

The Fire Within: The Consequences of Chronic Inflammation



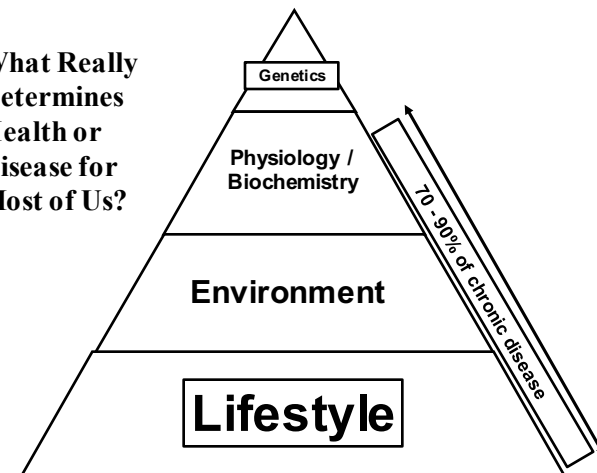
Tieraona Low Dog, MD

Director: Interprofessional
Fellowship in Integrative
Health & Medicine

Chair: Dietary
Supplements/Botanicals
Expert Information
Panel Admissions Sub-
Committee

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What Really
Determines
Health or
Disease for
Most of Us?



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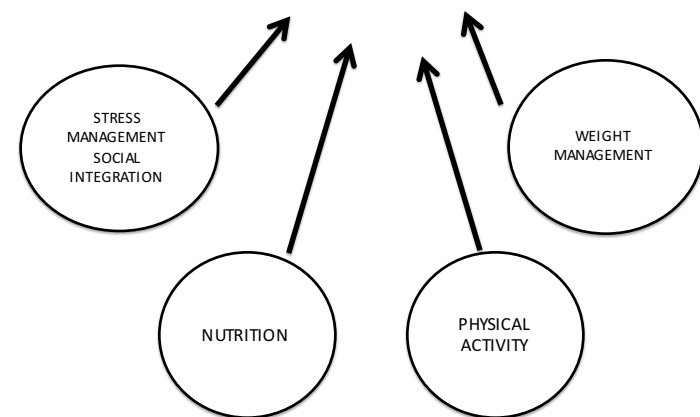
- If the American public embraced a healthier lifestyle:
 - *no smoking, no or moderate alcohol consumption*
 - *limited or no exposure to toxic chemicals*
 - *healthy nutrition*
 - *balance of exercise and rest*
 - *stress management*
 - *social integration*

93% of diabetes, 81% of heart attacks, 50% of strokes,
and 36% of all cancers could be prevented.

Ford, et al *Arch Intern Med.* 2009; 169(15):1355-62.

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RISK REDUCTION



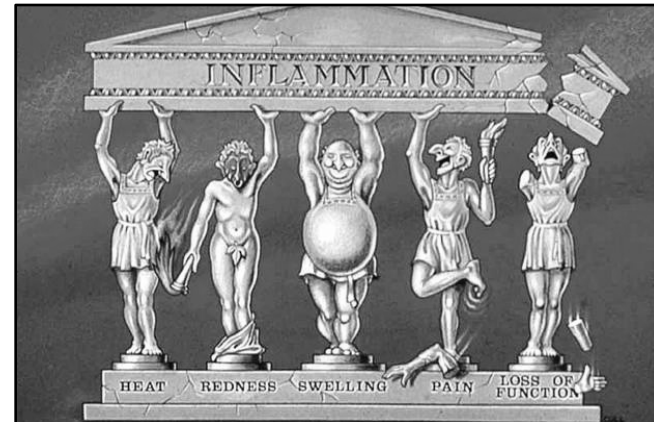
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Two Unifying Themes

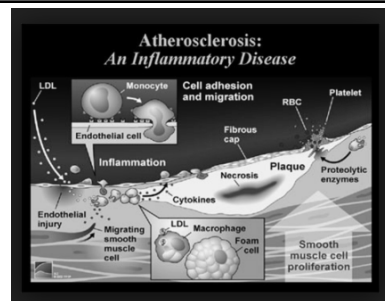
When we look at what appears to be driving much of our chronic disease, including some cancers, we see:

Chronic Inflammation and Insulin Resistance

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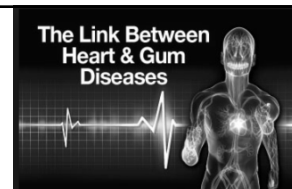


- CAD is leading cause of death in United States.
- CAD was considered primarily a lipid accumulation mediated disease; now shown to involve an ongoing inflammatory response.

Christodoulidis G, et al. Cardiol Rev 2014 Jan 15

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Periodontitis and Heart Disease



- Periodontitis recognized as an inflammatory disease of bacterial origin by American Academy of Periodontology.
- Plausibility of periodontal bacteria influencing vascular inflammation strengthened when *Porphyromonas gingivalis* isolated from human atheromatous plaques.

Friedewald VE, et al. J Periodontol 2009; 80:1021-1032

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Oral Health & Systemic Disease

- In recent years, periodontal diseases have been associated with systemic diseases such as rheumatoid arthritis, cardiovascular-disease, diabetes mellitus, chronic respiratory diseases and adverse pregnancy outcomes including pre-term low-birth weight (PLBW) and pre-eclampsia.
- Improving periodontal health before or during pregnancy may prevent or reduce the occurrences of these adverse pregnancy outcomes and, therefore, reduce the maternal and perinatal morbidity and mortality.

Parihar AS, et al. *J Int Oral Health* 2015; Jul;7(7):137-42.

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Periodontitis and Cancer?

- Almost 60,000 Americans develop head and neck cancer annually and 12,000 die from the disease.
- Chronic periodontitis may be independently associated with HNSCC through direct toxic effects of bacteria and their products, and/or through indirect effects of inflammation.
- It may also facilitate the acquisition and persistence of oral HPV infection, a recently recognized risk factor for HNSCC.

Han YW, et al. *Adv Dent Res* 2014; 26(1):47-55

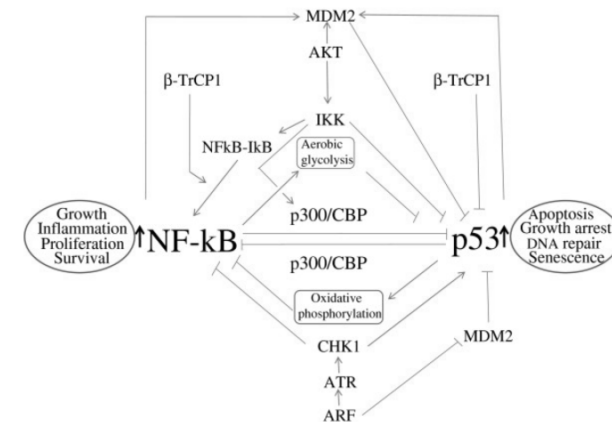
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Inflammation and Cancer

- Activation of NF- κ B is vital for our body's ability to defend itself against infection and is a central mediator of inflammation.
- Many things activate NF- κ B and when it is persistently "turned on" it induces genes that are responsible for increasing cell survival, proliferation, migration and invasion. It also turns down growth regulators (e.g., p53) that suppress tumor growth.

Pal S, et al. *J Inflamm* 2014; Aug 9; 11:23

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Pal S, et al. *J Inflamm* 2014; Aug 9; 11:23.

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Osteoporosis



- Growing evidence osteoporosis may be driven, in part, by chronic low grade inflammation.
- Pro-inflammatory cytokines (IL-1, IL-6, TNF-alpha), accelerate bone loss via activation of osteoclasts, inhibit collagen production in osteoblasts and enhance breakdown of the extracellular matrix.
- Large study of older women found almost a 50% increased risk of hip fracture in those with highest levels of inflammatory markers.

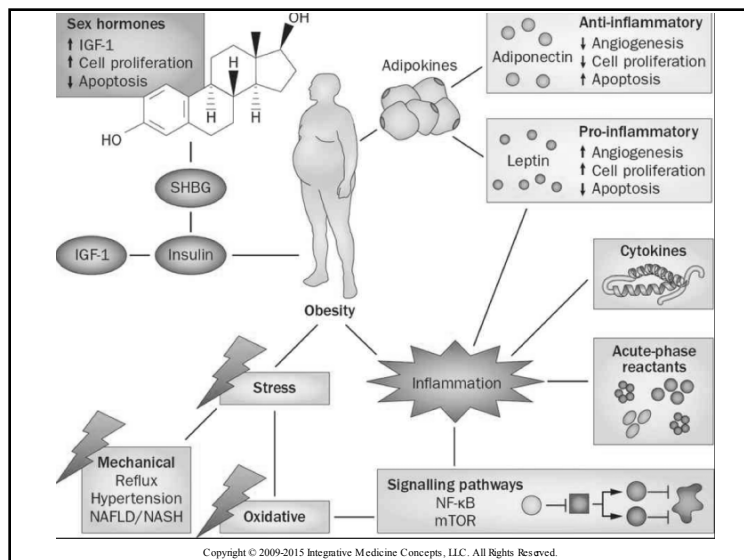
Barbour KE, et al. J Bone Miner Res 2014; 29(9):2057-64

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Factors That Drive Inflammation and Insulin Resistance

- Pattern of central obesity
- Western-dietary pattern, high fructose
- Sedentary lifestyle, lack of exercise
- Prolonged psychosocial stress
- Alterations in gut flora and intestinal permeability
- Environmental exposures (smoke, toxins)

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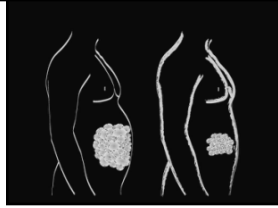


Obesity and Insulin Growth Factors

- Obesity associated with multiple factors that increase risk for heart disease, diabetes and certain cancers such as inflammation, insulin resistance, high blood sugar and insulin-growth factors (IGF).
- Elevated insulin increases tumor growth and aggressiveness.
- IGF-1 and IGF-2 have been identified as tumor promoters in multiple studies.

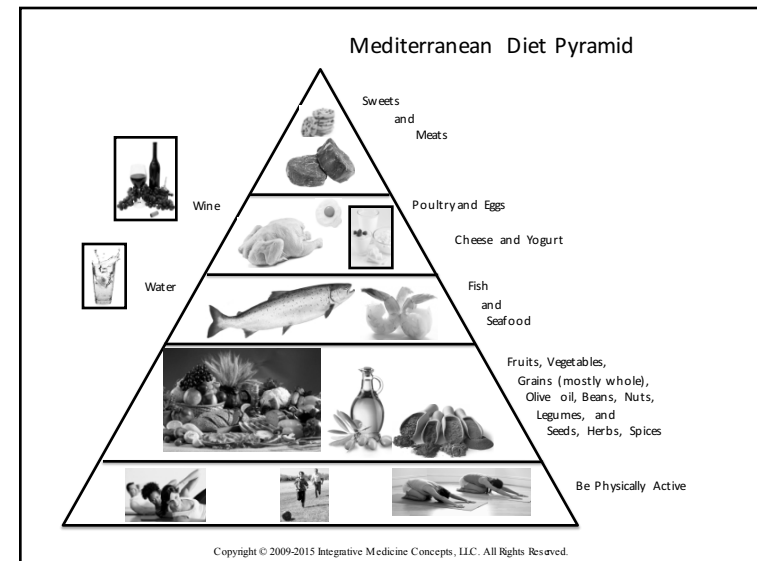
Belardi V et al. J Mammary Gland Biol Neoplasia 2013; 18(3-4):277-89

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- Waist measurements indicating increased risk:
 - 31.5 inches or more for women
 - 37 inches or more for men
- High risk
 - 35 inches or more for women
 - 40 inches or more for men

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Mediterranean Diet



- Traditional Mediterranean dietary pattern has shown superior anti-inflammatory effects when compared with typical North American and Northern European dietary patterns in most observational and interventional studies.

Galland L. Nutr Clin Pract 2010; Dec;25(6):634-40.

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- Study > 2000 women confirmed “Western” diet increased breast cancer risk, while Med Diet lowered risk of all **breast cancer** subtypes, particularly triple-negative tumors.
- Review found strong evidence of a beneficial role of the Mediterranean diet on **oral and pharyngeal cancer**.
- High adherence associated with significant reduction in overall cancer mortality (10%), colorectal cancer (14%), prostate cancer (4%) and aerodigestive cancer (56%).



Castello A, et al. Br J Cancer 2014; 111(7):1454-62

Filomeno M, et al. Br J Cancer 2014; 111(5):981-6.

Schwingshacki L, et al. Int J Cancer 2014; 135(8):1884-97.

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ORIGINAL CONTRIBUTION


Effect of a Mediterranean-Style Diet on Endothelial Dysfunction and Markers of Vascular Inflammation in the Metabolic Syndrome
A Randomized Trial

Esposito et al., JAMA 2004; 292:1440-1446

“Compared with patients consuming the control diet, patients consuming the intervention diet had significantly **reduced serum concentrations of hs-CRP, IL-6, IL-7, and IL-18**, as well as **decreased insulin resistance**.”

“A Mediterranean-style diet might be effective in **reducing the prevalence of the metabolic syndrome** and its **associated cardiovascular risk**.”

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- Traditional Mediterranean diet low in processed foods and fructose.
- High fructose consumption associated with increased intestinal permeability, elevated toll-like receptor 4, endotoxemia and development of non-alcoholic fatty liver disease.

Jin R, et al. Nutrients 2014; 6:3187-3201

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Non-alcoholic Fatty Liver Disease

- Small study found significant reductions in systolic blood pressure, body fat, liver enzymes ($P = .04$) and insulin resistance in children with NAFLD at 3 and 6 months ($P < .05$) on a *low fructose, low GL diet*.
- Four week study found low fructose diet in Hispanic adolescents increased insulin sensitivity and lowered hs-CRP.

Mager DR, et al. JPEN J Parenter Enteral Nutr 2013; Aug 23.
Jin R, et al. Nutrients 2014; 6:3187-3201

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WHO Recommends Limiting Sugar Consumption To 25g/d

Sugar verdict

The World Health Organization sets new draft guidelines for sugar in

WHAT PERCENTAGE OF YOUR DAILY RECOMMENDED SUGAR ALLOWANCE (25 GRAMS) DO THESE FOODS MAKE UP?

Food Item	Percentage of Daily Recommended Sugar Allowance (25g)	Amount
1 can sugar-sweetened pop	60% over	40 g
Blueberry muffin	62%	15.5 g
100-g fat-free, sweetened Greek yogurt	52%	13 g
Mars bar	28% over	32 g
20-oz Orange Gatorade	36% over	34 g

COMPILED BY KELLY GRANT, QUINCY, ILL. PHOTOGRAPHS BY THE OLIVE AND AVOCADO BOARD, PREVENTION MAGAZINE, UNIVERSE OF NATURE AND BEVERAGE COMPANIES

KELLY GRANT
HEALTH REPORTER
This is a changing scenario. If you drink a single can of pop a day, you're consuming the daily

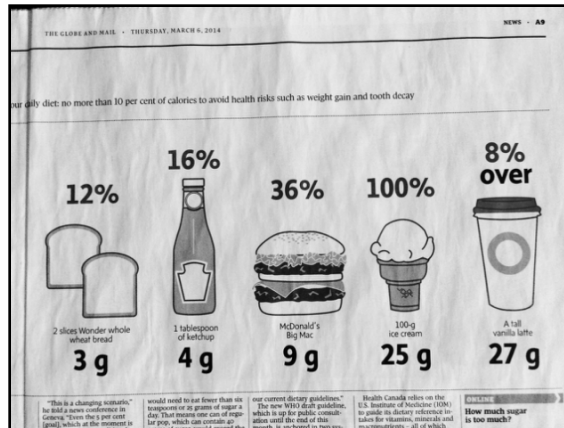
News:
The Canadian government is already under increasing pressure from health organizations to limit added sugars in foods.

In a separate statement, Health Canada said it was reviewing the WHO's draft recommendations. The WHO's move to update its guidelines is a landmark move.

cost:
"There'll be a lot of health advice and people who believe that sugar is really the

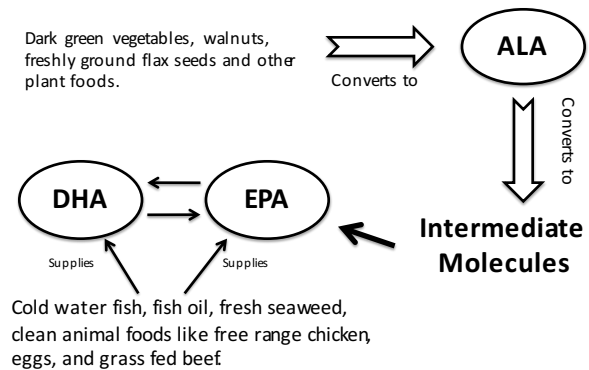
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Sugars added to foods, as well as those found naturally in honey, syrups, fruit juices and fruit concentrates. Not in fresh produce.



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Omega 3 Fatty Acids from Plants and Animals

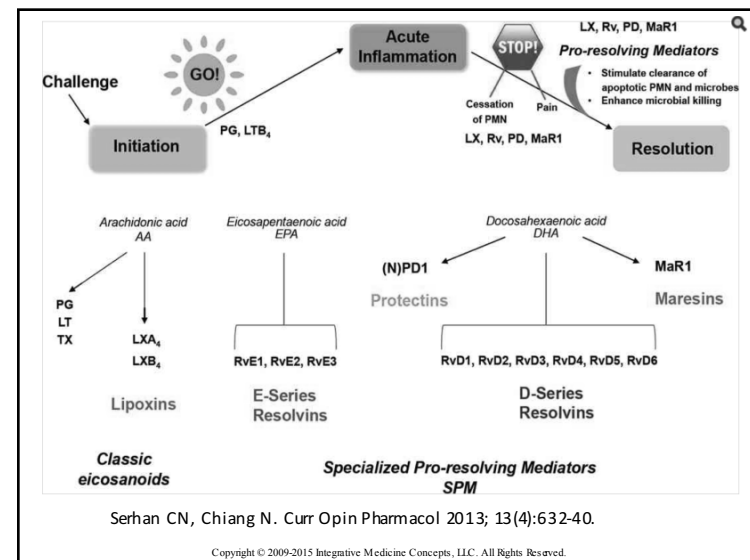


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Resolution Biology

- Inflammation always considered a passive process.
- Newer research shows that resolution of self-limited acute inflammation is an active, programmed response.
- Omega 3 fatty acids produce specialized pro-resolving mediators (SPM) – resolvins, protectins and maresins.

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DHA + Aspirin and Periodontitis

- Harvard/Beth Israel study: 55 adults with moderate periodontitis randomized to 2,000 mg of DHA or identical placebo plus 81 mg/d of aspirin.
- DHA supplementation decreased mean pocket depth and gingival index. Significant adjusted differences were found between DHA and control for both gingival crevicular fluid hs-CRP (-5.3 ng/mL) and IL-1 β ($p=.02$) but systemic hs-CRP, plaque index or bleeding on probing.

Naqvi AZ, et al. J Dent Res 2014; 93(8):767-773.

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Cardiovascular Health



Population studies and intervention trials show omega-3 fatty acids protect against cardiovascular morbidity and mortality.

Systematic reviews of clinical trials provide contradictory results for *secondary* prevention of cardiovascular disease.

Smith DA. Ann Intern Med 2012 Dec 18;157(12):JC6-5

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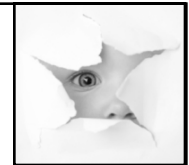
Canadians and Omega 3

- The Omega-3 Index indicates the percentage of EPA+DHA in red blood cell fatty acids.
- Canadian government found that the mean Omega-3 Index level of Canadians aged 20-79 was 4.5%.
 - Levels higher for women, older adults, Asians and other non-white Canadians, omega-3 supplement users, and fish consumers; levels lower for smokers and people who were obese.
- Fewer than 3% of adults had levels associated with low CHD risk; 43% had levels associated with high risk.

Langlois K, et al. Health Rep 2015; Nov 18;26(11):3-11

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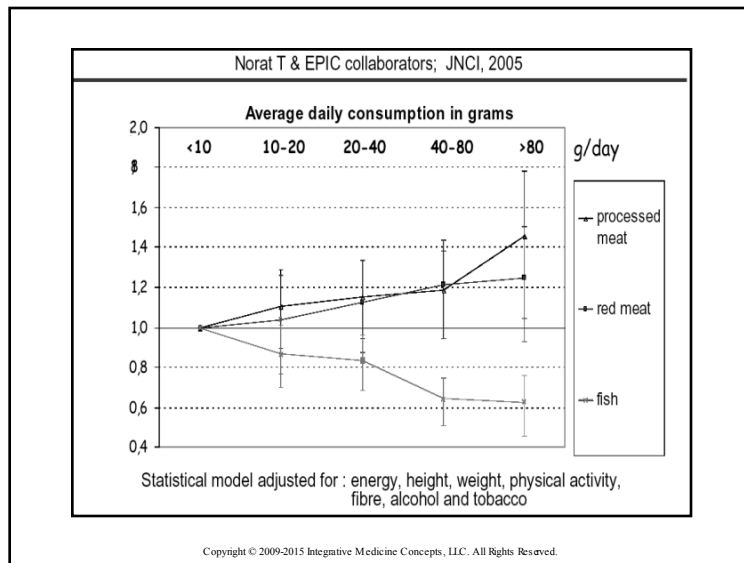
Pregnancy



- Maternal DHA intake during pregnancy and lactation can prolong high risk pregnancies, increase birth weight, head circumference; enhance visual acuity, hand and eye co-ordination, attention, and information processing.
- Maternal supplementation of omega 3 during pregnancy significantly reduced risk of childhood asthma and food allergies.

Morse NL. Nutrients 2012; 4(7): 799-840
Kiemens CM, et al. BJOG 2011; 118(8):916-25

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Seafood Calculator

www.ewg.org/research/ewg-s-consumer-guide-seafood/seafood-calculator

Calculations are based on 4 oz. serving size

CATEGORY	SPECIES	WEEKLY MERCURY	SUSTAINABILITY	CONCLUSION
EWG'S BEST BETS! Very High Omega-3s, Low Mercury, Sustainable	SALMON	NaN%	Best Choice: Wild Alaska	🍴⊗🍴
	SARDINES	NaN%	Best Choice: Pacific	🍴⊗🍴
	MUSSELS	NaN%	Best Choice: Farmed	🍴⊗🍴
	RAINBOW TROUT	NaN%	Best Choice: Farmed	🍴⊗🍴
	ATLANTIC MACKEREL	NaN%	Best Choice: Not Trawled	🍴⊗🍴

🍴⊗🍴 = should eat 1 Serving per week, but no other seafood

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Different Types of Fish Oil

- Supplementation is an alternative to eating fish; however, all supplements are not equal.
- Randomized, crossover study of 35 healthy individuals compared four popular brands/types of omega 3 fatty acids:
 - Concentrated triglyceride (rTG)
 - Ethyl ester (EE)
 - Phospholipid krill oil (PL)
 - Triglyceride salmon oil (TG)

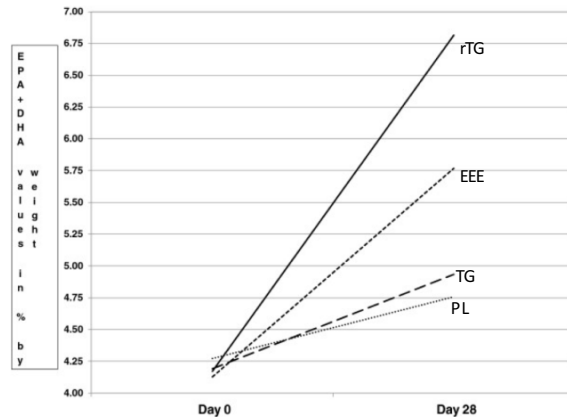
Laidlaw M, et al. Lipids Health Dis 2014; 13:99

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Dosing According to Manufacturer's Recommendations

TRT	Product	EPA & DHA per capsule*	Tested values	Label use: caps/day	Daily dosage of EPA + DHA
rTG	Nordic Naturals ProOmega®	325 mg EPA	329.6 mg EPA	2	EPA: 650 mg
	Triglyceride	225 mg DHA	226.0 mg DHA		DHA: 450 mg
EE	Minami MorEPA®	756 mg EPA	774.2 mg EPA	1	EPA: 756 mg
	Platinum Ethyl Ester	228 mg DHA	233.7 mg DHA		DHA: 228 mg
PL	Source Naturals ArcticPure®	75 mg EPA	78.0 mg EPA	2	EPA: 150 mg
	Krill Oil Phospholipid	45 mg DHA	46.7 mg DHA		DHA: 90 mg
TG	New Chapter				
	Wholemega® Salmon	90 mg EPA	96.4 mg EPA	2	EPA: 180 mg
	Oil Triglyceride	110 mg DHA	109.5 mg DHA		DHA: 220 mg

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Mean levels of EPA + DHA for four supplement groups at Day 0 and Day 28.

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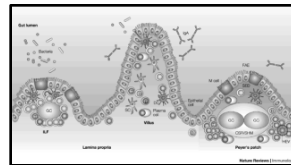
Intestinal Permeability and Systemic Inflammation

- When lipopolysaccharide (LPS), endotoxin from membrane of gram negative bacteria in intestinal lumen, enters bloodstream it binds Toll-like receptor 4, inflammation is activated, changing insulin signaling and triggering inflammatory mediators
- Chronic exposure to LPS may contribute to weight gain and type 2 DM. Obese people and diabetics have increased plasma LPS.

Boroni Moreira AP, et al. Nutr Hosp 2012; 27(2):382-90

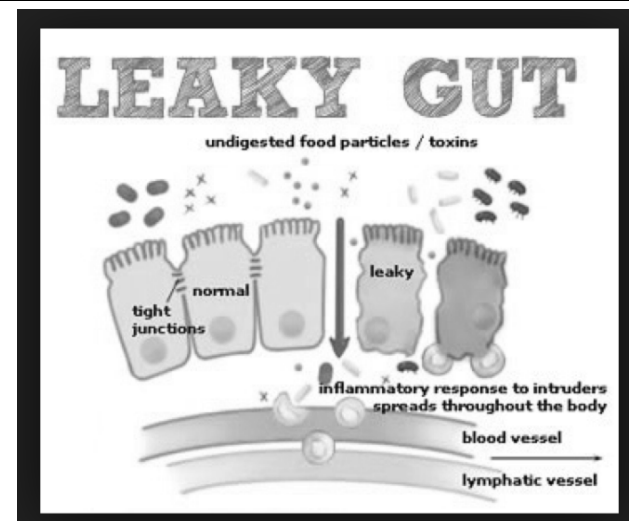
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Stress and The Gut



- Noradrenaline and adenosine released directly into gut mucosa from sympathetic nerve endings of ENS, causing mast cells to degranulate, releasing tryptase, histamine and other mediators.
- These neuromediators activate lymphocytes, stimulate epithelial chloride secretion and increase epithelial permeability.
- Subsequent movement of luminal bacteria into mucosa triggers further immune and inflammatory events.

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Leaky Gut and Depression?

- LPS found to be significantly higher in patients with chronic depression than in those without.
- Multiple linear regression analysis revealed that TLR4 is an independent risk factor relating to severity of major depression.

Maes M, et al. J Affect Disord. 2011;11:414-418.

Hung YY, et al. Psychiatry Res 2014; pii: S0165-1781(14)00653-2.

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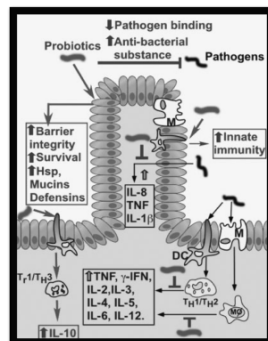
Pre and Probiotics

- Regulate/modulate immune functions, reduce risk intestinal infection.
- Improve intestinal barrier functions, reduce metabolic endotoxemia
- Induce hypo-responsiveness to food antigens
- Improve glucose control and reduce inflammatory cytokines.

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Anti-inflammatory effects of bifidobacteria by inhibition of LPS-induced NF- κ B activation

Christian U Riedel, Francis Foata, David Philippe, Oskar Adolfsson, Bernhard J Eikmanns, Stephanie Blum



Inflamm Bowel Dis • Volume 14, Number 11, November 2008

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Turmeric (*Curcuma longa*)



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Turmeric

- Curcumin is the yellow pigment in turmeric and has powerful health benefits.
- Human and animal data suggest beneficial for:
 - Brain health
 - Inflammation
 - Heart disease
 - Cancer
 - Depression
 - Skin Conditions

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Curcumin



- Beneficial effects on almost every known target or molecule involved in carcinogenesis.
- May prevent and be beneficial adjunctive treatment for colorectal cancer.
- Acts alone and synergistically with EGCG (green tea) to inhibit malignant changes in oral epithelium.

Irving GR, et al. Cancer Prev Res 2013; 6(2):119-28.

Khafif A, et al. Carcinogenesis 1998; 19(3):419-24.

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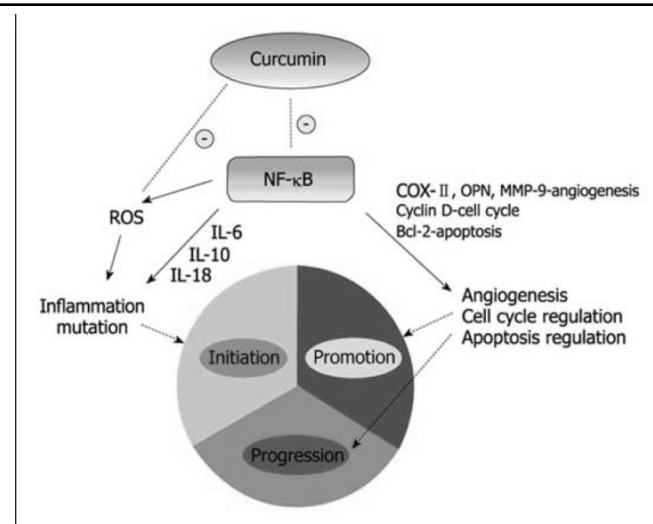


Mouthwash

- Turmeric mouthwash significantly reduced levels of radiation-induced oral mucositis at all time points.
- Lesser incidence of treatment breaks in first half of treatment schedule ($P < 0.01$) and reduced change in body weight ($P < 0.001$).

Rao S, et al. Integr Cancer Ther 2013; 13(3):201-210.

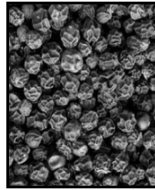
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Absorption



- Most research uses 1200-2000 mg of **curcumin**
- Curcumin is poorly absorbed from the GI tract.
- Preparations that increase absorption include: nanoformulations, phospholipid, and those with piperine.
- Doses up to 12 grams per day for three months not associated with toxicity **HOWEVER**, GI upset is common complaint.

Kanai M. World J Gastroenterol 2014; 20(28):9384-91.

Kakarala M, et al. Breast Cancer Res Treat 2009; 122:777-785

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Serving Size: 1 Vegetarian Capsule		
	Amount Per Serving	% Daily Value*
Turmeric root extract 4:1	500 mg	*
Serving Size: 1 Tablet		
Serving Per Container: 60		
	Amount Per Serving	% Daily Value
Total Carbohydrate	<1 g	<1%†
Turmeric extract (root), 95% curcuminoids	450 mg	**
Turmeric (root)	50 mg	**
Serving Size: 1 capsule		
Serving Per Container: 120		
	Amount Per Serving	% Daily Value
Turmeric (curcuma longa) extract (root) (standardized to contain 95% curcuminoids)	500 mg	*
Bioactive black pepper (piper nigrum) extract (fruit) (standardized to contain 95% piperine)	5.3 mg	*
Supplement Facts		
Serving Size: Two Capsules		
Servings Per Container: 60		
	Amount Per Serving	% DV
Two Capsules Contain:		
Curcumin Phytosome† (Curcuma longa extract (root) / Phosphatidylcholine complex)	500 mg	*

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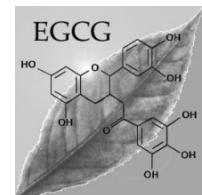
Green Tea (*Camellia sinensis*)



- **White, green, oolong and black teas** contain polyphenols and flavonoids, particularly catechins.
- Dominant catechin in green tea is epigallocatechin gallate (EGCG), which exerts potent anti-inflammatory and antioxidant activity.

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Green Tea in Cancer



- Potent inhibitor of NF- κ B and inducer of P53.
- Inhibits every step of carcinogenesis. Stimulates DNA repair and inhibits two proteins that promote tumor cell growth and migration—vascular endothelial growth factor (VEGF) and hepatocyte growth factor (HGF).

Butt MS, et al. Crit Rev Food Sci Nutr 2015; 55(6):792-805.

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Green Tea and Prostate Cancer



- RDBPCT 60 men with high-grade prostate intraepithelial neoplasia given 600 mg of EGCG or placebo for 1 year.
 - 3% in EGCG group converted to prostate cancer versus 30% in placebo group.
- UK study: 199 men (~74 years age) localized prostate cancer, randomized to oral capsule containing pomegranate, green tea, broccoli, turmeric; or identical placebo for 6 months.
 - Median rise in PSA in supplement group was 14.7% as opposed to 78.5% in the placebo group (P=0.0008).

Bettuzzi S, et al. Cancer Res 2006; 66(2):1234-40

Thomas R, et al. Prostate Cancer Prostatic Dis 2014; 17(2):180-6

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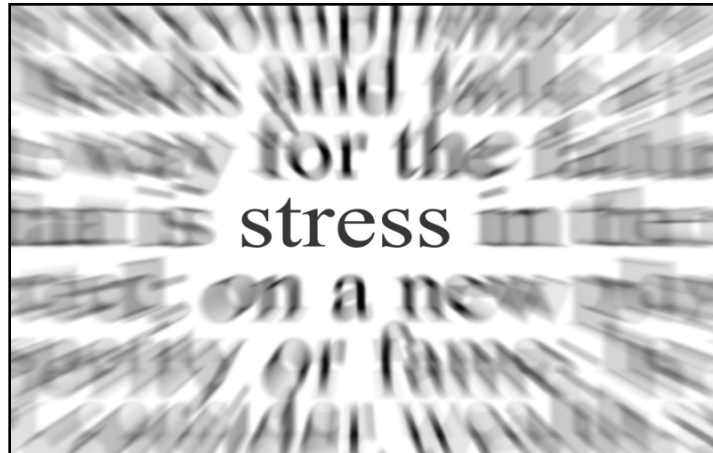
BENEFITS OF PHYSICAL ACTIVITY



- Maintain body weight and muscle tone.
- Resets stress response
- American Cancer Society, *exercise may reduce risk of cancer by reducing insulin and insulin-like growth factors levels, associated with increased cell/tumor growth.*
- Review of 73 studies found 25% average risk reduction for breast cancer amongst physically active women.

Lynch, et al. Recent Results Cancer Res 2011; 186:13-42

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How Prolonged Stress is Harmful

- Consequences of sustained high levels of stress hormones, principally cortisol, increases our risk for:
 - Obesity, heart disease, diabetes, irritable bowel syndrome, heartburn, low libido, infertility, hypothyroidism, infection, delayed healing, and even certain cancers.
- Scientists believe that prolonged elevation of stress hormones *may shorten our lifespan by 15 years.*

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A Nation on the Edge?



- According to CDC, 11% of Americans 12 and older take anti-depressant medications, a 400% increase from the 1980s, ~203 million prescriptions in 2011
- In 2011, ~63 million prescriptions for Xanax and Ativan (Xanax #1 psychiatric medication).
- Prevalence anxiety disorders ages 9 - 17 is 13%.
- 1 in 8 adolescents suffer from depression.

NCHS Data Brief Number 76, October 2011

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Mind-Heart



- InterHeart Trial, an international study conducted in 52 countries that included more than 27,000 participants, revealed that depression, social isolation and a feeling of hopelessness increased a woman's risk of having a heart attack **more** than diabetes, high blood pressure, smoking, or obesity.

Rosengren A, et al. *Lancet* 2004; 364:953-962.

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Social Isolation and Health



- 148 studies found that social isolation is:
 - As bad as smoking 15 cigarettes a day.
 - As dangerous as being an alcoholic.
 - As harmful as never exercising.
 - Twice as dangerous as obesity.

Holt-Lunstad J, et al. *PLoS Med* 2010; 7:e1000316

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Resiliency



- We are all born with innate resiliency, with the capacity to develop the traits seen in resilient survivors:
 - Social competence
 - Empathy, Caring, Communication skills, Humor
 - Autonomy
 - Sense of identity, Self-efficacy, Adaptive distancing from negative messages and conditions
 - A sense of purpose and belief in a bright future
 - Goal direction, Optimism, Spiritual connectedness

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The Power of Touch



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Neuroplasticity



- Brain's ability to change its structure and function; regularly used neural circuits are strengthened and expanded, those rarely engaged are weakened and contract.
- Long-time meditators have greater activation of areas responsible for sustaining attention, processing empathy, integrating emotion and cognition, and perceiving the mental and emotional state of others.

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Mindfulness Meditation Systematic Review

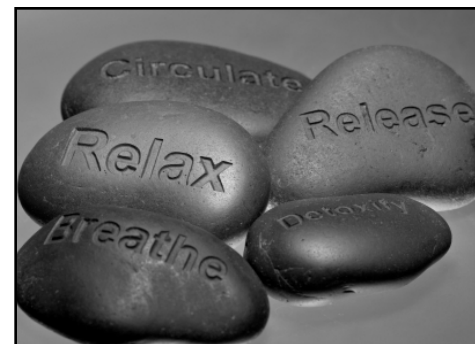


- 47 trials (n=3515) found it improved:
 - Anxiety
 - Depression
 - Pain

Goyal M, et al. JAMA Intern Med 2014; 174(3):357-68

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Just Breathe....



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Concluding Thoughts

- Chronic inflammation and insulin resistance are believed to be the root cause of many chronic diseases. Obesity is a major driver.
- Nutrition and exercise are vitally important for reducing disease risk.
- Chronic, persistent stress is also a significant cause of chronic inflammation and insulin resistance. Learning how to enhance resiliency and

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