

Nutrition and Lifestyle in Endometriosis

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- ❖ Epidemiological data on the relationship between diet endometriosis are scanty

- ❖ Associative studies > Interventional

- ❖ No clear Guideline

- ❖ **Preventive approach:** proliferation, vascularisation, peritoneal invasion, inflammation





Effectiveness of Dietary Interventions in the Treatment of Endometriosis: a Systematic Review

Konstantinos Nirgianakis¹  • Katharina Egger² • Dimitrios R. Kalaitzopoulos³ • Susanne Lanz¹ • Lia Bally⁴ • Michael D. Mueller¹

Nine human Studies:

- 2 RCT
- 2 Controlled
- 1 before after
- 1 qualitative study

12 animal studies:

- ✓ Supplementation with selected dietary components
- ✓ Exclusion of selected dietary components
- ✓ Complete diet modification.

Factors that may contribute to endometriosis and can be influenced by diet:

- ❖ Estrogen levels
- ❖ Inflammation
- ❖ Prostaglandin metabolism
- ❖ Angiogenesis
- ❖ Smooth muscle contractility
- ❖ Menstrual cyclicity

Estrogen Level

Since **1987** the role of diet in the development of **hormone-related diseases** has become a topic of interest

► Diet influence on:

- ✓ Ovarian and endometrial carcinogenesis
 - ✓ diet poor in vegetables and fruits and rich in fat increases the risk of endometrial cancer (Armstrong 1979)
- ✓ Development of benign gynaecological conditions
 - ✓ Fibroids (Chiaffarino 1999)

Foods to Eat & Foods to Avoid

Estrogen boosting foods

- ▶ Red meat
- ▶ Milk
- ▶ Alcohol
- ▶ Legumes
- ▶ Grains

- ▶ Low in fiber
- ▶ High in sugar & refined carbs
- ▶ Deficient in high quality “good fats”

Estrogen lowering foods

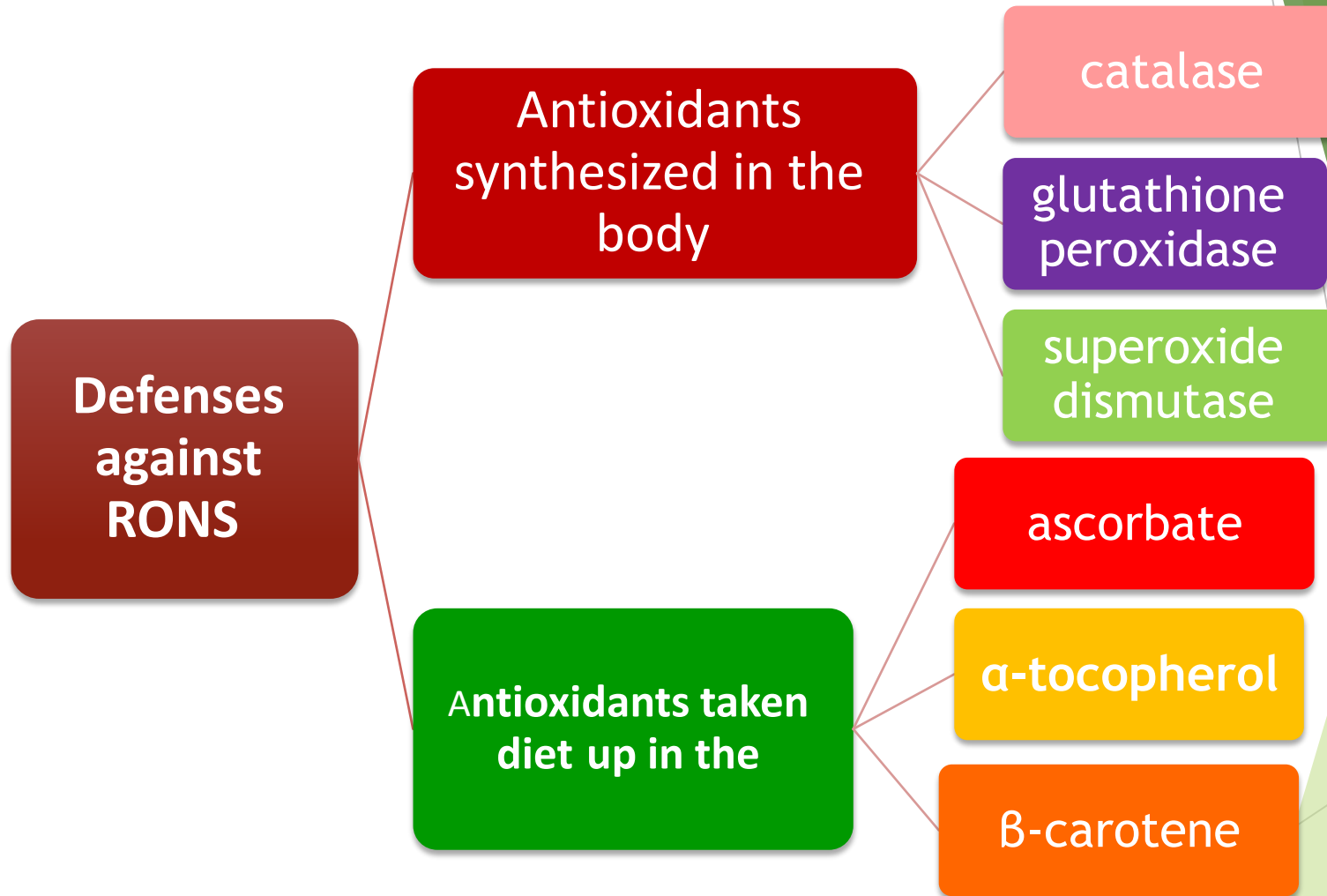
- ▶ Pomegranate
- ▶ Mushroom
- ▶ curcumin
- ▶ Whey protein
- ▶ Flax seed
- ▶ Grape
- ▶ Coconut
- ▶ Olive oil
- ▶ Garlic
- ▶ Cruciferous vegetables
- ▶ Nuts
- ▶ Eggs
- ▶ Avocados

Inflammation & Pain

The presence of elevated concentrations of free radicals and lowered antioxidant potential leads to oxidative stress

Increase in lipid peroxidation markers in the peripheral blood and peritoneal fluid of women with endometriosis





Research Article

**The Effect of Combined Vitamin C and Vitamin E
Supplementation on Oxidative Stress Markers in Women with
Endometriosis: A Randomized, Triple-Blind Placebo-Controlled
Clinical Trial**

Pain Research and Management Volume 2021

- vitamin C (1000 mg/day, 2 tablets of 500 mg)
- vitamin E (800 IU/day, 2 tablets of 400 IU)
- combination
- daily for 8 weeks.

**vitamins C and E, are
direct ROS scavengers**

The intake of vitamin C and vitamin E
supplements effectively reduced
dysmenorrhea severity and improved
dyspareunia and severity of pelvic pain.



Review

Towards Personalized Antioxidant Use in Female Infertility: Need for More Molecular and Clinical Studies

Over medication resulting in an opposite extreme, reductive stress, which can be counterproductive with regard to reproductive function

Efficacy of melatonin in the treatment of endometriosis: A phase II, randomized, double-blind, placebo-controlled trial

Pain: [June 2013 - Volume 154 - Issue 6 - p 874-881](#)

Melatonin has a particular position among antioxidants because it combines the properties of both a direct and an indirect antioxidant agent , **main pineal hormone** synthesized from **tryptophan** in response to darkness

melatonin modulates the secretion of brain-derived neurotrophic factor (BDNF)and pain through distinct mechanisms.

reduced the risk of using an analgesic by 80%

Melatonin activity and receptor expression in endometrial tissue and endometriosis FREE

A A Mosher, M W Tsoulis, J Lim, C Tan, S K Agarwal, N A Leyland, W G Foster ✉

Human Reproduction, Volume 34, Issue 7, July 2019, Pages 1215–1224,

<https://doi.org/10.1093/humrep/dez082>

Published: 18 June 2019 **Article history** ▼

melatonin receptors (melatonin receptor 1A (MR1A) and melatonin receptor 1B (MR1B)) expressed in human endometrium and endometriotic tissue

Beneficial effects of melatonin seen **in culture** have yet to be comprehensively evaluated in women with endometriosis.

Melatonin Boosters: Food to eat







Foods High in Melatonin

Bananas are great sliced over your cereal and yoghurt

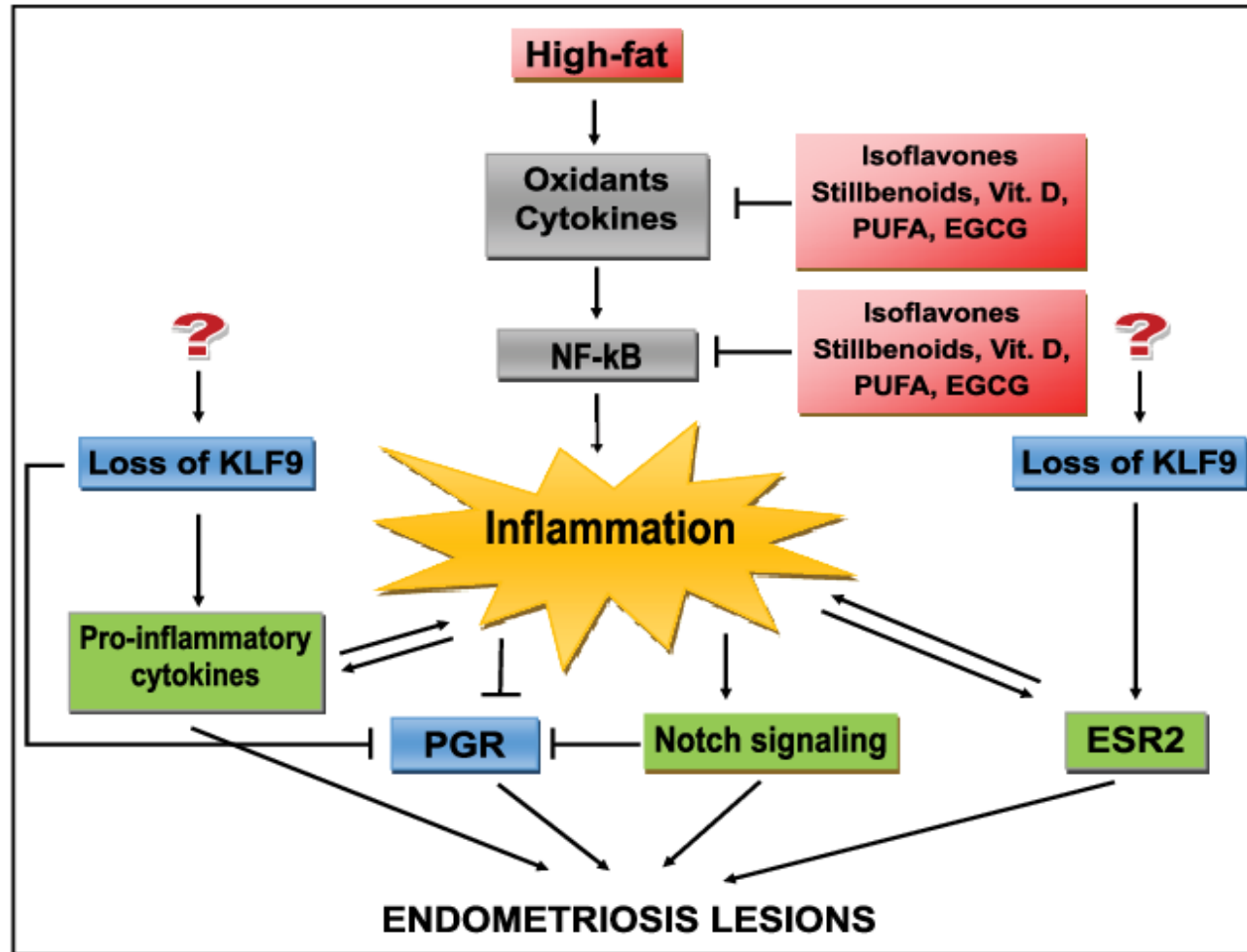
Nibble on half a dozen organic almonds before dinner

Organic spinach - swap lettuce for flat leaf spinach

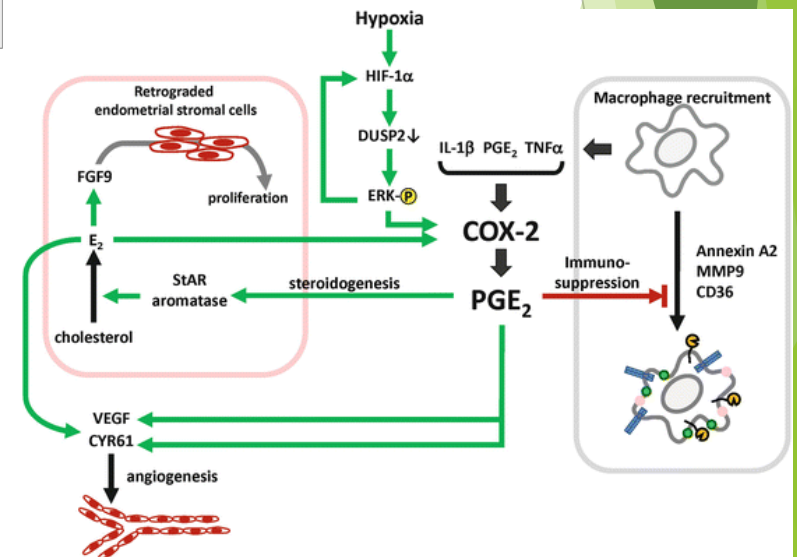
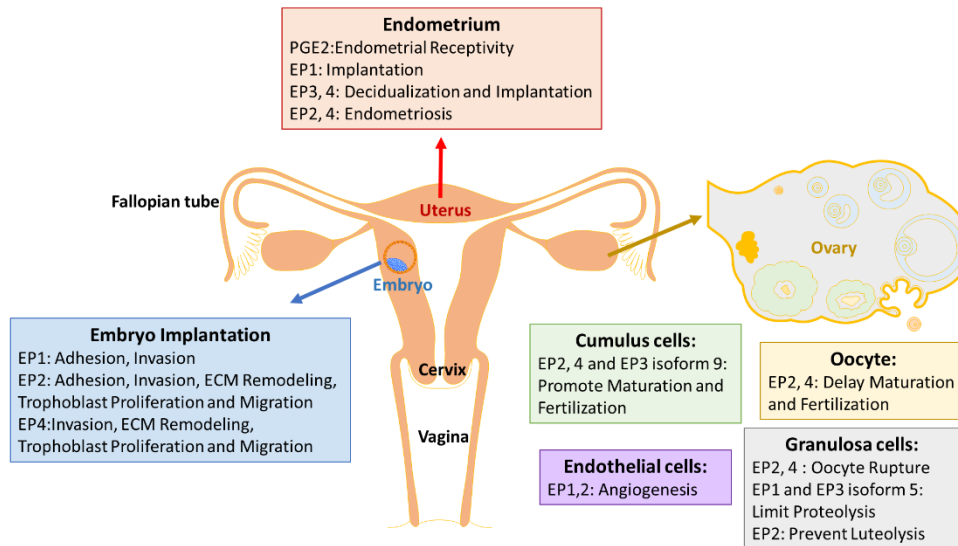
Fresh organic tomatoes chopped into salads



FAT consumption and inflammation



Prostaglandine Metabolism



Uterus

Estrogen/Progesterone

CXCL12/CXCR4

Endometrium autophagy

Recruit

Endometrial exfoliation

Menstruation

CD16⁺Grzm⁺IFN γ ⁺
NK cell

Immune defense

Retrograde

Endometriotic microenvironment (pelvic cavity)

High estrogen

ESR

Ectopic endometrium autophagy

PGE₂

Implantation
Growth
Angiogenesis

Endometriosis

IL-8

IL-23

IL-15

COX-2⁺CD16⁺

NK cell

IL-10

TGF- β

Immune escape

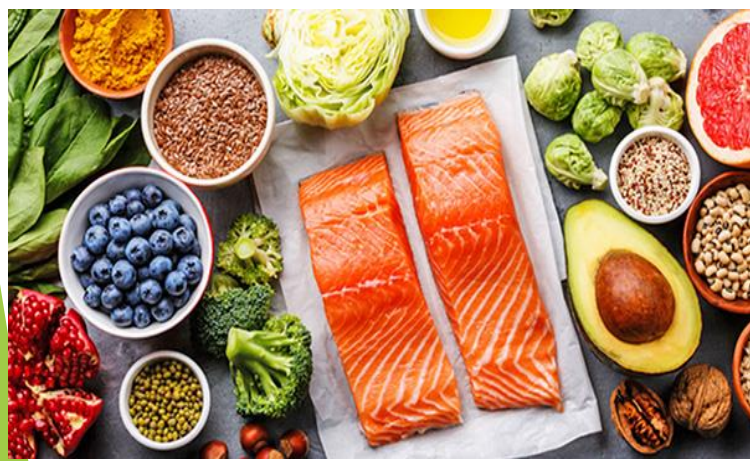
PGE₂

M2 macrophage

Activated T cell

SNCA, RGS19, IGF1, ATG9B, ATG12, ATG10, IFNG, PIK3CG, DAPK1, ATG16L1, IRGM, ULK1

CXCR4, ESR1, mTOR



Inflammatory Foods

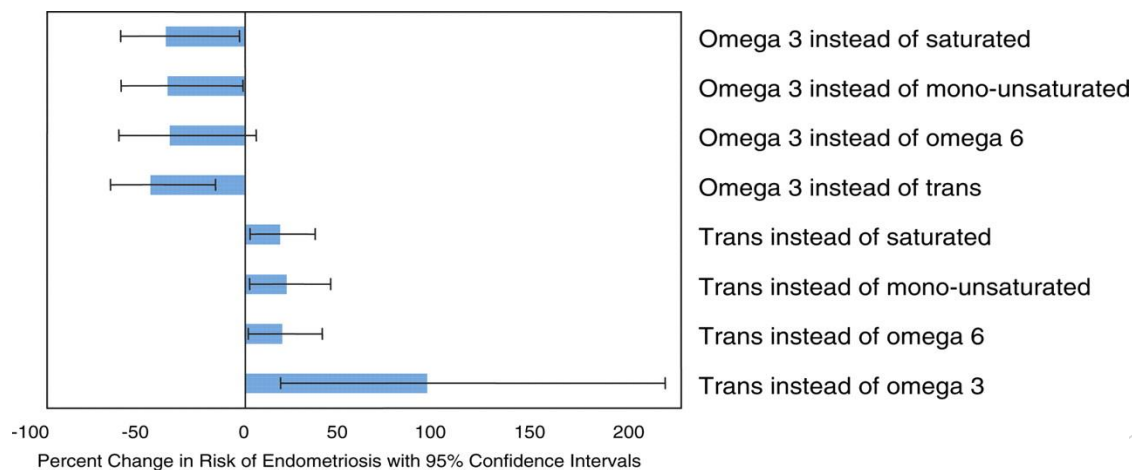
A prospective study of dietary fat consumption and endometriosis risk (1)

Hum Reprod (2010) 25(6): 1528-1535

- ▶ Nurses' Health Study II cohort from September 1989 to 1st June 2001
- ▶ Dietary fat was assessed via food frequency questionnaire in 1991, 1995 and 1999
- ▶ N= 1199 laparoscopically confirmed endometriosis

A prospective study of dietary fat consumption and endometriosis risk (2)

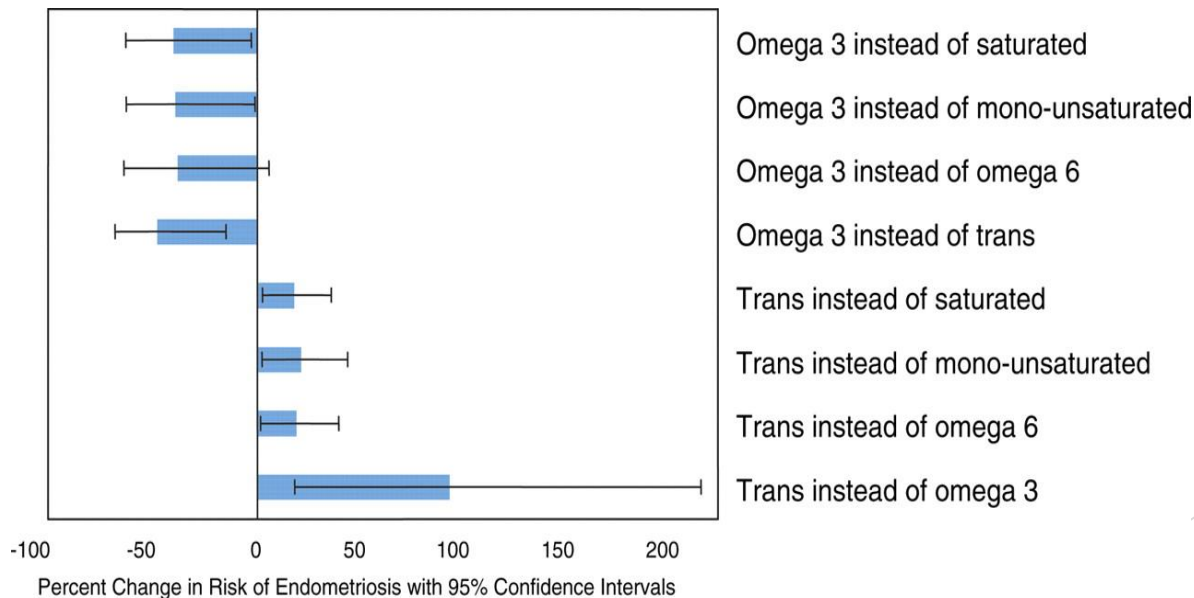
- ▶ Total fat consumption was not associated with endometriosis risk.
- ▶ Highest fifth of long-chain **omega-3** fatty acid consumption were **22% less** likely to be diagnosed with endometriosis compared with those with the lowest fifth of intake [95% confidence interval (CI) = 0.62-0.99; *P*-value, test for linear trend (Pt) = 0.03]



A prospective study of dietary fat consumption and endometriosis risk (3)

Hum Reprod (2010) 25(6): 1528-1535

- Highest quintile of **trans-unsaturated fat** intake were **48% more likely** to be diagnosed with endometriosis (95% CI = 1.17-1.88; Pt = 0.001).



- ▶ Observed the suggestion of an increased risk of endometriosis with animal fat consumption and specifically a significantly **increased risk of nearly 80% with palmitic acid** intake
- ▶ The primary contributors to **palmitic acid** consumption were animal products—**meats and dairy** foods—which perhaps supports the observation of increased endometriosis likelihood with greater red meat consumption observed within the sole human study published to date
- ▶ Fatty cuts of red meat, as well as **skin-on poultry**

Supplementation with vitamin D or ω -3 fatty acids in adolescent girls and young women with endometriosis (SAGE): a double-blind, randomized, placebo-controlled trial

Randomized Controlled Trial > Am J Clin Nutr. 2020 Jul 1;112(1):229-236.

Insight on Polyunsaturated Fatty Acids in Endometrial Receptivity

Biomolecules 2022, 12(1), 36; <https://doi.org/10.3390/biom12010036>

The effect of dietary supplementation with fish oil fatty acids on surgically induced endometriosis in the rabbit.

Fertil Steril 1988 Apr;49(4):698-703

- ▶ N= 38
- ▶ Fish oil containing eicosapentaenoic acid and docosahexaenoic acid (EPA/DHA) or olive oil (control).
- ▶ Peritoneal fluid **PGE2 and PGF2-alpha** concentrations were significantly lower in the EPA/DHA group versus controls ($P < 0.05$, $P = 0.05$).
- ▶ Total **endometrial implant diameter** 8 weeks after induction of endometriosis was significantly smaller in the experimental group (3.1 ± 0.2 cm) compared with the controls (4.0 ± 0.3 cm) ($P < 0.03$).

High omega-3:omega-6 fatty acid ratios in culture medium reduce endometrial-cell survival in combined endometrial gland and stromal cell cultures from women with and without endometriosis

Gazvani MR, Smith L, Haggarty P, Fowler PA, Templeton A
Fertil Steril 2001;76:717-722

- ▶ Endometrial cell **survival** is decreased in cultures containing a high proportion of long-chain **n-3** fatty acids (i.e. eicosapentaenoic acid).
- ▶ However, cell survival is not affected in cell cultures containing a high proportion of long-chain n-6 fatty acids (i.e. arachidonic acid) or equal amounts of n-3 and n-6 fatty acids.

Antiangiogenic foods: Foods To eat

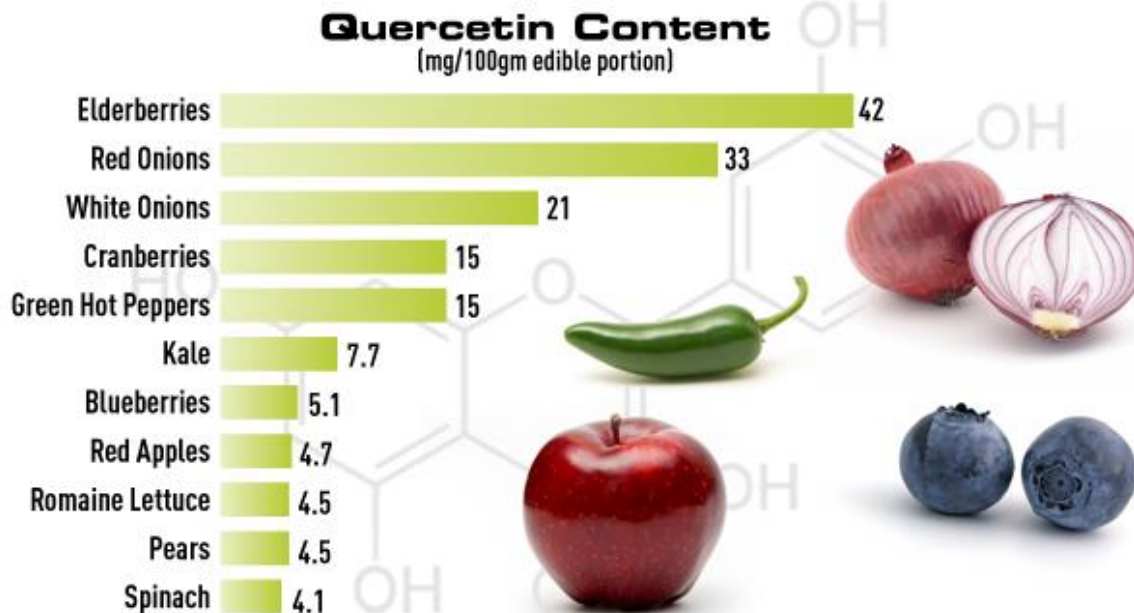
Green Tea	Dark Chocolate	Soy Beans
Artichokes	Tomatoes	Strawberries
Blackberries	Raspberries	Blueberries
Cranberries	Garlic	Apple
Pineapple	Cherries	Oranges
Grapefruit	Lemons	Red Grapes
Red Wine	Kale	Broccoli
Cauliflower	Brussels Sprouts	Bok Choy
Ginseng	Licorice	Lavender
Turmeric	Maitake Mushroom	Ginger
Parsley	Pumpkin	Olive Oil
Grape Seed Oil	Nutmeg	compiled by: Christianna Pierce, MA, RD

Modern Approaches

- ▶ Antioxidants
- ▶ Fatty acids
- ▶ Antiangiogenic foods
- ▶ Resvertrol
- ▶ Quercetin
- ▶ Epigalactocatechin
- ▶ Vit D
- ▶ Gut Microflora

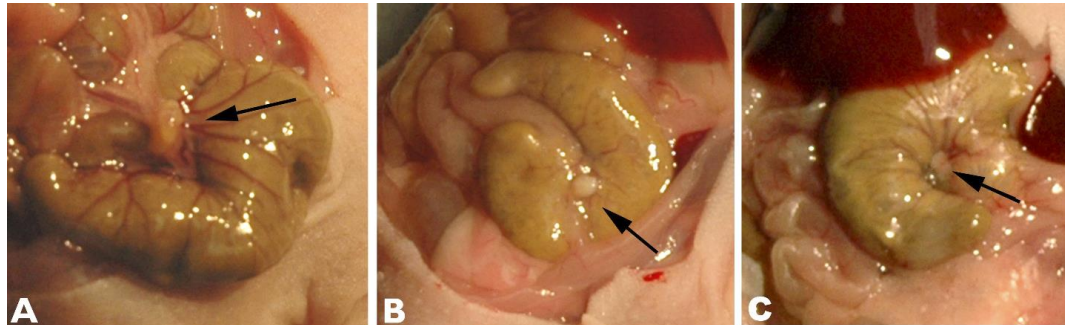
Inhibition effect and mechanisms of quercetin on surgically induced endometriosis

- ▶ 2009 Mar;40(2):228-31, 244.
- ▶ Quercetin inhibits surgically induced endometriosis in rats, and the possible mechanism is to inhibit the expression of Heat shock protein 70 and Vascular endothelial growth factor.



Resveratrol inhibits development of experimental endometriosis in vivo and reduces endometrial stromal cell invasiveness in vitro.

• BIOLOGY OF REPRODUCTION 84, 106-112 (2011)



- 1) Significant decrease in the number and size of endometriotic lesions
- 2) lesions exhibit evidence of increased apoptotic activity
- 3) Induces a concentration-dependent reduction of invasiveness.

A) after 10 days of treatment with vehicle
B) after 10 days of resveratrol treatment
C) after 20 days of resveratrol treatment



Green tea

- ▶ Anti-oxidant activity
- ▶ Anti-mitotic
- ▶ Anti-inflammatory
- ▶ Anti-angiogenic

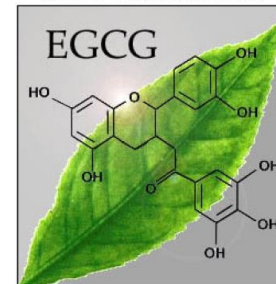


Epigallocatechin-3-gallate inhibits estrogen-induced activation of endometrial cells *in vitro* and causes regression of endometriotic lesions *in vivo*

Hum. Reprod. (2008) 23 (10): 2308-2318.

- ▶ Suppresses E₂-stimulated activation, proliferation and VEGF expression of endometrial cells *in vitro* (all $P < 0.05$)
- ▶ Might be a promising therapeutic agent in the treatment of endometriosis, preventing the establishment of new endometriotic lesions.

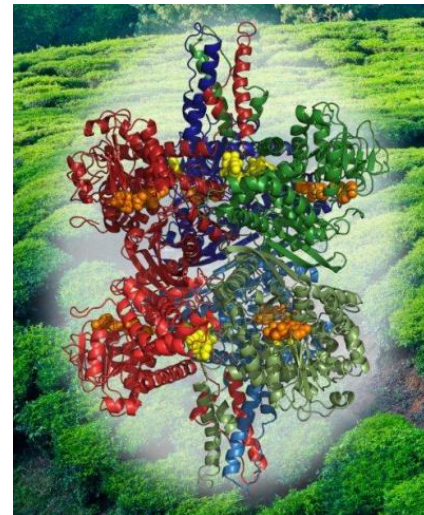
Galatul de Epigallocatechina
EGCG extr.stand. 50%



Anti-angiogenic effects of green tea catechin on an experimental endometriosis mouse model

Hum. Reprod. (2009) 24 (3): 608-618.

- ▶ EGCG significantly inhibits the development of experimental endometriosis through anti-angiogenic effects



Selected food intake and risk of endometriosis

Parazzini F, Chiaffarino F, Surace M

Hum Reprod 2004, 19:1755-1759

- ▶ Green vegetables (OR: 0.3)
- ▶ Fresh Fruits (OR: 0.6)
- ▶ High intake of beef and other red meat (OR:2.0)
- ▶ Ham (OR:1.8)
- ▶ Milk, liver, carrots, cheese, fish and whole-grain foods, as well as coffee and alcohol not significantly related to endometriosis

Endometriosis is associated with an altered profile of intestinal microflora in female rhesus monkeys

Hum. Reprod. (2002) 17(7): 1704-1708

Endometriosis is associated with an altered profile of intestinal microflora in rhesus monkeys.

It is possible that the microflora were affected by endometriosis-associated intestinal inflammation

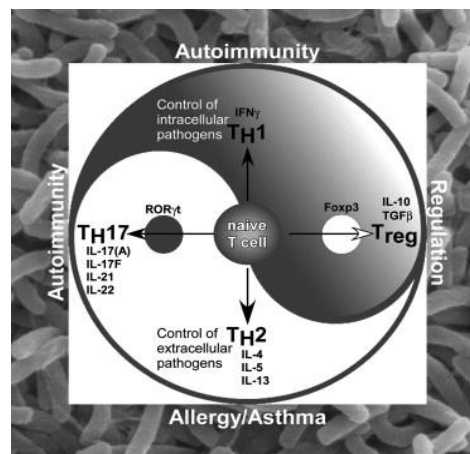


Review

Intricate Connections between the Microbiota and Endometriosis

Irene Jiang, Paul J. Yong, Catherine Allaire and Mohamed A. Bedaiwy *

- ▶ Dybiosis: Imbalances in gut and reproductive tract microbiota composition
- ▶ Disrupt normal immune function, leading to the elevation of proinflammatory cytokines
- ▶ Compromised immunosurveillance
- ▶ Altered immune cell profiles





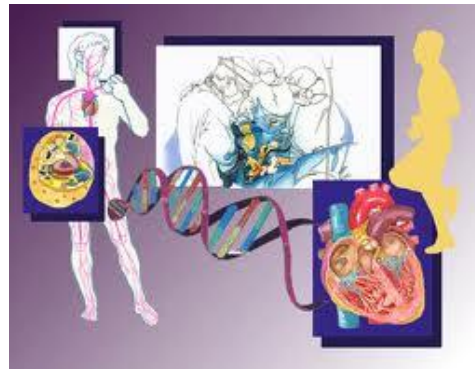
Our microbial census exceeds the total number of our own human cells by ~**10 fold**

Genomes of microbiome may contain >**100 fold** more genes than our 'own' genome

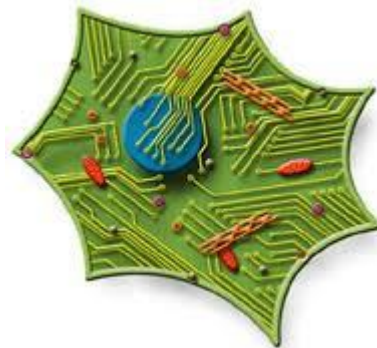
Integral part of our genetic landscape ('human metagenome') and of our genetic evolution

Systems biology has irrevocably altered the view that mammalian metabolism is solely influenced by the human genome

The concept of ‘personalized’ health care is therefore totally dependent on a better understanding of the gut **microbiome** from the top down and the bottom up



These approaches will have an impact across medicine and surgery, and they will deliver the next generation of drug therapies



Hormonal suppression treatment or dietary therapy versus placebo in the control of painful symptoms after conservative surgery for endometriosis stage III-IV. A randomized comparative trial

Francesco Sesti¹, Adalgisa Pietropolli, Talia Capozzolo, Patrizia Broccoli, Silvia Pierangeli, Maria Rosa Bollea, Emilio Diccione

vitamins (B6, A, C, E)

Minerals salts (Ca, Mg, Se, Zn, Fe)

VSL3 lactic ferments (Bifidobacterium breve, Bifidobacterium longum, Bifidobacterium infantis, Lactobacillus acidophilus, Lactobacillus casei, Lactobacillus bulgaricus, Streptococcus thermophilus)

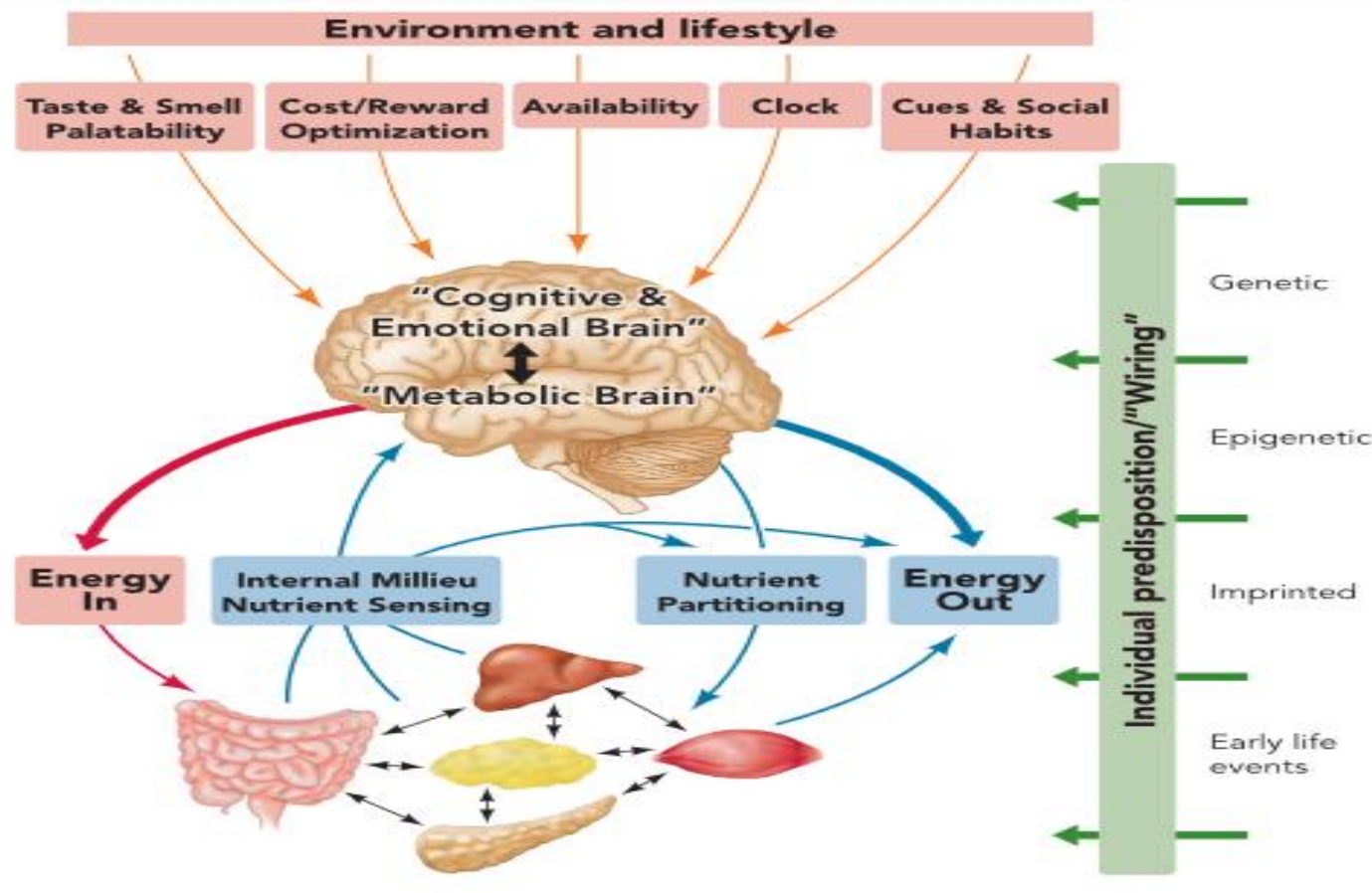
omega-3 and omega-6 fatty acids (fish oil)

Postoperative hormonal and dietary therapies were the most effective treatment, not only in terms of painful symptoms control, but also in terms of **general health** perception ($P < .001$) and **vitality** ($P < .001$), when compared with postoperative placebo administration

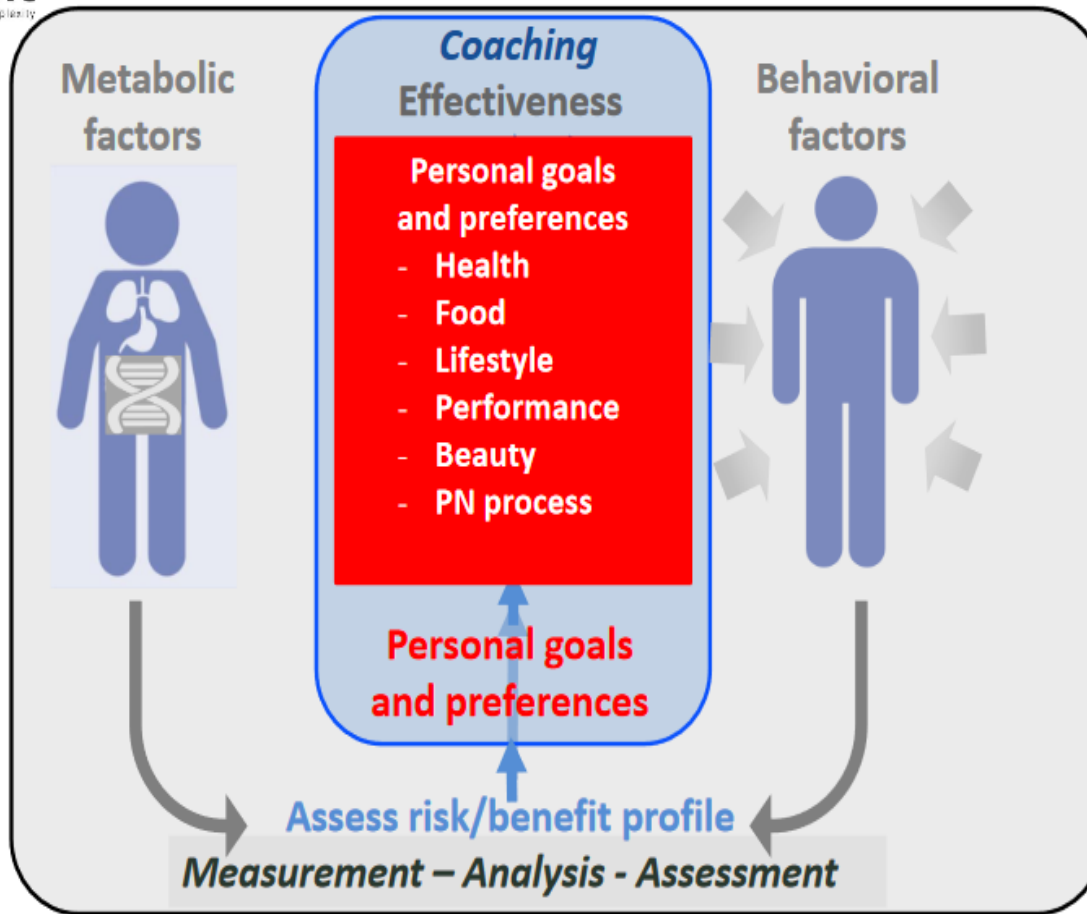
Dieting is more than this...



Neural Systems Controlling the Drive to Eat: Mind Versus Metabolism



...
complexity





Thanks For Your Attention



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Dr.ladangiahi