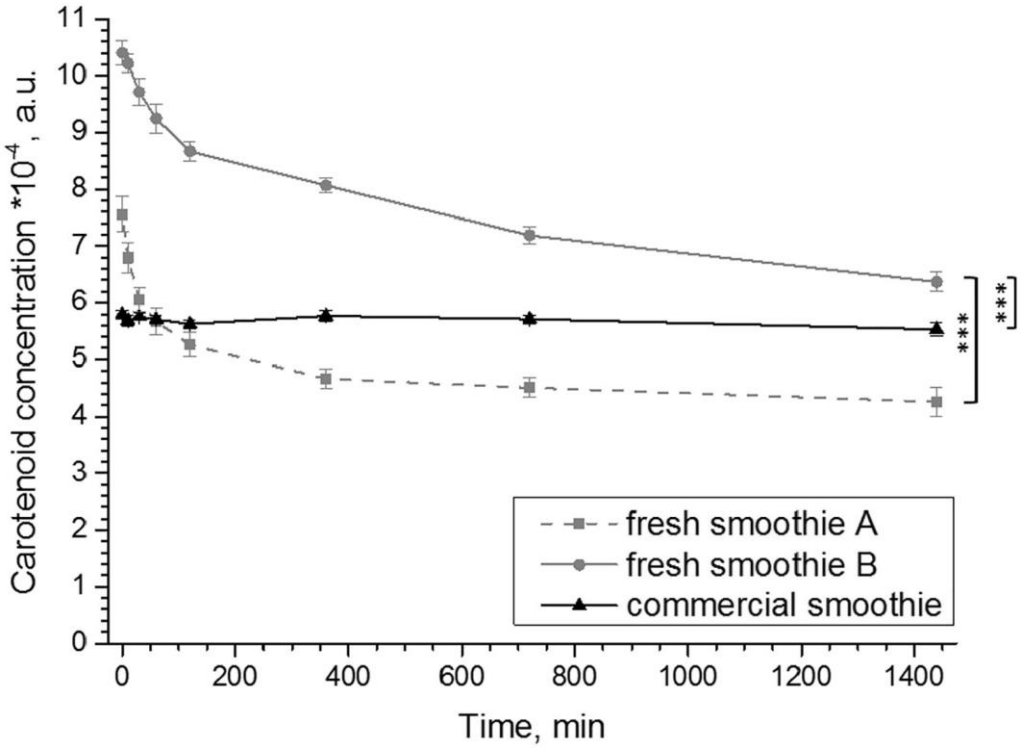


Heinz SA, Henson DA, Austin MD, Jin F, Nieman DC. Quercetin supplementation and upper respiratory tract infection: A randomized community clinical trial. Pharmacol Res. 2010 Sep;62(3):237-42. doi: 10.1016/j.phrs.2010.05.001. Epub 2010 May 15. PMID: 20478383; PMCID: PMC7128946.

Vegetable Drinks

Vegetable Drinks

- >300 clinical studies
- Best way to get these “un”important molecules
- Best consumed as soon as possible (graph shows loss rate at 4ºC)



Jung B, Darvin ME, Jung S, et al. Kinetics of the carotenoid concentration degradation of smoothies and their influence on the antioxidant status of the human skin in vivo during 8 weeks of daily consumption. Nutr Res. 2020 Sep;81:38-46. PMID: 32871403.

Clinical Benefit Calculation

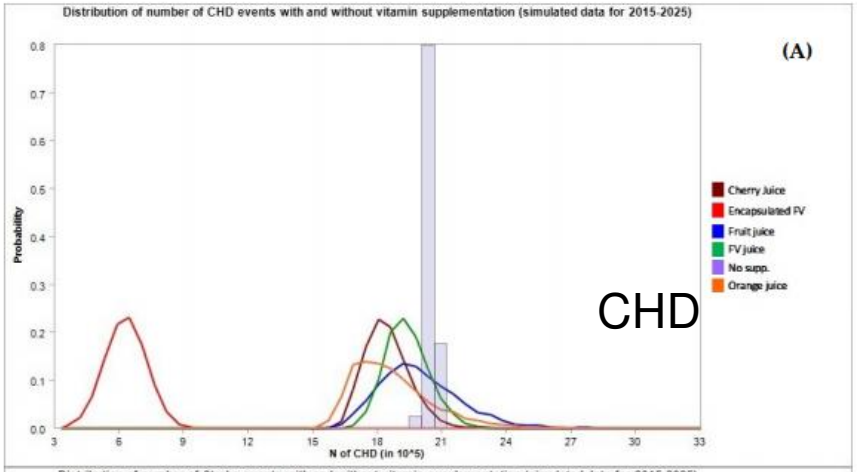
Table 2. Articles used to estimate the effect size of a single concentrate product on a specific clinical surrogate.

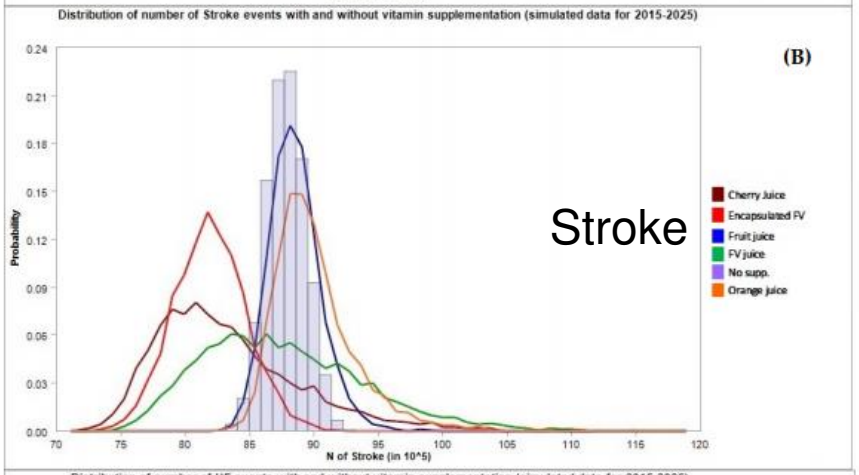
Surrogate	Link to Main Outcome	References
TC	1 mmol/L lower TC is associated with lower CHD mortality equal to: - hazard ratio 0.44 (0.42–0.48) in both sexes at ages 40–49 - hazard ratio 0.66 (0.65–0.68) in both sexes at ages 50–69 - hazard ratio 0.83 (0.81–0.85) in both sexes at ages 70–89	Prospective Studies Collaboration 2007 [34]
LDL	For a 10 mg/dL (0.26 mmol/L) reduction: - relative risk reduction is 7.1% (4.5% to 9.8%) for CHD events	Briel et al. 2009 [35]
HCY	For each 5 µmol/L increment: - pooled risk ratio is 1.52 (1.26–1.84) for CHD deaths	Peng et al. 2015 [36]
SBP	Every 10 mmHg reduction: - reduced the CHD events (relative risk (0.83, 0.78–0.88) - reduced the STR events (relative risk (0.73, 0.68–0.77) - reduced the HF (relative risk (0.72, 0.67–0.78)	Ettehad et al. 2016 [37]
BMI	The relative risk for a 5 unit increment is: - 1.41 (1.34–1.47) for HF incidence	Aune et al. 2016 [38]
TNF-α	The increase of 0.668 pg/mL in TNF-α is equal to an increase of STR risk with an odds ratio of 1.813 (1.194–2.748) 1-SD increment of TNF-α is associated with increased risk of CHD: - hazard ratio 1.09 (0.92–1.30)	Dong et al. 2015 [39] Kaptoge et al. 2014 [40]

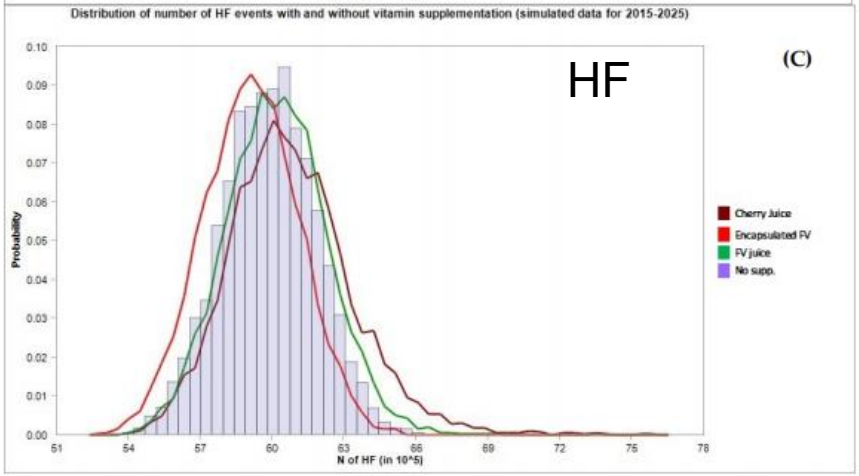
Lorenzoni G, Minto C, Vecchio MG, et al. Fruit and Vegetable Concentrate Supplementation and Cardiovascular Health: A Systematic Review from a Public Health Perspective. J Clin Med. 2019 Nov 8;8(11):1914. PMID: 31717327

Vegetable & Fruit Juices: Many Benefits

- Vegetable juice better than fruit juice
- Cherry juice most effective fruit juice
- Fruit and vegetable concentrates also beneficial







Lorenzoni G, Minto C, Vecchio MG, et al. Fruit and Vegetable Concentrate Supplementation and Cardiovascular Health: A Systematic Review from a Public Health Perspective. J Clin Med. 2019 Nov 8;8(11):1914. PMID: 31717327

Beetroot Juice Decreases Blood Pressure

- Metanalysis of 22 studies
- Diastolic BP
- >14 days better than <14 days
- Better results in unhealthy people

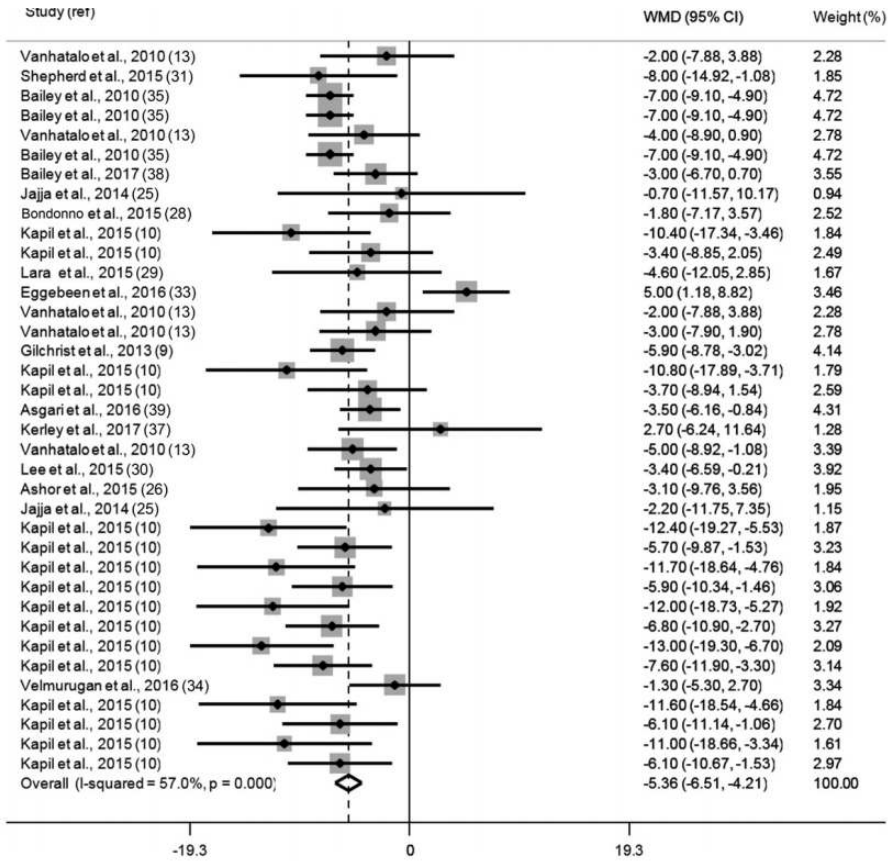


FIGURE 5 Forest plot of trials that investigated the effects of beetroot juice supplementation on diastolic blood pressure in relation to baseline values. Ref, reference; WMD, weighted mean difference.

Bahadoran Z, Mirmiran P, Kabir A, et al. The Nitrate-Independent Blood Pressure-Lowering Effect of Beetroot Juice: A Systematic Review and Meta-Analysis. Adv Nutr. 2017 Nov 15;8(6):830-838. PMID: 29141968

Pomegranate Fruit Decreases Inflammation

- The *Punica granatum* L.
- Rich source of phytochemicals with high antioxidant and anti-inflammatory activity
- Metanalysis of 16 studies
- Dosages 150-1,000 ml/d
- Length: Days to several weeks

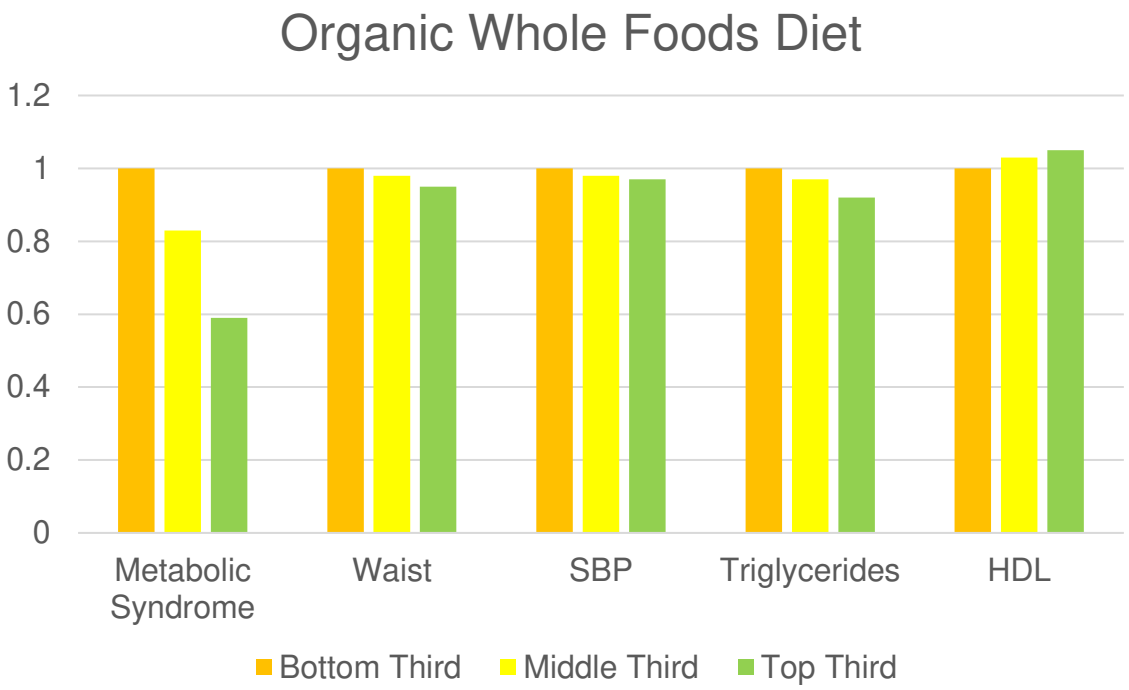
Improvement in many measures (averages):

- hsCRP: ↓ 6.57 mg/L
- CRP: ↓ 2.19 mg/dL
- TNF-α: ↓ 2.37 pg/mL
- IL-6: ↓ 1.68 pg/mL
- MDA: NS

Wang P, Zhang Q, Hou H, et al. The effects of pomegranate supplementation on biomarkers of inflammation and endothelial dysfunction: A meta-analysis and systematic review. Complement Ther Med. 2020 Mar;49:102358. PMID: 32147056.

Eating Organically

Eating Organic Whole Foods Clinically Impactful



Baudry J, Lelong H, Adriouch S, et al. Association between organic food consumption and metabolic syndrome: cross-sectional results from the NutriNet-Santé study. Eur J Nutr. 2018 Oct;57(7):2477-2488. PMID: 28770334

Conclusion

“Unimportant” Molecules Hugely Impact Health

- These molecules have been lost due to:
  - Changes in food choices
  - Growing foods with chemicals rather than organically
  - Excessive processing of food supply
- Increasing consumption of organically-grown, whole foods has huge clinical benefit